Facultad de Ciencias

Departamento de Química Orgánica

Oxidative dearomatization of phenols mediated by Oxone® or aerobic photooxidation.

TESIS DOCTORAL

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Content

Chapter 1

General introduction and objectives

General introduction

Over the years, the controlled oxidation of organic compounds has been deeply studied, particularly for aromatic derivatives bearing alkyl substituents that are prone to suffer over-oxidation. The oxidative dearomatization of phenols,[1] which is often present in the biosynthesis of many natural products with important biological properties,[2] gives rise to very interesting products from the synthetic point of view. Depending on the substitution and functionalities, phenols can be dearomatized into various species such as quinones, masked benzoquinones, acetates derived from quinols or quinols (*Figure 1.1*).[1, 3, 4] The variety of compounds that could be formed upon oxidation of a phenol reveals that the control of the transformation is essential looking for the final application of the procedure in the direct synthesis of the different products that can be prepared.

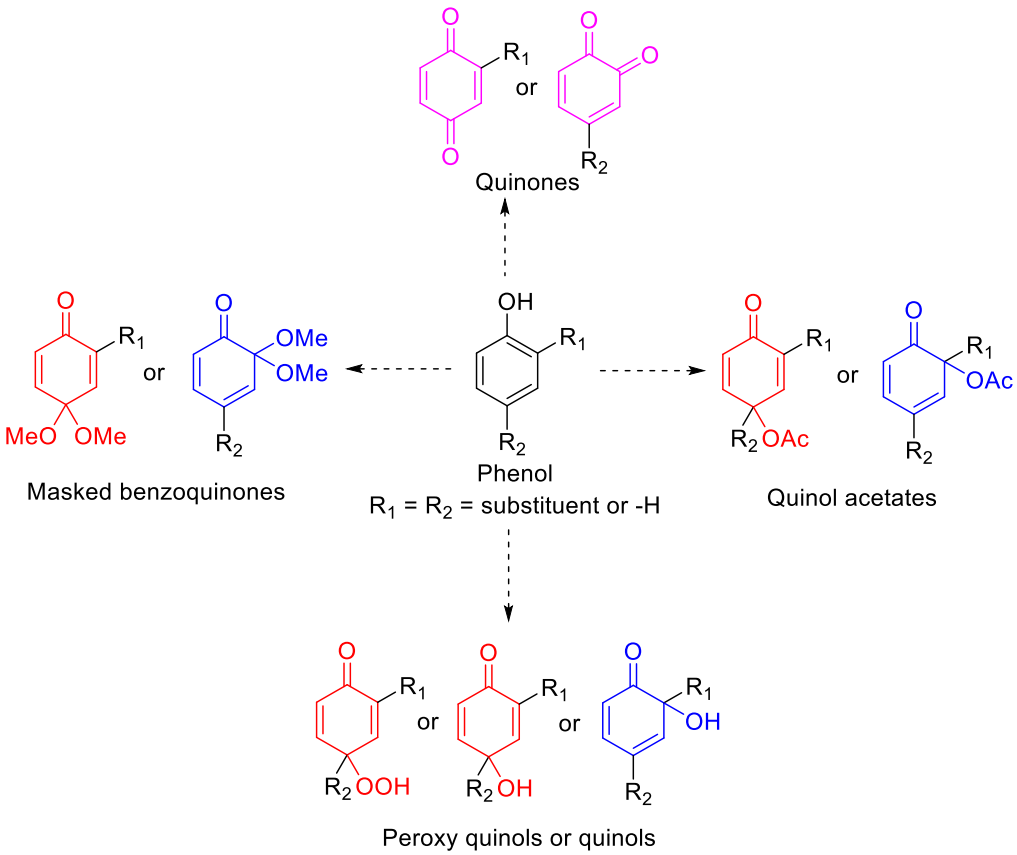


Figure 1.1. Possible oxidative dearomatization products resulting from substituted phenols

[1] a) S. Quideau, L. Pouysegu, P. A. Peixoto, D. Deffieux, *Top Curr Chem* **2016**, *373*, 25. b) S. P. Roche, J. A. Porco Jr., *Angew. Chem. Int. Ed.* **2011**, *50*, 4068.
[2] L. Pouysegu, D. Deffieux, S. Quideau, *Tetrahedron* **2010**, **66**, 2235.
[3] D. Magdziak, S. J. Meek, T. R. R. Pettus, *Chem. Rev.* **2004,** *104,* 1383.
[4] a) Q. Ding, Y. Ye, R. Fan, *Synthesis* **2013**, *45*, 1-16; b) C.-X. Zhuo, W. Zhang, S.-L. You, *Angew. Chem. Int. Ed.* **2012**, *51*, 12662-12686; c) S. P. Roche, J. A. Porco Jr., *Angew. Chem. Int. Ed.* **2011**, *50*, 4068-4093.

In the case of quinol derivatives, this transformation converts planar systems into new compounds bearing stereogenic centers, whose configuration can be controlled by asymmetric procedures, using starting materials with chiral substituents or chiral reagents, catalysts, or additives in a diastereo- or enantioselective manner.[1,4,5] Thus, the search for selective methods to effect the oxidative dearomatization of *para*-alkyl phenols into 4-alkyl-4-hydroperoxy-2,5-cyclohexadienones (*para*-peroxyquinols), 4-alkyl-4-hydroxy-2,5- cyclohexadienones (*para*-quinols) and/or 6-alkyl-6-hydroxy-2,4-cyclohexadienone (*ortho*-quinols) is of huge interest because of the essential role played by such derivatives in the skeletons of many natural products.[1,4] Although natural products with peroxide groups are relatively abundant,[6] there are only a few examples of natural derivatives possessing the *para*-peroxy-2,5-cyclohexadienone structure. Glutinosin C (**1**) shown in *Figure 1.2*, is an example of a natural *para*-peroxyquinol. [7] In contrast, both the *para*-quinol and the *ortho*-quinol moieties are found in a great number of natural products, such as dysideanone E (**2**)[8] and (+)-epoxysorbicillinol (**3**)[9] or involucratusol E (**4**),[10] respectively. (*Figure 1.2*).

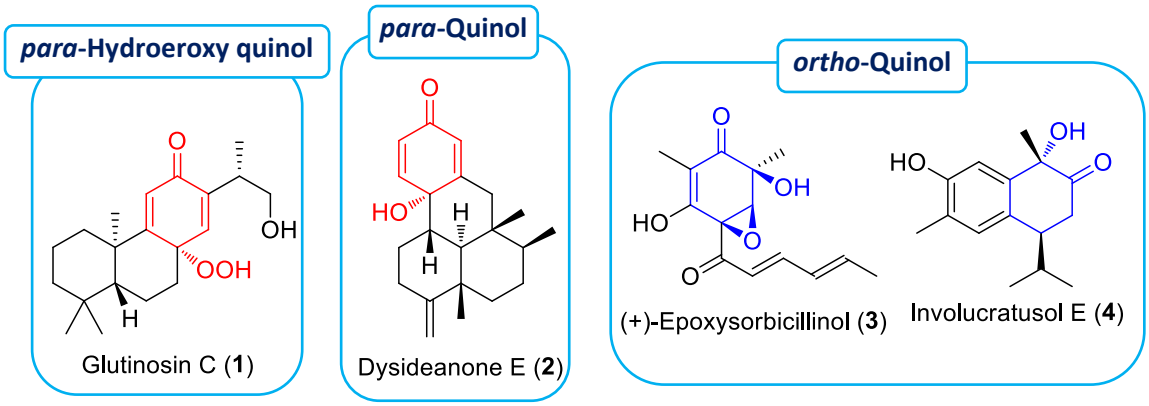


Figure 1.2. Examples of natural para-peroxy quinol, para-quinol and ortho-quinol structures.

[5] a) W.-T. Wu, L. Zhang, S.-L. You, *Chem. Soc. Rev.*, **2016**, *45*, 1570. b) W. Sun, G. Li, L. Hong, R. Wang, *Org. Biomol. Chem. 2016*, *14*, 2164. c) A. M. Harned, *Tetrahedron Lett.* **2014**, *55*, 4681. d) C.-X. Zhuo, W. Zhang, S.-L. You, *Angew. Chem. Int. Ed.* **2012**, *51*, 12662.

[6] a) M. T. Jamison, D. S. Dalisay, T. F. Molinski, *J. Nat. Prod.* **2016**, *79*, 555-563; b) M. D. Norris, M. V. Perkins, ***Nat. Prod. Rep*** **2016**, ***33***, 861-880; c) V. M. Dembitsky, *J. Mol. Genet. Med.* **2015**, *9*, 1-18

[7]. X. Niu, S. Li, Q. Zhao, Z. Lin, H. Sun, Y. Lu, L. Zhang, Q. Zheng, *Tetrahedron Lett.* **2002**, *43*, 5277-5280.

[8] W.-H. Jiao, G.-H. Shi, T.-T. Xu, G.-D. Chen, B.-B. Gu, Z. Wang, S. Peng, S.-P. Wang, J. Li, B.-N. Han, W. Zhang, H.-W. Lin, *J. Nat. Prod.* **2016**, *79*, 406-411

[9] A. M. Harned, K. A. Volp, *Nat. Prod. Rep.* **2011**, *28*, 1790-1810.

[10] Q. Li, J. Luo, Y. Zhang, H. Zhao, M. Yang, L. Kong, *Tetrahedron* **2016**, *72*, 6566-6571.

Moreover, these oxidized structures are valuable building blocks in organic synthesis because they could be used for further transformations to afford natural products or more complex molecules with novel therapeutic properties.[11]

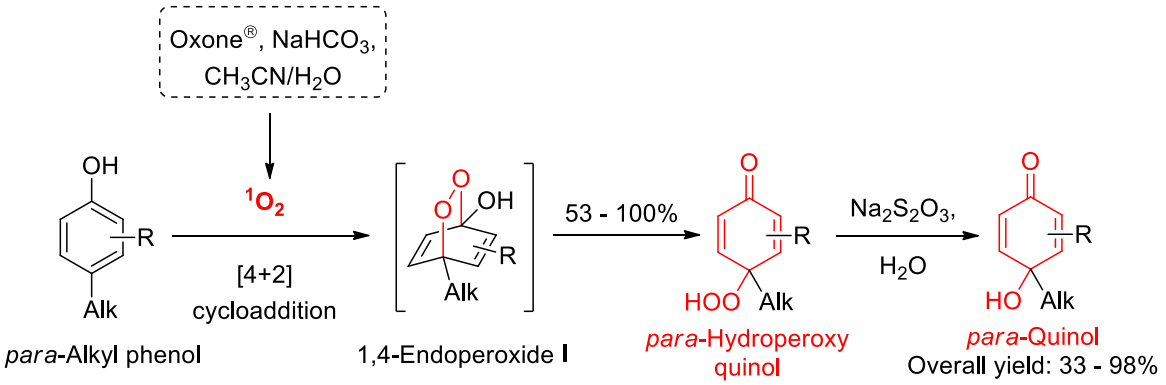
In 2006, our research group uncovered for the first time the use of Oxone® for the simple and selective oxidative dearomatization of differently substituted *para*-alkyl phenols into the corresponding *para*-peroxyquinols or *para*-quinols, after a subsequent reduction step with sodium thiosulfate ($Na_2S_2O_3$).[12] Oxone® is the trade name of the triple salt $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$. Peroxysulfuric acid ($H_2SO_5$), commonly called Caro's acid, is an explosive oxidizing agent, whose isolation and purification is difficult to carry out.[13] Nowadays, the stable triple salt is commercialized by Evonik under the trade name Caroat® and DuPont under the trade name Oxone®. This commercial triple salt is an easy to handle, not toxic, soluble in water, cheap and stable white crystallin solid that only contains about 50% of the active oxidant per mole, the anion peroxymonosulfate (HSO_5^-). The oxidative dearomatization process is carried out in the presence of a weak base such as $NaHCO_3$ in a mixture of CH_3CN and H_2O, affording the *para*-peroxyquinols with yields from good to excellent under very mild conditions. The proposed mechanism is initiated with the formation of singlet oxygen ($^1O_2$) by decomposition of Oxone® in the aqueous basic medium.[14] This singlet oxygen species is the responsible for the oxidative dearomatization of *para*-alkyl phenols through a [4+2] cycloaddition, giving rise to the unstable 1,4-endoperoxide **I**, which spontaneously evolved to the *para*-peroxyquinol structure, as shown in *Scheme 1.1*.

[11] J. E. Baldwin, R. M. Adlington, V. W.-W. Sham, R. Marquez, P. G. Bulger, Tetrahedron **2005**, *61*, 2353-2363. For recent examples, see: a) L. Pan, J. Dong, D. Xie, Y. Li, Q. Liu, *Adv. Synth. Catal.* **2018**, *360*, 958-964; b) N. J. Green, C. A. Connolly, K. P. W. Rietdijk, G. S. Nichol, F. Duarte, A. L. Lawrence, *Angew. Chem. Int. Ed.* **2018**, *57*, 6198-6202; c) J.-J. Xing, Y.-N. Gao, M. Shi, *Adv. Synth. Catal.* **2018**, *360*, 1-9.

[12] M. C. Carreño, M. González-López, A. Urbano, *Angew. Chem.Int. Ed.* **2006**, *45*, 2737-2741.

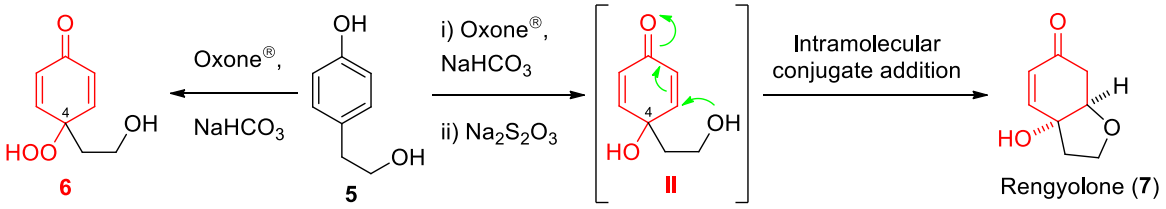
[13] a) H. Caro, *Angew. Chem.* **1898**, 845; b) F. Epifano, M. C. Marcotullio, M. Curini, *Trends Org. Chem.* **2003**, *10*, 21.

[14] a) W. Adam, D. V. Kazakov, V. P. Kazakov, *Chem. Rev.* **2005**, *105*, 3371-3387; b) D. F. Evans, M. W. Upton, *J. Chem. Soc. Dalton Trans.* **1985**, 1151-1153; c) D. L. Ball, J. O. Edwards, *J. Am. Chem. Soc.* **1956**, *78*, 1125-1129.



Scheme 1.1. Oxidative dearomatization of para-alkyl phenols with the system Oxone®/$NaHCO_3$/CH_3CN

When the starting phenol was adequately substituted, as in the case of *para*-(2-hydroxyethyl)phenol (**5**), the reaction with Oxone® afforded *para*-peroxy quinol **6**, and if this reaction was followed by the addition of $Na_2S_2O_3$ phenol **5** directly furnished rengyolone (**7**). This natural *cis*-fused hydrobenzofuran was formed by intramolecular conjugate addition of the hydroxy ethyl chain into the cyclohexadienone framework of the initially formed *para*-quinol **II** (*Scheme 1.2*).[15]



*Scheme 1.2. Synthesis of Rengyolone (**7**)*

Later, this efficient and mild oxidative dearomatization process was used as the key step in the total synthesis of more complex natural products such as cochinchinenone (**8**),[16a] cephalosporolide G (**9**),[16b] or cleroindicin D (**10**)[15] (*Figure 1.3*).

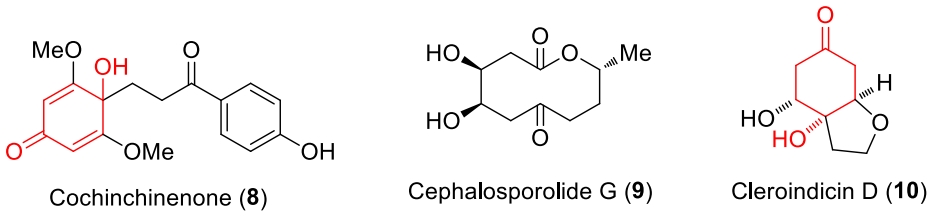


Figure 1.3. Natural products synthesized in our group using reaction with Oxone® / $NaHCO_3$ as the key step.

[15] S. Barradas, M. C. Carreño, M. González-López, A. Latorre, A. Urbano, *Org. Lett.* **2007**, *9*, 5019-5022.
[16] a) S. Barradas, G. Hernández-Torres, A. Urbano, M. C. Carreño, *Org. Lett.* **2012**, *14*, 5952-5955; b) S. Barradas, A. Urbano, M. Carmen Carreño, *Chem. Eur. J.* **2009**, *15*, 9286-9289.

Taking into account the results obtained by our research group, a project devoted to the synthesis of the aglycones of angularly oxygenated angucyclines, natural tetracyclic derivatives with important biological activity, was initiated, using the oxidative dearomatization of suitable phenols with Oxone® as the key step. This subgroup of angucyclinones is characterized by bearing hydroxy groups at the angular AB ring junction (C_{4a} and C_{12b} positions) as shown in *Figure 1.4* for the structures of the angucyclines aquayamycin (**11**) and urdamycinone F (**12**).[17] Also, this group of oxygenated derivatives displays important therapeutical activities and their total synthesis is still a synthetic challenge, not well solved up to date.[18]

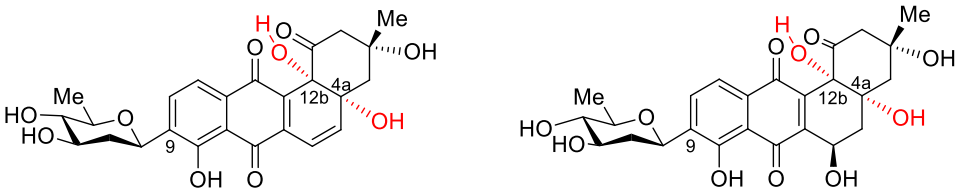
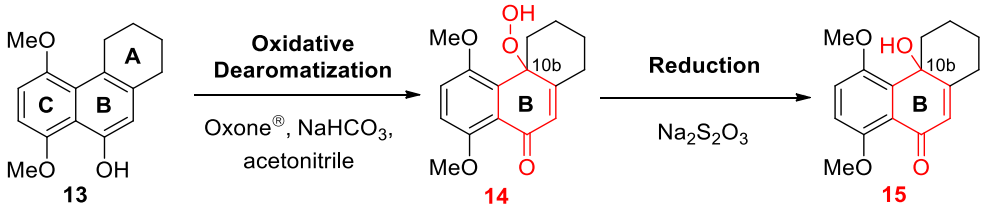


Figure 1.4. Angucyclines with angular hydroxy groups at C_{4a} and C_{12b}

The research began with a study on a tricyclic model, 5,8-dimethoxy-1,2,3,4-tetrahydrophenanthren-9-ol (**13**) (*Scheme 1.3*). The oxidative dearomatization of this phenol with the system Oxone® / $NaHCO_3$ in acetonitrile led to the tricyclic *para*-peroxy quinol **14** in a selective manner. Only the hydroxyl-substituted B ring was oxidized. Moreover, tricyclic *para*-quinol **15** could be synthesized after reduction of the intermediate peroxide with sodium thiosulfate.[19]



Scheme 1.3. Model studies towards ABC structures with angular hydroxyl groups

Further studies allowed the transformation of this tricyclic *para*-quinol **15** in a divergent and selective manner, into six differently substituted oxygenated tricyclic core models of several natural angucyclinones. A summary of the products obtained is depicted in *Figure 1.4* as well as

[17] S. I. Elshahawi, K. A. Shaaban, M. K. Kharel, J. S. Thorson, ***Chem. Soc. Rev.*** **2015**, ***44***, 7591-7697

[18] a) M. K. Kharel, P. Pahari, M. D. Shepherd, N. Tibrewal, S. E. Nybo, K. A. Shaaban, J. Rohr, *Nat. Prod. Rep.* **2012**, *29*, 264–325; b) M. C. Carreño, A. Urbano, *Synlett*. **2005**, 1-25; c) K. Krohn, J. Rohr, *Top. Curr. Chem.* **1997**,*188*, 127-195.

[19] S. Vila-Gisbert, A. Urbano, M. C. Carreño, *Chem. Commun*. **2013**, *49*, 3561-3563.

the structures of the natural oxygenated angucyclinones whose oxygenated moiety could be recognized in the tricyclic systems.

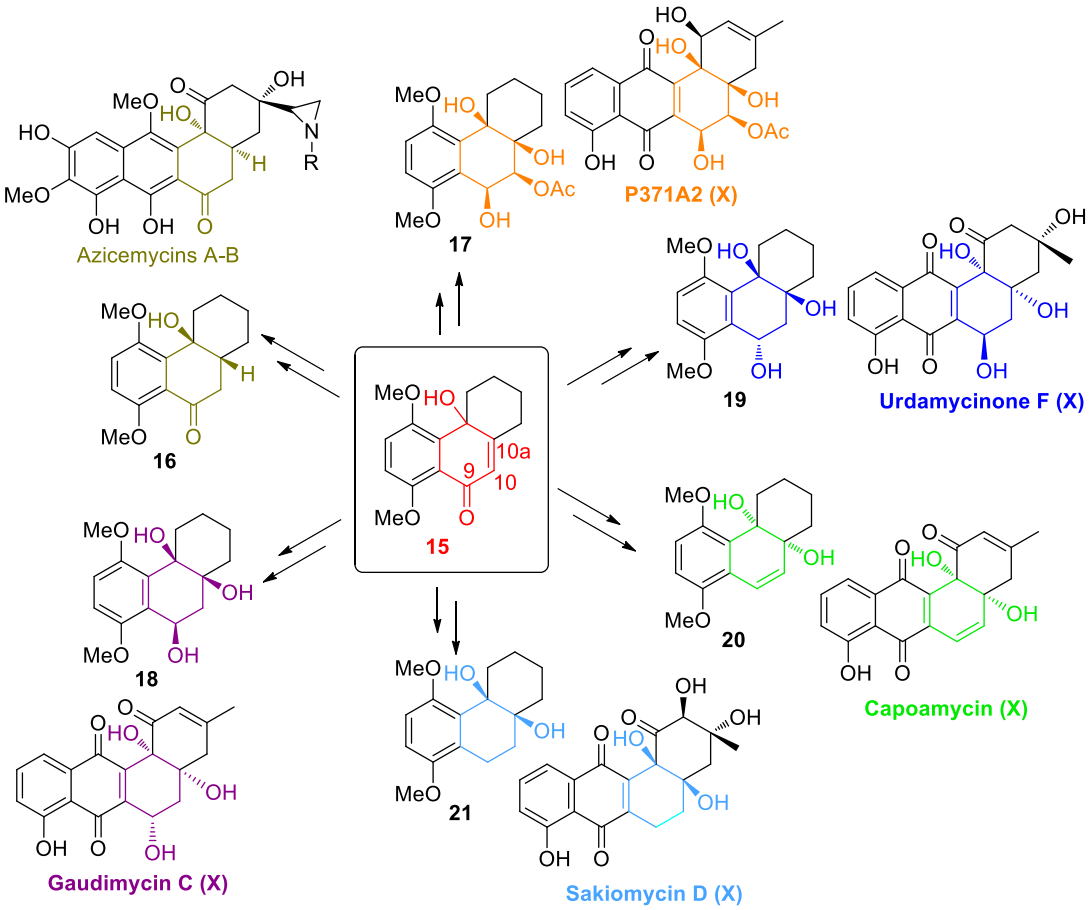


Figure 1.1. Substituted oxygenated tricyclic core models of natural angucyclinones

The excellent results obtained in the synthesis of these differently substituted tricyclic models of angularly oxygenated angucylinones using the oxidative dearomatization with Oxone® as the key step, prompted us to extend the methodology to more complex phenols. Thus, the first part of this Ph D work focused in this extension.

Objectives

The previous work detailed before was the direct precedent of the first objective of this PhD work, since the application of the model studies directed towards the oxygenated angucyclinones carried out on the tricyclic systems should be checked on analogue tetracyclic derivatives.

1. Oxidative dearomatization of angular tetracyclic phenols: Synthesis of angularly oxygenated angucyclinone derivatives.

En route to the synthesis of angularly oxygenated angucyclinones, final aim of the project, and thinking of applying the oxidative dearomatization of phenols described by us, based on the use of the system Oxone® / $NaHCO_3$ / acetonitrile as the key synthetic step to these targets, the synthesis of tetracyclic model *para*-alkyl phenol precursors was required.

The structures **22a** and **22b** shown in *Figure 1.5*, lacking the oxygenated function at C_1 and the CH_3 group at C-3 of the natural angucyclinones like Gaudimycin C, were chosen as tetracyclic models to evaluate the selectivity of the reaction with Oxone *versus* the three aromatic rings existent in these phenols that were prone to be dearomatized. In order to advance to the natural products, the tetracyclic phenol **22c**, with a carbonyl group at C_1, was also considered. The synthesis of these angular tetracyclic *para*-alkyl phenols: 7,12-dimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (**22a**), 7,8,12-trimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (**22b**) and 6-hydroxy-7,12-dimethoxy-3,4-dihydrotetraphen-1(2H)-one (**22c**), had not been previously reported.

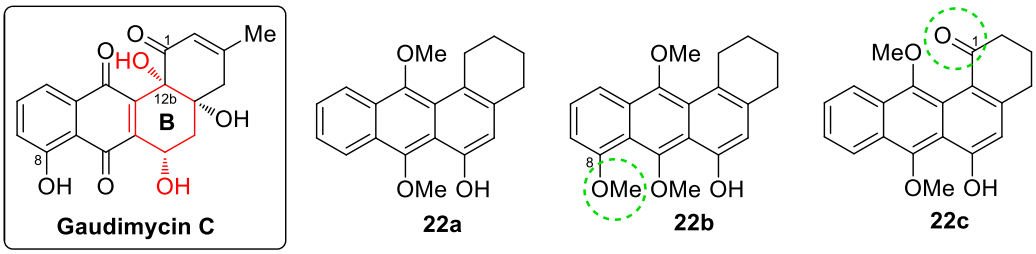
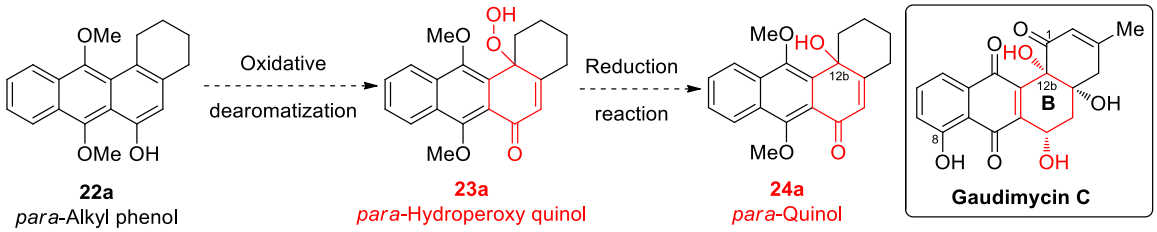


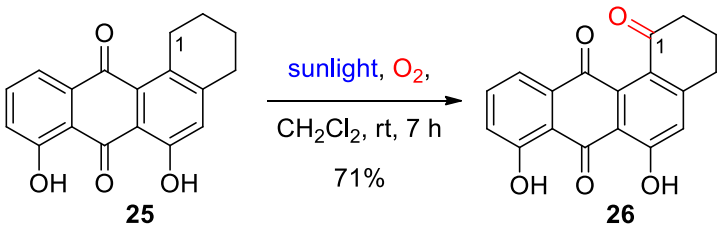
Figure 1.2. Angular tetracyclic para-alkyl phenols synthesized

Once synthesized, these tetracyclic *para*-alkyl phenols would be initially submitted to the oxidative dearomatization process with the system Oxone® / $NaHCO_3$ / acetonitrile, to obtain the corresponding tetracyclic *para*-peroxy quinols, which could be reduced into the tetracyclic *para*-quinols, as shown in *Scheme 1.4* for the phenol **22a**. This key step would allow the incorporation of the angular hydroxyl group at C_{12b} and the synthesis of 12b-hydroxy-7,12-dimethoxy-1,3,4,12b-tetrahydrotetraphen-6(2*H*)-one (**23a**) from 7,12-dimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (**22a**). The *para*-quinol **24a** would have the angular hydroxyl group at C_{12b} present in the natural angularly oxygenated angucyclinones, such as gaudimycin C.



*Scheme 1.4. Synthesis of tetracyclic para-quinol **24a***

During the development of the synthesis of the tetracyclic phenols **22**, we observed that some substrates, such as 7,12-dimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (**22a**), were sensitive to light and air and were transformed into different oxygenated products spontaneously. The direct photoinduced oxygenation of angucyclinone derivatives having a structure of 1,2,3,4-tetrahydrotetraphene-7,12-dione **25** to 1-keto substituted system **26**, had been reported by Kronh[20] in 1993 (*Scheme 1.5*), and later applied by other authors to the synthesis of some angucyclinone derivatives. [21]

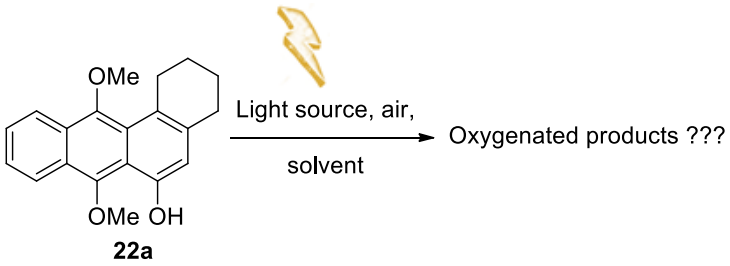


*Scheme 1.5. Photooxygenation at C_1 of 6,8-dihydroxy-3,4-dihydrotetraphene-1,7,12(2H)-trione (**25**) reported by Krohn*

Taking into account these precedents as well as our observations, we considered of high interest studying the photooxygenation of the tetracyclic phenols. Thus, a new objective of this Ph D work was to explore this photochemical process on the photosensitive phenols **22a**, **22b** and **22c** under different reaction conditions and different light sources. This exploration would allow the synthesis of unexpected peroxides and *para*-quinols and led to elucidate the mechanism of the reactions that were occurring (*Scheme 1.6*).

[20] a) R. Karmakar, D. Mal, *J. Org. Chem.* **2012**, *77*, 10235-10248; b) K. Krohn, M. H. Sohrab, U. Florke, *Tetrahedron*: *Asymmetry* **2004**, *15*, 713-718; c) K. Krohn, F. Ballwanz, W. Baltus, *Liebigs. Ann. Chem*. **1993**, 911–913.

[21] a) R. Karmakar, D. Mal, *J. Org. Chem.* **2012**, *77*, 10235-10248; b) K. Krohn, M. H. Sohrab, U. Florke, *Tetrahedron*: *Asymmetry* **2004**, *15*, 713-718; c) M. C Carreño, M. Ribagorda, A. Somoza, A. Urbano, *Angew. Chem., Int. Ed*., **2002**, *41*, 2755-2757.



*Scheme 1.6. Photooxidation study of 7,12-dimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (**22a**)*

All the results obtained in these studies are presented in this manuscript in the following parts:

- Synthesis of tetracyclic phenol precursors **22**
- Oxidative dearomatization using Oxone® as oxidant: Synthesis of angular tetracyclic *para*-quinols.
- Oxidative dearomatization of angular tetracyclic phenols **22** using irradiation under air.

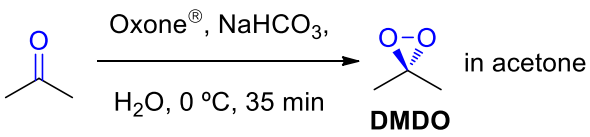
During the optimization experiments carried out in the reactions of our tetracyclic substrates with the system Oxone® / $NaHCO_3$ / acetonitrile, a new observation, due to the change of the solvent normally used in the oxidative dearomatization step from acetonitrile to acetone, prompted us to develop the studies presented in the second part of this work, devoted to the synthesis of *ortho*-quinols and epoxy *ortho*-quinols.

2. Synthesis of *ortho*-quinols by oxidative dearomatization of phenols using the system Oxone® / $NaHCO_3$ / acetone as the source of dimethyldioxirane.

When using acetone instead of acetonitrile in the Oxone® / $NaHCO_3$ mediated oxidative dearomatization of tetracyclic phenols, the results observed could not be explained considering only the presence of singlet oxygen in the reaction medium. It is well known that acetone, in the presence of Oxone® in basic medium is transformed into a reactive peroxide, dimethyldioxirane (DMDO)[22] which itself could act as an electrophilic oxidant. DMDO is a three-member ring

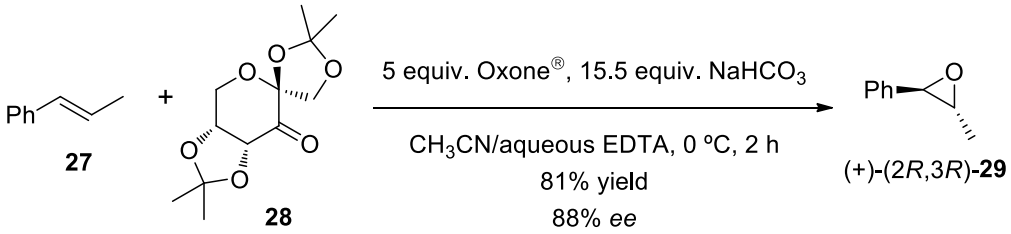
[22] a) H. Hussain, I. R. Green, I. Ahmed, *Chem. Rev.* **2013**, *113*, 3329-3371; b) P. Kachasakul, S. Assabumrungrat, P. Praserthdam, U. Pancharoen, *Chem. Eng. J.* **2003**, *92*, 131-139; c) N. Hashimoto, A. Kanda, *Org. Process. Res. Dev.* **2002**, *6,* 405-406.

peroxide derived from the oxidation of acetone. The most used and known DMDO preparation method is the oxidation reaction of acetone by Oxone®, shown in *Scheme 1.7*.[23, 24]



Scheme 1.7. Synthesis of dimethyldioxirane from acetone

An important application of the dioxiranes derived from ketones had been reported by Shi, who achieved the enantioselective epoxidation of olefins using a chiral dioxirane derived from a ketose, generated in situ with Oxone®. For instance, Shi reported the asymmetric epoxidation of (*E*)-prop-1-en-1-ylbenzene (**27**) using the chiral dioxirane derived from D-epoxone (**28**). The natural ketose **28** was transformed in situ into the enantiopure dioxirane by oxidation with Oxone® in presence of $NaHCO_3$ and an aqueous buffer solution (EDTA: 4×10^{-4}M). The mixture was able to epoxidize the *trans*-double bond, affording (2*R*,3*R*)-2-methyl-3-phenyloxirane (**29**) in 81% yield with 88% *ee* (*Scheme 1.8*), in an organocatalyzed process.[25]



*Scheme 1.8. Asymmetric epoxidation of (E)-prop-1-en-1-ylbenzene (**27**) by Shi and coworkers*

Taking into account the electrophilic nature of DMDO generated from Oxone® and acetone, we decided to deeply investigate the reactions of phenols with this system, that had been scarcely studied before. Thus, the second main objective of this PhD thesis was to study the oxidative dearomatization of phenols using the system Oxone® / $NaHCO_3$ in acetone. This research led to uncover a new process to synthesize *ortho*-quinols and epoxy *ortho*-quinols, depending on the substitution of the different phenols and naphthols studied (*Scheme 1.9*). The effect of the different functional groups in the reactivity of the phenols versus this oxidative dearomatization method was also studied.

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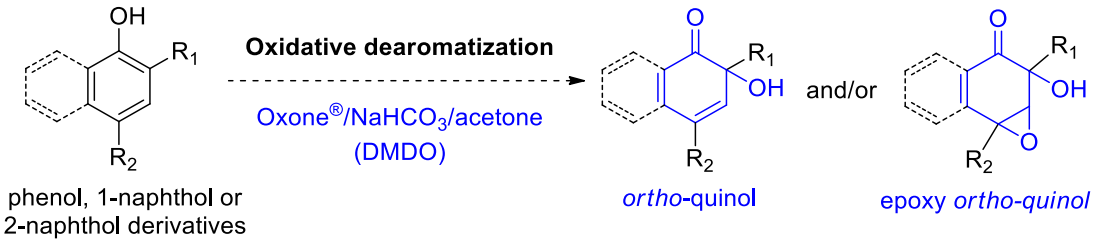
[23] a) H. Hussain, I. R. Green, I. Ahmed, *Chem. Rev.* **2013**, *113*, 3329-3371; b) P. Kachasakul, S. Assabumrungrat, P. Praserthdam, U. Pancharoen, *Chem. Eng. J.* **2003**, *92*, 131-139; c) N. Hashimoto, A. Kanda, *Org. Process. Res. Dev.* **2002**, *6,* 405-406.

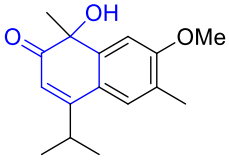
[24] D. F. Taber, P. W. DeMatteo, R. A. Hassan, *Org. Synth.* **2013**, *90*, 350-357.

[25] Y. Tu, Z.-X. Wang, Y. Shi, *J. Am. Chem. Soc.* **1996**, *118*, 9806−9807.



Scheme 1.9. Synthesis of ortho-quinols and epoxy ortho-quinols through hydroxylative dearomatization reaction

Finally, the last objective of this work was to explore the possible application of this new oxidative dearomatization methodology (Oxone® / $NaHCO_3$ / acetone) in the total synthesis of a natural product, such as lacinilene methyl ether (**30**) (*Figure 1.6*). We wanted to use this oxidative dearomatization reaction as the key step to introduce a hydroxyl group at the *ortho* position.



Lacinilene C ME (**30**)

*Figure 1.3. Lacinilene C methyl ether (**30**) structure*

The results obtained are presented in three parts:

- Oxidative dearomatization of 2,4,6-trisubstituted phenols with dimethyldioxirane
- Oxidative dearomatization of 1- and 2-naphthols with dimethyldioxirane
- Application of the oxidative dearomatization with dimethyldioxirane to the total synthesis of Lacinilene C methyl ether (**30**)

Chapter 2

Oxidative dearomatization of angular tetracyclic phenols: Synthesis of oxygenated angucyclinone derivatives.

2.1. Introduction

Angucyclines and their aglycones, named angucyclinones, are a large group of naturally occurring polycyclic aromatic polyketides, isolated from various members of the bacterial genus *Streptomyces*.[26, 27, 28, 29] These molecules exhibit a wide range of biological properties including antiviral, antifungal, antitumor, antimalarial and enzyme inhibitor activity.[26, 27, 28]

These natural products present some common features on their structure. All of them share a benz[*a*]anthracene ABCD angular tetracyclic skeleton with a methyl group at C_3 and oxygen functionalities at C_1, C_7, C_8 and C_{12} (*Figure 2.1*). Different degree of unsaturation and oxygenation exists among the members of the family. Some components show a modified carbon skeleton proceeding from the angular tetracyclic ABCD structure represented.

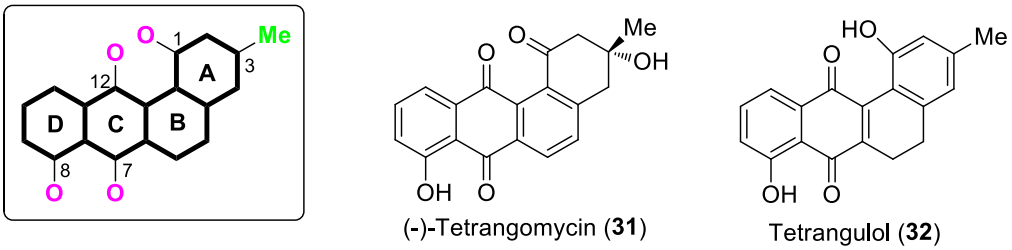


*Figure 2.4. Common structural features of angucyclinones: benz[a]anthracene skeleton and structure of tetrangomycin (**31**) and tetrangulol (**32**)*

The first angucyclines antibiotics to be isolated were tetrangomycin (**31**) and tetrangulol (**32**) in 1966 by Kuntsmann and Mitscher (*Figure 2.1*).[30] Since then, more than one hundred components of the group have been reported.[26]

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[26] M. K. Kharel, P. Pahari, M. D. Shepherd, N. Tibrewal, S. E. Nybo, K. A. Shaaban, J. Rohr, *Nat. Prod. Rep.* **2012**, *29*, 264−325.
[27] K. Krohn, J. Rohr, *Top. Curr. Chem.* **1997**,*188*, 127-195.
[28] J. Rohr, R. Thiericke, *Nat. Prod. Rep.* **1992**, *9*, 103-137.
[29] a) C. Huang, C. Yang, W. Zhang, L. Zhang, B. C. De, Y. Zhu, X. Jiang, C. Fang Q. Zhang, C.-S. Yuan, H.-w. Liu, C. Zhang, *Nat. Commun.* **2018**, *9*, 2088. b) Y.-J. Jiang, L.-S. Gan, W.-J. Ding, Z. Chen, Z.-J. Ma. *Tetrahedron Lett*. **2017**, *58*, 3747–3750. c) X. Zhu, Y. Duan, Z. Cui, Z. Wang, Z. Li, Y. Zhang, J. Ju, H. Huang, *J. Antibiotics,* **2017**, *70*, 819-822. d) S. M. Forget, A. W. Robertson, D. P. Overy, R. G. Kerr, D. L. Jakeman, *J. Nat. Prod*. **2017**, *80*, 1860-1866. e) Z. Xie, L. Zhou, L. Guo, X. Yang, G. Qu, C. Wu, S. Zhang, *Org. Lett*. **2016**, *18*, 1402-1405. f) M. Ma, M. E. Rateb, Q. Teng, D. Yang, J. D. Rudolf, X. Zhu, Y. Huang, L.-X. Zhao, Y. Jiang, X. Li, C. Rader, Y. Duan, B. Shen, *J. Nat. Prod*. **2015**, *78*, 2471−2480. g) H. B. Park, J. K. Le, K. R. Lee, H. C. Kwon, *Tetrahedron Lett.* **2014**, *55*, 63–66.
[30] M. P. Kuntsmann, L. A. Mitscher, *J. Org. Chem.* **1966**, *31*, 2920-2925.

2.1.1. Synthetic strategies towards the formation of the angularly tetracyclic core structure: Previous work

Due to the diverse range of biological activity and challenging structural features of the naturally occurring angucyclines, extensive studies on their synthesis[26, 31] and biosynthesis[1, 32] have been reported. The regio- and stereoselective construction of the tetracyclic benz[*a*]antraquinone skeleton have been achieved using different methods. The classical and most frequently synthetic strategies to form the tetracyclic angucycline backbone are the Diels-Alder reactions and a sequential nucleophilic/electrophilic addition process, but in recent years a variety of newer reactions and variants have been reported. The most general methods for the construction of the tetracyclic angular core could be summarized in five synthetic strategies: Diels-Alder cycloadditions, nucleophilic additions, electrophilic additions, transition metal catalyzed cross coupling and intramolecular cyclization reactions. Within the next sections we will focus on representative and recent examples of application of each strategy.

2.1.1.1. Diels–Alder reactions

The Diels-Alder reactions are one of the most versatile synthetic strategies employed in the construction of the angular tetracyclic core of angucyclines in a regio- and stereoselective manner. These cycloadditions allow a convergent synthetic approach leading to a variety of systems very useful due to the diversity in the structure of dienes and dienophiles that can be used. To simplify the presentation of this approach, this section will be divided in three parts based on the different methods used, depending on the rings (B, C or D) to be formed in the cycloaddition.

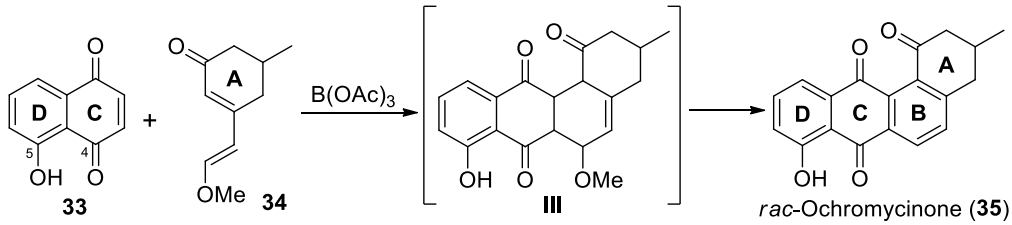
2.1.1.1.1. Formation of B Ring: DC+A Strategy

This strategy is the most used in the regioselective construction of the tetracyclic skeleton. The B ring was formed through a Diels-Alder cycloaddition reaction between a dienophile bearing the D and C rings and a diene with the A ring. The first application of this

[31] a) M. C. Carreño, A. Urbano, *Synlett*. **2005**, 1-25. Recent articles: b) M. M. Johnson, K. J. Ngwira, A. L. Rousseau, A. Lemmerer, C. B. de Koning, *Tetrahedron* **2018**, *74*, 12-18. c) K. J. Ngwira, A. L. Rousseau, M. M. Johnson, C. B. de Koning, *Eur. J. Org. Chem*. **2017**, *11*, 1479-1488. d) A. Saxena, F. Perez, M. J. Krische, *Angew. Chem. Int. Ed*. **2016**, *55*, 1493 –1497. e) L. W. K. Moodie, D. S. Larsen, *Eur. J. Org. Chem*. **2014**, 1684-1694. f) D. G. Vanga, K. P. Kaliappan, *RSC Adv.* **2014**, *4*, 12716-12722.

[32] D. R. Jackson, X. Yu, G. Wang, A. B. Patel, J. Calveras, J. F. Barajas, E. Sasaki, M. Metsä-Ketelä, H.-W. Liu, J. Rohr, S.-C. Tsai, *ACS Chem. Biol*. **2016**, *11*, 1137−1147.

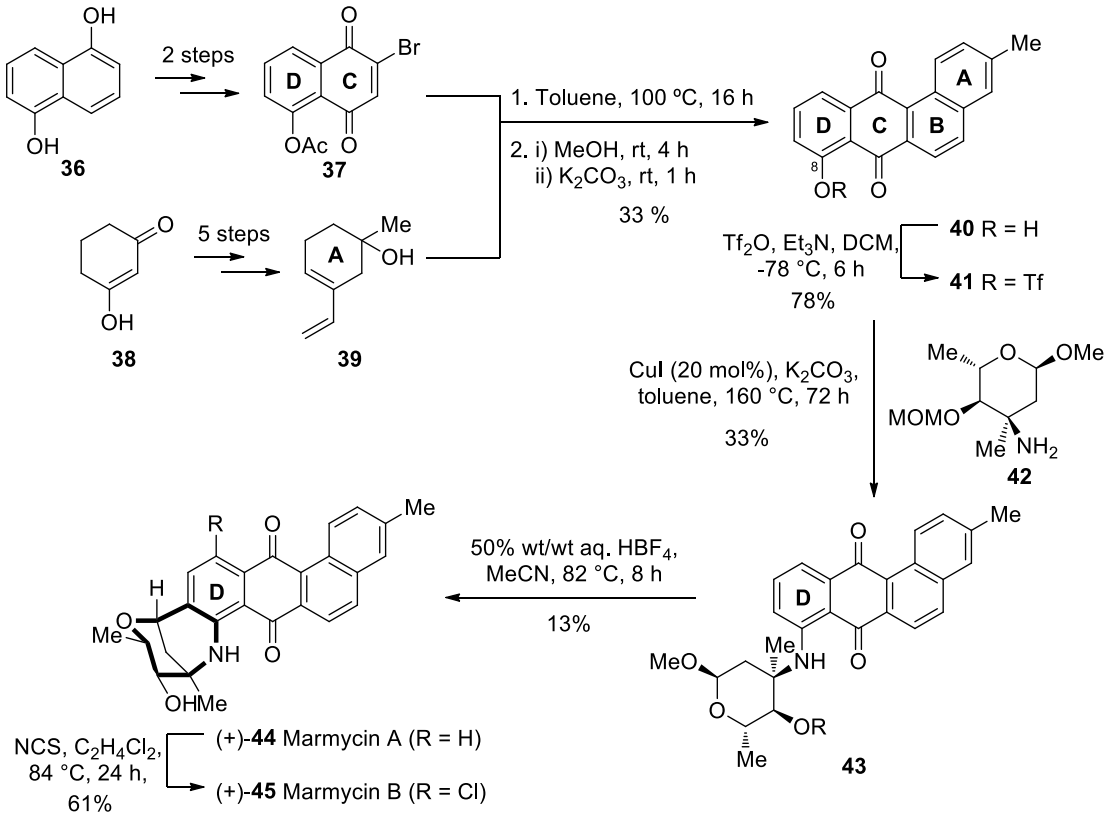
strategy in the synthesis of a natural angucyclinones was carried out by Guingant and Barreto in 1987.[33] They described the regioselective synthesis of racemic ochromycinone (**35**) by a boron triacetate catalyzed cycloaddition between the methoxyvinylcyclohexenone **34** and juglone **35**. This Diels-Alder reaction afforded the unstable adduct **III**, which evolved into racemic ochoromycinone (**35**) through methanol elimination and aromatization of B ring (*Scheme 2.1*).



*Scheme 2.10. Total synthesis of rac-ochromycinone (**X**) by Guingant and Barreto*

In 2015, Rodríguez and coworkers completed a total synthetic study towards marmycins A (**44**) and B (**45**), using as the key step the convergent formation of the B ring by Diels-Alder reaction between the brominated dienophile **37**, prepared in 2 steps from naphthalene-1,5-diol **36**, and diene **39**, synthesized in 5 steps from 1,3-cyclohexanedione **38** (*Scheme 2.2*)[34]. The Diels-Alder reaction between **37** and **39** was realized in toluene at reflux and was followed by stirring with potassium carbonate (K_2CO_3) in methanol to facilitate HBr elimination and aromatization, affording the desired tetracyclic cycloadduct **40** in 33% overall yield. The phenol at C_8 of the resulting tetracyclic compound was transformed using Tf_2O and Et_3N in the corresponding triflate **41**, which was coupled with the amino sugar **42** using a catalytic amount of cooper iodide (CuI) to achieve the formation of compound **43** with the carbohydrate incorporated into the skeleton. This protected derivative **43** was further treated with aq. fluoroboric acid (HBF_4) to give (+)-marmycin A (**44**) through an electrophilic aromatic substitution on ring D, where the anomeric carbon of the sugar moiety was acting as electrophile. This step allowed the installation of the C-glycoside in the structure. In the presence of N-chlorosuccinimide (NCS), (+)-marmycin A (**44**) evolved into the corresponding (+)-marmycin B (**45**) in good yield.

[33] A. Guingant, M. M. Barreto, *Tetrahedron Lett.* **1987**, *28*, 3107-3110.
[34] T. Cañeque, F. Gomes, T. T. Mai, G. Maestri, M. Malacria, R. Rodriguez, *Nature Chemistry* **2015**, *7*, 744-751.

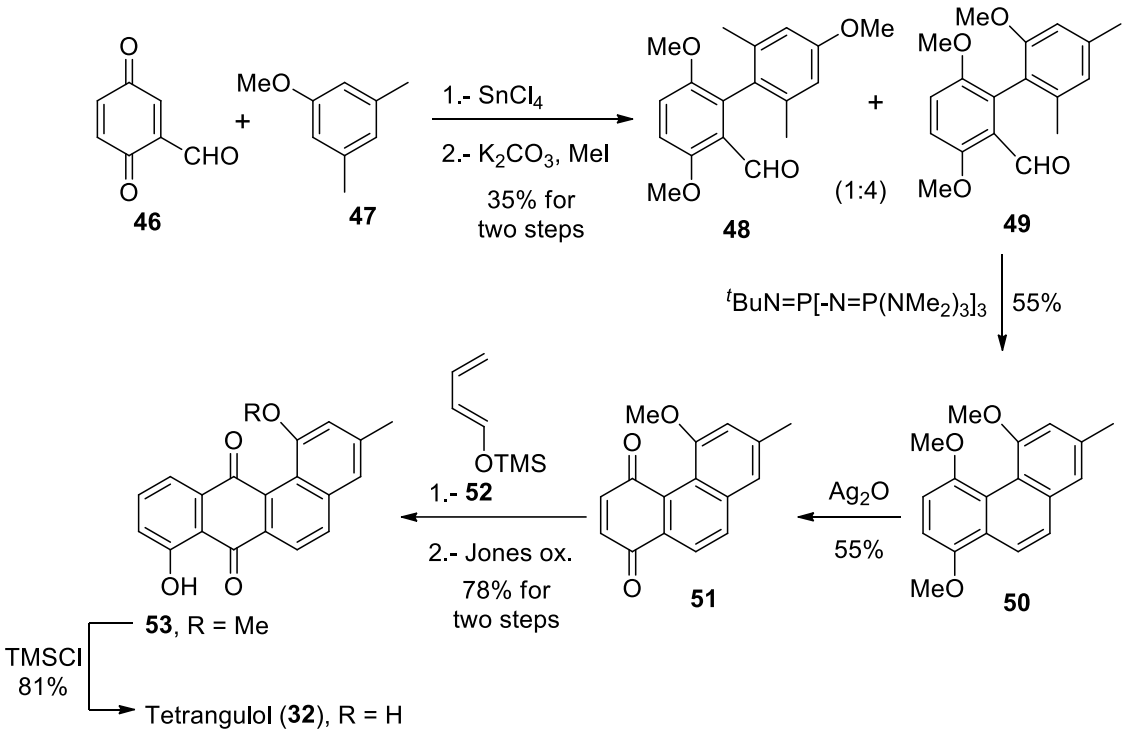


*Scheme 2.11. The total synthesis of marmycin A (**44**) and B (**45**) by Rodríguez and coworkers*

2.1.1.1.2. Formation of D Ring from a Dienophile Bearing the CBA Moiety

This strategy requires the use of an angular tricyclic dienophile bearing the A, B and C rings and a simple functionalized diene to form the D ring during the Diels-Alder cycloaddition reaction. Jensen and coworkers described in 2001 a total synthesis of tetrangulol (**32**) using this methodology for the formation of tetracyclic skeleton.[35] The synthesis shown in *Scheme 2.3* started with the reaction of 2-formyl-*para*-benzoquinone **46** with 3,5-dimethylanisole **47** using stannic chloride as catalyst, followed by reductive methylation to afford a 1:4 mixture of regioisomers **48** and **49**. These products were separated and the major regioisomer **49** was treated with *tert*-buthyl phosphazine base, giving the cyclization product phenantrene **50** through an aldol-like condensation. Then, an oxidative demethylation of phenantrene **50** with silver oxide afforded 1,4-phenanthrenequinone **51**, which was submitted to Diels-Alder reaction with 1-trimethylsilyloxy-1,3-butadiene (**52**). The sole regioisomer obtained was oxidized with the Jones reagent, a solution of chromium trioxide in diluted sulfuric acid, to afford tetracyclic derivative **53** in good yield. At the end, the oxygenated function at C_1 of **53** was demethylated using TMSCl to give tetrangulol (**32**) in high yield.

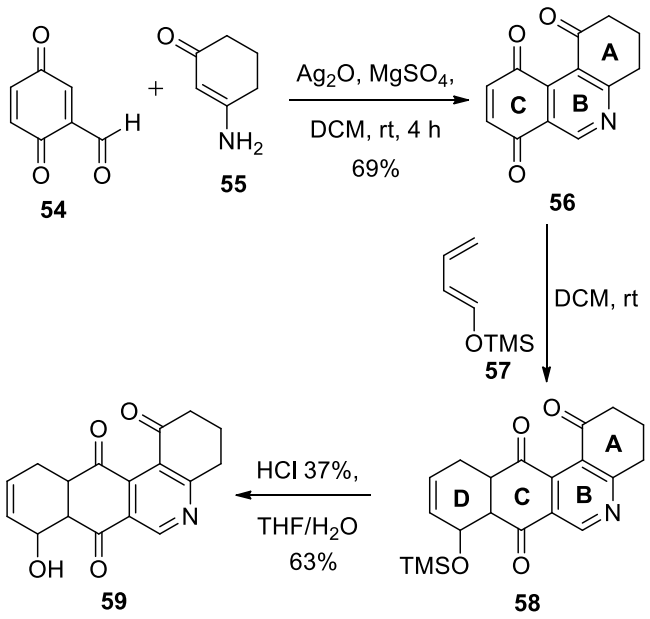
[35] G. A. Kraus, N. Zhang, A. Melekhov, J. H. Jensen, *Synlett* **2001**, 521-522.



*Scheme 2.12. Synthesis of tetrangulol (**32**) by Jensen and coworkers.*

Valderrama and coworkers reported in 2006 the construction of different 5-aza angucyclinone skeletons based on the Diels-Alder reaction between the 1,3-diene **57** and different substituted phenanthridine-7,10-dione to synthesize the D ring.[36] In the *Scheme 2.4* is explained the synthesis of one of 5-aza angucyclinones reported by them. The synthesis of phenantridine-7,10-dione **56** was achieved through a Michael addition / heterocyclization between the acyl benzoquinone **54** and cyclic enamine **55** with silver oxide (Ag_2O) and magnesium sulfate ($MgSO_4$). In this case, the Diels-Alder reaction between the dienophile **56** and diene **57** produced compound **58**, which finally was treated with hydrochloric acid (HCl 37%) in a mixture of THF/H_2O to afford the corresponding 8-hydroxy-aza-angucyclinone **59**.

[36] J. A. Valderrama, M. F. González, P. Colonelli, D. Vásquez, *Synlett* **2006**, *17*, 2777-2780.

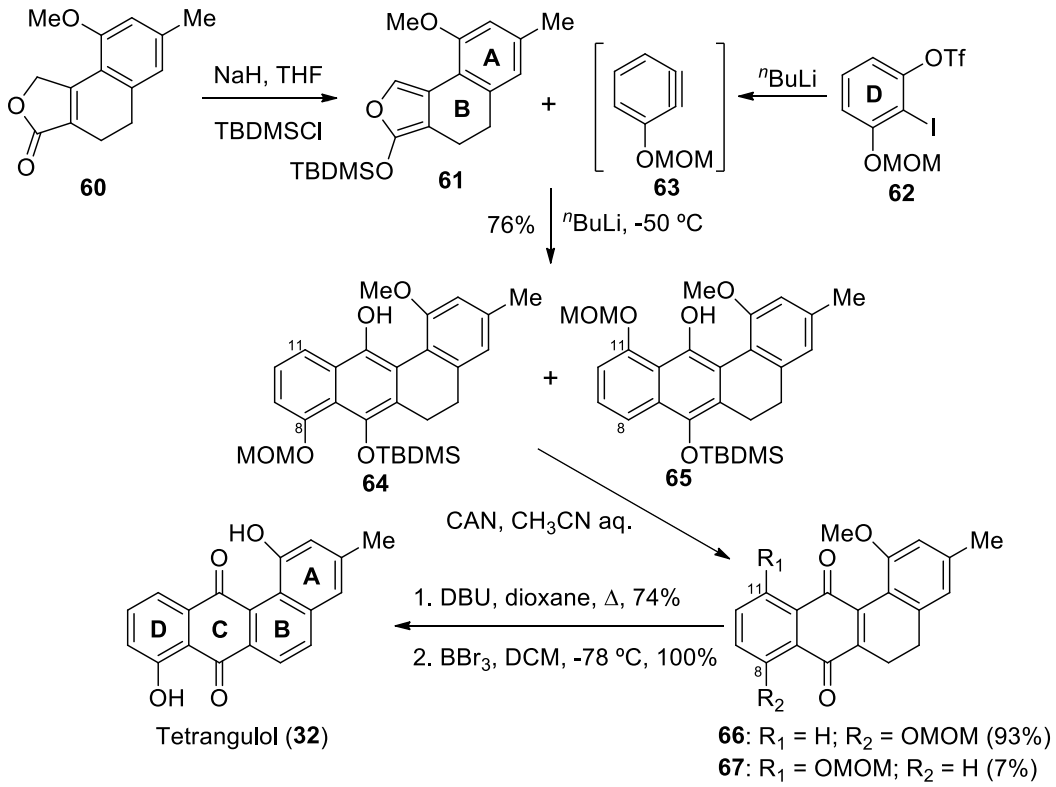


*Scheme 2.13. Synthesis of 5-aza angucyclinone **59** by Valderrama and co-workers*

2.1.1.1.3. Formation of C Ring: D+BA Strategy

This Diels-Alder strategy is based in the formation of the C ring of the tetracyclic core through a cycloaddition between a diene bearing the A and B rings and a dienophile with the D ring. Suzuki and coworkers synthesized in 1995 the angular tetracyclic benz[*a*]antraquinone core of tetrangulol (**32**), following this Diels-Alder strategy(*Scheme 2.5*).[37] The tricyclic diene 2-silyloxyfurane **61** was used to introduce the A and B rings in the final tetracyclic skeleton. This diene **61** was produced from butenolide **60** by treatment with NaH in presence of TBDMSCl. Reaction with the corresponding benzyne intermediate **63**, generated in situ from 2-iodoaryl triflate **62** by treatment with *n*-BuLi at low temperature, gave a 93:7 mixture of tetracyclic regiosisomers **64** and **65** with good yield. This mixture was oxidized by treatment with CAN to obtain the corresponding regioisomeric quinones **66** and **67**, separated by chromatographic column. The aromatization of B ring of the 8-methoxy substituted quinone **66**, using DBU, and the elimination of protecting groups (-OMOM and –OMe), using BBr_3, afforded tetragulol (**32**), identical to the natural product, in 74% yield for two step. Although the regioselectivity of the cycloaddition step was not complete, once both regioisomers were separated, the natural tetrangulol (**32**) could be synthesized in 52% overall yield.

[37] T. Matsumoto, T. Sohma, H. Yamaguchi, S. Kurata, K. Suzuki, *Synlett* **1995**, *3*, 263-266.



*Scheme 2.14. The synthesis of tetrangulol (**32**) by Suzuki and coworkers*

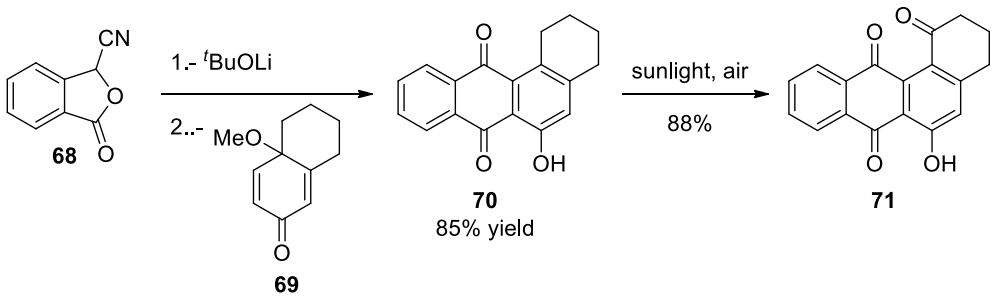
2.1.1.2. Nucleophilic additions

Other useful strategy allowing the regioselective construction of the tetracyclic framework is based on the inter- or intramolecular nucleophilic addition cyclization reactions. The anionic [4+2] cycloaddition between adequately substituted phtalides and several α,β-unsaturated ketones, commonly named Hauser-Kraus annulation or phtalide annulation, is the most commonly used type of nucleophilic addition. This strategy has been frequently applied to construct the tetracyclic framework, accessible in one-step if a cyclohexanone derivative is used as acceptor.

Mal and coworkers were the first to use this methodology in the construction of the tetracyclic core present in the natural angucyclinones. In 1997, they reported the synthesis of several benz[*a*]anthraquinone compounds using an annulation between an enone and phthalide.[38] In *Scheme 2.6*, the synthesis of one of these tetracyclic molecules is described. The Hauser-Kraus annulation process between the anion derived from cyianophthalide **68** and the bicyclic cyclohexenone **69** gave tetracyclic compound **70** in high yield. In this case, the tetracyclic

[38] D. Mal, H. N. Roy, N. K. Hazra, S. Adhikari, *Tetrahedron* **1997**, *53*, 2177-2184.

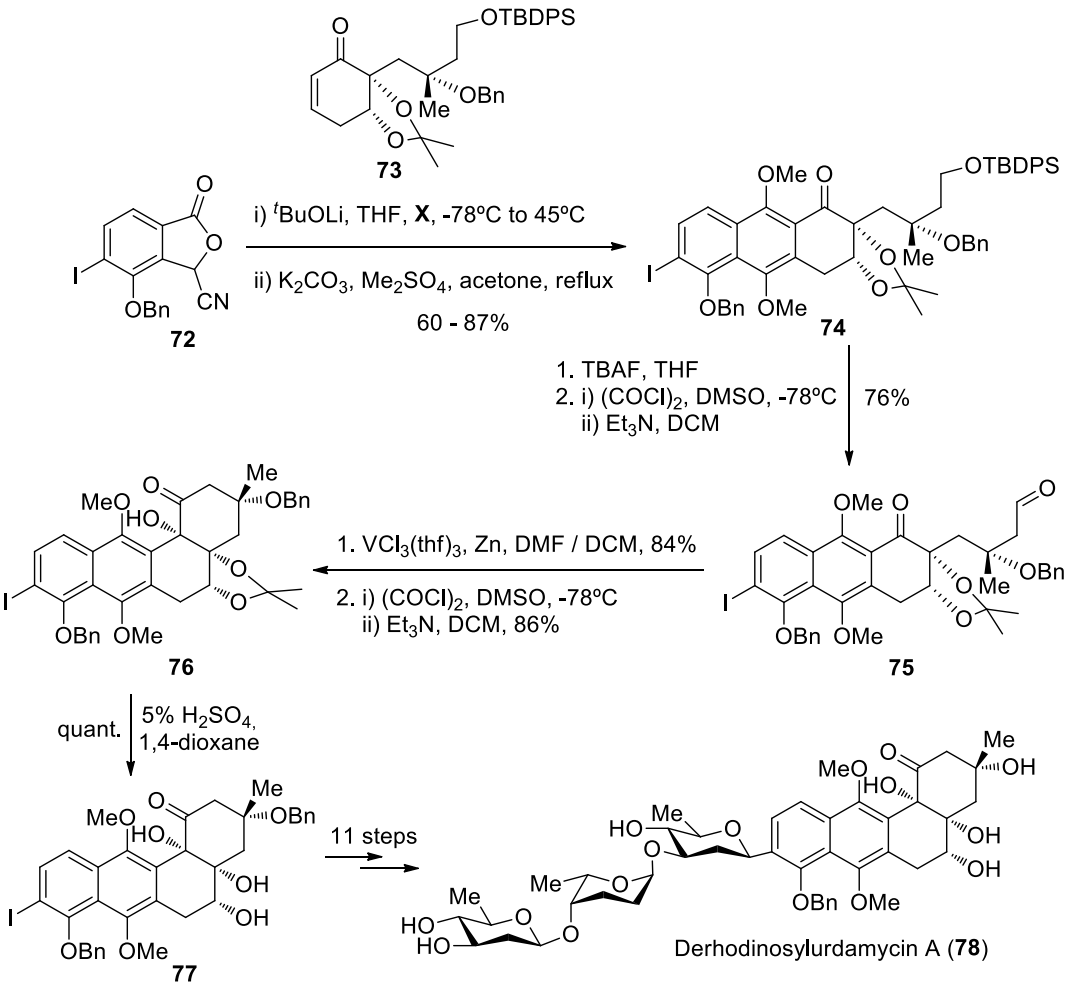
skeleton was achieved in one reaction step. Then, tetracyclic derivative **70** was exposure to sunlight under air to oxidize C_1 position and generate the tetracyclic derivative **71** in 88% yield.



Scheme 2.15. Synthesis of tetracyclic skeleton using the Hauser-Kraus annulation strategy by Mal and coworkers

In a recent publication, Zhu and coworkers applied this strategy to the total synthesis of derhodinosylurdamycin A (**78**) (*Scheme 2.7*).[39] The synthesis started with the coupling of the anion, resulting in the treatment of cyanophthalide **72** with *tert*-BuOLi and functionalized cyclohexenone **73**. This reaction gave rise to an unstable tricyclic hydroquinone, which was immediately methylated with dimethyl sulfate (Me_2SO_4) to generate tricyclic compound **74**. After removal the silyl group (TBDPS), the resulting primary alcohol was oxidized by Swern oxidation to afford the aldehyde **75**. Next, the tetracyclic derivative **76** was obtained by submitting the aldehyde **75** to a Perdersen-modified pinacol coupling[40] and subsequent Swern oxidation of the generated secondary alcochol. The deprotection of the acetonide afforded tetracyclic aryliodide **77**. Finally, after 11 synthetic steps, aryliodide **77** was transformed into derhodinosylurdamycin A (**78**).

[39] H. R. Khatri, H. Nguyen, J. K. Dunaway, J. Zhu, *Chem. Eur. J.* **2015**, *21*, 13553- 13557.
[40] a) P. M. Takahara, J. H. Freudenberger, A. W. Konradi, S. F. Pedersen, *Tetrahedron Lett*. **1989**, 30, 7177; b) J. H. Freudenberger, A. W. Konradi, S. F. Pedersen, *J. Am. Chem. Soc*. **1989**, 111, 8014.



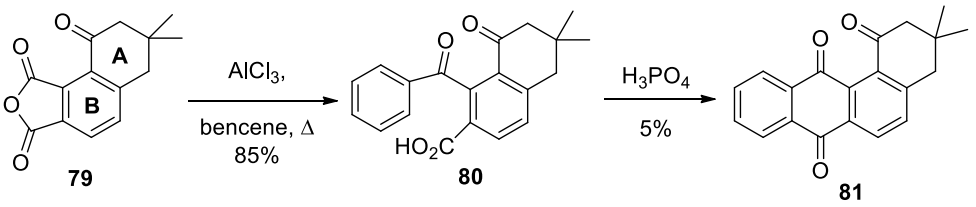
*Scheme 2.16. Total synthesis of derhdinosylurdamycin A (**78**) by Zhu and coworkers*

2.1.1.3. Electrophilic additions

This strategy is based on the initial formation of an adequately substituted aromatic precursor, further transformed into the tetracyclic framework applying an electrophilic addition or a Friedel-Crafts acylation as the key step.

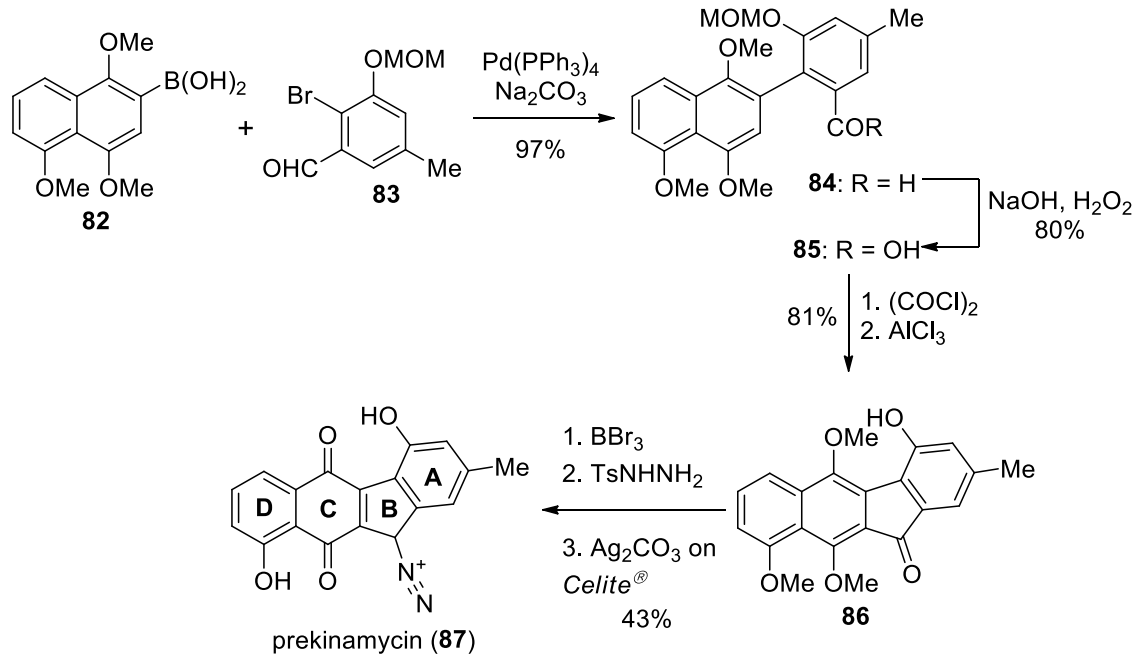
In 1998, Bowie and coworkers described the synthesis of tetracyclic compound **81** by two successive Friedel-Crafts acylations.[41] This two acylation steps are depicted in *Scheme 2.8*. Thus, the reaction of anhydride **79** with aluminum trichloride in benzene and heating led to compound **80** in high yield. Although, the treatment of **80** with phosphoric acid afforded the tetracyclic cyclization product in a very low yield, this was the first example of the use a Friedel-Crafts acylation with this aim.

[41] T. Rozek, W. Janowski, J. M. Hevko, E. R. T. Tieknink, S. Dua, D. J. M. Stone, J. H. Bowie, *Aust. J. Chem.* **1998**, *51*, 515-524.



Scheme 2.17. Synthesis of tetracyclic skeleton using the Friedel-Crafts acylation strategy by Bowie and coworkers

Recently, Kumamoto and coworkers applied this methodology for the synthesis to the tetracyclic benzofluorene system of prekinamycin (**87**) (Scheme 2.9).[42] The synthesis started with a palladium catalyzed Suzuki cross-coupling between naphthyl boronic acid **82** and bromo benzaldehyde derivative **83**, leading to the corresponding naphthyl-fused benzaldehyde **84** in 97% yield. The oxidation of the aldehyde **84** into acid **85**, with NaOH and H_2O_2, and subsequent acid chloride formation was followed by an intramolecular Friedel-Crafts reaction in the presence of $AlCl_3$, which generated the tetracyclic compound **86** in 81% yield for two steps. Finally, prekinamycin (**87**) was obtained in 3 steps with good yield from tetracyclic **86**: demethylation reaction with BBr_3, followed by hydrazone formation with $TsNHNH_2$ and oxidation with Fetizone's reagent (Ag_2CO_3 on *Celite®*).



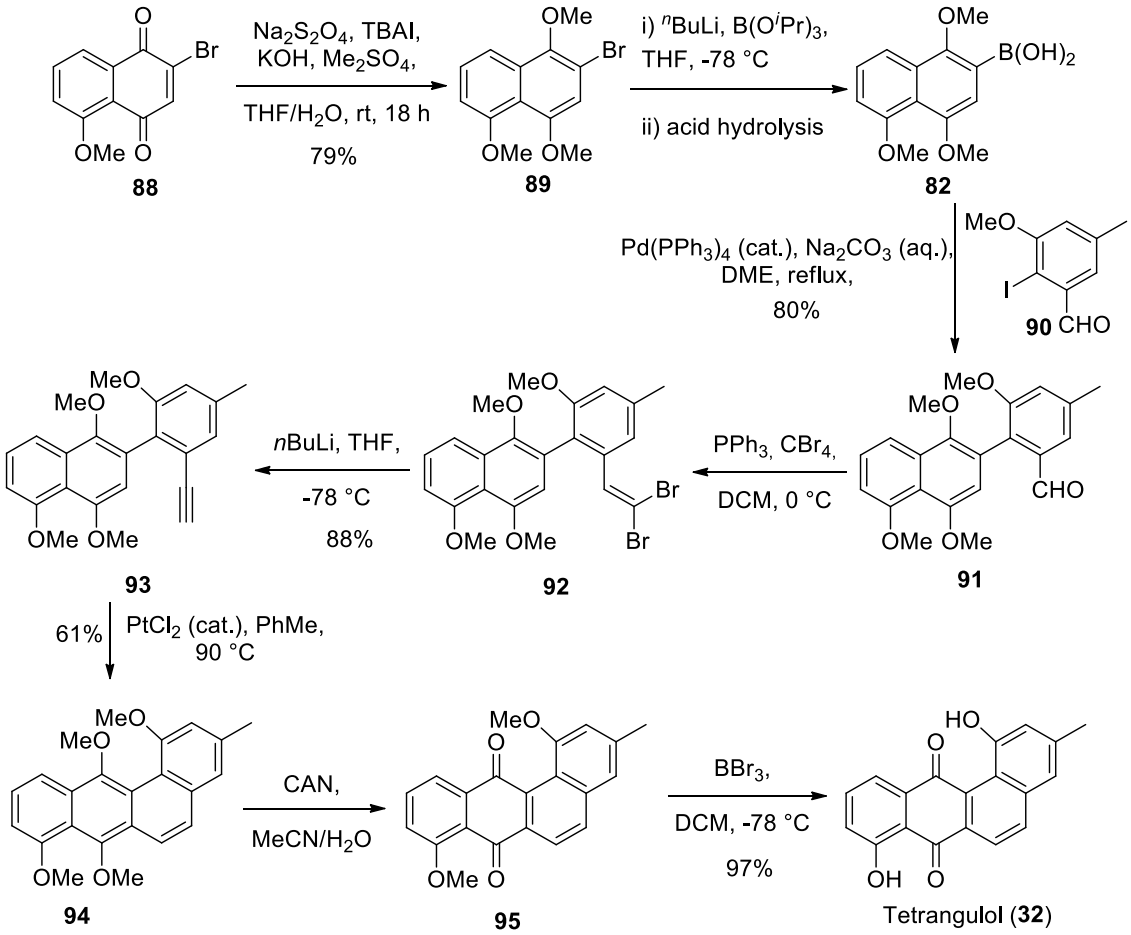
*Scheme 2.18. The synthesis of prekinamycin (**87**) by Kumamoto and coworkers*

[42] S. Kimura, S. Kobayashi, T. Kumamoto, A. Akagi, N. Sato, T. Ishikawa, *Helv. Chim. Acta* **2011**, *94*, 578-591

2.1.1.4. Transition metal-catalyzed cross-coupling reactions

In the recent years, transition metal catalyzed cross-coupling reactions have proven to be a useful tool in the synthesis of skeletons of angucyclines and their derivatives. In 2017, de Koning and coworkers utilized this methodology for the construction of the tetracyclic benz[*a*]anthracene core structure of tetrangulol (**32**) (*Scheme 2.10*).[43] Thus, bromo-naphthoquinone **88** was transformed into bromo-trimethoxynaphthalene **89** by the classical reductive methylation procedure using sodium dithionite ($Na_2S_2O_4$) and dimethyl sulfate (Me_2SO_4) in good yield. Bromo-trimethoxynaphthalene **89** was transformed into the boronic acid **82** after reaction with ^{n}BuLi and triisopropylborate, followed by acidic hydrolysis in the work-up. Then, the Suzuki-Miyaura coupling reaction between the boronic acid **82** and iodobelzaldehyde **90** afforded 3-methoxy-5-methyl-2-(1,4,5-trimethoxynaphthalen-2-yl)benzaldehyde derivative (**91**) in 80% yield. This aldehyde was later transformed into alkyne **93** by a Corey-Fuchs reaction from **91** via formation of intermediate **92**. Next, the cycloisomerization of alkyne **93** was achieved by treatment with a catalytic amount of platinum(II) chloride to generate the tretracyclic derivative **94** in 61% yield, which possess the tetrangulol core. Finally, compound **94** was later oxidized with CAN to give quinone **95**, which was demethylated with boron tribromide to afford tetrangulol (**32**) in 97% yield.

[43] K. J. Ngwira, A. L. Rousseau, M. M. Johnson, C. B. de Koning, *Eur. J. Org. Chem.* **2017**, *11*, 1479-1488.



*Scheme 2.19. The total synthesis of Tetrangulol (**32**) by de Koning and coworkers*

2.1.1.5. Intramolecular cyclization strategies

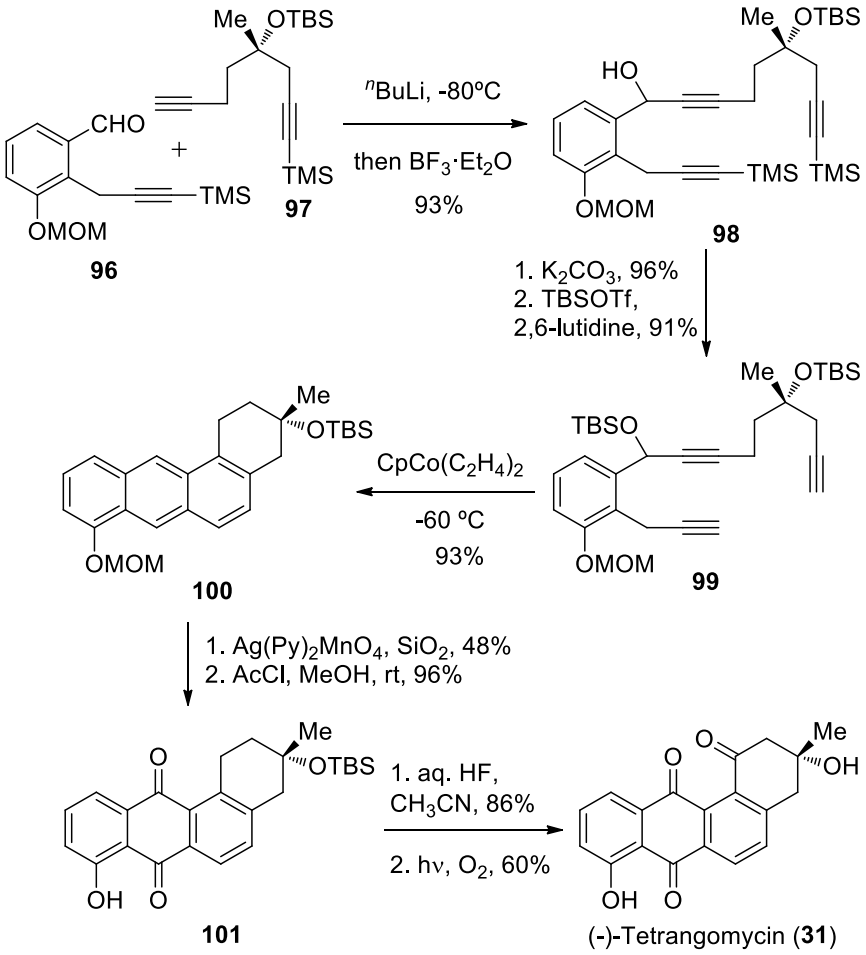
Intramolecular processes including [2+2+2] or [4+2]-cycloaddition reactions effected by combining thermal or ring opening electrocyclizations catalyzed by transition metals (cobalt or gold) or by heating, allowed a one-step synthesis of angucyclines skeletons.

2.1.1.5.1. Metal-Mediated [2+2+2] Cycloadditions

This approach is exemplified by the stereoselective total synthesis of (-)-tetrangomycin (**31**), realized by Groth and coworkers who reported, in 2010, an intramolecular [2+2+2] cyclization, catalyzed by cobalt, as the key step. [44] The synthesis of (-)-tetrangomycin (**31**), shown in *Scheme 2.11*, started with the coupling of the lithiated octadiyne, formed in situ from the reaction of octadiyne **97** with *n*-BuLi, with the substituted benzaldehyde **96** in presence of $BF_3{\cdot}Et_2O$, to afford the triyne **98** in 93% yield. Trimethylsilyl group was removed under basic

[44] C. Kesenheimer, A. Kalogerakis, A. Meißner, U. Groth, *Chem. Eur. J.* **2010**, *16*, 8805-8821.

conditions in the presence of potassium carbonate (K_2CO_3) and the secondary alcohol was protected as silyl ether using TBSOTf and 2,6-lutidine to generate the triyne derivate **99** in 87% yield for two steps. Then, the angular tetracyclic skeleton was synthesized in high yield in one-step from the enantiopure triyne **99** through an intramolecular [2+2+2] cyclization catalyzed by a cobalt complex catalyst. The tetracyclic derivative **100** obtained was oxidized using a mixture of silver complex $Ag(Py)_2MnO_4$ and silica gel (1:2), followed by a deprotection of methoxy methyl ether group (-MOM), giving rise the tetracyclic quinone **101** in moderate yield. Finally, a deprotection of silyl ether group using aqueous hydrofluoric acid and a regioselective photooxidation at C_1 by irradiation under oxygen afforded (-)-tetrangomycin (**31**) in good yield from the tetracyclic quinone **101**.

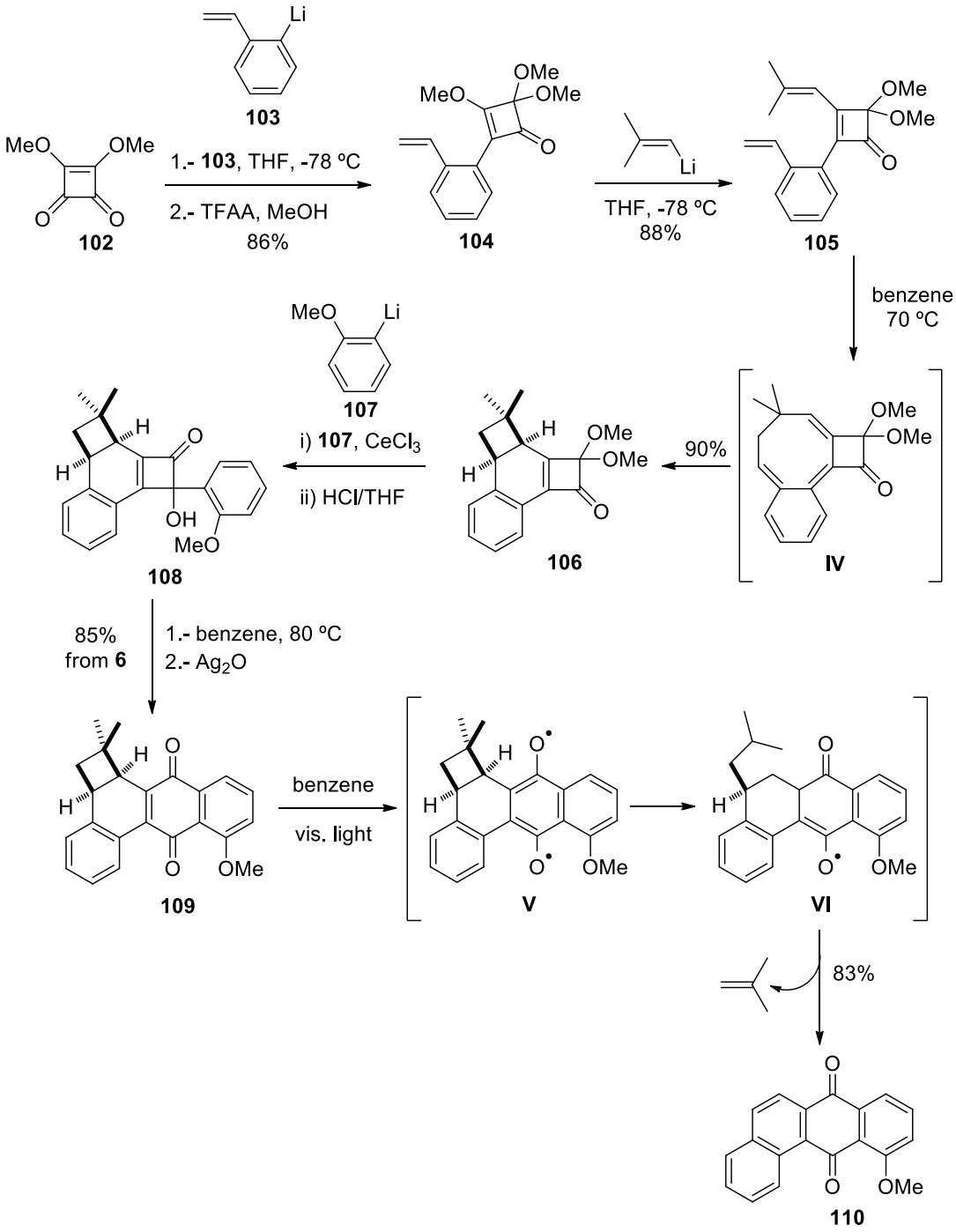


*Scheme 2.20. Total synthesis of (-)-tetrangomycin (**31**) by Groth and co-workers*

2.1.1.5.2. Electrocyclic reactions from cyclobutenones combined with pinacol-like cyclizations

This electrocyclic reaction is based on an initial thermal benzocyclobutenone ring opening followed by a subsequent electrocyclic ring closure reaction of the resulting triene fragment to synthesize the 2-phenyl naphthalene skeleton. In 1998, Moore and coworkers was the pioneer to use this methodology in the formation of the tetracyclic core present in angucyclinones (*Scheme 2.12*).[45] Dimethyl squarate **102** was transformed into alkenyl aryl cyclobutenone **105** in three reaction steps: treatment with 2-lithiostyrene **103** and methanolysis with TFAA-MeOH to give compound **104**, followed by treatment with 1-lithio-2-methylpropene to afford compound **105**. Then, upon mild thermolysis conditions (benzene, 70 ºC), alkenyl aryl cyclobutenone **105** underwent ring-closure through 8π-electrocyclization to cyclooctatriene intermediate **IV**, followed by 6π-electcyclic ring-closure to achieve compound **106** in 90% yield. The reaction of 6 with 2-lithioanisole (**107**) in the presence of cerium(III) chloride followed by acid hydrolysis led to cyclobutenone **108**. A ring expansion by a thermolysis conditions (benzene, 80 ºC), followed by a directly oxidation with silver oxide gave quinone **109** in 85% overall yield from compound **106**. Finally, the exposure of a benzene solution of quinone 9 to visible light gave tetracyclic benz[a]anthraquinone **110** in 83% yield, through a photofragmentation via formation of the diradical **V**, cleavage of the cyclobutane to **VI** and expulsion of isobutylene.

[45] M. J. Heileman, R. Tiedemann, H. W. Moore, *J. Am. Chem. Soc.* **1998**, *120*, 3801-3802.

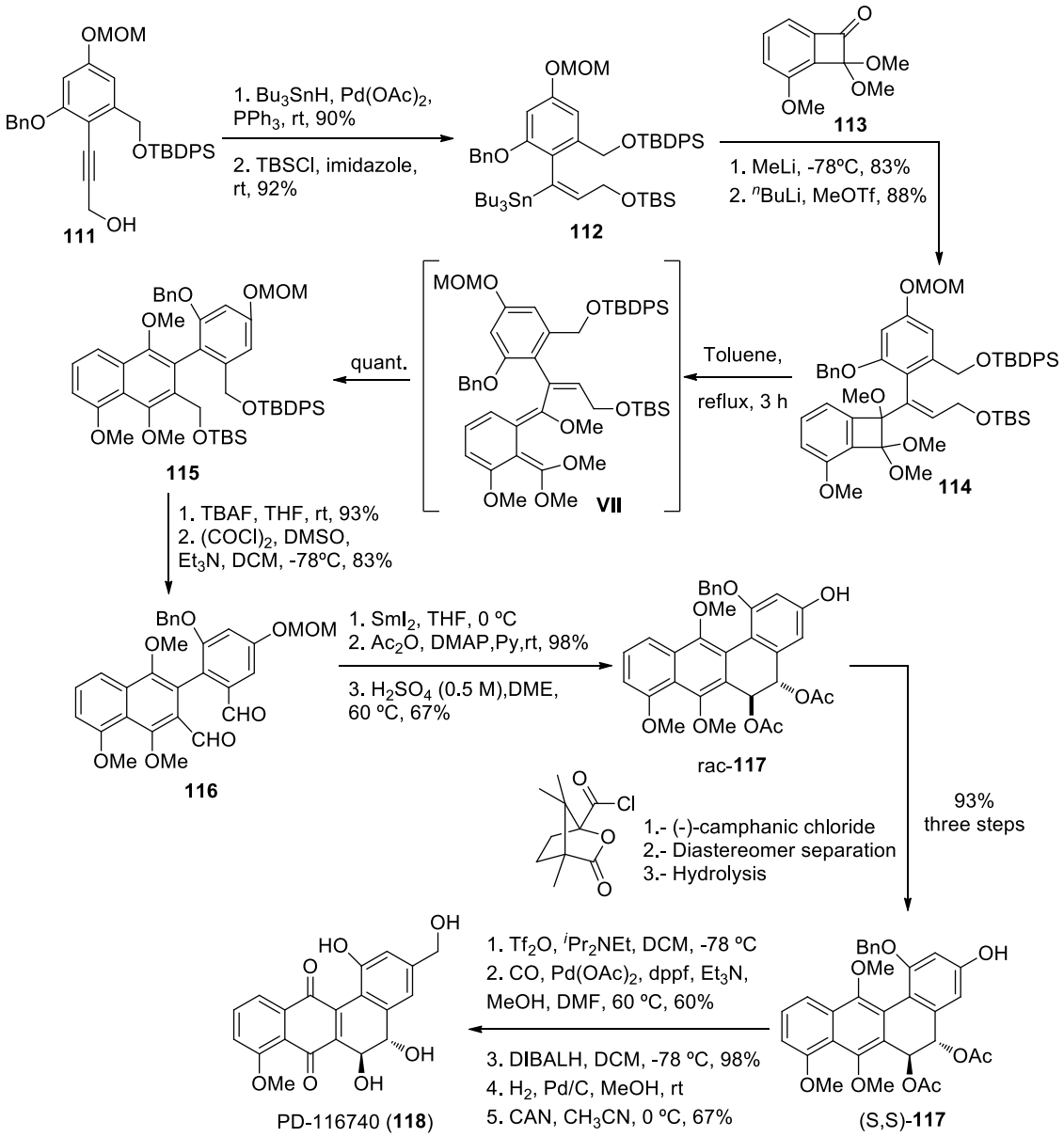


*Scheme 2.21. Synthesis of tetracyclic compound **110** by Moore and coworkers*

More recently, in 2008, Suzuki and coworkers utilized a cyclobutenone electrocyclic ring opening strategy in the synthesis of the oxygenated angucyclinones natural product PD-11640 (**118**) (*Scheme 2.13*).[46] The vinyl stannane **112** was synthesized in good yield with the necessary E geometry from arylalkyne **111** by a Pd-catalyzed hydrostannylation. Coupling of vinyl stannane **112** with cyclobutenone **113**, mediated by methyl lithium and followed by methylation of the

[46] K. Mori, Y. Tanaka, K. Ohmori, K. Suzuki, *Chem. Lett.* **2008**, *37*, 470-471.

resulting carbinol, afforded **114**, which on refluxing in toluene underwent an initial 4 π-electrocyclic ring opening of the benzocyclobutenone forming the intermediate **VII**, which evolved through a 6π-electrocyclization into 2-phenyl naphthalene **115**. Deprotection of silyl ether groups followed by Swern oxidation gave rise to dialdehyde **116**. The dialdehyde **116** formed was then cyclized through pinacol-type reaction in the presence of SmI_2 to obtain mostly the trans-isomer of tetracyclic derivative **117**. This step not only allowed the construction of the tetracyclic core but also installed a vicinal diol at C_5-C_6 of the system. Next, the racemic compound **117** was resolved by reaction with (-)-camphanic chloride, allowing the separation of (*S*,*S*)- and the (*R*,*R*)-enantiomers of **117** after a diastereomer separation and removal of chiral moeity. Finally, both isomers were transformed into PD-11640 (**118**) in 39% yield after a 5-step reaction sequence: triflation of C_3 hydroxy group followed by Pd catalyzed carbonyl insertion, reduction of the formed carbonyl group using diisobutylaluminium hydride (DIBALH) and standard deprotections with H_2 and cerium ammonium nitrate (CAN).



*Scheme 2.22. The total synthesis of PD-116740 (**118**) by Suzuki and co-workers*

2.1.2. Angularly oxygenated angucyclinones

Within angucyclines, there is an important subgroup bearing additional hydroxy groups at the angular AB ring junction (C_{4a} and C_{12b} positions), and/or in other positions. This group of oxygenated angucyclines displays important therapeutical activities and their total synthesis still represents a significant challenge. In addition, this subgroup is called "aquayamycin-type", because the structure of angular *cis*-diol at C_{4a} and C_{12b} is represented by aquayamycin (**11**).[47]

[47] S. I. Elshahawi, K. A. Shaaban, M. K. Kharel, J. S. Thorson, ***Chem. Soc. Rev.*** **2015**, ***44***, 7591-7697

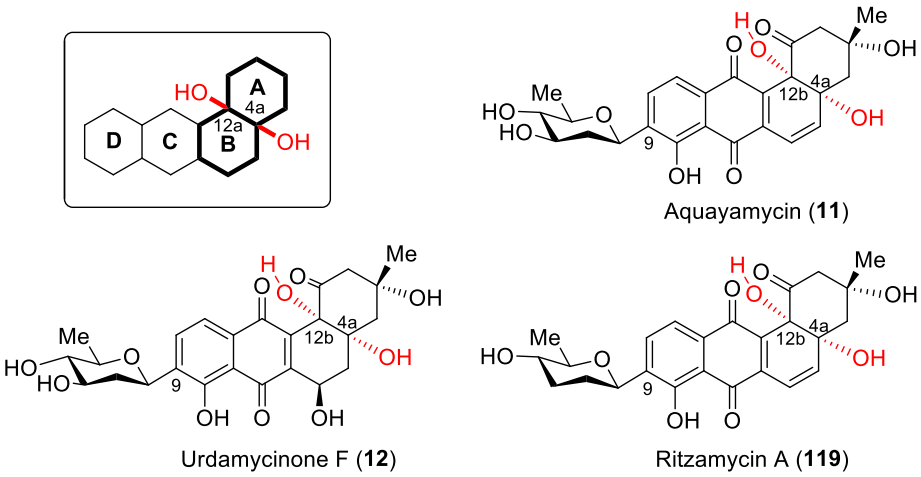


Figure 2.5. Aquayamycin-type: angucycline with angular hydroxy groups at C_{12b} and C_{4a}

Some examples of members of this group are show in *Figure 2.2*. Aquayamycin (**11**) shows the characteristic ben[*a*]anthraquinone structure with oxygen functions at C_1, C_3 and C_8 and a methyl group at C_3 shared by all the family, and a *cis*-diol at C_{12b} and C_{4a}. This is a C-aryl glycoside with a deoxysugar linked at C_9. Urdamycinone F (**12**), other representative member of the group, has a similar structure with an additional hydroxy group at position C_6. Ritzamycin A (**119**) is an analogue of aquayamycin (**11**), but the sugar moiety lacks one of the hydroxy groups.

The structures of other oxygenated angucyclinones are shown in *Figure 2.3*, UWM6 (**120**) and prejadomycin (**121**), bear a single hydroxy group at C_{4a}, and urdamycinone E (**122**), urdamycin J (**123**) and I (**124**), WP 3688 (**125**), gaudimycin A (**126**), B (**127**) and C (**128**) and SS-22BY (**129**), have in their structure the angular *cis*-diol at C_{4a} and C_{12b}.[26, 27]

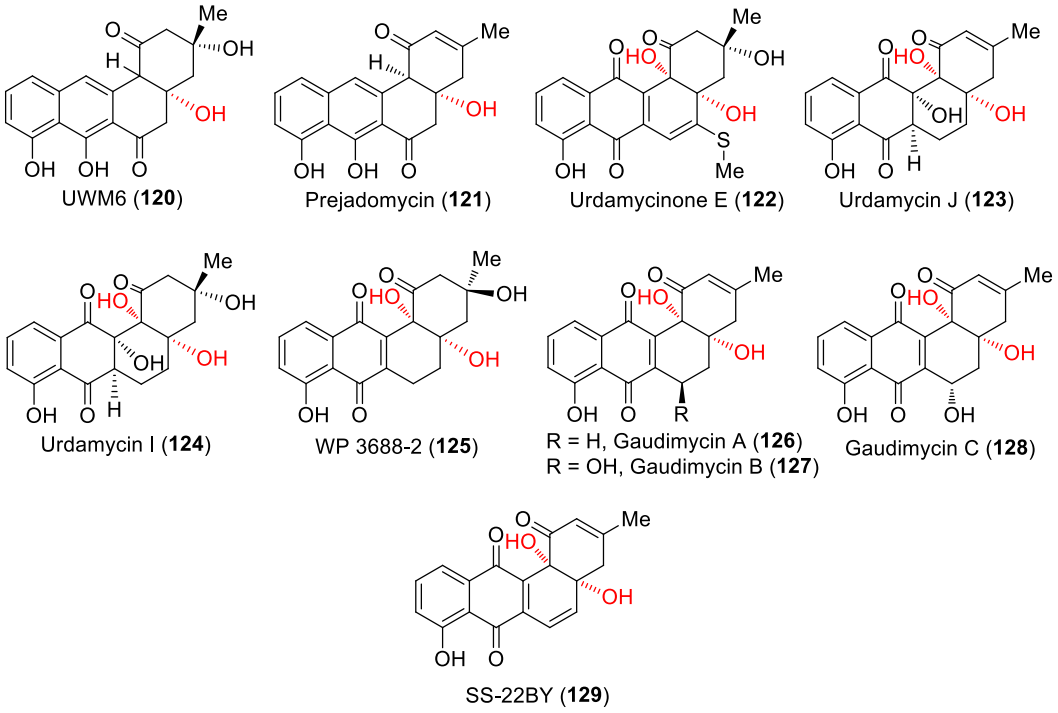


Figure 2.6. Some examples of naturally occurring angucyclinones with one or two angular hydroxy groups at C_{4a} and/or C_{12b}

Other more complex oxidized natural angucyclinones have been also isolated from natural sources. Some representative examples are depicted in *Figure 5*. Thus, panglimycin A (**130**), B (**131**) and C (**132**) have one or two hydroxy groups at C_6 and/or C_{6a},[48] whereas panglimycin F (**133**) and chemomycin (**137**) are characterized by possessing an epoxy functionalization between C_{6a} and C_{12a} positions.26 Oviedomycin (**139**) is including a bisquinone in the tetracyclic structure[49] and kyamicin (**136**) has a cyclic ether between C_1 and C_{12}.[50] In geophyromycins B (**134**) and C (**135**), a cyclic ether bridge exists between C_3 and C_{12a}.[51] Grisemycin (**138**), a new angucyclinone including a tetrahydrofuran ketal at C_1 and C_{12}, a bridged ether (C_{4a} and C_7) and a methyl sulfinyl moiety at C_6, has been recently isolated (*Figure 2.4*).[52]

[48] S. Fotso, T. Mahmud, T. M. Zabriskie, D. A. Santosa, P. Sulastri, J. Philip, *J. Nat. Prod*. **2008**, *71*, 61-65.
[49] C. Méndez, E. Künzel, F. Lipata, F. Lombó, W. Cotham, M. Walla, D. W. Bearden, A. F. Braña, J. A. Salas, J. Rohr, *J. Nat. Prod*. **2002**, *65,* 779-782.
[50] Z. Xie, B. Liu, H. Wang, S. Yang, H. Zhang, Y. Wan, N. Ji, S. Qin, H. Laatsch, *Mar. Drugs* **2012**, *10*, 551-558.
[51] a) G. Bringmann, G. Lang, K. Maksimenka, A. Hamm, T. A. M. Gulder, A. Dieter, A. T. Bull, J. E. M. Stach, N. Kocher, W. E. G. Mueller, H. P. Fiedler, *Phytochemistry* **2005**, *66*, 1366-1373. b) Y.-J. Ji, L.-S. Gan, W.-J. Ding, Z. Chen, Z.-J. Ma, *Tetrahedron Lett.* 2017, *58*, 3747-3750.
[52] Z. Xie, L. Zhou, L. Guo, X. Yang, G. Qu, C. Wu, S. Zhang, *Org. Lett*. **2016**, *18*, 1402-1405.

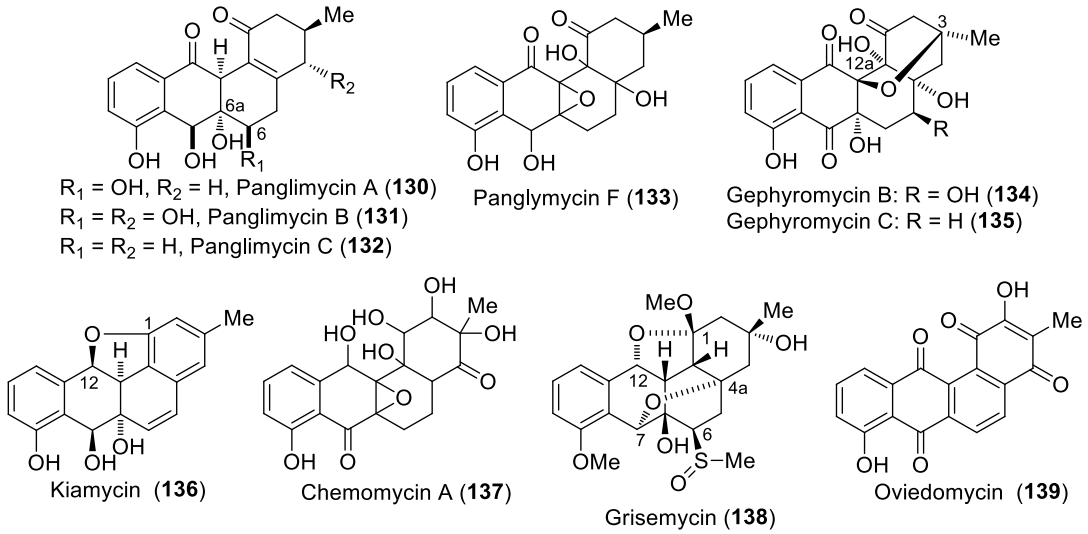


Figure 2.7. Another interesting naturally occurring angucyclinones with additional oxygenated functions

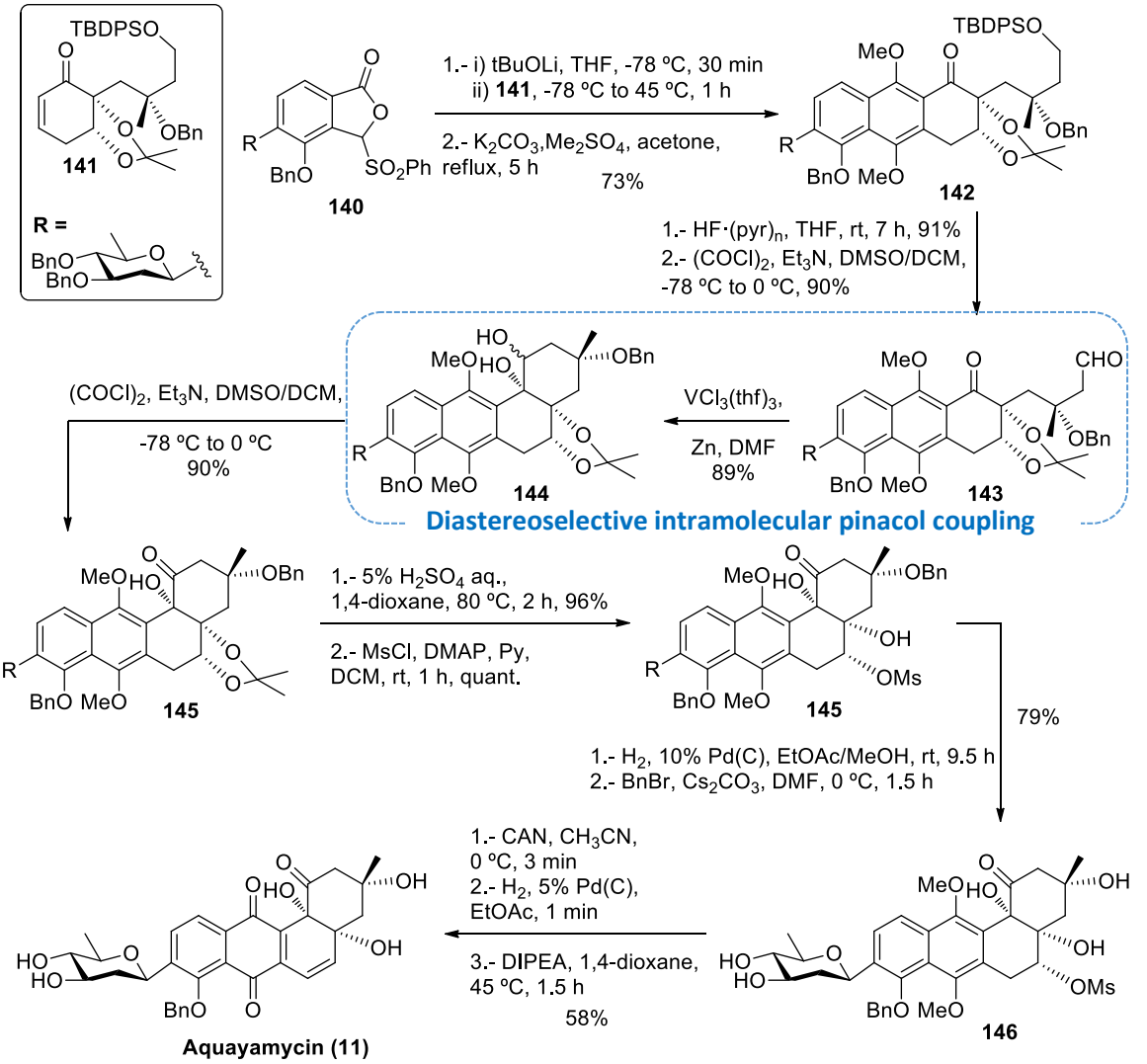
A few total syntheses of angucyclines and angucycline-derivatives with angular hydroxy groups at C_{4a} and C_{12b}, such as aquayamycin-type, have been achieved.[39, 53] Formation of the vicinal *cis*-diol at C_{4a} and C_{12b} has been reported in the literature using two procedures: a diatereoselective intramolecular pinacol coupling [53a,b] and SmI_2 mediated cyclization of a dicarbonyl derivative. [53c].

In the literature, there are some examples for the incorporation of the *cis*-diol motifs using the diastereoselective intramolecular pinacol coupling. The first to use this strategy in the construction of the tetracyclic C_{4a} and C_{12b} cis-diol structure was Suzuki and coworkers.[53b] In 2000, they reported the first total synthesis of aquayamycin (**11**) using as key steps a Hauser-Kraus annulation between cyclohexenone **141** and 3-(phenylsulfonyl)phthalide **140** to synthesize the preliminary linear BCD tricyclic structure, and an intramolecular pinacol coupling of keto aldehyde **143** to furnish the cis-diol tetracyclic core of aquayamycin (**11**) (*Scheme 2.14*). The synthesis started with the Hauser-Kraus annulation between the cyclohexenone **141** and the anion of phatalide **140**, formed by treatment with *tert*-BuOLi, followed by a methylation of the unstable hydroquinone formed with dimethyl sulfate and potassium carbonate to give dimethoxy tricyclic derivative **142** in 73% yield for two steps. Compound **142** was later treated with hydrogen fluoride-pyridine complex ($HF{\cdot}(pyr)_n$) to remove the silyl ether protecting group (TBSDPS-) and was subjected to a Swern oxidation to generate the tricyclic keto aldehyde **143** in high yield. This aldehyde **143** was submitted to an intramolecular pinacol coupling through the Pedersen

[14] H. R. Khatri, H. Nguyen, J. K. Dunaway, J. Zhu, *Chem. Eur. J*. **2015**, *21*, 13553-13557

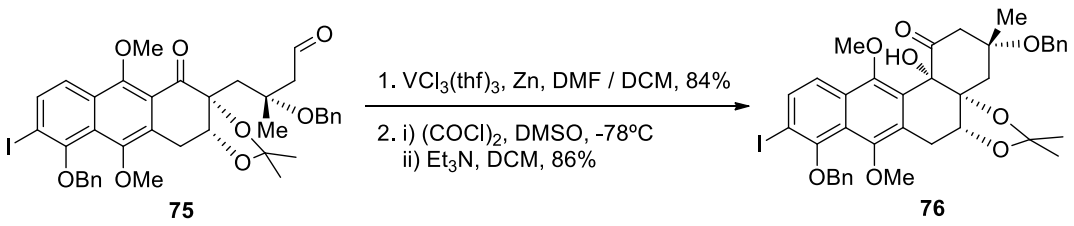
[53] a) S. Kusumi, H. Nakayama, T. Kobayashi, H. Kuriki, Y. Matsumoto, D. Takahashi, K. Toshima, *Chem. Eur. J*, **2016**, 22, 18733-18736; b) T. Matsumoto, H. Yamaguchi, M. Tanabe, Y. Yasui, K. Suzuki, *Tetrahedron Lett*. **2000**, 8393-8396; c) K. Krohn, P. Frese, U. Florke, *Chem. Eur. J.,* **2000**, *6*, 3887-3896.

procedure using $VCl_3{\cdot}(thf)_3$ and Zn. The A ring and *cis*-diol moiety present in aquayamycin (**11**) were installed with this methodology. Thus, tetracyclic pinacol derivative **144** was synthesized in 89% yield as a mixture of C_1-epimers. Then, the mixture was oxidized by Swern oxidation into the same ketone **145** in high yield, which was transformed into tetracyclic derivative **146** in 96% yield through two reaction steps: removal of the acetonide with an aqueous solution of 5% of sulfuric acid and a selective mesylation of hydroxyl group at C_5 with MsCl in presence of DMAP. A deprotection of all benzyl protecting group under hydrogen catalytic conditions and a selective re-protection of hydroxyl group at C_8 as benzyl group using BnBr in presence of Cs_2CO_3 afforded tetracyclic derivative **147** in 79% yield. Finally, aquayamycin (**11**) was obtained in 58% yield after three reaction steps: oxidation with CAN, deprotection by a catalytic hydrogenolysis and removal of methanesulfonic acid with DIPEA.



*Scheme 23. Total synthesis of aquayamycin (**11**) using the intramolecular pinacol coupling to introduce the cis-diol motif by Suzuki and coworkers.*

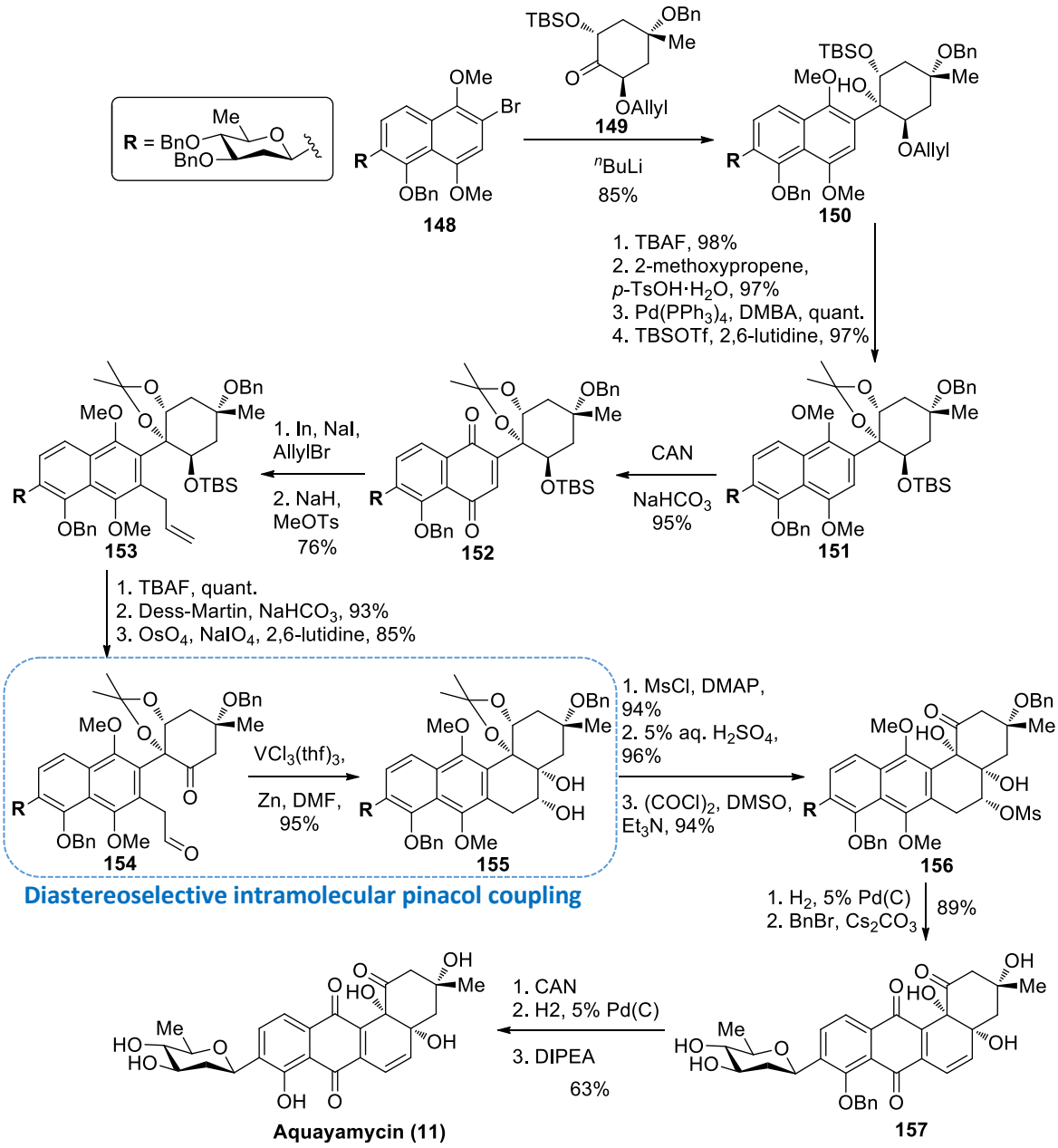
In 2015, Zhu and coworkers used the same synthetic strategy described previously y Suzuki. They synthesized derhdinosylurdamucin A (**78**) through two key steps: a Hauser-Kraus annulation and intramolecular pinacol coupling strategy to incorporate the *cis*-diol motif at C_{4a} and C_{12b} (*Scheme 2.15*).[39] We already discussed this synthesis before, so we only highlighted here the formation step of the *cis*-diol motif. Tetracyclic compound **76** was obtained by submitting the keto aldehyde **75** to a Perdersen-modified pinacol coupling using $VCl_3(thf)_3$ and Zn, followed by Swern oxidation of generated secondary alcochol into ketone at C_1.



*Scheme 2.24. Intramolecular pinacol coupling to introduce the cis-diol motif present in derhdinosylurdamycin A (**78**) by Zhu and coworkers*

Most recently, Toshima and coworkers published in 2016 the total synthesis of aquayamycin (**11**) (*Scheme 2.16*).[53a] The strategy utilized to form the *cis*-diol and the B ring moiety (diol **155**) was again the intramolecular pinacol coupling of ketoaldehyde **154** using a Pedersen modified procedure.[40] The first step in construction of ketoaldehyde **154** involved a nucleophilic addition between the cyclic ketone **149** and the naphthyllithium derivative resulting from the bromonaphthalene **148** by treatment with ^{n}BuLi. The resulting compound **150** was transformed into **151** in 4 synthetic steps: desilylation, acetonide protection of the vicinal diol, deallilation and silylation, which occurred in high yields. The resulting product **151** was oxidized with CAN to obtain naphthoquinone **152**. Then, compound **153** was formed in two reaction steps: an allylation with a solution of allylindium species prepared in situ from indium, sodium iodide and allylbromide, followed by one-pot rearrangement-methylation using NaH and MeOTs. Transformation of the allylnaphthalene **153** into the key intermediate keto aldehyde **154** was achieved in 3 steps: removal of the silyl group, Dess-Martin oxidation and mild oxidative cleavage of the terminal double bond using OsO_4 and $NaIO_4$. Once synthesized diol **155**, mesylation of hydroxy group at C_5, followed by removal of acetonide group and Swern oxidation, gave the intermediate **156**. Deprotection of benzyl group with H_2 and Pd(C) and re-protection of the phenol at C_8 as benzyl group with BnBr and $CsCO_3$, afforded compound **157**. Finally, **157** was transformed into aquayamycin (**11**) in 5 steps, including protection and deprotection group reactions: deprotection of all benzyl groups under catalytic hydrogenation, mono-benzylation of phenol at

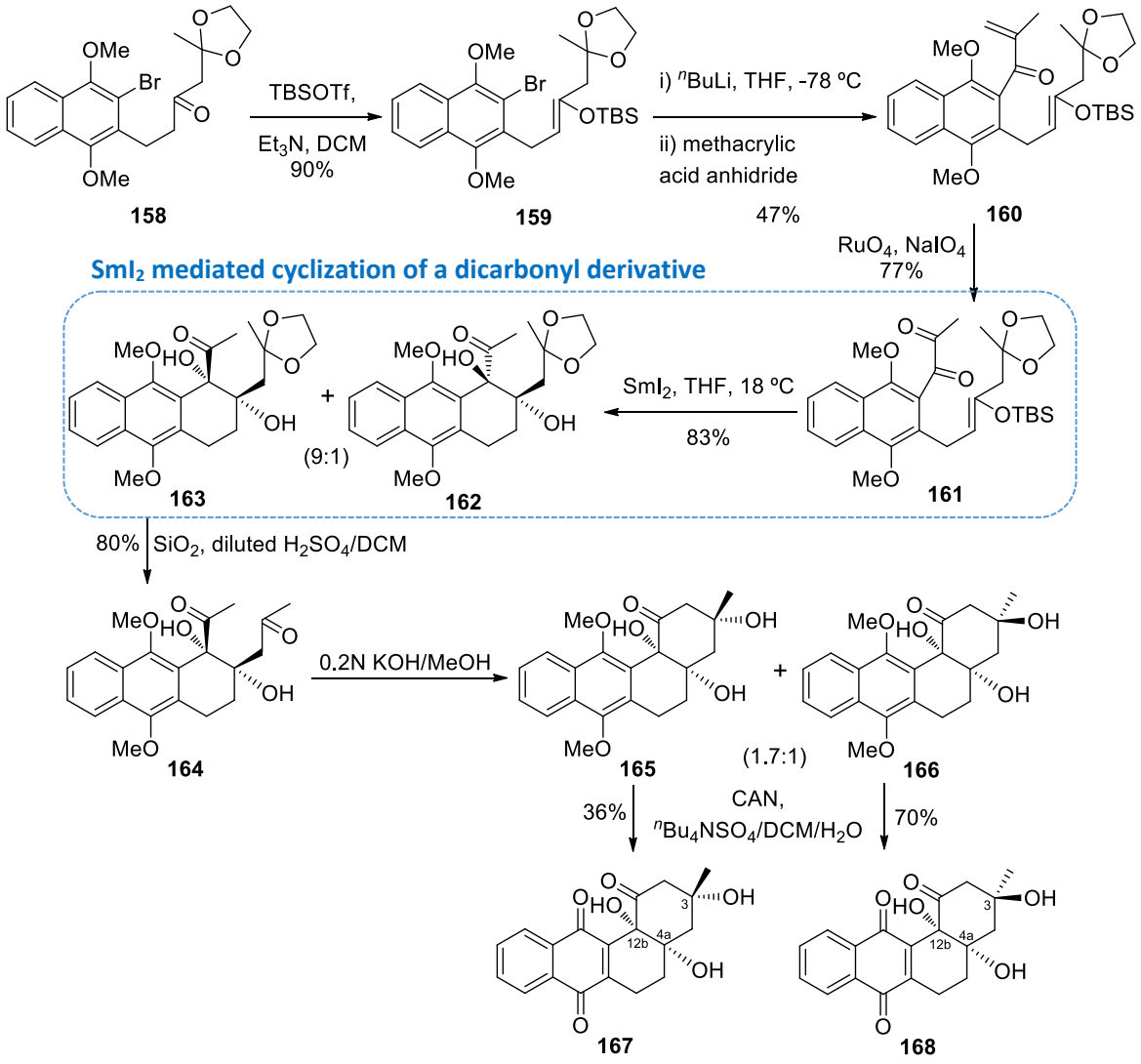
C_8 with BnBr and Cs_2O_3, oxidation with CAN, debenzylation with H_2 and Pd (C) and elimination of mesylate group.



*Scheme 2.25. Total synthesis of aquayamycin (**11**) by Toshima and coworkers*

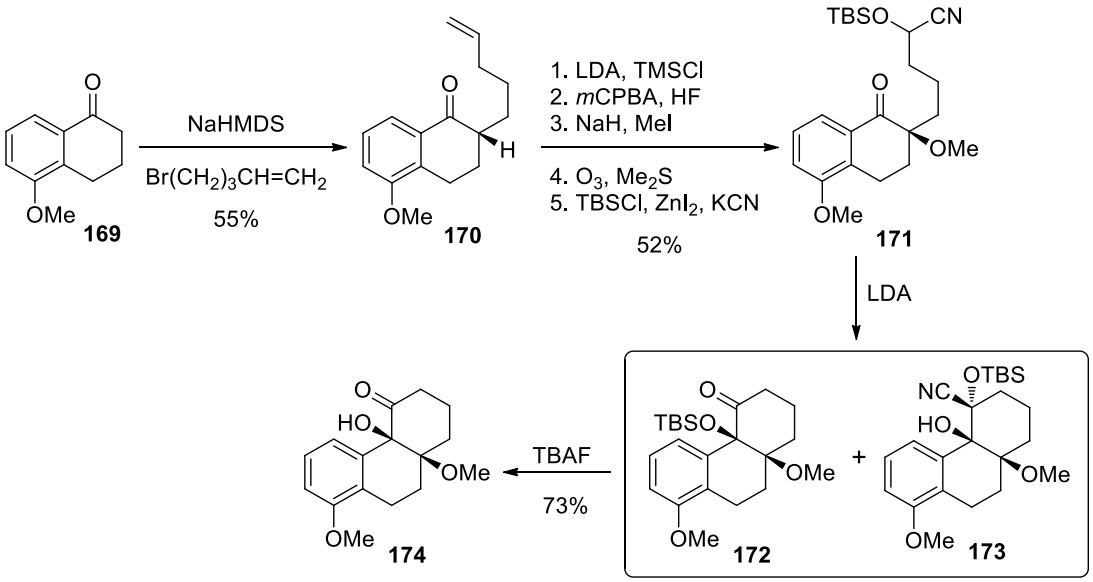
In 2000, Krohn and coworkers reported the first total synthesis of racemic 8-deoxy WP3688-2 angucycline antibiotic **168** with characteristic *cis*-hydroxy groups at C_{4a} and C_{12b}, using as the key step an intramolecular coupling cyclization of the bicyclic dicarbonyl **161** mediated by samarium diiodie (SmI_2) (*Scheme 2.17*).[53c] The synthesis began with the protection of ketone of substituted naphthalene **158** as silyl enol ether using TBSCl and Et_3N to afford derivative **159**. Then, the coupling reaction between the lithiated compound, formed from the reaction of bromo

derivative **159** with *n*-BuLi and methacrylic acid anhydride gave the unsaturated product **160** in 47% yield. The double bond was cleaved using ruthenium tetroxide and sodium periodate, generating diketone **161** in 77% yield, which was treated later with samarium diiodide. The cyclization mediated by SmI_2 afforded a mixture of the stereoisomeric *cis*-diol **163** and *trans*-diol **162** in 83% yield in a ratio 9:1, which were separated. Then, the dioxolane was removed through an acid-catalyzed on silica gel according to the procedure of Huet et al. to afford dione **164** in 80% yield. This dione **164** was treated with a solution of potassium hydroxide in methanol, obtaining three compounds: the desired tetracyclic 3,4a-cis diol **165** and 3,4a-trans diol **161** in 1.7:1.0 ratio and a small amount of the open chain retro-aldol product. Both tetracyclic compounds were oxidized separately by cerium ammonium nitrate (CAN) to obtained the 8-deoxy-5,6-dihydro analogue **167** of aquayamycin (**11**) and the 8-deoxy WP3688-2 **168**, respectively.



*Scheme 2.26. Synthesis of 8-deoxy WP3688-2 **168** and 8-deoxy-5,6-dihydro analogue **167** of aquayamycin (**11**) by Krohn and coworkers*

Other method used to install a *cis*-diol moiety into the ABC ring system consisted in an intramolecular addition of an anion derived from a protected cyanohydrin to a ketone. This method was applied by Kraus and Wan to the synthesis of the angular diol tricyclic model **174** (*Scheme 2.18*).[54] Thus, starting from methoxy substituted tetralone **169** treatment with sodium bis(trimethylsilyl)amide (NaHDMS) and 5-bromo-1-pentene ($Br(CH_2)_3CH=CH_2$) afforded the α-alkylated ketone derivative **170** with 55% yield. Then, silylated cyanohydrin **171** was synthesized from ketone **170** in 5 steps in 52% overall yield. These 5 synthetic steps involved an enol silyl ether formation with LDA and trimethylsilyl chloride (TMSCl), oxidation with *m*-chloroperbenzoic acid (*m*CPBA) and hydrofluoric acid (HF), methylation with sodium hydride (NaH) and methyl iodide (MeI) in DMF, ozonolysis of the alkene and the treatment with *tert*-buthyldimethylsilyl chloride (TBSCl), zinc iodide (ZnI_2) and potassium cyanide (KCN), respectively. Reaction of **171** with LDA at -78ºC gave a mixture of hydroxy ketone **172** and silyl protected cyanohydrin **173**, which reacted with tetra-n-butylammonium fluoride (TBAF) to afford the angularly oxygenated ketone **174** in 73% overall yield from **171**.



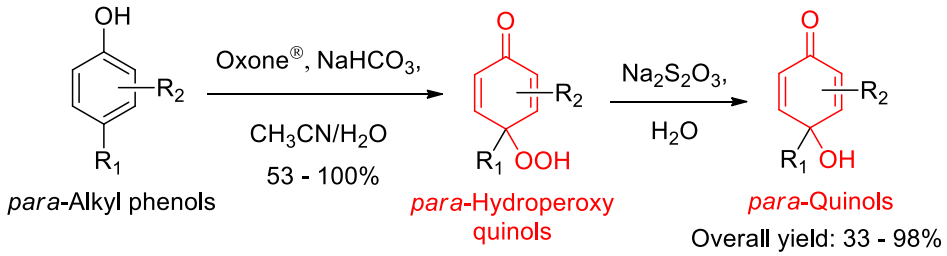
Scheme 2.27. Synthesis of tricyclic model aquayamycin-type by Kraus and Wan

2.1.2.1. Model studies towards the synthesis of angucyclinones with angularly oxygenated substituents.

A precedent work directly related with the research developed in this PhD thesis corresponds to a model study carried out in our research group focused on the synthesis of tricyclic ABC angularly oxygenated systems. The starting point of this study was the finding of a

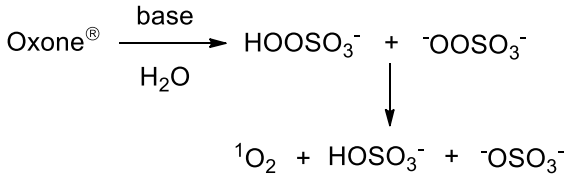
[54] G. A. Kraus, Z. Wan, *Tetrahedron Lett.* **1997**, *38*, 6509-6512.

practical method for the oxidative dearomatization of differently substituted *para*-alkyl phenols into the corresponding *para*-peroxyquinols. In 2006, the group uncovered a new application of the oxidant Oxone® to the synthesis of *para*-peroxyquinols based on the treatment of *para*-alkyl substituted phenols with the system Oxone® / $NaHCO_3$. [55] The resulting *para*-peroxy quinols were later reduced with sodium thiosulfate ($Na_2S_2O_3$) into the corresponding *para*-quinols as shown in *Scheme 2.19*. The method was very general and could be applied to differently substituted *para*-alkyl phenols, using acetonitrile as solvent.



Scheme 2.28. Oxidative dearomatization of para-alkyl phenols with the system Oxone® / $NaHCO_3$

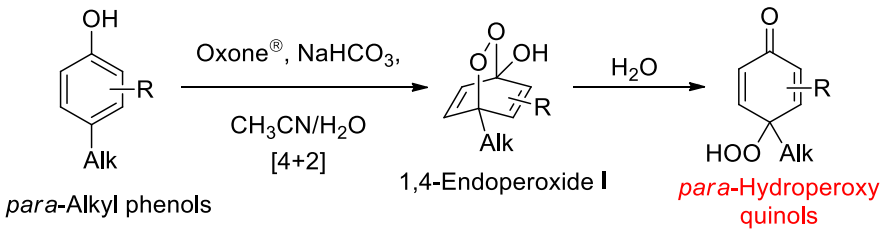
The active ingredient of Oxone®, potassium peroxymonosulfate ($KHSO_5$) was known to decomposed in aqueous basic medium to generate singlet oxygen ($^1O_2$) (*Scheme 2.20*).[56]



Scheme 2.29. Decomposition of Oxone® in singlet oxygen.

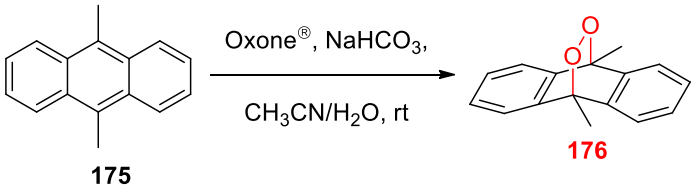
The singlet oxygen species, generated from an excess of Oxone® in the presence of sodium bicarbonate ($NaHCO_3$), is the species responsible for the oxidative dearomatization of *para*-alkyl phenols to *para*-peroxy quinols (*Scheme 2.21*).

[55] M. C. Carreño, M. González-López, A. Urbano, *Angew. Chem.Int. Ed.* **2006**, *45*, 2737-2741.
[56] a) W. Adam, D. V. Kazakov, V. P. Kazakov, *Chem. Rev.* **2005**, *105*, 3371-3387; b) D. F. Evans, M. W. Upton, *J. Chem. Soc. Dalton Trans.* **1985**, 1151-1153; c) D. L. Ball, J. O. Edwards, *J. Am. Chem. Soc.* **1956**, *78*, 1125-1129.



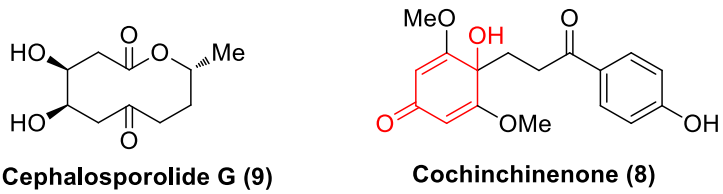
Scheme 2.30. Formation of para-peroxyquinols from oxidative dearomatization of para-alkyl phenols

From the mechanistic point of view, the process involves a [4+2] cycloaddition between singlet oxygen and electron-rich *para*-alkyl phenols giving a 1,4-endoperoxide **I**, which immediately evolves to the corresponding 4-peroxy-2,5-cyclohexadienones as a result of its unstable peroxyhemiaketal structure. This mechanistic proposal was supported by the synthesis of the known endoperoxide **176** derived from 9,10-dimethylanthrecene (**175**) by treatment with Oxone® / $NaHCO_3$ in acetonitrile/water, under similar conditions (*Scheme 2.22*).



*Scheme 2.31. Formation of (9s,10s)-9,10-dimethyl-9,10-dihydro-9,10-epidioxyanthracene (**176**)*

This efficient and mild oxidative dearomatization process was later used as the key step in the total synthesis of some natural products such cephalosporolide G (**9**)[57a] or cochinchinenone (**8**)[57b] (*Scheme 2.23*).

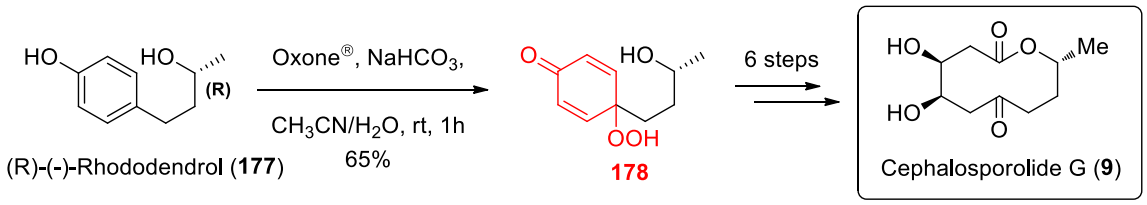


Scheme 2.32. Natural products synthesized in our group using the system Oxone® / $NaHCO_3$

In the total synthesis of cephaslosporolide G (**9**), the oxidative dearomatization was carried out on (*R*)-(-)-rhododendrol (**177**), a *para*-alkyl substituted phenol, which was submitted to the reaction with singlet oxygen, generated from Oxone® in the presence of $NaHCO_3$, to give the

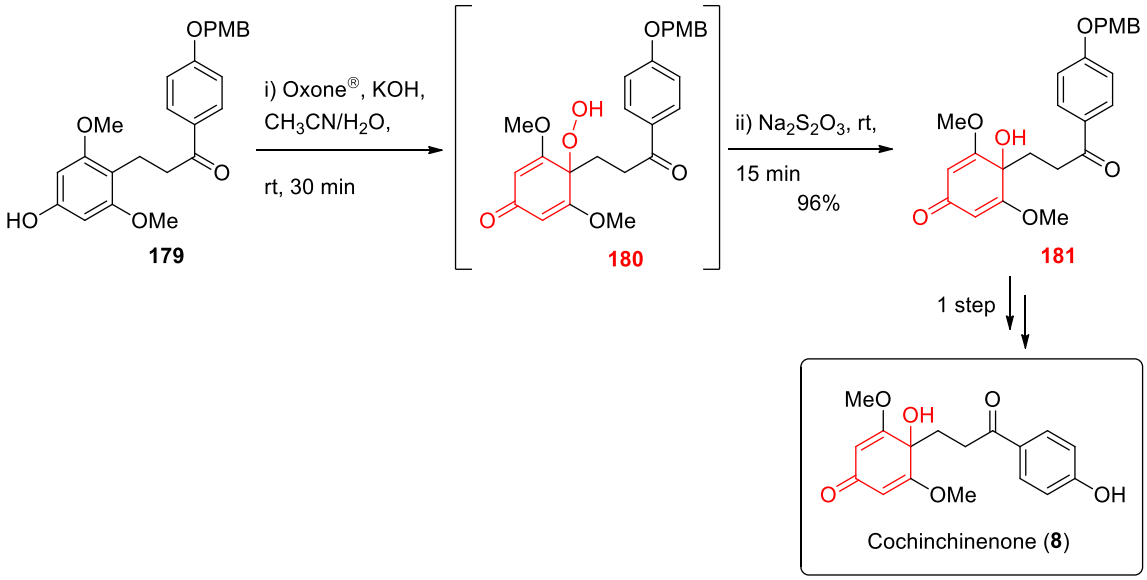
[57] a) S. Barradas, A. Urbano, M. C. Carreño, *Chem. Eur. J.* **2009**, *15*, 9286-9289; b) S. Barradas, G. Hernández-Torres, A. Urbano, M. C. Carreño, *Org. Lett.* **2012**, *14*, 5952-5955.

para-peroxy quinol **178** in 65% yield (*Scheme 2.24*). The transformation of the *para*-peroxy quinol **178** into the natural product, cephalosporolide G (**9**), required six additional synthetic steps.



*Scheme 2.33. Oxidative dearomatization key step in the synthesis of cephalosporolide G (**9**)*

On the other hand, the oxidative dearomatization of *para*-alkyl phenol **179** was realized in the latest steps of the total synthesis of cochinchinenone (**8**). The oxidative dearomatization of *para*-alkyl phenol **179**, having the carbon skeleton of cochinchinenone (**8**), with the system Oxone® / KOH at rt for 30 min, followed by in situ reduction with $Na_2S_2O_3$ of the initially formed *para*-peroxy quinol **180**, afforded the corresponding *para*-quinol **181** in 96% yield (*Scheme 2.25*).

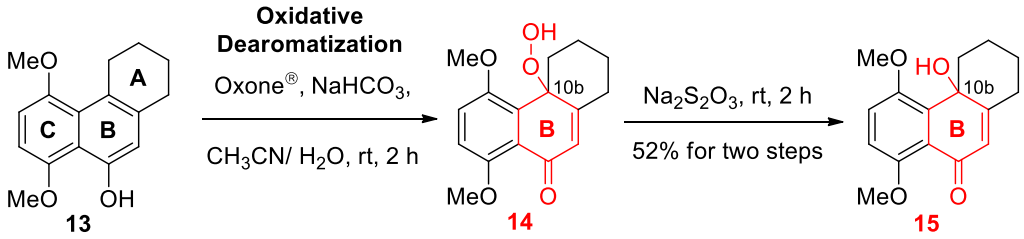


*Scheme 2.34. Oxidative dearomatization key step in the synthesis of cochinchinenone (**8**)*

Taking into account these results, a new approach to the synthesis of angularly oxygenated angucyclinones was envisaged. [58] A model study was initially carried out on the tricyclic structure 5,8-dimethoxy-1,2,3,4-tetrahydrophenanthren-9-ol (**13**). This was considered a simple *para*-alkyl substituted phenol precursor of the angularly oxygenated tricyclic analogues of the natural products. Based on the reported oxidative dearomatization method reaction of **13**

[58] a) M. C. Carreño, A. Urbano, C. Di Vitta, *J. Chem. Soc., Chem. Commun.* **1999**, 817-818; b) M. C. Carreño, A. Urbano, C. Di Vitta, *Chem. Eur. J.* **2000**, *6*, 906-913; c) M. C Carreño, M. Ribagorda, A. Somoza, A. Urbano, *Angew. Chem., Int. Ed.*, **2002**, *41*, 2755-2757.

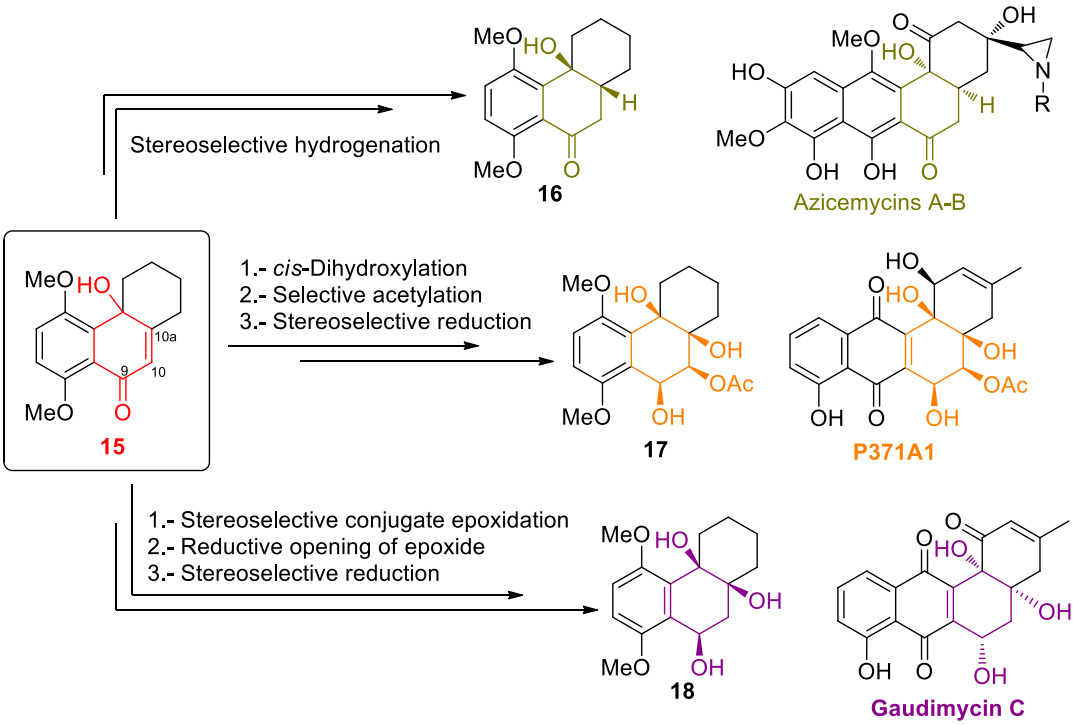
with Oxone® / $NaHCO_3$ (*Scheme 2.26*) gave a selective access to the tricyclic *para*-peroxy quinol **14**.[59]



Scheme 2.35. Model studies towards ABC structures with angular hydroxyl groups

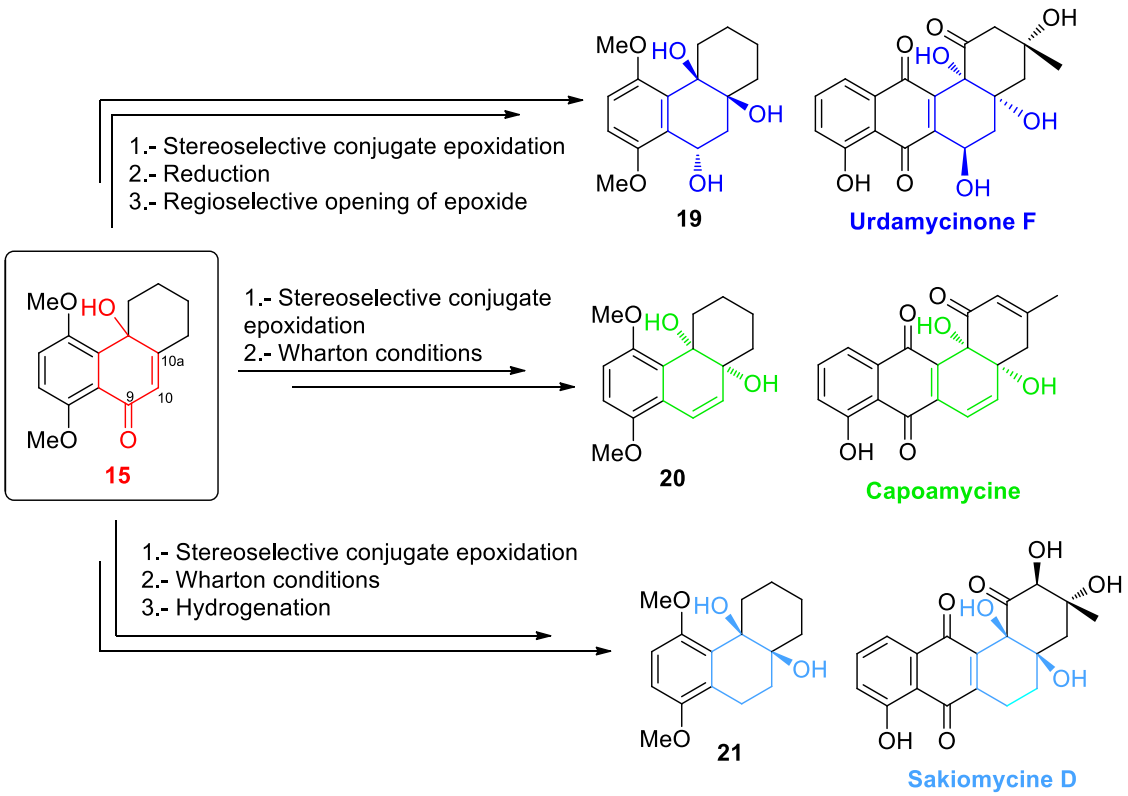
The peroxide **14** was later reduced in situ into *para*-quinol **15** with sodium thiosulfate in 52% yield from *para*-alkyl phenol **13**. Later, *para*-quinol **15** was transformed in a divergent and selective manner into 6 differently substituted oxygenated tricyclic core models of natural angucyclinones such as the tricyclic aquayamycin-type derivative **16** as show in *Schemes 2.27* and *2.28*. The tricyclic *para*-quinol **15** was transformed into the azicemycin-type tricyclic model **16** by a stereoselctive hydrogenation of the conjugated double bond. Then, tryciclic derivative **17**, which possesses the *cis*-tetraoxygenated B ring present in the structure of angucyclinones P371A1, was synthesized after three reaction steps: a *cis*-dihydroxylation of conjugated double bond, a selective acetylation the hydroxyl group at C_{10} and a stereoselective reduction of carbonyl group. The tricyclic model **18** of guadimycin C was synthesis from *para*-quinol **15** in another three steps: a stereoslective conjugated epoxidation, a reductive opening of epoxide and a stereoselective reduction of carbonyl group.

[59] S. Vila-Gisbert, A. Urbano, M. C. Carreño, *Chem. Commun*. **2013**, *49*, 3561-3563.



Scheme 2.36. Substituted oxygenated tricyclic core models of natural angucyclinones

Scheme 2.28 showed the transformation of *para*-quinol **15** into the tricyclic model **19** of urdamycinone F, the tricyclic model **20** of capoamycin and the tricyclic model **21** of sakyomycin D. Tricyclic derivative **19** was synthesized after a stereoselective conjugated epoxidation followed by the reduction of the carbonyl group and the regioselective opening of the epoxide. Finally, the tricyclic model **21** was afforded through formation of the tricyclic model **20**. First, a stereoselective conjugated epoxidation followed by a reduction of α,β-epoxy ketone using Wharton reaction conditions gave compound **20**, which evolved to tricyclic derivative **21** through an hydrogenation of the conjugated double bond.



Scheme 2.37. Substituted oxygenated tricyclic core models of natural angucyclinones

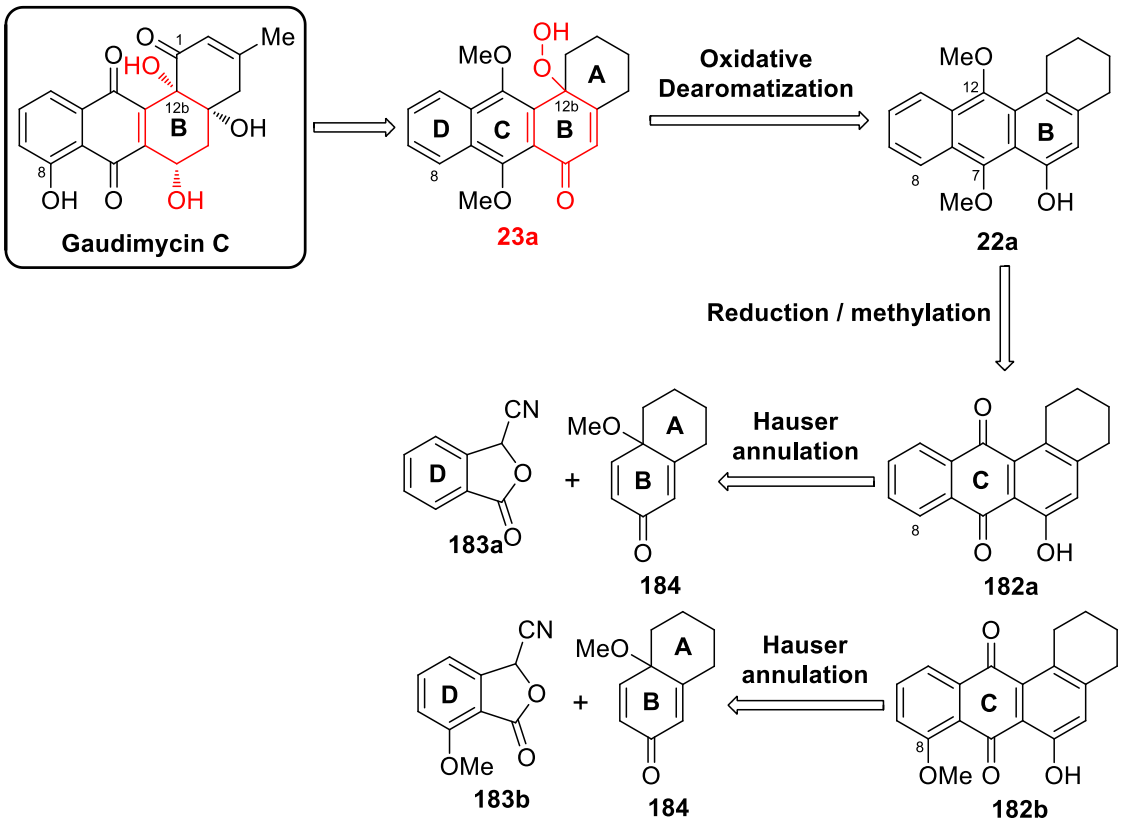
These results led us to consider a similar route to the angularly oxygenated tetracyclic angucyclinones starting from adequately substituted angular tetracyclic phenols.

2.2. Results and Discussion

2.2.1. Synthesis of 12b-peroxy-7,12-dimethoxy-1,3,4,12b-tetrahydrotetraphen-6(2H)-one (23a): Retrosynthesis analysis.

Based on our previous studies,[55, 57, 59] we reasoned that tetracyclic hydroperoxy derivative **23a** could be adequate model precursors to further install other oxygenated functions in the different positions of the skeleton, *en route* to the angularly oxygenated angucyclinone-type targets, such as gaudimycin C. To check this possibility, the simplified tetracyclic precursor **22a**, lacking the oxygenated functions at C_1 and C_8 and the methyl group at C_3, was chosen to check the oxidative dearomatization because it would be synthetically more accessible. The retrosynthetic analysis indicated in *Scheme 2.29* evidences that C_{12b} oxygenated compound **23a** would proceed from phenol **22a**. In the case of phenols **22b** and **22c**, having the oxygenated functions at C_8 C_1,

respectively, as in the natural angucyclinones (e.g. Gaudamycin C), the retrosynthetic analysis would be similar. These systems were chosen as models to evaluate the selectivity of the oxidative dearomatization, since different aromatic rings prone to react, exist in their structures. The presence of two methoxy groups at ring C in all cases was necessary to further transform this moiety into the anthraquinone existent in the natural products. Thus, a simple retrosynthetic analysis of **22a** (*Scheme 2.29*) led to consider the availability of *para*-peroxy quinol **23a** through an oxidative dearomatization of phenol **22a**. A direct reduction / methylation reaction of angular tetracyclic anthraquinones **182a** with an orthogonal protecting group at the –OH would allow the access to the phenol **22a**. In turn, compound **182a** should be obtained through a Hauser-Kraus annulation[60] of commercially available cyanophtalide **183a** and 4a-methoxy-5,6,7,8-tetrahydronaphthalen-2(4a*H*)-one (**184**). This method has been already used *en route* to the construction of the tetracyclic skeleton. Phenols **22b** and **22c** would be available in a similar manner from the adequately substituted precursors.



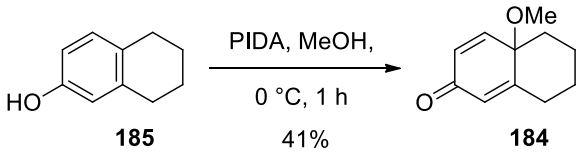
*Scheme 2.38. Retrosynthesis of 12b-hydroperoxy-7,12-dimethoxy-1,3,4,12b-tetrahydrotetraphen-6(2H)-one (**23a**)*

[60] a) F. M. Hauser, R. P. Rhee, *J. Org. Chem.* **1978**, *43*, 178-180; b) G. Kraus, H. Sugimoto, *Tetrahedron Lett.* **1978**, *19*, 2263-2266; c) D. Mal, P. Pahari, *Chem. Rev*. **2007**, *107*, 1892-1918.

2.2.2. Synthesis of tetracyclic phenol precursors 22

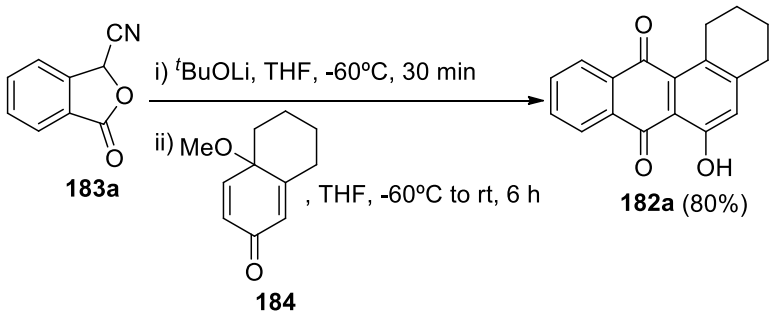
2.2.2.1. Synthesis of 7,12-dimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (22a)

To apply this retrosynthetic scheme, cyanophthalide **183a** and bycyclic cyclohexadienone **184** were required. Cyanophthalide **183a** was commercially available, but 4a-methoxy-5,6,7,8-tetrahydronaphthalen-2(4a*H*)-one (**184**) had to be synthetized. Cyclohexadienone **184** was prepared in one-step by an oxidative dearomatization of 5,6,7,8-tetrahydro-β-naphthol (**185**) using (diacetoxyiodo)benzene (PIDA) in dry methanol, following the reported procedure (*Scheme 2.30*). [61]



*Scheme 2.39. Synthesis of 4a-methoxy-5,6,7,8-tetrahydronaphthalen-2(4a*H*)-one (**184**)*

With cyclohexadienone **184** in hand, a Hauser-Kraus annulation was achieved by reaction with the α-cyano carbanion resulting in the treatment of commercially available 3-cyanophthalide (**183a**) with lithium *tert*-butoxide (^{t}BuOLi) in dry tetrahydrofuran (THF) at -60 ºC to room temperature (rt), following the reported procedure.[62] 6-Hydroxy substituted benz[*a*]anthraquinone **182a** could be isolated in 80% yield (*Scheme 2.31*).

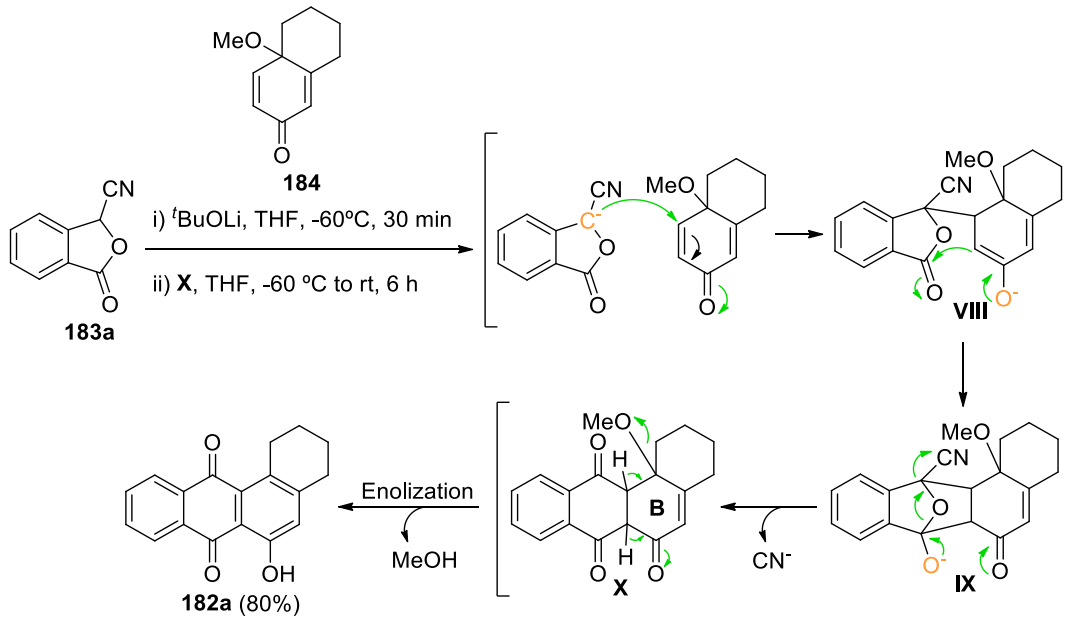


*Scheme 2.40. Synthesis of 6-hydroxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (**182a**) through Hauser-Kraus annulation*

As shown in *Scheme 2.32*, once the intermediate α-cyano carbanion was formed, the mechanism of the Hauser-Kraus annulation involves a 1,4-conjugate addition to the reactive

[61] a) H. N. Roy, M. S. Sarkar, D. Mal, *Synth. Commun.* **2005**, *35*, 2183-2188; b) D. Mal, H. N. Roy, N. K. Hazra, S. Adhikari *Tetrahedron*. **1997**, *53*, 2177-2184.
[62] a) D. Mal, S. Dey *Tetrahedron* **2006**, *62*, 9589-9602; b) D. Mal, P. Pahari, *Chem. Rev.* **2007**, *107*, 1892-1918.

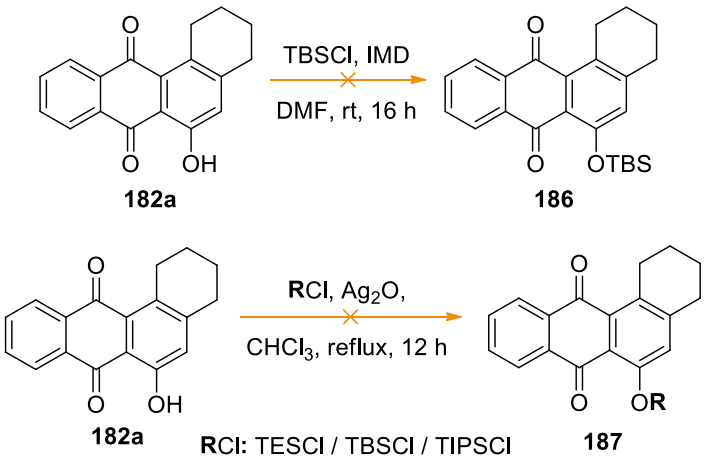
enone moiety, followed by the attack of the intermediate enolate to the lactone. The tetracyclic intermediate **IX** later evolves through the opening of the lactone and cyanide anion elimination.



Scheme 2.41. Mechanism of the Hauser-Kraus annulation

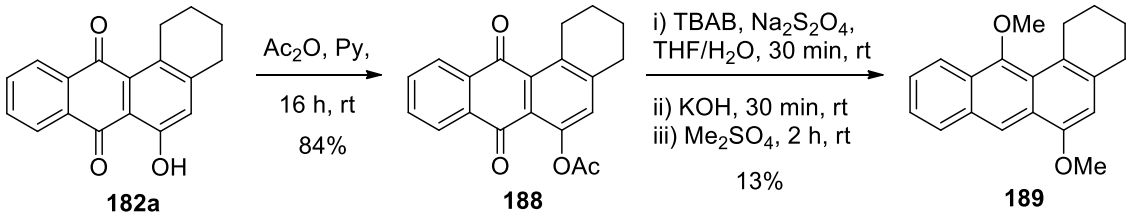
Protection of the phenol of **182a** was the next step in the synthetic plan. Different protecting groups were checked with poor results. Initially, a silyl ether was considered as protecting group. Various conditions for the silyl ether formation were checked. We used *tert*-butyldimethylsilyl chloride (TBSCl) with imidazole (IMD) dissolved in N,N-dimethylformamide (DMF) 16h at rt,[63] whithout observing the desired product. Others alkylsilyl ethers such as triethylsilyl chloride (TESCl), triisopropylsilyl chloride (TIPSCl) and TBSCl were tested in the presence of silver oxide (Ag_2O) and dissolved in chloroform for 12 hours at reflux.[64] In all reaction conditions, the starting material remained unchanged (*Scheme 2.33*)

[63] M. N. Bakola, K. K. Apazidou *OPA*, **1996**, *113*, 245-253.
[64] N. Lebrasseur, G.-J. Fan, M. Oxoby, M. A. Looney, S. Quideau, *Tetrahedron*, **2005**, *61*, 1551-1562.



Scheme 2.42. Essays of protection of phenol at C_6 with different alkylsilyl ethers

Protection of 6-hydroxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (**182a**) could be achieved as acetate with acetic anhydride in pyridine (Py) for 16 hours at rt.[62a, 65] 7,12-dioxo-1,2,3,4,7,12-hexahydrotetraphen-6-yl acetate (**188**) could be isolated in 84% yield. However, the acetate group was not robust enough to support the strong basic conditions necessary in the next reduction/methylation process.[66] Upon treatment of the acetylated phenol **188** with sodium dithionite under phase transfer conditions followed by adding potassium hydroxide solution and dimethyl sulfate (Me_2SO_4), the expected product was not detected. Under these conditions, 6,12-dimethoxy-1,2,3,4-tetrahydrotetraphene (**189**) was the only product detected, that was isolated in a poor 13% yield from the resulting complex mixture (*Scheme 2.34*).

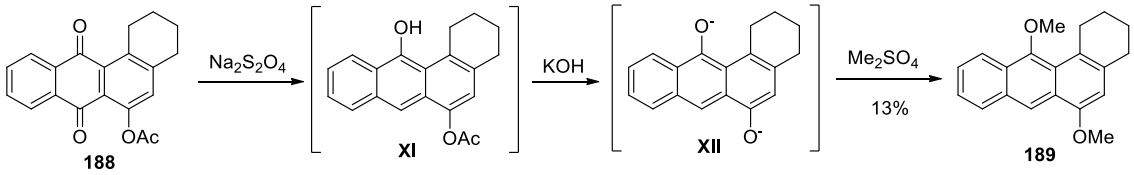


*Scheme 2.43. Formation of 6,12-dimethoxy-1,2,3,4-tetrahydrotetraphene (**189**)*

Formation of this dimethoxy derivative **189** could be a consequence of the initial reduction of compound **188** leading to intermediate **XI** with sodium dithionite ($Na_2S_2O_4$). This process had been previously reported in the literature.[67] Then, the addition of potassium hydroxide produced the saponification of the ester and the deprotonation of the phenols at C_6

[65] M. O'Keefe, D. M. Mans, D. E. Kaelin Jr., S. F. Martin, *Tetrahedron* **2011**, *67*, 6524-6538.
[66] K. Wu, M. Wang, Q. Yao, A. Zhang, *Chin. J. Chem.* **2013**, *31*, 93-99.
[67] H. Prinz, W. Wiegrebe, K. Müller, *J. Org. Chem.* **1996**, *61*, 2853-2856.

and C_{12}. Finally, the phenoxy groups were methylated by the addition of dimethyl sulfate (Me_2SO_4) (*Scheme 2.35*). It is important to highlight the role of tetra-*n*-butylammonium bromide (TBAB), a quaternary ammonium salt used as a phase transfer catalyst.



*Scheme 2.44. Mechanism of the synthesis of 6,12-dimethoxy-1,2,3,4-tetrahydrotetraphene (**189**)*

The structure of 6,12-dimethoxy-1,2,3,4-tetrahydrotetraphene (**189**) was confirmed from the HBMC correlations. The most significant data correspond to the correlations observed between the proton at C_7 (H_7) with C_8 and C_9 (*Figures 2.5*and *2.6*).

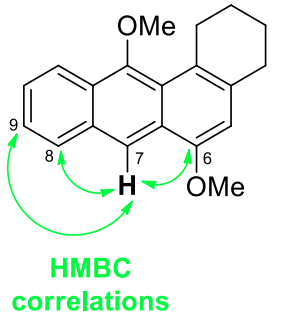


Figure 2.8. HMBC correlations

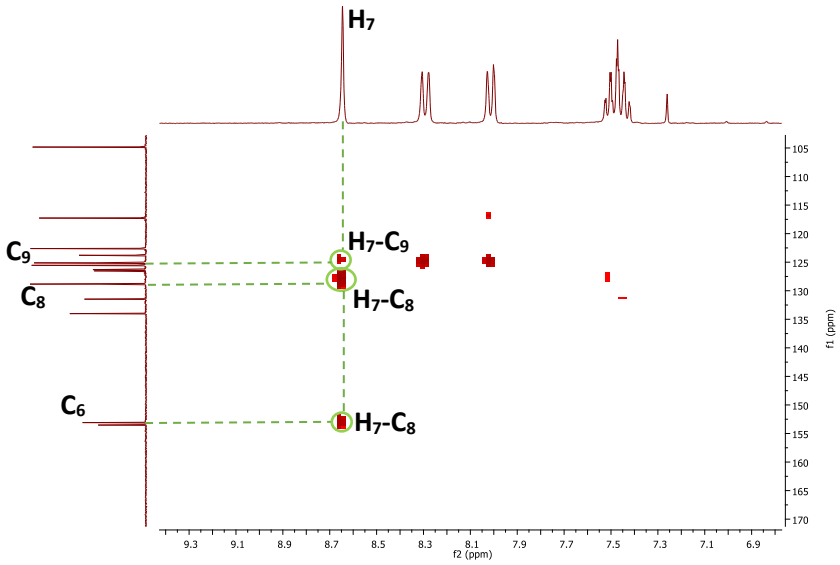
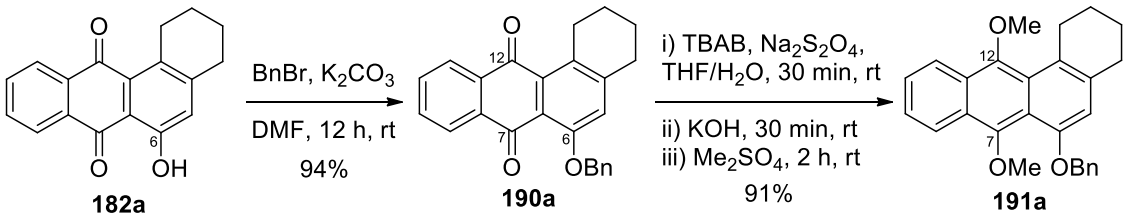


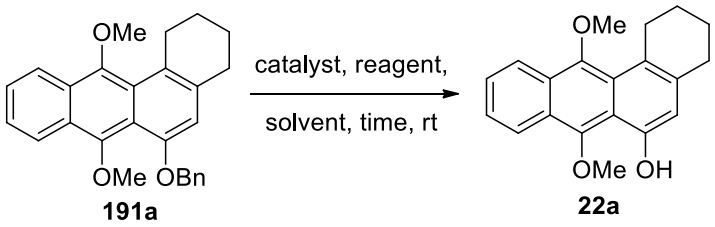
Figure 2.9. HMBC experiment

Finally, the 6-hydroxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (**182a**) could be adequately protected as benzyl group with benzyl bromide (BnBr) and potassium carbonate (K_2CO_3) in DMF at rt.[66] The resulting 6-(benzyloxy)-1,2,3,4-tetrahydrotetraphene-7,12-dione (**190a**) was isolated after flash chromatography in 94% yield. We later carried out the reduction of the quinone with $Na_2S_2O_4$ and methylation in situ of the intermediate hydroquinone with KOH and Me_2SO_4. The benzyl protected derivative 6-(benzyloxy)-7,12-dimethoxy-1,2,3,4-tetrahydrotetraphene (**191a**) could be isolated pure after flash chromatography in 91% yield (*Scheme 2.36*).



*Scheme 2.45. Synthesis of 6-(benzyloxy)-7,12-dimethoxy-1,2,3,4-tetrahydrotetraphene (**191a**) in two steps*

Compound **191a** was then submitted to a reductive debenzylation process. This proved to be a challenging task requiring a number of experiments checking different conditions, as shown in *Table 2.1*.



entry	catalyst	reagent	time (h)	solvent	conversion %[a] (yield %)[b]
1	**Pd/C**	H_2	24	THF	0
2	**Pd/C**	H_2	24	AcOEt	5
3	**Pd/C**	H_2	24	MeOH/THF	0
4	**Pd/C**	H_2	24	MeOH	0
5	**Pd/C**	H_2, AcOH	24	AcOEt	13
6	**$Pd(OH)_2$**	H_2, Py	24	MeOH/AcOEt	0
7	**$Pd(OH)_2$**	H_2	24	MeOH/THF	0
8	**Pd-black**	H_2	24	AcOEt	0
9	**Pd-black**	H_2, HCl 2M	16	MeOH	95 (63)
10	**Pd-black**	HCOOH	2	Acetone	100 (83)

a: Determined by ^{1}H-NMR of the crude mixture. b: Isolated yield.

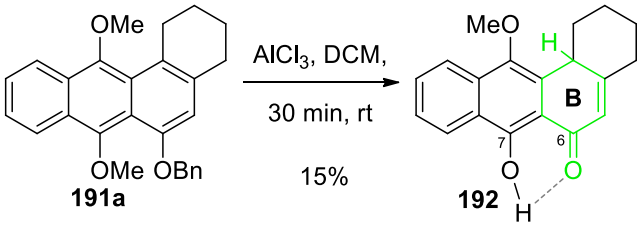
Table 2.1 .- Different reductive debenzylation conditions.

We checked different palladium catalysts [palladium on carbon {Pd/C), palladium hydroxide [$Pd(OH)_2$] and Pd-black} and sources of H_2 [hydrogen gas and formic acid (HCOOH)], as well as the addition of additives [acetic acid (AcOH), Py, and HCl 2M] and different solvents [THF, ethyl acetate (EtOAc), methanol (MeOH) and acetone].[68] Using Pd/C we did not observed any conversion (*Table 2.1*, *entries 1-4*), except when acetic acid was included to the reaction (*Table 2.1*, *entry 5*), where a poor 13% conversion was observed by ^{1}H-NMR. Changing the catalyst to $Pd(OH)_2$ compound **191**a remained unchanged (*Table 2.1*, *entries 6 and 7*) and the same result was obtained using hydrogen gas and Pd-black (*Table 2.1*, *entry 8*). The first time we observed a high conversion reaction (95%) was when hydrogen gas and Pd-black in presence of an aqueous solution of HCl 2M were used (*Table 2.1*, *entry 9*). Under these conditions, deprotected phenol **22a** could be isolated in 63% yield. However, in all cases that the debenzylated phenol **22a** was detected, a complex reaction mixture was obtained. We observed that the experiments were not easy to reproduce. All the results evidenced that laboratory light was affecting the final result, leading to non-reproducible yields of the desired phenol **22a**. Finally, **22a** could be obtained with a high yield (83%) using Pd-black and HCOOH in acetone[Error! Bookmark not defined.] and working in the dark (*Table 2.1*, *entry 10*).

Other debenzylation method for similar substrates, described in the literature, used aluminum chloride anhydrous ($AlCl_3$) in DCM.[69] Surprisingly, the reaction of benzyl protected derivative **191a** with 3 equivalents of $AlCl_3$ (30 min at rt) afforded a complex mixture from which the unexpected 7-hydroxy-12-methoxy-1,3,4,12b-tetrahydrotetraphen-6(2H)-one (**192**) could be isolated in a low yield (15%) (*Scheme 2.37*). The relative stability of **192**, a keto form of a phenol, could be due to the hydrogen bond formed between the hydroxyl group at C_7 and the carbonyl group at C_6.

[68] a) K. Wu, M. Wang, Q. Yao, A. Zhang, *Chin. J. Chem.* **2013**, *31*, 93-99; b) G. Stork, P. C. Tang, M. Casey, B. Goodman, M. Toyota, *J. Am. Chem. Soc.* **2005**, *127*, 16255-16262; c) D. Enders, G. Geibel, S. Osborne, *Chem. Eur. J.* **2000**, *6*, 1302-1309; d) D. A. Evans, J. C. Barrow, J. L. Leighton, A. J. Robichaud, M. Sefkow, *J. Am. Chem. Soc.* **1994**, *116,* 12111-12112; e) B. M. O'Keefe, D. M. Mans, D. E. Kaelin Jr., S. F. Martin *J. Am. Chem. Soc.* **2010**, *132*, 15528-15530; f) X. Cai, K. Ng, H. Panesar, S.-J. Moon, M. Paredes, K. Ishida, C. Hertweck, T. G. Minehan, *Org. Lett.* **2014**, *16*, 2962-2965; g) M. Nakata, S. Wada, K. Tatsuta, M. Kinoshita, *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1801-1806; h) A. Ben, D.-S. Hsu, T. Matsumoto, K. Suzuki, *Tetrahedron* **2011**, *67*, 6460-6468; i) G. Hernández-Torres, M. C. Carreño, A. Urbano, F. Colobert, *Chem. Eur.* **2011**, *17*, 1283-1293.

[69] K. C. Nicolaou, A. L. Nold, H. Li, *Angew. Chem. Int. Ed.* **2009**, *48*, 5860-5863.



*Scheme 2.46. Reaction of 6-(benzyloxy)-7,12-dimethoxy-1,2,3,4-tetrahydrotetraphene (**192a**) with $AlCl_3$*

Compound **192** was the result of a double deprotection of oxygenated substituents at C_6 and C_7 positions, followed by dearomatization of ring B. The structure of **192** was determined by its spectroscopic data. Thus, in the ^{13}C-NMR spectrum, the characteristic signal for a ketone group appeared at 195.1 ppm, while a doublet of doublets at δ: 3.73 ppm due to the proton at C_{12b} (H_{12b}) and a highly deshielded signal at 14.32 ppm (s) corresponding to the associated hydroxyl group could be found in the ^{1}H-NMR spectrum (*Figures 2.7*, *2.8* and *2.9*).

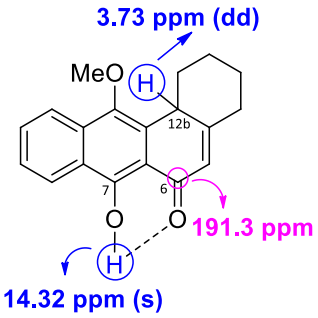


Figure 2.10. Characteristic signals

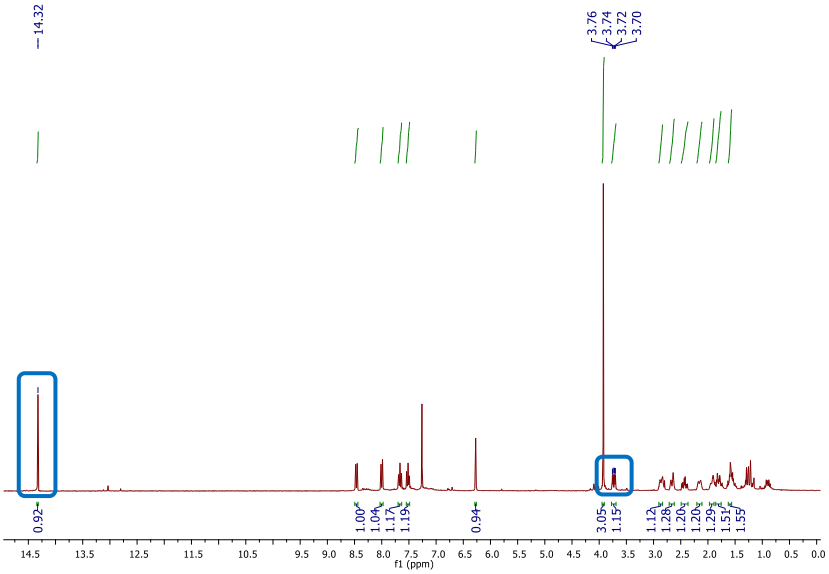


Figure 2.11. ^{1}H-NMR spectrum

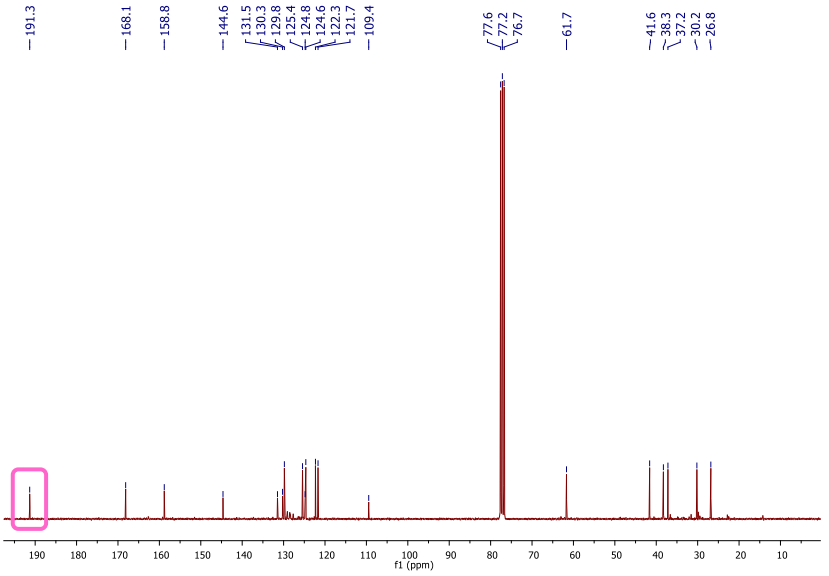


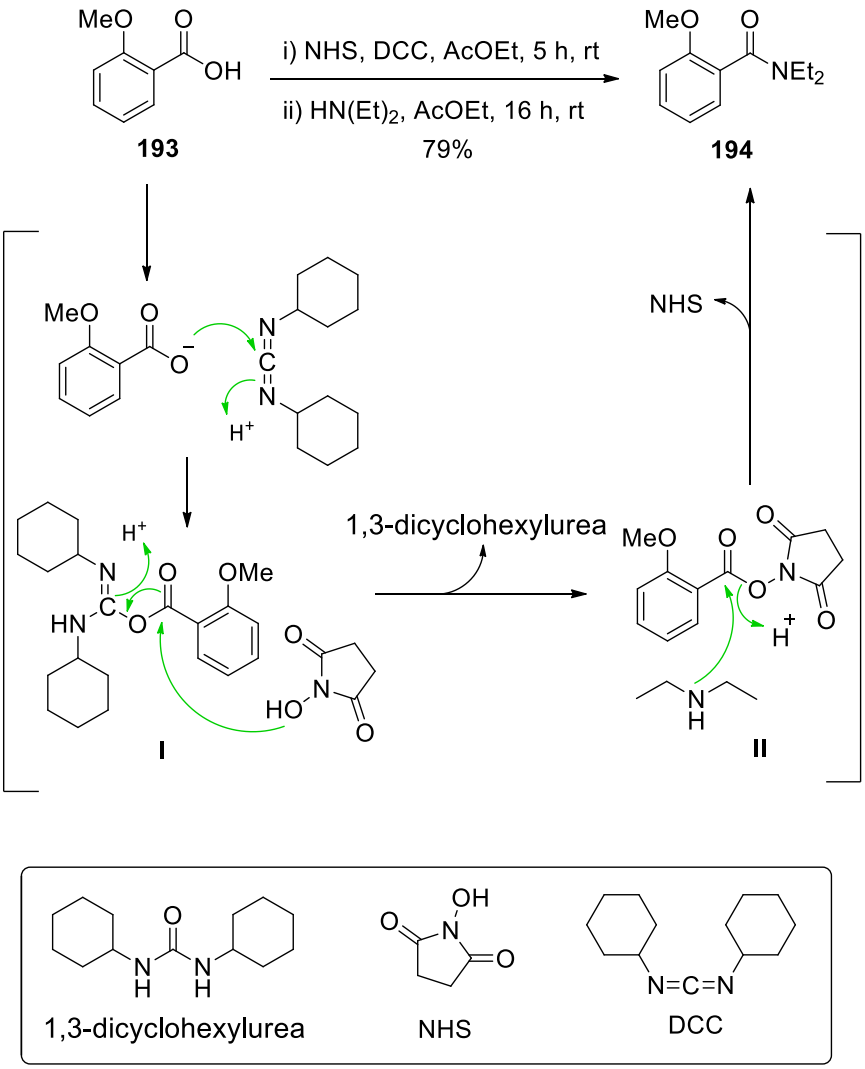
Figure 2.12. ^{13}C-NMR spectrum

2.2.2.2. Synthesis of 7,8,12-trimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (22b)

7,8,12-trimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (**22b**) was obtained following a similar synthetic sequence starting from 7-methoxy-3-cyanophtalide **183b**. This starting material was not commercially available and was prepared in 3 steps from 2-methoxybenzoic acid following a reported procedure.[70] As shown in *Scheme 2.38* the first step in the synthesis of cyanophtalide **183b** was the formation of *N*,*N*'diethyl amide **193** from 2-methoxybenzoic acid using *N*-hydroxysuccinimide (NHS) and *N*,*N*-dicyclohexylcarbodiimide (DCC), as activating agents, followed

[70] B. J. Naysmith, M. A. Brimble, *Org. Lett.* **2013**, *15*, 2006-2009.

by the addition of diethylamine. After 21 hours, *N*,*N*-diethyl-2-methoxybenzamide (**194**) could be isolated in 79% yield.

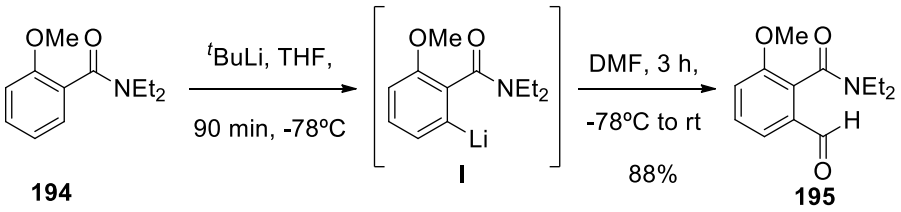


*Scheme 2.47. Synthesis of N,N-diethyl-2-methoxybenzamide (**194**)*

Thus, the carboxylic acid group of 2-methoxybenzoic acid was activated with DCC to produce the reactive intermediate **I**, which was later attacked by the hydroxy group of NHS, affording the corresponding derivative **II** and releasing 1,3-dicyclohexylurea. Finally, the activated ester group of **II** reacted with diethylamine through a nucleophilic addition / elimination process, giving the desired product **194** and NHS (*Scheme 2.38*).

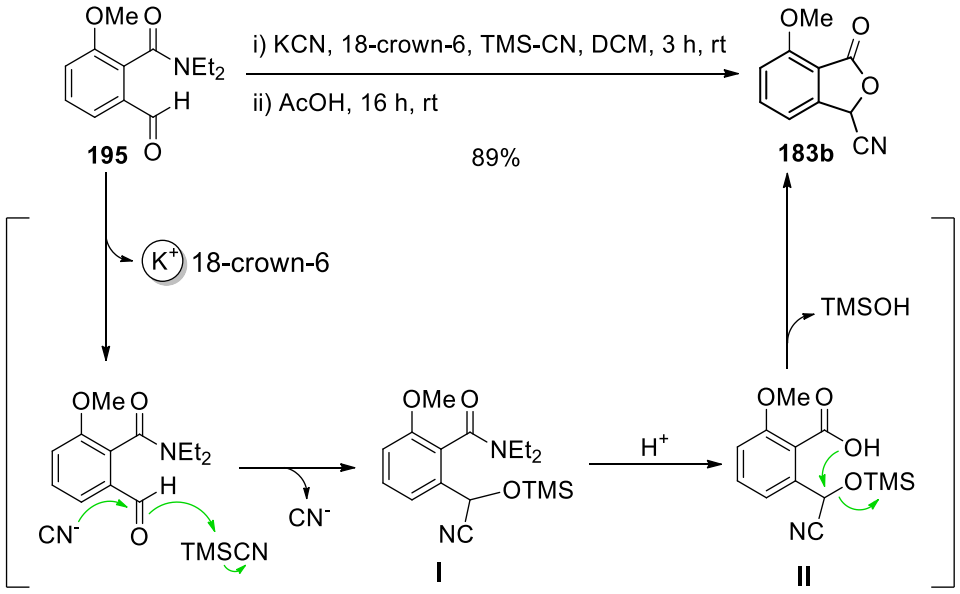
The second step in the synthesis of 7-methoxy-3-cyanophtalide **183b** involved an *ortho*-directed lithiation of amide **194** to introduce an aldehyde group at the vicinal position. Thus, amide **194** was treated with tert-buthyllitium (^{t}BuLi) at -78 ºC under inert atmosphere, affording

the lithium intermediate **I**. This reactive intermediate was treated *in situ* with a formylating agent (DMF), generating *N*,*N*-diethyl-2-formyl-6-methoxybenzamide (**195**) in 88% yield (*Scheme 2.39*).



*Scheme 2.48. Synthesis of N,N-diethyl-2-formyl-6-methoxybenzamide (**195**)*

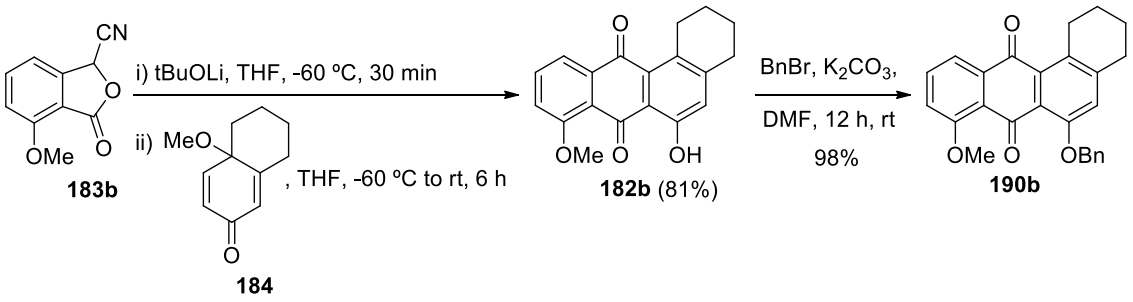
The last step in the synthesis of cyanophtalide **183b** involved the formation of the cyclic esther by an intramolecular condensation. This was achieved by adding KCN, TMSCN and 18-crown-6 to the formyl amide **X**, followed by addition of AcOH. The final 7-methoxy-3-cyanophtalide **183b** could be isolated in 89% yield (*Scheme 2.40*).



*Scheme 2.49. Synthesis of 4-methoxy-3-oxo-1,3-dihydroisobenzofuran-1-carbonitrile (**183b**)*

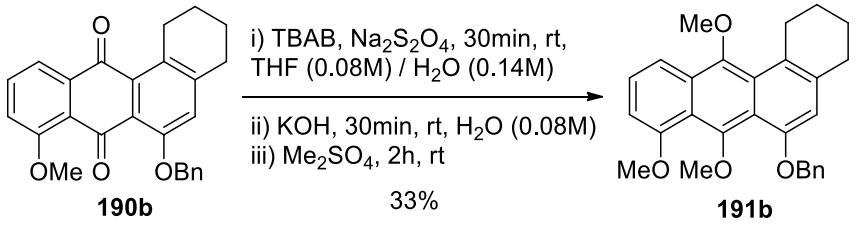
The role of 18-crown-6 was to trap the potassium cation (K^+), leaving the cyanide anion (CN^-) naked, thus increasing its nucleophilicity. Free CN^- reacted through a nucleophilic addition with the aldehyde group of compound **195** and later with TMSCN, affording the silylated cyanohydrin **I**, and recovering free CN^-. Then, the amide group was cleaved by the addition of acetic acid, giving the corresponding carboxylic acid that evolved to the desired 7-methoxy-3-cyanophtalide **183b** by an intramolecular nucleophilic substitution between the carboxylic acid group and the silylated cyanohydrin (*Scheme 2.40*).

The next step in the synthetic sequence to obtain 7,8,12-trimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (**182b**) was the Hauser-Kraus annulation. In this way, reaction between 7-methoxy-3-cyanophtalide **183b** and cyclohexadienone **184** was carried out as above. Thus, the lithium anion derived from 7-methoxy-3-cyanophtalide **183b** after treatment with lithium *tert*-butoxide reacted with 4a-methoxy-5,6,7,8-tetrahydronaphthalen-2(4a*H*)-one (**184**) giving rise to 6-hydroxy-8-methoxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (**182b**) isolated in 81% yield.[62, 71] Then, the phenol **182b** was protected as benzyl group by reaction with BnBr, leading to 6-(benzyloxy)-8-methoxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (**190b**) in 98% yield (*Scheme 2.41*).



*Scheme 2.50. Synthesis of 6-(benzyloxy)-8-methoxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (**190b**)*

The quinone reductive methylation process was achieved following the reported procedure previously used in the synthesis of benzyl protected dimethoxy analogue **191a**, by treatment with $Na_2S_2O_4$ and TBAB in a mixture of THF / water. After 30 min, KOH was added to the mixture and stirred other 30 min. Finally, Me_2SO_4 was added and stirred 2 hours more at rt. This allowed the isolation of 6-(benzyloxy)-7,8,12-trimethoxy-1,2,3,4-tetrahydrotetraphene (**191b**) in 33% yield (*Scheme 2.42*).

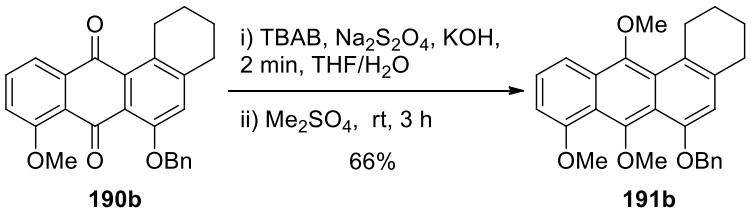


*Scheme 2.51. Synthesis of 6-(benzyloxy)-7,8,12-trimethoxy-1,2,3,4-tetrahydrotetraphene (**191b**)*

The low yield obtained in the reduction / methylation process of the benz[*a*]anthraquinone **190b** was a drawback in the synthetic sequence. To improve the yield of

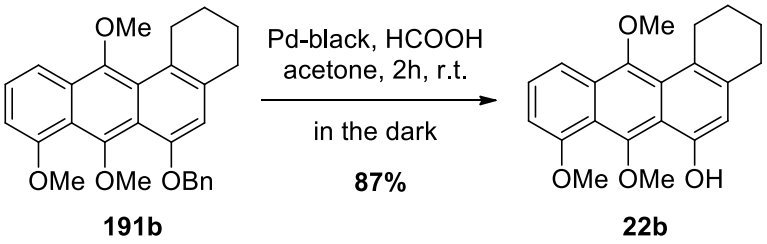
[71] D. Mal, H. Nath Roy, *J. Chem. Soc. Perkin Trans. 1* **1999**, 3167-3171.

this step, we checked different reaction conditions such as different solvents, concentrations, temperature, reaction time or/and reducing agents. During the optimization studies, some interesting results, not directly related to the main objective of this PhD work, were obtained. They will be presented in the *subchapter 2.6*. Finally, we could improve the yield to 66% through a one-pot reaction, where TBAB, $Na_2S_2O_4$ and KOH were mixed together with 6-(benzyloxy)-8-methoxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (**191b**) in a mixture of THF/water at rt under inert atmosphere and, after 2 min Me_2SO_4 was added to the reaction mixture and stirred for 2 hours. (*Scheme 2.43*).



*Scheme 2.52. Improved synthesis of 6-(benzyloxy)-7,8,12-trimethoxy-1,2,3,4-tetrahydrotetraphene (**191b**)*

Reductive debenzylation of 6-(benzyloxy)-7,8,12-trimethoxy-1,2,3,4-tetrahydrotetraphene (**191b**), using Pd-black and HCOOH in acetone under the conditions previously optimized, lead to 7,8,12-trimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (**22b**) in 87% yield, working in the dark (*Scheme 2.44*).

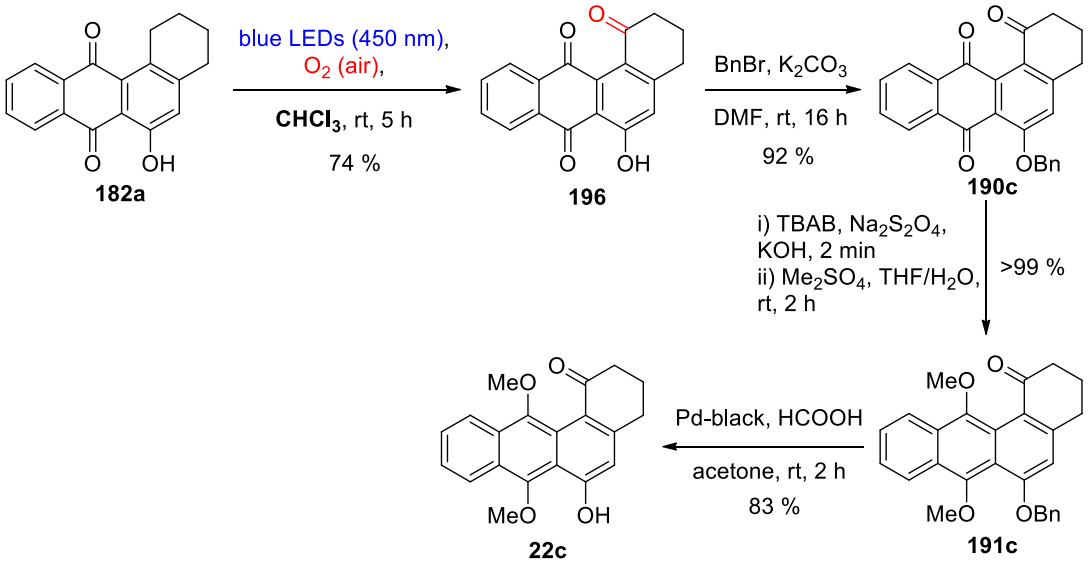


*Scheme 2.53. Synthesis of 7,8,12-trimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (**22b**)*

2.2.2.3. Synthesis of 6-hydroxy-7,12-dimethoxy-3,4-dihydrotetraphen-1(2*H*)-one (22c)

The synthesis of 6-hydroxy-7,12-dimethoxy-3,4-dihydrotetraphen-1(2*H*)-one (**22c**) was achieved starting from 6-hydroxy substituted benz[*a*]anthraquinone **182a**, obtained previously.

Following a modified Krohn's photooxidation procedure,[72] 6-hydroxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (**182a**) was dissolved in $CHCl_3$, stirred in a flask open to the air and irradiated with blue LEDs (450 nm) at rt. After 6 hours, the oxidized compound 6-hydroxy-3,4-dihydrotetraphene-1,7,12(2H)-trione (**196**) could be isolated in 47% yield, as it was described in the literature.[73] [38] The phenol motif present in the tetracyclic structure of **196** was protected as benzyl group with BnBr, affording 6-(benzyloxy)-3,4-dihydrotetraphene-1,7,12(2H)-trione (**190c**) in 92% yield. Then, the quinone was submitted to one pot reduction / methylation process under the conditions we had previously optimized. TBAB, $Na_2S_2O_4$ and KOH were mixed together with compound **190c** in a mixture of THF / water at rt under inert atmosphere and, after 2 min Me_2SO_4 was added to the reaction mixture and stirred for 2 hours. In this case, 6-(benzyloxy)-7,12-dimethoxy-3,4-dihydrotetraphen-1(2H)-one (**191c**) was formed in quantitative yield. Finally, the target structure of 6-hydroxy-7,12-dimethoxy-3,4-dihydrotetraphen-1(2H)-one (**22c**) was obtained by reductive debenzylation, using Pd-black and HCOOH in acetone with 83% yield, working in the dark (*Scheme 2.45*).



*Scheme 2.54. Synthesis of 6-hydroxy-7,12-dimethoxy-3,4-dihydrotetraphen-1(2H)-one (**22c**) from 6-hydroxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (**182a**) in 4 steps*

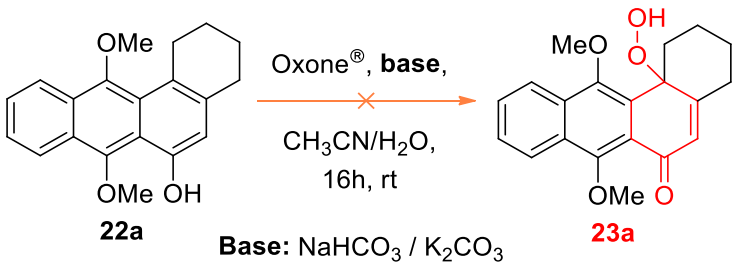
[72] a) R. Karmakar, D. Mal, *J. Org. Chem.* **2012**, *77*, 10235-10248; b) K. Krohn, M. H. Sohrab, U. Florke, *Tetrahedron*: *Asymmetry* **2004**, *15*, 713-718; c) K. Krohn, F. Ballwanz, W. Baltus, *Liebigs. Ann. Chem*. **1993**, 911–913.

[73] D. Mal, H. N. Roy, N. K. Hazra, *Tetrahedron* **1997**, *53*, 2177-2184.

2.2.3. Oxidative dearomatization using Oxone® as oxidant: Synthesis of angular tetracyclic *para*-quinols **24**.

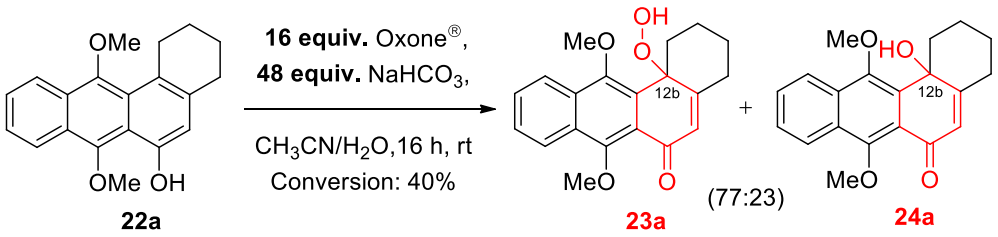
With the angular tetracyclic phenols in hand, we began the study of the oxidative dearomatization *en route* to the corresponding *para*-quinols using 7,12-dimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (**22a**) as the starting material. It is important to mention that the substrate submitted to this process had three aromatic rings prone to react. Thus, the ring selectivity of this reaction was an essential issue to consider.

7,12-dimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (**22a**) was initially submitted to the oxidative dearomatization reaction using Oxone® as the oxidant, under the experimental conditions previously established in our group to synthesize *para*-peroxyquinols: Oxone® (8 equiv.) and $NaHCO_3$ (24 equiv.) in a mixture of CH_3CN/H_2O.[Error! Bookmark not defined.] Unfortunately, under these conditions the starting material remained unchanged. When $NaHCO_3$ was changed to K_2CO_3, a stronger base, phenol **22a** was also recovered unchanged (*Scheme 2.46*).



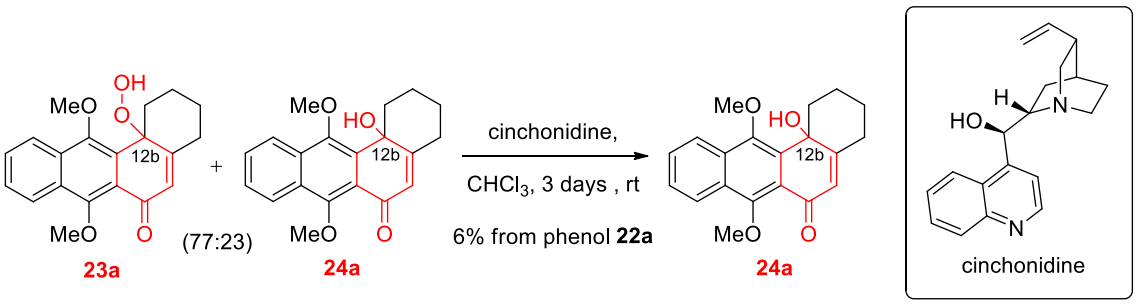
Scheme 2.55. Application of oxidative dearomatization condition using the system Oxone® / base

When the amount of Oxone® and $NaHCO_3$ was increased to 16 equiv. and 48 equiv., respectively, phenol **22a** evolved and 40% of conversion was observed after 16 hours. Tetracyclic *para*-peroxy quinol **23a** and *para*-quinol **24a** were obtained in a 77:23 ratio mixture, determined by ^{1}H-NMR spectrum of the crude reaction. Separation of both compounds could not be achieved (*Scheme 2.47*). We carried out this oxidative dearomatization reaction in the presence of light and, as we will comment later, the photosensitivity of phenol **22a** would be an explanation in the formation of the unexpected *para*-quinol **24a**.



*Scheme 2.56. Obtaining of a mixture of para-peroxy quinol **23a** and para-quinol **24a***

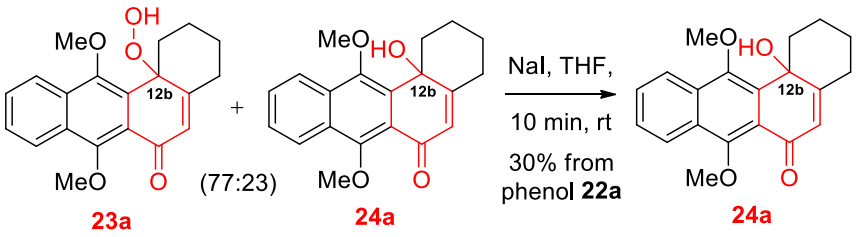
Without further purification, the mixture of *para*-peroxy quinol **23a** and *para*-quinol **24a** was submitted to a reduction process. Initially, the mixture was treated with sodium thiosulfate and water and was stirred at rt. Although stirring was prolonged up to 16 hours, the mixture remained unchanged. Other method reported by our research group to reduce *para*-peroxy quinols to the corresponding *para*-quinols was based in the use of cinchonidine in chloroform under inert atmosphere.[74] Under this conditions, after stirring the mixture at rt for 3 days, *para*-quinol **24a** was obtained in a poor 6% global yield from phenol **22a** (*Scheme 2.48*). This result was not good and we needed other reducing conditions to improve the final yield of *para*-quinol **24a**.



Scheme 2.57. Reduction of the mixture with cinchonidine

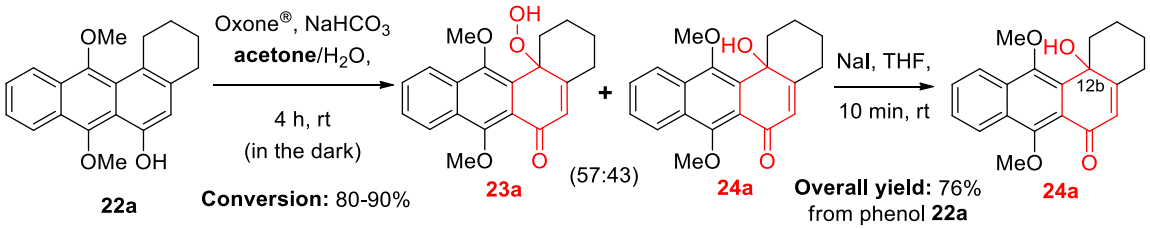
Looking for other reduction procedures for peroxides, we found in the literature an easy, clean and quick method to reduce peroxides into alcohols using sodium iodide.[75] Thus, the 77:23 mixture of *para*-peroxy quinol **23a** and *para*-quinol **24a** was treated with NaI in THF at rt for 5 min to obtain *para*-quinol **24a**, in 30% overall yield from phenol **22**a, as a sole product (*Scheme 2.49*).

[74] Thesis Marcos González López, 2006
[75] E. Schöttner, M. Wiechoczek, P. G. Jones, T. Lindel, *Org. Lett.*, **2010**, *12*, 784-787.



*Scheme 2.58. Reduction of the mixture with NaI: Synthesis of 12b-hydroxy-7,12-dimethoxy-1,3,4,12b-tetrahydrotetraphen-6(2H)-one (**24a**)*

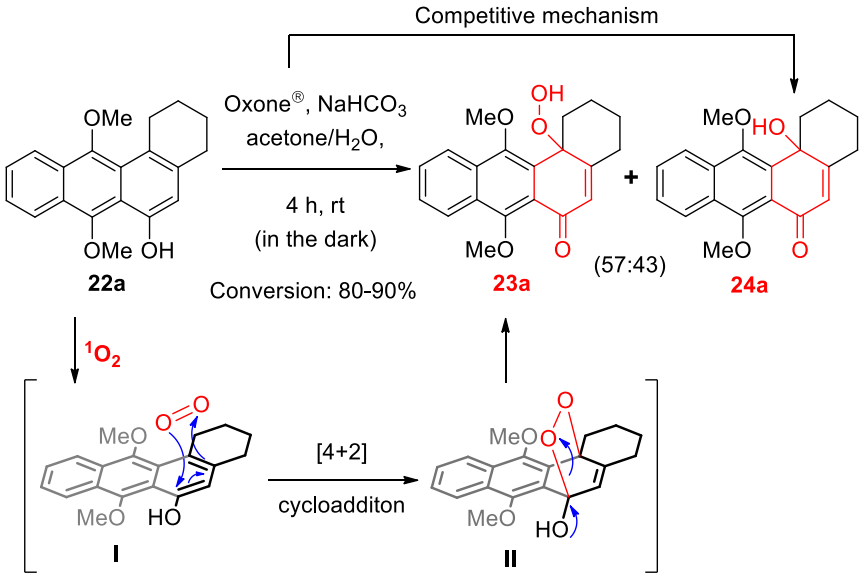
The low conversion observed for 7,12-dimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (**22a**) in the treatment with Oxone® and $NaHCO_3$ in acetonitrile / water (40%) could be due to its low solubility in acetonitrile. In order to improve the yield of this oxidative dearomatization process, we checked other solvent miscible with water. Carrying out the reaction under the conditions depicted in *Scheme 2.50*, using acetone instead acetonitrile, and working in the dark, the conversion of the starting phenol **22a** increased to 80-90%, but again a mixture of *para*-peroxy quinol **23a** and *para*-quinol **24a** was obtained. Without further purification, the mixture was treated with NaI in THF, to obtain the tetracyclic *para*-quinol **24a** as a sole product in 76% overall yield from phenol **22a**.



*Scheme 2.59. Optimized synthesis of 12b-hydroxy-7,12-dimethoxy-1,3,4,12b-tetrahydrotetraphen-6(2H)-one (**24a**)*

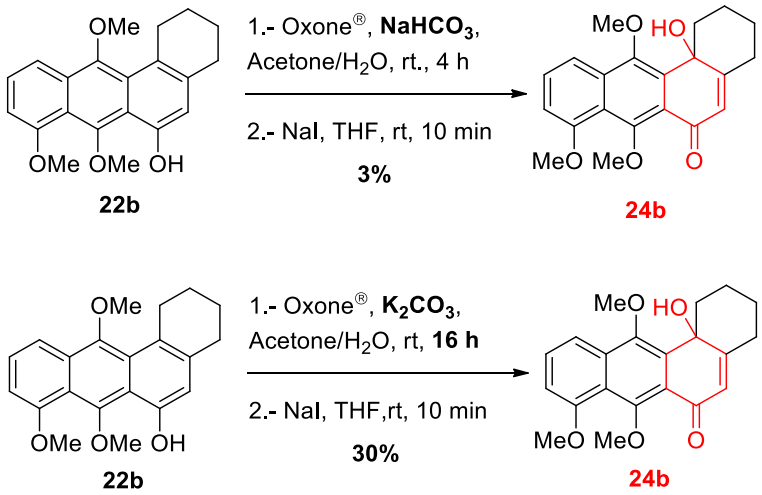
According with the mechanism previously proposed for the oxidative dearomatization of *para*-alkyl phenols with Oxone® in the presence of $NaHCO_3$, the process must occur through a [4+2] cycloaddition between singlet oxygen, generated in situ by decomposition of potassium peroxymonosulphate in the aqueous basic medium, and the electron-rich *para*-alkyl phenol **22a**. This reaction would lead to the formation of the corresponding endoperoxide intermediate **II**, which immediately would evolve to the *para*-peroxy quinol **23a** due to its unstable peroxyhemiketal structure.[55] This process was carried out in the dark, because the starting phenol **22a** had been shown to be sensitive to ambientl ight. In spite of these precautions, a mixture of *para*-peroxy quinol **23a** and *para*-quinol **24a** was still obtained. Taking into account that this reaction was effected using acetone as solvent, we assumed that the direct formation of *para*-

quinol **24a** in the mixture could probably occurred through a competitive process due to the presence of another reagent formed in the reaction of Oxone® and acetone (*Scheme 2.51*).



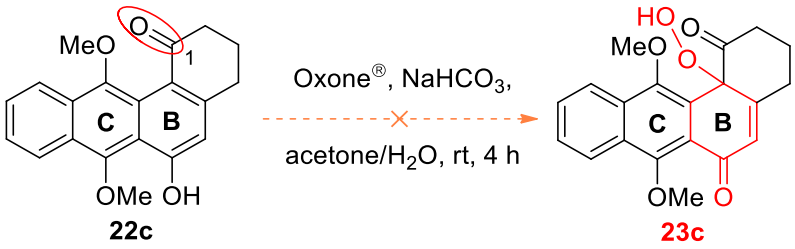
Scheme 2.60. Mechanistic hypothesis of oxidative dearomatization with the system Oxone®/$NaHCO_3$

The oxidative dearomatization with Oxone® was also carried out on 7,8,12-trimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (**22b**). Thus, treatment of phenol **22b** with the system Oxone® (16 equiv.) and $NaHCO_3$ (48 equiv.) in a mixture of acetone / water, followed by reduction of the resulting mixture with NaI in THF, gave *para*-quinol **24b** with a very low 3% global yield from phenol **22b**. The isolated yield of final *para*-quinol **24b** was later improved to 30%, changing sodium bicarbonate by a stronger base (potassium carbonate) and increasing the reaction time to 16 h (*Scheme 2.52*).



*Scheme 2.61. Optimized synthesis of 12b-hydroxy-7,8,12-trimethoxy-1,3,4,12b-tetrahydrotetraphen-6(2H)-one (**24b**)*

Treatment of 6-hydroxy-7,8,12-trimethoxy-3,4-dihydrotetraphen-1(2H)-one (**22c**) under the conditions used above for the oxidation process (Oxone®, $NaHCO_3$ in acetone/water) was also checked. In this case, the carbonyl-bearing tetracyclic substrate **22c** remained unchanged. In accordance with the mechanistic proposed for this transformation, begining with a [4+2] cycloaddition between singlet oxygen and the elctron-rich hydroxy substituted ring, the lack of reactivity of this substrate could be due to the presence of the carbonyl group at C_1, which deactivated the rings B and C, decreasing the electron-density and making impossible to apply the oxidative dearomatization method with Oxone® to oxidize ring B (*Scheme 2.53*).

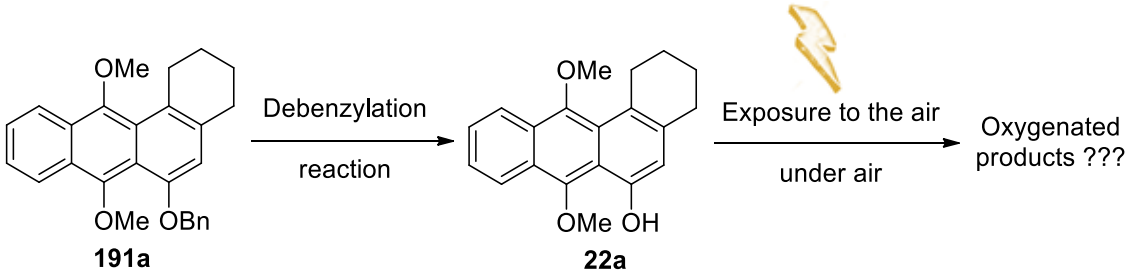


*Scheme 2.62. Attempt to oxidative dearomatization of 6-hydroxy-7,8,12-trimethoxy-3,4-dihydrotetraphen-1(2H)-one (**22c**)*

In order to decrease the electron-withdrawing effect of the carbonyl group on ring B, we thought to protect this ketone before the deprotection of the benzyl group. We tried different methods and protecting reagents (ethylene glycol, acetic anhydride, TBDMSCl, etc.), but unfortunately it was not possible to protect this carbonyl group. Details of the experiments performed are included in *subchapter 2.2.6.3*.

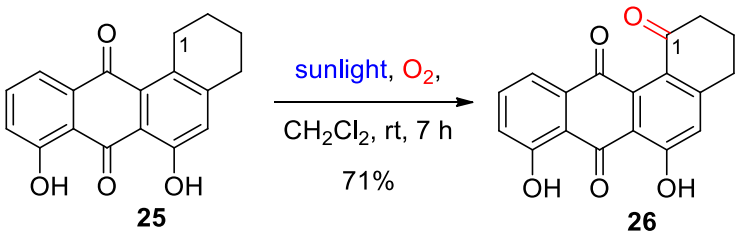
2.2.4. Oxidative dearomatization of angular tetracyclic phenols 22 by irradiation under air.

Earlier in this document, we indicated the observed light sensitivity of 7,12-dimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (**22a**) and its evolution into mixtures of different products upon exposure to light. This photosensitivity of phenol **22a** was detected during the debenzylation and the oxidative dearomatization process, when the reactions or the purifications were carried out under the laboratory light (*Scheme 2.54*).



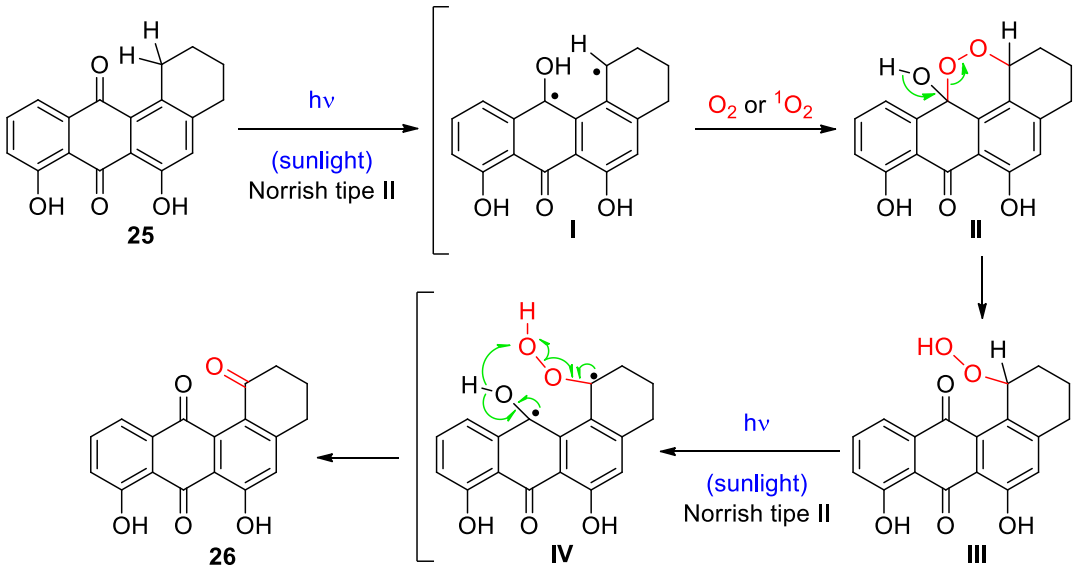
*Scheme 2.63. Photosensitive of 7,12-dimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (**22a**) to light*

As we previously commented in *Chapter 1*, in 1993, Krohn discovered a mild oxidation reaction of angucyclinone derivatives having a structure of 1,2,3,4-tetrahydrotetraphene-7,12-dione to 1-keto substituted systems, based on a photoinduced oxygenation by simple irradiation of the precursors with sunlight under oxygen (*Scheme 1.5*).[72] This procedure was later applied with success in the synthesis of different angucyclinones derivatives.[58c, 72a,b]



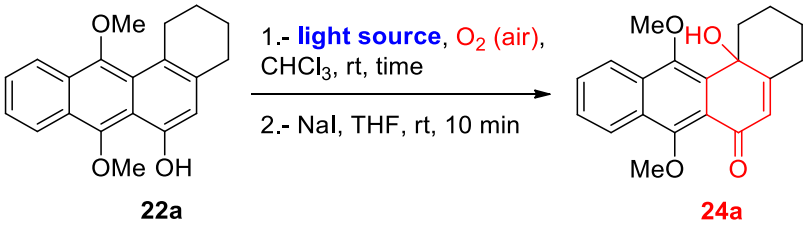
*Scheme 1.5. Photooxygenation at C_1 of 6,8-dihydroxy-3,4-dihydrotetraphene-1,7,12(2H)-trione (**25**) reported by Krohn*

The mechanistic hypothesis proposed by Krohn for this photooxygenation is shown in *Scheme 2.55*. The process could start with a Norrish type II reaction, in which a photoinduced intramolecular γ-hydrogen abstraction of one of the hydrogens at C_1 by the excited neighboring carbonyl group produced the 1,4-biradical **I**. This biradical could be trapped by triplet or singlet oxygen to form the unstable tetracyclic peroxyhemiketal **II**, which evolved in the medium to the corresponding hydroperoxide **III**. This peroxide suffered a second photoinduced hydrogen abstraction, affording the 1,4-biradical **IV** and, this biradical was finally transformed into 6,8-dihydroxy-3,4-dihydrotetraphene-1,7,12(2H)-trione (**26**).[72c]



*Scheme 2.64. Proposed mechanism for the photooxidation of 6,8-dihydroxy-3,4-dihydrotetraphene-1,7,12(2H)-trione (**X**) by Krohn.*

Taking into account this precedent as well as the observed light sensitivity of the angular tetracyclic phenols, previously synthesized in this PhD work, we decided to investigate deeply the photochemical behavior of our substrates. We initiated the study with 7,12-dimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (**22a**) using similar conditions reported by Krohn. The irradiation reactions were monitorized by TLC and the time of irradiation of the different experiments was determined after consumption of the starting phenol **22a**. Thus, a $CHCl_3$ solution of phenol **22a** was exposed to the laboratory fluorescent light under air with stirring and found its slow evolution (24 h) to an inseparable mixture of *para*-peroxy quinol **23a** and *para*-quinol **24a** in a ratio of 75:25, approximately. This mixture of products was reduced with NaI in THF to afford the tetracyclic *para*-quinol **24a** in 44% isolated yield after 10 min, as a sole product (*Table 2.2*, *entry 1*). Under identical conditions, other light sources were checked (household lamp, a red bulb and green LEDs). In all the experiments, after irradiation, the resulting mixture was treated with NaI. 12b-Hydroxy-7,12-dimethoxy-1,3,4,12b-tetrahydrotetraphen-6(2H)-one (**24a**) was always formed and could be isolated with 34% yield (household lamp; *Table 2.2*, *entry 2*) or 35% yield (red bulb; *Table 2.2*, *entry 3*). When the irradiation was effected with green LEDs, a complex mixture was observed (*Table 2.2*, *entry 4*).



22a **24a**

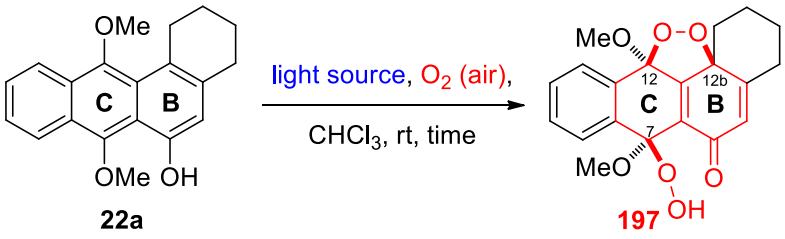
entry	light sources	time of irradiation	overall yield [a]
1	Laboratory light	24 h	44 %
2	Household lamp	12 h	34 %
3	Red bulb (618 - 780 nm)	3 days	35 %
4	Green LEDs (525 nm)	12 h	Complex mixture

a: Isolated yield

*Table 2.2.- The aerobic photooxidation of **22a** to synthesize para-quinol **24a** with different sources of visible light.*

This photochemical oxidation seemed to be a very interesting process, producing the same oxidative dearomatization than the system Oxone® / $NaHCO_3$, but under environmentally benign conditions (visible-light irradiation under air), without addition of other oxidants or photosensitizers.

More interestingly, when tetracyclic phenol **22a** was exposed to sunlight in chloroform under air for 6 hours a new oxidized single product, identified as the pentacyclic double peroxide **197**, was obtained with 31% isolated yield after chromatographic purification (*Table 2.3*, *entry 1*).



22a **197**

entry	light sources	time of irradiation	yield [a]
1	sunlight	6 h	31 %
2	UV lamp (370 nm)	6 h	39 %
3	Blue LEDs (450 nm)	2 h	47 %

a: Isolated yield.

*Table 2.3.- Different aerobic photooxidation conditions to synthesize bisperoxy quinone bisketal **197**.*

Under these conditions, an unprecedented double oxidative dearomatization process had occurred on the electron-rich aromatic rings B and C of the phenol precursor **22a**. Moreover, two molecules of oxygen had been incorporated to the tetracyclic derivative producing three new stereogenic centers at C_7, C_{12} and C_{12b} with the formation of a single diastereomer. The structure of (7S*,11bR*,13aS*)-7-hydroperoxy-7,11b-dimethoxy-3,4,7,11b-tetrahydro-1H-tetrapheno[12-cd][1,2]dioxol-6(2H)-one (**197**) was assigned on the base of its spectroscopic parameters (see below) and confirmed by X-ray diffraction. Interestingly, compound **197** had a masked anthraquinone fragment in the form of a double peroxy bisketal situated at ring C. Its relative configuration evidenced that both oxygen molecules had been incorporated from the same face in a highly stereoselective fashion (*Figure 2.10*).

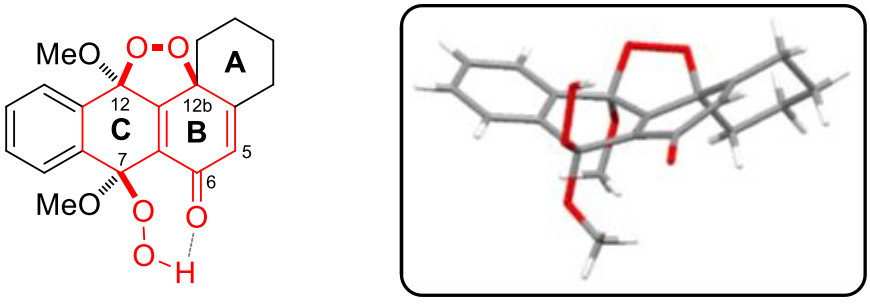


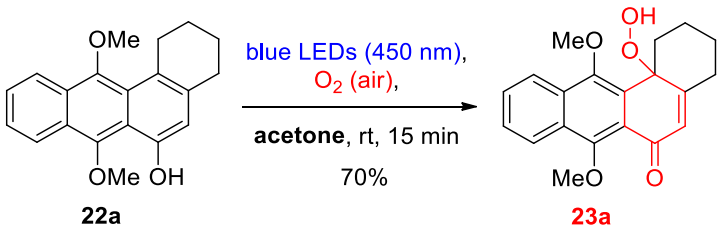
Figure 2.13. Structure of (7S,11bR*,13aS*)-7-hydroperoxy-7,11b-dimethoxy-3,4,7,11b-tetrahydro-1H-tetrapheno[12-cd][1,2]dioxol-6(2H)-one (**197**) and its X-ray*

The double oxidative dearomatization of rings B and C of phenol **22a** upon irradiation with sunlight (*Table 2.3*, *entry 1*) contrasted with the mixture of products obtained with the other light sources (400-700 nm) used (see *Table 2.3*), where only the ring B of phenol **22a** was oxidized. We reasoned that such difference could be due to the range of UV wavelength provided by sunlight. Then, we decided to evaluate other light sources with maximum emissions at the near UV to achieve the double dearomatization process. Thus, irradiation of tetracyclic phenol **22a** with an UV lamp (λ_{max} 370 nm) in chloroform for 6 hours under air gave rise to double peroxide **197** in

39% yield (*Table 2.3*, *entry 2*). The best result was obtained upon irradiation of tetracyclic phenol **22a** with blue LEDs (λ_{max} 450 nm) under air in chloroform. Under these conditions, after only 2 hours, the double peroxide **197** could be isolated pure in 47% yield after chromatographic purification (*Table 2.3*, *entry 3*).

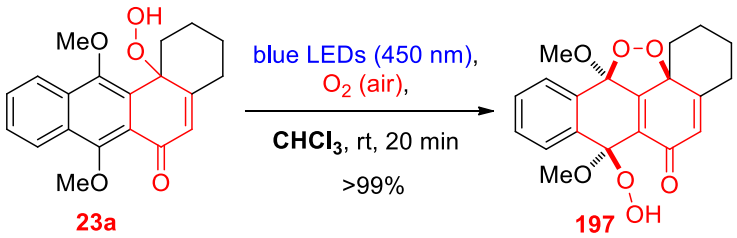
Once studied the effects of irradiation with different wavelengths on the oxidative daromatization of phenol **22a**, we thought of studying the influence of a polar aprotic solvent on the photooxidation of substrate **22a**. Thus, we changed chloroform by acetone, where phenol **22a** had an excellent solubility. Moreover, a precedent work in the literature described the oxidation process of a triterpene by oxygen, in which acetone was used as solvent.[76]

Surprisingly, when phenol **22a** was irradiated with blue LEDs (λ_{max} 450 nm) under air in acetone solution, the *para*-peroxy quinol derivative **23a** was exclusively formed after only 15 min and it could be isolated pure in 70 % yield (*Scheme 2.56*).



*Scheme 2.65. Synthesis of 12b-hydroperoxy-7,12-dimethoxy-1,3,4,12b-tetrahydrotetraphen-6(2H)-one (**23a**) upon irradiation with blue LEDs.*

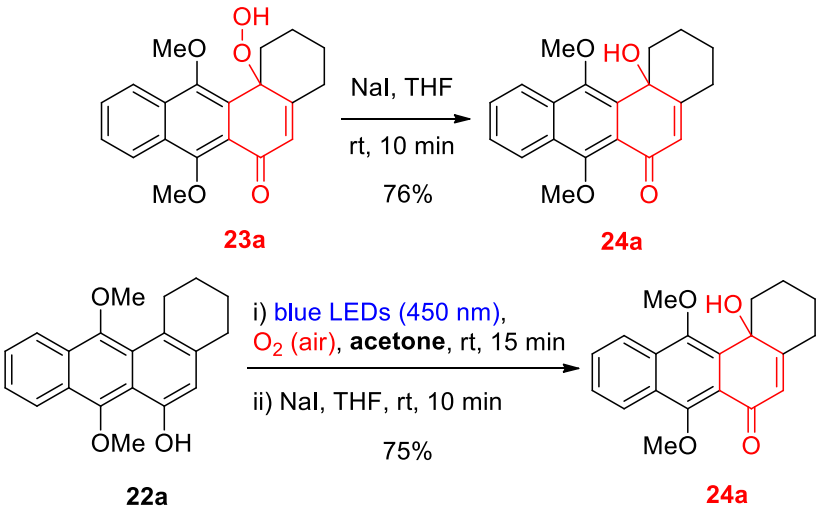
This result suggested that *para*-peroxy quinol **23a** could be the intermediate in the double dearomatization process on phenol **22a** leading to the double peroxide **197**. This assumption was confirmed when a solution of *para*-peroxy quinol **23a** was irradiated with blue LEDs (λ_{max} 450 nm) under air in chloroform. Under these conditions, the bisperoxy bisketal **197** was formed and isolated in quantitative yield after only 20 min (*Scheme 2.57*).



Scheme 2.66. Synthesis of (7S,11bR*,13aS*)-7-hydroperoxy-7,11b-dimethoxy-3,4,7,11b-tetrahydro-1H-tetrapheno[12-cd][1,2]dioxol-6(2H)-one (**197**) from 12b-hydroperoxy-7,12-dimethoxy-1,3,4,12b-tetrahydrotetraphen-6(2H)-one (**23a**)*

[76] A. Chung, M. R. Miner, K. J. Richert, C. J. Rieder, K. A. Woerpel, *J. Org. Chem.* **2015**, *80*, 266-273.

Besides, *para*-peroxy quinol **23a** was reduced with NaI in THF to afford the *para*-quinol **24a** in a 76% yield after 10 min.75 The overall yield of *para*-quinol **24a** was improved to 75% from phenol **22a**, using this two-step procedure: initial irradiation of phenol **22a** in acetone and further treatment with NaI in THF, previous elimination of the acetone under reduced pressure and without purification of the intermediate *para*-peroxy quinol **23a** (*Scheme 2.58*).

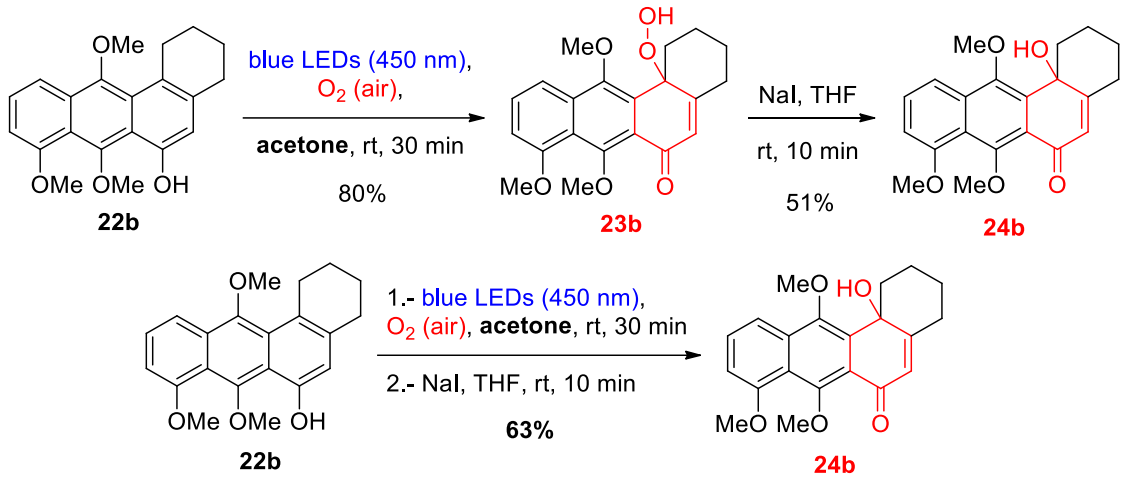


*Scheme 2.67. Synthesis of 12b-hydroxy-7,12-dimethoxy-1,3,4,12b-tetrahydrotetraphen-6(2H)-one (**24a**)*

Once the best reaction conditions for the oxidative dearomatization with light and oxygen (air) were determined, these conditions were applied to the other phenolic precursors **22**, previously synthesized in this work.

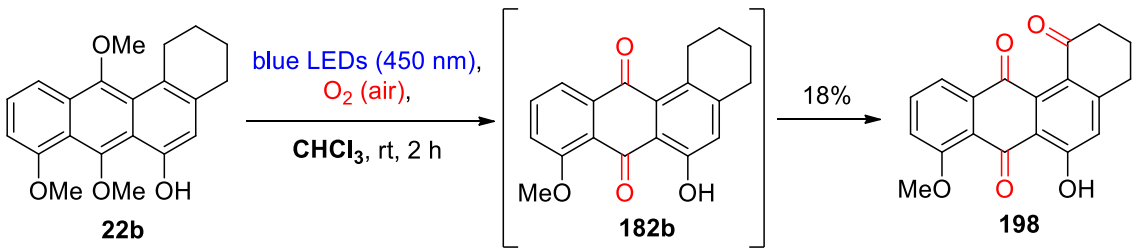
2.2.4.1. Photooxidation of 7,8,12-trimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (22b)

Irradiation of phenol **22b** with blue LEDs (λ_{max} 450 nm) under air in acetone for 15 min, furnished *para*-peroxy quinol **23b** in 81% isolated yield after chromatographic purification. Further treatment of **23b** with NaI in THF, gave rise to *para*-quinol **24b** in 51% yield. Without purification of *para*-peroxy quinol **23b**, *para*-quinol **24b** could be synthesized in 63% overall yield from phenol **22b** (*Scheme 2.59*).



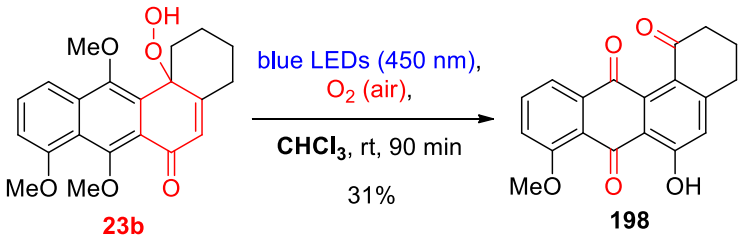
*Scheme 2.68. Synthesis of 12b-hydroxy-7,8,12-trimethoxy-1,3,4,12b-tetrahydrotetraphen-6(2H)-one (**24b**)*

When the photooxidation of 7,8,12-trimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (**22b**) was carried out by irradiation with blue LEDs under air for 2 hours in chloroform, a complex reaction mixture was formed, from which tetracyclic quinone **198**, proceeding from oxidative dearomatization of ring C and oxidation at C_1, could be isolated in a poor 18% yield (*Scheme 2.60*). This result suggested that phenol **22b** was initially oxidized to tetracyclic quinone **182b**, that reacted immediately by a radical oxidative process promoted by light, as reported in the literature.[72]



*Scheme 2.69. Irradiation of 7,8,12-trimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (**22b**) with blue LEDs in $CHCl_3$*

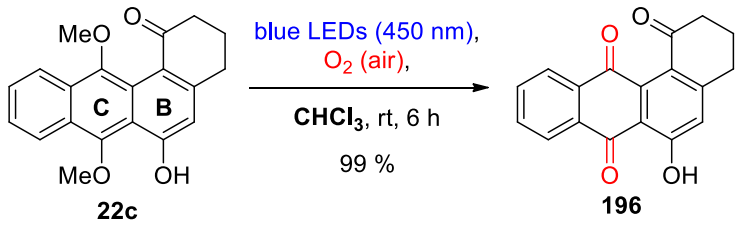
Also, when *para*-peroxy quinol **23b** was irradiated in a chloroform solution with blue LEDs (λ_{max} 450 nm) under air after 90 min, 6-hydroxy-8-methoxy-3,4-dihydrotetraphene-1,7,12(2H)-trione (**198**) was formed and isolated from a complex mixture in 31% yield (*Scheme 2.61*).



*Scheme 2.70. Irradiation of 12b-hydroperoxy-7,8,12-trimethoxy-1,3,4,12b-tetrahydrotetraphen-6(2H)-one (**23b**) with blue LEDs in $CHCl_3$*

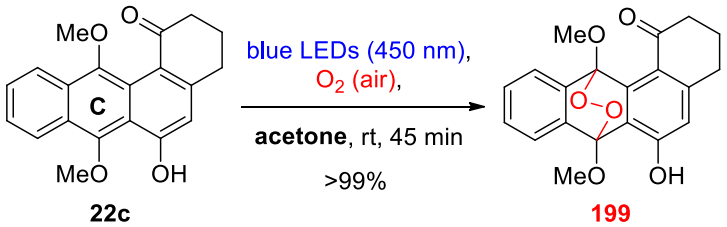
2.2.4.2. Photooxidation of 6-hydroxy-7,12-dimethoxy-3,4-dihydrotetraphen-1(2H)-one (22c)

Irradiation of a chloroform solution of 6-hydroxy-7,12-dimethoxy-3,4-dihydrotetraphen-1(2*H*)-one (**22c**) with blue LEDs (λ_{max} 450 nm) under air after 6 hours, gave quinone **196** in an excellent 99% yield. This quinone resulted from the oxidation of the more electron rich *para*-dimethoxy substituted aromatic C ring of **22c** (*Scheme 2.62*).



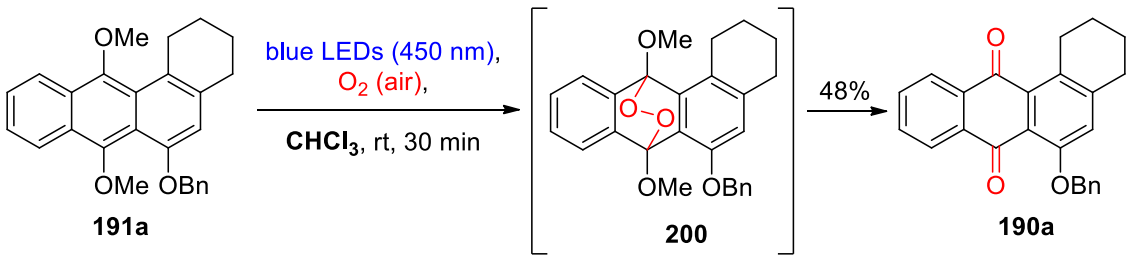
*Scheme 2.71. Irradiation of a $CHCl_3$ solution of 6-hydroxy-7,12-dimethoxy-3,4-dihydrotetraphen-1(2H)-one (**22c**) with blue LEDs*

When this 1-oxosubstitued phenol **22c** was irradiated in acetone, the endoperoxide **199**, shown in the *Scheme 2.63*, was isolated in quantitative yield. The structure of endoperoxide **199**, having a masked quinone bisketal at C ring, was determined by its spectroscopic data.



*Scheme 2.72. Irradiation of an acetone solution of 6-hydroxy-7,12-dimethoxy-3,4-dihydrotetraphen-1(2H)-one (**22c**) with blue LEDs*

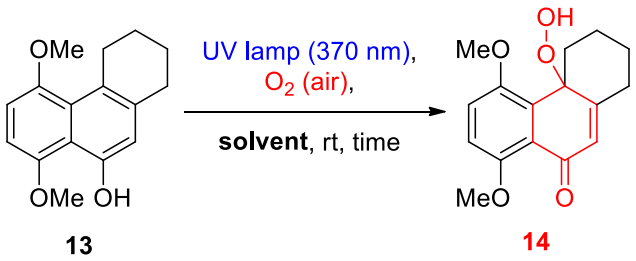
All the results obtained in the photooxidation process studied evidenced a selectivity for the oxidative dearomatization highly dependent on the electronic density of the aromatic rings existent in the tetracyclic phenol precursors **22**. When the structure of the phenols bears a *para*-alkyl substituted group, like in compounds **22a** and **22b**, the phenolic ring was initially suffering the oxidative dearomatization giving rise to the corresponding *para*-peroxy quinols **23**. If the starting phenol has a ketone in the para position, like in compound **22c**, the oxidative dearomatization occurred at the *para*-dimethoxy substituted aromatic ring leading to an endoperoxide. In order to evaluate the ability of the free hydroxyl group to control the selective oxidation, the benzyl protected analogue **191a** was submitted to the photooxidation process. As indicate in *Scheme 2.64*, the irradiation of **191a**, with blue LEDs (λ_{max} 450 nm) under air in chloroform for 30 min, gave quinone **190a** in 48% yield. Quinone **190a** could be formed as a result of the exclusive oxidation of the more electron rich *para*-dimethoxy substituted C ring of **191a**, probably through the corresponding endoperoxide intermediate **200**, which could not be detected. This result corroborated that the electronic density of the aromatic ring in the polyaromatic precursors, is an essential factor in controlling the selectivity of the oxidative dearomatization process.



*Scheme 2.73. Irradiation of a $CHCl_3$ solution of 6-(benzyloxy)-7,12-dimethoxy-1,2,3,4-tetrahydrotetraphene (**191a**) with blue LEDs*

2.2.4.3. Photooxidation of 5,8-dimethoxy-1,2,3,4-tetrahydrophenanthren-9-ol (13)

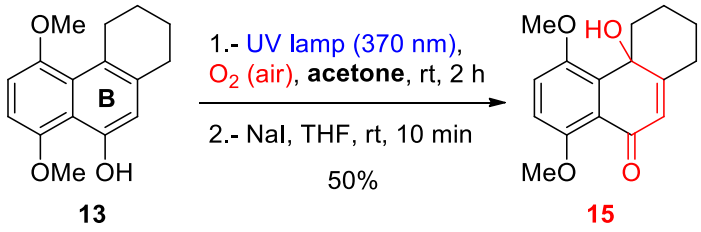
We also checked the behavior of 5,8-dimethoxy-1,2,3,4-tetrahydrophenanthren-9-ol (**13**) under the photooxidation conditions. Thus, irradiation of the tricyclic phenol **13** with UV lamp (λ_{max} 370 nm) under air in chloroform for 2 hours and 30 min, furnished tricyclic *para*-peroxy quinol **14** with a 32% isolated yield, but the yield was improved to 39% yield when the solvent was changed to acetone (*Table 2.4*).



entry	solvent	time	isolated yield
1	chloroform	2 h 30 min	32%
2	Acetone	2 h	39%

*Table 2.4.- Irradiation conditions for tricyclic phenol **13**.*

Finally, the irradiation of tricyclic phenol **13** followed by reduction of the *para*-peroxy quinol **14** with NaI in THF, without its prior purification, gave rise to tricyclic *para*-quinol **15** in 50% overall yield from 5,8-dimethoxy-1,2,3,4-tetrahydrophenanthren-9-ol (**13**) (*Scheme 2.65*).



*Scheme 2.74. Synthesis of 4a-hydroxy-5,8-dimethoxy-2,3,4,4a-tetrahydrophenanthren-9(1H)-one (**15**)*

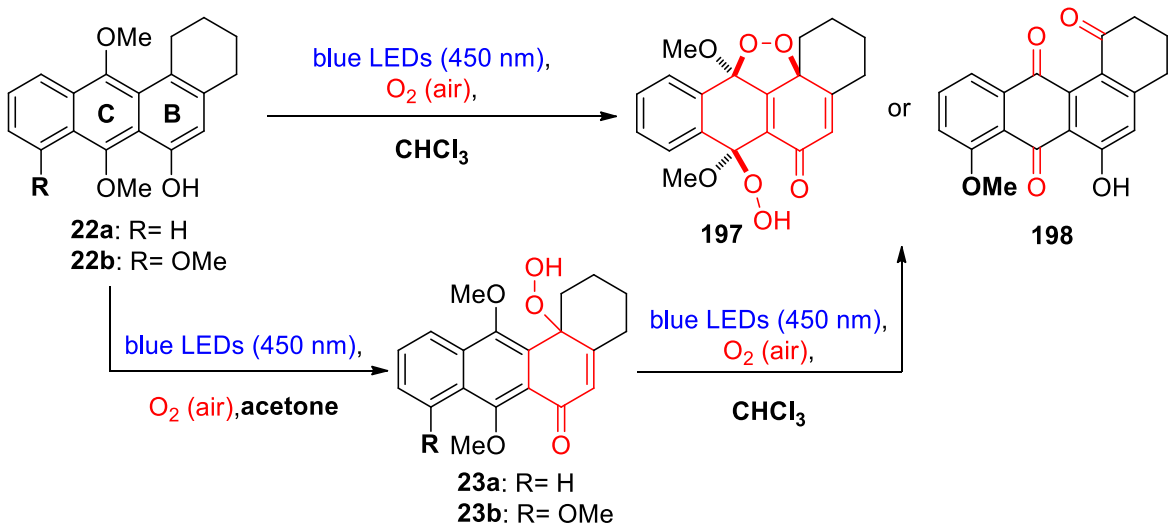
Again, the selectivity of this oxidative dearomatization process was controlled by the electron density of the ring, being in this case only the *para*-alkyl phenol B ring reacting.

2.2.4.4. Mechanism of the photosensitizer- and oxidant-free oxidative dearomatization

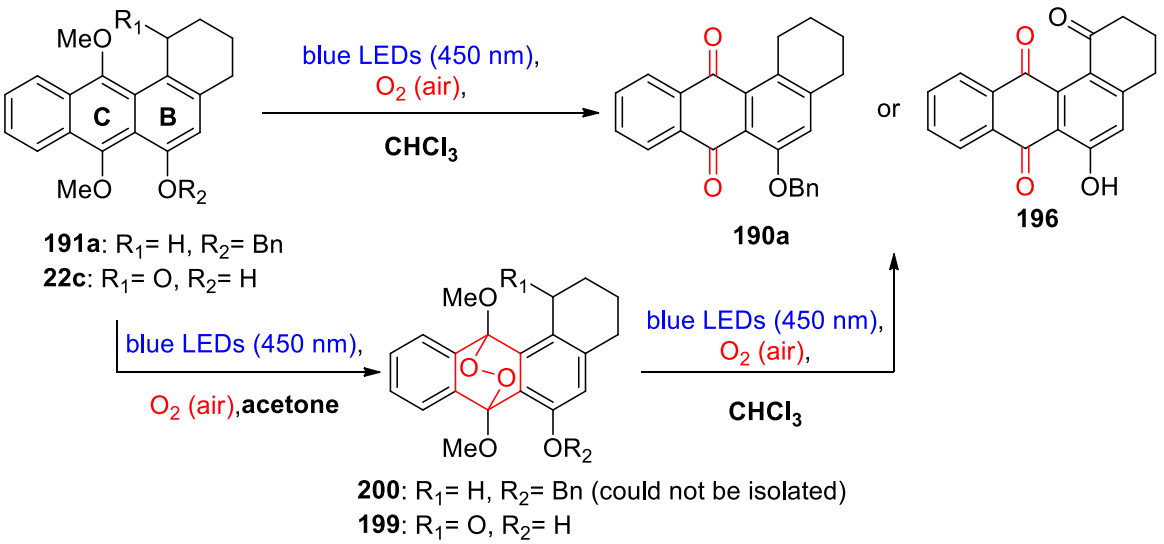
Not only the high ring selectivity observed, in the photooxidation process is noteworthy. Other remarkable features of the oxidative dearomatization of the starting phenols **22** were the mild reaction conditions, only light and air were used. Molecular oxygen is an ideal oxidant for organic synthesis because it is abundant, environmentally friendly and inexpensive. However, controlled incorporation of oxygen to organic substrates requires activation of molecular oxygen

by metal catalysts,[77, 78] organocatalysts[79 80 81] or using photosensitizers to produce singlet oxygen.[82] Outstandingly, the oxidative dearomatization of the angularly tetracyclic phenols **22** observed by us has been achieved under exceptionally mild conditions in the absence of any added metal, photosensitizer and oxidant. These transformations fulfill the requirements of green chemistry and open a direct access to peroxides or quinone derivatives, just using oxygen from air as the oxidant.

As illustrated in the summary shown in *Scheme 2.66*, the solvent employed was essential to produce substrates with different degrees of oxidation in a controlled manner. In this way, in most cases when the solvent used was the acetone, the products obtained were the corresponding *para*-peroxy quinols **23a** or endoperoxide **199**, while chloroform must be chosen to synthesize more oxidized products such as peroxyquinone bisketals **197** or the benz[*a*]anthraquinones **198**, **190a** and **196**. The final transformations observed were also dependent on the substituent existent in the tetracyclic precursors whose influence on the electron density of the different rings is the key.



[77] N. Yoshikai, E. Nakamura, *Chem Rev*, **2012**, *105*, 2339-2372.
[78] J. Piera, J. E. Bäckvall, *Angew. Chem. Int. Ed.* **2008**, *47*, 3506-3523.
[79] J. Scoccia, M. D. Perretti, D.M. Monzón, F. P. Crisóstomo, V. S. Martín, R. Carrillo, *Green Chem*. **2016**, *18*, 2647-2650.
[80] F. G. Gelalcha, *Chem. Rev.* **2007**, *107*, 3338-3361.
[81] a) Y. Imada, H. Iida, S. Ono, S. I. Murahashi, *J. Am. Chem. Soc*. **2003**, *125*, 2868-2869; b) S. Chen, F. W. Foss Jr., *Org. Lett*. **2012**, *14,* 5150-5153.
[82] a) A.G. Griesbeck, M. Bräutigam, M. Kleczka, A. Raabe, *Molecules* **2017**, *22*, 1-14. b) A.G. Griesbeck, D. Blunk, T.T. El-Idreesy, A. Raabe, *Angew. Chem. Int. Ed.* **2007**, *46*, 8883-8886.



Scheme 2.75. Summary of results upon irradiation with blue LEDs using different solvent

Considering that, this photooxidation process is a practical and straightforward method to synthesize a variety of oxidized products from aromatic precursors, several mechanistic studies were performed to elucidate a plausible mechanism. 7,12-Dimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (**22a**) was chosen as model substrate for these studies.

The system Oxone® / $NaHCO_3$ had been shown to provide singlet oxygen ($^1O_2$) which, upon reaction with *para*-alkyl phenols led to *para*-peroxy quinols through the intermediate formation of endoperoxides based on a [4+2] cycloaddition process.[55] Biosynthetic studies carried out by Rohr on aquayamycin (**11**)[83] by culturing the *Streptomyces* precursor under $^{18}O_2$ atmosphere, revealed incorporation of the heavy isotope at the C_{12b} position. The oxygenated groups introduced at C_{12b} in our angucyclinone-type derivatives **23** and **197**, were thus incorporated in a biomimetic manner from molecular oxygen. Taking these precedents into account we reasoned that *para*-peroxy quinols **23a** resulting from irradiation of the phenol **22a** in the presence of air, could be formed by reaction with a reactive oxygen species (ROS) such as singlet oxygen ($^1O_2$).

The presence of singlet oxygen in the reactions effected under our conditions, in the presence of air and light could be confirmed by a trapping experiment. It is well known that anthracenes are $^1O_2$ trapping compounds[84] and that some anthracenes act themselves as photosensitizers, when they are irradiated with a 405 nm LED source affording the corresponding

[83] G. Udvarnoki, T. Henkel, R. Machinek, J. Rohr, *J. Org. Chem.,* **1992**, *57*, 1274-1276.
[84] a) H. Kotani, K. Ohkubo, S. J. Fukuzumi, *J. Am. Chem. Soc.* **2004**, *126*, 15999-16006; b) R. L. Donkers, M. S. Workentin, *J. Am. Chem. Soc.* **2004**, *126*, 1688-1698.

anthracene endoperoxides.[85] 9,10-Dimethylanthracene (**175**) has been shown to react with singlet oxygen leading to 9,10-dimethyl-9,10-dihydro-9,10-epidioxyanthracene (**176**). The UV-visible spectrum of 9,10-dimethylanthracene (**175**), presented in *Figure 2.12*, evidenced an absorption band within the range 331-418 nm. Thus, irradiation with a blue LEDs ($\lambda_{max.}$ 450 nm) used for us, could produce excitation of the anthracene **175**, which could then act as self-sensitizer facilitating the generation of singlet oxygen. Thus, when 9,10-dimethylanthracene (**175**) was irradiated with blue LEDs (λ_{max} 450 nm) in an open flask and stirred at rt 30 min in chloroform, 9,10-dimethyl-9,10-dihydro-9,10-epidioxyanthracene (**176**) was formed and isolated in 93% yield (*Scheme 2.67*). Thus, the formation of singlet oxygen occurred without adding an external photosensitizer. This result confirmed and evidenced that 9,10-dimethylanthracene (**175**) was acting as a self-photosensitizer producing $^1O_2$ which was later reacting with the substrate though a [4+2] cycloaddition leading to **176**.[86]

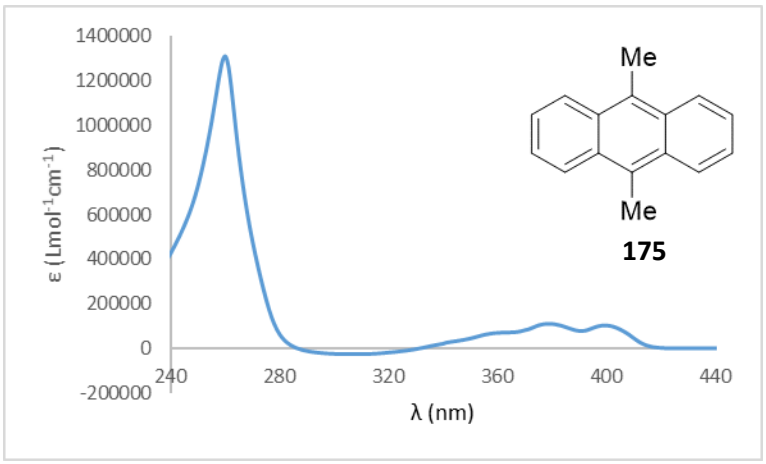
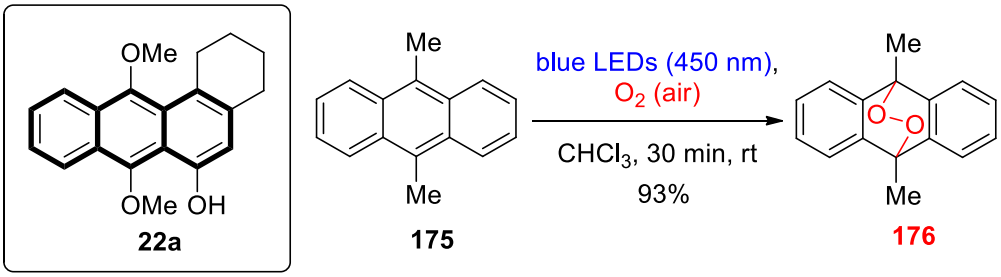


*Figure 2.14. Optical absorption spectra recorded in chloroform in quartz cuvettes (1 cm path). 9,10-Dimethylanthracene (**X**) (c: 1.31 x 10^{-6} M). λ_{max1}: 261 nm (ε_1: 1277393 $Lmol^{-1}cm^{-1}$) and λ_{max2}: 381 nm (ε_2: 107687 $Lmol^{-1}cm^{-1}$).*

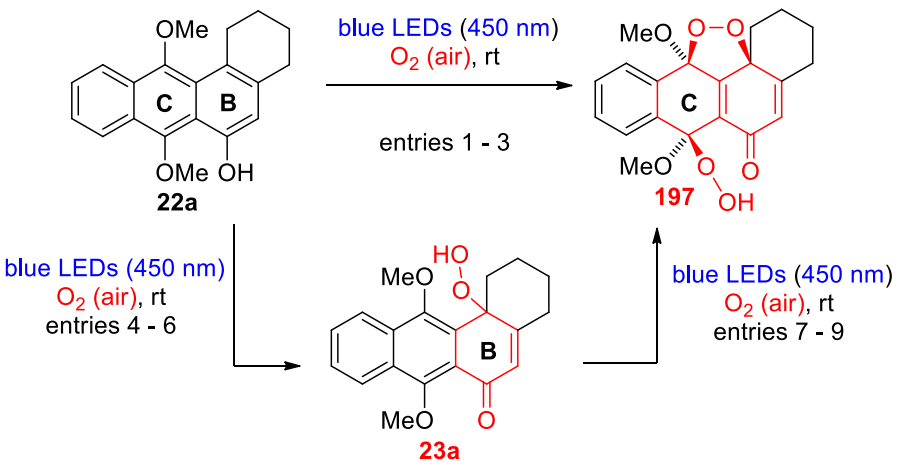


*Scheme 2.76. Formation of 9,10-dimethyl-9,10-dihydro-9,10-epidioxyanthracene (**176**) under our photooxidation conditions.*

[85] J. M. Carney, R. J. Hammer, M. Hulce, C. M. Lomas, D. Miyashiro, *Tetrahedron Lett.* **2011**, *52*, 352-355.
[86] K. Kim, M. Min, S. Hong, *Adv. Synth. Catal.* **2017**, *359*, 848-852.

The structure of the angular tetracyclic phenol **22a** has an aromatic tricyclic fragment analogue to the anthracenes and could behave in a similar manner.

Moreover, different mechanistic experiments were carried out to confirm the presence of singlet oxygen and to propose a mechanism for the two steps transformation of phenol **22a** into bisperoxy quinone bisketal **197**, through the intermediate *para*-peroxy quinol **23a** (*Table 2.5*). These experiment were realized in the presence of a deuterated solvent ($CDCl_3$), which is known to increase the lifetime of singlet oxygen, the singlet oxygen inhibitor 1,4-diazabicyclo[2.2.2]octane (DABCO),[87] and a radical inhibitor (2,2,6,6-tetramethylpiperidin-1-yl)oxyl free radical (TEMPO).[88] All these experiments were carried out using 10 mg of the corresponding starting substrate, phenol **22a** or *para*-peroxy quinol **23a**, and following the experimental procedures used to synthesize compounds **23a** and **197**, but adding the corresponding additive (DABCO or TEMPO) or changing the solvent by the deuterated one.



entry	starting comp.	solvent	time (min)	additive (5 equiv.)	22a (%)[a]	23a (%)[a]	197 (%)[a]
1	**22a**	$CHCl_3$	120	-----	0	0	47[b]
2	**22a**	$CDCl_3$	15	-----	0	0	47[b]
3	**22a**	$CDCl_3$	15	TEMPO	40	60	0
4	**22a**	acetone	15	-----	0	70[b]	-----
5	**22a**	acetone	15	DABCO	64	36	-----
6	**22a**	acetone	15	TEMPO	25	75	-----

[87] S. K. Silverman, C. S Foote, *J Am. Chem. Soc.* 1991, *113*, 7672-7675.
[88] P. B. Arockiam, L. Guillemard, J. Wencel-Delord, *Adv Synth Cat.* **2017**, *359*, 2571-2579

7	**23a**	$CHCl_3$	20	-----	-----	0	>99[b]
8	**23a**	$CHCl_3$	20	DABCO	-----	100	0
9	**23a**	$CHCl_3$	20	TEMPO	-----	100	0

a: Determined by NMR of the crude mixture. b: Isolated yield

Table 2.5.- Mechanistic experiment data

The role of singlet oxygen as the oxidant in the synthesis of bisperoxy bisketal **197** from phenol **22a**, under our aerobic photooxidation conditions, was supported by the increased reaction rate observed when irradiation of **22a** was carried out in a deuterated solvent such as $CDCl_3$ (15 min *vs* 120 min in $CHCl_3$), which is known to increase the lifetime of singlet oxygen, as mentioned above (*Table 2.5*, *entries 1* and *2*).[89] The presence of singlet oxygen was also supported by the results obtained upon addition of DABCO.[87] When phenol **22a** was irradiated (blue LEDs, air, acetone, 15 min) in the presence of DABCO (5 equiv), a 64% of starting phenol **22a** remained unchanged (*Table 2.5*, *entry 5*), in comparison with the same reaction without DABCO (*Table 2.5*, *entry 4*), where a 100% conversion of **22a** and 70% isolated yield of **23a** were achieved. Thus, the presence of DABCO is difficulting the reaction with singlet oxygen.

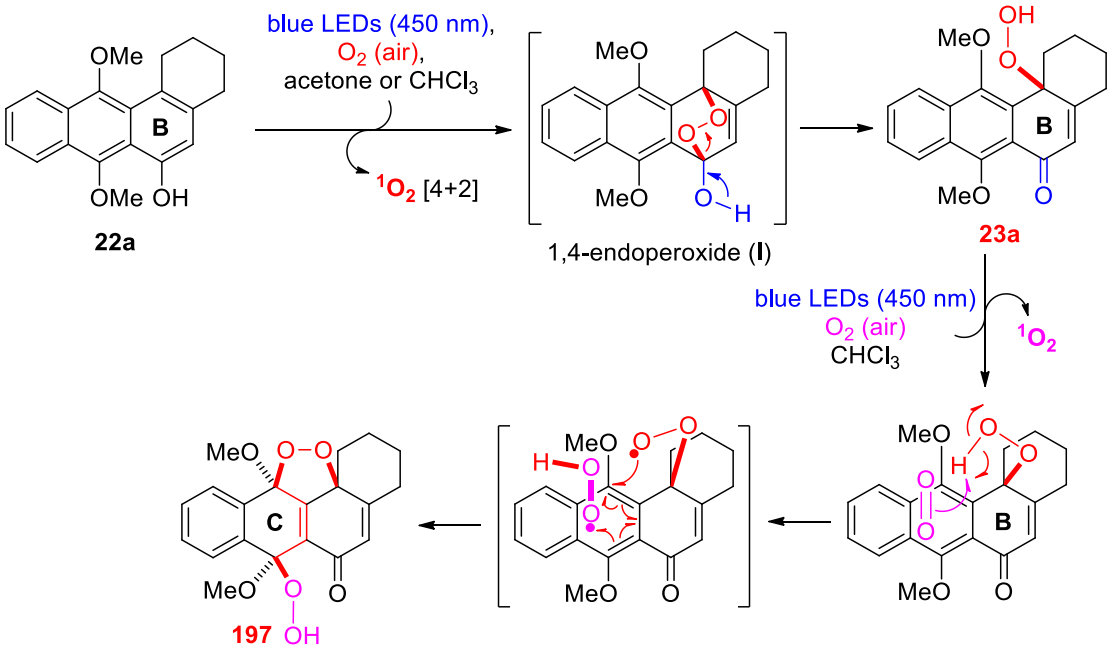
On the other hand, the irradiation of **22a** in acetone in the presence of TEMPO (5 equiv) gave rise to the exclusive formation of hydroperoxide **23a**, although in slightly lower conversion in 15 min (*Table 2.5*, *entry 6*). Moreover, we irradiated **22a** in $CDCl_3$ in the presence of TEMPO (5 equiv) and detected the formation of the intermediate hydroperoxide **23a**, but the bisperoxy bisketal **197** was not detected (*Table 2.5*, *entry 3*). These results were suggesting that singlet oxygen was the oxidant responsible of the formation of the *para*-peroxy quinol **23a** which could later evolve into thebisperoxy bisketal **197** by a radical mechanistic pathway inhibited by TEMPO.

We also checked the influence of both additives in the transformation of **23a** into **197**. Thus, when *para*-peroxy quinol **23a** was irradiated (blue LEDs under air in $CHCl_3$, 20 min) in the presence of DABCO or TEMPO (*Table 2.5*, *entries 8* and *9*), the starting hydroperoxide **23a** remained unchanged, whereas under these conditions, in the absence of both additives, **23a** was quantitatively transformed into **197** (*Table 2.5*, *entry 7*). These experiments were suggesting that free radicals must be involved in the transformation of **23a** into **197** and that singlet oxygen must also have an essential role.

[89] Hurst, J. R.; McDonald, J. D.; Schuster, G. B. *J. Am. Chem. Soc.* **1982**, *104*, 2065–2067.

2.2.4.4.1. Mechanistic proposal

In light of these studies and precedents from the literature, we propose a mechanism for the formation of *para*-peroxy quinol **23a** and the *bis*-peroxy bisketal **197** from angular tetracyclic phenol **22a** (*Scheme 2.68*). After irradiation with blue leds, the starting phenol **22a**, acting as photosensitizer, was able to generate singlet oxygen which reacted, through a [4+2] cycloaddition, selectively at the most electron rich *para*-alkyl substituted B ring of tetracyclic phenol **22a**, leading to 1,4-endoperoxide **I**. This intermediate, immediately evolved into the *para*-peroxy quinol **23a** as result of its unstable peroxyhemiketal structure. Once **23a** is formed, a radical process, favored by irradiation in the chlorinated solvent and triggered by $^1O_2$[90] through abstraction of the hydrogen of the hydroperoxide **23a**, affords the peroxy radicals [**23a**]$^{\cdot}$ and HOO·. Intramolecular attack of [**23a**]$^{\cdot}$ to the C_{12} position from the face containing the peroxy radical, gave the cyclic peroxide moiety. This attack triggers the movement of electrons represented, favoring reaction at C_7 with the HOO· situated at the same face, giving the *bis*-peroxide **197** and explaining the exclusive formation of the diastereomer with the *cis* relative configuration of the peroxide and hydroperoxide groups.



*Scheme 2.77. Mechanistic proposal for the aerobic photooxidation of **22a** into **23a** and **197***

As already mentioned, two aspects of this process are noteworthy. First, the mild conditions and short time required for a process incorporating four oxygen atoms to the system and occurring without any added reagent or photosensitizer, only in the presence of light and

[90] J.-G. Sun, H. Yang, P. Li, B. Zhang, *Org. Lett*. **2016**, *18*, 5114−5117.

oxygen from air. Second, the exclusive formation of one diastereomer with a *cis* relative configuration of the peroxide and hydroperoxide groups.

2.2.4.4.2. UV-visible spectra of the photosensitive tetracyclic substrates

The reactivity shown by 7,12-dimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (**22a**) by irradiation under an aerobic atmosphere, could be explained observing its UV-vis spectrum, which apart from intense absorption bands at λ 240 and 273 nm, displayed a broad absorption band in a range of λ 338-457 nm (*Figure 2.12*). The visible light sources such as household lamp, emitted at higher wavelengths and the overlap with this absorption band was very little. The emission wavelengths of sunlight are higher and overlap all the absorption spectrum of phenol **22a**. In addition, the phenol **22a** band emissions was partially overlap with the emission band of blue LEDs (λ_{max} 450 nm) (*See Experimental part*).

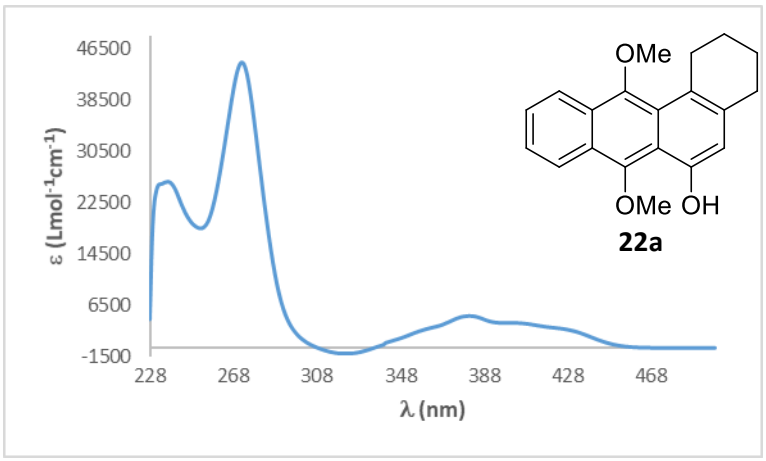


*Figure 2.15. Optical absorption spectra recorded in chloroform in quartz cuvettes (1 cm path). 7,12-dimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (**22a**) (c: 1.90 x 10^{-5} M). λ_{max1}: 240 nm (ε_1: 25817 $Lmol^{-1}cm^{-1}$), λ_{max2}: 273 nm (ε_2: 43248 $Lmol^{-1}cm^{-1}$) and λ_{max3}: 384 nm (ε_3: 4961 $Lmol^{-1}cm^{-1}$).*

The UV-visible spectrum of *para*-peroxy quinol **23a** showed a broad absorption band in a range of λ 340-410 nm (*Figure 2.13*), which overlapped with the emission band of blue LEDs used in the aerobic photooxidation and could interact and react with oxygen from the air, oxidizing it.

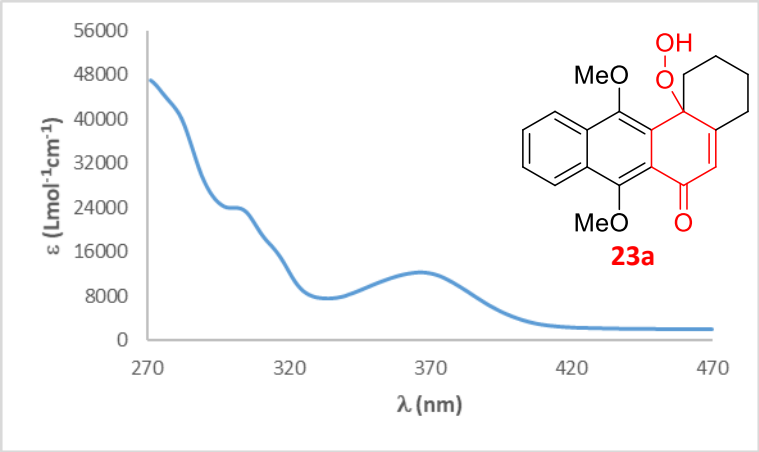


*Figure 2.16. Optical absorption spectra recorded in chloroform in quartz cuvettes (1 cm path). 12b-hydroperoxy-7,12-dimethoxy-1,3,4,12b-tetrahydrotetraphen-6(2H)-one (**23a**) (c: 2.11 x 10^{-5} M). λ_{max1}: 304 nm (ε_1: 23640 $Lmol^{-1}cm^{-1}$) and λ_{max2}: 368 nm (ε_2: 12311 $Lmol^{-1}cm^{-1}$)*

The UV-visible spectrum of 7,8,12-trimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (**22b**) showed a broad absorption band in a range of 340-452 nm (*Figure 2.14*), similar to the phenol **22a**, lacking the 8-methoxy substituent Therefore, phenol **22b** could have a similar behavior and reactivity to phenol **22a**. This justifies a similar reactivity of both phenols under the same irradiation conditions.

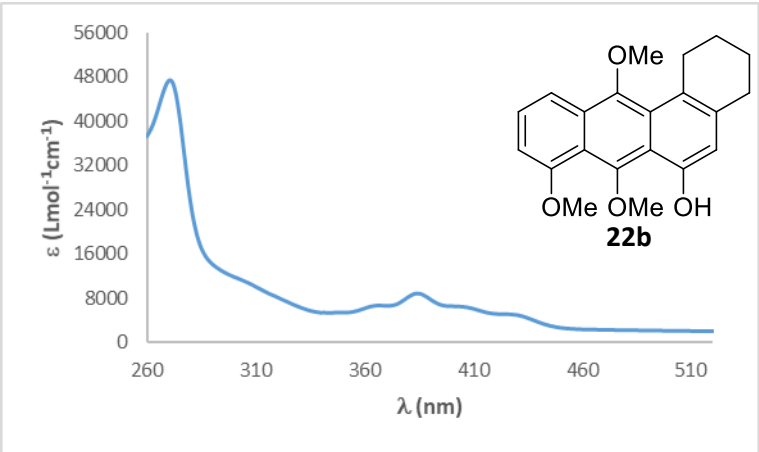


*Figure 2.17. Optical absorption spectra recorded in chloroform in quartz cuvettes (1 cm path). 7,8,12-trimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (**22b**) (c: 2.01 x 10^{-5} M). λ_{max1}: 272 nm (ε_1: 46986 $Lmol^{-1}cm^{-1}$) and λ_{max2}: 386 nm (ε_2: 8737 $Lmol^{-1}cm^{-1}$).*

On the other hand, the UV-visible spectrum of *para*-peroxy quinol **23b** showed a broad absorption band in a range of 340-436 nm (*Figure 2.15*), similar to *para*-peroxy quinol **22a**. However, irradiation of *para*-peroxy quinol **23b** did not led to an homologous *bis*-peroxide, but its irradiation genetared a complex mixture, where 6-hydroxy-8-methoxy-3,4-dihydrotetraphene-1,7,12(2H)-trione (**198**) could be isolated.

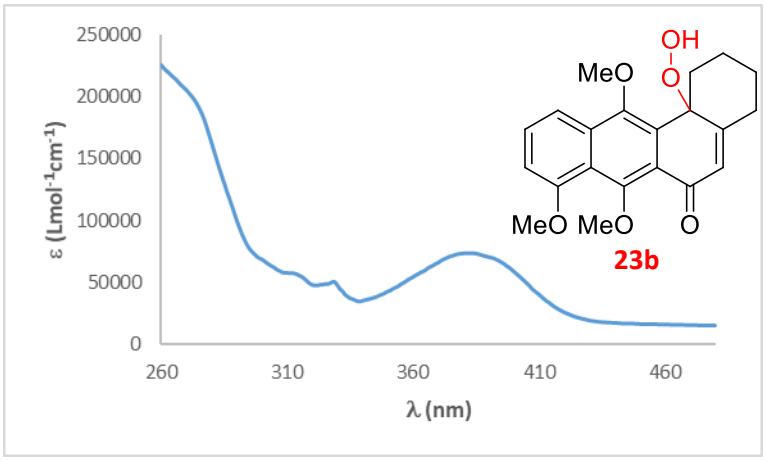


*Figure 2.18. Optical absorption spectra recorded in chloroform in quartz cuvettes (1 cm path). 12b-hydroperoxy-7,8,12-trimethoxy-1,3,4,12b-tetrahydrotetraphen-6(2H)-one (**23b**) (c: 2.70 x 10^{-6} M). λ_{max1}: 274 nm (ε_1: 197984 $Lmol^{-1}cm^{-1}$) and λ_{max2}: 385 nm (ε_2: 74100 $Lmol^{-1}cm^{-1}$).*

The UV-visible spectrum of 6-hydroxy-7,12-dimethoxy-3,4-dihydrotetraphen-1(2H)-one (**22c**) showed a broad absorption band in a range of 335-470 nm (*Figure 2.16*) and penol **22c** could present a similar reactivity to phenol **22a**. However, unlike phenol **22a**, the more electron rich ring of phenol **22c** was the C ring and thus, this is the reactive and oxidized this ring.

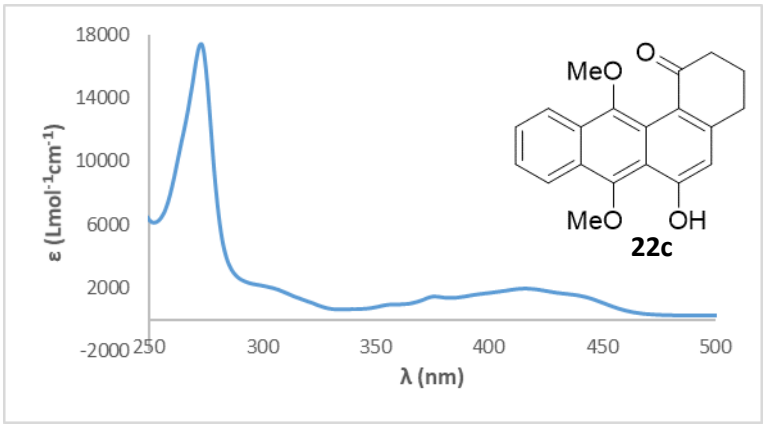


Figure 2.19. Optical absorption spectra recorded in chloroform in quartz cuvettes (1 cm path). 6-hydroxy-7,12-dimethoxy-3,4-dihydrotetraphen-1(2H)-one (**22c**) (c: 1.49 x 10^{-4} M). λ_{max1}: 273 nm *(ε_1: 16858 $Lmol^{-1}cm^{-1}$)* and λ_{max2}: 417 nm *(ε_2: 1974 $Lmol^{-1}cm^{-1}$)*.

The UV-visible spectrum of 6-(benzyloxy)-7,12-dimethoxy-1,2,3,4-tetrahydrotetraphene (**191a**) showed a broad absorption band in a range of 320-440 nm (*Figure 2.17*).

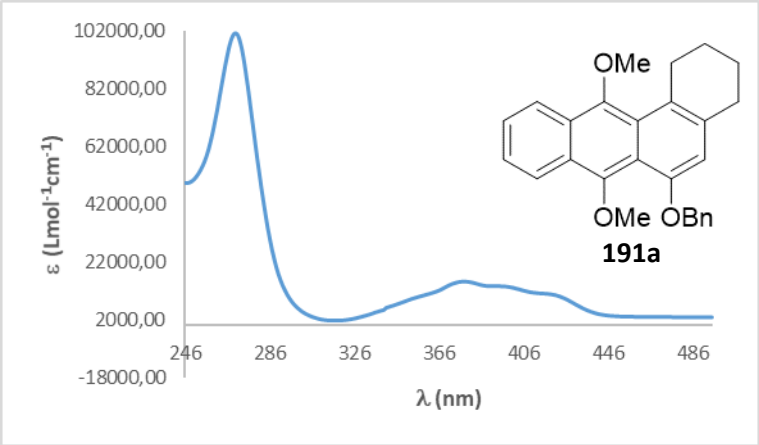


*Figure 2.20. Optical absorption spectra recorded in chloroform in quartz cuvettes (1 cm path). 6-(benzyloxy)-7,12-dimethoxy-1,2,3,4-tetrahydrotetraphene (**191a**) (c: 8.99 x 10^{-6} M). λ_{max1}: 271 nm (ε_1: 100238 $Lmol^{-1}cm^{-1}$) and λ_{max2}: 400 nm (ε_2: 12969 $Lmol^{-1}cm^{-1}$).*

Finally, the UV-visible spectrum of 5,8-dimethoxy-1,2,3,4-tetrahydrophenanthren-9-ol (**13**) showed some absorption bands in a range of 280-370 nm (*Figure 2.18*). These bands were in the near UV and did not overlap with the emission band of blue LEDs (λ_{max} 450 nm), but they did with the emission band of UV lamp (λ_{max} 370 nm).

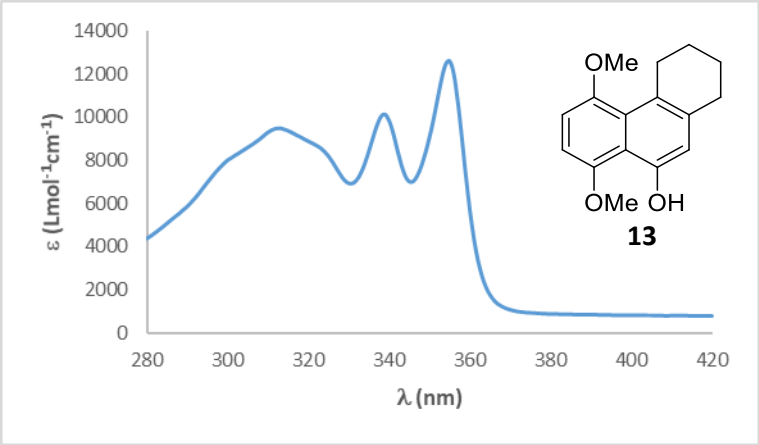


*Figure 2.21. Optical absorption spectra recorded in chloroform in quartz cuvettes (1 cm path). 5,8-dimethoxy-1,2,3,4-tetrahydrophenanthren-9-ol (**13**) (c: 5.53 x 10^{-5} M). λ_{max1}: 314 nm (ε_1: 9514 $Lmol^{-1}cm^{-1}$), λ_{max2}: 340 nm (ε_2: 9868 $Lmol^{-1}cm^{-1}$) and λ_{max3}: 355 nm (ε_3: 12631 $Lmol^{-1}cm^{-1}$).*

All these spectroscopic features justified that these phenols could be excited by irradiation with blue LEDs (λ_{max} 450 nm), with the exception of 5,8-dimethoxy-1,2,3,4-tetrahydrophenanthren-9-ol (**13**).

2.2.4.4.3. ^{1}H NMR spectra of the mechanistic studies

To support the mechanism previously proposed, we also studied the ^{1}H-NMR crude spectra, of each mechanistic experiment previously commented. The ^{1}H-NMR spectra of the starting materials and final products (phenol **22a**, *para*-peroxy quinol **23a** and *bis*-peroxide **197** are included by the sequel for comparison with the ^{1}H-NMR spectra of crude mechanistic experiments. To determine approximately the conversion of each experiment, we compared the signal of the proton at C_5 position (H_5) because of the ppm range in which these signal appear was cleaner, making easier to follow them in each case. Moreover, to understand better the results shown in the ^{1}H-NMR crude spectra it is necessary to know the chemical shifts of the additives. Thus, the chemical shift for DABCO is δ: 2.80 ppm (singlet), and the radical oxygen present in TEMPO interferes in the proton experiment and we cannot have a clear ^{1}H-NMR spectrum.

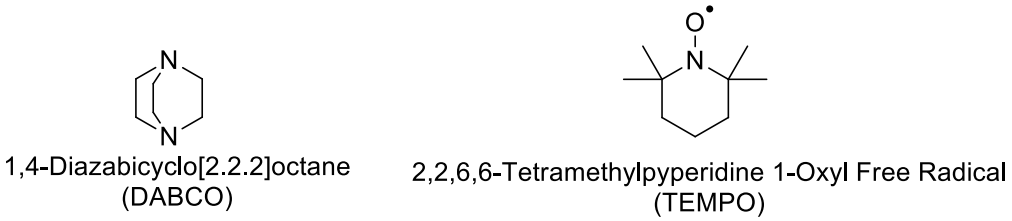


Figure 2.22. Structure of DABCO and TEMPO

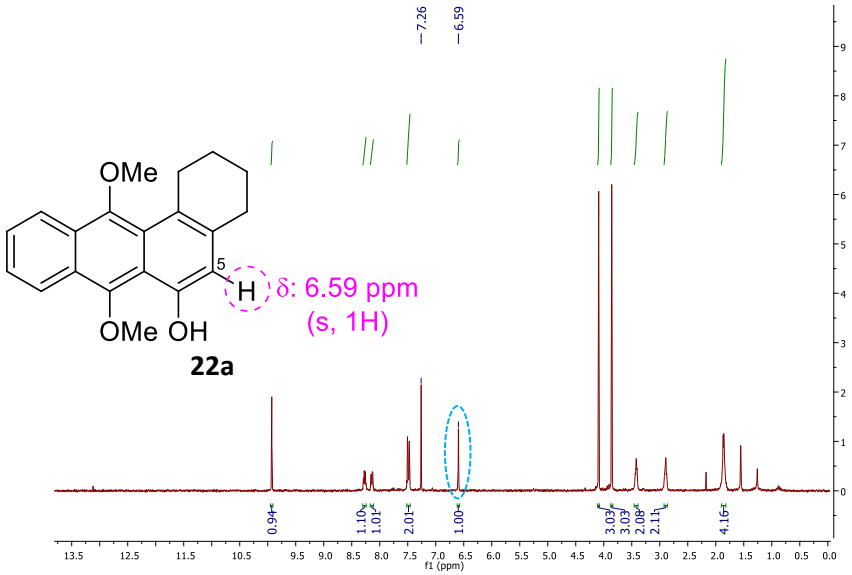


Figure 2.23. ^{1}H-NMR of *7,12-dimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (**22a**) in* $CDCl_3$

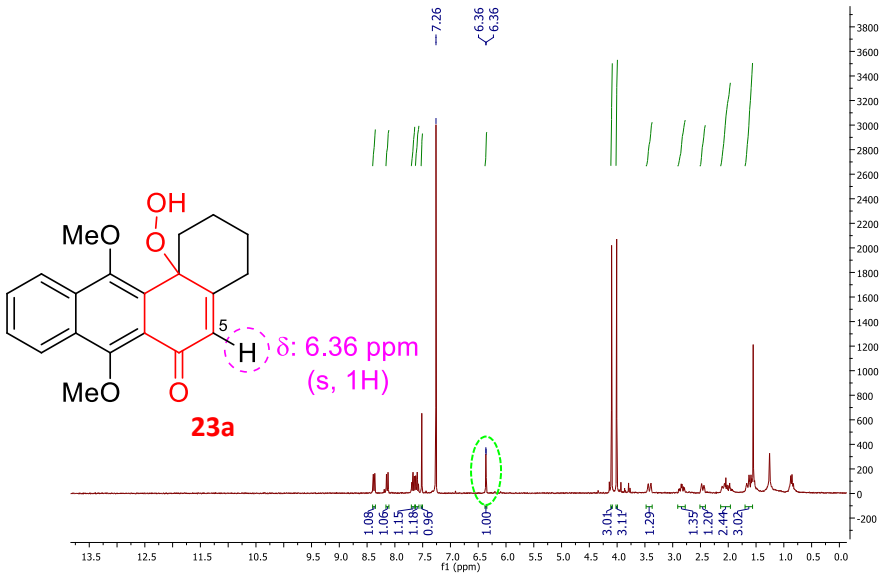


Figure 2.24 . ^{1}H-NMR of *12b-Hydroperoxy-7,12-dimethoxy-1,3,4,12b-tetrahydrotetraphen-6(2H)-one (**23a**) in $CDCl_3$*

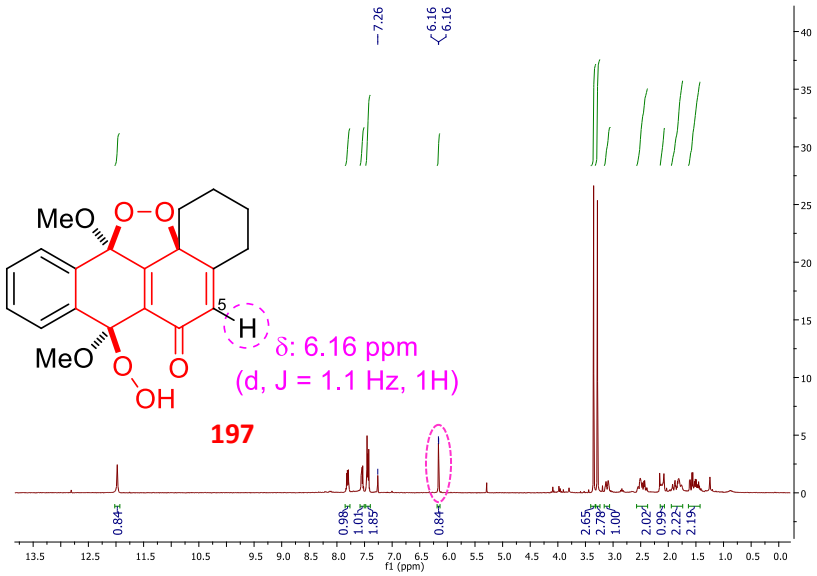


Figure 2.25. ^{1}H-NMR of *(7S*,11bR*,13aS*)-7-hydroperoxy-7,11b-dimethoxy-3,4,7,11b-tetrahydro-1H-tetrapheno[12-cd][1,2]dioxol-6(2H)-one (**197**) in $CDCl_3$*

As can be seen by comparison of spectra of the starting phenol **22a** and *para*-peroxy quinol **23a**, the crude reaction mixture in $CDCl_3$ (*Figure 2.23*) displayed a 40:60 mixture of **22a** and **23a** after 15 min of irradiation in CDCl3 [δ: 6.72 ppm (H_{5Xa}) and δ: 6.47 ppm (H_{5Xa})].

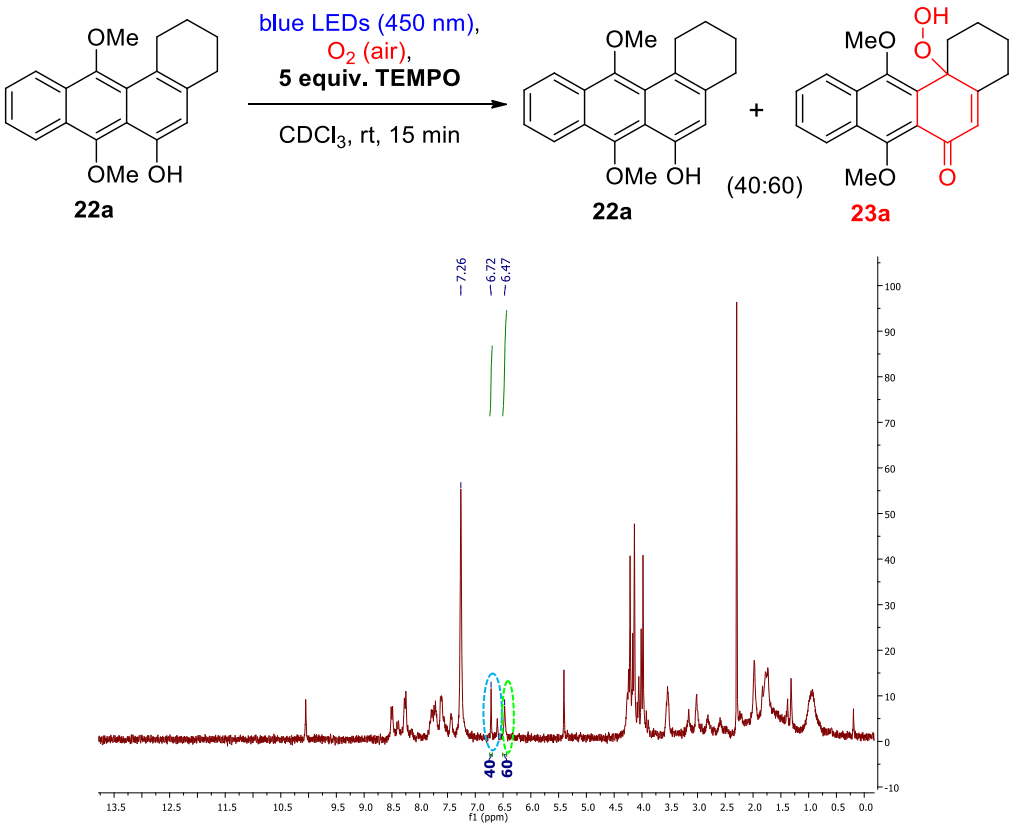
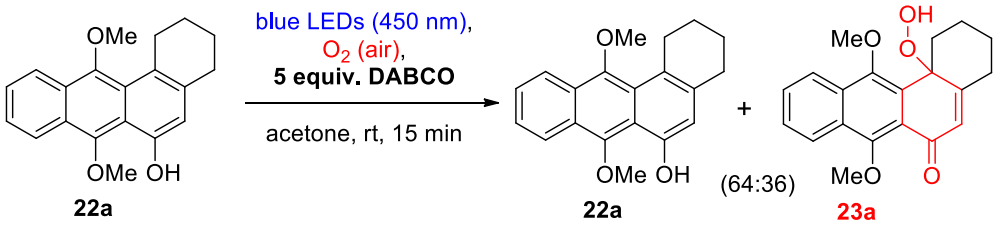


Figure 2.26. ^{1}H-NMR crude in $CDCl_3$, adding 5 equiv. of TEMPO in the reaction of **22a** with blue LEDs and air in $CDCl_3$. *Table 2.5, entry 3*.

Figure 2.24 showed the crude reaction mixture in acetone of the photooxidation of phenol **22a** in acetone in presence of DABCO. A 64:36 mixture of **22a** and **23a** was determined after 15 min of irradiation [δ: 6.56 ppm (H_{5Xa}) and δ: 6.17 ppm (H_{5Xa})].



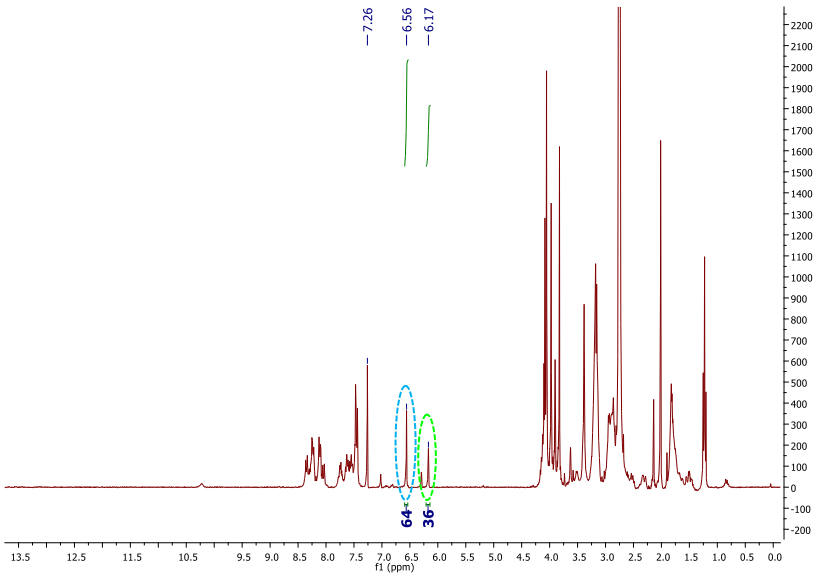
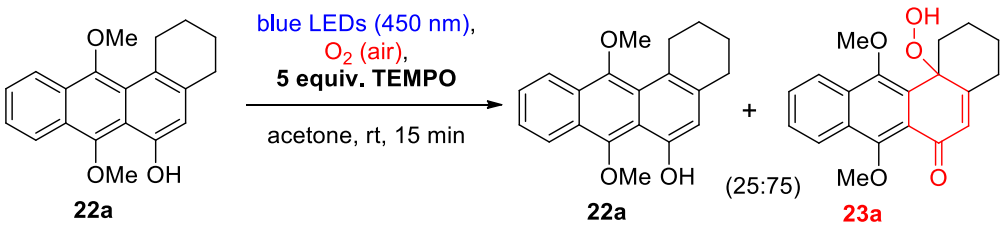


Figure 2.27. ^{1}H-NMR crude in $CDCl_3$, adding 5 equiv. of DABCO in the reaction of **22a** with blue LEDs and air in acetone. *Table 2.5, entry 5*.

The crude reaction mixture in $CHCl_3$ of the photooxidation of phenol **22a** in acetone in the presence of TEMPO are exhibited in *Figure 2.25*. After 15 min of irradiation, a 25:75 mixture of **22a** and **23a** was determined in the ^{1}H-RMN crude [δ: 6.65 ppm (H_{5Xa}) and δ: 6.37 ppm (H_{5Xa})].



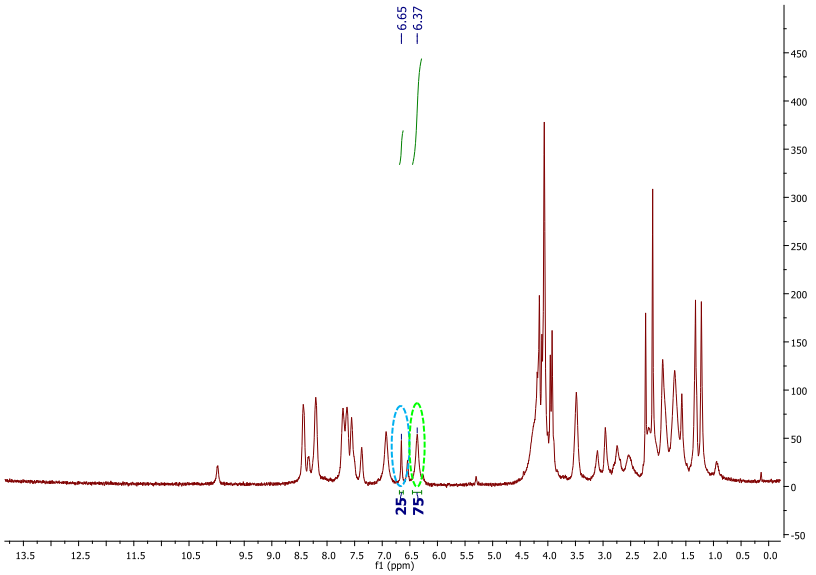


Figure 2.28. ^{1}H-NMR crude in $CDCl_3$, adding 5 equiv. of TEMPO in the reaction of **22a** with blue LEDs and air in acetone. *Table 2.5, entry 6*.

The irradiation of a chloroform solution of *para*-peroxy quinol **23a** with blue LEDs (λ_{max} 450 nm) did not afford the bisperoxy bisketal **197** in presence of both inhibitors (DABCO and TEMPO), but remained unchanged as we can see in the ^{1}H-NMR crude in $CDCl_3$ of both mechanistic experiments in *Figure 2.26* and *2.27*, respectively.

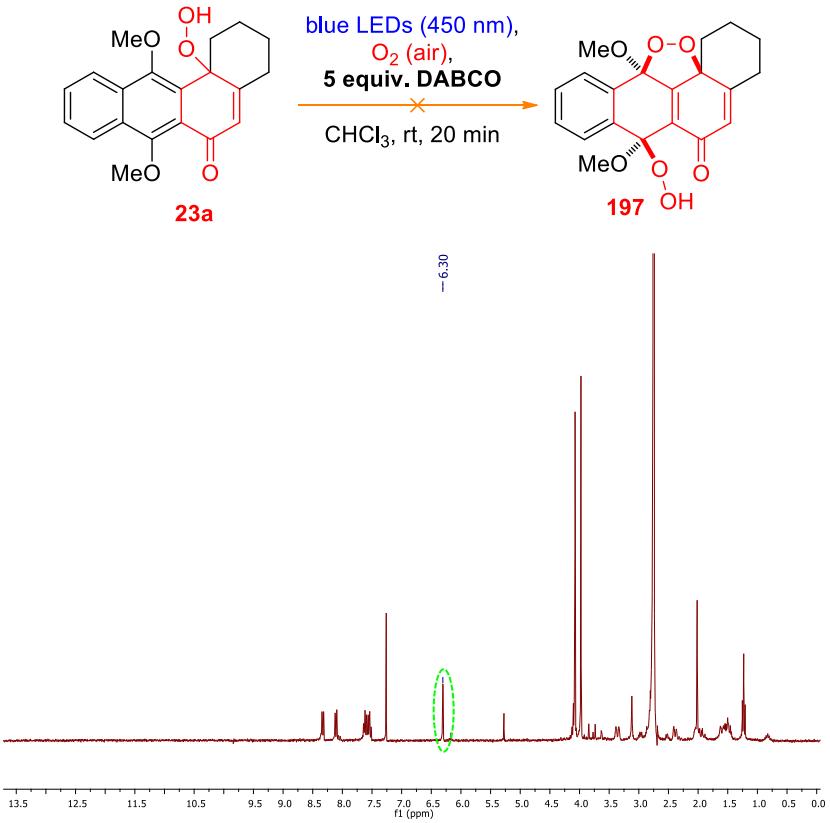
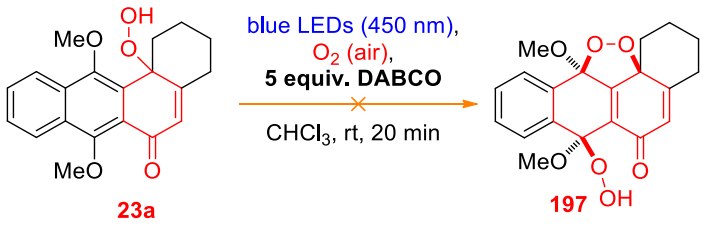


Figure 2.29. ^{1}H-NMR crude in $CDCl_3$, adding 5 equiv. of DABCO in the reaction of **23a** with blue LEDs and air in $CHCl_3$. *Table 2.5, entry 8*.



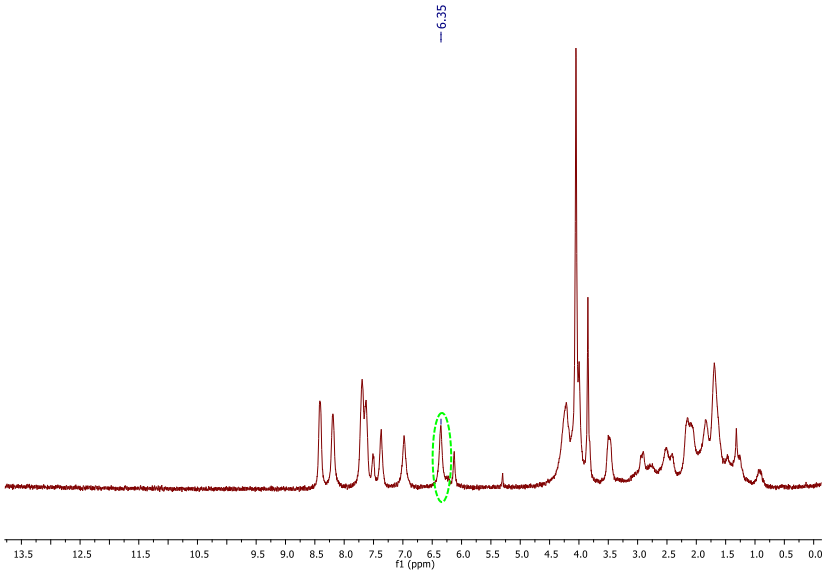


Figure 2.30. ^{1}H-NMR crude in $CDCl_3$, adding 5 equiv. of TEMPO in the reaction of **23a** with blue LEDs and air in $CHCl_3$. *Table 2.5, entry 9*.

2.2.4.5. Structural assignment of bisperoxy bisketal 197 and endoperoxide 199

The structures of all the compounds synthesized were unequivocally establish on the base of their spectroscopic data: HRMS, ^{1}H and ^{13}C-NMR and in one case, corroborated by X-ray diffraction studies.

*2.2.4.5.1. 7-Hydroperoxy-7,11b-dimethoxy-3,4,7,11b-tetrahydro-1H-tetrapheno[12-cd][1,2]dioxol-6(2H)-one (**197**)*

The ^{1}H-NMR spectrum of *bis*-peroxy bisketal **197** presented some characteristic signals for its structural assignment. Apart from the aromatic protons H_8, H_9, H_{10} and H_{11} and the aliphatic CH_2- groups of rings D and A, respectively, the most significant signals are shown in *Figure 2.28* and *2.29*. Thus, the singlet at δ: 12.01 ppm (s, 1H), correspond to the hydrogen of peroxide group at C_7 which is forming a hydrogen bond with the close ketone at C_6 as evidence in the X-ray. The appearing doublet at 6.16 (d, *J* = 1.1 Hz, 1H), is assigned to the hydrogen at C_5. The singlets at δ: 3.37 ppm and δ: 3.29 ppm, correspond to the hydrogens of methoxy groups at C_7 and C_{12}. The chemical low shift of methoxy groups signals suggested that these groups are at the aliphatic part of the molecule, thus, ring C had lost its aromaticity. In addition, the asymmetry observed in the signals for the aliphatic hydrogens of ring A suggested a substitution in one of the angularly positions (C_{4a} or C_{12b}) and/or at C_{12} position (*Figures 2.28* and *2.29*).

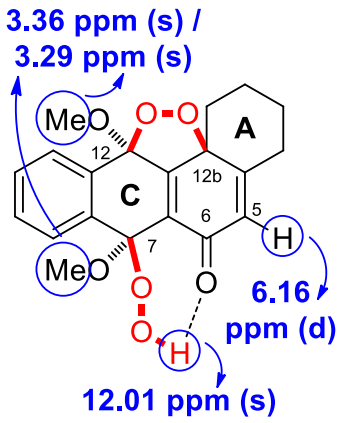


Figure 2.31. Characteristic signals in ^{1}H-NMR

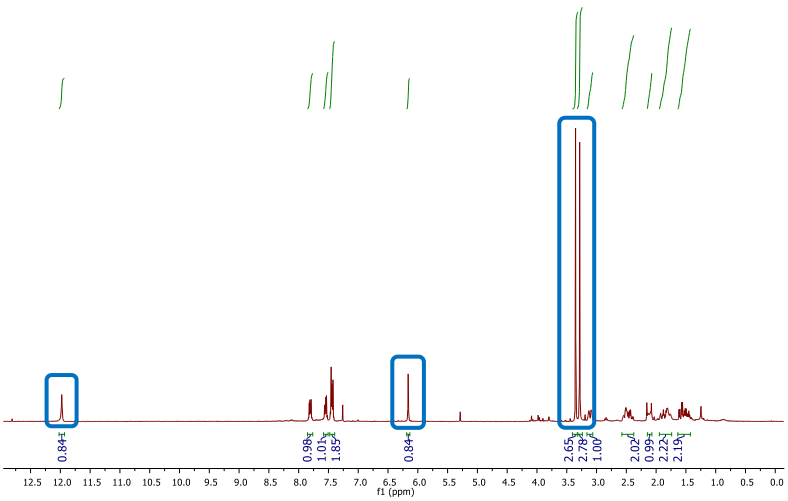


*Figure 2.32. ^{1}H-RMN spectrum of bisperoxy bisketal **197***

The ^{13}C-NMR spectrum with DEPT experiment, showed a signal at 184.5 ppm, corresponding to the ketone group at C_6. Two signals for quaternary carbons at 101.3 ppm were assigned to the aliphatic ketal carbons at C_7 and C_{12}, and a signal at 81.4 ppm, corresponded to the quaternary C_{12b} carbon joined to oxygen (*Figures 2.30* and *2.31*).

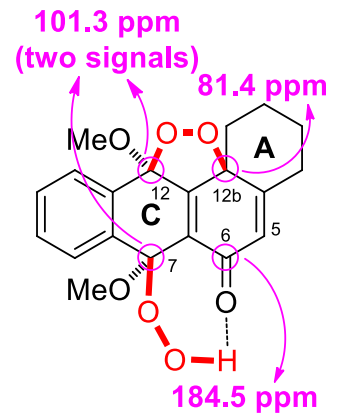


Figure 2.33. Characteristic signals in ^{13}C-NMR

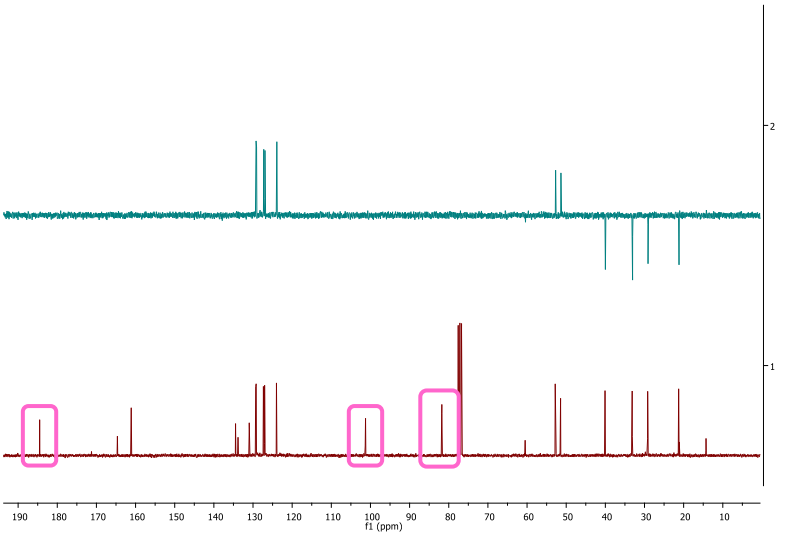


*Figure 2.34. DEPT 135 experiments with ^{13}C-NMR of double peroxide **197**.*

In addition, the HMBC experiment showed correlations between the proton at C_5 with the carbons at C_4, C_{4a}, C_{12b} and C_6, as shown in *Figures 2.32* and *2.33*.

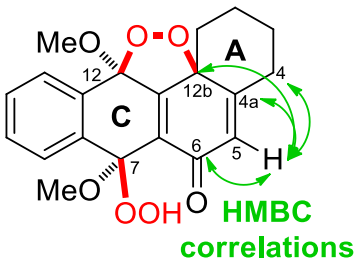


Figure 2.35. HMBC correlations

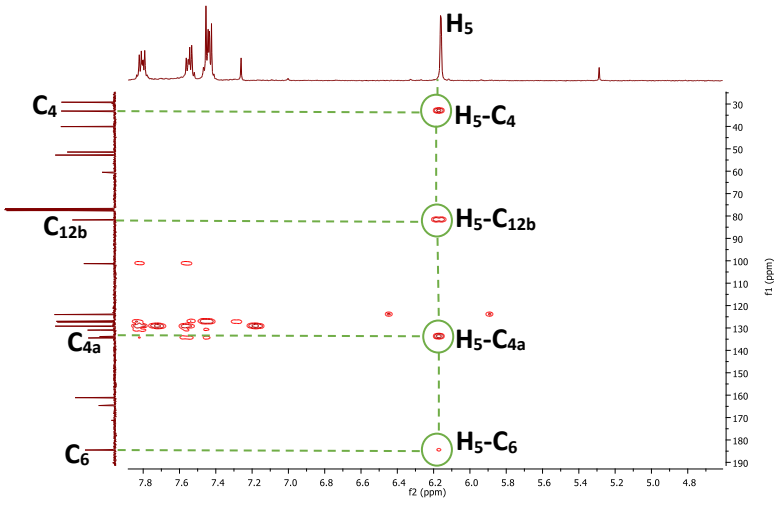


Figure 2.36. HMBC experiment

Finally, the structure of 7-Hydroperoxy-7,11b-dimethoxy-3,4,7,11b-tetrahydro-1H-tetrapheno[12-cd][1,2]dioxol-6(2H)-one (**197**) was confirmed by a X-ray diffraction study (*Figure 2.34*).

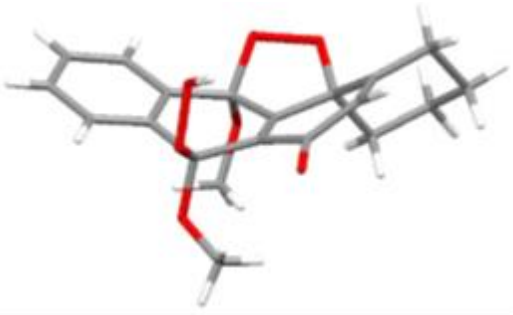


*Figure 2.37. X-ray of 6-Hydroxy-7,12-dimethoxy-3,4,7,12-tetrahydro-7,12-epidioxytetraphen-1(2H)-one (**X**)*

The apparition of the molecular ion ($[M+Na]^+$) at 395.1109 amu determined by High-Resolution Mass Spectroscopy is agreed with the molecular weight calculated for 6-hydroxy-7,12-dimethoxy-3,4,7,12-tetrahydro-7,12-epidioxytetraphen-1(2*H*)-one (**197**), that is 395.1106 amu.

*2.2.4.5.2. 6-Hydroxy-7,12-dimethoxy-3,4,7,12-tetrahydro-7,12-epidioxytetraphen-1(2H)-one (**199**)*

The structure of endoperoxide **199**, having a masked quinone *bis*-ketal at C ring, was also determined by its spectroscopy data of ^{1}H-NMR, ^{13}C-NMR, and DEPT experiment. The most characteristic signals of the ^{1}H-NMR spectrum are indicated in *Figures 2.35* and *2.36*. Thus, the singlet at 8.69 ppm (s, 1H), corresponds to the hydrogen of phenol at C_6 and the singlets at δ: 4.05

ppm (s, 3H) and δ: 3.74 ppm (s, 3H), are assigned to the hydrogens of the methoxy groups at C_7 and C_{12}.

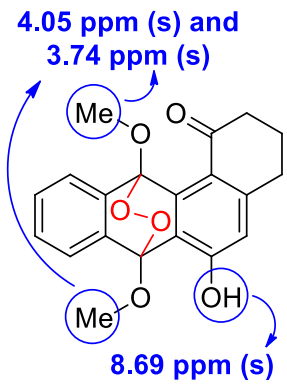


Figure 2.38. Characteristic signals in ^{1}H-NMR

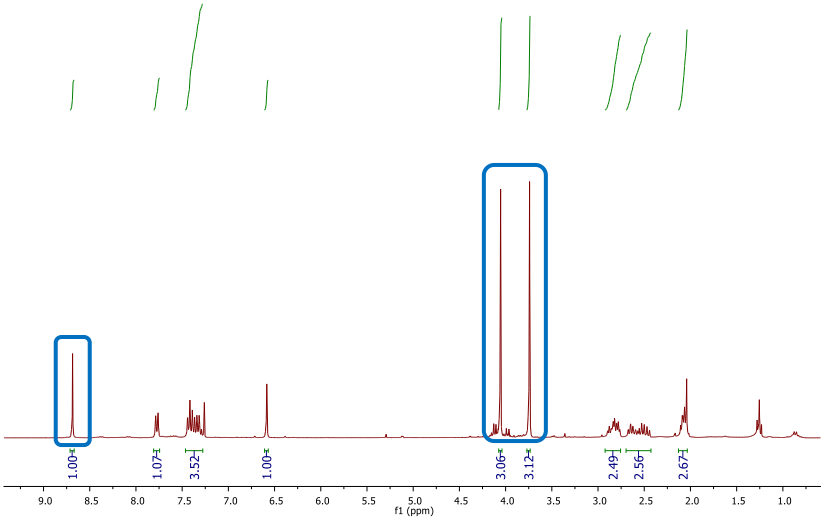


*Figure 2.39. ^{1}H-NMR spectrum of endoperoxide **X***

On the other hand, the ^{13}C-NMR spectrum showed a characteristic signal at 197.0 ppm, corresponding to the ketone at C_1 and two signals at 104.8 ppm and 103.9 ppm, assigned to the ketal quaternary carbons at C_7 and C_{12}. The DEPT 135 experiment supported the different degree of substitution of all carbons presented in tetracyclic endoperoxide **199** (*Figures 2.37* and *2.38*).

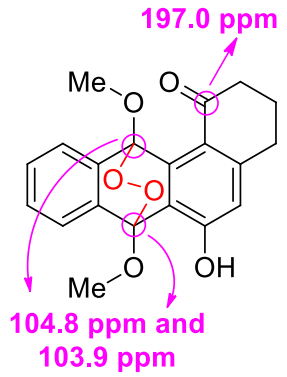


Figure 2.40. Characteristic signals in ^{13}C-NMR

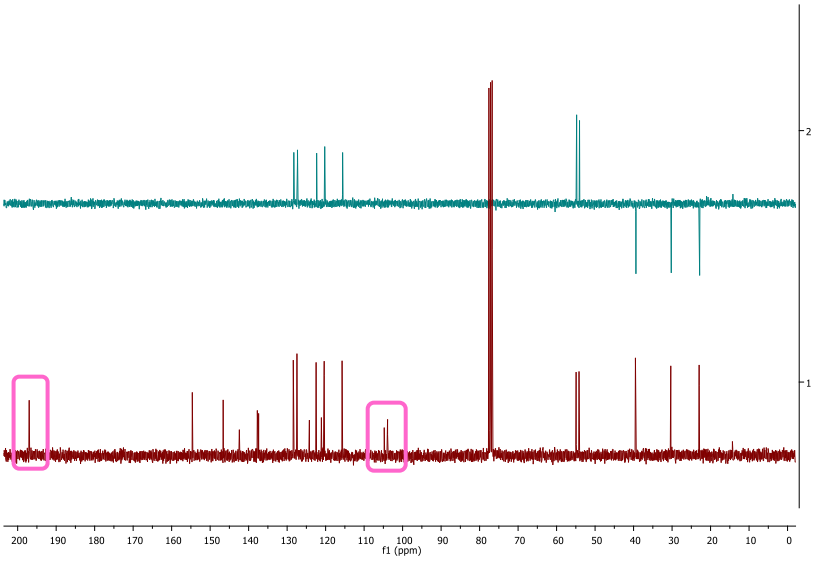


*Figure 2.41. DEPT 135 experiment with ^{13}C-NMR of endoperoxide **X***

The presence of molecular ion ([M+H]$^+$) at 355.1168 amu determined by High-Resolution Mass Spectroscopy is also agreed with the molecular weight calculated for 6-hydroxy-7,12-dimethoxy-3,4,7,12-tetrahydro-7,12-epidioxytetraphen-1(2*H*)-one (**199**), 355.1176 amu.

2.2.5. Biological activity of (7*S**,11b*R**,13a*S**)-7-hydroperoxy-7,11b-dimethoxy-3,4,7,11b-tetrahydro-1H-tetrapheno[12-cd][1,2]dioxol-6(2*H*)-one (197)

Taking into account that reactive oxygen species (ROS) such as peroxides can be exploited for therapeutic benefits against cancer,[91] the cytotoxicity of the double peroxide **197** was tested in selected cancer cell lines. Similar to our synthetized compound, other angucyclinones,[12] have demonstrated antitumoral activity, producing apoptosis in various cancer cell lines (doxorubicin, MDA-MB-231, A549, and HT29). The biological evaluation of *bis*-peroxide **197** was carried out by Dr. Silvia Lucena and Prof. Ángeles Juarranz at the Departamento de Biología, Facultad de Ciencias, Universidad Autónoma de Madrid.

The new angucyclinone-type derivative **197** was tested in three different established human cell lines, larynx Hep-2, breast MDA-MB and cervix HeLa cells. First, we evaluated the cytotoxicity of double peroxide **197** in these cell lines by using two different conditions of treatment: long-incubation period (24 hours) with a low concentration of drug (10^{-8} M) and a short-term incubation (5 hours) with higher drug concentration (10^{-7} M, $5x10^{-7}$ M, $2.5x10^{-7}$ M and 10^{-6} M). The final concentration of acetone in the culture medium was always lower than 5%.

When treating cells with 10^{-8} M for 24 h, only Hep-2 and MDA-MB lines significantly decreased their survival compared with the untreated control cells (*Figure 2.39*). The most sensible line was MDA-MB, with a percentage of 25% of lethality. When incubating cells for 5 h, the survival rate was dependent on the drug concentration. No effects were seen for DMEM / acetone 5%. The lower concentration of the drug tested (10^{-7} M) did not cause a relevant effect in any of the lines; the induced toxicity was lower than 10%. However, the rest of the tested concentrations were highly effective, inducing more than 90% of toxicity for all cell lines, with the exception of Hep-2 cells treated with concentrations of $2.5x10^{-7}$ M in which only 70% of cell death

[91] a) M. H. Raza, S. Siraj, A. Arshad, U. Waheed, F. Aldakheel, S. Alduraywish, M. Arshad, *J Cancer Res Clin. Oncol*. **2017**, *143*, 1789-1809; b) C. Gorrini, I. S. Harris, T. W. Mak, *Nat. Rev. Drug Discov.* **2013**, *12*, 931-947; c) F. Lombó, M. S. Abdelfattah, A. F. Braña, J. A. Salas, J. Rohr, C. Méndez, *Chembiochem*. **2009**, *10,* 296-303.

was detected. Therefore, with long-term incubation, the most sensitive cell line in terms of survival was MDA-MB and Hep-2 was the most resistant (*Figure 2.40a* and *2.40b*).

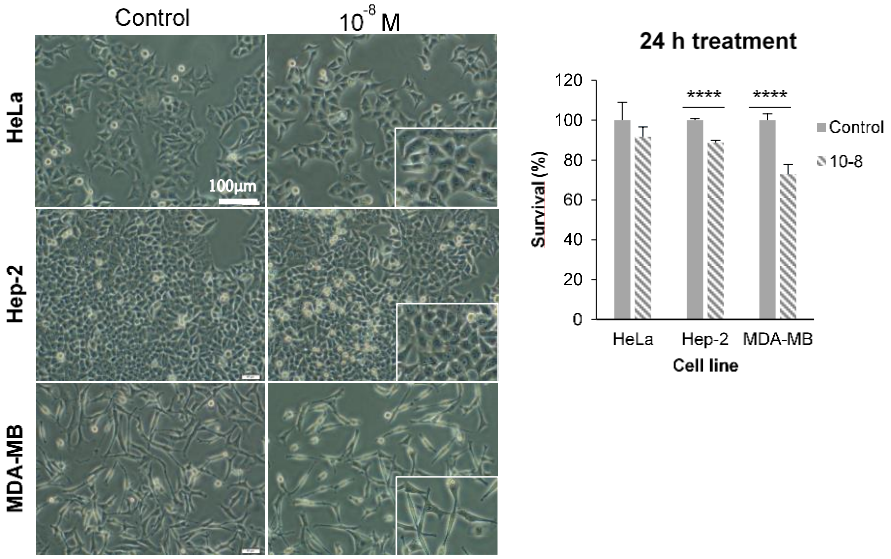


*Figure 2.42. Effect of the peroxide **197** after a long-incubation period with a low concentration of drug. The morphology and survival rate of HeLa, Hep-2 and MDA-MB cells was analysed by phase contrast microscopy and MTT, respectively, after 24 h of treatment with 10^{-8} M in acetone of **197***

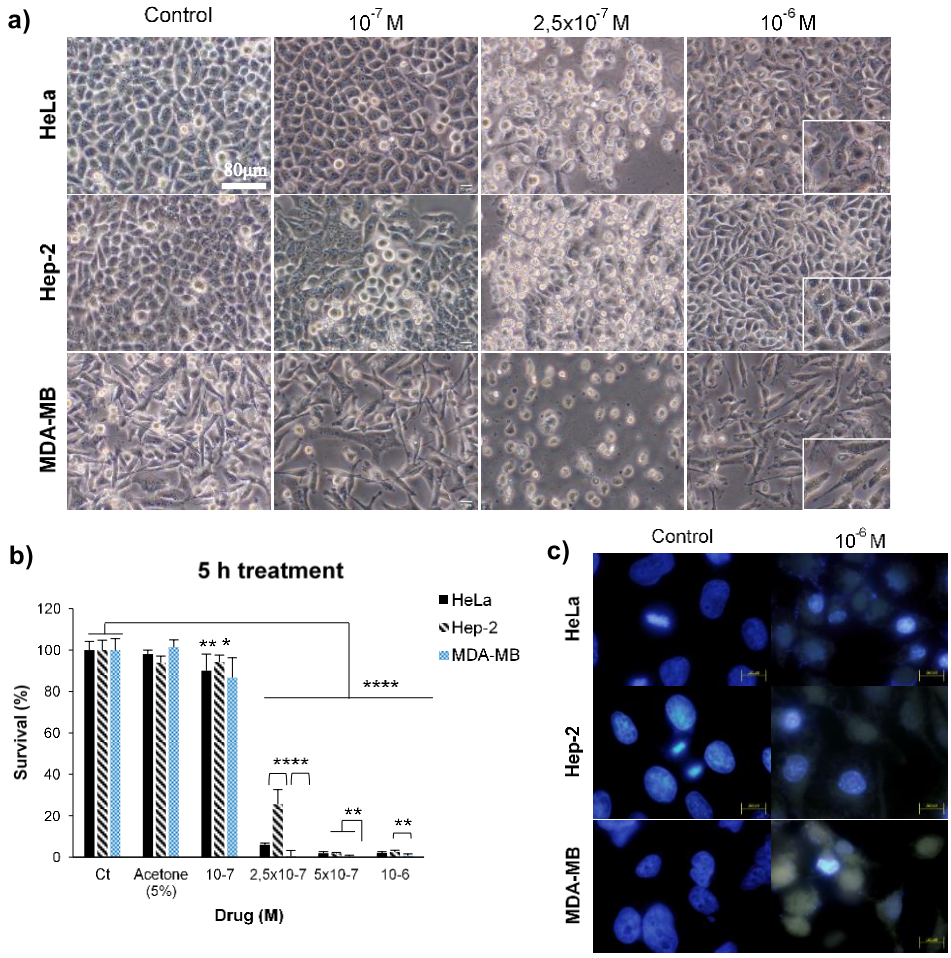


*Figure 2.43. Effect of the peroxide **197** after a short-incubation period with increasing concentration of drug.*

This drug demonstrates an extremely high effectivity at short-term treatment from a concentration of $2.5x10^{-7}$ M, being even more effective (in terms of lethality) than Doxorubicin (Doxo), a comparative compound whose use is extended in patients with cancer. Doxo presented an IC_{50} of $5x10^{-7}$ M in two mammary cancer cell lines (MDA-MB-231 and MCF-7)[92] and it was even higher in other studies, presenting an IC_{50} of $1.84x10^{-5}$ M in MDA-MB-231,[93] between 9.16 $x10^{-6}$ M and $5.46x10^{-6}$ M for Hep-2, HeLa and MCF-7 cell lines.[94] Comparing the efficiency of Doxo with four angucyclinones of new synthesis employed for the treatment of the breast MCF-7 cell line, again, our bisperoxide **197** was more lethal at lower concentrations, presenting these four compounds an IC_{50} between $3.4x10^{-7}$ M and $51.3x10^{-7}$ M.[95]

[92] L. Sapio, L. Sorvillo, M. Illiano, E. Chiosi, A. Spina, S. Naviglio, *Molecules*. **2015**, *20*, 15910-15928.
[93] Z. L. Li, C. Chen, Y. C. Yang, T. Wang, X. Yang, S. Yang, C. Liu, *Int. J. Clin. Exp. Pathol.* **2015**, *8*, 4378-4387.
[94] M. M. Mohammed, N. A. Ibrahim, N. E. Awad, A. A. Matloub, A. G. Mohamed-Ali, E. E. Barakat, A. E. Mohamed, P.L. Colla, *Nat Prod Res*. **2012**, *26*, 1565-1575.
[95] C. Boonlarppradab, C. Suriyachadkun, P. Rachtawee, W. Choowong, *J. Antibiot*. **2013**, *66*, 305-309.

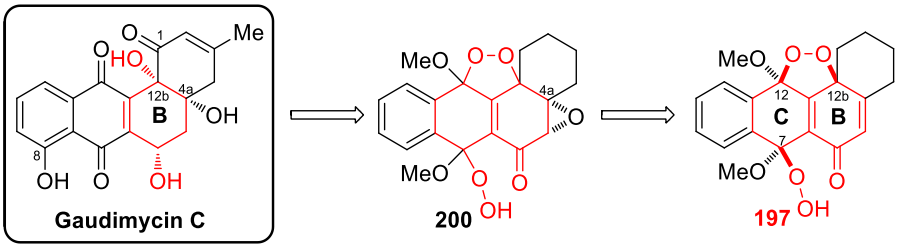
We have also evaluated the changes induced in the cell and nuclear morphology after treatments Control HeLa and Hep-2 cells present a polygonal morphology, typical of keratinocytes, while the features of the MDA-MB cells were more spindled. These morphologies were maintained in cultures treated with low drug concentrations and in control acetone (5%). In incubations with drug concentrations of $2.5x10^{-7}$ M, cells become rounded and detach from the substrate. Conversely, concentrations of 10^{-6} M, cells remained attached to the well but exhibited an irregular shape. In this case, the 3D structure of the cells seemed to be lost.

Nuclear morphology was evaluated 5 hours after treatment with the highest concentrations ($5x10^{-7}$ M and 10^{-6} M). Whereas control cells showed rounded nuclei and brilliant blue fluorescent chromatin (after DAPI staining), treated cultures showed nuclei with chromatin irregularly distributed forming highly fluorescent discrete aggregates or with a very low or null blue fluorescence; thus indicating a loss of the DNA content of the nucleus (*Figure 2.40c*).

2.2.6. Miscellaneous

2.2.6.1. Study of the reactivity of bisperoxy bisketal 197

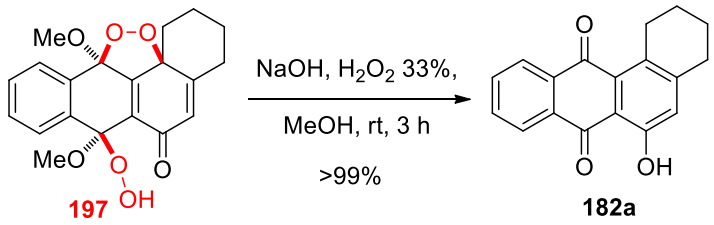
The interesting structural characteristics of double peroxide **197** led us to consider its behavior as a reactive oxygen species (ROS) that could be used for further reaction in a controlled manner. Moreover, transformation of the double peroxide into oxygenated angucyclinone analogues was the ultimate objective of this work. For instance, en route to the final trihydroxylated core of gaudimycin C, following the model studies previously reported by us on tricyclic models (*Scheme 2.69*).[59]



Scheme 2.78. Retrosynthesis analysis en route to gaudimycin C

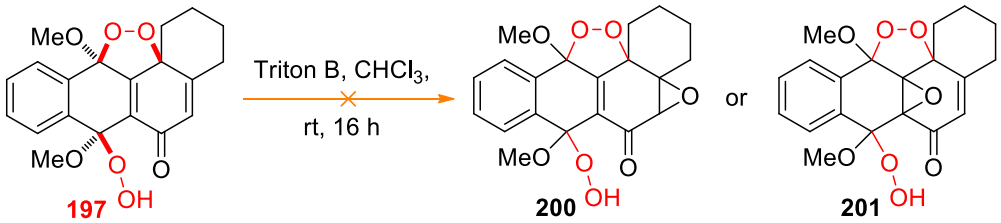
Initially, we decided to evaluate the possible epoxidation of the enone present in the double peroxide **197**. As shown in *Scheme 2.70*, we treated the bisperoxy bisketal **197** with hydrogen peroxide and sodium hydroxide in MeOH.[59] Bisperoxy bisketal **197** reacted under these

conditions at rt, giving in 3 hours 6-hydroxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (**182a**) in quantitative yield.



*Scheme 2.79. Reaction of double peroxide **197** under epoxidation conditions (H_2O_2 and NaOH)*

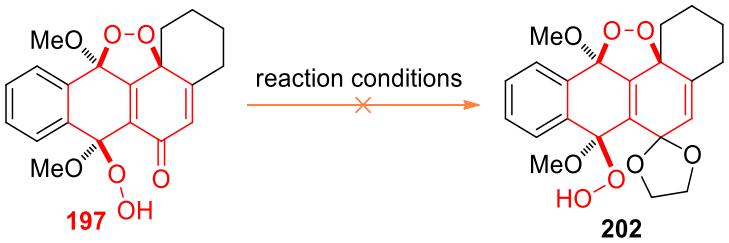
We also treated (7*S**,11b*R**,13a*S**)-7-hydroperoxy-7,11b-dimethoxy-3,4,7,11b-tetrahydro-1H-tetrapheno[12-cd][1,2]dioxol-6(2*H*)-one (**197**) with benzyltrimethylammonium hydroxide (Triton B) to epoxide the enone motif Δ 4a-5 or Δ 6a-12a.[96] Nevertheless, the bisperoxy bisketal **197** remained unchanged after 16 hours of reaction (*Scheme 2.71*).



*Scheme 2.80. Reaction of bisperoxide bisketal **197** with Triton B*

Unfortunately, no traces of the expected peroxide **200** were detected in any case. With the aim of protecting the carbonyl group of the enone of the double peroxide **197** to avoid such evolution, we treated compound **197** with ethylene glycol under the conditions indicated in *Table 2.6*. Different reactions conditions were applied on bisperoxy bisketal **197** under different catalytic systems: *para*-toluenesulfonic acid (PTSA), cerium trifluoromethanesulfonate [$Ce(OTf)_3$] / triisopropyl orthoformate [$HC(O^iPr)_3$] and boron trifluoride etherate ($BF_3{\cdot}OEt_2$). The classical reaction conditions to protect ketone as acetal (PTSA, $HO(CH_2)_2OH$, toluene, reflux) give a complex mixture after 16 hours (*Table 2.6*, *entry 1*).[97] Under mild condition reactions using $HO(CH_2)_2OH$, $Ce(OTf)_3$ and $HC(O^iPr)_3$ in hexane also afforded a complex mixture after 24 hours (*Table 2.6*, *entry 2*).[98] Finally, we tried to protect the ketone at C_6 with $BF_3{\cdot}OEt_2$ and ethylene glycol in THF, but a complex mixture was also obtained after 16 hours (*Table 2.6*, *entry 3*).

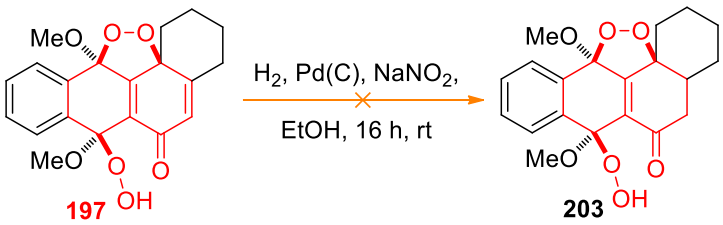
[96] S. Barradas, A. Urbano, M. C. Carreño, *Chem. Eur. J.* **2009**, *15*, 9286-9289.
[97] S. Danishefsky, K. Vaughan, R. Gadwood, K. Tsuzuki, *J. Am. Chem. Soc.* **1981**, *103*, 4136-4141.
[98] F. Ono, H. Takenaka, T. Fujikawa, M. Mori, T. Sato, *Synthesis* **2009**, *8*, 1318-1322.



entry	reaction conditions
1	PTSA, ethylene glycol, toluene, reflux, 16 h
2	$Ce(OTf)_3$, $HC(O^iPr)_3$, ethylene glycol, hexane , rt, 24 h
3	$BF_3{\cdot}OEt_2$, ethylene glycol, THF, rt, 16 h

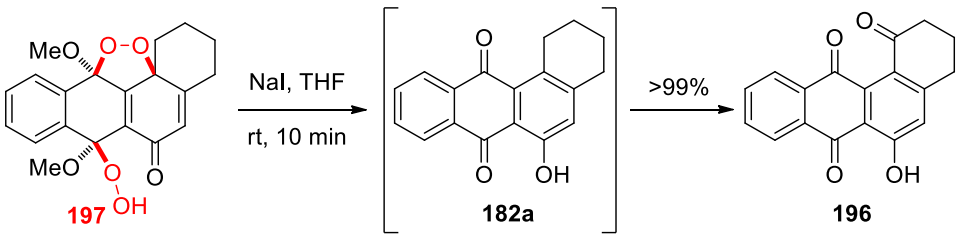
Table 2.6.- Experimental conditions of protection of carbonyl group

We also tried to reduce the conjugated double bond with hydrogen gas in the presence of sodium nitrite ($NaNO_2$).[99] However, a complex mixture was obtained after 16 hours (*Scheme 2.72*)



*Scheme 2.81. Reaction of bisperoxy bisketal **197** with hydrogen gas under catalytic conditions*

Finally, when we applied the reductive conditions by employing NaI in THF,[75] the double peroxide **197** evolved into 6-hydroxy-3,4-dihydrotetraphene-1,7,12(2H)-trione (**196**) in a quantitative manner (*Scheme 2.73*). In a first step, bisperoxide **197** could transform into quinone **182a** and, then, C_1 position could be oxidized in a similar way to that described by Krohn, giving quinone **196**.



*Scheme 2.82. Reduction reaction of double peroxide **197** using NaI*

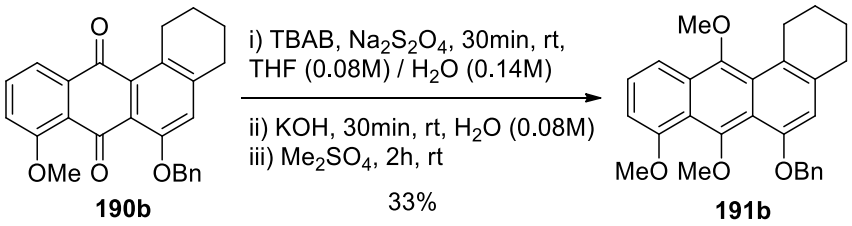
[99] A. Suksamrarn, T. Tanachatchairatana, C. Sirigarn, *Tetrahedron* **2002**, *58*, 6033-6037

In view of the obtained results in these experiments, we could conclude that bisperoxy bisketal **197** could act as an oxygen storage.

2.2.6.2. Optimization experiments for the reduction / protection process of 6-(benzyloxy)-8-methoxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (190b)

2.2.6.2.1. Reduction / methylation process of quinone moiety.

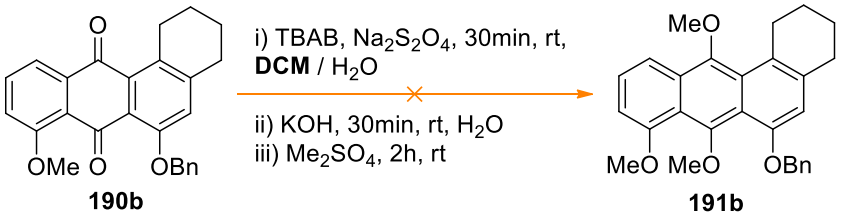
As we previously mentioned in *subchapter 2.2.2.2*, the low yield obtained in the reduction / methylation process of the 6-(benzyloxy)-8-methoxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (**190b**), displayed is *Scheme 2.42*, was a drawback in the synthetic sequence en route to the synthesis of 7,8,12-trimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (**191b**).



*Scheme 2.42. Synthesis of 6-(benzyloxy)-7,8,12-trimethoxy-1,2,3,4-tetrahydrotetraphene (**191b**)*

To improve the yield of this step, we carried out different experiments. Considering that the low conversion could be due to a poor solubility of 6-(benzyloxy)-8-methoxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (**190b**) in THF, the reaction was carried out in DCM instead of THF (*Table 2.7*).[100] Using a 0.08M solution of DCM, no evolution was observed when 6-benzyloxy derivative Xa was sequentially treated with sodium dithionite, potassium hydroxide and dimethyl sulfate, in the presence of TBAB (*Table 2.7, entry 1*). 6-(Benzyloxy)-8-methoxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (**190b**) also remained unchanged when the concentration of DCM solution was increased up to 0.32M (*Table 2.7, entry 2*).

[100] T. Iwanaga, K. Miyamoto, K. Tahara, K. Inukai, S. Okuhata, Y. Tobe, S. Toyota, *Chem. Asian J.* **2012**, *7*, 935-943.

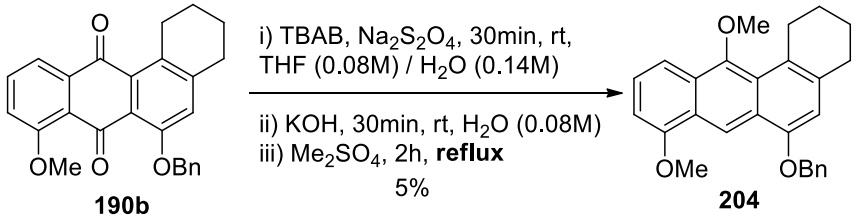


entry	first Step (i)	conversion (%)[a]
1	DCM (0.08M)/ H_2O	0
2	DCM (0.32M)/ H_2O	0

a: Determined by ^{1}H-NMR of the crude mixture.

Table 2.7 .- Reduction conditions in a two-phase transfer reaction using DCM

In view of these results, we thought of using a solvent miscible with water to have a homogeneous reaction mixture because the TBAB had not facilitated the process acting as a phase transfer catalyst. We thus went to back to THF. After stirring a mixture of 6-(Benzyloxy)-8-methoxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (**190b**) and sodium dithionite in THF (0.08M) and water (0.14M) 30 min at rt, potassium hydroxide and dimethyl sulfate were added and the mixture was then refluxed during 2 hours. Under these conditions a complex reaction mixture resulted from which 6-(benzyloxy)-8,12-dimethoxy-1,2,3,4-tetrahydrotetraphene (**204**) could be isolated in low 5% yield (*Scheme 2.74*). Under these conditions, the desired product **191b** was not detected by ^{1}H-NMR of the crude.



Scheme 2.83. Reductive methylation at reflux condition

The structure of 6-(benzyloxy)-8,12-dimethoxy-1,2,3,4-tetrahydrotetraphene (**204**) was determined on the base of its spectroscopic data of ^{1}H-NMR, ^{13}C-NMR and DEPT and NOESY experiments. The most significant ^{1}H-NMR data for the structural assignment correspond to the presence of a singlet at 9.12 ppm which was assigned to proton at C_7 (H_7). The NOESY experiment depicted in *Figure 2.43* allowed to stablish the position of H_7 showing correlations with the protons of -CH_2- at C_1 (δ: 3.48 ppm) and the protons of methoxy group appearing at δ: 3.90 ppm, assigned to the C_8 substituent.

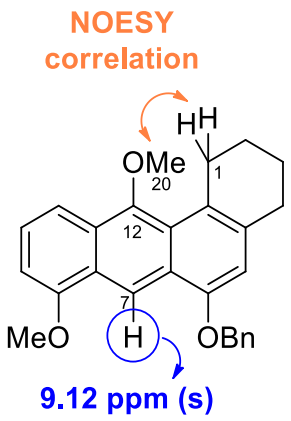


Figure 2.44. NOESY correlation

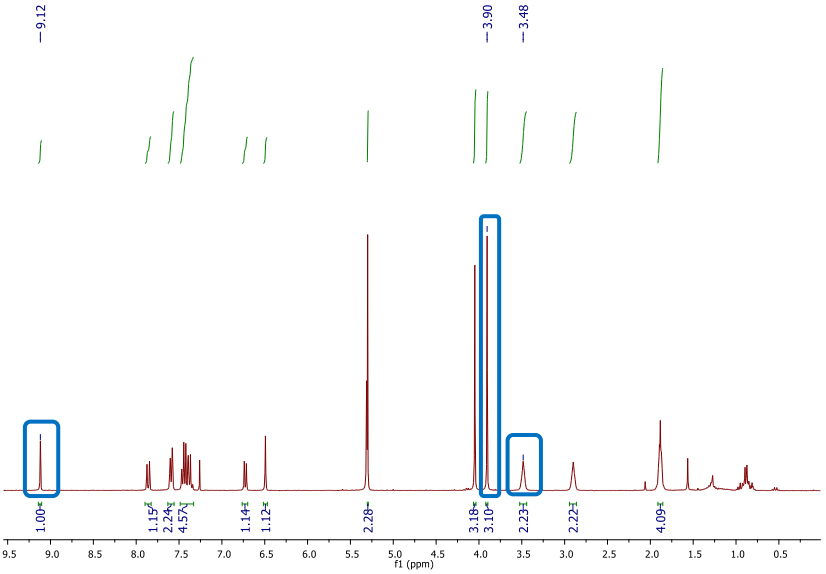


Figure 2.45. ^{1}H-NMR spectrum

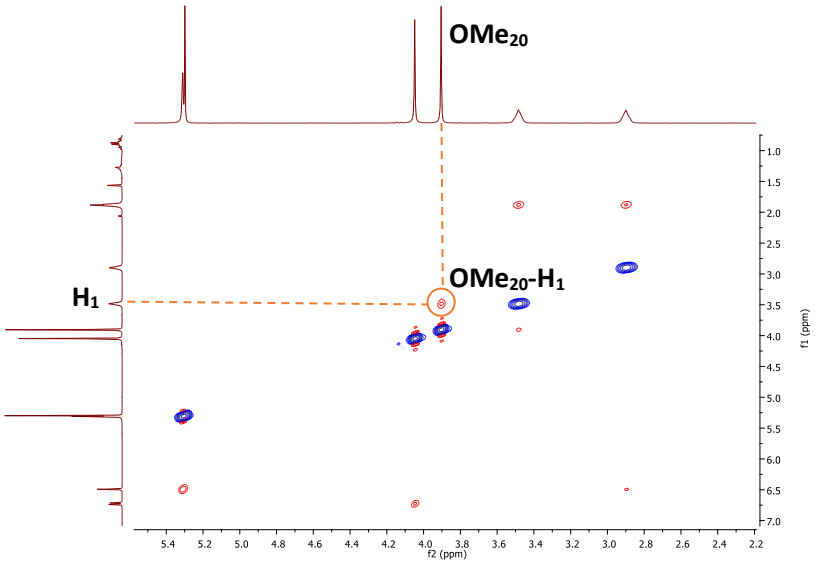
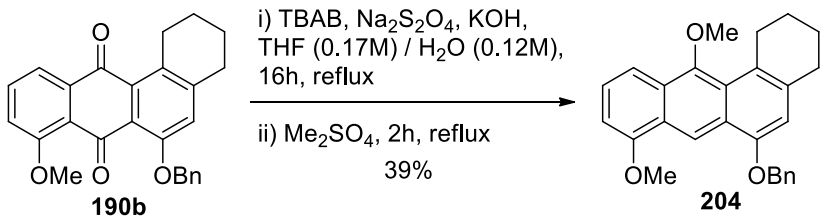


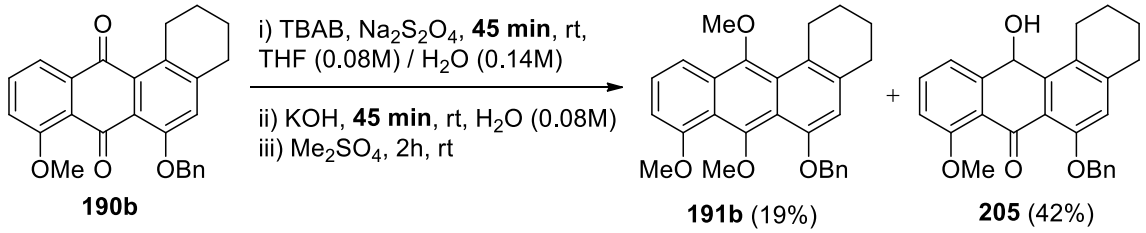
Figure 2.46. NOESY experiment

Taking into account these results, we could improve the yield of 6-(benzyloxy)-8,12-dimethoxy-1,2,3,4-tetrahydrotetraphene (**204**) in 39% yield, by increasing the reaction time of the first reaction step to 16 hours. Thus, the treatment of 6-(benzyloxy)-8-methoxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (**190b**) with sodium dithionite and potassium hydroxide in a solution of THF (0.17M) and water (0.12M) for 16 hours at reflux, followed by addition of dimethyl sulfate for 2 hours at reflux, gave rise 6-benziloxy-7,12-dimethoxy derivative **204** (*Scheme 2.75*).



*Scheme 2.84. Synthesis of 6-(benzyloxy)-8,12-dimethoxy-1,2,3,4-tetrahydrotetraphene (**204**)*

Increasing the reaction time from 30 min to 45 min in the first two steps of the sequential process, the starting material was not observed in the ^{1}H-NMR of the crude, but the target structure 6-(benzyloxy)-7,8,12-trimethoxy-1,2,3,4-tetrahydrotetraphene (**191b**) was obtained in low 19% yield. The major product obtained under these conditions was 6-(benzyloxy)-12-hydroxy-8-methoxy-1,2,3,4-tetrahydrotetraphen-7(12H)-one (**205**), resulting from a partial reduction of the quinone in 42% yield (*Scheme 2.76*).



Scheme 2.85. Reductive methylation increasing the reaction times

The structure of 6-(benzyloxy)-12-hydroxy-8-methoxy-1,2,3,4-tetrahydrotetraphen-7(12H)-one (**205**) was determined on the base of its spectroscopic data of ^{1}H-NMR, ^{13}C-NMR and DEPT and NOESY experiments. The most significant ^{13}C-NMR data for the structural assignment correspond to the signal for the carbonyl group at C_7 at 187.1 ppm and the carbon joined to the hydroxyl group at C_{12} at 56.1 ppm (*Figures 2.44* and *2.45*). And the most important data for ^{1}H-RMN are the doublets at δ: 6.43 ppm and 3.08 ppm correspond to the hydroxyl group or the proton (H_{12}) at C_{12}. Also, the NOESY experiment showed a correlation between the proton of the hydroxyl group or the proton H_{12} [δ: 3.08 ppm (d, 2H)] with the protons at C_1 of the ring A δ: 3.44 – 3.31 (m, 1H) (*Figures 2.46* and *2.47*).

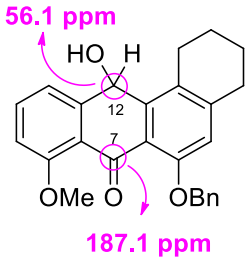


Figure 2.47. Characteristic signals at ^{13}C-NMR

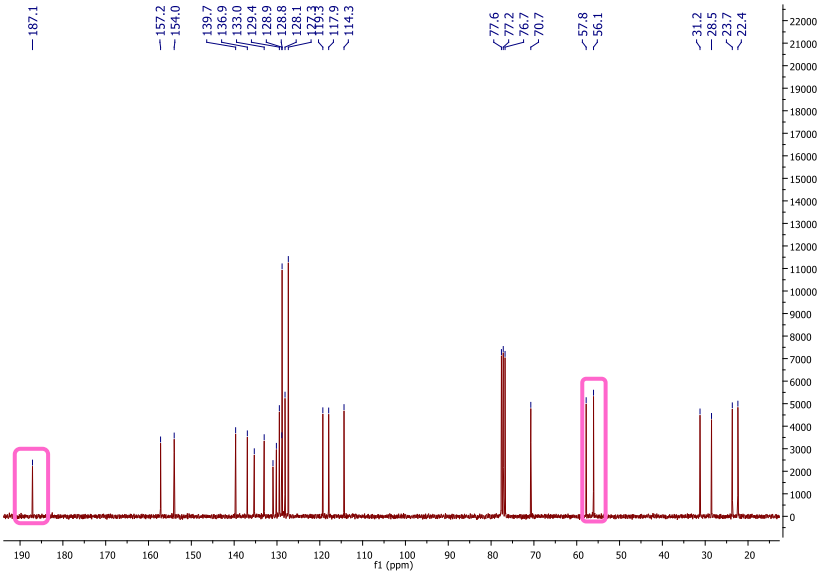


Figure 2.48. ^{13}C-NMR spectrum

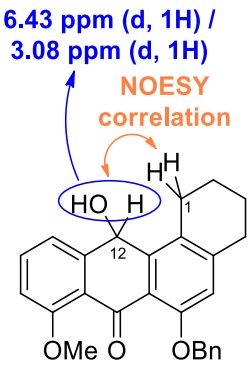


Figure 2.49. NOESY correlation

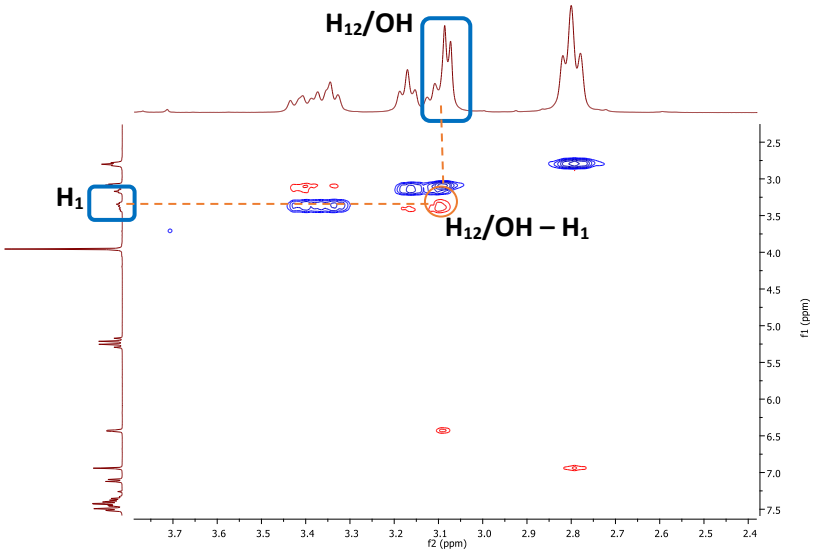
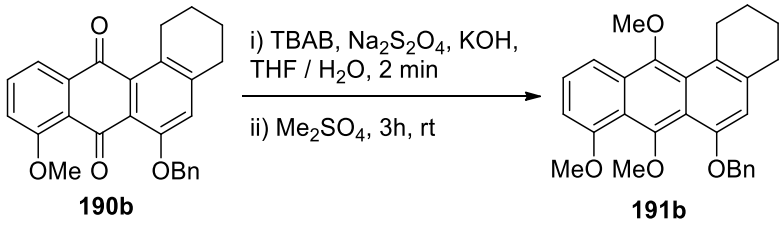


Figure 2.50. NOESY experiment

To minimize the formation of this undesired byproduct **205**, we carried out the reduction/methylation reaction in one-pot, adding all the reagents at the same time. We also studied the effect that concentration could have in this process (*Table 2.8*). Using the same reaction conditions described in the literature (a solution of 0.08M of THF and 0.05 of water)66, but realizing the addition in one-pot, 6-benzyloxy-7,8,12-trimethoxy derivative **191b** was isolated in 16% yield (*Table 2.8, entry 1*). The result was improved increasing the concentration of the THF solution to 0.17M, obtaining 6-benzyloxy-7,8,12-trimethoxy derivative **191b** in 54% yield (*Table 2.8, entry 2*). The yield of final product **191b** decreased when the concentration decreased to

0.25M (*Table 2.8, entry 4*) or quinone motif of **190b** did not react at higher concentrations (*Table 2.8, entry 5*). Finally, the best result with a total conversion was obtained in one-pot reaction as indicated in *Table 2.8, entry 3* (stir all the reagents together 3 hours at rt) with a concentration of 0.17M of THF and 0.12M of water, affording the desired 6-(benzyloxy)-7,8,12-trimethoxy-1,2,3,4-tetrahydrotetraphene (**191b**) in 66% yield.



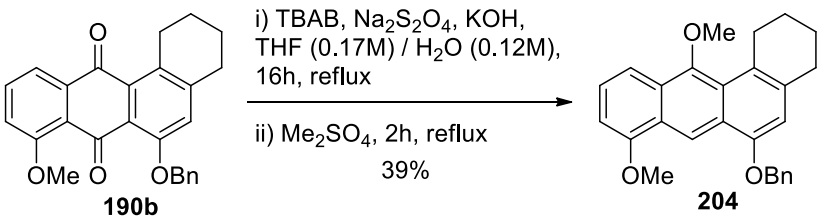
entry	Solvents Concentration	Yield (%)[a]
1	THF (0.08M) / H_2O (0.14M)	16
2	THF (0.17M) / H_2O (0.14M)	54
3	THF (0.17M) / H_2O (0.12M)	66
4	THF (0.25M) / H_2O (0.14M)	30
5	THF (0.5M) / H_2O (0.5M)	0

a: Isolated yield.

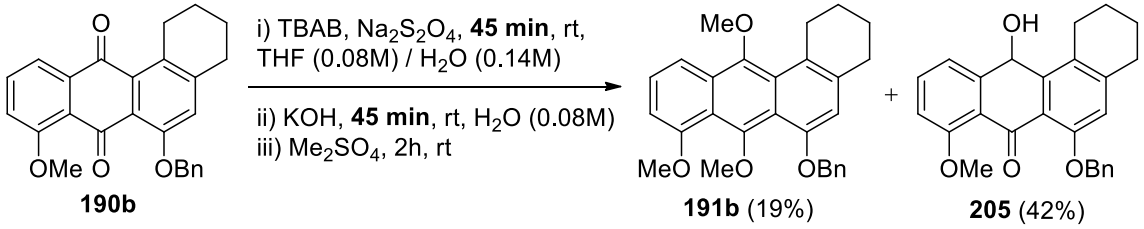
Table 2.8 .- Checking different concentration reaction in the reductive methylation process

2.2.6.2.2. Study of the partial reduction of the quinone motif in tetracyclic derivatives.

In order to understand the partial reduction of the quinone moiety, we had observed in the formation of 6-(benzyloxy)-12-hydroxy-8-methoxy-1,2,3,4-tetrahydrotetraphen-7(12H)-one (**205**) or 6-(benzyloxy)-8,12-dimethoxy-1,2,3,4-tetrahydrotetraphene (**204**), whose synthesis was described in *Scheme 2.75* and *Scheme 2.76*., we performed a searching in the literature to find similar reactions.

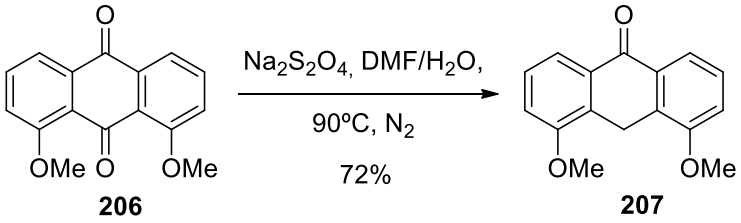


*Scheme 2.75. Synthesis of 6-(benzyloxy)-8,12-dimethoxy-1,2,3,4-tetrahydrotetraphene (**204**)*



Scheme 2.76. Reductive methylation increasing the reaction times

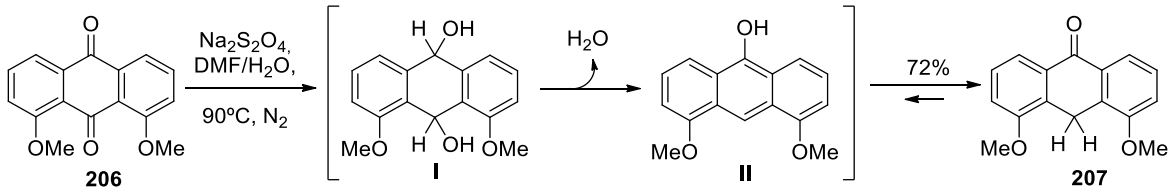
We found some publications where the reduction of 1,8-disubstituted 9,10-anthracenediones, using different reduction conditions, led to the corresponding anthracenone**s**. Thus, the reduction of 1,8-dimethoxyanthracene-9,10-dione (**206**), carried out by Müller et al., occurred at the keto group situated in relative 1,3-position with respect to the methoxyl groups, using sodium dithionite as reducing agent in a mixture of DMF / water at 90 ºC under inert atmosphere. They isolated 4,5-dimethoxyanthracen-9(10*H*)-one (**207**) in 72% yield (*Scheme 2.77*).[101]



*Scheme 2.86. Reduction of 1,8-dimethoxyanthracene-9,10-dione (**206**) realized by Müller and coworkers*

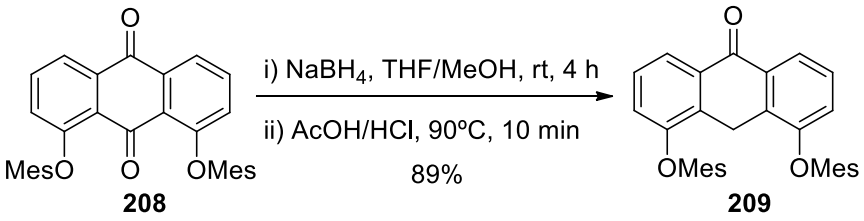
The authors suggested a possible mechanism for this reduction of one of the keto groups, that could start with the formation of the corresponding 9,10-dihydro-9,10-dihydroxyanthracene **I**, evolving into 9-hydroxyanthracene **II** by loss of water and, finally, by a tautomerization, 4,5-dimethoxyanthracen-9(10H)-one **207** was formed (*Scheme 2.78*).[101]

[101] H. Prinz, W. Wiegrebe, K. Müller, *J. Org. Chem.* **1996**, *61*, 2853-2856.



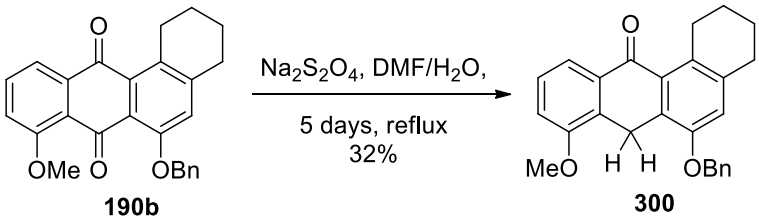
Scheme 2.87. Reduction mechanism suggested by Müller and coworkers

Other reducing agent reported in the literature was the sodium borohydride, used by Osuka et al. to reduce 1,8-*bis*(mesityloxy)anthracene-9,10-dione (**208**) to 4,5-*bis*(mesityloxy)anthracen-9(10*H*)-one (**209**) in 89% yield (*Scheme 2.79*).[102]



*Scheme 2.88. Partial reduction of 1,8-bis(mesityloxy)anthracene-9,10-dione (**208**) with sodium borohydride by Osuka et al.*

To check if our substrate could behave in a similar way, we decided to apply these reaction conditions on 6-(benzyloxy)-8-methoxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (**190b**). Thus, we treated derivative **190b** with sodium dithionite in DMF/water at reflux.[101]. After 5 days, we could isolate 6-(benzyloxy)-8-methoxy-1,2,3,4-tetrahydrotetraphen-12(7*H*)-one (**300**), in 32% yield, the expected final product coming from the partial quinone reduction (*Scheme 2.80*).



*Scheme 2.89. Reduction of 6-(benzyloxy)-8-methoxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (**190b**) with sodium dithionite*

The structure of 6-(benzyloxy)-8-methoxy-1,2,3,4-tetrahydrotetraphen-12(7H)-one (**300**) was determined on the base of its spectroscopic data of ^{1}H-NMR, ^{13}C-NMR and DEPT and NOESY experiments. The most significant ^{1}H-NMR and ^{13}C-NMR data for the structural assignment correspond to the singlet at 4.12 ppm, assigned to the protons at C_7 and the signal at 187.3 ppm

[102] K. Naoda, H. Mori, N. Aratani, B. S. Lee, D. Kim, A. Osuka, *Angew. Chem. Int. Ed.* **2012**, *51*, 9856-9859.

for the carbonyl group at C_{12}. With the NOESY experiment, we could confirm the substitution of C_7, due to the correlation between the protons H_7 with those of the methyl group (Me_{19}) at 3.94 ppm (*Figures 2.48* and *2.49*).

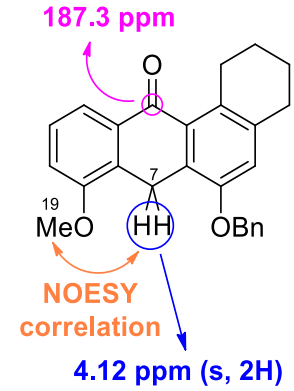


Figure 2.51. Characteristic signals and NOESY correlations

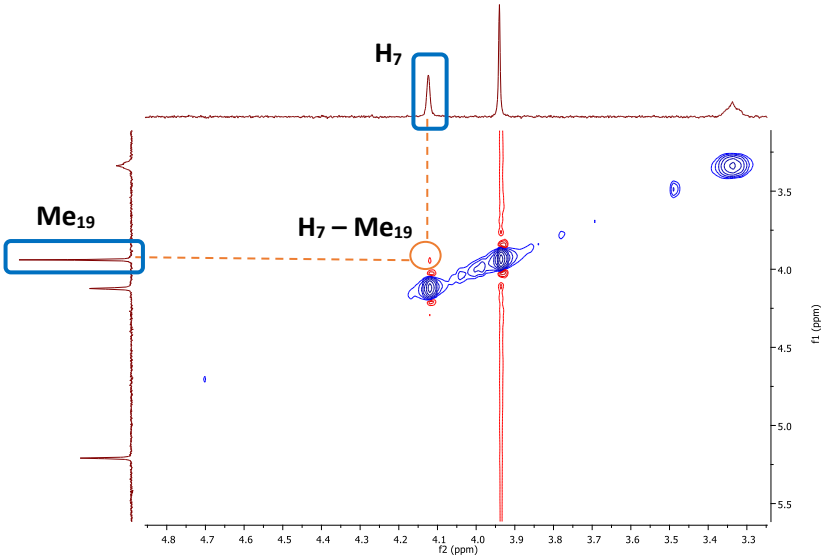
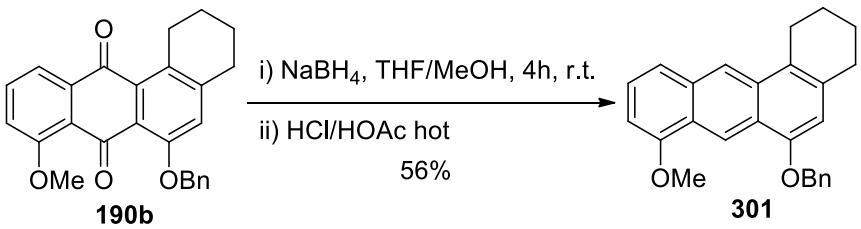


Figure 2.52. NOESY experiment

On the other hand, the product of complete reduction of the quinone ring of **190b** was obtained, with a moderate yield (56%), when sodium borohydride was used as reducing agent in a mixture of THF and MeOH for 4 hours at rt, followed by addition of a hot mixture of HCl 37% and acetic acid (*Scheme 2.81*).[102]



*Scheme 2.90. Reduction of 6-(benzyloxy)-8-methoxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (**190b**) with sodium borohydride*

The structure of 6-(benzyloxy)-8-methoxy-1,2,3,4-tetrahydrotetraphene (**301**) was determined on the base of its spectroscopic data of ^{1}H-NMR, ^{13}C-NMR and DEPT. The most significant ^{1}H-NMR data for the structural assignment correspond to the singlets at δ: 9.28 ppm and 8.37 ppm, assigned to the protons (H_7 and H_{12}) at C_7 and C_{12} (*Figures 2.50* and *2.51*).

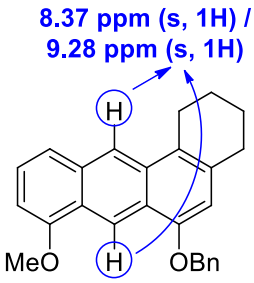


Figure 2.53. Characteristic signals at ^{1}H-NMR

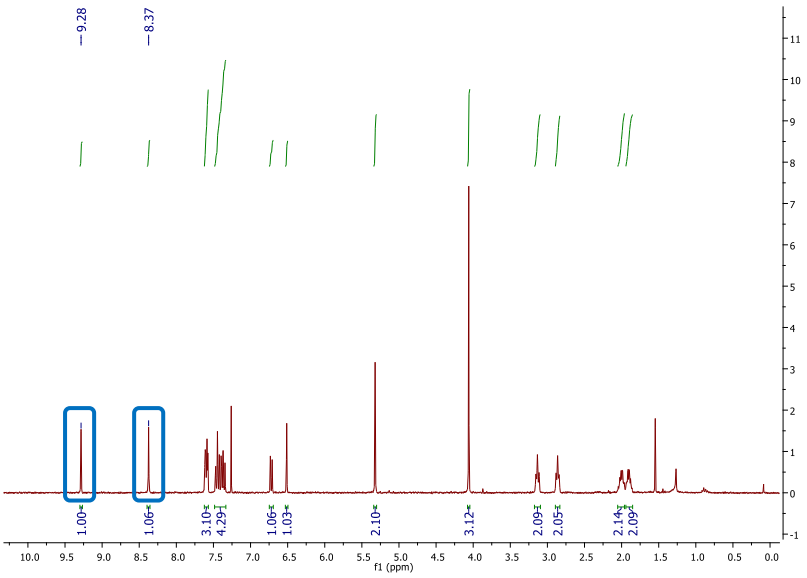
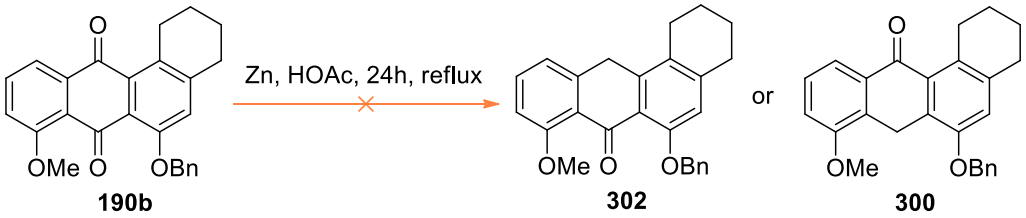


Figure 2.54. ^{1}H-NMR spectrum

We also checked zinc, another reagent reported for reducing quinones.[103] However, after treatment of **190b** with zinc in acetic acid at reflux, 6-(benzyloxy)-8-methoxy-1,2,3,4-tetrahydrotetraphene-7,12-dione(**190b**) remained unchanged (*Scheme 2.82*).

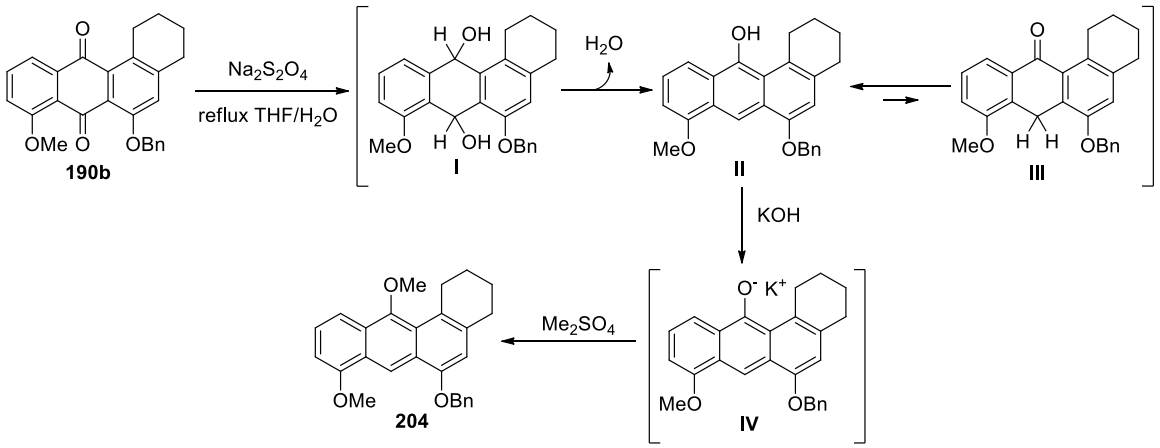


*Scheme 2.91. Attempt to reduce 6-(benzyloxy)-8-methoxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (**190b**) with zinc*

Taking into account the work by Müller and coworkers,[101] we could suggest a similar mechanistic explanation for the formation of 6-(benzyloxy)-8,12-dimethoxy-1,2,3,4-tetrahydrotetraphene (**204**) from 6-(benzyloxy)-8-methoxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (**190b**) (*Scheme 2.83*). First, the treatment of **190b** with sodium dithionite at reflux of THF/water could deliver the corresponding 7,12-dihydro-7,12-dihydroxy tetracyclic derivative **I**, which would undergo a loss of water generating the 12-hydroxy tetracyclic derivative **II**. A keto-enol tautomeric equilibrium between the tetracyclic tautomers ketone **III** and enol **II**, must exist in this intermediate. In this case, the enol form was most favored due to the formation of tetracyclic

[103] a) P. Kissel, F. Weibel, L. Federer, J. Sakamoto, A. D. Schlüter, *Synlett* **2008**, *12*, 1793-1796; b) H. Prinz, T. Burgemeister, W. Wiegrebe, K. Müller**,** *J. Org. Chem.* **1996**, *61*, 2857-2860.

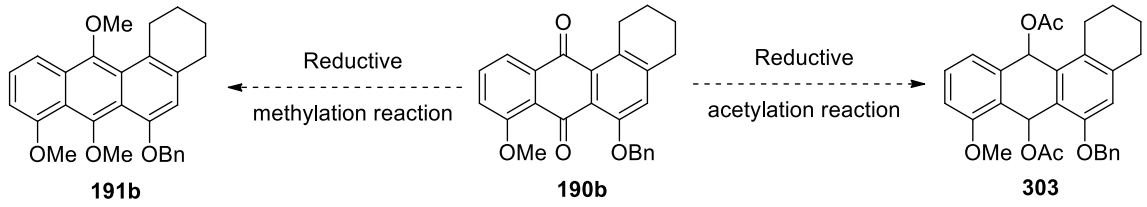
anion **IV** by action of potassium hydroxide. Finally, 6-(benzyloxy)-8,12-dimethoxy-1,2,3,4-tetrahydrotetraphene (**204**) was formed through methylation of anion **IV** with dimethyl sulfate.



*Scheme 2.92. Mechanism of formation of 6-(benzyloxy)-8,12-dimethoxy-1,2,3,4-tetrahydrotetraphene (**204**)*

*2.2.6.2.3. Reduction / acetylation process of the quinone moiety of 6-(benzyloxy)-8-methoxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (**190b**).*

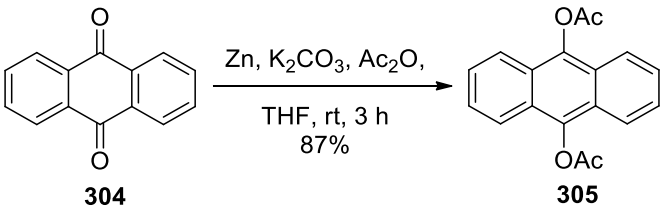
While we optimized the reduction / methylation process of 6-(benzyloxy)-8-methoxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (**190b**) to obtain **191b**, an alternative reduction / acetylation process to access **303** was studied in order to check if the acetate could be a better protecting group of the phenolic -OH and if we could obtain better yields in the reductive acetylation process.



Scheme 2.93. Protection of quinone motif as methoxys or as acetates

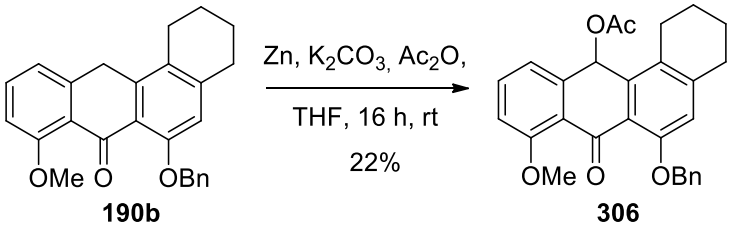
In the literature there were some examples of acetylation conditions for molecules with similar structures, such as the reduction-acetylation of anthracene-9,10-dione (**304**) carried out by Thongpanchang and coworkers (*Scheme 2.85*).[104] This process was carried out using acetic anhydride in the presence of Zn and potassium carbonate to afford anthracene-9,10-diyl diacetate (**305**) in 87 yield.

[104] C. Nerungsi, P. Wanitchang, S. Sahasithiwat, K. Sadorn, T. Thongpanchang, *Tetrahedron Letters* **2010**, *51*, 6392-6395.



*Scheme 2.94. Reductive acetylation reaction of anthracene-9,10-dione (**304**) by Thongpanchang and coworkers*

Using the same reaction conditions (Zn, Ac_2O, THF, K_2CO_3, rt) on derivative **190b**, but increasing the reaction time to 16 hours,[104] 6-(benzyloxy)-8-methoxy-7-oxo-1,2,3,4,7,12-hexahydrotetraphen-12-yl acetate (**306**) could be isolated in 22% yield. When a stronger base was used (sodium hydroxide), a complex mixture of reaction was obtained (*Scheme 2.86*).



*Scheme 2.95. Reductive acetylation of 6-(benzyloxy)-8-methoxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (**190b**) with Ac_2O*

The structure of 6-(benzyloxy)-8-methoxy-7-oxo-1,2,3,4,7,12-hexahydrotetraphen-12-yl acetate (**306**) was determined on the base of its spectroscopic data of ^{1}H-NMR, ^{13}C-NMR and DEPT and NOESY and HMBC experiments. The most significant ^{1}H-NMR and 13C-NMR data for the structural assignment correspond to the singlet at δ: 7.11 ppm, assigned to the proton at C_{12} and the signals 184.9 ppm and 170.8 ppm, correspond to the carbonyl group at C_7 and the carbonyl of the acetate group, respectively. The structure was confirmed on the base of the NOESY and HMBC correlations (*Figures 2.52* and *2.54*). NOESY experiment showed a correlation between the proton H_{12} with the protons at C_1 of A ring (*Figure 2.53*). Also, HMBC experiments displayed a correlation between the proton (H_5) at C_5 with the carbonyl group at C_7 and a correlation between the proton H_{12} with the carbon at C_{11} (*Figure 2.55*).

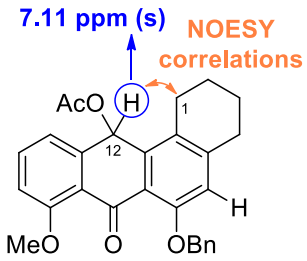


Figure 2.55. NOESY correlation

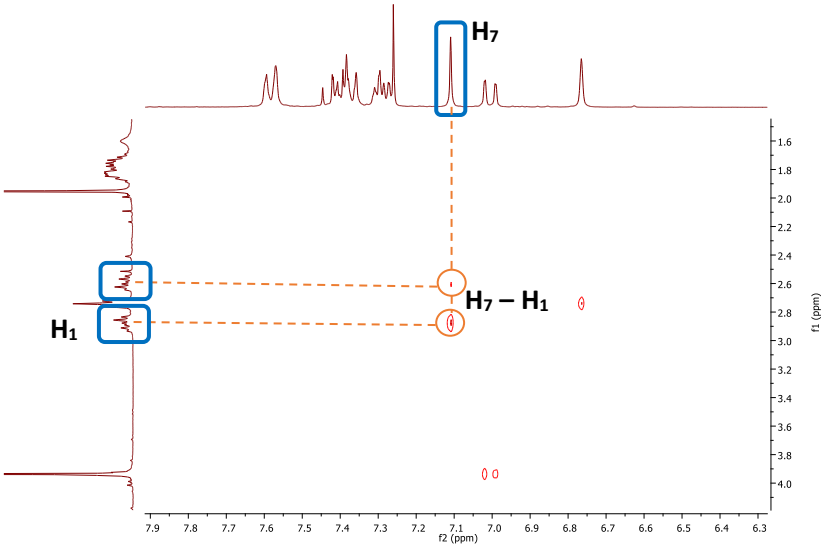


Figure 2.56. NOESY experiment

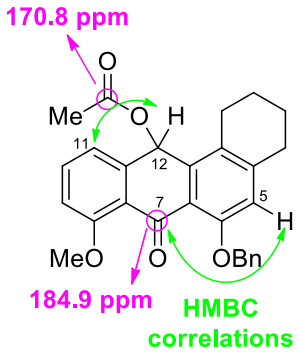


Figure 2.57. HMBC correlations

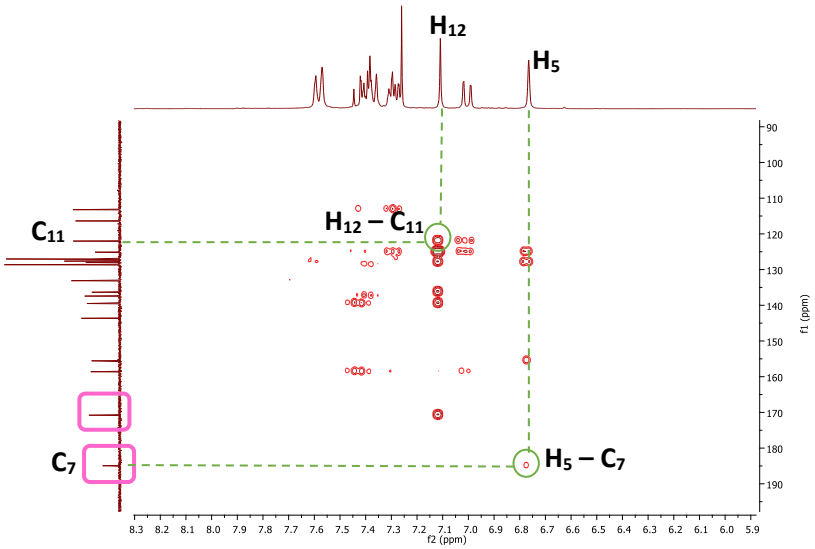
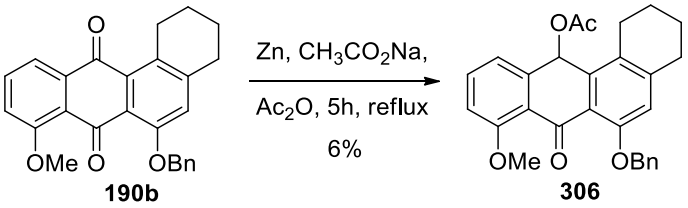


Figure 2.58. HMBC experiment

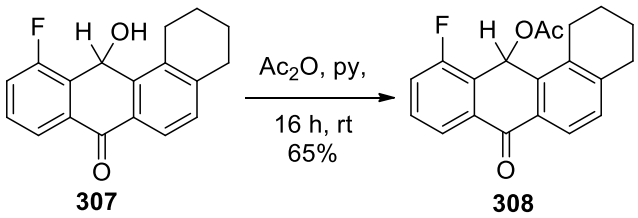
Another method of reductive acetylation, zinc and sodium acetate in a reflux of acetic anhydride was also checked.[105] Under these conditions 6-(benzyloxy)-8-methoxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (**190b**) evolved in a very low conversion and only a 6% of isolated yield into 6-(benzyloxy)-8-methoxy-7-oxo-1,2,3,4,7,12-hexahydrotetraphen-12-yl acetate (**306**) (*Scheme 2.87*).

[105] R. Uddin, P. Hodge, M. S. Chisholm, P. Eustace, *J. Mater. Chem.* **1996**, *6*, 527-532.



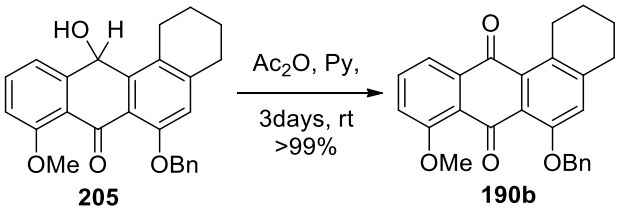
*Scheme 2.96. Reductive acetylation of 6-(benzyloxy)-8-methoxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (**306**) with Ac_2O*

Moreover, we tried to protect the hydroxyl group of 6-(benzyloxy)-12-hydroxy-8-methoxy-1,2,3,4-tetrahydrotetraphen-7(12H)-one (**205**), using a reported procedure for the acetylation of 11-fluoro-12-hydroxy-1,2,3,4-tetrahydrotetraphen-7(12H)-one (**307**) carried out by Witiak and coworkers (*Scheme 2.88*).[106] They protected the hydroxyl group using acetic anhydride in pyridine and afforded 11-fluoro-7-oxo-1,2,3,4,7,12-hexahydrotetraphen-12-yl acetate (**308**) in 65% yield after 16 hours of reaction.



*Scheme 2.97. Acetylation of 11-fluoro-12-hydroxy-1,2,3,4-tetrahydrotetraphen-7(12H)-one (**307**) by Witiak and coworkers*

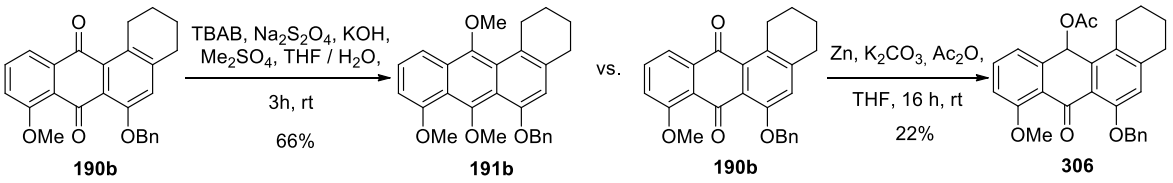
Applying these reaction conditions (Ac_2O, pyridine, rt) on our substrate 6-(benzyloxy)-12-hydroxy-8-methoxy-1,2,3,4-tetrahydrotetraphen-7(12H)-one (**205**), 6-(benzyloxy)-8-methoxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (**190b**) was isolated in quantitative yield after three days (*Scheme 2.89*).



*Scheme 2.98. Attempt to acetylate 6-(benzyloxy)-12-hydroxy-8-methoxy-1,2,3,4-tetrahydrotetraphen-7(12H)-one (**205**) with Ac_2O*

[106] D. T. Witiak, S. Goswami, G. E. Milo, *J. Org. Chem.* **1988**, *53*, 345-352.

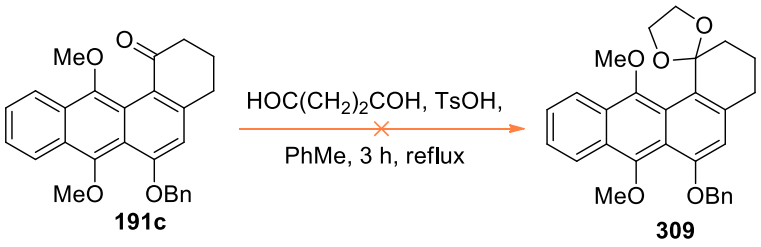
In summary, sodium dithionite was a better reducing agent than zinc for these systems, because we observed better conversions of 6-(benzyloxy)-8-methoxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (**190b**) with this reducing agent. Applying the reduction / methylation process we could access to the desired 6-(benzyloxy)-7,8,12-trimethoxy-1,2,3,4-tetrahydrotetraphene (**191b**) with a moderate yield (66%), while with the reduction / acetylation process only 6-(benzyloxy)-8-methoxy-7-oxo-1,2,3,4,7,12-hexahydrotetraphen-12-yl acetate (**306**) could be obtained with a low yield (22%) (*Scheme 2.90*).



Scheme 2.99. Summary and comparison between the reductive methylation and the reductive acetylation

2.2.6.3. Attempts to protect the carbonyl group at C_1 of 6-hydroxy-7,12-dimethoxy-3,4-dihydrotetraphen-1(2*H*)-one (190c)

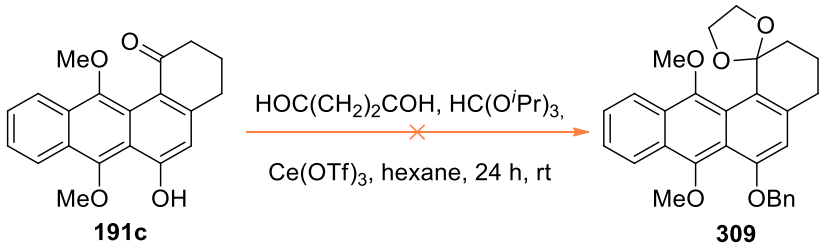
Taking into account the lack of reactivity observed in the oxidative dearomatization of 6-hydroxy-7,8,12-trimethoxy-3,4-dihydrotetraphen-1(2H)-one (**22c**) having a carbonyl electron-withdrawing group (EWG) at the para position of the phenol, we decided to change the electron-withdrawing character of the carbonyl group by transformation into the corresponding dioxolane. A classical acetalization method was initially tried on compound **191c** adding ethylene glycol ($HOC(CH_2)_2COH$) and *para*-toluenesulfonic acid (TsOH) at reflux using a Dean-Stark (*Scheme 2.91*).[97] Unfortunately 6'-(benzyloxy)-7',12'-dimethoxy-3',4'-dihydro-2'H-spiro[[1,3]dioxolane-2,1'-tetraphene] (**309**) was not formed and the starting material remained unchanged.



Scheme 2.100. Classical acetalization conditions with $HOC(CH_2)_2COH$ in presence of TsOH at toluene reflux

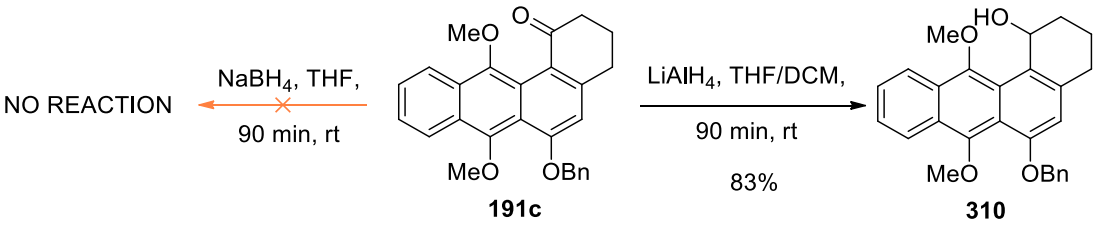
Another protecting method used was ethylene glycol ($HOC(CH_2)_2COH$), triisopropyl orthoformate $HC(OC^iPr)_3$, and a catalytic amount of cerium(III) trifluoromethanesulfonate

[Ce(OTf)$_3$] in hexane at rt, but the starting material **191c** also remained unchanged (*Scheme 2.92*).98



Scheme 2.101. Acetalization conditions with OHC(CH$_2$)$_2$OH in presence of HC(O^{i}Pr)$_3$ and Ce(OTf)$_3$

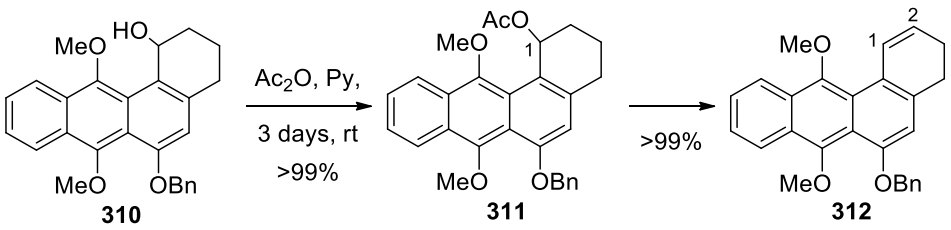
Taking into account the difficulties encountered in the protection of the carbonyl group, we decided to reduce it to transform the ketone group into a secondary alcohol substituent to check if this change in the electron density of the aromatic ring would favor the oxidative dearomatization process. However, 6-(benzyloxy)-7,12-dimethoxy-3,4-dihydrotetraphen-1(2H)-one (**191c**) did not react with sodium borohydride in THF at rt,X but in the presence of lithium aluminum hydride (LiAlH$_4$) in a mixture of THF / DCM at rt,[107] 6-(benzyloxy)-7,12-dimethoxy-1,2,3,4-tetrahydrotetraphen-1-ol (**310**) was obtained in 83% yield (*Scheme 2.93*).



*Scheme 2.102. Reduction reactions of the carbonyl group at C$_1$ of 6-(benzyloxy)-7,12-dimethoxy-3,4-dihydrotetraphen-1(2H)-one (**191c**)*

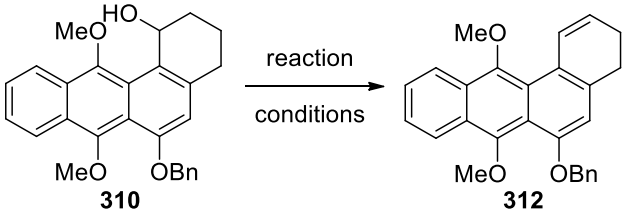
Then, several synthetic methods to protect the secondary benzylic hydroxy group of **310** were checked. Initially, acetylation of the hydroxyl group was achieved using acetic anhydride (Ac$_2$O) in pyridine (Py)[62a, 65] to afford 6-(benzyloxy)-7,12-dimethoxy-1,2,3,4-tetrahydrotetraphen-1-yl acetate (**311**) in quantitative yield. The acetate **311** proved to be very unstable and evolved over time into 6-(benzyloxy)-7,12-dimethoxy-3,4-dihydrotetraphene (**312**) with a conjugated double bond between C$_1$ and C$_2$, resulting from the β-elimination of the acetate (*Scheme 2.94*).

[107] Patent WO2005/113527, 2005, A1



*Scheme 2.103. Acetylation of hydroxyl group at C_1 of 6-(benzyloxy)-7,12-dimethoxy-1,2,3,4-tetrahydrotetraphen-1-ol (**310**)*

Other trials to protect the hydroxyl group of 6-(benzyloxy)-7,12-dimethoxy-1,2,3,4-tetrahydrotetraphen-1-ol (**310**) utilized TBDMSCl, TBDMSOTf, BzCl and benzoic acid as reagents.[64, 108] The results of these experiments are depicted in *Table 2.9*. When the system TBDMSCl/AgO_2 was used in DCM, the starting material remained unchanged after 3 days stirring (*Table 2.9, entry 1*). The same result was observed under BzCl in presence of Et_3N and 4-dimethylaminopyridine (DMAP) in DCM at rt for 5 days (*Table 2.9, entry 5*). Typical conditions for silylation in the presence of imidazole (IMD) and DMAP, in DMF at rt, gave a complex mixture after 1 hour of reaction (*Table 2.9, entry 2*). A similar complex mixture resulted when a more reactive silylating agent TBDMOTf was used in DCM and in the presence of DIPEA (*Table 2.9, entry 3*). When 6-(benzyloxy)-7,12-dimethoxy-1,2,3,4-tetrahydrotetraphen-1-ol (**310**) reacted with TBDMSCl and IMD in DMF, the elimination product 6-(benzyloxy)-7,12-dimethoxy-3,4-dihydrotetraphene (**312**) was formed after 2 hours of reaction (*Table 2.9, entry 4*).



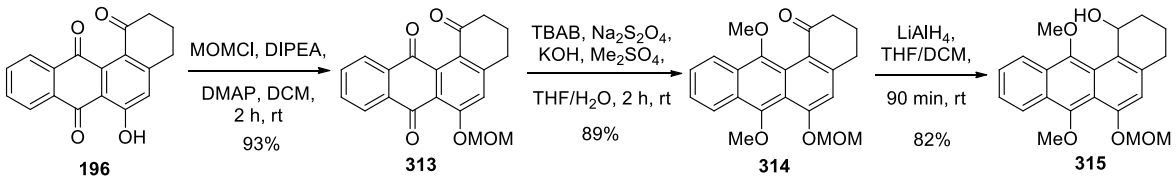
[108] a) C. Xie,M. T. C. Runnegar, B. B. Snider, *J. Am. Chem. Soc.* **2000**, *122*, 5017-5024 b) S. V. Ley, A. Abad-Somovilla, J. C. Anderson, C. Ayats, R. Bänteli, E. Beckmann, A. Boyer, M. G. Brasca, A. Brice, H. B. Broughton, B. J. Burke, E. Cleator, D. Craig, A. A. Denholm, R. M. Denton, T. Durand-Reville, L. B. Gobbi, M. Göbel, B. L. Gray, R. B. Grossmann, C. E. Gutteridge, N. Hahn, S. L. Harding, D. C. Jennens, L. Jennens, P. J. Lovell, H. J. Lovell, M. L. de la Puente, H. C. Kolb, W.-J. Koot, S. L. Maslen, C. F. McCusker, A. Mattes, A. R. Pape, A. Pinto, D. Santafianos, J. S. Scott, S. C. Smith, A. Q. Somers, C. D. Spilling, F. Stelzer, P. L. Toogood, R. M. Turner, G. E. Veitch, A. Wood, C. Zumbrunn, *Chem Eur. J.* **2008**, *14*, 10683-107004 c) M. N. Bakola-christianopoulou, K. K. Apazidou, *Phosphorus, Sulfur and Silicon* **1996**, *113*, 245-253. d) J. D. Winkler, M. B. Rouse, M. F. Greaney, S J. Harrison, Y. T. Jeon, *J. Am. Chem. Soc.* **2002**, *124*, 9726-9728.

Entry	Reaction conditions	Yield[a]
1	TBDMSCl, Ag_2O, DCM, rt, 3 days	Did not react
2	TBDMSCl, IMD, DMAP, DMF, rt, 1 h	Complex mixture
3	TBDMSOTf, DIPEA, DCM, rt, 2 h	Complex mixture
4	TBDMSCl, IMD, DMF, rt, 2 h	88%
5	BzCl, Et_3N, DMAP, DCM, rt, 5 days	Did not react

a: Isolated yield

Table 2.9.- Protection reaction conditions

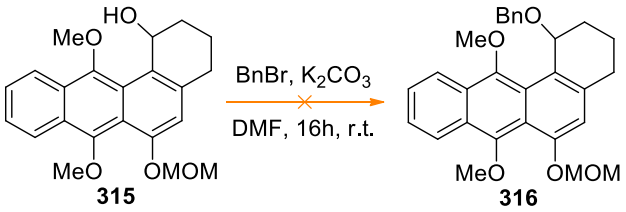
In view of the impossibility to protect the hydroxy group at C_1 of 6-(benzyloxy)-7,12-dimethoxy-1,2,3,4-tetrahydrotetraphen-1-ol (**310**), we thought to change the benzyloxy group at C_6 to a methoxy methyl ether (-MOM) and later protect the secondary alcohol as benzyl group. Thus, the protection of 6-hydroxy-3,4-dihydrotetraphene-1,7,12(2*H*)-trione (**196**) with chloromethyl methyl ether (MOMCl), DIPEA and DMAP in DCM,[109] afforded 6-(methoxymethoxy)-3,4-dihydrotetraphene-1,7,12(2H)-trione (**313**) in 93% yield. A reductive methylation process ($Na_2S_2O_4$, KOH, Me_2SO_4) of the quinone moiety of **313** followed by $LiAlH_4$ reduction of the ketone group of the resulting **314** afforded 7,12-dimethoxy-6-(methoxymethoxy)-1,2,3,4-tetrahydrotetraphen-1-ol (**315**) in 73% yield in two steps from **313** (*Scheme 2.95*).



*Scheme 2.104. Synthesis of 7,12-dimethoxy-6-(methoxymethoxy)-1,2,3,4-tetrahydrotetraphen-1-ol (**315**) from 6-hydroxy-3,4-dihydrotetraphene-1,7,12(2H)-trione (**196**) in 3 steps*

However, 7,12-dimethoxy-6-(methoxymethoxy)-1,2,3,4-tetrahydrotetraphen-1-ol (**315**) remained unchanged when treated with sodium carbonate and benzyl bromide in DMF (*Scheme 2.96*).

[109] L. N. Mander, M. M. McLachlan, *J. Am. Chem. Soc.* **2003**, *125*, 2400-2401.

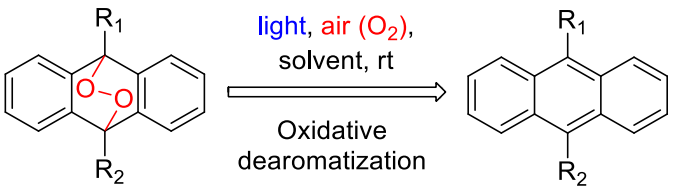


*Scheme 2.105. Benzylation reaction of 7,12-dimethoxy-6-(methoxymethoxy)-1,2,3,4-tetrahydrotetraphen-1-ol (**315**)*

2.2.6.4. Aerobic photooxidation of anthracene derivatives: Synthesis of anthracene endoperoxides through oxidative dearomatization by irradiation with light under air.

Anthracene endoperoxides are usually prepared by [4+2] cycloaddition of anthracenes with singlet oxygen, generated by irradiation in the presence of a photosensitizer such as methylene blue or rose bengal.[85, 110] In some examples, this transformation did not need an external photosensitizer, because the anthracenes acted as self-photosensitizer leading to the photooxidation product [85] This photooxidation process is thermally reversible for some anthracenes, producing singlet oxygen and regenerating the corresponding anthracenes. Therefore, these endoperoxides could act as singlet oxygen storage batteries,[111] and have been used in photodymanic therapy (PDT) being of great interest in the cancer treatment.[112]

Considering all this information, we decided to evaluate the behavior of different anthracenes under our photooxidaton conditions (*Scheme 2.97*) with a previous optimization of the reaction conditions.



Scheme 2.106. retrosynthetic scheme in the formation of anthracene endoperoxides.

Anthracene (**317a**) was chosen as the substrate model to optimize the oxidative dearomatization conditions through irradiation with light under air. First, we studied its UV-vis spectrum, which displayed a broad absorption band in a range of λ 326 – 391 nm (*Figure 2.56*), similar to tetracyclic phenols **22**, apart from the intense absorption band at λ 252 nm.

[110] M. Klaper, T. Linker, *J. Am. Chem. Soc.* **2015**, *137*, 13744-13747.
[111] C. Pierlot, J. M. Aubry, K. Briviba, H. Sies, P. Di Mascio, *Methods Enzymol.* **2000**, *319*, 3-20.
[112] D. Posavec, M. Zabel, U. Bogner, G. Bernhardt, G. Knör, *Org. Biomol. Chem.* **2012**, *10*, 7062-7069.

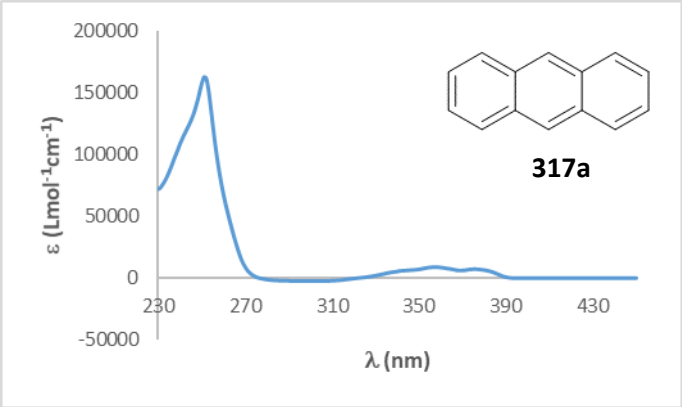
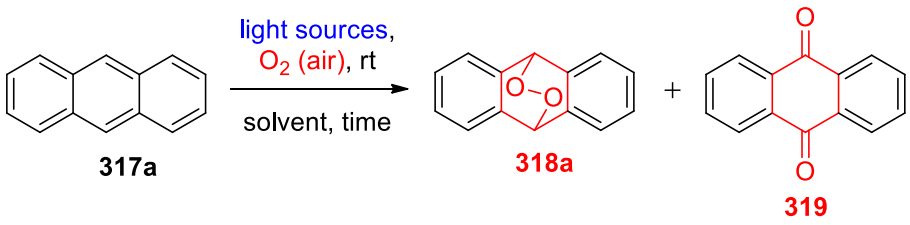


*Figure 2.59. Optical absorption spectra recorded in chloroform in quartz cuvettes (1 cm path). Anthracene (**317a**) (c: 1.06 x 10^{-5} M). λ_{max1}: 252 nm (ε_1: 161252 $Lmol^{-1}cm^{-1}$) and λ_{max2}: 359 nm (ε_2: 8656 $Lmol^{-1}cm^{-1}$).*

Among the light sources that we had in the laboratory, only blue LEDs (λ_{max} 450 nm) and UV lamp (λ_{max} 370 nm) overlapped with the absorption band of anthracene (**317a**), so we decided to evaluate them for the photooxidation process using different solvents (chlroroform, acetone and acetonitrile) with the idea of synthesized the endoperoxide (EPO) **318a**. The results of different experiments are indicated in *Table 2.10*.



entry	light sources	solvent	time	318a (%)[a]	319 (%)[a]
1	Blue LEDs (λ_{max} 450 nm)	$CHCl_3$	24 h	14	42
2	Blue LEDs	acetone	5 days	-	95
3	Blue LEDs	CH_3CN	2 days	-	47
4	UV lamp (λ_{max} 370 nm)	$CHCl_3$	6 h	48	22
5	UV lamp	acetone	24 h	-	92
6	UV lamp	CH_3CN	24 h	-	46

a: Isolated yield

*Table 2.10. Photooxidation of anthracene **317a** under different conditions*

Endoperoxide **318a**[85] could be synthesized using chloroform as solvent and irradiating the anthracene (**317a**) solution with both blue LEDs (λ_{max} 450 nm) and the UV lamp (λ_{max} 370 nm) (*Table 2.10*, *entries 1* and *4*). However, a significant amount of anthracene-9,10-dione (**319**) was observed with blue LEDs (42% yield) (*Table 2.10*, *entry 1*) and a non-negligible amount of the quinone **319** (22% yield) was formed irradiating at 370 nm (*Table 2.10*, *entries 4*). Using acetone and acetonitrile, only the quinone **319** was formed, probably by evolution of endoperoxide **318a**, due to the very long reaction times (24 hours to 5 days) with high to moderate yields (95% to 46%) (*Table 2.10*, *entries 2*, *3*, *5* and *6*). The best result was thus obtained with the UV lamp (λ_{max} 370 nm) in chloroform, giving rise to a mixture of the endoperoxide **318a** (48% yield) and quinone **319** (22% yield) after 6 hours of irradiation (*Table 2.10*, *entry 4*).

With the optimal photooxidation conditions in hands (UV lamp in $CHCl_3$ under air) for the formation of the endoperoxides, we focused on other substrates. First, the UV-vis spectra of four anthracene derivatives were analyzed. These four anthracenes showed the same broad absorption bands within a range of wavelength from 327 to 412 nm (*Figures 2.57, 2.58, 2.59* and *2.60*), thus we would expect a similar reactivity to anthracene (**317a**).

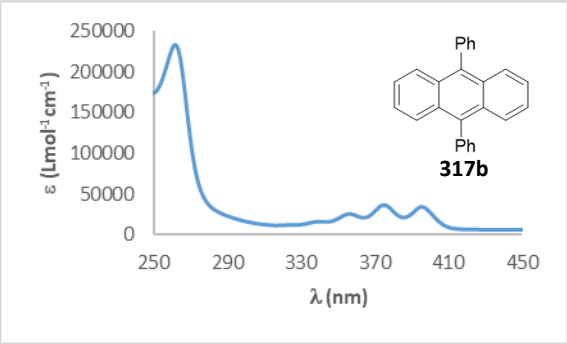


*Figure 2.60. Optical absorption spectra recorded in chloroform in quartz cuvettes (1 cm path). 9,10-Diphenylanthracene (**317b**) (c: 6.05 x 10^{-6} M). λ_{max1}: 263 nm (ε_1: 229197 $Lmol^{-1}cm^{-1}$) and λ_{max2}: 376 nm (ε_2: 33408 $Lmol^{-1}cm^{-1}$).*

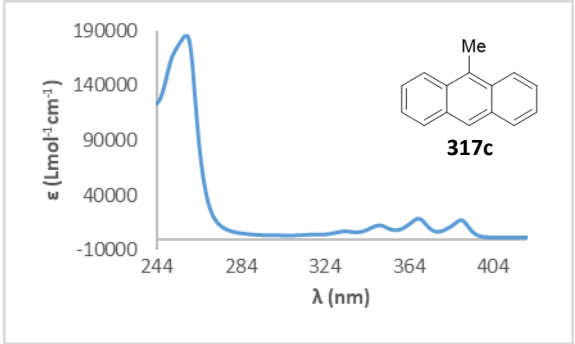


*Figure 2.61. Optical absorption spectra recorded in chloroform in quartz cuvettes (1 cm path). 9-methylanthracene (**317c**) (c: 2.08 x 10^{-5} M). λ_{max1}: 259 nm (ε_1: 185466 $Lmol^{-1}cm^{-1}$) and λ_{max2}: 370 nm (ε_2: 18350 $Lmol^{-1}cm^{-1}$).*

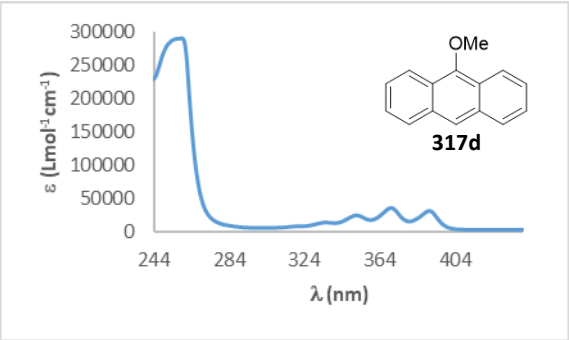


*Figure 2.62. Optical absorption spectra recorded in chloroform in quartz cuvettes (1 cm path). 9-Methoxyanthracene (**317d**) (c: 1.34 x 10^{-5} M). λ_{max1}: 257 nm (ε_1: 284372 $Lmol^{-1}cm^{-1}$) and λ_{max2}: 371 nm (ε_2: 34784 $Lmol^{-1}cm^{-1}$).*

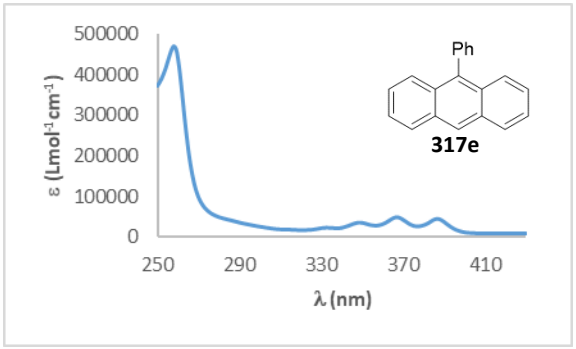
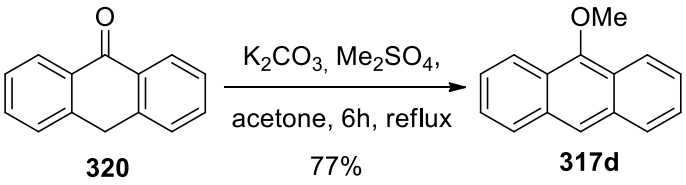


*Figure 2.63. Optical absorption spectra recorded in chloroform in quartz cuvettes (1 cm path). 9-Phenylanthracene (**317e**) (c: 3.93 x 10^{-6} M). λ_{max1}: 259 nm (ε_1: 463280 $Lmol^{-1}cm^{-1}$) and λ_{max2}: 368 nm (ε_2: 49251 $Lmol^{-1}cm^{-1}$).*

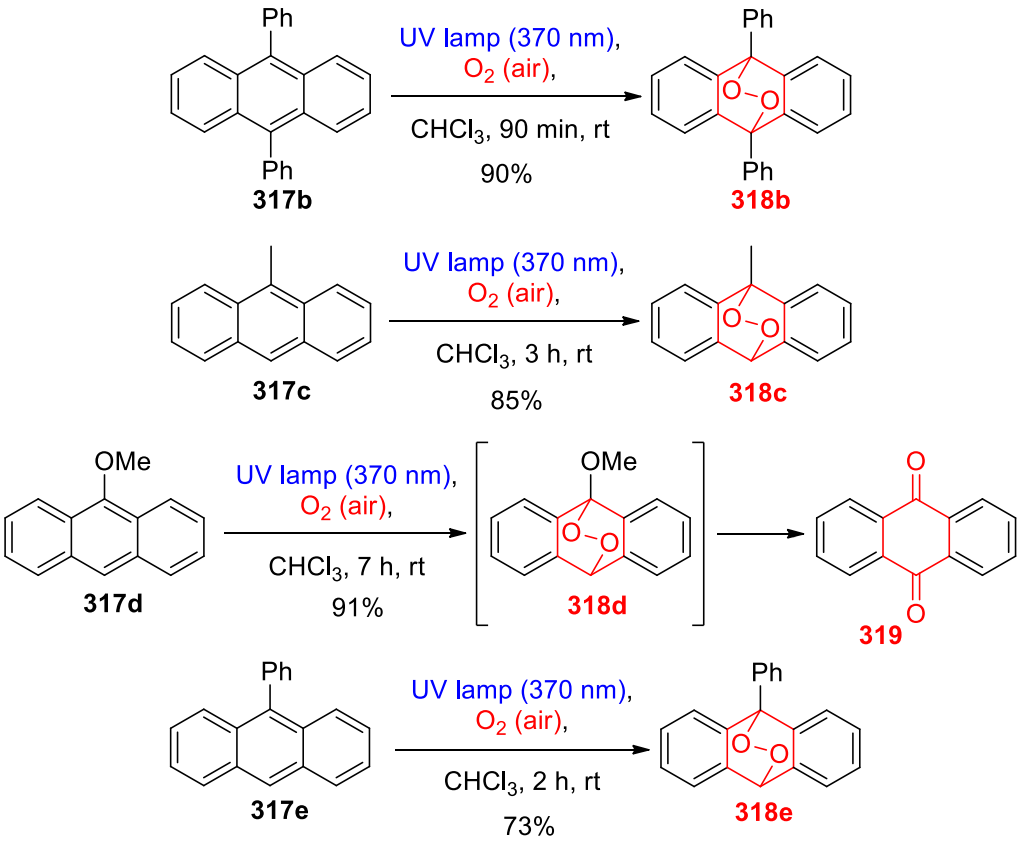
The anthracenes we used were commercially available unless 9-methoxyanthracene (**317d**), which was generated in 77% isolated yield from anthracen-9(10*H*)-one (**320**) through a one-pot reduction/methylation process with potassium carbonate (K_2CO_3) and dimethyl sulfate (Me_2SO_4) in acetone (*Scheme 2.98*).[113]



*Scheme 2.107. Reductive methylation reaction of anthracen-9(10H)-one (**320**) with K_2CO_3 and Me_2SO_4*

The irradiation of these four anthracenes **317b-e** with the UV lamp (λ_{max} 370 nm) in chloroform under air gave rise to the corresponding described endoperoxides in good to excellent yields (75-90% yield) (*Scheme 2.99*). However, 9-methoxyanthracene (**317d**) afforded the quinone **319** in 91% yield, probably through evolution of the unstable endoperoxide **318d**.

[113] Yasukazu Hirao, Tohru Saito, Hiroyuki Kurata, Takashi Kubo, *Angew. Chem. Int. Ed.* **2015**, *54*, 2402-2405.



Scheme 2.108. Summary of photooxidation reaction of different anthracenes

The anthracenes **317** were acting as self-photosensitizers and generating singlet oxygen when they were irradiated with light of the adequate wavelenght. The singlet oxygen generated from the self-photosensitizers reacted with the anthracenes through a [4+2] Diels-Alder cycloaddition to afford the corresponding photooxidized products.

2.3. Experimental part

2.3.1. Synthesis data

2.3.1.1. General Information

General Experimental Procedures. All starting materials were purchased from commercial sources (Merck and Alpha Aesar), and used without further purification. Solvents used for reactions, extractions and purifications were reagent grade and used as received from Carlo Erba. When necessary, solvents were dried under standard conditions. Reactions were

monitored by thin layer chromathography (TLC) using TLC silicagel coated aluminium plates 60 F_{254} (Merck) and visualized by ultraviolet light lamp (254 nm) and by staining with phosphomolybdic acid, followed by heating. Column chromatography was performed with silicagel 60 (0.040-0.063 mm), packed with the corresponding eluent and run under positive air pressure. Irradiation was effected using Blue (λ_{max} 450 nm, Ref. 2040694) and green (λ_{max} 525 nm, Ref. 2040693) LEDs lamps from Segainvex UAM (18 W), compact UV lamp (λ_{max} 370 nm, JIADI-36 *JD 818*), red lamp (λ 618 to 780 nm, Lexman E27 15W *EQ5S10*) and white lamp (λ 400 to 700 nm, Ikea 11W, Ref. ES11G0601). The experimental conditions for the reactions are indicated in each case.

Instrumentation. ^{1}H-NMR and ^{13}C-NMR spectra were performed on Bruker, Advance 300 (300 MHz for ^{1}H and 75 MHz for ^{13}C). Chemical shifts are expressed in ppm using the residual non-deuterated solvent as internal standard ($CDCl_3$ from Carlo Erba, ^{1}H-NMR: δ 7.26 ppm, ^{13}C-NMR: δ 77.16 ppm). The abbreviations used for the multiplicities are s (singlet), d (doublet), dd (doublet of doublets), t (triplet), td (triplet of doublets), tt (triplet of triplets) and m (multiplet); and the coupling constants (*J*) are reported in Hertz (Hz). High Resolution Mass Spectrometry (HRMS) and X-Ray crystallographic experiments were carried out by Servicio Interdepartamental de Investigación (SIdI) of Universidad Autónoma de Madrid. Melting points were performed on a BÜCHI B-540 capillary melting point apparatus and are uncorrected. UV/vis absorption spectra were recorded on a JASCO ETCS-761 V-660 spectrophotometer. Measurements were collected using a 1 cm path-length quartz cuvette. The following parameters were used: bandwidth 1 nm, response time 1 sec, wavelength scan range 187–900 nm.

Description of the irradiation sources used. Relative spectral power distribution and reaction set-up with blue LEDs (λ_{max} 450 nm, from Segainvex UAM, 18 W):

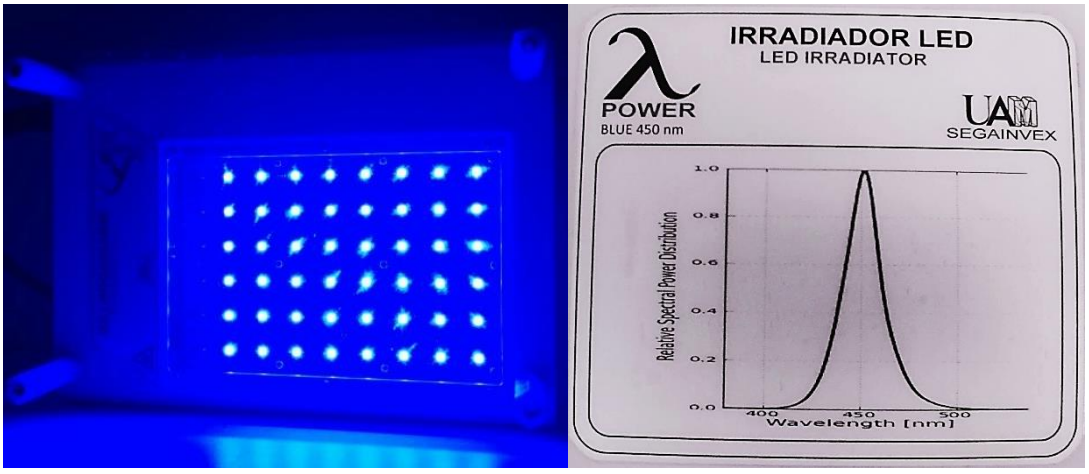


Figure 2.64. Relative Spectral Power Distribution of blue LEDs.

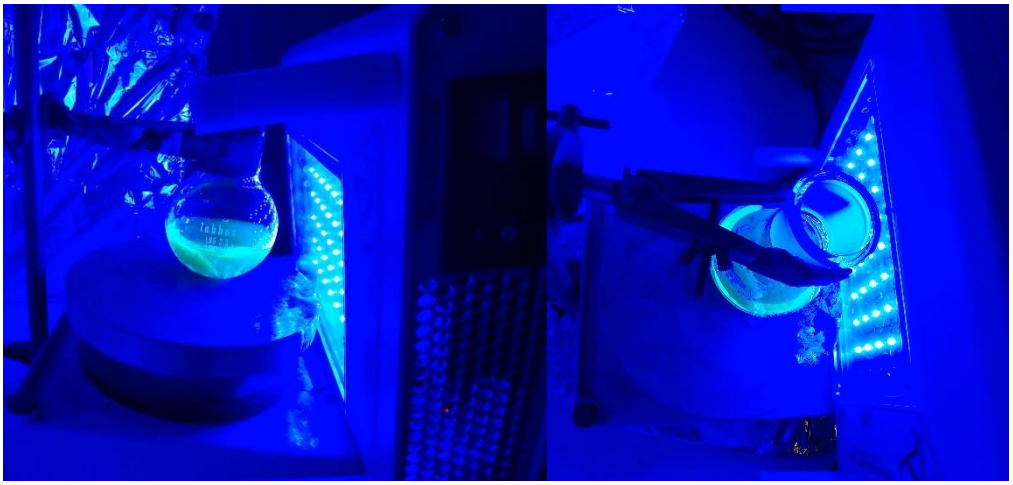


Figure 2.65. Reaction set-up with blue LEDs.

Relative spectral power distribution and reaction set-up with Green LEDs (λ_{max} 525 nm, from Segainvex UAM, 18 W):

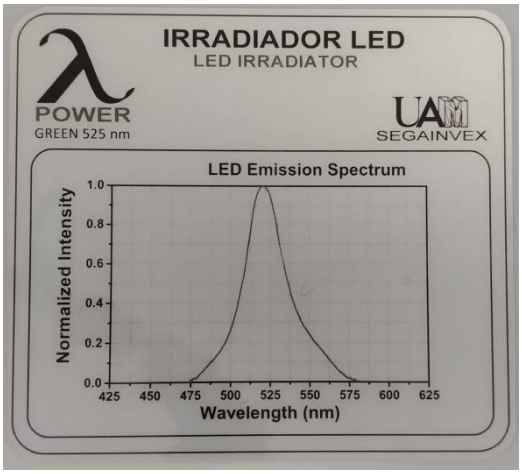


Figure 2.66. Relative Spectral Power Distribution of green LEDs.

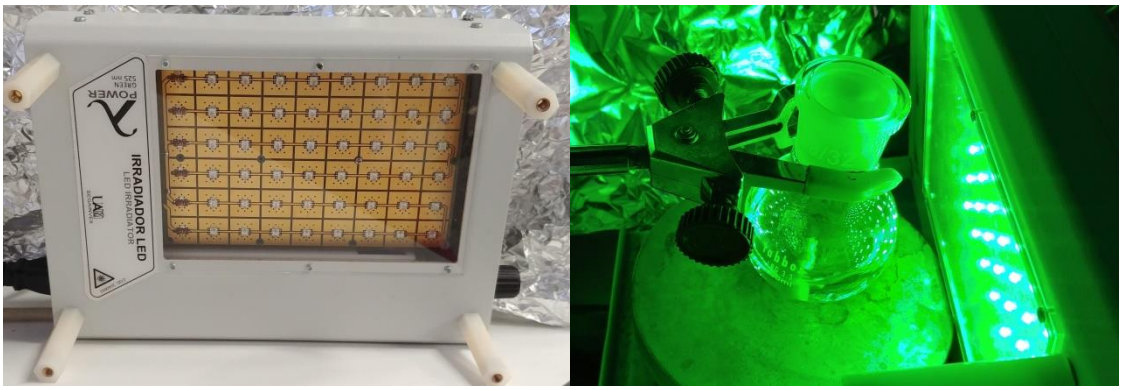


Figure 2.67. Reaction set-up with green LEDs.

Reaction set-up with compact UV lamp (λ_{max} 370 nm, JIADI-36 *JD 818*)

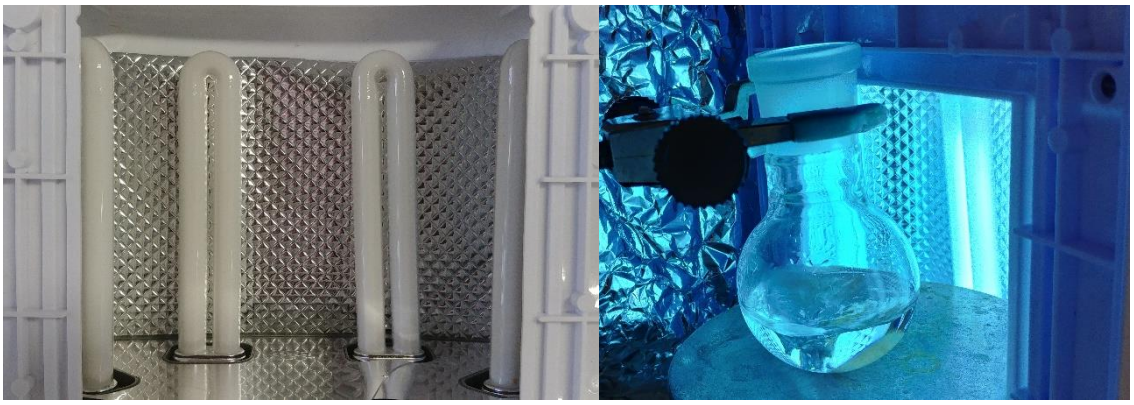


Figure 2.68. Reaction set-up with compact UV lamp.

Reaction set-up with red bulb lamp (λ 618 to 780 nm, Lexman E27 15W *EQ5S10*)

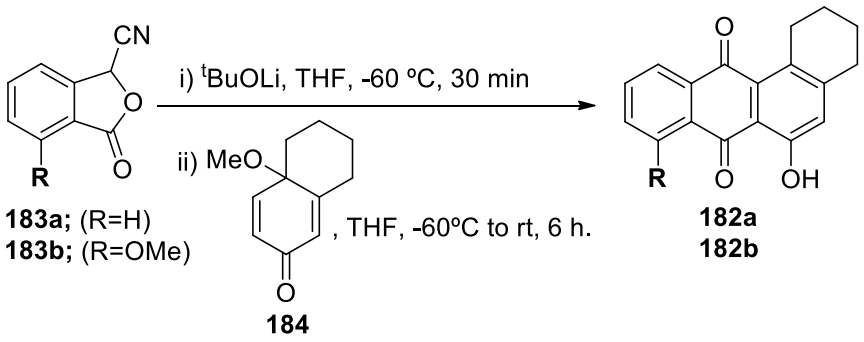
Figure 2.69. Reaction set-up with red bulb lamp.

Reaction set-up with white bulb lamp (λ 400 to 700 nm, Ikea 11W, Ref. ES11G0601)

Figure 2.70. Reaction set-up with white bulb lamp.

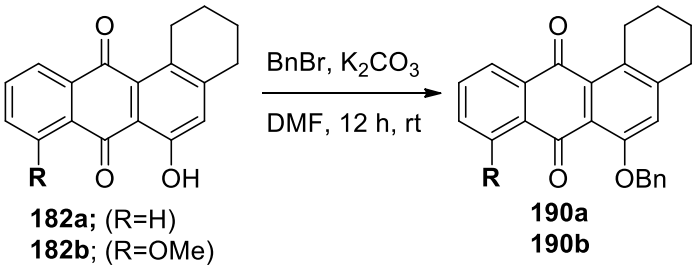
2.3.1.2. Experimental Procedures and Product Characterization

Method A. General method for Hauser-Kraus annulation.[114]



To a stirred solution of 1M lithium *tert*-butoxide (^{t}BuOLi, 3 equiv.) in THF, a solution of phthalide **183** (1 equiv.) in dry THF (0.66 M) was added, at -60 ºC. The resulting yellow solution was stirred for 30 min at -60 ºC and then, a solution of **184** (1.5 equiv.) in dry THF (0.66 M) was added. The reaction was stirred at -60 ºC for 1 h, brought to rt over 1h and stirred for 4 h. The reaction was quenched with NH_4Cl sat. and extracted with EtOAc (x3). The combined organic layers were washed with brine (x2), dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The crude mixture was purified by flash chromatography to give the desired products **182**.

Method B. General method for benzylation.*[115]*



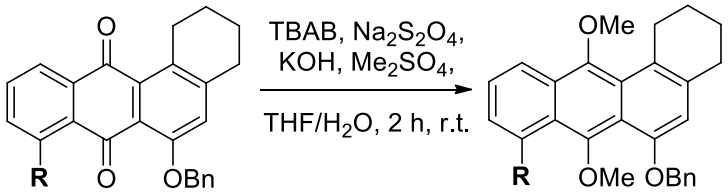
To a solution of **182** (1 equiv.) and potassium carbonate (K_2CO_3, 2 equiv.) in DMF (0.10 M), benzyl bromide (BnBr, 2 equiv.) was added. The mixture was stirred overnight at rt and quenched with water. The suspension was extracted with DCM (x3) and the organic phase was washed with water (x3). The organic layer was dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography to give compounds **190**.

---

[114] a) D. Mal, S. Dey *Tetrahedron* **2006**, *62*, 9589-9602; b) D. Mal, P. Pahari, *Chem. Rev.* **2007**, *107*, 1892-1918.

[115] K. Wu, M. Wang, Q. Yao, A. Zhang, *Chin. J. Chem.* **2013**, *31*, 93-99.

Method C. General method for reduction and methylation of quinones.[115]

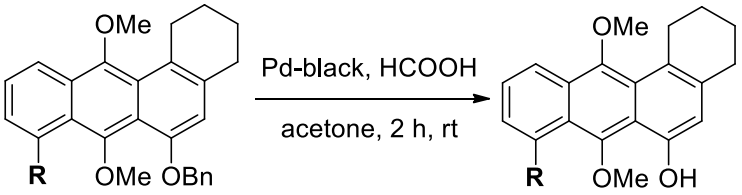


190a; (R=H)
190b; (R=OMe)

191a
191b

To a solution of quinone **190** (1 equiv.), tetrabutyl ammonium bromide (TBAB, 0.3 equiv.), sodium dithionite ($Na_2S_2O_4$, 8 equiv.) and potassium hydroxide (KOH, 25 equiv.) in THF (0.17 M) and water (0.12 M), under an inert atmosphere, dimethyl sulfate (Me_2SO_4, 40 equiv.) was added dropwise. The mixture was stirred at rt for 2 h until the starting material was consumed and, then, quenched with aqueous ammonia solution. The mixture was extracted with EtOAc (x3) and the combined organic layers were washed with brine (x2), dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The crude mixture was purified by flash chromatography to afford the desired product **191**.

Method D. General method for the reductive debenzylation.[116]



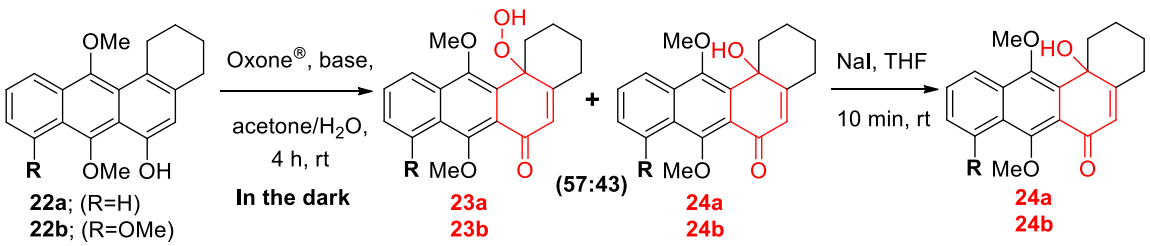
191a; (R=H)
191b; (R=OMe)

22a
22b

To a suspension of benzyl derivative **191** (1 equiv.) and Pd-black (1.2 equiv.) in acetone (0.20 M), under an inert atmosphere, formic acid (HCOOH, 10 equiv.) was added in the dark. The mixture was stirred at rt in the dark for 2 h, and monitored by TLC. When the reaction was finished, it was filtered through Celite® and the solvent was evaporated in the dark. The resulting crude mixture was purified by flash chromatography in the dark, to afford compounds **22**.

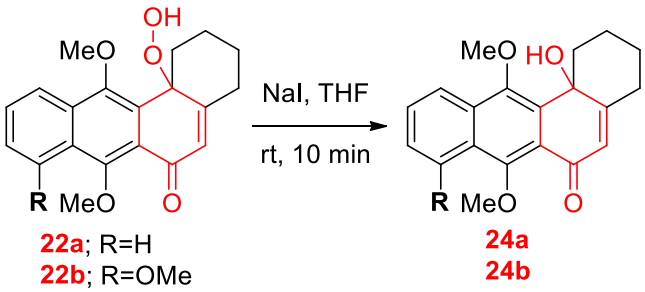
[116] G. Hernández-Torres, M. C. Carreño, A. Urbano, F. Colobert, *Chem. Eur.* **2011**, *17*, 1283-1293.

Method E. General method for the synthesis of *para*-quinols with Oxone® as oxidant.[117]



A mixture of Oxone® and a base ($NaHCO_3$ for **22a** and K_2CO_3 for **22b**) previously ground into powder, was slowly added in one portion to a vigorously stirred solution of phenol **22** in water (0.06 M) and acetone (0.1 M). A septum with an empty balloon was immediately placed to avoid overpressure into the flask and loss of generated singlet oxygen. The reaction was monitored by TLC and when the starting material was consumed, it was quenched with water. The crude reaction mixture was extracted with EtOAc (x3) and the combined organic layers were washed with brine (x2), dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The crude mixture of **23** and **24** was then dissolved in THF (0.012 M) and treated with sodium iodide (NaI, 5 equiv.) at rt. After stirring for 10 min, the mixture was quenched with brine, and extracted with EtOAc (x3). The organic layer was washed with brine (x2), dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography to give *para*-quinols **24**.

Method F: General method for the reduction of *para*-peroxy quinols.[118]

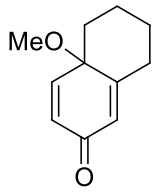


To a solution of *para*-peroxy quinols **23** (1 equiv.) in THF (0.012 M) at rt, sodium iodide (NaI, 5 equiv.) was added. The reaction changed the color to dark brown and, after stirring for 10 min, the mixture was quenched with brine and extracted with EtOAc (x3). The organic layer was

[117] S. Vila-Gisbert, A. Urbano, M. C. Carreño, *Chem. Commun*. **2013**, *49*, 3561-3563.
[118] E. Schöttner, M. Wiechoczek, P. G. Jones, T. Lindel, *Org. Lett.*, **2010**, *12*, 784-787.

washed with brine (x2), dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography to give *para*-quinols **24**.

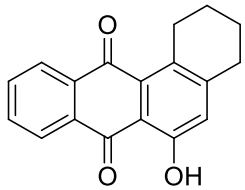
4a-Methoxy-5,6,7,8-tetrahydronaphthalen-2(4a*H*)-one (184)[119]



Compound **184** was prepared according to a previously published procedure.119 To a stirred solution of 5,6,7,8-tetrahydronaphthalen-2-ol (**185**) (1.20 g, 8.23 mmol) in dry MeOH (24 mL) at 0 ºC under inert atmosphere, *bis*(triacetoxy)]-iodobenzene (PIDA, 2.70 g, 8.03 mmol) was added. After 1 h, MeOH was evaporated and the resulting oil was dissolved in CH_2Cl_2 and washed with water, $NaHCO_3$ (5%) and water, respectively. The organic layer was dried over Na_2SO_4, concentrated to dryness under reduced pressure and the residue purified by flash chromatography (heptane/EtOAc : 8/1) to afford **184** (599.5 mg, 3.28 mmol, 41% yield), as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.65 (d, *J* = 10.0 Hz, 1H), 6.31 (dd, *J* = 10.0, 1.8 Hz, 1H), 6.19 (m, 1H), 3.03 (s, 3H), 2.46 – 2.26 (m, 2H), 2.16 – 2.06 (m, 1H), 2.05 – 1.82 (m, 2H), 1.65 – 1.54 (m, 1H), 1.42 – 1.21 (m, 2H).

6-Hydroxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (182a)[0120]

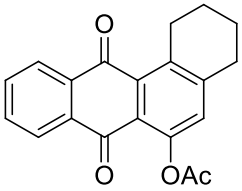


[119] H. N. Roy, M. S. Sarkar, D. Mal, *Synth. Commun.* **2005**, *35*, 2183-2188.
[120] D. Mal, S. Dey, *Tetrahedron* **2006**, *62*, 9589-9602.

Following **Method A**, compound **182a** was obtained in 80% yield (461.9 mg, 1.66 mmol), as an orange solid, from phthalide **183a** (333.1 mg, 2.05 mmol) and compound **184** (554.5m g, 3.08 mmol). The crude mixture was purified by flash chromatography (heptane/EtOAc : 9/1).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 13.04 (s, 1H), 8.23 – 8.13 (m, 2H), 7.78 – 7.68 (m, 2H), 6.97 (s, 1H), 3.25 – 3.17 (m, 2H), 2.88 – 2.79 (m, 2H), 1.85 – 1.72 (m, 4H).

7,12-Dioxo-1,2,3,4,7,12-hexahydrotetraphen-6-yl acetate (188)



To a stirred solution of **182a** (102.8 mg, 0.37 mmol) in pyridine (Py, 1.5 mL), acetic anhydride (Ac_2O, 0.5 mL, 5.3 mmol) was added and the reaction stirred at rt overnight. Then, the reaction was poured into crushed ice, extracted with EtOAc (x3), and the combined extracts were washed several times with an aqueous $CuSO_4$ sat. solution. The organic layer was washed with brine (x2), dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The crude product was purified by flash chromatography (heptane/EtOAc : 1/9) to give **188** (100.1 mg, 0.31 mmol, 84% yield) as a yellow solid.

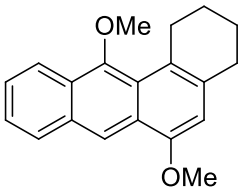
mp: 125.6 – 127.0 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.18 – 8.09 (m, 2H), 7.76 – 7.67 (m, 2H), 7.12 (s, 1H), 3.38 – 3.30 (m, 2H), 2.96 – 2.88 (m, 2H), 2.48 (s, 3H), 1.88 – 1.79 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 185.6, 182.7, 170.1, 147.8, 147.3, 140.2, 134.6, 133.8, 133.5, 133.4, 133.3, 130.1, 126.8, 126.4, 124.4, 31.3, 29.4, 23.2, 21.7, 21.3.

HRMS (ESI): calculated for $C_{20}H_{16}O_4$ ($[M]^+$) 320.1049, found 320.1035.

6,12-Dimethoxy-1,2,3,4-tetrahydrotetraphene (189)



Following **Method C**, compound **189** was obtained in 13% yield (6.3 mg, 0.02 mmol), as a brown solid, from compound **188** (54.9 mg, 0.17 mmol). The crude mixture was purified by flash chromatography (heptane/EtOAc : 9/1).

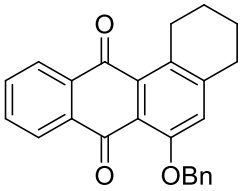
mp: 161.1 – 163.5 ºC.

^{1}H NMR (300 MHz, CDCl3) δ: 8.65 (s, 1H), 8.29 (d, J = 8.5 Hz, 1H), 8.01 (d, J = 7.9 Hz, 1H), 7.53 – 7.42 (m, 2H), 6.42 (s, 1H), 4.04 (s, 3H), 3.93 (s, 3H), 3.53 – 3.46 (m, 2H), 2.98 – 2.91 (m, 2H), 1.93 – 1.87 (m, 4H).

^{13}C NMR (75 MHz, CDCl3) δ: 153.5, 153.1, 134.0, 131.5, 128.8, 126.5, 126.3, 125.6, 125.5, 125.1, 123.8, 122.6, 117.3, 104.8, 63.5, 55.5, 32.2, 28.5, 24.3, 22.8.

HRMS (APCI): calculated for $C_{20}H_{21}O_2$ ($[M+H]^+$) 293.1172, found 293.1170.

6-(Benzyloxy)-1,2,3,4-tetrahydrotetraphene-7,12-dione (190a)



From 182a. Following **Method B**, compound **190a** was obtained in 94% yield (576.7 mg, 1.56 mmol) as a yellow solid from hydroxy quinone **182a** (461.9 mg, 1.66 mmol). The crude mixture was purified by flash chromatography (heptane/DCM : 1/1).

mp: 165.5 – 166.7 ºC.

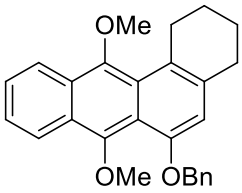
^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.23 – 8.16 (m, 1H), 8.14 – 8.09 (m, 1H), 7.75 – 7.67 (m, 2H), 7.63 (d, *J* = 7.3 Hz, 2H), 7.43 (t, *J* = 7.4 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.08 (s, 1H), 5.28 (s, 2H), 3.31 – 3.20 (m, 2H), 2.90 – 2.80 (m, 2H), 1.88 – 1.73 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 186.7, 183.2, 156.8, 146.9, 136.8, 134.5, 134.4, 134.2, 133.8, 133.3, 133.0, 128.7, 127.9, 127.0, 126.4, 122.2, 120.9, 76.7, 71.2, 31.7, 29.1, 23.5, 22.0.

HRMS (ESI): calculated for $C_{25}H_{21}O_3$ ($[M+H]^+$) 369.1491, found 369.1451.

From 191a (Aerobic photooxidation). A solution of phenol **191a** (22.4 mg, 0.06 mmol) in $CHCl_3$ (7.0 mL) was irradiated with blue LEDs (λ_{max} 450 nm) in an open flask and stirred at rt for 30 min. After this time, the solvent was evaporated and the residue purified by flash chromatography (heptane/DCM : 1/1) to give compound **190a** in 48% yield (10.0 mg, 0.03 mmol), as a yellow solid.

6-(Benzyloxy)-7,12-dimethoxy-1,2,3,4-tetrahydrotetraphene (191a)



Following **Method C**, compound **191a** was obtained in 91% yield (541.3 mg, 1.36 mmol), as a yellow solid, from compound **190a** (552.6 mg, 1.50 mmol). The crude mixture was purified by flash chromatography (heptane/DCM : 7/3).

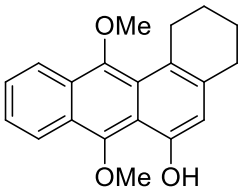
mp: 149.4 – 149.8 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.40 – 8.33 (m, 1H), 8.33 – 8.25 (m, 1H), 7.67 (d, J = 7.0 Hz, 2H), 7.56 – 7.35 (m, 5H), 6.60 (s, 1H), 5.25 (s, 2H), 3.89 (s, 3H), 3.87 (s, 3H), 3.50 – 3.38 (m, 2H), 2.93 (t, J = 5.8 Hz, 2H), 1.98 – 1.82 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 153.1, 149.7, 149.6, 137.5, 134.2, 128.6, 127.9, 127.9, 127.6, 127.0, 126.1, 126.0, 125.2, 124.8, 123.3, 122.6, 118.9, 109.0, 71.7, 63.7, 63.3, 31.8, 29.2, 24.4, 22.8.

HRMS (ESI): calculated for $C_{27}H_{27}O_3$ ($[M+H]^+$) 399.1960, found 399.1942.

7,12-Dimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (22a)



Following **Method D**, compound **22a** was obtained in 83% yield (131.4 mg, 0.43 mmol), as a yellow solid, from compound **191a** (200 mg, 0.50 mmol). The crude mixture was purified by flash chromatography (heptane/DCM : 7/3).

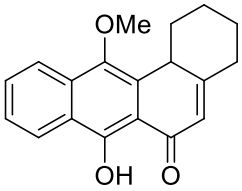
mp: decomposed.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.93 (s, 1H), 8.30 – 8.24 (m, 1H), 8.17 – 8.11 (m, 1H), 7.52 – 7.46 (m, 2H), 6.59 (s, 1H), 4.09 (s, 3H), 3.86 (s, 3H), 3.46 – 3.39 (m, 2H), 2.93 – 2.86 (m, 2H), 1.90 – 1.81 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 151.0, 150.8, 147.9, 136.0, 127.0, 126.7, 125.9, 125.7, 123.6, 123.3, 123.0, 121.6, 116.9, 111.1, 64.3, 63.5, 31.7, 28.8, 24.3, 22.7.

HRMS (ESI): calculated for $C_{20}H_{21}O_3$ ($[M+H]^+$) 309.1485, found 309.1478.

7-Hydroxy-12-methoxy-1,3,4,12b-tetrahydrotetraphen-6(2H)-one (192).



To a solution of **191a** (50.0 mg, 0.12 mmol) in DCM (1.5 mL), $AlCl_3$ (48.0 mg, 0.36 mmol) was added slowly and the reaction stirred for 30 min at rt. The reaction was quenched with an aqueous solution of HCl 10% and extracted with DCM (x3). The organic layer was dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 20:1) to give **192** in 15% yield (5.5 mg, 0.02 mmol), as an orange solid.

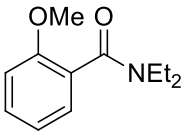
mp: 28.9 – 30.5 ºC

^{1}H NMR (300 MHz, CDCl3) δ: 14.32 (s, 1H), 8.46 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 8.4 Hz, 1H), 7.70 – 7.63 (m, 1H), 7.52 (t, J = 7.6 Hz, 1H), 6.27 (s, 1H), 3.92 (s, 2H), 3.73 (dd, J = 11.6, 4.4 Hz, 1H), 2.90 – 2.83 (m, 1H), 2.71 – 2.62 (m, 1H), 2.43 (td, J = 12.5, 5.1 Hz, 1H), 2.20 – 2.11 (m, 1H), 1.97 – 1.89 (m, 1H), 1.86 – 1.76 (m, 1H), 1.63 – 1.56 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 191.3, 168.1, 158.8, 144.6, 131.5, 130.2, 129.8, 125.4, 124.8, 124.6, 122.3, 121.7, 109.4, 61.8, 41.6, 38.3, 37.2, 30.2, 26.8.

HRMS (ESI): calculated for $C_{19}H_{19}O_3$ ($[M+H]^+$) 295.1328, found 295.1336.

***N*,*N*-Diethyl-2-methoxybenzamide (194)[121]**

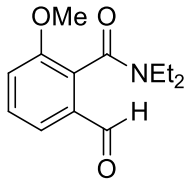


N,*N*-Diethyl-2-methoxybenzamide (**194**) was prepared according to a previously published procedure.[121] 2-Methoxybenzoic acid (**193**) (3.04 g, 19.70 mmol) and *N*-hydroxysuccinimide (2.69 g, 22.70 mmol) were dissolved in EtOAc (150 mL) and then, *N*,*N*-dicyclohexylcarbodiimide (DCC, 4.25 g, 20.30 mmol) was added at rt and the mixture stirred for 5 h. Then, diethylamine (14.9 mL, 142.60 mmol) was added and the mixture stirred overnight at rt. The reaction was quenched with AcOH (75 mL) and the resulting solid was removed by filtration and washed with EtOAc. The filtrate was concentrated and filtered again. The crude concentrate was diluted in EtOAc and washed with aqueous NaOH (1M). The organic layer was washed with brine (x2), dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 3/2) to afford *N*,*N*-diethyl-2-methoxybenzamide (**194**) in 79% yield (3.22 g, 15.53 mmol), as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.37 – 7.27 (m, 1H), 7.18 (dd, *J* = 7.4, 1.8 Hz, 1H), 6.95 (dt, *J* = 7.4, 1.0 Hz, 1H), 6.90 (d, *J* = 7.9 Hz, 1H), 3.80 (s, 3H), 3.65 – 3.49 (m, 2H), 3.13 (q, *J* = 7.0 Hz, 2H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.02 (t, *J* = 7.1 Hz, 3H).

[121] B. J. Naysmith, M. Brimble, *Org. Lett.* **2013**, *15*, 2006-2009.

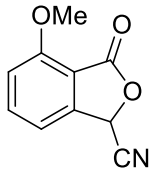
***N*,*N*-Diethyl-2-formyl-6-methoxybenzamide (195)[121]**



N,*N*-Diethyl-2-formyl-6-methoxybenzamide (**195**) was prepared according to a previously published procedure.[121] To a solution of *N*,*N*-diethyl-2-methoxybenzamide (**194**) (3.22 g, 15.53 mmol) in dry THF (32 mL) at -78 ºC, under inert atmosphere, *tert*-BuLi 1.6M in THF (15.3 mL, 155.34 mmol) was added dropwise and the mixture was stirred for 90 min at -78 ºC. Then, dry DMF (32 mL) was added and the reaction was stirred at -78ºC for 3 h, quenched with NH_4Cl sat. and extracted with EtOAc (x3). The combined organic layers were washed with brine (x2), dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The residue was purified by flash chromatography (heptane/EtOAc : 1/1) to give *N*,*N*-diethyl-2-formyl-6-methoxybenzamide (**195**) in 88% yield (3.20 g, 13.58 mmol), as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.02 (s, 1H), 7.53 (dd, *J* = 7.4, 1.0 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.16 (dd, *J* = 8.2, 1.2 Hz, 1H), 3.90 (s, 3H), 3.80 – 3.65 (m, 1H), 3.65 – 3.51 (m, 1H), 3.12 (q, *J* = 7.4, 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.04 (t, *J* = 7.1 Hz, 3H).

4-Methoxy-3-oxo-1,3-dihydroisobenzofuran-1-carbonitrile (183b) [121]

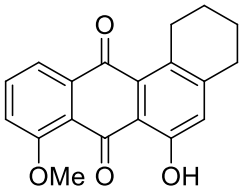


Compound **183b** was prepared according to a previously published procedure.[121] To a solution of *N*,*N*-Diethyl-2-formyl-6-methoxybenzamide (**195**) (3.20 g, 13.58 mmol), 18-crown-6 (189.7 mg, 0.68 mmol) and KCN (spatula tip) in dry CH_2Cl_2 (57 mL), TMS-CN (2.2 mL, 18.20 mmol) was added at 0 ºC. The reaction was stirred at 0 ºC for 2h and then, brought to rt. The solvents were removed carefully and AcOH (57 mL) was added dropwise to the crude oil at 0 ºC. The mixture was left to reach rt and stirred overnight. The reaction was quenched with aqueous NaOH (1M) and extracted with EtOAc (x3). The organic layer was washed with brine (x2), dried over $MgSO_4$

and concentrated to dryness under reduced pressure. The crude product was purified by flash chromatography (heptane/EtOAc : 1/1) to give **183b** in 89% yield (2.29 g, 12.10 mmol), as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.77 (dd, *J* = 8.3, 7.6 Hz, 1H), 7.22 (d, *J* = 7.6 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 6.00 (s, 1H), 4.03 (s, 3H).

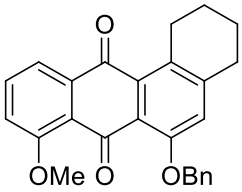
6-Hydroxy-8-methoxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (182b)[122]



Following **Method A,** compound **182b** was obtained in 81% yield (680.4 mg, 2.20 mmol), as an orange solid, from phthalide **183b** (515.4 mg, 2.72 mmol) and compound **184** (736.6 mg, 4.09 mmol). The crude was purified by flash chromatography (heptane/DCM : 3/1).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 13.22 (s, 1H), 7.86 (dd, J = 7.7, 1.0 Hz, 1H), 7.70 (t, J = 8.1 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.01 (s, 1H), 4.06 (s, 3H), 3.26 – 3.16 (m, 2H), 2.89 – 2.79 (m, 2H), 1.83 – 1.75 (m, 4H).

6-(Benzyloxy)-8-methoxy-1,2,3,4-tetrahydrotetraphene-7,12-dione (190b)



Following **Method B**, compound **190b** was obtained in 98% yield (629.2 mg, 1.58 mmol), as a yellow solid, from compound **182b** (500 mg, 1.62 mmol). The crude was purified by flash chromatography (heptane/DCM : 1/1).

[122] D. Mal, H. N. Roy, *J. Chem. Soc., Perkin Trans. 1* **1999**, 3167-3171.

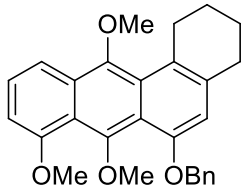
mp: 187.2 – 188.3 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.66 (dd, *J* = 7.7, 1.1 Hz, 1H), 7.62 – 7.55 (m, 3H), 7.43 – 7.36 (m, 2H), 7.34 – 7.27 (m, 1H), 7.21 (dd, *J* = 8.2, 1.0 Hz, 1H), 6.99 (s, 1H), 5.27 (s, 2H), 3.99 (s, 3H), 3.22 – 3.11 (m, 2H), 2.84 – 2.74 (s, 2H), 1.83 – 1.72 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 187.1, 183.6, 158.4, 155.5, 145.2, 137.1, 137.0, 133.7, 133.0, 132.8, 128.7, 127.8, 127.1, 124.9, 123.9, 121.2, 118.6, 116.8, 71.4, 56.6, 31.4, 28.5, 23.5, 22.1.

HRMS (FAB): calculated for $C_{26}H_{23}O_4$ ($[M+H]^+$) 399.1596, found 399.1592.

6-(Benzyloxy)-7,8,12-trimethoxy-1,2,3,4-tetrahydrotetraphene (191b)



Following **Method C**, compound **191b** was obtained in 66% yield (141.8 mg, 0.33 mmol), as a yellow solid, from compound **190b** (200.0 mg, 0.50 mmol). The crude was purified by flash chromatography (heptane/AcOEt : 7/3).

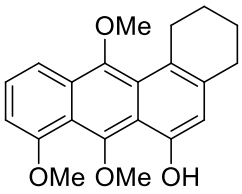
mp: 52.2 – 54.0 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.88 (d, *J* = 8.7 Hz, 1H), 7.64 (d, *J* = 7.3 Hz, 2H), 7.49 – 7.32 (m, 5H), 6.77 (d, *J* = 7.5 Hz, 1H), 6.57 (s, 1H), 5.22 (s, 2H), 4.03 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.39 (t, *J* = 5.1 Hz, 2H), 2.88 (t, *J* = 5.7 Hz, 2H), 1.96 – 1.77 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.2, 153.9, 151.0, 149.2, 137.8, 134.8, 129.2, 128.5, 127.9, 127.8, 125.9, 124.4, 119.7, 118.8, 115.0, 109.6, 104.0, 71.9, 64.0, 62.9, 56.3, 31.6, 29.3, 24.3, 22.8.

HRMS (FAB): calculated for $C_{28}H_{28}O_4$ ($[M]^+$) 428.1988, found 428.1995.

7,8,12-Trimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (11b) (22b)



Following **Method D**, compound **22b** was obtained in 87% yield (33.9 mg, 0.10 mmol), as a yellow solid, from **191b** (50 mg, 0.12 mmol). The crude was purified by flash chromatography (heptane/DCM : 7/3).

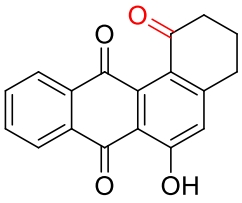
mp: decomposed.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.34 (s, 1H), 7.89 (d, *J* = 8.8 Hz, 1H), 7.35 (dd, *J* = 7.7 Hz, 1H), 6.80 (d, *J* = 7.5 Hz, 1H), 6.59 (s, 1H), 4.07 (s, 3H), 3.97 (s, 3H), 3.81 (s, 3H), 3.41 (t, *J* = 4.7 Hz, 2H), 2.89 (t, *J* = 5.2 Hz, 2H), 1.95 – 1.76 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.8, 151.6, 150.4, 149.0, 136.7, 128.9, 127.4, 125.7, 122.5, 117.2, 116.5, 115.7, 111.3, 104.3, 64.6, 63.1, 56.3, 31.5, 29.9, 28.8, 24.3, 22.7.

HRMS (ESI): calculated for $C_{21}H_{23}O_4$ ($[M+H]^+$) 339.1590, found 339.1579.

6-Hydroxy-3,4-dihydrotetraphene-1,7,12(2H)-trione (196)[123]



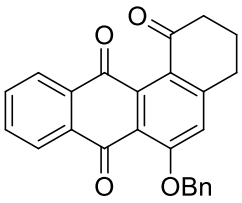
From 182a (Aerobic photooxidation). A solution of phenol **182a** (147.4 mg, 0.53 mmol) in $CHCl_3$ (62 mL) was irradiated with blue LEDs (λ_{max} 450 nm) in an open flask and stirred at rt for 6 h. After this time, the solvent was evaporated and the residue purified by flash chromatography (heptane/EtOAc : 3/1) to give compound **196** in 74% yield (114.8 mg, 0.39 mmol), as an orange solid.

[123] D. Mal, H. N. Roy, N. K. HaTra, S. Adhikari, *Tetrahedron* **1997**, *53*, 2177-2184.

^{1}H NMR (300 MHz, $CDCl_3$) δ 12.79 (s, 1H), 8.24 – 8.17 (m, 1H), 8.16 – 8.09 (m, 1H), 7.82 – 7.73 (m, 2H), 6.99 (s, 1H), 2.84 (t, *J* = 6.7 Hz, 4H), 2.22 – 2.12 (m, 2H).

From 182c (Aerobic photooxidation). A solution of compound **182c** (56.8 mg, 0.18 mmol) in $CHCl_3$ (21 mL) was irradiated with blue LEDs (λ_{max} 450 nm) in an open flask and stirred at rt for 6 h. After this time, the solvent was evaporated and the residue purified by flash chromatography (heptane/EtOAc : 3/1) to give compound **196** in 99% yield (51.0 mg, 0.17 mmol), as an orange solid.

6-Benzyloxy-3,4-dihydrotetraphene-1,7,12(2H)-trione (190c)



Following **Method B**, compound **190c** was obtained in 92% yield (137.9 mg, 0.36 mmol), as a brown solid, from compound **196** (114.8 mg, 0.39 mmol). The crude was purified by flash chromatography (heptane/EtOAc : 1/1).

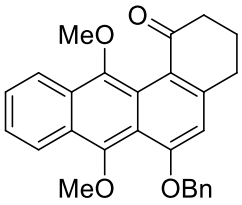
mp: 190.7 – 191.5 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.20 – 8.14 (m, 1H), 8.09 – 8.03 (m, 1H), 7.77 – 7.67 (m, 2H), 7.61 (d, *J* = 7.4 Hz, 2H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.02 (s, 1H), 5.33 (s, 2H), 2.89 – 2.80 (m, 4.7 Hz, 4H), 2.24 – 2.13 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 198.2, 185.1, 181.3, 160.2, 152.1, 140.2, 135.7, 134.2, 134.1, 133.6, 133.3, 129.5, 128.7, 128.0, 126.7, 126.6, 126.1, 122.6, 116.0, 70.9, 39.0, 30.4, 22.6.

HRMS (FAB): calculated for $C_{25}H_{19}O_4$ ($[M+H]^+$) 383.1283, found 383.1273.

6-Benzyloxy-7,12-dimethoxy-3,4-dihydrotetraphen-1(2*H*)-one (191c)



Following **Method C**, compound **191c** was obtained in >99% yield (268.1 mg, 0,65 mmol), as a yellow solid, from compound **190c** (248.8 mg, 0.65 mmol). The crude was purified by flash chromatography (heptane/EtOAc/DCM : 3/1/0.5).

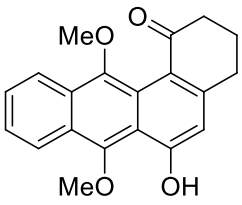
mp: 205.7 – 206.6 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.38 – 8.29 (m, 2H), 7.66 – 7.59 (m, 2H), 7.59 – 7.36 (m, 5H), 6.54 (s, 1H), 5.32 (s, 2H), 3.84 (s, 3H), 3.75 (s, 3H), 2.91 (t, *J* = 5.9 Hz, 2H), 2.85 (t, *J* = 6.8 Hz, 2H), 2.28 – 2.17 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 195.2, 159.3, 149.9, 149.0, 148.1, 136.1, 128.7, 128.2, 127.7, 127.1, 126.7, 125.8, 123.89, 123.2, 123.0, 122.1, 118.4, 104.4, 71.3, 63.9, 61.3, 38.9, 31.1, 22.5.

HRMS (FAB): calculated for $C_{27}H_{25}O_4$ ($[M+H]^+$) 413.1753, found 413.1754.

6-Hydroxy-7,12-dimethoxy-3,4-dihydrotetraphen-1(2*H*)-one (22c)



Following **Method D**, compound **22c** was obtained in 83% yield (173.0 mg, 0.54 mmol), as a yellow solid, from **191c** (268,1 mg, 065 mmol). The crude was purified by flash chromatography (heptane/EtOAc : 3/1).

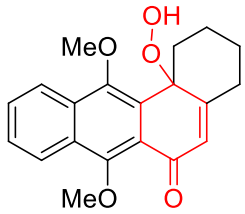
mp: 167.5 – 169.3 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.50 (s, 1H), 8.42 – 8.35 (m, 1H), 8.16 – 8.09 (m, 1H), 7.58 – 7.49 (m, 2H), 6.57 (s, 1H), 4.10 (s, *J* = 2.4 Hz, 3H), 3.74 (s, 3H), 2.90 (t, *J* = 6.0 Hz, 2H), 2.82 (t, *J* = 6.8 Hz, 2H), 2.24 – 2.14 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 194.9, 158.0, 150.4, 150.0, 148.1, 127.9, 126.7, 126.5, 124.6, 123.9, 122.8, 121.7, 121.5, 116.5, 108.3, 76.7, 64.6, 61.4, 39.1, 31.1, 22.6.

HRMS (ESI): calculated for $C_{20}H_{19}O_4$ ($[M+H]^+$) 323.1277, found 323.1273.

12b-Hydroperoxy-7,12-dimethoxy-1,3,4,12b-tetrahydrotetraphen-6(2*H*)-one (23a)



A solution of phenol **22a** (131.4 mg, 0.43 mmol) in acetone (50 mL), was irradiated with blue LEDs (λ_{max} 450 nm) in an open flask and stirred at rt for 15 min. After this time, the solvent was evaporated and the residue purified by flash chromatography (heptane/EtOAc : 4/1) to give *para*-peroxy quinol **23a** in 70% yield (101.9 mg, 0.30 mmol), as a pale brown solid.

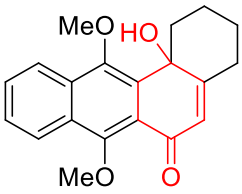
mp: 163.8 – 164.3 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.37 (d, *J* = 8.1 Hz, 1H), 8.14 (d, *J* = 8.6 Hz, 1H), 7.70 – 7.57 (m, 2H), 7.52 (s, 1H), 6.36 (s, 1H), 4.10 (s, 3H), 4.01 (s, 3H), 3.47 – 3.37 (m, 1H), 2.84 (td, J = 14.0, 6.1 Hz, 1H), 2.50 – 2.41 (m, 1H), 2.14 – 1.92 (m, 2H), 1.72 – 1.57 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 184.7, 161.3, 155.2, 151.5, 131.8, 130.8, 130.0, 128.9, 127.7, 127.1, 124.6, 122.9, 120.7, 82.5, 63.5, 62.8, 37.5, 32.7, 28.6, 21.6.

HRMS (ESI): calculated for $C_{20}H_{20}O_5Na$ $[M+Na]^+$ 363.1202, found 363.1190.

12b-Hydroxy-7,12-dimethoxy-1,3,4,12b-tetrahydrotetraphen-6(2*H*)-one (24a)



From 22a (with Oxone®). Following **Method E**, compound **24a** was obtained in 76% yield for two steps (84.9 mg, 0.26 mmol), as a pale brown solid, from phenol **22a** (105.2 mg, 0.34 mmol) using Oxone® (8 equiv.) and $NaHCO_3$ (24 equiv.) in water (0.06 M) and acetone (0.1 M) after 4 h stirring. The crude was purified by flash chromatography (heptane/EtOAc : 4/1).

mp: 179.3 – 180.9 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.38 (d, *J* = 8.6 Hz, 1H), 8.05 (d, *J* = 8.3 Hz, 1H), 7.70 – 7.55 (m, 2H), 6.19 (s, 1H), 4.35 (s, 1H), 4.14 (s, 3H), 4.00 (s, 3H), 2.97 (td, *J* = 12.2, 4.2 Hz, 1H), 2.73 – 2.62 (m, 1H), 2.40 – 2.30 (m, 1H), 2.21 (tt, *J* = 13.4, 4.1 Hz, 1H), 2.15 – 2.05 (m, 1H), 1.74 – 1.66 (m, 1H), 1.60 (td, *J* = 13.5, 4.4 Hz, 1H), 1.49 (tt, *J* = 13.2, 4.4 Hz, 1H).

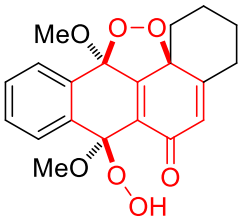
^{13}C NMR (75 MHz, $CDCl_3$) δ: 184.0, 163.0, 155.1, 150.2, 134.7, 130.5, 129.8, 128.8, 126.8, 124.9, 124.6, 122.3, 119.2, 71.8, 63.7, 63.0, 42.7, 32.3, 29.2, 21.6.

HRMS (ESI): calculated for $C_{20}H_{21}O_4$ $[M+H]^+$ 325.1434, found 325.1443.

From 22a (Aerobic photooxidation). A solution of phenol **22a** (75.8 mg, 0.25 mmol) in acetone (29 mL) was irradiated with blue LEDs (λ_{max} 450 nm) in an open flask and stirred at rt for 15 min. After this time, the solvent was evaporated and the residue was treated with NaI in THF, following **Method F**. Purification by flash chromatography (heptane/EtOAc : 4/1) gave *para*-quinol **24a** in 75% yield (59.7 mg, 0.18 mmol), as a pale brown solid.

From 23a. Following **Method F**, *para*-quinol **24a** was obtained in 76% yield (44.6 mg, 0.14 mmol), as a pale brown solid, from *para*-peroxy quinol **23a** (61.3 mg, 0.18 mmol). The crude was purified by flash chromatography (heptane/EtOAc : 4/1).

(7*S,11b*R**,13a*S**)-7-Hydroperoxy-7,11b-dimethoxy-3,4,7,11b-tetrahydro-1*H*-tetrapheno[12-cd][1,2]dioxol-6(2*H*)-one (197)**



From 22a. A solution of phenol **22a** (127.6 mg, 0.41 mmol) in $CHCl_3$ (48 mL) was irradiated with blue LEDs (λ_{max} 450 nm) in an open flask and stirred at rt for 2 hours. After this time, the solvent was evaporated and the residue was purified by flash chromatography (heptane/EtOAc : 4/1) to give compound **197** in 47% yield (70.7 mg, 0.19 mmol), as a pale brown solid.

mp: 157.1 – 157.7 ºC.

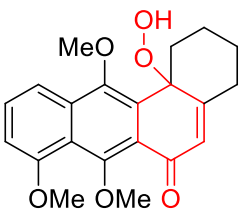
^{1}H NMR (300 MHz, $CDCl_3$) δ: 11.98 (s, 1H), 7.84 – 7.77 (m, 1H), 7.58 – 7.51 (m, 1H), 7.47 – 7.41 (m, 2H), 6.16 (d, *J* = 1.1 Hz, 1H), 3.35 (s, 3H), 3.28 (s, 3H), 3.16 – 3.06 (m, 1H), 2.57 – 2.49 (m, 1H), 2.44 (td, *J* = 12.5, 3.9 Hz, 1H), 2.15 – 2.09 (m, 1H), 1.87 (tt, *J* = 13.6, 10.7, 3.8 Hz, 1H), 1.82 – 1.73 (m, 1H), 1.56 (td, *J* = 13.6, 3.8 Hz, 1H), 1.54 – 1.39 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 184.5, 164.6, 161.1, 134.5, 133.8, 131.0, 129.3, 129.2, 127.3, 127.0, 124.0, 101.3, 101.3, 81.8, 52.8, 51.4, 40.1, 33.1, 29.2, 21.3.

HRMS (ESI): calculated for $C_{20}H_{20}O_7Na$ ([M+Na]$^+$) 395.1106, found 395.1109.

From 23a. A solution of **23a** (31.9 mg, 0.09 mmol) in $CHCl_3$ (10.6 mL) was irradiated with blue LEDs (λ_{max} 450 nm) in an open flask and stirred at rt for 20 min. After this time, the solvent was evaporated to give compound **197** pure in >99% yield (35.8 mg, 0.10 mmol), as a pale brown solid.

12b-Hydroperoxy-7,8,12-trimethoxy-1,3,4,12b-tetrahydrotetraphen-6(2*H*)-one (12b) (23b)



A solution of phenol **22b** (37.5 mg, 0.11 mmol) in acetone (13.0 mL) was irradiated with blue LEDs (λ_{max} 450 nm) in an open flask and stirred at rt for 15 min. After this time, the solvent was evaporated and the residue was purified by flash chromatography (heptane/EtOAc : 3/1) to give *para*-peroxy quinol **23b** in 81% yield (33.1 mg, 0.09 mmol), as a pale brown solid.

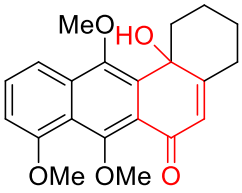
mp: 154.7 – 155.9 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (s, 1H), 7.70 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.51 (t, *J* = 8.1 Hz, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 6.22 (s, 1H), 4.05 (s, 3H), 3.96 (s, 3H), 3.85 (s, 3H), 3.44 – 3.33 (m, 1H), 2.83 (td, *J* = 12.9, 4.2 Hz, 1H), 2.35 (d, *J* = 12.9 Hz, 1H), 2.07 – 1.92 (m, 2H), 1.64 – 1.45 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 184.5, 159.7, 158.7, 156.5, 151.1, 134.3, 131.5, 129.2, 128.2, 122.0, 121.8, 115.2, 107.5, 82.4, 63.3, 62.9, 56.6, 37.3, 32.5, 28.5, 21.6.

HRMS (ESI): calculated for $C_{21}H_{23}O_6$ ($[M+H]^+$) 371.1489, found 371.1485.

12b-Hydroxy-7,8,12-trimethoxy-1,3,4,12b-tetrahydrotetraphen-6(2*H*)-one (13b) (24b)



From 22b (with Oxone®). Following **Method E**, compound **24b** was obtained in 30% yield for two steps (4.8 mg, 0.01 mmol), as a pale brown solid, from phenol **22b** (15.2 mg, 0.04 mmol) using Oxone® (16 equiv.) and K_2CO_3 (48 equiv.) in water (0.06 M) and acetone (0.1 M) after 4 h stirring. The crude was purified by flash chromatography (heptane/EtOAc : 3/1).

mp: 168.5 – 170.1 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.57 – 7.49 (m, 1H), 6.90 (d, *J* = 7.0 Hz, 1H), 6.13 (s, 1H), 4.61 (d, *J* = 168.7 Hz, 1H), 4.07 (s, 3H), 4.00 (s, 3H), 3.90 (s, 3H), 2.94 (td, *J* = 12.2, 4.6 Hz, 1H), 2.71 – 2.61 (m, 1H), 2.35 – 2.25 (m, 1H), 2.25 – 2.13 (m, 1H), 2.12 – 2.02 (m, 1H), 1.72 – 1.64 (m, 1H), 1.64 – 1.44 (m, 3H).

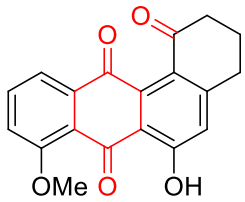
^{13}C NMR (75 MHz, $CDCl_3$) δ 183.9, 161.6, 159.0, 156.6, 149.9, 135.5, 133.1, 129.2, 125.1, 121.9, 120.2, 114.6, 107.2, 71.8, 63.6, 63.0, 56.6, 42.7, 32.1, 29.3, 21.6.

HRMS (ESI): calculated for $C_{21}H_{23}O_5$ ($[M+H]^+$) 355.1540, found 355.1531.

From 22b (Aerobic photooxidation). A solution of phenol **22b** (40.9 mg, 0.12 mmol) in acetone (14.0 mL) was irradiated with blue LEDs (λ_{max} 450 nm) in an open flask and stirred at rt for 15 min. After this time, the solvent was evaporated and the residue was treated with NaI in THF, following **Method F**. Purification by flash chromatography (heptane/EtOAc : 3/1) gave *para*-quinol **24b** in 63% yield (27.0 mg, 0.08 mmol), as a pale brown solid.

From 23b. Following **Method F**, *para*-quinol **24b** was obtained in 51% yield (14.9 mg, 0.04 mmol), as a pale brown solid, from *para*-peroxy quinol **23b** (30.6 mg, 0.09 mmol). The crude was purified by flash chromatography (heptane/EtOAc : 3/1).

6-Hydroxy-8-methoxy-3,4-dihydrotetraphene-1,7,12(2*H*)-trione (198)122

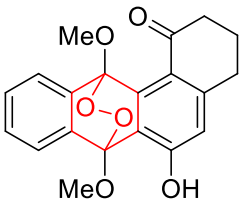


From phenol 22b (Aerobic photooxidation). A solution of phenol **22b** (36.4 mg, 0.11 mmol) in $CHCl_3$ (13.0 mL) was irradiated with blue LEDs (λ_{max} 450 nm) in an open flask and stirred at rt for 6 h. After this time, the solvent was evaporated and the residue was purified by flash chromatography (heptane/AcOEt : 4/1) to give compound **198** in 18% yield (6.4 mg, 0.02 mmol), as a red solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 13.05 (s, 1H), 7.77 – 7.71 (m, 2H), 7.31 (dd, J = 6.8, 2.8 Hz, 1H), 6.97 (s, 1H), 4.05 (s, 3H), 2.83 (dt, J = 11.4, 6.5 Hz, 4H), 2.21 – 2.10 (m, 2H).

From *para*-peroxy quinol 23b (Aerobic photooxidation). A solution of *para*-peroxy quinol **23b** (37.7 mg, 0.10 mmol) in $CHCl_3$ (12.0 mL) was irradiated with blue LEDs (λ_{max} 450 nm) in an open flask and stirred at rt for 90 min. After this time, the solvent was evaporated and the residue was purified by flash chromatography (heptane/EtOAc : 2/1) to give compound **198** in 31% yield (10.1 mg, 0.03 mmol), as a red solid.

6-Hydroxy-7,12-dimethoxy-3,4,7,12-tetrahydro-7,12-epidioxytetraphen-1(2*H*)-one (199)



A solution of phenol **22c** (18.9 mg, 0.06 mmol) in acetone (7.0 mL) was irradiated with blue LEDs (λ_{max} 450 nm) in an open flask and stirred at rt for 45 min. After this time, the solvent was evaporated to obtain endoperoxide **199** in >99% yield (20.7mg, 0.06 mmol), as a pale brown solid.

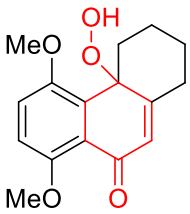
mp: 77.0 – 79.0 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.69 (s, 2H), 7.77 (d, J = 7.8 Hz, 2H), 7.47 – 7.27 (m, 7H), 6.58 (s, 2H), 4.05 (s, 6H), 3.74 (s, 7H), 2.91 – 2.75 (m, 5H), 2.69 – 2.43 (m, 5H), 2.13 – 2.05 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 197.0, 154.6, 146.6, 142.4, 137.7, 137.4, 128.4, 127.4, 124.2, 122.5, 121.1, 120.4, 115.7, 104.8, 103.9, 54.9, 54.2, 39.5, 30.3, 23.0.

HRMS (ESI): calculated for $C_{20}H_{19}O_6$ ($[M+H]^+$) 355.1176, found 355.1168.

4a-Hydroperoxy-5,8-dimethoxy-2,3,4,4a-tetrahydrophenanthren-9(1*H*)-one (14)[124]

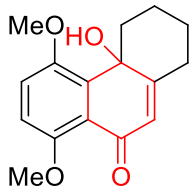


A solution of phenol **13** (20.0 mg, 0.08 mmol) in acetone (9.4 mL) was irradiated with blue LEDs (λ_{max} 450 nm) in an open flask and stirred at rt for 2 h. After this time, the solvent was evaporated and the residue purified by flash chromatography (heptane/EtOAc : 2/1) to give compound **14** in 39% yield (8.8 mg, 0.03 mmol), as a beige solid.

[124] S. Vila-Gisbert, A. Urbano, M. C. Carreño, *Chem. Commun*. **2013**, *49*, 3561-3563.

^{1}H NMR (300 MHz, CDCl3) δ: 7.70 (s, 1H), 7.15 (d, J = 9.2 Hz, 1H), 7.00 (d, J = 9.2 Hz, 1H), 6.26 (s, 4H), 3.88 (s, 3H), 3.88 (s, 3H), 3.24 – 3.09 (m, 1H), 2.82 (td, J = 12.3, 4.3 Hz, 1H), 2.39 (d, J = 12.6 Hz, 1H), 2.05 (d, J = 9.3 Hz, 1H), 1.98 – 1.83 (m, 1H), 1.67 – 1.53 (m, 1H), 1.46 – 1.33 (m, 2H).

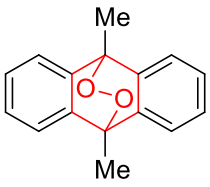
4a-hydroxy-5,8-dimethoxy-2,3,4,4a-tetrahydrophenanthren-9(1H)-one (15)124



A solution of phenol **13** (20.0 mg, 0.08 mmol) in acetone (9.4 mL) was irradiated with blue LEDs (λ_{max} 450 nm) in an open flask and stirred at rt for 2 min. After this time, the solvent was evaporated and the residue was treated with NaI in THF following **Method F**. Purification by flash chromatography (heptane/EtOAc : 2/1) gave *para*-quinol **15** in 50% yield (10.5 mg, 0.04 mmol), as a beige solid.

^{1}H NMR (300 MHz, CDCl3) δ: 7.11 (d, J = 9.1 Hz, 1H), 6.95 (d, J = 9.1 Hz, 1H), 6.13 (s, 1H), 4.49 (s, 1H), 3.94 (s, 3H), 3.89 (s, 3H), 2.88 (td, J = 12.6, 4.6 Hz, 1H), 2.72 (d, J = 12.1 Hz, 1H), 2.30 (d, J = 11.9 Hz, 1H), 2.18 – 1.96 (m, 2H), 1.71 – 1.55 (m, 1H), 1.53 – 1.28 (m, 2H).

9,10-Dimethyl-9,10-diydro-9,10-epidioxyanthracene (X)[125]

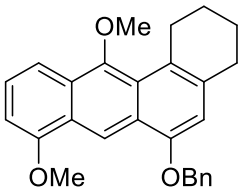


A solution of 9,10-dimethylanthracene (**X**) (20.0 mg, 0.10 mmol) in $CHCl_3$ (11.8 mL) was irradiated with blue LEDs (λ_{max} 450 nm, Ref. 2040694) in an open flask and stirred at rt for 30 min. After this time, the solvent was evaporated and the residue purified by flash chromatography (heptane/AcOEt 3/1), to give endoperoxide **X** in 93% yield (24.6 mg, 0.09 mmol), as a white solid.

[125] a) J. M. Carney, R. J. Hammer, M. Hulce, C. M. Lomas, D. Miyashiro, *Tetrahedron Lett.* **2011**, *52*, 352-355; b) H. Kotani, K. Ohkubo, S. Fukuzumi, *J. Am. Chem. Soc.* **2004**, *126*, 15999-16006.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.42 – 7.36 (m, 2H), 7.32 – 7.26 (m, 2H), 2.16 (s, 3H).

6-Benzyloxy-8,12-dimethoxy-1,2,3,4-tetrahydrotetraphene (204)



A solution of **190b** (21.7 mg, 0.05 mmol), TBAB (4.9 mg, 0.01 mmol), $Na_2S_2O_4$ (57.5 mg, 0.40 mmol) and KOH (70.2 mg, 1.25 mmol) in THF (0.3 mL) and water (0.4 mL), under an inert atmosphere, was stirred for 16 hours at reflux. Then, Me_2SO_4 (56.0 µL, 0.59 mmol) was added dropwise to the mixture, stirred for 5 h and quenched with aqueous ammonia solution. The mixture was extracted with EtOAc (x3) and the combined organic layers were washed with brine (x2), dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The residue was purified by flash chromatography (heptane/DCM : 8/2) to afford **204** in 39% yield (8.5 mg, 0.02 mmol), as a pale yellow solid.

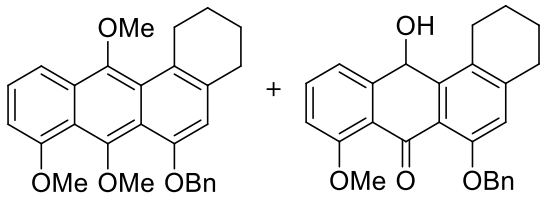
mp: 163.9 – 164.7 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.12 (s, 1H), 7.86 (d, *J* = 8.8 Hz, 1H), 7.59 (d, *J* = 7.0 Hz, 2H), 7.48 – 7.34 (m, 4H), 6.73 (d, *J* = 7.4 Hz, 1H), 6.49 (s, 1H), 5.31 (s, 2H), 4.05 (s, 3H), 3.91 (s, 3H), 3.53 – 3.45 (m, 2H), 2.94 – 2.86 (m, 2H), 1.94 – 1.84 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.3, 153.3, 152.6, 137.6, 134.3, 128.7, 127.9, 127.7, 127.4, 126.0, 125.8, 125.6, 124.7, 124.0, 114.9, 112.0, 106.4, 101.8, 70.2, 63.4, 55.7, 53.6, 32.2, 28.5, 24.3, 22.8.

HRMS (ESI): calculated for $C_{27}H_{26}O_3Na$ ($[M+Na]^+$) 421.1774, found 421.1758.

6-Benzyloxy-7,8,12-trimethoxy-1,2,3,4-tetrahydrotetraphene (191b) and 6-benzyloxy-12-hydroxy-1,2,3,4-tetrahydrotetraphen-7(12H)-one (205)



Compound **190b** (20.4 mg, 0.05 mmol), TBAB (4.8 mg, 0.01 mmol) and $Na_2S_2O_4$ (211.9 mg, 1.34 mmol) were dissolved, under inert atmosphere, in a mixture of THF (0.3 mL) and water (0.2 mL) and stirred for 30 min at rt. Then, a solution of KOH (164.0 mg, 2.92 mmol) in water (0.2 mL) was added and the reaction mixture was stirred for 30 min at rt. After this time, Me_2SO_4 (0.19 mL, 2.00 mmol) was added dropwise to the reaction, the mixture was stirred at rt for 2 h until the starting material was consumed, and finally, quenched with aqueous ammonia solution. The mixture was extracted with EtOAc (x3) and the combined organic layers were washed with brine (x2), dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The residue was purified by flash chromatography (heptane/DCM : 8/2) to afford **191b** in 19% yield (4.1 mg, 0.01 mmol), as a yellow solid, and **205** in 42% yield (8.6 mg, 0.02 mmol), as a beige solid.

6-Benzyloxy-7,8,12-trimethoxy-1,2,3,4-tetrahydrotetraphene (**191b**):

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.88 (d, *J* = 8.7 Hz, 1H), 7.64 (d, *J* = 7.3 Hz, 2H), 7.49 – 7.32 (m, 5H), 6.77 (d, *J* = 7.5 Hz, 1H), 6.57 (s, 1H), 5.22 (s, 2H), 4.03 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.39 (t, *J* = 5.1 Hz, 2H), 2.88 (t, *J* = 5.7 Hz, 2H), 1.96 – 1.77 (m, 4H).

6-Benzyloxy-12-hydroxy-1,2,3,4-tetrahydrotetraphen-7(12H)-one (**205**):

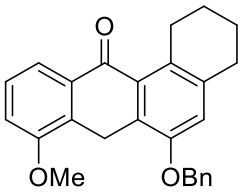
mp: 177.5 – 179.5 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.75 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 7.0 Hz, 2H), 7.47 – 7.32 (m, 4H), 7.11 (d, *J* = 8.1 Hz, 1H), 6.94 (s, 1H), 6.43 (d, J = 3.7 Hz, 1H), 5.23 (q, *J* = 12.1 Hz, 2H), 3.96 (s, 3H), 3.44 – 3.31 (m, 1H), 3.22 – 3.08 (m, 1H), 3.08 (d, J = 4.0 Hz, 1H), 2.80 (t, *J* = 5.9 Hz, 2H), 1.96 – 1.61 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 187.1, 157.2, 154.0, 139.7, 136.9, 135.3, 133.0, 130.9, 130.1, 129.4, 128.9, 128.8, 128.1, 127.3, 119.3, 117.9, 114.3, 70.7, 57.8, 56.1, 31.2, 28.5, 23.7, 22.4.

HRMS (ESI): calculated for $C_{26}H_{24}O_4Na$ ($[M+Na]^+$) 423.1566, found 423.1560.

6-Benzyloxy-8-methoxy-2,3,4,7-tetrahydrotetraphen-12(1*H*)-one (300)



Compound **190b** (21.4 mg, 0.05 mmol) and $Na_2S_2O_4$ (122.4 mg, 0.86 mmol) were dissolved in a mixture of DMF (0.3 mL) and water (0.4 mL), under an inert atmosphere. The solution was stirred for 30 min at 90 ºC and 5 days at rt. The reaction mixture was quenched with water, extracted with DCM (x3), and the organic layers dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The residue was purified by flash chromatography (heptane/EtOAc : 9/1) to afford **300** in 32% yield (6.7 mg, 0.02 mmol), as a pale yellow solid.

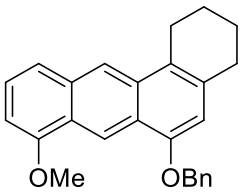
mp: 149.1 – 150.0 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.85 (d, *J* = 7.9 Hz, 1H), 7.50 (d, *J* = 7.2 Hz, 2H), 7.46 – 7.34 (m, 4H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.88 (s, 1H), 5.21 (s, 2H), 4.12 (s, 2H), 3.94 (s, 3H), 3.38 – 3.31 (m, 2H), 2.85 – 2.78 (m, 2H), 1.85 – 1.74 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 187.3, 156.6, 153.3, 137.4, 136.9, 135.2, 132.6, 131.2, 129.6, 128.9, 128.8, 128.0, 127.3, 127.2, 119.0, 116.2, 112.5, 70.2, 55.8, 31.3, 29.0, 23.9, 23.0, 22.6.

HRMS (ESI): calculated for $C_{26}H_{25}O_3$ ($[M+H]^+$) 385.1798, found 385.1806.

6-Benzyloxy-8-methoxy-1,2,3,4-tetrahydrotetraphene (301)



To a solution of **190b** (19.6 mg, 0.05 mmol) in THF (1.2 mL), sodium borohydride (76.0 mg, 2.01 mmol) and methanol (0.24 mL) were added ($NaBH_4$: 19.0 mg, 0.50 mmol, every 1h / MeOH: 0.12 mL every 2h). After 4 h, the excess of $NaBH_4$ was filtered off and the solvent was removed under reduced pressure. Then, a hot mixture of acetic acid (0.6 mL) and HCl (0.6 mL) was added to the

crude, and the solution was stirred for 10 min. The precipitates were filtered and washed with a saturated solution of $NaHCO_3$ and water, respectively. The residue was purified by flash chromatography (heptane/EtOAc : 9/1) to afford **301** in 56% yield (10.2 mg, 0.03 mmol), as a white solid.

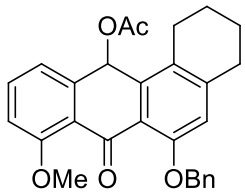
mp: 124.3 – 125.7 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.28 (s, 1H), 8.37 (s, 1H), 7.63 – 7.56 (m, 3H), 7.48 – 7.33 (m, 4H), 6.72 (d, *J* = 7.4 Hz, 1H), 6.51 (s, 1H), 5.32 (s, 2H), 4.06 (s, 3H), 3.13 (t, *J* = 6.3 Hz, 2H), 2.86 (t, *J* = 6.0 Hz, 2H), 2.06 – 1.95 (m, 2H), 1.95 – 1.85 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.0, 153.0, 137.7, 133.9, 133.1, 132.6, 128.7, 127.9, 127.5, 125.6, 124.1, 123.8, 123.4, 120.7, 120.6, 116.2, 106.0, 101.5, 70.1, 55.6, 31.3, 25.5, 23.5, 23.3.

HRMS (ESI): calculated for $C_{26}H_{24}O_2$ ($[M+H]^+$) 368.1770, found 368.1763.

6-Benzyloxy-8-methoxy-7-oxo-1,2,3,4,7,12-hexahydrotetraphen-12-yl acetate (306)



To a mixture of **190b** (28.4 mg, 0.07 mmol), zinc (46.6 mg, 0.71 mmol) and K_2CO_3 (98.12 mg, 0.71 mmol) in THF (0.6 mL), under an inert atmosphere, Ac_2O (70.0 µL, 0.74 mmol) was added and the reaction mixture stirred at rt for 16 h. Then, zinc and K_2CO_3 were filtered off and washed with DCM. To the crude mixture, HCl 0.1M was added and the solvent was removed under reduced pressure. The mixture was extracted with DCM (x3), washed with water, dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The residue was purified by flash chromatography (heptane/EtOAc : 2/1) to afford **306** in 22% yield (6.8 mg, 0.01 mmol), as a yellow solid.

mp: 159.0 – 161.2 ºC.

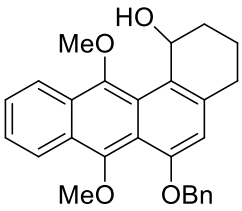
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.58 (d, *J* = 7.4 Hz, 2H), 7.45 – 7.34 (m, 3H), 7.33 – 7.26 (m, 2H), 7.11 (s, 1H), 7.01 (dd, *J* = 8.4, 0.8 Hz, 1H), 6.77 (s, 1H), 5.23 (dd, *J* = 38.4, 12.7 Hz, 2H), 3.93 (d, *J* = 3.6

Hz, 3H), 2.88 (dt, *J* = 16.6, 6.5 Hz, 1H), 2.74 (t, *J* = 6.0 Hz, 2H), 2.60 (dt, *J* = 16.6, 6.0 Hz, 1H), 1.95 (s, 3H), 1.90 – 1.68 (m, 4H), 1.66 – 1.49 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 184.9, 170.8, 158.6, 155.5, 143.6, 139.5, 137.4, 136.3, 133.1, 128.6, 128.0, 127.6, 127.0, 125.1, 122.0, 116.4, 113.2, 71.1, 66.1, 56.4, 31.0, 25.2, 23.2, 22.4, 21.3.

HRMS (FAB): calculated for $C_{28}H_{27}O_5$ ($[M+H]^+$) 443.1858, found 443.1852.

6-Benzyloxy-7,12-dimethoxy-1,2,3,4-tetrahydrotetraphen-1-ol (310)



To a stirred suspension of lithium aluminium hydride ($LiAlH_4$, 36.8 mg, 0.97 mmol) in dry THF (0.35 mL), under an inert atmosphere, a solution of compound **191c** (100.0 mg, 0.24 mmol) in dry DCM (0.81 mL) was added dropwise at rt. The reaction mixture was stirred for 90 min and quenched with a slow addition of EtOAc and some drops of water. After stirring for 15 min, the crude mixture was dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography with neutral silica gel (heptane/EtOAc : 9/1) to give **310** in 83% yield (83.5 mg, 0.20 mmol), as a pale yellow solid.

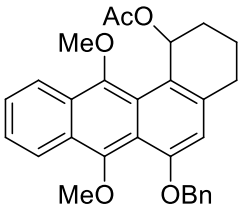
mp: 151.6 – 152.4 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.36 (d, J = 7.9 Hz, 1H), 8.25 (d, J = 8.3 Hz, 1H), 7.64 (d, J = 7.2 Hz, 2H), 7.60 – 7.33 (m, 6H), 6.57 (s, 1H), 5.44 (t, *J* = 5.0 Hz, 1H), 5.25 (s, 2H), 4.28 (s, 1H), 4.03 (s, 3H), 3.86 (s, 3H), 3.05 – 2.81 (m, 2H), 2.26 – 2.07 (m, 3H), 1.92 – 1.78 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.5, 150.8, 147.1, 137.1, 136.6, 128.6, 128.0, 127.8, 126.8, 126.6, 126.2, 125.8, 125.3, 123.5, 122.4, 119.1, 107.9, 71.4, 65.7, 64.4, 63.8, 32.7, 32.4, 18.8.

HRMS (FAB): calculated for $C_{27}H_{26}O_4$ ($[M+H]^+$) 414.1831, found 414.1828.

6-Benzyloxy-7,12-dimethoxy-1,2,3,4-tetrahydrotetraphen-1-yl acetate (311)



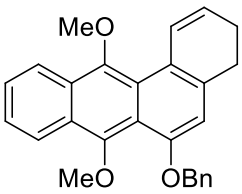
To a solution of compound **310** (51.8 mg, 0.12 mmol) in pyridine (0.7 mL), Ac_2O (0.24 mL, 2.50 mmol) was added and the reaction mixture stirred at rt for 16 h. Then, the reaction was quenched with HCl 1M and extracted with EtOAc (x3). The organic layers were washed with brine (x2), dried over $MgSO_4$ and concentrated to dryness under reduced pressure. Compound **311** was obtained in >99% yield (57.0 mg, 0.12 mmol), as a yellow oil, without further purification.

^{1}H NMR (300 MHz, CDCl3) δ: 8.33 (dd, J = 7.2, 2.2 Hz, 1H), 8.23 (dd, J = 7.2, 2.0 Hz, 1H), 7.64 (d, J = 7.1 Hz, 2H), 7.56 – 7.35 (m, 6H), 6.75 (t, J = 4.3 Hz, 1H), 6.57 (s, 1H), 5.26 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.00 – 2.90 (m, 2H), 2.31 – 2.02 (m, 4H), 1.99 (s, 3H), 1.97 – 1.79 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.3, 155.5, 150.0, 149.1, 138.1, 137.1, 128.7, 128.1, 127.8, 127.2, 126.5, 126.3, 125.4, 125.4, 123.3, 122.8, 120.7, 119.0, 107.6, 71.4, 69.6, 63.7, 63.4, 32.1, 29.9, 21.7, 17.9.

HRMS (ESI): calculated for $C_{28}H_{28}O_4Na$ ([M+Na] $^+$) 451.1879, found 451.1876. The mass was determined in MeOH and, under these conditions, the –OAc group was exchanged for the –OMe group.

6-Benzyloxy-7,12-dimethoxy-3,4-dihydrotetraphene (312)



To a solution of compound **311** (20.0 mg, 0.05 mmol) and imidazole (20.4 mg, 0.30 mmol) in DMF (0.15 mL) at 0 ºC, under an inert atmosphere, *tert*-butyldimethylsilyl chloride (TBDSCl, 21.8 mg, 0.14 mmol) was added. The reaction was stirred at rt for 2 h and quenched with water. The crude

mixture was extracted with DCM (x3), dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The residue was purified by flash chromatography with neutral silica gel (heptane/EtOAc : 9/1) to give **312** in 88% yield (16.8 mg, 0.04 mmol), as a yellow solid.

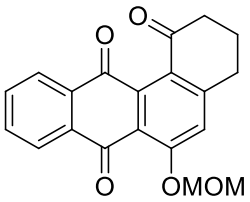
mp: 82.3 – 83.0 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.31 (td, J = 7.5, 2.1 Hz, 2H), 7.90 (d, J = 10.1 Hz, 1H), 7.65 (d, J = 7.2 Hz, 3H), 7.55 – 7.32 (m, 7H), 6.73 (d, J = 6.2 Hz, 1H), 6.13 (dt, J = 9.7, 4.7 Hz, 1H), 5.28 (s, 2H), 3.92 – 3.87 (m, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 2.91 – 2.82 (m, 2H), 2.38 – 2.28 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.6, 149.6, 149.4, 137.3, 134.9, 128.7, 128.0, 127.9, 127.6, 127.0, 126.2, 125.9, 125.3, 124.1, 123.3, 122.6, 122.2, 119.0, 108.2, 71.7, 63.8, 62.4, 30.2, 21.8.

HRMS (ESI): calculated for $C_{27}H_{24}O_3Na$ ($[M+Na]^+$) 419.1617, found 419.1606.

6-(Methoxymethoxy)-3,4-dihydrotetraphene-1,7,12(2*H*)-trione (313)



To a solution of compound **196** (49.7 mg, 0,17 mmol), *N*,*N*-diisopropylethylamine (DIPEA, 56.0 µL, 0.32 mmol) and 4-dimethylaminopyridine (DMAP, 7.1 mg, 34 mmol %) in dichloromethane (2.3 mL) at 0 ºC, chloromethyl methyl ether (MOMCl, 40.0 µL, 0.51 mmol) was added dropwise. The reaction mixture was stirred at rt for 16 h, quenched with aqueous 0.5M NaOH solution (5 mL) and stirred for 1 h to eliminate the excess of MOMCl. The crude mixture was diluted with DCM and washed with water, aqueous 1M HCl solution, water and brine, consecutively. The organic layer was dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The residue was purified by flash chromatography with neutral silica gel (heptane/EtOAc : 1/1) to give **313** in 93% yield (53.1 mg, 0.16 mmol), as a yellow solid.

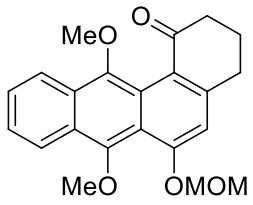
mp: 156.5 – 157.0 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.10 – 8.03 (m, 1H), 8.01 – 7.95 (m, 1H), 7.70 – 7.61 (m, 2H), 7.18 (s, 1H), 5.34 (s, 2H), 3.50 (s, 3H), 2.79 (dd, J = 13.8, 6.8 Hz, 4H), 2.19 – 2.06 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 198.3, 184.9, 181.5, 158.8, 151.9, 139.8, 134.2, 134.1, 133.6, 133.4, 130.5, 126.6, 126.2, 122.9, 118.4, 94.9, 56.7, 39.0, 30.3, 22.6.

HRMS (ESI): calculated for $C_{20}H_{16}O_5Na$ ([M+Na]$^+$) 359.0889, found 359.0889.

7,12-Dimethoxy-6-(methoxymethoxy)-3,4-dihydrotetraphen-1(2*H*)-one (314)



Following **Method C**, compound **314** was obtained in 89% yield (50.3 mg, 0,14 mmol), as a yellow solid, from compound **313** (52.0 mg, 0.15 mmol). The crude was purified by flash chromatography (heptane/EtOAc : 2/1).

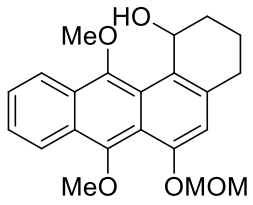
mp: 118.7 – 120.8 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.38 – 8.27 (m, 2H), 7.58 – 7.45 (m, 2H), 6.72 (s, 1H), 5.44 (s, 2H), 4.01 (s, 3H), 3.74 (s, 3H), 3.63 (d, *J* = 8.9 Hz, 3H), 2.88 (t, *J* = 5.9 Hz, 2H), 2.83 (t, *J* = 6.8 Hz, 2H), 2.25 – 2.13 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 195.4, 157.2, 149.5, 149.0, 147.7, 127.5, 127.0, 126.6, 125.9, 124.8, 123.0, 122.1, 118.3, 107.5, 95.4, 63.7, 61.4, 56.8, 39.0, 30.9, 22.6.

HRMS (ESI): calculated for $C_{22}H_{22}O_5Na$ ([M+Na]$^+$) 389.1359, found 389.1342.

7,12-Dimethoxy-6-(methoxymethoxy)-1,2,3,4-tetrahydrotetraphen-1-ol (315)



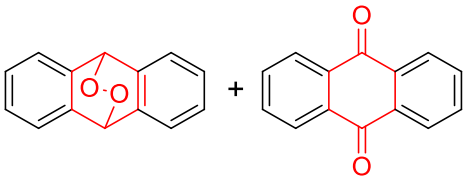
To a stirred suspension of $LiAlH_4$ (20.8 mg, 0.55 mmol) in dry THF (0.20 mL), under an inert atmosphere, a solution of compound **314** (50.3 mg, 0.14 mmol) in dry DCM (0.47 mL) was added dropwise. The reaction mixture was stirred for 90 min and quenched with a slow addition of EtOAc and some drops of water. After stirring for 15 min, the crude mixture was dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The residue was purified by flash chromatography with neutral silica gel (heptane/EtOAc : 4/1) to give **314** in 82% yield (41.3 mg, 0,11 mmol), as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.36 (dd, *J* = 7.5, 1.7 Hz, 1H), 8.25 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.59 – 7.45 (m, 2H), 6.78 (s, 1H), 5.44 (dd, *J* = 9.3, 5.0 Hz, 1H), 5.40 – 5.35 (m, 2H), 4.29 (d, *J* = 4.0 Hz, 1H), 4.02 (s, 3H), 4.01 (s, 3H), 3.63 (s, 3H), 3.05 – 2.79 (m, 2H), 2.25 – 1.99 (m, 3H), 1.90 – 1.76 (m, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 152.4, 150.2, 147.2, 136.7, 127.1, 126.6, 126.5, 126.1, 125.7, 125.4, 123.2, 122.4, 119.1, 112.0, 96.2, 65.7, 64.4, 63.5, 56.6, 32.5, 32.4, 18.7.

HRMS (ESI): calculated for $C_{22}H_{24}O_5Na$ ($[M+Na]^+$) 391.1515, found 391.1512.

9,10-Dihydro-9,10-epidioxyanthracene (318a)[125, 126] and anthracene-9,10-dione (319)[126]



A solution of anthracene (**317a**) (21.0 mg, 0.12 mmol) in $CHCl_3$ (14.1 mL) was irradiated with a UV lamp (λ_{max} 370 nm) in an open flask and stirred at rt for 6 h. After this time, the solvent was evaporated and the residue purified by flash chromatography (heptane/EtOAc 10/1) to afford a mixture of endoperoxide **318a** in 48% yield (11.5 mg, 0.05 mmol), as a white solid, and anthracene-9,10-dione (**319**) in 22% yield (4.6 mg, 0.02 mmol), as a yellow solid.

9,10-Dihydro-9,10-epidioxyanthracene (**318a**):

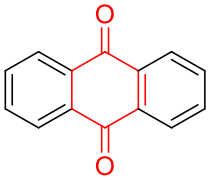
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.42 (dd, *J* = 5.4, 3.2 Hz, 2H), 7.29 (dd, *J* = 5.4, 3.2 Hz, 2H), 6.03 (s, 1H).

Anthracene-9,10-dione (**319**):

[126] M. E. Sigman, S. P. Zingg, R. M. Pagni, J. H. Burns, *Tetrahedron Lett.* **1991**, *32*, 5737-5740.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.33 (dd, *J* = 5.8, 3.3 Hz, 1H), 7.81 (dd, *J* = 5.8, 3.3 Hz, 1H).

Anthracene-9,10-dione (319)[126]

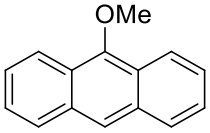


From 317a. A solution of anthracene (**317a**) (21.9 mg, 0.10 mmol) in acetone (11.8 mL) was irradiated with a UV lamp (λ_{max} 370 nm) in an open flask and stirred at rt for 24 h. After this time, the solvent was evaporated and the residue purified by flash chromatography (heptane/EtOAc : 9/1) to give anthracene-9,10-dione (**319**) in 92% yield (23.5 mg, 0.11 mmol), as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.33 (dd, *J* = 5.8, 3.3 Hz, 1H), 7.81 (dd, *J* = 5.8, 3.3 Hz, 1H).

From 317d. A solution of anthracene (**317d**) (35 mg, 0.17 mmol) in acetone (20 mL) was irradiated with a UV lamp (λ_{max} 370 nm) in an open flask and stirred at rt for 8 h. After this time, the solvent was evaporated and the residue purified by flash chromatography (heptane/EtOAc : 9/1) to give anthracene-9,10-dione (**319**) in 91% yield (31.6 mg, 0.15 mmol) as a yellow solid.

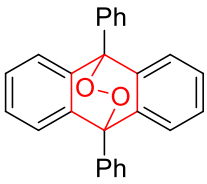
9-Methoxyanthracene (317d)[113]



To a solution of anthrone (**320**) (40.0 mg, 0.21 mmol) and K_2CO_3 (125.2 mg, 0.91 mmol) in acetone (0.4 mL), Me_2SO_4 (41 µL, 0.43 mmol) was added and the reaction was refluxed for 6 h. The mixture was cooled to rt, quenched with an aqueous solution of ammonia, extracted with DCM. The organic layer was washed with water and saturated NaCl solution, and concentrated to dryness under reduced pressure. The residue was purified by flash chromatography (heptane/EtOAc : 40/1) to obtain 9-methoxyanthracene **317d** in 77% yield (46.4 mg, 0.22 mmol), as a white solid.

^{1}H NMR (300 MHz, $CDCL_3$) δ: 8.35 (d, *J* = 8.7 Hz, 2H), 8.25 (s, 1H), 8.03 (d, *J* = 7.7 Hz, 2H), 7.56 – 7.46 (m, 4H), 4.18 (s, 3H).

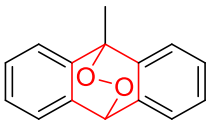
9,10-Diphenyl-9,10-dihydro-9,10-epidioxyanthracene (318b)[125a]



A solution of 9,10-diphenylanthracene (**317b**) (20.0 mg, 0.06 mmol) in $CHCl_3$ (7.0 mL) was irradiated with a UV lamp (λ_{max} 370 nm) in an open flask and stirred at rt for 90 min. After this time, the solvent was evaporated and the residue purified by flash chromatography (heptane/EtOAc : 4/1) to afford endoperoxide **318b** in 90% yield (21.2 mg, 0.06 mmol), as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.72 (d, *J* = 7.4 Hz, 4H), 7.64 (t, *J* = 7.5 Hz, 4H), 7.56 (d, *J* = 7.2 Hz, 2H), 7.25 – 7.17 (m, 8H).

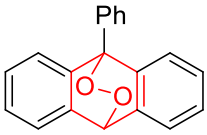
9-Methyl-9,10-dihydro-9,10-epidioxyanthracene (318c)[125b]



A solution of 9-methylanthracene (**317c**) (20.7 mg, 0.11 mmol) in $CHCl_3$ (12.9 mL) was irradiated with a UV lamp (λ_{max} 370 nm) in an open flask and stirred at rt for 3 h. After this time, the solvent was evaporated and the residue purified by flash chromatography (heptane/EtOAc : 3/1) to afford endoperoxide **318c** in 85% yield (20.5 mg, 0.09mmol), as a beige solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45 – 7.38 (m, 4H), 7.33 – 7.27 (m, 4H), 6.00 (s, 1H), 2.17 (s, 3H).

9-Phenyl-9,10-dihydro-9,10-epidioxyanthracene (318e)



A solution of 9-phenylanthracene (**317e**) (20 mg, 0.08 mmol) in $CHCl_3$ (9.4 mL) was irradiated with a UV lamp (λ_{max} 370 nm) in an open flask and stirred at rt for 2 h 15 min. After this time, the

solvent was evaporated and the residue purified by flash chromatography (heptane/EtOAc : 10/1) to afford endoperoxide **318e** in 73% yield (16.3 mg, 0.06 mmol), as a white solid.

mp: 151.8-153.2 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.66 – 7.56 (m, 4H), 7.55 – 7.48 (m, 3H), 7.31 (td, *J* = 7.4, 1.3 Hz, 2H), 7.21 (td, *J* = 7.6, 1.3 Hz, 2H), 7.14 – 7.09 (m, 2H), 6.13 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 140.3, 138.3, 132.9, 128.4, 128.3, 128.0, 127.8, 127.5, 123.7, 123.6, 83.9, 80.3, 77.6.

HRMS (ESI): calculated for $C_{20}H_{14}O_2Na$ $[M+Na]^+$ 309.0886, found 309.0889.

2.3.2. Biological data

2.3.2.1. Materials and methods

2.3.2.1.1. Cell cultures

Three human carcinoma cell lines were used in this study: HEp-2 (epidermoid carcinoma), MDA-MB (derived from a breast adenocarcinoma) and HeLa (derived from a cervical carcinoma) cells. All cell lines were cultured using Dulbecco's modified Eagle's medium (DMEM), supplemented with 10% (v/v) fetal bovine serum (FBS), 50 units/mL penicillin and 50 mg/mL streptomycin (all from GE Healthcare Life Sciences, HyClone Laboratories, Logan, Utah, USA). Cell cultures were performed under standard conditions at 37 ºC, 95% of humidity and 5% of CO2 and the medium was changed every two days.

2.3.2.1.2. Compound administration

Stock solutions were prepared in acetone (Panreac). The work solutions were obtained by dissolving the compounds in DMEM with 1% FBS. The final concentration of acetone was always lower than 5% (v/v), and the lack of toxicity of this solvent for the cells was also tested and confirmed. All the treatments were performed when cultures reached around 60e70% of confluence.

2.3.2.1.3. Viability assays

Cell viability was assessed 24 h after treatments using the MTT assay. For this assay, following treatments, 3-[4,5- dimethylthiazol-2-yl]-2,5-diphenyltetrazoliumbromide (MTT Sigma, St Louis,

USA) solution was added to each well at a final concentration of 50 mg/mL, and plates were incubated at 37 ºC for 3 h. The formazan crystals were dissolved in DMSO and the absorbance at 542 nm was measured using a spectrophotometer (Spectra Fluor 4, Tecan). The results were expressed as cell survival percentage related to non-treated cells (control).

2.3.2.1.4. Cell and nuclear morphology

Cell morphology was evaluated by phase contrast microscopy at the end of the treatment. Nuclear morphology was analysed using a dark field microscope after its staining with DAPI (4',6-diamidino-2-phenylindole) (Invitrogen).

2.3.2.1.5. Microscopical observations and statistical analysis

Microscopic observation was carried out using a fluorescence microscope (Olympus BX61) equipped with an ultraviolet filter (UV, 365 nm, exciting filter UG-1), set for fluorescence microscopy. Images were obtained with the digital camera Olympus CCD DP70 and processed using the Adobe Photoshop CS5 extended version 12.0 software (Adobe Systems Inc., USA). Data are expressed as the mean value ± standard deviations (SD). Statistical analysis was carried out with SPSS Statistics 24.0 (IBM®). The statistical significance was determined using the T test for independent samples (**: $P < 0.05$; ***: $P < 0.01$; ****: $P < 0.0001$).

Chapter 3

Synthesis of ortho-quinols by oxidative dearomatization of phenols using Oxone®/acetone as the source of dimethyldioxirane

3.1. Introduction

6-Alkyl-6-hydroxy-2,4-cyclohexadienone motif, commonly known as *ortho*-quinol, and its derivatives are of great interest in organic synthesis because they can undergo a large variety of useful transformations. Looking at the *ortho*-quinol structure, it is easy to identify these possible transformations. The 2,4-cyclohexadienone moiety is a Michael acceptor because 1,4- or 1,6-conjugate addtions of nucleophiles can take place at the α,β- or γ,δ-conjugated double bond of the di-enone motif. Also, it is a single 1,2-acceptor of nucleophiles on the carbonyl group and the conjugated double bonds could act as diene or/and as dienophile in Diels Alder reactions with itself or with another diene/dienophile.[127] All these transformations can lead to highly functionalized cyclohexane systems. Moreover, the tertiary hydroxyl group at C_6 can behave as a nucleophile site and the stereogenic center existent at C_6 could provide enantio- or diastereoselective opportunities for inducing asymmetry in subsequent reactions (*Figure 3.1*).

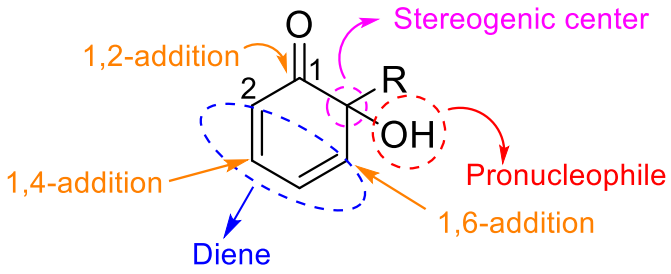


Figure 3.71.- ortho-Quinol structure.

All these structural features make the *ortho*-quinol structure and the products derived from these transformations very useful and attractive intermediates for the synthesis of natural products and other complex derivatives.[128]

Unfortunately, it is often difficult to exploit the interesting reactivity of their linearly conjugated dienone system in a controlled manner because the *ortho*-quinols derived from the oxidative dearomatization of the corresponding *ortho*-alkyl substituted phenols, undergo spontaneous self-dimerization via regio- and steroselective intramolecular [4+2] cyclodimerization (Diels-Alder reaction) to afford the corresponding bicycle[2.2.2]octenones (*Figure 3.2*).[129]

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[127] S. Dong, K. J. Cahill, M.-Il Kang, N. H. Colburn, C. J. Henrich, J. A. Wilson, J. A. Beutler, R. P. Johnson, J. A. Porco Jr., *J. Org. Chem.* **2011**, *76*, 8944-8954.
[128] S. P. Roche and J. A. Porco, Jr., *Angew. Chem. Int. Ed.* **2011**, *50*, 4068-4093.
[129] J. K. Boppisetti, V. B. Birman, *Org. Lett.* **2009**, *11*, 1221-1223.

Nevertheless, their propensity to dimerize via [4+2] cycloaddition can be significantly diminished in sterically congested substrates.

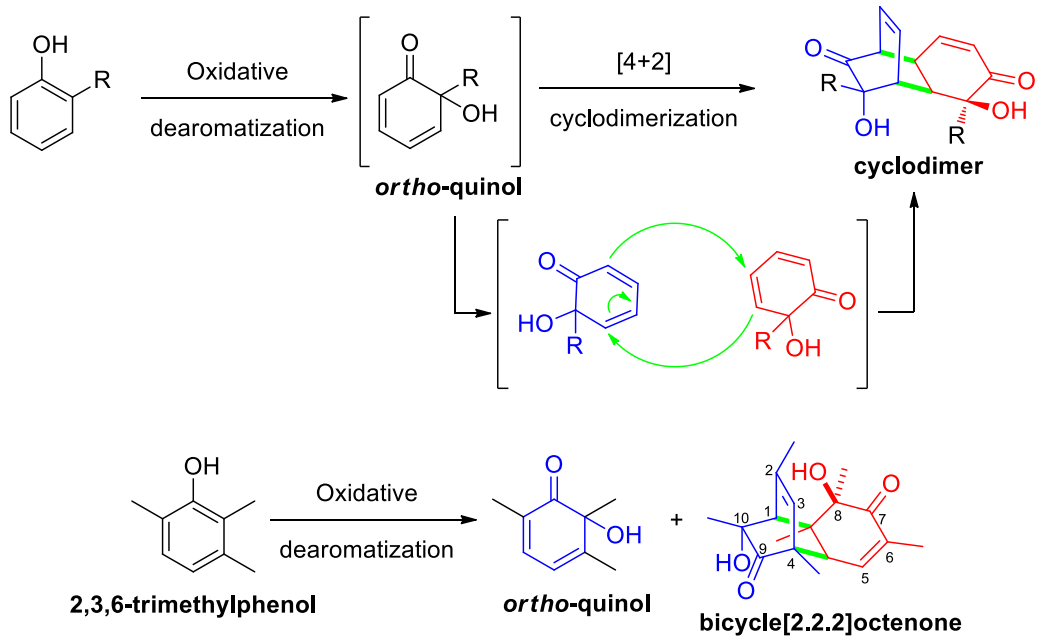


Figure 3.72. Spontaneous [4+2] cyclodimerization of ortho-quinols

3.1.1ortho-Quinol moiety in Nature.

ortho-Quinol fragments are present in various natural products such as (+)-aquaticol (**320**) or (+)-grandifloracin (**321**), in the form of its derived cyclodimers (*Figure 3.3*). (+)-Aquaticol (**320**) is a bis-sesquiterpene, isolated in 1999 by Jia and coworkers from *Veronica anagallis-aquatica*, a plant used in traditional Chinese medicine.[130] (-)-Glandiforacin (**321**) was isolated for the first time in 1997 by Sun et al. from the stem and leaves of Uvaria grandiflora, but did not present biological activity.[131] Later, Awale and coworkers extracted (+)-grandifloracin (**321**) from the stem of Uvaria dac.[132] (+)-Grandifloracin (**321**) was shown to be a potent agent in the treatment of pancreatic cancer and induced autophagic PANC-1 pancreatic cancer cell death.[132, 133]

[130] B.-N. Su, Q.-X. Zhu, Z.-J. Jia, *Tetrahedron Lett.* **1999**, *40*, 357-358.
[131] Y.-H. Liao, L.-Z. Xu, S.-H. Yang, J. Dai, Y.-S. Zhen, M. Zhu, N.-J. Sun, *Phytochemistry* **1997**, *45*, 729-732.
[132] S. Awale, J.-Y. Ueda, S. Athikomkulchai, S. Abdelhamed, S. Yokoyama, I. Saiki, R. J. Miyatake, *Nat. Prod.* **2012**, *75*, 1177-1183
[133] J.-y. Ueda, S. Athikomkulchai, R. Miyatake, I. Saiki, H. Esumi, S. Awale, *Drug Design, Development and Therapy* **2014**, *8*, 39-47

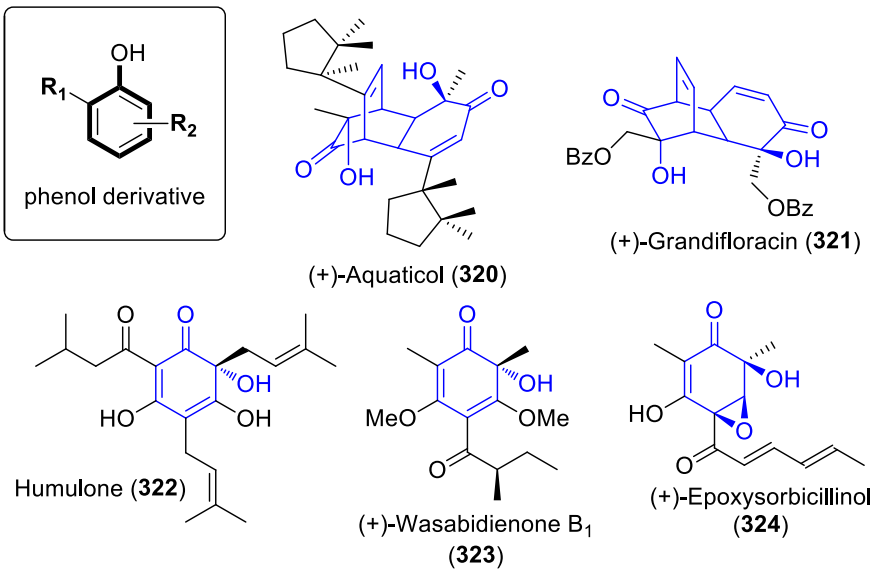


Figure 3.73.- Natural ortho-quinols derived from phenol derivatives

Few examples of natural non-dimerizing *ortho*-quinols derived from phenols have been reported. Some of these natural derivatives, shown in *Figure 3.3*, are humulone (**322**), wasabidienone B_1 (**323**), and (+)-epoxysorbicillinol (**324**), an example of natural epoxy *ortho*-quinol. Humulone (**322**) was isolated from the cones and resin of *Humulus lupulus* (hops) by Cook and Harris in 1950. [134] Humulone possess diverse biological activities in vitro such as antioxidant, cyclooxygenase-2 inhibitory, antiviral and antibacterial.[135] (+)-Wasabidienone B_1 (**323**) is a fungal polyketide metabolite isolated from a potato culture of *Phoma wasabiae* in 1980s by Soga and coworkers.[136] Later, it could be extracted from *Phoma lingam* or *Aspergillus Viridinutans* cultures.[137] (+)-Epoxysorbicillinol (**324**) is a vertinoid polyketide possessing an epoxide functionality isolated from Trichodera and shows interesting biological activity, including TNF-R production and DPPH radical scavenging activity.[138]

There are also examples of natural *ortho*-quinols derived from naphthols, which cannot form the corresponding cyclodimers. Thus, fluostatin K (**325**) and lacinilene D (**326**) have the *ortho*-quinol moiety that could come from a 2-methyl-1-naphthol derivative or a 1-methyl-2-naphthol derivative, respectively (*Figure 3.4*). Fluostatin K (**325**) was isolated from the culture of

[134] A. H. Cook, G. Harris, *J. Chem. Soc.* **1950**, 1873-186.
[135] N. Yamaguchi, K. Satoh-Yamaguchi, M. Ono, *Phytomedicine* **2009**, *16*, 369-376.
[136] a) O. Soga, H. Iwamoto, K. Hata, R. Maeba, A. Takuwa, T. Fujiwara, Y.- H. Hsu, M. Nakayama, *Agric. Biol. Chem.* **1988**, *52*, 865; b) O. Soga, H. Iwamoto, Y. Ota, M. Odoi, K. Saito, A. Takuwa, M. Nakayama, *Chem. Lett.* **1987**, 815
[137] a) M. S. C. Pedras, J. L. Taylor, V. M. Morales, *Phytochemistry* **1995**, *38*, 1215-1222; b) J. O. Omolo, H. Anke, S. Chhabra, O. Sterner, *J. Nat. Prod.* **2000**, *63*, 975-977.
[138] S. Sperry, G. J. Samuels, P. Crews, *J. Org. Chem.* **1998**, *63*, 10011-10014.

M. rosaria SCSIO N160 and displays antimicrobial and cytotoxic activities.[139] Lacinilene D (**326**) is a phytoalexine isolated from the cotton plant *Gossypium hirsutum* and has been used as inhibiting growth of cotton bacterial pathogens, such as *Xanthomonas campestris* or *malvacearum*.[140]

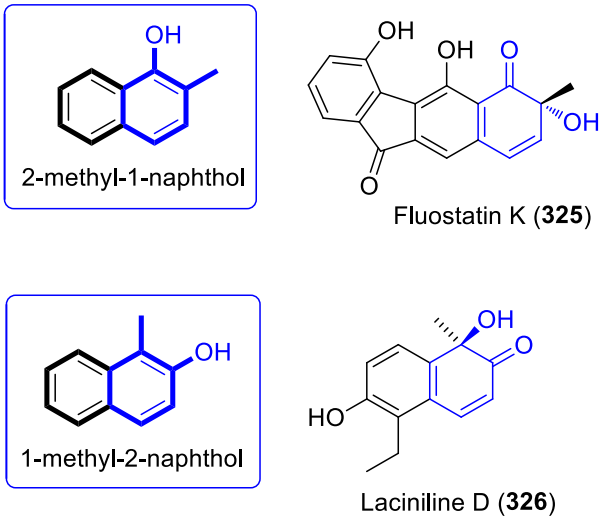


Figure 3.74.- Natural ortho-quinols derived from alkyl substituted 1- and 2-naphthols.

3.1.2. Synthesis of ortho-quinols: antecedents

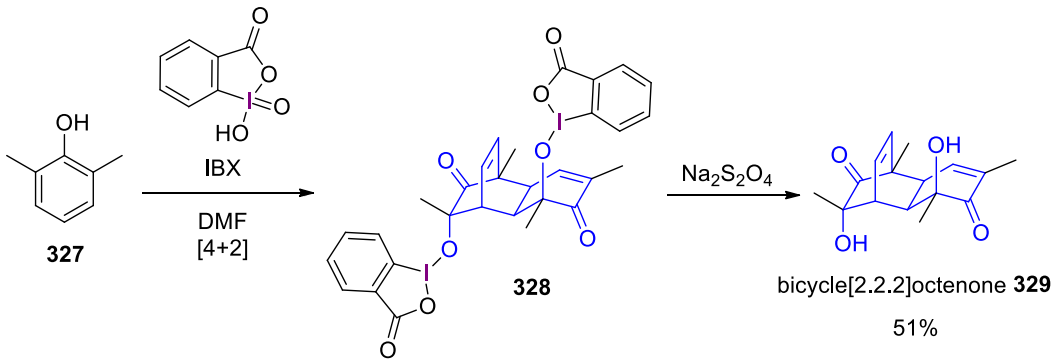
The synthesis of *ortho*-quinols is less studied than the synthesis of the corresponding *para*-quinol derivatives. In the literature we can find different oxidizing methods to synthesize the 6-carbo-6-hydroxy-2,4-cyclohexadienone moiety from the oxidative dearomatization of adequately substituted phenols and naphthols. These oxidants are oxaziridines, copper complexes or selenium compounds. Nevertheless, the most frequently used and studied method to synthesize *ortho*-quinols utilized hypervalent λ^5-organoiodide reagents as oxidants.[141] In this chapter, we will review the most outstanding examples of these synthesizes as well as some recent examples of synthesis and study of *ortho*-quinols.

3.1.2.1. Hypervalent organoiodine (λ^5-iodide) reagents

Pettus and coworkers were the first to use hypervalent organoiodide (λ^5-iodide) reagents in the synthesis of *ortho*-quinols. They reported a regioselective *ortho*-oxygenation of 2,6-

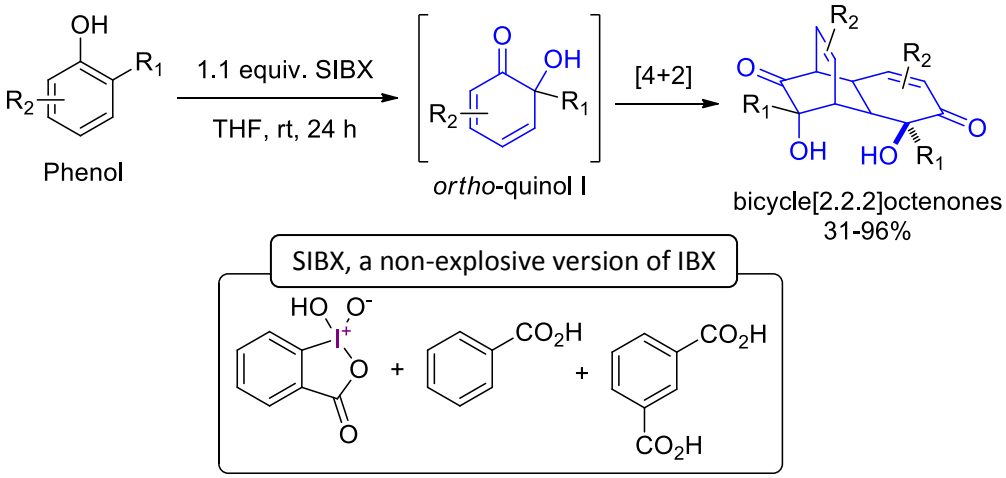
[139] W. Zhang, Z. Liu, S. Li, Y. Lu, Y. Chen, H. Zhang, G. Zhang, Y. Zhu, G. Zhang, W. Zhang, J. Liu, C. Zhang, *J. Nat. Prod.* **2012**, *75*, 1937-1943.
[140] K. Nishikawa, S. Yasuda, M. Hanzawa, *Mokuzai Gakkaishi* **1972**, *18*, 623
[141] a) S. Quideau, L. Pouysegu, P. A. Peixoto, D. Deffieux, *Top Curr Chem* **2016**, *373*, 25. b) S. P. Roche, J. A. Porco Jr., *Angew. Chem. Int. Ed.* **2011**, *50*, 4068.

dimethylphenol (**327**) using IBX (2-Iodoxybenzoic acid) to furnish the dimer **329** in 51% yield as the sole diastereomeric product, after a reduction with sodium dithionite (Scheme 2).[142] They isolated the intermediate product **328** formed in the synthesis of bicycle[2.2.2]octenone **329**, which resulted from a Diels-Alder dimerization of the corresponding monomeric *ortho*-quinol.



Scheme 3.109. Oxidative dearomatization of 2,6-dimethylphenol by Pettus and coworkers

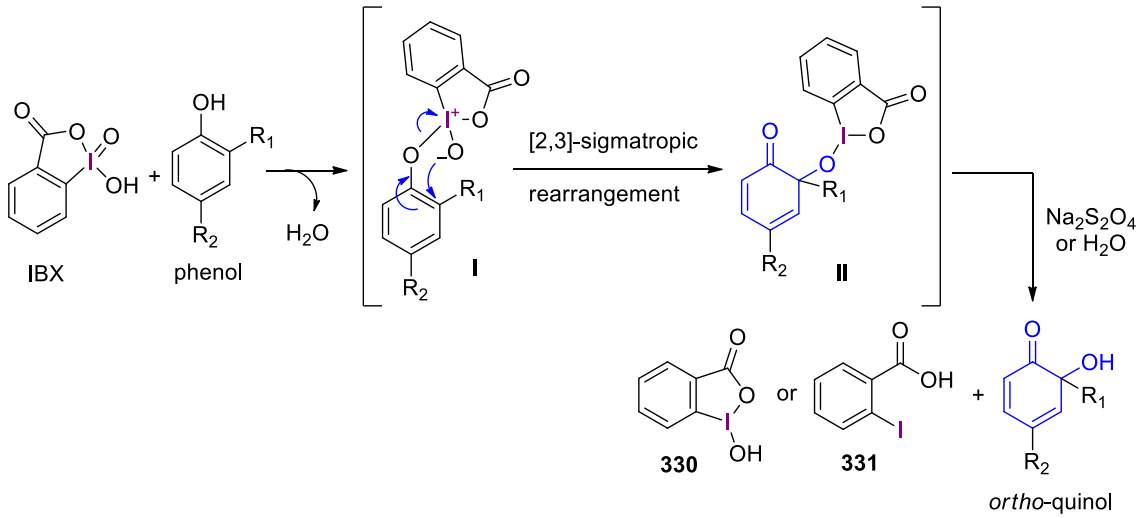
Later, Quideau and coworkers reported a safety and efficient oxidative dearomatization reaction to transform 2-alkyl substituted phenols into their corresponding [4+2] cyclodimers in moderate to high yield, using 1.1 equiv. of stabilized 2-iodoxybenzoic acid (SIBX) in THF after 24 hours at rt (*Scheme 3.2*).[143] SIBX is the non-explosive and non-moisture sensitive version of the λ^5-iodide IBX (49% IBX, 22% benzoic acid, 29% isophtalic acid).



Scheme 3.110.- Oxidative dearomatization of phenols by Quideau and coworkers

[142] D. Magdziak, A. A. Rodriguez, R. W. Van De Water, T. R. R. Pettus, *Org. Lett.* **2002**, *4*, 285-288.
[143] a) S. Quideau, L. Pouységu, D. Deffieux, A. Ozanne, J. Gagnepain, I. Fabre, M. Oxoby, *ARKIVOC* **2003**, *6*, 106-119. b) N. Lebrasseur, J. Gagnepain, A. Ozanne-Beaudenon, J.-M. Léger, S. Quideau, *J. Org. Chem.* **2007**, *72*, 6280-6283.

The mechanistic proposal commonly accepted in the literature for the formation of *ortho*-quinols from IBX (λ^5-iodide), start with an initial ligand exchange between IBX and the phenol, which could generate intermediate **I**. Then, a [2,3]-sigmatropic rearrangement resulted in oxygenation at the *ortho*-position, bearing the alkyl group, and concomitant reduction of the iodine atom (λ^3-iodide). Finally, the intermediate **II** could suffer a ligand exchange to afford *ortho*-iodosobenzoic acid **330** and *ortho*-quinol or a reductive cleavage to give *ortho*-iodobenzoic acid **331** and the *ortho*-quinol (*Scheme 3.3*).[144]



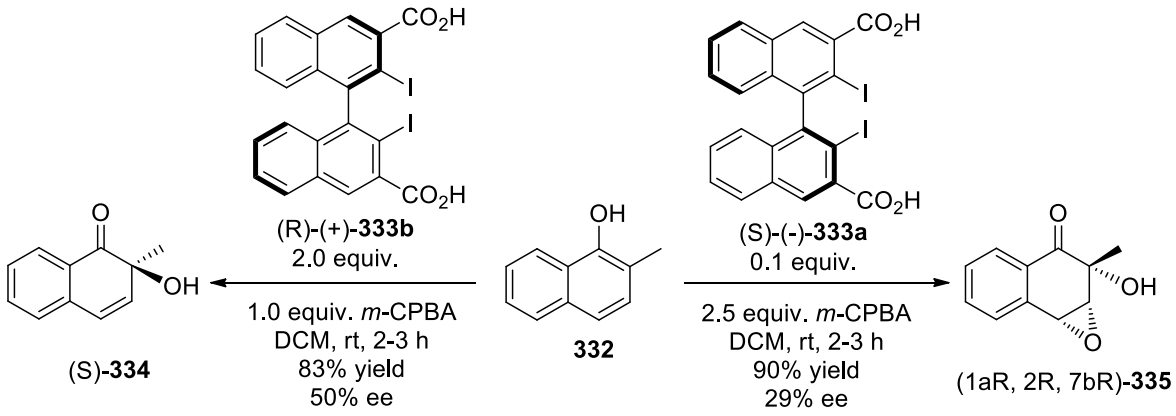
Scheme 3.111. Mechanism of ortho-quinol formation by action of IBX

According with this mechanism the λ^5-iodide-mediated dearomatizations can only occur at the *ortho* position of the phenol. Furthermore, using these oxidizing agents (λ^5-iodide) external nucleophiles, instead of the hydroxy group, could not be inserted at the *ortho* position.

In 2009 Quideau and coworkers were the first to study the asymmetric oxidative dearomatization of phenols through the use of chiral iodoarenes in the presence of an external oxidizing agent.[145] They achieved a regio- and diastereoselective hydroxilative dearomatization and epoxidation utilizing iodoarenes with axial chirality as organocatalysts with *m*-CPBA as co-oxidant. The best results achieved, are represented in *Scheme 3.4* using chiral iodobinaphthyl (R)-**333b** in the oxidative dearomatization of 2-methylnaphthalen-1-ol (**332**). They could modulate the epoxidation of the double bond Δ 3-4 of the ortho-quinol initially formed with the equivalents of *m*-CPBA. Thus, they synthesized the epoxy *ortho*-quinol (1aR,2R,7bR)-**335** in 90% yield with 29% ee, using 0.1 equiv. of iodobnaphthyl (S)-**33a** and 2.5 equiv. of *m*-CPBA. Using 2.0 equiv. of

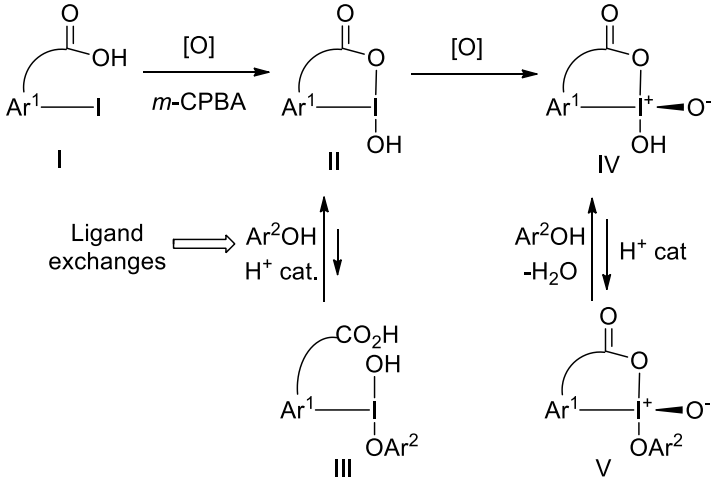
[144] A. M. Harned, *Tetrahedron Lett.* **2014**, *55*, 4681-4689.
[145] S. Quideau, G. Lyvinec, M. Marguerit, K. Bathany, A. Ozanne-Beaudenon, T. Buffeteau, D. Cavagnat, A. Chénedé, *Angew. Chem.* **2009**, *121*, 4675-4679.

iodoarene **33b** and 1.0 equiv. of *m*-CPBA they obtained the *ortho*-quinol **334** in 83% yield with 50% ee.



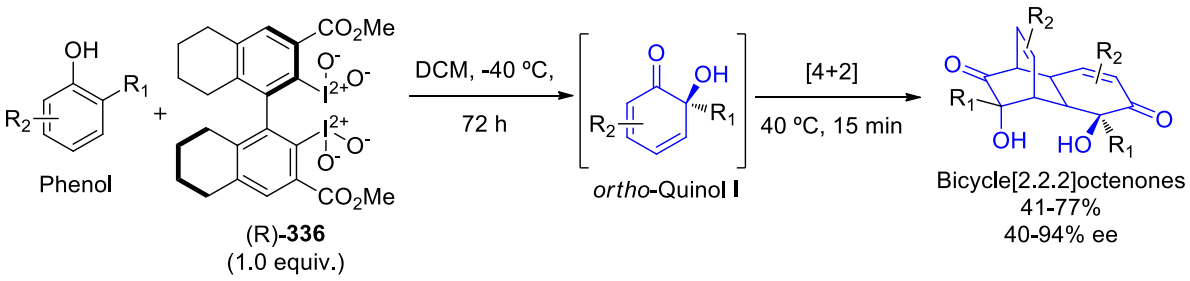
*Scheme 3.112. Enantioselective oxidative daromatization of 2-methylnaphthalen-1-ol (**332**) by Quideau and coworkers*

They also proposed a mechanism that explained the important role of the co-oxidant and the phenolic substrates in the oxidation of the iodoarenes. Initially, m-CPBA could oxidize iodoarene **I** into hypervalent organoiodide III species **II**, which could react with the phenolic substrates by ligand exchange to give intermediate **III** (λ^3-iodide). On the other hand, *m*-CPBA could oxidize λ^3-iodide into λ^5-iodide species **IV**, which could also react with the phenolic substrates by ligand exchange to give intermediate **V** (λ^5-iodide) (*Scheme 3.5*). To investigate what hypervalent organoiodide species is formed during the reaction, they monitored the reaction with electrospray ionization mass spectrometric (ESI-MS) and found evidence to support the formation of the λ^5-iodide species, but they did not dismiss the formation of λ^3-iodide. Both of them could be the reactive intermediate in the formation of *ortho*-quinols.



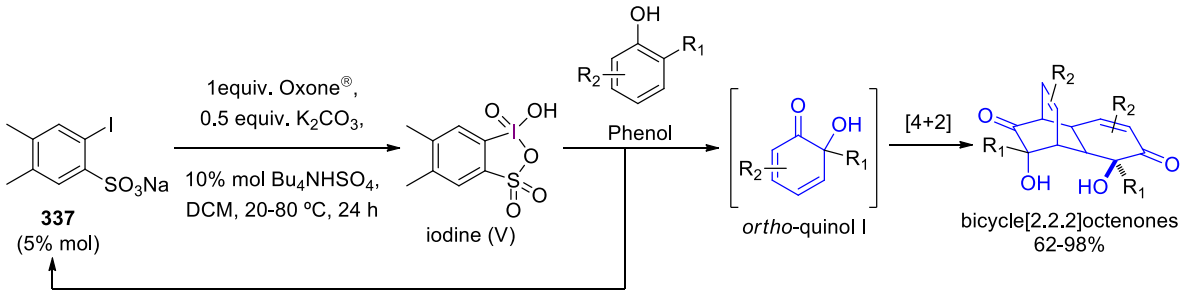
Scheme 3.113. Mechanism for the oxidation of organo iodide compound using a co-oxidant proposed by Quideau and coworkers

Later, Quideau and coworkers developed the enantioselective oxidative dearomatizations of phenols using a chiral biphenyl C_2-symmetrical bisiodide(λ^5-iodane) (*R*)-**336**.[146] They evaluate the enantioselective methodology on different 2-alkylphenols to obtained the corresponding bicyclo-[2.2.2]octenone framework, after dimerization of the initially formed *ortho*-quinol, in a regio- and stereoselective manner. Thus, the reaction of different phenols with hypervalent organoiodide (*R*)-**336** led to the corresponding cyclodimers in 41-77% yield with 40-94% ee after 72 hours at -40 ºC, followed by 15 min at 40 ºC (*Scheme 3.6*).



Scheme 3.114. Enantioselective hydroxylative dearomatization of phenols by Quideau and coworkers

More recently, Ishihara and coworkers described the first site-selective oxidative dearomatization of phenols, using IBS (sodium salts of 2-iodobenzenesulfonic acids) / Oxone® catalytic system (*Scheme 3.7*).[147] The reaction of different 2-alkyl substituted phenols with 1 equiv. of Oxone and 10 mol% of Bu_4NHSO_4, in the presence of 5 mol% of iodide **337**, gave rise to the corresponding [4+2] cyclodimers in good to high yields, after heating. The iodo derivative **337** was oxidized with Oxone® in presence of Bu_4NHSO_4 and dissolved in a buffer solution to give the necessary organoiodine (V).

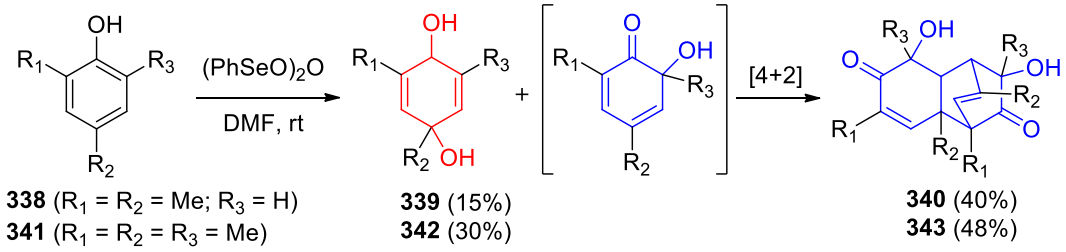


Scheme 3.115.- Selective oxidative dearomatization of phenols by Ishihara and coworkers

[146] C. Bosset, R. Coffinier, P. A. Peixoto, M. El Assal, K. Miqueu, J.-M. Sotiropoulos, L. Pouységu, S. Quideau, *Angew. Chem. Int. Ed.* **2014**, *53*, 9860-9864.
[147] M. Uyanik, T. Mutsuga, K. Ishihara, *Angew. Chem. Int. Ed.* **2017**, *56*, 3956-3960.

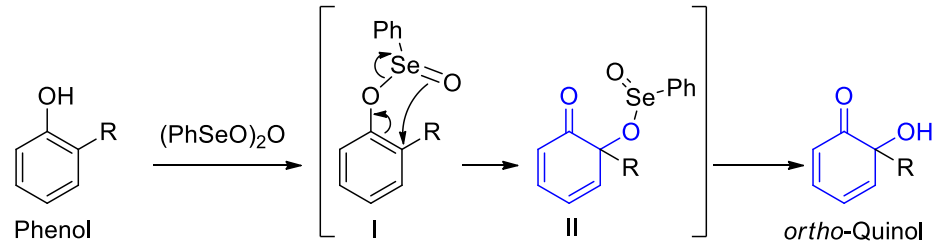
3.1.2.2. Selenium compounds as oxidants

In 1977, Barton and coworkers reported a new methodology to obtain the corresponding *ortho*-quinols from different phenols using benzeneseleninic anhydride, $(PhSeO)_2O$,[148] a stable white solid synthesized for the first time by Doughty.[149] One of the examples described by Barton was the reaction of 2,4-dimethylphenol (**338**) with benzeneseleninic anhydride in dimethylformamide giving rise to a mixture of *para*-quinol **389** in 15% yield and the cyclodimer **340** in 40% yield (*Scheme 3.8*). The same reactivity was observed for 2,4,6-trimethylphenol (**341**), which afforded *para*-quinol **342** in 30% yield and dimer **343** in 48% yield.



Scheme 3.116. Hydroxylative dearomatization of 2,4-dimethylphenol with benzeneseleninic anhydride by Barton and coworkers

Barton suggested a mechanism similar to that described for the IBX in the hydroxilative dearomatization process (*Scheme 3.3*). He proposed that the oxidative transformation could start with an initial ligand exchange between benzeneseleninic anhydride and the phenol, which could generate intermediate **I**. Then, a 2,3-sigmatropic rearrangement resulted in oxygenation at the *ortho*-position, generating intermediate **II**. Finally, **II** would evolve to the corresponding *ortho*-quinol by regeneration of benzeneseleninic anhydride (*Scheme 3.9*).

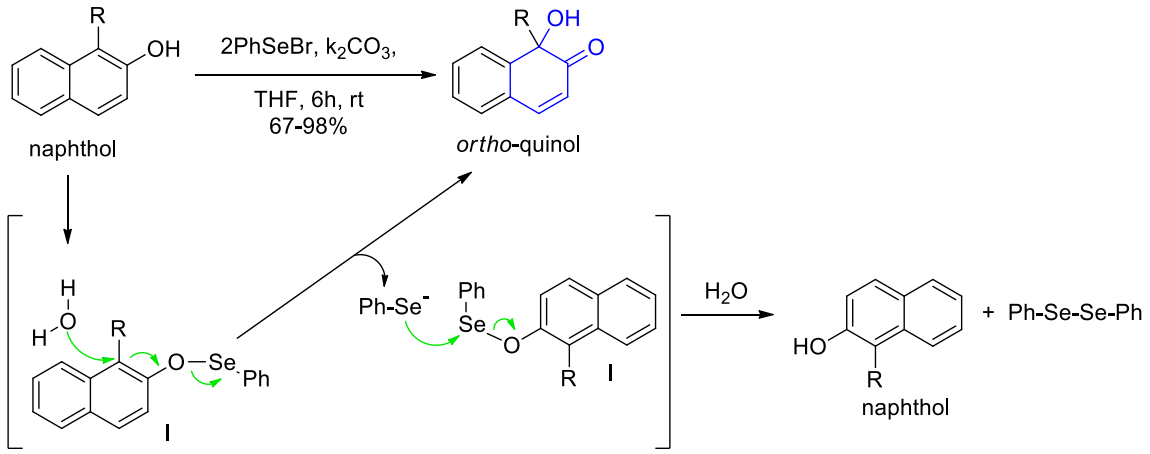


Scheme 3.117 Proposed mechanism by Barton in the formation of ortho-quinol by Barton and coworkers

Recently, Sarkar and coworkers have described in 2016 an easy method for the one-pot synthesis of *ortho*-quinols in good to high yields from different substituted naphthols (Scheme

[148] D. R. H. Barton, S. V. Ley, P. D. Magnus, M. N. Rosenfeld, *J. Chem. Soc. Perkin Trans.1* **1977**, 567.
[149] H. W. Dougthy, *J. Am. Chem.* **1909**, *41*, 326

X).[150] This methodology consisted in the oxidative dearomatization of naphthols by two equivalents of phenyl selenyl bromide (PhSeBr) in the presence of potassium carbonate in THF, without the need of an inert atmosphere.



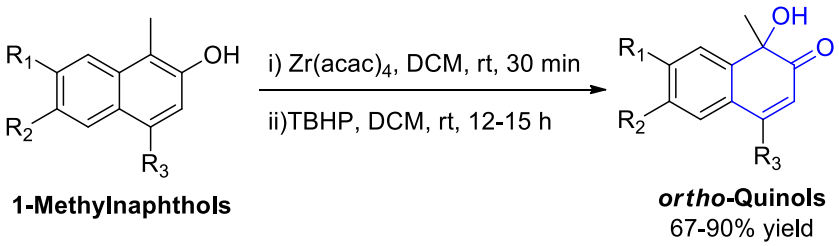
Scheme 3.118. Oxidative dearomatization of naphthols using phenyl selenyl bromide by Sarkar and coworkers

Compared with the mechanism described by Barton, the one proposed by Sarkar for the reaction of a naphthol with PhSeBr started with the formation of a seleno-naphthoxy intermediate **I**, but Sarkar suggested an important role for water. He proposed a nucleophilic attack at carbon C_1 of **I** by a water molecule, followed by a migration of the double bond and loss of phenyl selenyl anion to afford the desired *ortho*-quinol. Then, the leaving phenyl selenide anion could react with another intermediate **I** to give diphenyldiselenide and to regenerate the naphthol.

3.1.2.3. Metal complexes catalysis

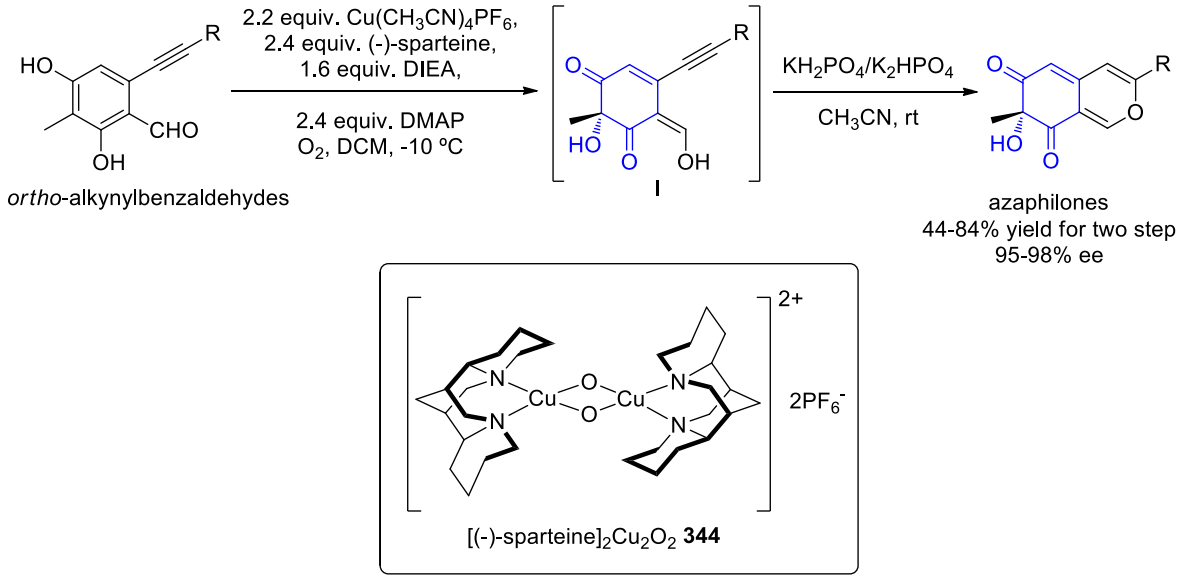
Krohn and Zimmermann reported in 1998 a new methodology to obtain *ortho*-quinols from different 1-methylnaphthols using the stable zirconium tetraacetylacetonate [Zr $(acac)_4$] as catalyst in the presence of *tert*-butylhydroperoxide (TBHP).[151] They obtained differently substituted *ortho*-quinols in high yields (67-90% yield) after 12-15 hours of reaction (*Scheme 3.11*).

[150] D. Sarkar, M. K. Ghosh, N. Routa, S. Giri, *RSC Adv*. **2016**, *6*, 26886-26894.
[151] K. Krohn, G. Zimmermann, *J. Org. Chem.* **1998**, *63,* 4140-4142.



Scheme 3.119. Oxidative dearomatizaton of 1-methylnaphthols using [Zr (acac)$_4$] and TBHP described by Krohn and Zimmermann

Later, In 2005, Porco and coworkers developed a copper-mediated catalyzed hydroxylative dearomatization of *ortho*-alkynylbenzaldehydes by the chiral Copper-sparteine-dioxygen complex **344**, obtained from $Cu(CH_3CN)_4PF_6$ and (-)-sparteine, en route to synthesize azaphilones.[152] Firstly, *ortho*-alkynylbenzaldehyde was transformed into the enantioenriched enol **I**, which could be subsequently cycloisomerized by KH_2PO_4 / K_2HPO_4 buffer to afford azaphilones in moderate yields and excellent enantioselectivities (*Scheme 3.12*).

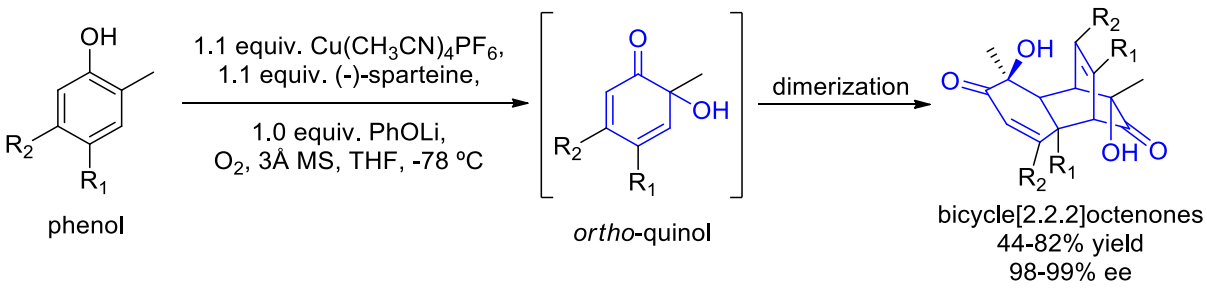


Scheme 3.120. Synthesis of azaphilones through oxidative dearomatization by Porco and coworkers

In 2008, the same author developed a general methodology for the enantioselective oxidative hydroxylation of phenols to generate bicycle[2.2.2]octenones, using the same catalytic system used in the synthesis of azaphilone, [(-)-sparteine]$_2Cu_2O_2$ **344**.[153] This transformation involved an asymmetric oxidation of substituted 2-methylphenols to the corresponding *ortho*-

[152] J. Zhu, N. P. Grigoriadis, J. P. Lee, J. A. Porco, Jr., *J. Am. Chem. Soc.* **2005**, *127*, 9342- 9343.
[153] S. Dong, J. Zhu, J. A. Porco, Jr., *J. Am. Chem. Soc.* **2008**, *130*, 2738- 2739.

quinols followed by homochiral dimerization to afford the corresponding enantiopure cyclodimer (*Scheme 3.13*).



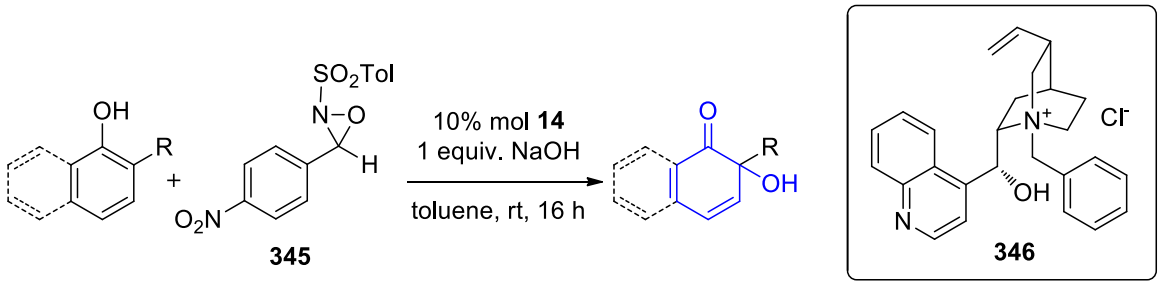
Scheme 3.121. Enantioselective oxidative hydroxylation of phenols by Porco and coworkers

However, the scope of this reaction showed that it was limited to the use of 2-methyl 5-susbtituted phenols or 2-methyl 4-susbtituted phenols because 2,3-dimethylphenol, 2,6-dimethylphenol and 2-isopropyl-5-methylphenol led to the formation of the corresponding dimer or catechol products.

3.1.2.4. Oxaziridines as oxidants

Oxaziridines are organic aprotic heterocyclic oxidizing reagents mainly known for their ability to act as electrophilic oxygen transfer agents.[154] Emmons was the first to synthesize them in 1957.[155] Grandclaudon and Toullec were the first to apply oxaziridines in the oxidative dearomatization of phenolic and naphtholic substrates. They developed an oxidative dearomatization of phenols and naphthols under phase-transfer conditions (benzylcinchonidinium chloride **346** as a phase-transfer agent) in the presence of oxaziridine **345** as electrophilic reagents to generate the corresponding *ortho*-quinols in moderate to good yields (*Table 3.1*).[156]

[154] a) K. S. Williamson, D. J. Michaelis, T. P. Yoon, *Chem. Rev.* **2014**, *114*, 8016; b) Y. Zhu, Q. Wang, R. G. Cornwall, Y. Shi, *Chem. Rev.* **2014**, *114*, 8199.
[155] W. D. Emmons *J. Am. Chem. Soc.* **1957**, *79*, 5739.
[156] C. Grandclaudon, P. Y. Toullec, *Eur. J. Org. Chem.* **2016**, *2*, 260-264.



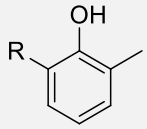
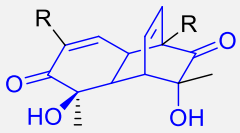
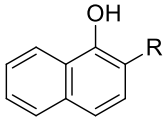
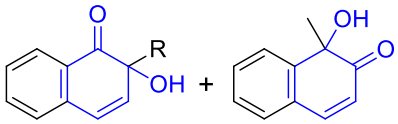
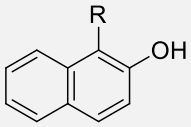
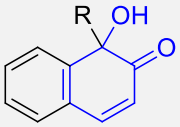
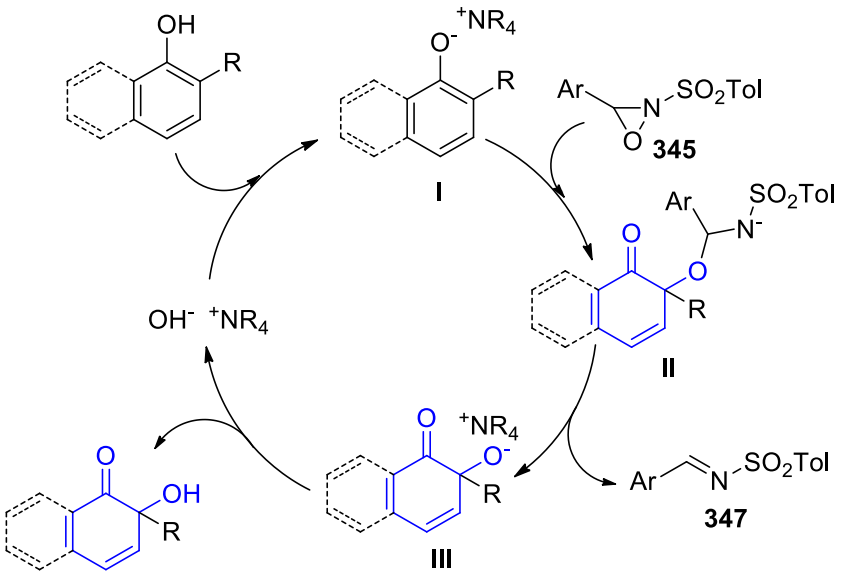
entry	equiv. of 345	starting material	final product	yield (%)
1	1 equiv.	 2-methyl phenol	 bicycle[2.2.2]octenones	23-64
2	1 equiv.	 2-substituted-1-naphthol	 *ortho*-quinols	11-61
3	1.25 equiv.	 1-substituted-2-naphthol	 *ortho*-quinol	56-87

Table 3.11.- Oxidative dearomatization of phenols and naphthols using oxaziridines by Grandclaudon and Toullec

They carried out a scope of this methodology on differents susbtrates to study its limitations. The oxidative dearomatization of 2-methyl-6-substituted phenols afforded the corresponding dimers in moderate to good yields, in most of the cases (*Table 3.1*, *entry 1*). The best results were obtained when R- was not a hindered functional group. Then, the reaction of 2-substituted-1-nahthols gave rise the corresponding *ortho*-quinol in low to good yield, because an α-ketol rearrangement took place (*Table 3.1*, *entry 2*). They obtained the best results with the transformation of 1-substituted-2-naphthols into the corresponding *ortho*-quinols in good to high yields (*Table 3.1*, *entry 3*).

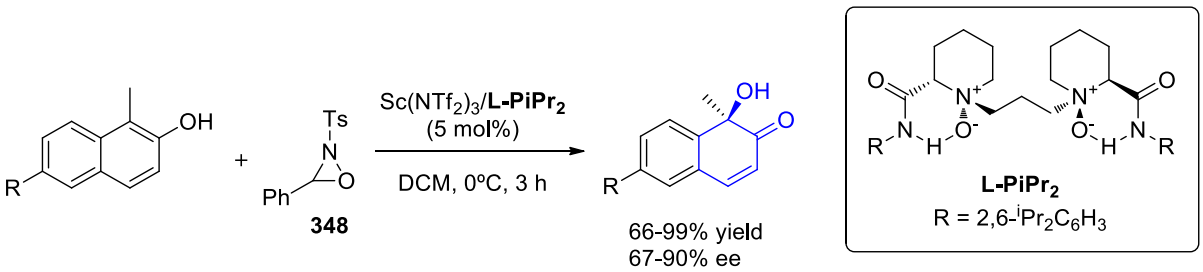
Grandclaudon and Toullec proposed a catalytic mechanism for the oxidative dearomatization of phenols / naphthols by oxaziridines (*Scheme 3.14*). The reaction could begin with the formation of the corresponding phenolate/naphtholate anion **I**, upon a phase transfer of the hydroxide anion in the presence of the ammonium salt. Next, **I** would react with N-sulfonyloxaziridine **345** to afford the intermediate **II**, which would evolve to intermediate **III** by

the imine **347** removal. Finally, **III** would be protonated to give the corresponding *ortho*-quinol and regenerating the ammonium salt.



Scheme 3.122. Proposed mechanism for the oxidative dearomatization of phenols and naphthols with oxaziridines by Grandclaudon and Toullec

More recently, Feng and coworkers described a highly chemo- and enantioselective oxidative dearomatization of 6-substituted-1-methyl-2-naphthols with 3-phenyl-2-tosyl-1,2-oxaziridine (**348**) catalyzed by a 5 mol% of chiral N,N'-dioxide-Sc(NTf$_2$)$_3$ complex catalyst. The desired enantiopure *ortho*-quinols were obtained in good to high yields with moderate to high enantioselectivities (*Scheme 3.15*).[157]

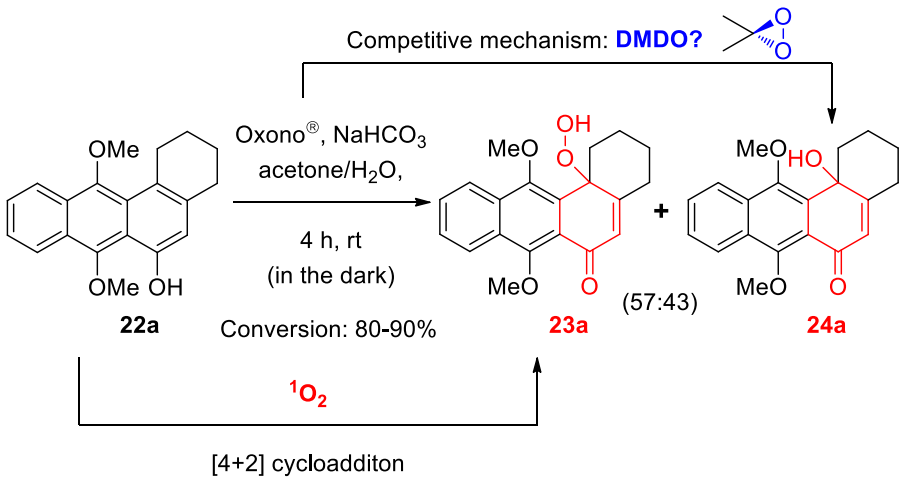


Scheme 3.123. Enantioselective oxidative dearomatization of 6-substituted-1-methyl-2-naphthols by Feng and coworkers

[157] Y. Zhang, Y. Liao, X. Liu, L. Lin, X. Feng, *Chem. Sci.* **2017**, *8*, 6645- 6649.

3.1.3. Oxidative dearomatization using dimethyldioxirane (DMDO) as oxidizing agent: Previous work

In the previous *Chapter 2*, we have shown that the oxidative dearomatization of 7,12-dimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (**22a**) using the system Oxone® / $NaHCO_3$ / acetone afforded a mixture of the corresponding *para*-peroxy quinol **23a** and *para*-quinol **24a** (*Scheme 2.51*). The formation of the *para*-peroxy quinol **23a** could be explained by reaction of the starting angular tetracyclic phenol **22a** with singlet oxygen generated in situ through decomposition of Oxone® in the basic medium, as occurred under our classical conditions using the system Oxone® / $NaHCO_3$ / acetonitrile. Nevertheless, the presence of the corresponding *para*-quinol in the crude reaction mixture when using acetone, suggested the possible existence of another competitive reactive species when the oxidative dearomatization is carried out in acetone. It is well known that Oxone® in basic medium is able to oxidize acetone to dimethyldioxirane (DMDO) and we reasoned that the formation of *para*-quinol **24a** could be possible by direct oxidation of the angular tetracyclic phenol X through reaction with DMDO formed in situ.

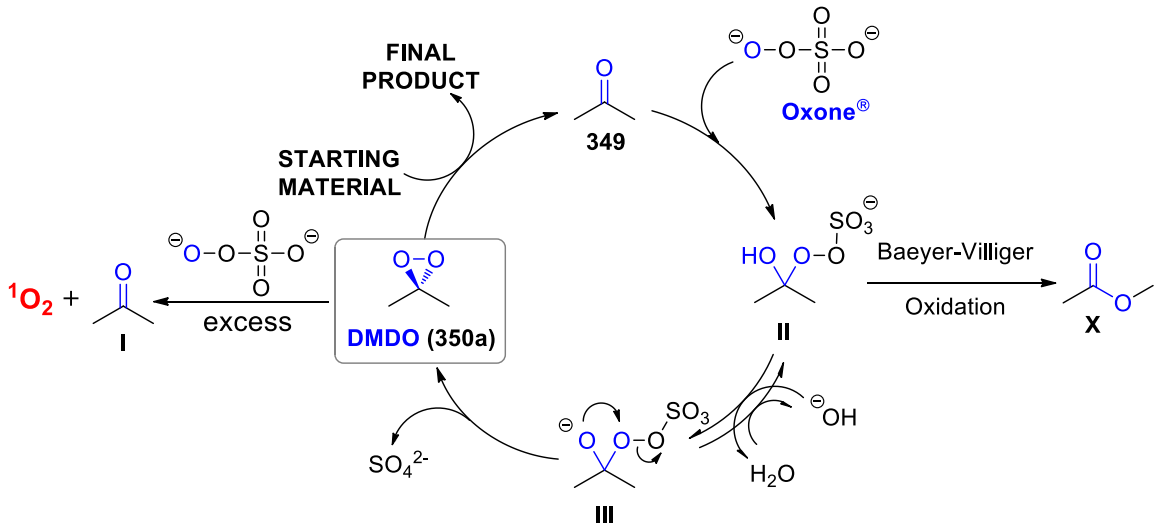


Scheme 2.51. Mechanistic hypothesis of oxidative dearomatization with the system Oxone®/$NaHCO_3$

In 1979, Edwards and coworkers were the first to perform a reaction between Oxone® and acetone further achieving a stereospecific epoxidation of alkenes.[158] They generated dioxiranes with the system Oxone / acetone at pH 7.8-8.0. Later, the groups of Yang,[159] Denmark[160] and Shi[161] synthesized different chiral dioxiranes from Oxone® and chiral ketones to study the enantioselective epoxidation of alkenes.

[158] J. O. Edwards, R. H. Pater, R. Curci, F. DiFuria, *Photochem. Photobiol.* 1979, *30*, 63.
[159] D. Yang, M.-K. Wong, Y.-C. Yip, *J. Org. Chem.* **1995**, *60*, 3887–3889.
[160] S. E. Denmark, D. C. Forbes, D. S. Hays, J. S. DePue, R. G. Wilde, *J. Org. Chem.* **1995**, *60*, 1391–1407.

Dioxiranes are three-membered-ring peroxides, the smallest cyclic peroxide, and are known to be highly efficient and selective oxidants capable of performing a variety of oxidative transformations, usually prepared from solutions of the corresponding ketone. The most used and known dioxirane preparation method is an oxidation reaction of a ketone by Oxone® (*Scheme 3.16*). The oxidation of a ketone with Oxone® started with the nucleophilic attack of potassium peroxymonosulfate ($KHSO_5$) to the ketone **349** to generate the intermediate **II**. The proton abstraction in the basic medium afforded intermediate **III**, which evolved through ring closure by loss of sulfate anion, a good leaving group, to furnish dioxirane **350a**. Finally, dioxirane **350a** could oxidize a substrate to form an oxygenated final product, regenerating the ketone **349**.[162]



Scheme 3.124. DMDO formation from Oxone® and acetone

It is necessary to carry out the dioxirane synthesis in a buffered aqueous solution to maintain an adequate basic pH to avoid a possible Baeyer-Villiger secondary reaction of intermediate **II** to form the corresponding ester **V**. In addition, it is also described in the literature that, in presence of an excess of potassium peroxymonosulfate ($KHSO_5$), dioxirane **350a** decomposed releasing singlet oxygen and regenerating the ketone **349**.[163]

Specifically, the oxidations using dimethyldioxirane (DMDO) have some advantages over other oxidation methods. For example, the solvent can be recycled, it is a cheap and environment friendly methodology, the oxidative reaction can be realized at ambient or low temperature, the

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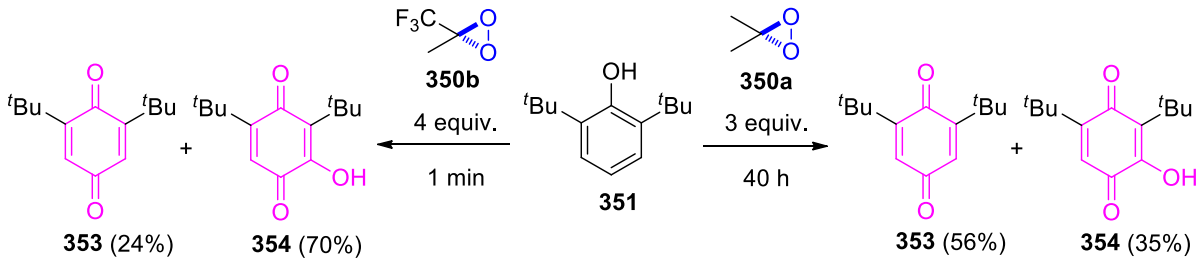
[161] Y. Tu, Z.-X. Wang, Y. Shi, *J. Am. Chem. Soc.* **1996**, *118*, 9806–9807.

[162] a) H. Hussain, I. R. Green, I. Ahmed, *Chem. Rev.* **2013**, *113*, 3329-3371; b) P. Kachasakul, S. Assabumrungrat, P. Praserthdam, U. Pancharoen, *Chem. Eng. J.* **2003**, *92*, 131-139; c) N. Hashimoto, A. Kanda, *Org. Process. Res. Dev.* **2002**, *6,* 405-406.

[163] a) W. Adam, D. Kazakov, V. Kazakov, *Chem. Rev.* **2005**, *105*, 3371-3387; b) A. Lange, H. J. Brauer, *Chem. Soc. Perkin Trans. 2* **1996**, 805

short reaction times, not need stronger conditions of reactions and sometimes the final products can be obtained pure after simple evaporation of the solvent.[164] DMDO is an useful oxidizing agent and has been widely studied in the oxidation of different heteroatoms (sulfur, nitrogen, iodine, selenium, phosphorus), metals to form metal organic frameworks (MOFs), alkenes, alkynes and in the epoxidation of α,β-unsaturated esters, 1,3-cyclohexadienes and 1,3-cyclooctadienes.[164, 165] However, there are described only a few examples of oxidative dearomatizations of phenols using dimethyldioxirane as oxidizing agent. In these examples, the authors reported the formation of mixtures of different oxidation products in low to moderate yields, being in most cases the major compounds the corresponding quinones.

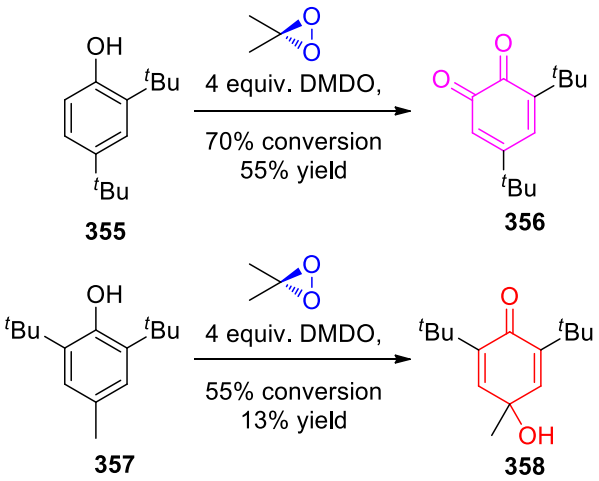
Curci and coworkers described in 1991 the oxidation studies of 2,6-di-*tert*-butylphenol (**351**) with isolated 3-methyl-3-(trifluoromethyl)dioxirane (**350b**) or dimethyldioxirane (**350a**) (*Scheme 3.17*).[166] The oxidative dearomatization of the hindered phenol **351** afforded a mixture of 2,6-di-tert-butylcyclohexa-2,5-diene-1,4-dione (**353**) and 3,5-di-tert-butyl-2-hydroxycyclohexa-2,5-diene-1,4-dione (**354**) and the proportion of isolated yield of **353** and **354** depended on the dioxirane used in the reaction. Thus, with 3-methyl-3-(trifluoromethyl)dioxirane (**350b**), 3,5-di-tert-butyl-2-hydroxycyclohexa-2,5-diene-1,4-dione (**354**) was obtained as the major product in 70% yield *vs.* 24% isolated yield of 2,6-di-tert-butylcyclohexa-2,5-diene-1,4-dione (**353**). Instead, using dimethyldioxirane (**350a**) the major product was quinone **353**, isolated in 56% yield *vs.* 35% yield of **354**, because the trifluoromethyl substituted dioxirane **350b** is more reactive than dioxirane **350a**. This fact was supported by the reactions time, 1 min using dioxirane **350b** *vs.* 40 hours with dioxirane **350a**, and the conversion of phenol **351**, 96% of conversion when the oxidant was dioxirane **350b** *vs.* 33% of conversion using dioxirane **350a**.



*Scheme 3.125. Oxidative dearomatization of 2,6-di-tert-butylcyclohexa-2,5-diene-1,4-dione (**351**) using isolated dioxiranes by Curci and coworkers*

[164] A. Saeed, F. A. Larik, B. Lal, M. Faisal, H. El-Seedi, P. A. Channar, *Synth. Commun.* **2017**, *47*, 835-852
[165] W. Adam, C.-G Zhao, K. Jakka, *Organic Reactions* **2008**, *69*, 1–346
[166] A. Altamura, C. Fusco, L. D'Accolti, R. Mello, T. Prencipe, R. Curci, *Tetrahedron Lett.* **1991**, *132*, 5445-5448.

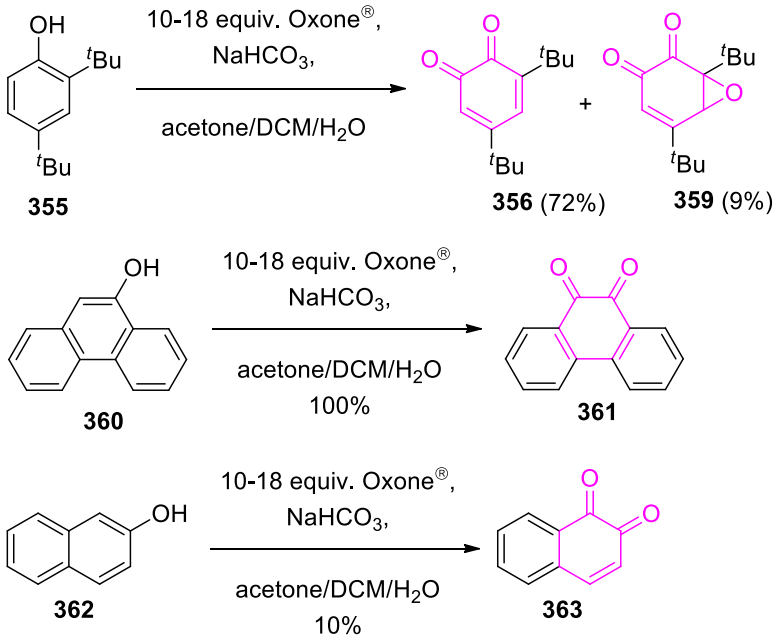
Crandall and coworkers also reported in 1991 an oxidation study of different phenols, utilizing isolated dimethyldioxirane (**350a**) as the reagent (*Scheme 3.18*).[167] The reaction of 2,4-di-*tert*-butylphenol (**355**) with 4 equiv. of a solution of DMDO in acetone gave rise to ortho-quinone **356** in 55% yield with 70% conversion. However, 2,6-di-tert-butyl-4-methylphenol (**357**) reacted with 55% of conversion under the same conditions, affording *para*-quinol **358** in 13% yield.



Scheme 3.126. Oxidative dearomatization of different ortho-substituted phenol with isolated DMDO by Crandall and coworkers

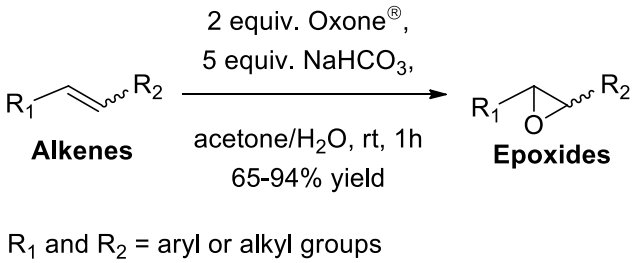
In addition, the same authors described a method to synthesize in situ the necessary DMDO from Oxone® and acetone in an aqueous solution of sodium bicarbonate (*Scheme 3.19*). Thus, 2,4-di-*tert*-butylphenol (**355**) was added to the mixture of Oxone®, acetone and $NaHCO_3$ in water and phenol was completely converted into *ortho*-quinone **356** in 72% yield and a small amount of epoxy *ortho*-quinone **359** in 9% yield. This methodology was applied to different substrates, such as phenanthren-9-ol (**360**) and naphthalen-2-ol (**362**), to afford the corresponding *ortho*-quinones, phenanthrene-9,10-dione (**362**), in 100% yield, and naphthalene-1,2-dione (**365**), in a poor 10% yield.

[167] J. K. Crandall, M. Zucco, R. S. Kirsch, D. M. Coppert, *Tetrahedron Lett.* **1991**, 132, 5441-5441.



Scheme 3.127. Oxidative dearomatization of different substrates (phenols, naphthols and phenanthrenols) with Oxone® / $NaHCO_3$ / acetone by Crandall and coworkers

The oxidation reactions utilizing dioxiranes can be carried out with the "isolated" dioxirane dissolved in the corresponding solvent or by generating the dioxirane "in situ", under mild conditions, by adding Oxone® in one portion. These methods require a buffer solution to regulate de pH for the correct formation of the dioxirane. Nevertheless, in 2002 Hashimoto and Kanda described an epoxidation method of double bonds using dimethyldioxirane formed in situ by slow addition of an aqueous solution of Oxone® with a syringe pump to a solution of different alkenes and sodium bicarbonate in acetone/water, open to the air.[168] The epoxidation of (E)-1,2-disubstitutedethenes, using 2 equiv. of Oxone and 5 equiv. of sodium bicarbonate, afforded 2,3-disubstituted dioxiranes in high yield after 1 hour, without the need of a buffer solution (*Scheme 3.20*).



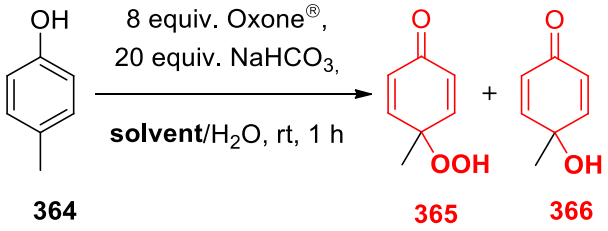
Scheme 3.128. Epoxidation of alkenes through DMDO generated in situ by slow addition of Oxone®.

[168] N. Hashimoto, A. Kanda, *Org Proc. Res. Dev.* **2002**, *6*, 405-406.

3.2. Results and Discussion

3.2.1. Preliminary results

Taking into account all these information and precedents, we decided to realize some experiments trying to understand the mechanism involved in the direct formation of angular tetracyclic *para*-quinol **24a** from phenol **22a** (*Scheme 2.51*) using *para*-cresol as the simplest model substrate (*Table 3.2*). In a first approach, we carried out a control experiment under the oxidative dearomatization conditions developed in our group in 2006 to synthesize *para*-peroxy quinols through the in situ formation of singlet oxygen ($^1O_2$).[169] Thus, the addition of a grounded mixture of Oxone® and $NaHCO_3$ in one portion to a solution of *para*-cresol (**364**) in acetonitrile / water gave *para*-peroxy quinol **365** in 99% yield (*Table 3.2*, *entry 1*). Following the same procedure, but changing acetonitrile by acetone, a mixture of the corresponding *para*-peroxy quinol **365** and *para*-quinol **366** was obtained, in low yield, in a ratio 26:74, respectively (*Table 3.2*, *entry 2*). This result suggested that both oxidizing agents, singlet oxygen and dimethyldioxirane (DMDO), were formed in the reaction medium, singlet oxygen arising from dioxirane in the presence of an excess of Oxone®.



entry	addition of Oxone®	solvent	formed reagent	365 (%)[a]	366 (%)[a]	yield (%)[b]
1	Fast (one portion)	CH_3CN	$^1O_2$	100	0	90
2	Fast (one portion)	Acetone	$^1O_2$ + DMDO	26	74	10
3	Slow (with a syringe pump)	acetone	DMDO	0	100	19

a: Conversion determined by ^{1}H-NMR of the crude reaction; b: Isolated yield of majority product

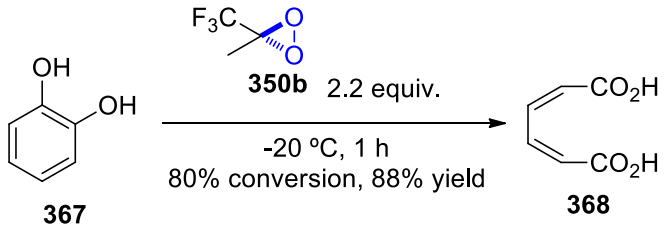
*Table 3.12. Oxidative dearomatization experiments of 4-methylphenol (**364**) using the system Oxone® / $NaHCO_3$ / acetone*

In order to minimize the formation of singlet oxygen, responsible of the formation of the *para*-peroxy quinol **365** as the sole product, we decided to apply the methodology reported by

[169] M. C. Carreño, M. González-López, A. Urbano, *Angew. Chem.Int. Ed.* **2006**, *45*, 2737-2741.

Hashimoto and Kanda (*Scheme 3.20*). Thus, the slow addition of an aqueous solution of 8 equiv. of Oxone® using a syringe pump, to a solution of *para*-cresol (**364**) and sodium bicarbonate in a mixture of acetone / Milli-Q water (1:1) afforded *para*-quinol **366** as the unique product, albeit in a very low 19% yield (*Table 3.2*, *entry 3*).

These results indicated that DMDO, generated from the slow reaction of Oxone® with acetone in a basic medium, was able to achieve the oxidative dearomatization of phenols, although, in the case of *para*-cresol (**366**) in a very low yield. We reasoned that this low yield could be a consequence of the possible competitive oxidation of the free *ortho* positions of *para*-cresol (**364**) generating the corresponding *ortho*-quinone, which could be decomposed under the basic conditions employed. This hypothesis was supported by a reference found in the literature, where the reaction of catechol **367** with isolated dioxirane **350b** gave rise to (2Z,4Z)-hexa-2,4-dienedioic acid (**368**) in good yield after 1 hour of reaction (*Scheme 27*).[170] An oxidative cleavage of **367** occurred by action of dioxirane **350**b, through an intermediate oxidation product such as its semiquinone and / or 1,2-benzoquinone. In our case, this type of very polar derivatives would remain in the basic aqueous phase, explaining the low yield of the *para*-quinol obtained.

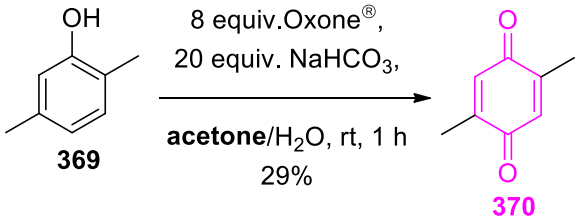


*Scheme 3.129. Reaction of catechol **367** with isolated dioxirane **350**b to afford the dicarboxylic acid X*

For this reason, in order to continue with our reactivity studies of the oxidative dearomatization of different phenols using Oxone® / acetone, as the source of dimethyldioxirane, we decided to use phenols with substituents at the *ortho* positions, starting with 2,5-dimethylphenol (**369**).

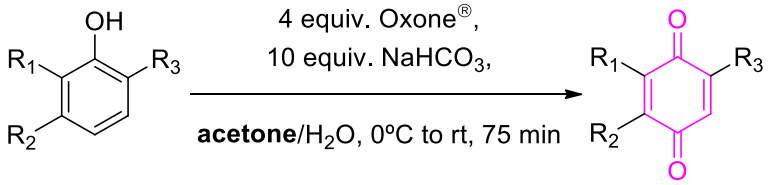
Thus, the reaction of 2,5-dimethylphenol (**369**) with 8 equiv. of Oxone® (slow addition) and 20 equiv. of sodium bicarbonate in a mixture of acetone / Milli-Q water gave rise to quinone **370** in 29% yield after 1 hour of reaction (*Scheme 3.22*).

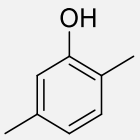
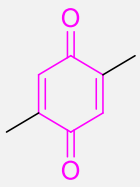
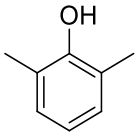
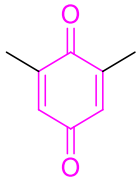
[170] A. Altamura, C. Fusco, L. D'Accolti, R. Mello, T. Prencipe, R. Curci, *Tetrahedron Lett.* **1991**, *32*, 5445-5448.

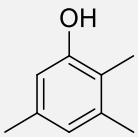
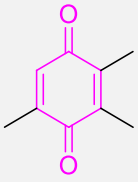
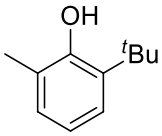
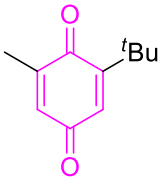


*Scheme 3.130. Formation of para-quinone 370 using the system Oxone® / $NaHCO_3$ / acetone from 2,5-dimethylphenol (**X**)*

After optimization of several reaction conditions, the best result was obtained when an aqueous solution of 4 equiv. of Oxone® was added at 0 ºC to a solution of 2,5-dimethylphenol (**369**) and 10 equiv. of $NaHCO_3$ in acetone / Milli-Q water for 30 min, followed by stirring at rt for additional 45 minutes (*Table 3.3*, *entry 1*). Under these conditions, quinone **370** was obtained in 32% yield. A little scope of this kind of substrates using these optimized conditions demonstrated that these type of phenols with the unsubstituted *para*-position afforded the corresponding *para*-quinones in moderate yields (*Table 3.3*). The final yield of these quinones could not be improved because the crude reaction mixtures were not clean and required further purification, in which we observed some quinone decomposition.



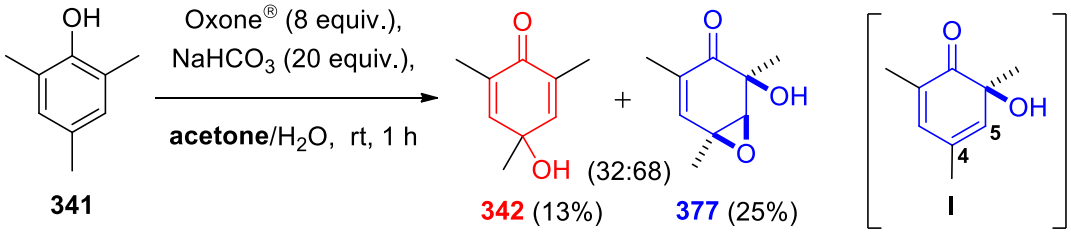
entry	starting phenol	final product	yield (%)[a]
1	 369	 370	32
2	 371	 372	39

3	 373	 374	43
4	 375	 376	35

a: Isolated yield

Table 3.13. Oxidative dearomatization of different ortho-disubstituted phenol with the system Oxone® / $NaHCO_3$ / acetone

The next step was to test our oxidative dearomatization conditions in 2,4,6-trisubstituted phenols. We chose the simplest 2,4,6-trimethylphenol (**341**) as the model to study the reactivity of these type of phenols under our conditions. Initially, an aqueous solution of 8 equiv. of Oxone® was slowly added, using a syringe pump, to a solution of 2,4,6-trimethylphenol (**341**) and 10 equiv. of $NaHCO_3$ in acetone / Milli-Q water at rt for 1 hour. Under these conditions, we obtained a 32:68 mixture of 4-Hydroxy-2,4,6-trimethylcyclohexa-2,5-dienone (**342**) and (1*R**,2*S**,6*S**)-2-Hydroxy-2,4,6-trimethyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (**377**), which could be isolated in 13% and 25% yield, respectively, after chromatographic separation (*Scheme 3.23*).



*Scheme 3.131. Oxidative dearomatization reaction of 2,4,6-trimethylphenol (**341**) using Oxone® / $NaHCO_3$ / acetone*

This result was very interesting because, besides the *para*-quinol obtained, as in the case of the oxidative dearomatization of 7,12-dimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (**22a**) (see *Scheme 2.51*), we observed the oxidative dearomatization at one *ortho* position for the first time. We believe that the *ortho*-quinol **I** was initially formed, followed by a rapid epoxidation at the C_4-C_5 double bond, from the same face of the OH group, effected by an excess of dimethyldioxirane (*Scheme 3.23*).

The structure of epoxy *ortho*-quinol **377** was determined from its spectroscopic data, while the relative *cis* configuration of both the hydroxyl group and the epoxide was established through a NOESY correlation between H_1 and the protons of the methyl groups 8 and 9 situated at C_2 and C_6, respectively (*Figures 3.5* and *3.6*).

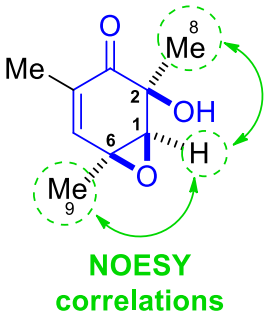


Figure 3.75. NOESY correlations

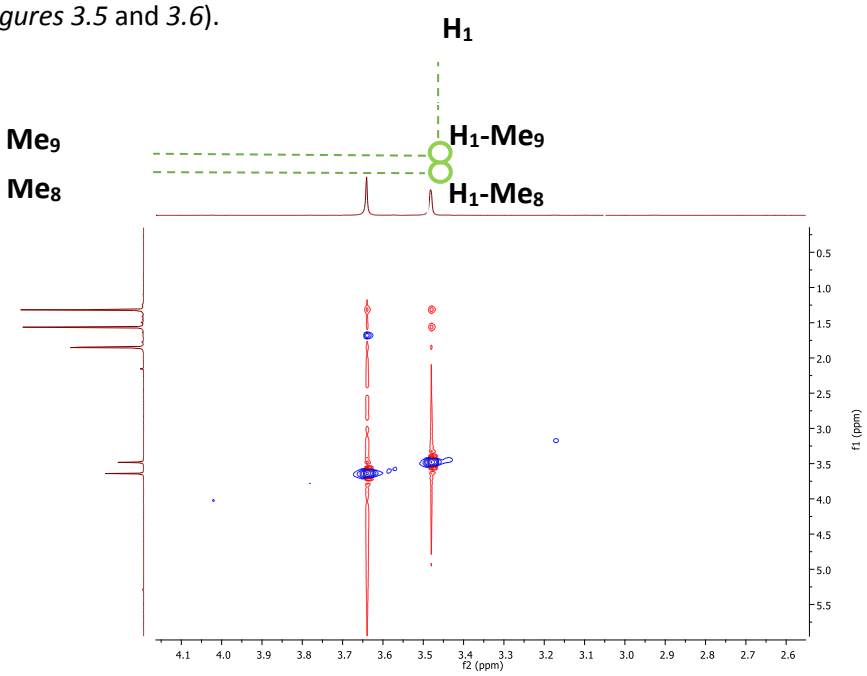
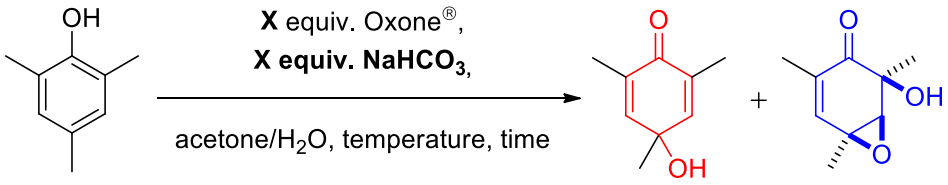


Figure 3.76. NOESY experiment of (1R,2S*,6S*)-2-hydroxy-2,4,6-trimethyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (X)*

This promising result encouraged us to try to improve the yield of this process as well as to enhance the ratio of the epoxy *ortho*-quinol **377** with respect to the *para*-quinol **341**. With this aim, we carried out an optimization of this transformation, varying different conditions and parameters such as the concentration, temperature during the addition, addition time and equiv. of Oxone® and $NaHCO_3$ as well as the final reaction time. The results obtained are summarized in the *Table 3.4*.



341 **342** **377**

entry	equiv. Oxone® /$NaHCO_3$	temp.	addition time	total reaction time	final concentration	**342** (%)[a] (yield)[b]	**377** (%)[a] (yield)[b]
1	8/20	rt	1 h	1 h	0.017 M	32	68
2	4/10	rt	1 h	1 h	0.017 M	27	73
3	2/5	rt	1 h	1 h	0.017 M	31	59
4	4/10	0 ºC	1 h	2 h	0.017 M	23	77
5	4/10	0 ºC	2 h	3 h	0.017 M	23	77
6	4/10	0 ºC	1 h	2 h	0.034	23 (23%)	77 (55%)

*a: Conversion of phenol **341** determined by ^{1}H-NMR of the crude reaction; b: Isolated yield*

Table 3.14. Summary of the different conditions tested to optimized the oxidative dearomatization process

Initially, we checked different equiv. of Oxone® and $NaHCO_3$, maintaining a ratio of 1 to 2.5 between Oxone® and $NaHCO_3$. The other variants remained fixed, 1 hour of addition and reaction at rt with a final concentration of 0.017M in a mixture of acetone / Milli-Q water (1:2). Using 8 equiv. of Oxone® and 20 equiv. of $NaHCO_3$ (*Table 3.4*, *entry 1*), a 32:68 mixture of *para*-quinol **342** and epoxy *ortho*-quinol **377** was obtained. As we detected by TLC that phenol **341** was consumed after 30 min of addition, we decided to use 4 equiv. of Oxone® and 10 equiv. of $NaHCO_3$ (*Table 3.4*, *entry 2*). Under these conditions, a 27:73 mixture of **342** and **377** was achieved. When decreasing the equiv. of Oxone® and $NaHCO_3$ to 2 and 5, respectively (*Table 3.4*, *entry 3*), phenol **341** did not completely react and we observed a conversion of 90%. In any case, we detected the presence of the *ortho*-quinol **I** in the reaction mixtures, suggesting that the epoxidation process is faster than the oxidative dearomatizaton at the *ortho*-position under our experimental conditions.

Next, we studied the influence of the temperature keeping fixed the equiv. of the reagents (4 equiv. of Oxone® and 10 equiv. of $NaHCO_3$), the time of the addition (1 hour) and the final concentration of the reaction mixture (0.017M of a mixture of acetone / Milli-Q water (1/2)).

Thus, when the slow addition of Oxone® was performed at low temperature (the reaction flask was cooled at 0 ºC in an ice / water bath), a 23:77 mixture of **342** and **377** was obtained (*Table 3.4*, entry 4), in comparison with the addition at room temperature (27:73 mixture; *Table 3.4*, entry 3). When the Oxone® addition was performed at low temperature, it was necessary to continue stirring the reaction mixture for an additional hour at rt to consume all the starting phenol **341**.

The next step was to study the effect of the addition time of the Oxone® aqueous solution. Without changing the other conditions [4 equiv. of Oxone® and 10 equiv. of $NaHCO_3$, addition at 0 ºC followed by stirring 1 hour at rt and with a final concentration of 0.017M of a mixture of acetone / Milli-Q water (1:2)], we carried out the addition of Oxone® during 2 hours, by means of a syringe pump (*Table 3.4*, *entry 5*). Under these conditions, we observed exactly the same results than in entry 4 (2 hours vs 3 hours of total reaction time). When adding the aqueous solution of Oxone® during 30 min, we observed a loss of reactivity, because phenol **341** did not react at all.

Finally, we studied the effect of the concentration without changing the acetone / Milli-Q water ratio (1:2) and keeping constant the other variables (4 equiv. of Oxone® and 10 equiv. of $NaHCO_3$, 1 hour of addition at 0 ºC, and 1 hour of stirring at rt). When the reaction was performed increasing the final concentration from 0.017M to 0.034M (*Table 3.4*, *entry 6*), the same 27:73 mixture of **342** and **377** was obtained. At lower or higher concentrations, the final conversion of phenol **341** decreased.

Therefore, the best conditions to achieve the oxidative dearomatization of 2,4,6-trimethylphenol (**341**) were the addition of 4 equiv. of Oxone® at 0 ºC during 1 hour to a solution of phenol **341** and 10 equiv. of $NaHCO_3$, with an additional hour of stirring at rt and with a final reaction concentration of 0.034M (*Table 3.4*, *entry 6*). Under these conditions, a 23% yield of *para*-quinol **342** and a 55% yield of epoxy *ortho*-quinol **377** could be isolated after chromatographic separation of the initially obtained 23:77 mixture.

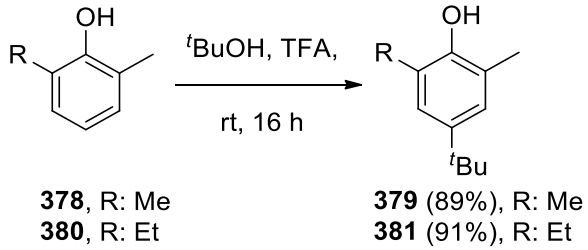
Once optimized our oxidative dearomatization process and found the standard reaction conditions (4 equiv. of Oxone® and 10 equiv. of $NaHCO_3$ at rt for 1 hour), our next step was to carry out a scope of this methodology using diverse substrates, such as differently trisubstituted phenols and substituted 1- and 2-naphthols.

3.2.2. Oxidative dearomatization of 2,4,6-trisubstituted phenols with dimethyldioxirane

3.2.2.1. Synthesis of starting 2,4,6-trisubstituted phenols

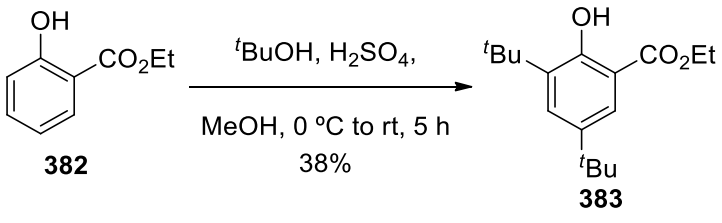
To perform the study of the scope of our oxidative dearomatization process, diverse commercially available 2,4,6-trisubstituted phenols were used, while we had to synthesize other phenols to complete the study. In this section, we describe the synthetic sequences en route to the necessary phenol precursors to perform the reactivity study of our method.

Thus, 4-(*tert*-butyl)-2,6-dimethylphenol (**379**) was synthesized in 89% yield, following a described method, after a Friedel-Crafts alkylation of 2,6-dimethylphenol (**378**) using *tert*-butanol in trifluoroacetic acid at rt for 16 hours (*Scheme 3.24*).[171] 4-(tert-Butyl)-2-ethyl-6-methylphenol (**381**) was obtained from 2-ethyl-6-methylphenol (**380**) in 91% yield, using the same reactions conditions.



*Scheme 3.132. Friedel-Crafts alkylation of phenols **378** and **380** to introduce a tert-butyl group at C_4 position*

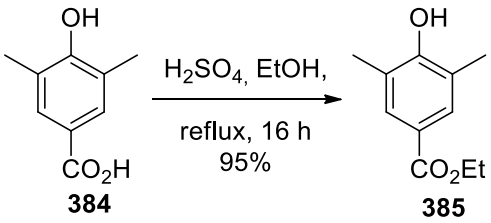
A similar Friedel-Crafts alkylation, but under different reaction conditions (concentrated sulfuric acid in a mixture of *tert*-butanol and methanol at 0 ºC, stirring at rt for 5 hours),[172] allowed the transformation of ethyl 2-hydroxybenzoate (**382**) into ethyl 3,5-di-tert-butyl-2-hydroxybenzoate (**383**) in 38% yield (*Scheme 3.25*).



*Scheme 3.133. Double Friedel-Crafts alkylation of phenol **382** to introduce tert-butyl groups at ortho and para position*

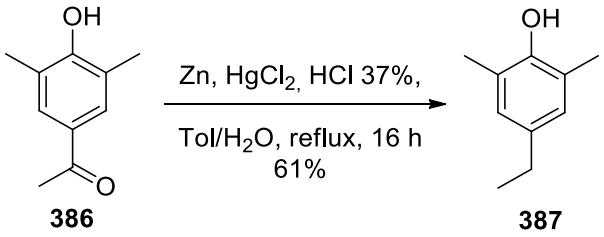
[171] U. Svanholm, V. D. Parker, *J. Chem. Soc., Perkin Trans 1* **1973**, 562-566.
[172] C. A. Jiménez, J. B. Belmar, *Synth. Commun.* **2007**, *37*, 2391-2397.

Under a Fischer esterification conditions, carboxylic acid (**384**) was transformed into ester (**385**) in 95% yield by treatment with a catalytic amount of concentrated sulfuric acid in ethanol after 16 hours at reflux (*Scheme 3.26*).[173]



*Scheme 3.134. Synthesis of ester **385** through a Fischer esterification reaction from carboxylic acid **384***

4-Ethyl-2,6-dimethylphenol (**387**) was obtained in 61% yield, after a Clemmensen reduction of 1-(4-hydroxy-3,5-dimethylphenyl)ethanone (**386**) effected by zinc amalgam (generated by zinc and mercury (II) chloride in concentrated HCl), in a mixture of water and toluene for 16 hours at reflux (*Scheme 3.27*).[174]



*Scheme 3.135. Clemmensen reduction of ketone **386** with a zinc amalgam*

We synthesized three different phenyl-substituted phenols under mild conditions through Suzuki-Miyaura cross-coupling between phenylboronic acid and the corresponding phenol bromides, using tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) and potassium carbonate as described in the literature (*Scheme 3.28*).[175] Thus, 4-bromo-2,6-dimethylphenol (**388**) led to 3,5-dimethyl-[1,1'-biphenyl]-4-ol (**389**) in 75% yield, 2-bromo-4,6-dimethylphenol (**390**) was transformed into 3,5-dimethyl-[1,1'-biphenyl]-2-ol (**391**) in quantitative yield and 5'-methyl-[1,1':3',1''-terphenyl]-2'-ol (**393**) was synthesized in 33% yield from2,6-dibromo-4-methylphenol (**392**).

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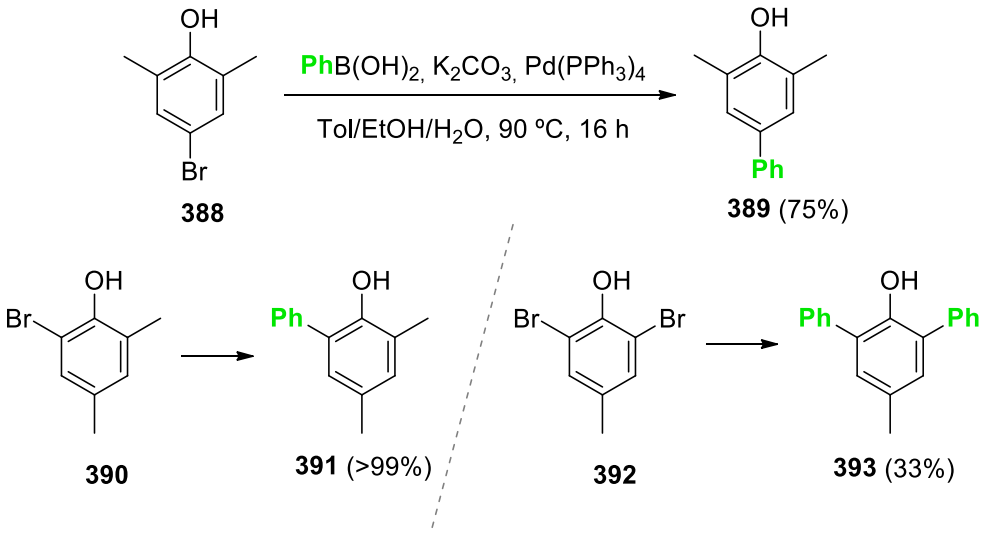
[173] J. Deng, N. Li, H. Liu, Z. Zuo, O. W. Liew, W. Xu, G. Chen, X. Tong, W. Tang, J. Zhu, J. Zuo, H. Jiang, C.-G. Yang, J. Li, W. Zhu, *J. Med. Chem.* **2012**, *55*, 6278-6293.

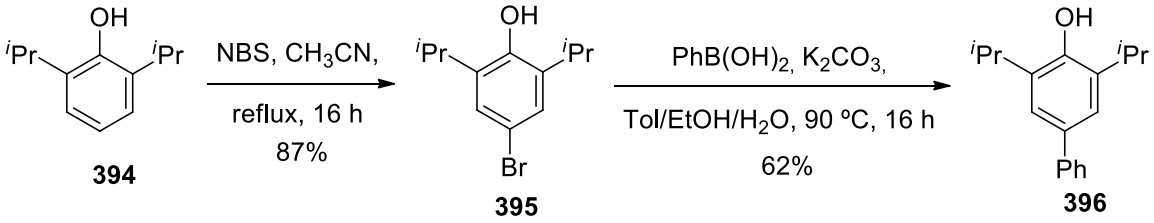
[174] a) Patent WO2012/101244, 2012, A1. b) R. Read, J. Wood, *Organic Synthesis, Wiley: New York* **1995**, *3*, 444.

[175] a) I. Khan, S. R. Chidipudi, H. W. Lam, *Chem. Commun.* **2015**,*51*, 2613-2616. b) Y. Wu, L. Hu, Z. Li, L. Deng, *Nature* **2015**, *523*, 445-450. c) P. H. Bos, M. T. Antalek, J. A. Porco Jr., C. R. J. Stephenson, *J. Am. Chem. Soc.* **2013**, *135*, 17978-17982.



Scheme 3.136. Suzuki-Miyaura cross-coupling between different phenol bromides and phenyl bornic acid

Finally, 3,5-diisopropyl-[1,1'-biphenyl]-4-ol (**396**) was obtained from 2,6-diisopropylphenol (**394**) in two reaction steps (*Scheme 3.29*). Firstly, the bromination of 2,6-diisopropylphenol (**394**) in *para*- position was performed using NBS in acetonitrile affording the intermediate 4-bromo-2,6-diisopropylphenol (**395**) in 87% yield, following a reported procedure.[176] Next, 4-bromo-2,6-diisopropylphenol (**395**) was submitted to a Suzuki-Miyaura cross-coupling with phenylboronic acid, potassium carbonate and tetrakis(triphenylphosphine)palladium(0),[175] generating the desired phenol **396** in 62% yield.



*Scheme 3.137. Synthesis of 3,5-diisopropyl-[1,1'-biphenyl]-4-ol (**396**) in two steps: a bromination followed by a Suzuki-Miyaura cross coupling*

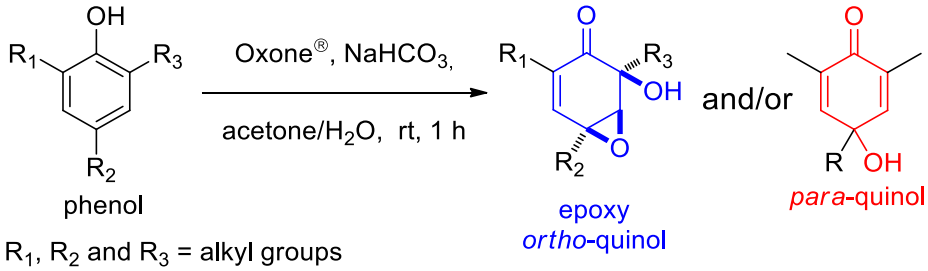
3.2.2.2. Oxidative dearomatization of 2,4,6-trisubstituted phenols with dimethyldioxirane

With our standard conditions in hand, we submitted differently 2,4,6-trisubstituted phenols to the oxidative dearomatization process using 4 equiv. of Oxone® and 10 equiv. of $NaHCO_3$ in 1 hour of addition at rt (all the starting phenol was consumed, being 1 hour of addition

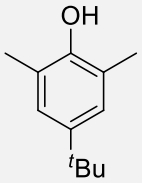
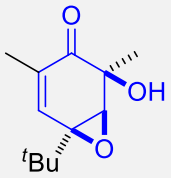
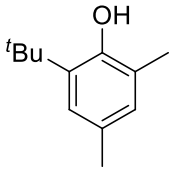
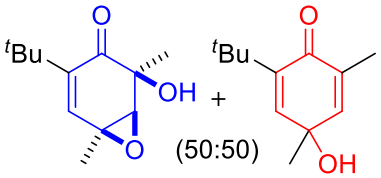
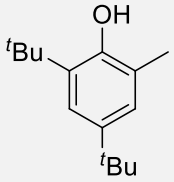
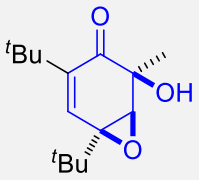
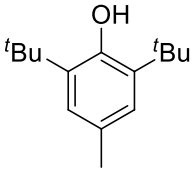
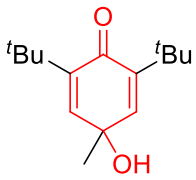
[176] T. Jähnert, M. D. Hager, U. S. Schubert, *Macromol. Rapid Commun.* **2016**, *37*, 725–730.

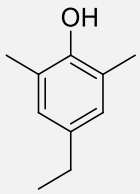
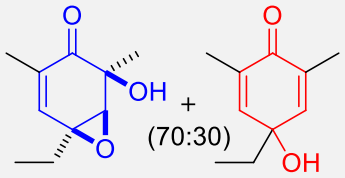
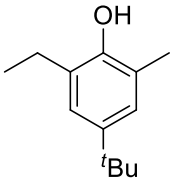
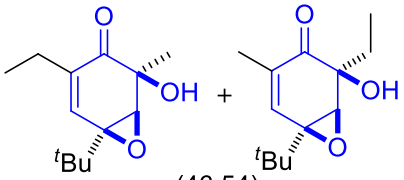
/ reaction). Only when more than one product was formed, the addition of Oxone® was carried out at 0 ºC during 1 hour followed by stirring for an additional hour.

When we carried out the oxidative dearomatization with phenols having alkyl substituents (*tert*-butyl, ethyl and / or methyl), the corresponding epoxy *ortho*-quinols and / or *para*-quinols were obtained (*Table 3.5*).



R_1, R_2 and R_3 = alkyl groups

entry	Oxone® / $NaHCO_3$	phenol	final products	yield (%)[b]
1	4 equiv. / 10 equiv.	 **379**	 **397**	66
2	4 equiv. / 10 equiv	 **398**	 **399** + **400** (50:50)	**399**: 46 **400**: 45
3	6 equiv. / 15 equiv	 **401**	 **402**	67
4	8 equiv. / 20 equiv	 **357**	 **358**	56[c]

5[a]	4 equiv. / 10 equiv	 **387**	 (70:30) **403** **404**	**403**: 64 **404**: 12
6[a]	6 equiv. / 15 equiv	 **380**	 (46:54) **405** **406**	**405**: 43 **406**: 51

a: 1hour of addition at 0 ºC followed by 1 hour of stir at rt; b: Isolated yield; c: 77% conversion.

Table 3.15. Oxidative dearomatization of 2,4,6-trialkyl phenols with Oxone® / $NaHCO_3$ / acetone

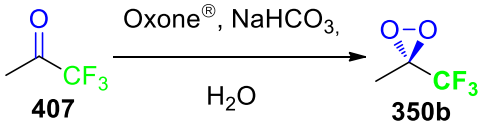
The position oxidized was dependent on the nature of the substituents present in the phenol ring. Thus, very bulky groups, such as *tert*-butyl, blocked the position in which the substituent was located thus inhibiting the approach of DMDO and the oxidation of this position. For example, 4-(*tert*-butyl)-2,6-dimethylphenol (**379**), with a *tert*-butyl group situated at *para* position, completely blocked this C_4 position and DMDO oxidized C_2 and / or C_6 positions. Thus, the oxidative dearomatization of 4-(*tert*-butyl)-2,6-dimethylphenol (**379**) under the standard conditions led to the (1R*,2S*,6R*)-6-(*tert*-Butyl)-2-hydroxy-2,4-dimethyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (**397**) as a sole product, in 66% yield (*Table 3.5*, *entry 1*).

When the bulky *tert*-butyl group was situated in one of the *ortho* positions, the oxidation probability at the alternative *ortho* and *para* positions was balanced by 50%. Accordingly (*Table 3.5*, *entry 2*), the oxidative dearomatization of 2-(*tert*-butyl)-4,6-dimethylphenol (**398**) using 4 equiv of Oxone® and 10 equiv of $NaHCO_3$ (1 hour of addition / reaction at rt) afforded a 50:50 mixture of (1*R**,2S*,6*S**)-4-(*tert*-Butyl)-2-hydroxy-2,6-dimethyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (**399**) and 2-(*tert*-Butyl)-4-hydroxy-4,6-dimethylcyclohexa-2,5-dienone (**400**), from which a 46% yield of **399** and a 45% yield of **400**, could be isolated, after chromatographic separation.

In the case of the oxidative dearomatization of 2,4-di-*tert*-butyl-6-methylphenol (**401**), we need to increase the amount of Oxone® and $NaHCO_3$ to 6 and 15 equiv., respectively, in order to achieve a complete conversion, giving (1*R**,2*S**,6*R**)-4,6-Di-*tert*-butyl-2-hydroxy-2-methyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (**402**), as the unique compound, in 67% yield (*Table 3.5*, *entry 3*). Moreover, the oxidative dearomatization of 2,6-di-*tert*-butyl-4-methylphenol (**357**) to give the 2,6-Di-*tert*-butyl-4-hydroxy-4-methylcyclohexa-2,5-dienone (**358**), in 56% yield, was troublesome (*Table 3.5*, *entry 4*). To achieve only a 77% of conversion, it was necessary to use 8 equiv. of

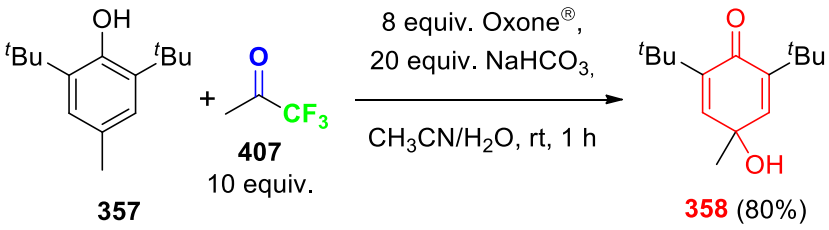
Oxone® and 20 equiv of $NaHCO_3$ and the concentration was decreased to 0.017M, in order to be able to dissolve the reagents.

With the aim of achieving a complete conversion of phenol **357**, we thought of employing a more reactive dioxirane such as methyl trifluoromethyl dioxirane (MTMD).[177] This dioxirane can be prepared from the reaction of 1,1,1-trifluoropropan-2-one (**407**) with Oxone® in basic medium (*Scheme 3.30*) and has been employed as a more reactive alternative to DMDO in different type of oxidations.



*Scheme 3.138. Oxidation of 1,1,1-trifluoropropan-2-one (**407**) with Oxone® to give MTMD*

Thus, the reaction of 2,6-di-*tert*-butyl-4-methylphenol (**357**) with 8 equiv. of Oxone®, 20 equiv. of $NaHCO_3$ and 10 equiv. of 1,1,1-trifluoropropan-2-one (**407**) gave *para*-quinol **358**, in 80% yield, after 1 hour of addition/reaction at rt (*Scheme 3.31*). It was necessary to use acetonitrile as the co-solvent in order to completely dissolve the phenol **357** and to have a homogeneous solution, so the reaction might take place.



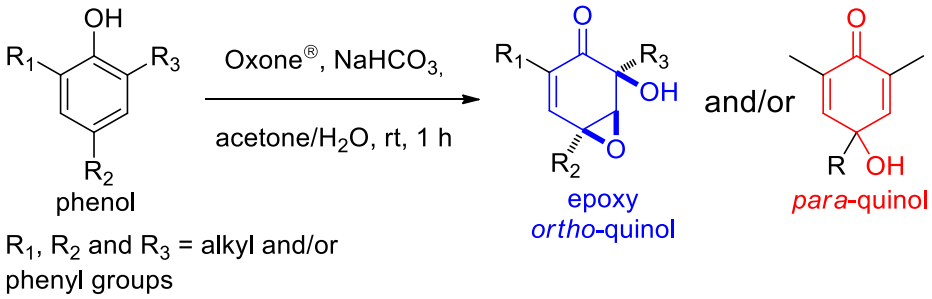
*Scheme 3.139. Oxidative dearomatization of phenol **357** using a more reactive ketone [1,1,1-trifluoropropan-2-one (**407**)]*

The oxidative dearomatization of 4-ethyl-2,6-dimethylphenol (**387**) was another example evidencing that the oxidative dearomatization at the C_2 and C_6 *ortho* positions, adjacent to –OH group, was most favored. Thus, the treatment of 4-ethyl-2,6-dimethylphenol (**387**) with 4 equiv. of Oxone® and 10 equiv. of $NaHCO_3$ (1 hour of addition at 0 ºC followed by 1 hour at rt), afforded (1*R**,2*S**,6*S**)-6-Ethyl-2-hydroxy-2,4-dimethyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (**403**) in 64% yield and 4-Ethyl-4-hydroxy-2,6-dimethylcyclohexa-2,5-dienone (**404**) in 12% yield, after chromatographic separation of the 70:30 mixture initially obtained (*Table 3.5*, *entry 5*).

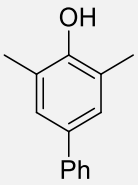
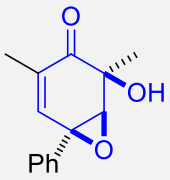
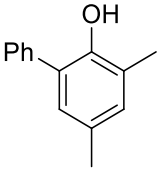
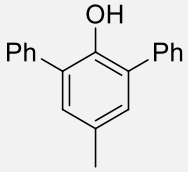
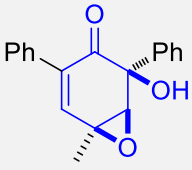
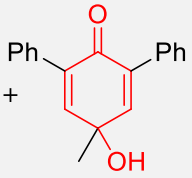
[177] W. Adam, C. R. Saha-Möller, P. A. Ganeshpure, *Chem. Rev.* **2001**, *101*, 3499-3548.

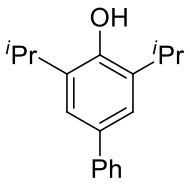
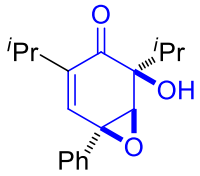
Finally, when 4-(*tert*-butyl)-2-ethyl-6-methylphenol (**380**) was reacted with 6 equiv. of Oxone® and 15 equiv. of $NaHCO_3$ (1 hour of addition at 0 ºC followed by 1 hour at rt) a 43% yield of (1*R**,2*S**,6*R**)-6-(*tert*-Butyl)-4-ethyl-2-hydroxy-2-methyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (**405**) and a 51% yield of (1*R**,2*S**,6*R**)-6-(*tert*-Butyl)-2-ethyl-2-hydroxy-4-methyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (**406**) could be obtained, after chromatographic separation of the 46:54 mixture initially obtained (*Table 3.5*, *entry 6*). We had to increase the equivalents of Oxone® and $NaHCO_3$ to 6 and 15, respectively, to achieve the complete conversion of all phenol **380**.

We were also interested to study the effect of the phenyl group situated at different positions of the phenol ring in the reactivity and selectivity of the process (*Table 3.6*).



R_1, R_2 and R_3 = alkyl and/or phenyl groups

entry	Oxone® / $NaHCO_3$	phenol	final products	yield (%)[b]
1	4 equiv. / 10 equiv.	 **398**	 **408**	70
2	4 equiv. / 10 equiv.	 **391**	complex mixture	-
3[a]	6 equiv. / 15 equiv	 **393**	 **409** (43:57)  **410**	**409**: 24 **410**: 47

4	4 equiv. / 10 equiv	 **396**	 **411**	39[d]

a: 1hour of addition at 0 ºC followed by 1 hour at rt; b: Isolated yield; d: 60% conversion.

Table 3.16. Oxidative dearomatization of phenyl substituted phenols with Oxone® / $NaHCO_3$ / acetone

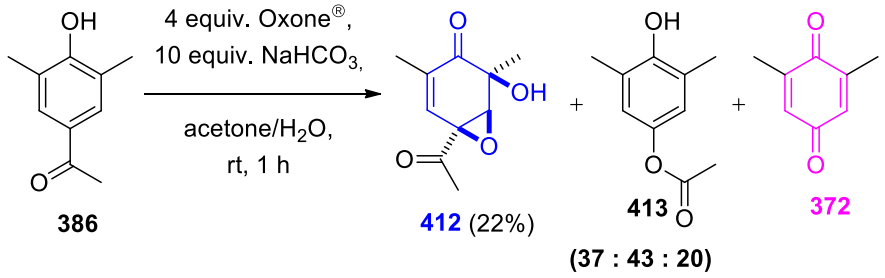
Thus, the oxidative dearomatization of 3,5-dimethyl-[1,1'-biphenyl]-4-ol (**389**) in the presence of 4 equiv. of Oxone® and 10 equiv. of $NaHCO_3$, after 1 hour of addition / reaction at rt, gave rise to (1*R**,2*S**,6*R**)-2-Hydroxy-2,4-dimethyl-6-phenyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (**408**) in 70% yield as a sole product (*Table 3.6*, *entry 1*). This result suggested that a phenyl group situated at the *para* position completely blocked the oxidation at this position, in a similar way to the *tert*-butyl group, favoring initially the oxidation at the *ortho* positions

The treatment of 3,5-dimethyl-[1,1'-biphenyl]-2-ol (**391**) with 4 equiv. of Oxone® and 10 equiv. of $NaHCO_3$, after 1 hour of addition / reaction at rt, generated a complex reaction mixture (*Table 3.6*, *entry 2*).

Nevertheless, the reaction of 5'-methyl-[1,1':3',1''-terphenyl]-2'-ol (**393**) with 6 equiv. of Oxone® and 15 equiv. of $NaHCO_3$ after 1 hour of addition at 0 ºC followed by 1 hour at rt, afforded a 43:57 mixture of (1*R**,2*S**,6*S**)-2-Hydroxy-6-methyl-2,4-diphenyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (**409**) and 5'-hydroxy-5'-methyl-[1,1':3',1''-terphenyl]-2'(5'H)-one (**410**), from which a 24% yield of **409** and a 47% yield of **410** could be isolated, after chromatographic separation (*Table 3.6*, *entry 3*). In this case, the phenyl groups situated at the *ortho* positions made the oxidation at this position difficult, but a significant amount of the *ortho*-oxidation could be observed, demonstrating again the preference for the oxidative dearomatization of the ortho positions under our standard conditions.

This fact was again corroborated when we carried out the oxidative dearomatization of 3,5-diisopropyl-[1,1'-biphenyl]-4-ol (**396**) with 4 equiv. of Oxone® and 10 equiv. of $NaHCO_3$ after 1 hour of addition / reaction at rt (*Table 3.6*, *entry 4*). Although only a 60% of conversion was achieved, the (1*R**,2*S**,6*R**)-2-Hydroxy-2,4-diisopropyl-6-phenyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (**411**) was the unique product obtained, and isolated in 39% yield, after chromatographic purification. This result indicated the preference for the oxidation at the *ortho* positions containing the bulky isopropyl groups than the oxidation at the para position occupied by the phenyl group, since the formed epoxide must proceed from the initially formed *ortho*-quinol.

We also carried out the oxidative dearomatization of phenol **386**, bearing a methyl ketone at the para position (*Scheme 3.32)*. Thus, the reaction of 1-(4-hydroxy-3,5-dimethylphenyl)ethanone (**386**) with 4 equiv. of Oxone® and 10 equiv. of $NaHCO_3$, after 1 hour of addition / reaction at rt, afforded a 37:43:20 mixture of (1*R**,2*S**,6*S**)-6-Acetyl-2-hydroxy-2,4-dimethyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (**412**), ester **413** and 2,6-dimethylcyclohexa-2,5-diene-1,4-dione (**372**), from which epoxy *ortho*-quinol **412** could be isolated in 22% yield.



*Scheme 3.140. Oxidative dearomatization of phenol **386** with a Baeyer-Villeger secondary reaction*

The relative *cis* configuration between the hydroxyl and epoxide groups could be confirmed through the NOESY correlations indicated in the *Figures 3.7* and *3.8* between H_1 and the protons of the methyl groups 9 and 10 situated at C_6 and C_2, respectively.

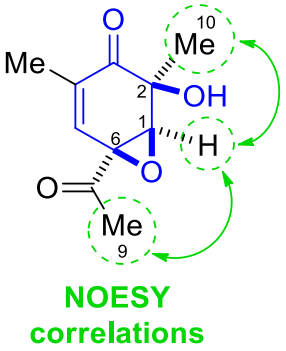


Figure 3.77. NOESY correlations

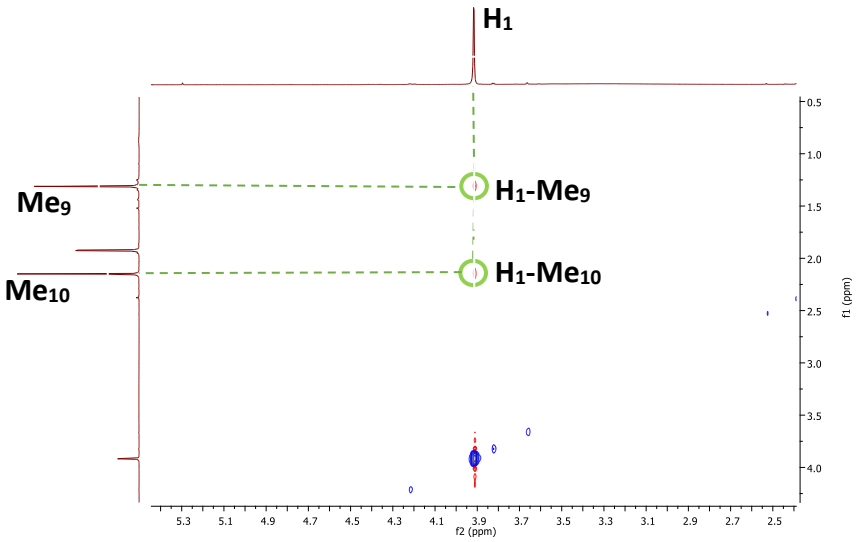
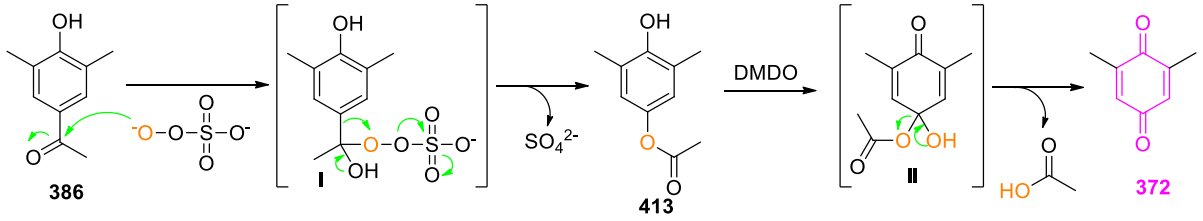


Figure 3.78. NOESY experiment

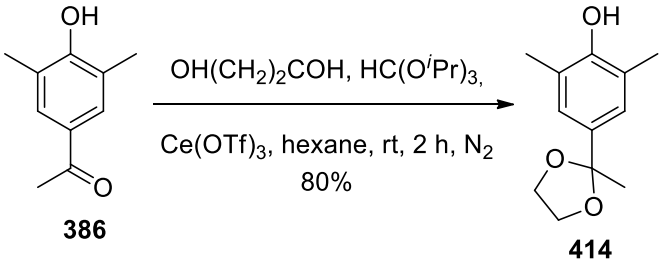
A possible explanation of the result shown in *Scheme 3.33* could be that the ketone group of phenol **386** could suffer a nucleophilic attack of the Oxone® present in the reaction medium, forming intermediate **I**, which would evolve to ester **413** through a Baeyer-Villiger reaction with

the consequent loss of sulfate anion (*Scheme 3.33*). Next, DMDO formed in situ could give an oxidative dearomatization at the para position, leading to the non-stable hemiketal intermediate **II**, which could evolve to quinone **372** by loss of acetic acid.



*Scheme 3.141. Baeyer-Villiger mechanism to finally obtained quinone **372** via formation of ester **413***

In order to avoid this non-desirable secondary reaction, we decided to protect the ketone group of **386** as acetal. Thus, using a described method, the treatment of ketone **386** with ethylene glycol, triisopropyl orthoformate and a catalytic amount of cerium(III) trifluoromethanesulfonate in hexane at rt for 2 h,[178] afforded acetal **414** in 80% yield (*Scheme 3.34*).

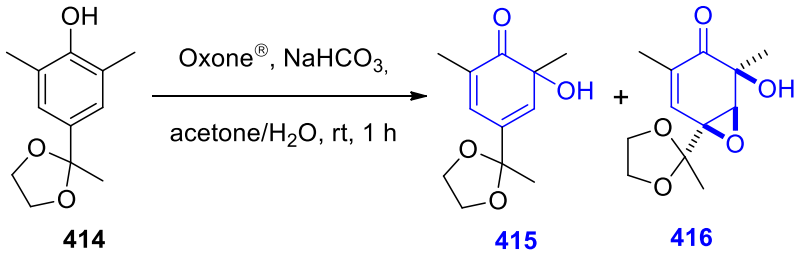


*Scheme 3.142. Protection of carbonyl group of **386** as acetal using ethylene glycol*

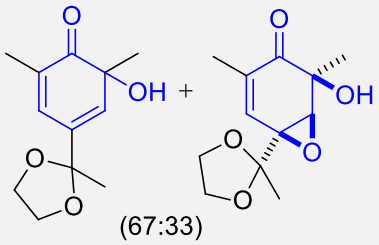
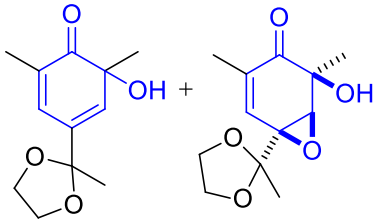
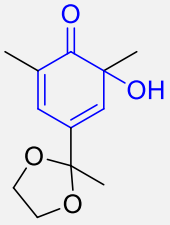
The oxidative dearomatization of acetal **414** with 4 equiv. of Oxone® and 10 equiv. of $NaHCO_3$, after 1 hour of addition/reaction at rt, afforded a 67:33 mixture of 6-hydroxy-2,6-dimethyl-4-(2-methyl-1,3-dioxolan-2-yl)cyclohexa-2,4-dienone (**415**) and (1*R**,2*S**,6*S**)-2-Hydroxy-2,4-dimethyl-6-(2-methyl-1,3-dioxolan-2-yl)-7-oxabicyclo[4.1.0]hept-4-en-3-one (**416**) from which a 47% of **415** and a 27% of **416** could be isolated, after chromatographic separation (*Table 3.7*, *entry 1*). This result was the first example in which the initially formed *ortho*-quinol could be isolated indicating that derivative **415** was less reactive than the previously generated *ortho*-quinols, which only could be isolated as the derivative epoxy *ortho*-quinols. We did not

[178] F. Ono, H. Takenaka, T. Fujikawa, M. Mori, T. Sato, *Synthesis* **2009**, *8*, 1318-1322.

observe at all the possible spontaneous dimerization of *ortho*-quinol **415** through Diels-Alder reaction.



414 **415** **416**

entry	Oxone® / $NaHCO_3$	final products	yield (%)[b]
1	4 equiv. / 10 equiv	 (67:33)	**415**: 47 **416**: 27
2	8 equiv. / 20 equiv	 (38:62)	**415**: 27 **416**: 48
3[a]	2 equiv. / 5 equiv.		64

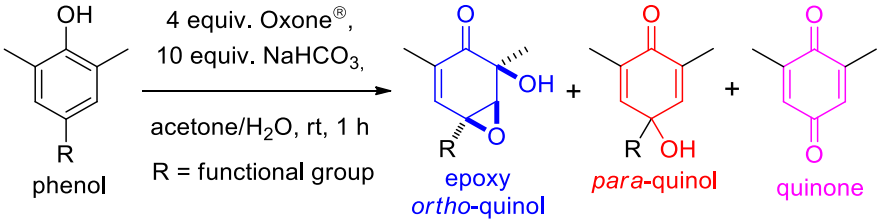
a: 1 hour of addition at 0 ºC followed by 1 hour of stir at rt; b: Isolated yield.

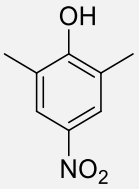
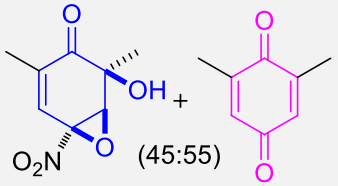
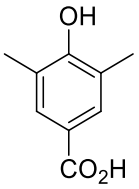
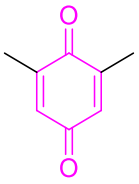
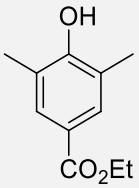
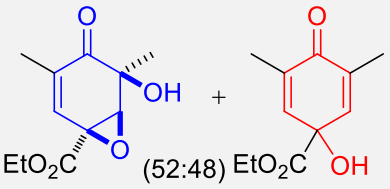
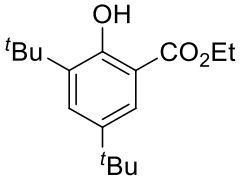
*Table 3.17. Oxidative dearomatization of phenol **414** under different conditions*

The ratio of the epoxy *ortho*-quinol **416** could be increased when 8 equiv. of Oxone® and 20 equiv. of $NaHCO_3$ were used, giving rise to a 38:62 mixture of **415** an **416**, from which a 27% yield of ortho-quinol **415** and a 48% yield of epoxy *ortho*-quinol **416** could be isolated, after chromatographic separation (*Table 3.7, entry 2*). Finally, the treatment of acetal **414** with 2 equiv.

of Oxone® and 5 equiv. of $NaHCO_3$, after 1 hour of addition at 0 ºC followed by 1 hour at rt, gave rise to *ortho*-quinol **415**, as the sole product, in 64% yield (*Table 3.7*, *entry 3*).

We were also interested in checking how different electron-withdrawing substituents such as nitro, carboxylic acid or ester groups could affect the reactivity and selectivity under our oxidative dearomatization conditions (*Table 3.8*).



entry	phenol	final products	yield (%)[c]
1[a]	 417	 418 (45:55) 372	**418**: 44 **372**: 9
2	 384	 372	-
3[a]	 385	 419 (52:48) 420	**419**: 34 **420**: 30
4[b]	 383	-	-

a: 1 hour of addition at 0 ºC followed by 1 hour of stir at rt; b: 8 equiv. Oxone® and 20 equiv. $NaHCO_3$; c: Isolated yield.

Table 3.18. Oxidative dearomatization of 2,4,6-trisubstituted phenols with Oxone® / $NaHCO_3$ / acetone

Thus, the oxidative dearomatization of 2,6-dimethyl-4-nitrophenol (**417**) with 4 equiv. of Oxone® and 10 equiv. of $NaHCO_3$, after 1 hour of addition at 0 ºC followed by 1 hour at rt (*Table*

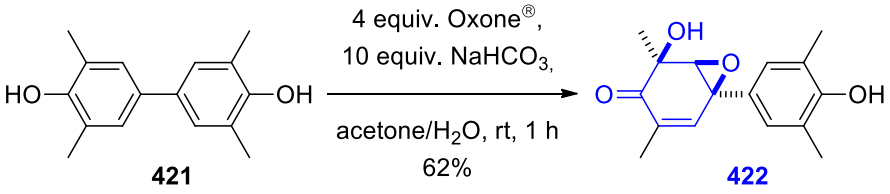
3.8, *entry 1*), afforded a 45:55 mixture of (1*R**,2*S**,6*S**)-2-Hydroxy-2,4-dimethyl-6-nitro-7-oxabicyclo[4.1.0]hept-4-en-3-one (**418**) (44% isolated yield) and quinone **372** (9% isolated yield). The low isolated yield of quinone **372** could be explained because of a loss of product by sublimation. We suggested that quinone **372** could come from a Nef reaction between nitro group and Oxone® or the oxidation product at para position, which evolved in the medium to quinone **372** by loss of nitrogen dioxide (NO_2).

On the other hand, the oxidative dearomatization of 4-hydroxy-3,5-dimethylbenzoic acid (**384**) (*Table 3.8*, *entry 2*), generated quinone **372** after 1 hour of addition / reaction at rt**,** as the sole product, probably after loss of carbon dioxide (CO_2) from the corresponding initially formed *para*-quinol, which could not be detected.

When we carried out the same reaction on the corresponding ethyl ester **385** and after 1 hour of addition at 0 ºC followed by 1 hour at rt, a 52:48 mixture of (1*S**,5*S**,6*R**)-Ethyl-5-hydroxy-3,5-dimethyl-4-oxo-7-oxabicyclo[4.1.0]hept-2-ene-1-carboxylate (**419**) (34% isolated yield) and ethyl 1-hydroxy-3,5-dimethyl-4-oxocyclohexa-2,5-dienecarboxylate (**420**) (30% isolated yield), could be obtained (*Table 3.8*, *entry 3*).

Finally, ethyl 3,5-di-tert-butyl-2-hydroxybenzoate (**383**) remained unchanged under our oxidative dearomatization conditions, even increasing the equivalents to 8 equiv. of Oxone® and 20 equiv. of $NaHCO_3$ (*Table 3.8*, *entry 4*).

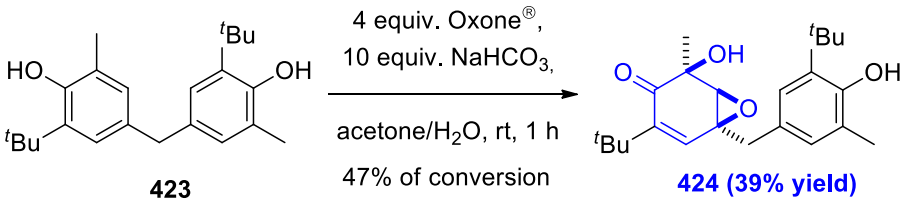
We also applied our oxidative dearomatization process to a series of commercially available more complex *bi*-phenols. Thus, the reaction of 3,3',5,5'-tetramethyl-[1,1'-biphenyl]-4,4'-diol (**421**) with 4 equiv. of Oxone® and 10 equiv. of $NaHCO_3$, after 1 hour of addition/reaction at rt, furnished as the unique product epoxy *ortho*-quinol **422**, which could be isolated in 62% yield (*Scheme 3.35*). We only detected the product of oxidative dearomatization of one of the rings, even doubling the equivalents of Oxone® (8 equiv.) and $NaHCO_3$ (20 equiv.).



*Scheme 3.143. Oxidative dearomatization of bi-phenol **421** with Oxone® / $NaHCO_3$ / acetone*

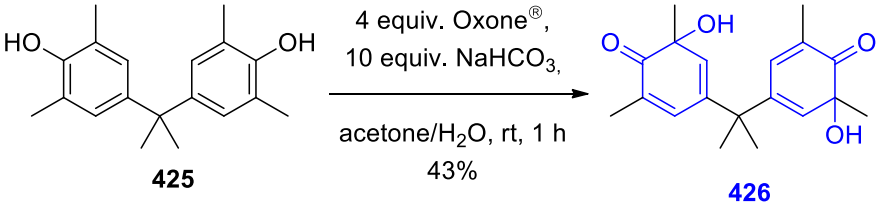
A similar result was observed when 4,4'-methylenebis(2-(*tert*-butyl)-6-methylphenol) (**423**) was submitted to the same conditions as before (*Scheme 3.36*). In this case, we observed

only a of 47% conversion of *bis*-phenol **423** which was transformed into epoxy *ortho*-quinol **424** in 39% yield as the sole product. Doubling the equivalents of Oxone® (8 equiv.) and $NaHCO_3$ (20 equiv.) gave rise to the same result.



*Scheme 3.144. Oxidative dearomatization of bis-phenol **423** with Oxone® / $NaHCO_3$ / acetone*

Finally, the treatment of 4,4'-(propane-2,2-diyl)bis(2,6-dimethylphenol) (**425**) with 4 equiv. of Oxone® and 10 equiv. of $NaHCO_3$, after 1 hour of addition / reaction at rt afforded *bis-ortho*-quinol **426** in 43% yield, as the sole product (*Scheme 3.37*). Unlike the other substrates, with *bis*-phenol **425** a double oxidative dearomatization process occurred but we never detected the corresponding epoxides, even with a higher excess of reactive.



*Scheme 3.145. Oxidative dearomatization of bis-phenol **425** with Oxone® / $NaHCO_3$ / acetone*

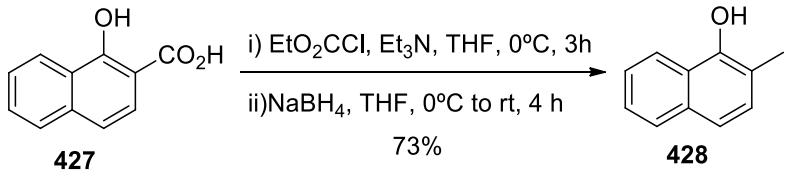
It should be noted that the oxidative dearomation products at the para position were not observed in none of these substrates under our reaction conditions.

3.2.3. Oxidative dearomatization of naphthols with dimethyldioxirane

Once studied the oxidative dearomatization of 2,4,6-trisubstituted phenols with the sytem Oxone / $NaHCO_3$ / acetone as the source of dimethyldioxirane, we were interested in extending the scope of our new methodology to differently substituted 1- and 2-naphthols. Again, we used as standard conditions 4 equiv. of Oxone® and 10 equiv. of $NaHCO_3$ in 1 hour of addition/reaction at rt, but the addition was carried out at 0 ºC for 1 hour followed by 1 hour at rt, when more than one product was formed. In this case, the required substituted 1- and 2-naphthols were not commercially available and had to be synthesized.

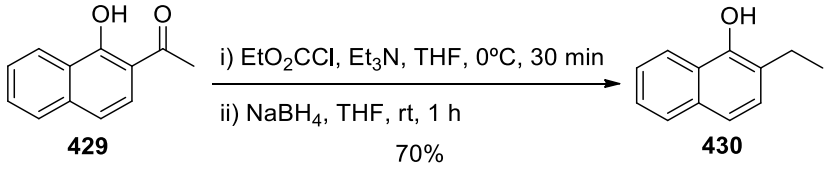
3.2.3.1. Synthesis of 2-substituted-1-naphthols

2-Methylnaphthalen-1-ol (**428**) could be obtained in 73% yield from 1-hydroxy-2-naphthoic acid (**427**), following a described procedure for the reduction of carboxylic group into methyl group with ethyl chloroformate and sodium borohydride at 0 ºC (*Scheme 3.38*).[179]



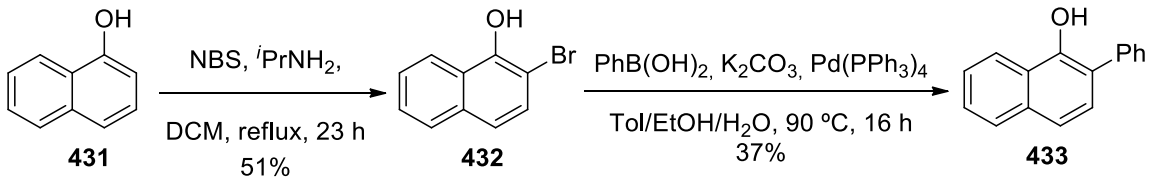
*Scheme 3.146. Synthesis of phenol **428** using ethyl chloroformate*

Through a similar reduction method, commercially available ketone **429** was transformed into 2-ethylnaphthalen-1-ol (**430**) in 70% yield, using ethyl chloroformate and sodium borohydride at 0 ºC (*Scheme 3.39*).[180]



*Scheme 3.147. Synthesis of phenol **430** with ethyl chloroformate*

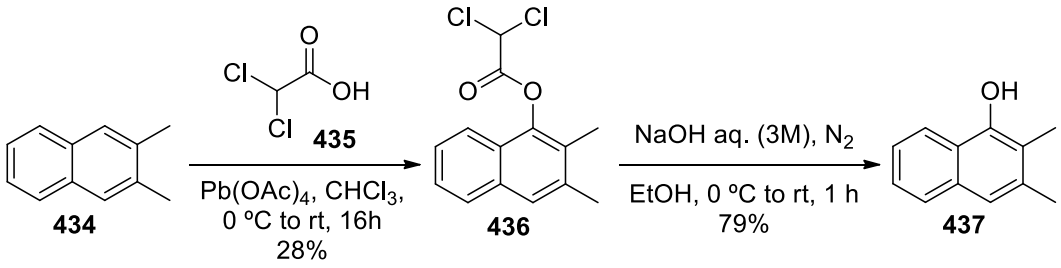
2-Phenylnaphthalen-1-ol (**433**) was prepared in a two-step procedure. Firstly, a reported bromination of naphthalen-1-ol (**431**) with NBS in the presence of isopropylamine in DCM afforded 2-bromonaphthalen-1-ol (**432**) in 51% yield.[181] Next, a Suzuki-Miyaura cross-coupling between 2-bromonaphthalen-1-ol (**432**) and phenylboronic acid in the presence of $Pd(PPh_3)_4$ and potassium carbonate[175a] gave rise to 2-phenylnaphthalen-1-ol (**433**) in 37% yield (*Scheme 3.40*).



*Scheme 3.148. Synthesis of phenol **433** from 1-naphthol **431** in two steps: bromination and Suzuki-Miyaura cross-coupling*

[179] F. Mazzini, P. Salvadori, *Synthesis* **2005**, *15*, 2479-2481.
[180] C. Grandclaudon, P. Y. Toullec, *Eur. J. Org. Chem.* **2016**, *2*, 260-264.
[181] K. Fuchibe, T. Morikawa, K. Shigeno, T. Fujita, J. Ichikawa, *Org. Lett.* **2015**, *17*, 1126-1129.

2,3-Dimethylnaphthalen-1-ol (**437**) was synthesized following a reported procedure from 2,3-dimethylnaphthalene (**434**) in two reaction steps (*Scheme 3.41*).[182] The oxidation of 2,3-dimethylnaphthalene (**434**) with lead tetraacetate and dichloroacetic acid (**435**) in chloroform at rt generated 2,3-dimethylnaphthalen-1-yl 2,2-dichloroacetate (**436**) in 28% yield. Next, **436** was transformed into 2,3-dimethylnaphthalen-1-ol (**437**) in good yield by basic hydrolysis using an aqueous solution of NaOH 3M in ethanol for 1 hour.



*Scheme 3.149. Synthesis of phenol **437** from naphthalene **434** through oxidation followed by basic hydrolysis*

3.2.3.2. Oxidative dearomatization of 2-substituted-1-naphthols with dimethyldioxirane

Taking into account the previously obtained results, we could predict the possible reactivity of 2-substituted 1-naphthols without substituents at C_4 position. It would exist a competitive oxidation competition between the *para* and *ortho* positions and the amount of oxidation product in the *para* position will depend on the size and nature of R_1. If R_1 is not very bulky, the oxidation at C_2 could afford the corresponding *ortho*-quinol and/or epoxy ortho-quinol, while the oxidation at C4 could give the unstable semihydroquinone I, which would evolve into the corresponding quinone (*Figure 3.9*).

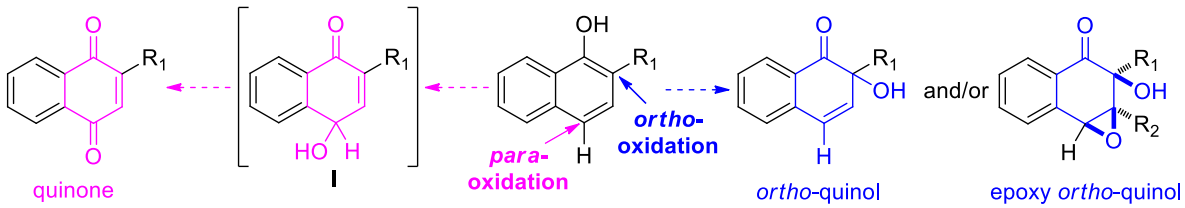
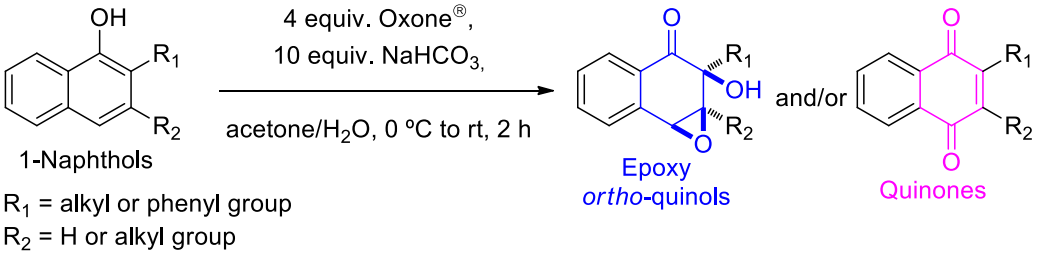


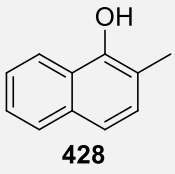
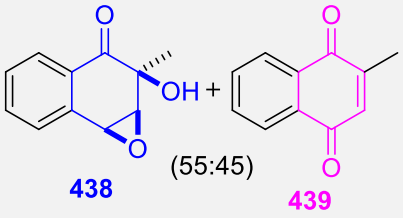
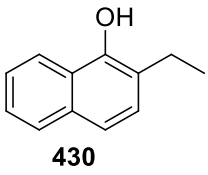
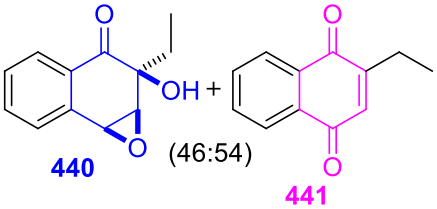
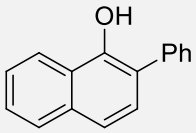
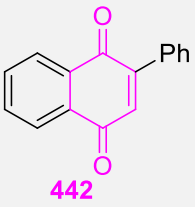
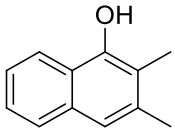
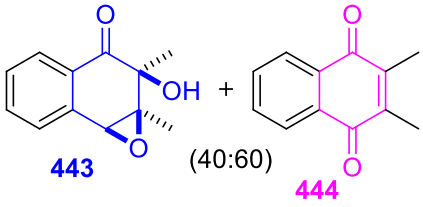
Figure 3.79. Possible oxidized products formed by oxidative dearomatization of 2-substituted-1-naphthols

Thus, we applied our oxidative dearomatization conditions (4 equiv. of Oxone® and 10 equiv. of $NaHCO_3$, for 1 hour of addition at 0 ºC followed by 1 hour at rt) on different 2-

[182] H Greenland, J. T. Pinhey, S Sternhell, *Aust. J. Chem.* **1987**, *40*, 325-331.

substituted 1-naphthols. Under these conditions, a mixture of epoxy *ortho*-quinol and quinone was formed in moderate yields, but we never observed the intermediates *ortho*-quinol, that must be the precursor of the epoxy *ortho*-quinol (*Table 3.9*).



entry	phenol	final products	yield (%)[b]
1	 428	 438 (55:45) 439	**438**: 50 **439**: 34
2[a]	 430	 440 (46:54) 441	**440**: 46 **441**: 54
3[a]	 433	 442	Complex mixture
4	 437	 443 (40:60) 444	**443**: 40 **444**: 56

a: quinone **442** was not purified; b: Isolated product

Table 3.19. Oxidative dearomatization of 2-substituted-1-naphthols with Oxone® / $NaHCO_3$ / acetone

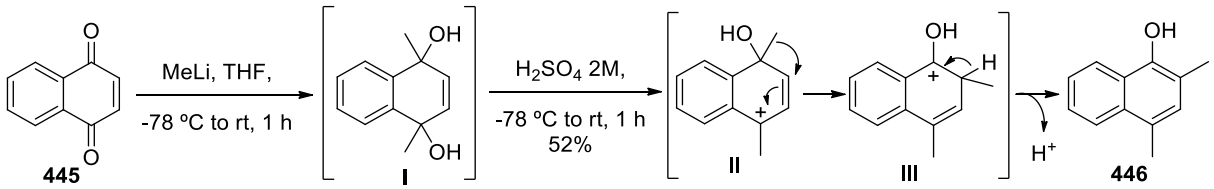
Thus, the oxidative dearomatization of 2-methylnaphthalen-1-ol (**428**) with the system Oxone® / $NaHCO_3$ / acetone led to a 55:45 mixture of (1a*S**,2*S**,7b*S**)-2-Hydroxy-2-methyl-1a,2-dihydronaphtho[1,2-b]oxiren-3(7b*H*)-one (**438**) and 2-methylnaphthalene-1,4-dione (**439**). We separated the products by column chromatography to isolate the epoxy *ortho*-quinol **438** in 50% yield and quinone **439** in 34% yield (*Table 3.9*, *entry 1*). 2-Ethylnaphthalen-1-ol (**430**) was oxidized

into a 46:54 mixture of (1a*S**,2*S**,7b*S**)-2-Ethyl-2-hydroxy-1a,2-dihydronaphtho[1,2-b]oxiren-3(7b*H*)-one (**440**) (46% isolated yield) and 2-ethylnaphthalene-1,4-dione (**441**) (54% isolated yield) (*Table 3.9*, *entry 2*). 2-Phenylnaphthalen-1-ol (**433**) gave rise to a complex mixture, in which we could detect the signals of the 2-phenylnaphthalene-1,4-dione (**442**), but we did not isolate (*Table 3.9*, *entry 3*). In this case, the phenyl group of 2-phenylnaphthalen-1-ol (**433**) inhibited the oxidation at ortho position, so we could only detect the formation of the corresponding quinone **442**. Also, we also checked the reactivity of a naphthol bearing a substituent at meta position and we chose 2,3-dimethylnaphthalen-1-ol (**437**) as model substrate. The reaction of 2,3-dimethylnaphthalen-1-ol (**437**) with 4 equiv. of Oxone® and 10 equiv. of $NaHCO_3$ afforded a 40:60 mixture of (1aS*,2S*,7bS*)-2-Hydroxy-1a,2-dimethyl-1a,2-dihydronaphtho[1,2-b]oxiren-3(7b*H*)-one (**443**) (40% isolated yield) and 2,3-dimethylnaphthalene-1,4-dione (**444**) (56% isolated yield) (*Table 3.9*, *entry 4*). The methyl group at C_3 did not inhibit the formation of epoxide and favored the oxidation at para position.

With the aim of avoiding the undesired oxidation at the para position of 2-substituted 1-naphthols without substituents at C_4, we decided to study the oxidative dearomatization, under our standard conditions, of 2,4-disubstituted 1-naphthols bearing different substituents at C_4. These derivatives were not commercially available and had to be previously synthesized.

3.2.3.3. Synthesis of 2,4-disubstituted-1-naphthols

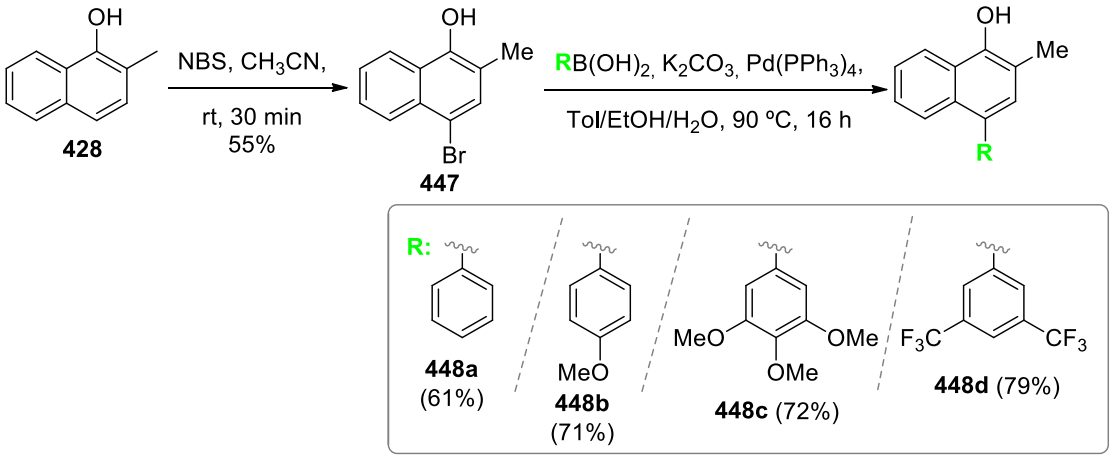
2,4-Dimethylnaphthalen-1-ol (**446**) was synthesized from naphthoquinone **445** by a nucleophilic addition followed by dehydration, migration and deprotonation (*Scheme 3.42*).[183] The reaction between naphthalene-1,4-dione (**445**) and excess of methyllithium afforded diol **I**, which evolved to carbocation **II** after an acid catalyzed dehydration of intermediate **I** when sulfuric acid was added. Then, carbocation **II** underwent a 1,2-methyl migration leading the most stable oxocabenium ion **III**. Finally, 2,4-dimethylnaphthalen-1-ol (**446**) was obtained by a deprotonation of **III**.



*Scheme 3.150. Formation of naphthol **446** from quinone **445** using MeLi*

[183] C. T. Wigal, J. D. McKinley, J. Coyle, D. J. Porter, D. E. Lehman, *J. Org. Chem.* **1995**, *60*, 8421-8423.

4-Aryl-substituted 2-methyl-1-naphthols **448a-d** were synthesized in a two-step procedure from 2-methylnaphthalen-1-ol (**428**). Firstly, this naphthol was treated with NBS in acetonitrile, affording the 4-brominated product **447** in 55% yield after 30 min, as described in the literature.[184] Next, a Suzuki-Miyaura cross-coupling between 4-bromo-2-methylnaphthalen-1-ol (**447**) and the arylboronic acids Xa-d, using tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) in the presence of potassium carbonate,[175a] gave rise to the corresponding 4-aryl-2-methyl-1-naphthols **448a-d**, in good yields (*Scheme 3.43*).

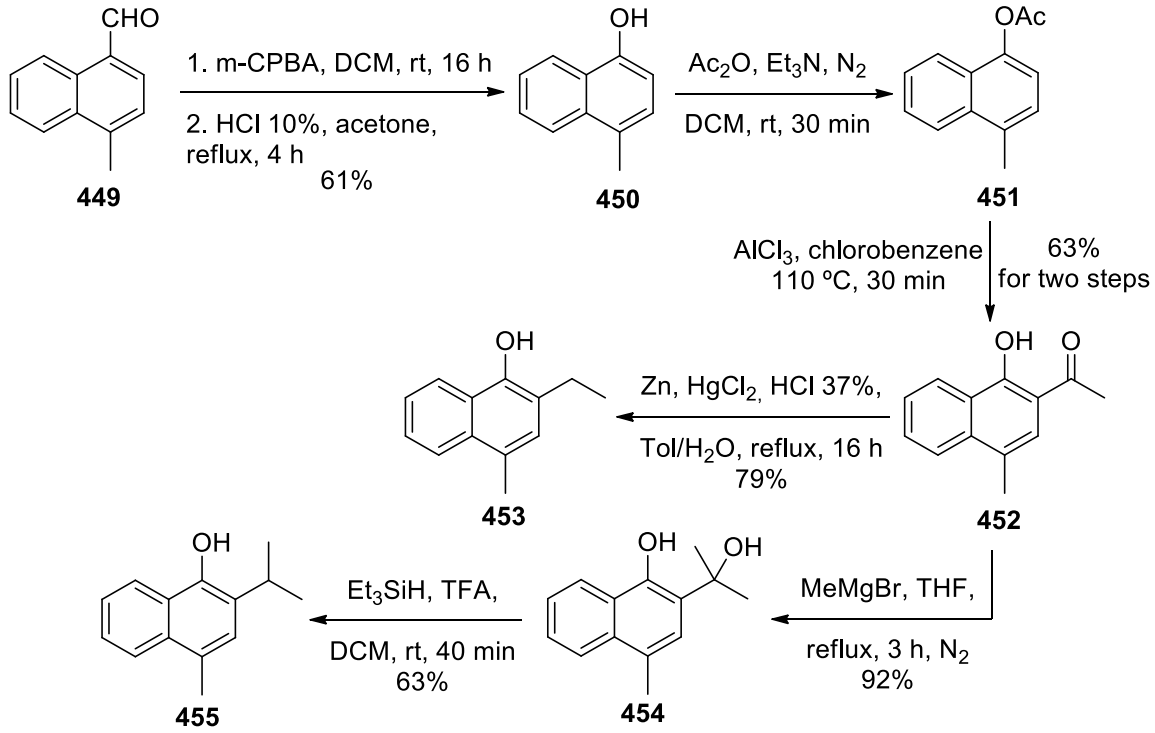


*Scheme 3.151. Synthesis of 4-Aryl-substituted 2-methyl-1-naphtholes **448a-d** from naphthol **428** in two steps: bromination and Suzuki-Miyaura cross-coupling*

2-Ethyl-4-methylnaphthalen-1-ol (**453**) and 2-isopropyl-4-methylnaphthalen-1-ol (**455**) were synthesized in a divergent manner from a common intermediate, 1-(1-hydroxy-4-methylnaphthalen-2-yl)ethanone (**452**), which was obtained from commercially available 4-methyl-1-naphthaldehyde (**449**), in three reaction steps (*Scheme 3.44*). Firstly, the treatment of aldehyde **449** with *m*-CPBA for 16 hours followed by an acid treatment in refluxing acetone for 4 hours afforded 4-methyl-1-naphthol **450**, in 61% yield, after a Baeyer-Villiger reaction.[185] Then, protection of the naphthol as acetate, using acetic anhydride in the presence of triethylamine in DCM under inert atmosphere,[184] gave 4-methylnaphthalen-1-yl acetate (**451**), after 30 min of reaction. Finally, a Fries rearrangement achieved by the treatment of acetate **451** with aluminum trichloride in chlorobenzene at 110 ºC for 30 min, gave rise to methyl ketone **452**, in 63% yield for the two last steps.[184] Once the common intermediate **452** was obtained, a Clemmensen reduction[174] of the keto group present in **452** afforded the desired 2-ethyl-4-methylnaphthalen-1-ol (**453**) in 79% yield. On the other hand, a nucleophilic addition of methyl magnesium bromide to

[184] S. Companys, P. A. Peixoto, C. Bosset, S. Chassaing, K. Miqueu, J.-M. Sotiropoulos, L. Pouysegu, S. Quideau, *Chem. Eur. J.* **2017**, *23*, 13309-13313.
[185] T. Takeya, H. Doi, T. Ogata, T. Otsuka, I. Okamoto, E. Kotani, *Tetrahedron* **2004**, *60*, 6295-6310.

ketone **452** afforded, in 92% yield, carbinol **454**,[Error! Bookmark not defined.] whose transformation into the desired 2-isopropyl-4-methylnaphthalen-1-ol (**455**) was effected, in 63% yield, after acid-catalyzed ionic cleavage of the C-O bond using triethylsilane in the presence of trifluoroacetic acid.[186]

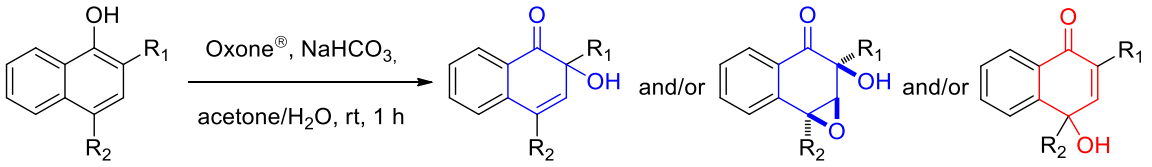


*Scheme 3.152. Synthesis of naphthol **453** and naphthol **455** from aldehyde **449** in 4 steps and 5 steps, respectively.*

3.2.3.4. Oxidative dearomatization of 2,4-disubstituted-1-naphthols with dimethyldioxirane

The oxidative dearomatization of 1-naphthols substituted at C_2 y C_4 positions, under our standard conditions gave rise to the corresponding *ortho*-quinols, epoxy *ortho*-quinols and/or *para*-quinols. The equivalents of Oxone® and $NaHCO_3$ needed to consume the starting naphthol, depended on the size and the electronic characteristics of the substituents (*Table 3.10*).

[186] Patent, US20070049610, 2007, A1.



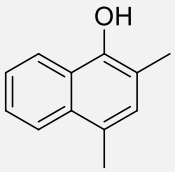
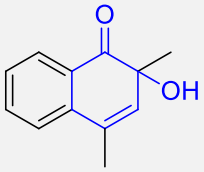
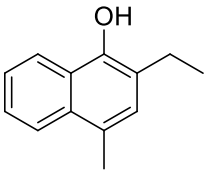
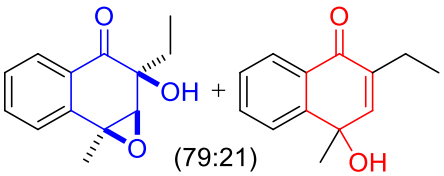
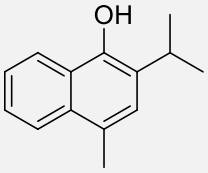
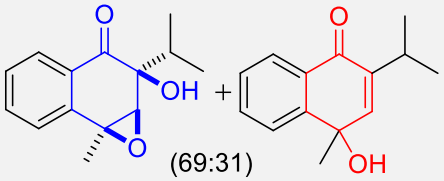
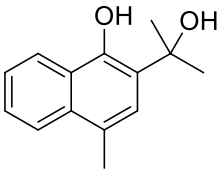
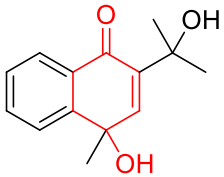
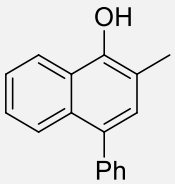
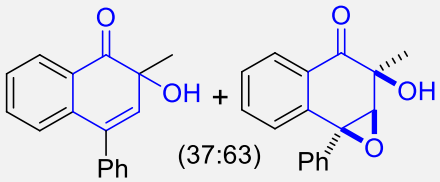
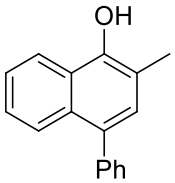
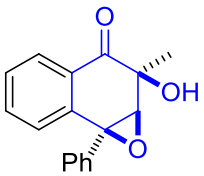
1-naphthol

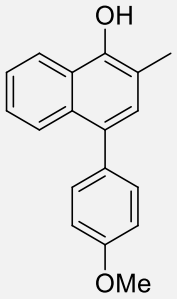
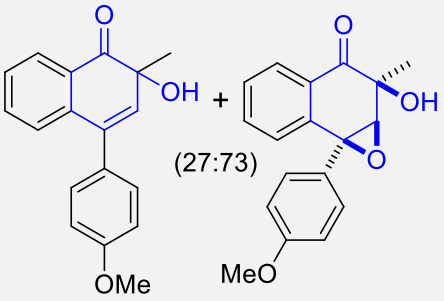
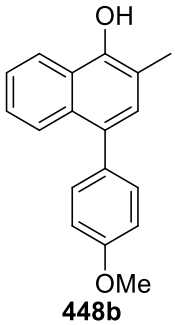
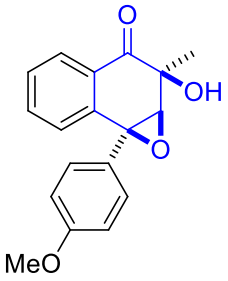
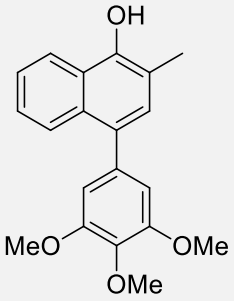
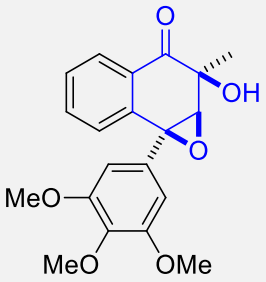
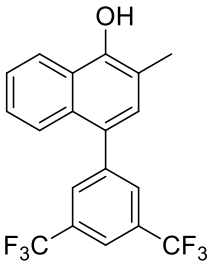
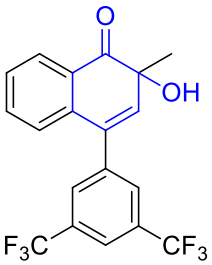
ortho-quinol

epoxy *ortho*-quinol

para-quinol

R_1 and R_2 = alkyl and/or aryl

entry	Oxone® / $NaHCO_3$	phenol	final products	yield (%)[b]
1	2 equiv. / 5 equiv.	 **445**	 **456**	63
2b[a]	2 equiv. / 5 equiv	 **453**	 **457** + **458** (79:21)	**457**: 62 **458**: 21
3[a]	2 equiv. / 5 equiv	 **455**	 **459** + **460** (69:31)	**459**: 29 **460**: 17
4	4 equiv. / 10 equiv	 **454**	 **461**	46
5	2 equiv. / 5 equiv	 **448a**	 **462** + **463** (37:63)	**462**: 30 **463**: 51
6	4 equiv. / 10 equiv	 **448a**	 **463**	95

7	2 equiv. / 5 equiv	 **448b**	 **464** + **465** (27:73)	**464**: 17 **465**: 66
8	4 equiv. / 10 equiv	 **448b**	 **465**	76
9	4 equiv. / 10 equiv	 **448c**	 **466**	25
10	2 equiv. / 5 equiv	 **448d**	 **467**	57

a: 1hour of addition at 0 ºC followed by 1 hour of stir at rt; b: Isolated yield.

Table 3.20. Oxidative dearomatization of 2,4-disubstituted naphthols with Oxone® / $NaHCO_3$ / acetone

Thus, reaction of 2,4-dimethylnaphthalen-1-ol (**445**) with 4 equiv. of Oxone® and 10 equiv. of $NaHCO_3$, after 1 hour of addition/reaction at rt, afforded 2-Hydroxy-2,4-dimethylnaphthalen-1(2*H*)-one (**456**), in 43% yield, as the sole product. This result was improved by decreasing the equivalents of Oxone® (2 equiv.) and $NaHCO_3$ (5 equiv.), giving rise to the *ortho*-quinol **456** in 63% yield (*Table 3.10, entry 1*). This result suggested that in these systems the ortho position was much more reactive than the para position, because the corresponding *para*-quinol was not detected (*Figure 3.10*).

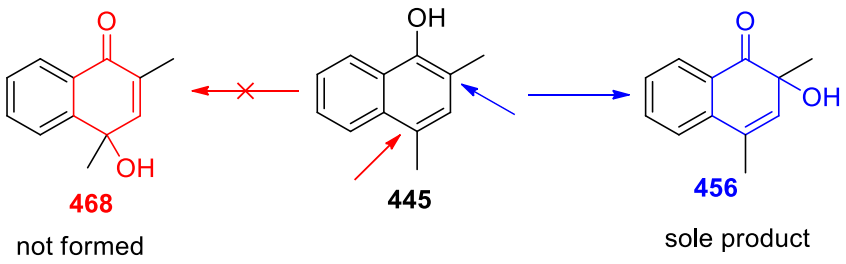


*Figure 3.80. Possible oxidized products in the oxidative dearomatization of naphthol **445**: only formation of ortho-quinol **456***

The structure of *ortho*-quinol **456** was determined from the analysis of HMBC and NOESY spectra (*Figures 3.12* and *3.14*). Thus, in the HMBC spectrum, two correlations between the carbonyl carbon at C_1 (205 ppm) and the protons of hydroxyl group (3.7 ppm) and the methyl group (1.5 ppm) at C_2 were observed. On the other hand, in the NOESY spectrum, it could be observed correlations between protons at C_3 (6.1 ppm) and C_5 (7.5 ppm) with the protons of methyl group at C_4 (2.4 ppm).

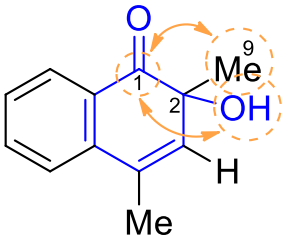


Figure 3.81. HMBC correlations

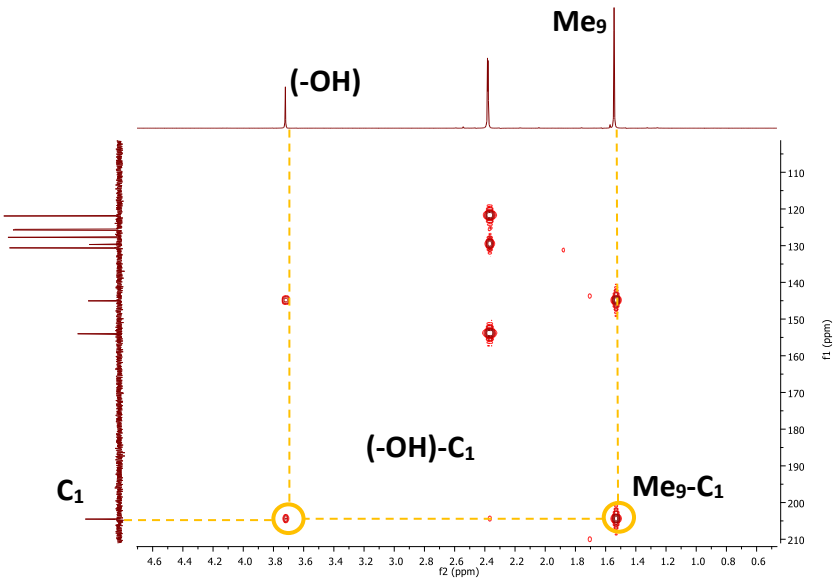


*Figure 3.82. HMBC of 2-hydroxy-2,4-dimethylnaphthalen-1(2H)-one (**456**)*

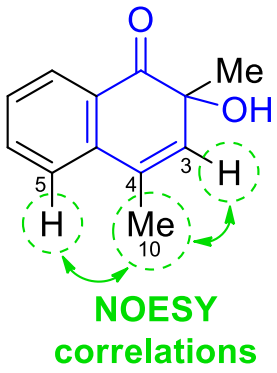


Figure 3.83. NOESY correlations

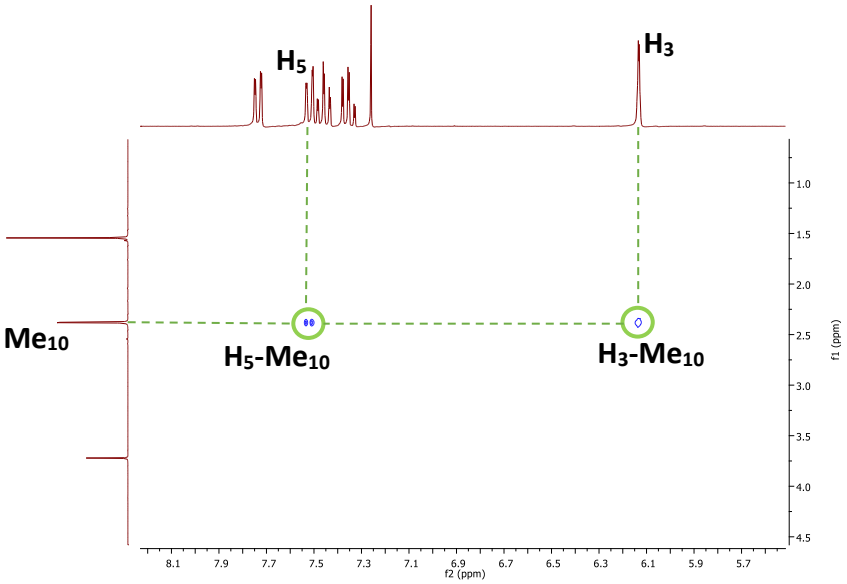


*Figure 3.84. NOESY of 2-hydroxy-2,4-dimethylnaphthalen-1(2H)-one (**456**)*

Treatment of 2-ethyl-4-methylnaphthalen-1-ol (**453**) with 2 equiv. of Oxone® and 5 equiv. of $NaHCO_3$, for 1 hour of addition at 0 ºC followed by 1 hour at rt, afforded a 79:21 mixture of (1a*R**,2*S**,7b*S**)-2-Ethyl-2-hydroxy-7b-methyl-1a,2-dihydronaphtho[1,2-b]oxiren-3(7b*H*)-one (**457**) (62% yield) and 2-ethyl-4-hydroxy-4-methylnaphthalen-1(4*H*)-one (**458**) (21% yield) (*Table 3.10*, *entry 2*).

The structure of epoxy *ortho*-quinol **457** was determined from the analysis of their HMBC spectrum (*Figure 3.16*), in which three correlations between the carbonyl carbon at C_3 (199.3 ppm) and the protons of hydroxyl group (3.89 ppm), at C1 (3.69 ppm) and one of the proton of CH_2- of the ethyl group (1.84-1.74 ppm) at C_8 were observed.

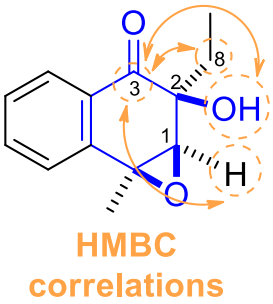


Figure 3.85. HBMC correlations

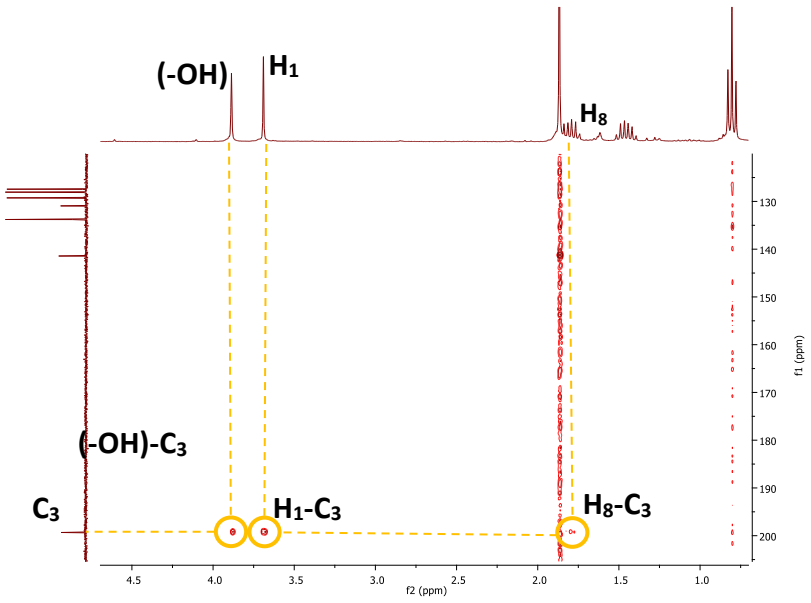


*Figure 3.86. HMBC of (1a*R**,2*S**,7b*S**)-2-ethyl-2-hydroxy-7b-methyl-1a,2-dihydronaphtho[1,2-b]oxiren-3(7b*H*)-one (**457**)*

When 2-isopropyl-4-methylnaphthalen-1-ol (**455**) was submitted to the same oxidative dearomatization conditions (2 equiv. of Oxone® and 5 equiv. of $NaHCO_3$ for 1 hour of addition at 0 ºC followed by 1 hour at rt), a 69:31 mixture of (1a*R**,2*S**,7b*S**)-2-Hydroxy-2-isopropyl-7b-methyl-1a,2-dihydronaphtho[1,2-b]oxiren-3(7b*H*)-one (**459**) (29% yield) and 4-hydroxy-2-isopropyl-4-methylnaphthalen-1(4*H*)-one (**460**) (17% yield) was obtained (*Table 3.10*, *entry 3*).

As ethyl and isopropyl groups are bulkier that methyl group, the *ortho* position was more difficult to be oxidized and we started to see the formation of oxidative dearomatization products at C_4, although the *ortho* position was more reactive than the *para* position.

In the case of the oxidative dearomatization of 2-(2-hydroxypropan-2-yl)-4-methylnaphthalen-1-ol (**454**), the carbinol group present at *ortho* position completely blocked the oxidation at C_2 and DMDO only could access the C_4, less reactive position (*Table 3.10*, *entry 4*). Thus, the treatment of 1-naphthol **454** with 4 equiv. of Oxone® and 10 equiv. of $NaHCO_3$ afforded 4-Hydroxy-2-(2-hydroxypropan-2-yl)-4-methylnaphthalen-1(4*H*)-one (**461**), in 46% yield, as the sole product.

On the other hand, when 2-methyl-4-phenylnaphthalen-1-ol (**448a**) was reacted with 2 equiv. of Oxone® and 5 equiv. of $NaHCO_3$, after 1 hour of addition / reaction at rt, a 37:63 mixture of 2-Hydroxy-2-methyl-4-phenylnaphthalen-1(2*H*)-one (**462**) (30% yield) and (1a*R**,2*S**,7b*S**)-2-hydroxy-2-methyl-7b-phenyl-1a,2-dihydronaphtho[1,2-b]oxiren-3(7b*H*)-one (**463**) (51% yield) was obtained (*Table 3.10*, *entry 5*). After increasing the equivalents of Oxone® (4 equiv.) and $NaHCO_3$

(10 equiv.), only the epoxy *ortho*-quinol **463** was formed and isolated in 95% yield (*Table 3.10*, *entry 6*).

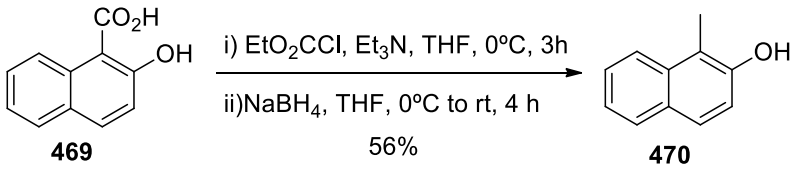
A similar reactivity was observed for naphthols **448b** and **448c**, having electron donating groups (-OMe) at the aryl substituent. Thus, the treatment of 4-(4-methoxyphenyl)-2-methylnaphthalen-1-ol (**448b**) with 2 equiv. of Oxone® and 5 equiv. of $NaHCO_3$, after 1 hour of addition / reaction at rt, gave rise to a 27:73 mixture of 2-Hydroxy-4-(4-methoxyphenyl)-2-methylnaphthalen-1(2*H*)-one (**464**) (17% yield) and (1a*R**,2*S**,7b*S**)-2-hydroxy-7b-(4-methoxyphenyl)-2-methyl-1a,2-dihydronaphtho[1,2-b]oxiren-3(7b*H*)-one (**465**) (66% yield) (*Table 3.10*, *entry 7*). Increasing the equivalents of Oxone® (4 equiv.) and $NaHCO_3$ (10 equiv.) led to the exclusive formation of epoxy *ortho*-quinol **465**, which could be isolated pure in 76% yield (*Table 3.10*, *entry 8*). Epoxy ortho-quinol **465** is not very stable and decomposes spontaneously at rt. On the other hand, the reaction of 2-methyl-4-(3,4,5-trimethoxyphenyl)naphthalen-1-ol (**448c**) with 4 equiv. of Oxone® and 10 equiv. of $NaHCO_3$, after 1 hour of addition / reaction at rt, generated (1a*R**,2*S**,7b*S**)-2-Hydroxy-2-methyl-7b-(3,4,5-trimethoxyphenyl)-1a,2-dihydronaphtho[1,2-b]oxiren-3(7b*H*)-one (**466**) in 25% yield (*Table 3.10*, *entry 9*). The low yield could be due to the low stability of the product.

Finally, the introduction of electron withdrawing substituents, such as the CF_3 groups at the 1-naphthols only allowed the formation of 4-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxy-2-methylnaphthalen-1(2H)-one (**467**). Thus, the oxidative dearomatization of 4-(3,5-bis(trifluoromethyl)phenyl)-2-methylnaphthalen-1-ol (**448**d) with 2 equiv. of Oxone® and 5 equiv. of $NaHCO_3$, after 1 hour of addition/reaction at rt, afforded *ortho*-quinol **467**, as the sole product, in 57% yield (*Table 3.10*, *entry 10*). The epoxide was not observed, probably due to the decreased reactivity of the Δ 3,4 double bond bearing the electron-withdrawing group substituent.

Once studied the oxidative dearomatization of differently 2-substituted 1-naphthols with the sytem Oxone / $NaHCO_3$ / acetone as the source of dimethyldioxirane, we continued to extend the scope of our new methodology to the corresponding 1-substitued 2-naphthols. As commented before, the required substituted 2-naphthols were not commercially available and had to be synthesized.

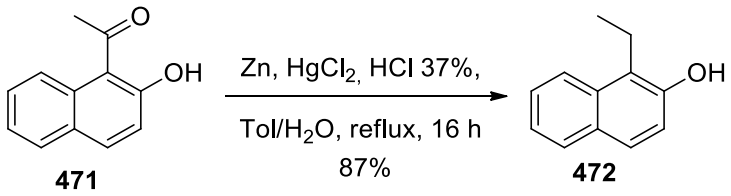
3.2.3.5. Synthesis of 1-substituted-2-naphthols

1-Methylnaphthalen-2-ol (**470**) could be obtained in 56% yield from 2-hydroxy-1-naphthoic acid (**469**), following a described procedure for the reduction of carboxylic group into methyl group with ethyl chloroformate and sodium borohydride at 0 ºC (*Scheme 3.45*).[187]



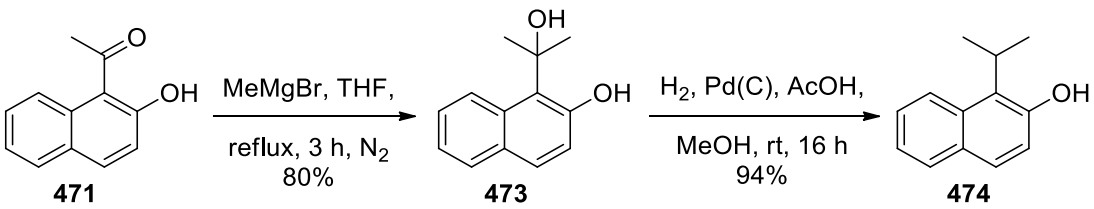
*Scheme 3.153. Synthesis of nahthol **470** by reduction of carboxylic group of **469***

The corresponding 1-ethylnaphthalen-2-ol (**472**) was synthesized, in 87% yield, after Clemmensen reduction of 1-(2-hydroxynaphthalen-1-yl)ethanone (**471**),[174] using zinc amalgam generated in situ (*Scheme 3.46*).



*Scheme 3.154. Synthesis of naphthol **472** through Clemmensen reduction of **471***

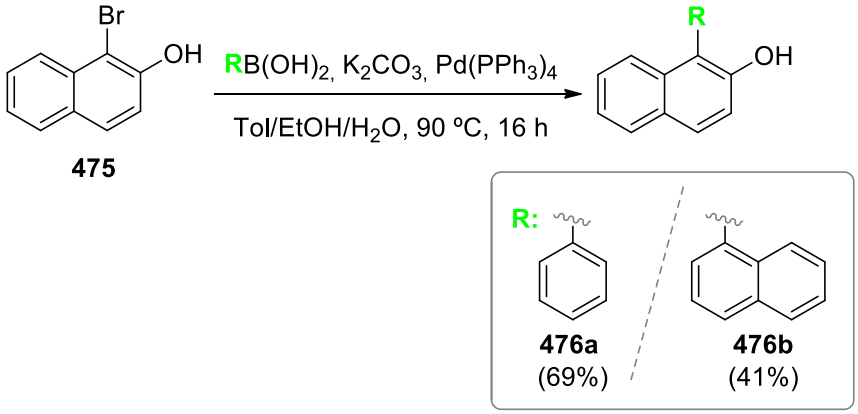
The same starting material, 1-(2-hydroxynaphthalen-1-yl)ethanone (**471**), was used to prepare 1-isopropylnaphthalen-2-ol (**474**) in two reaction steps (*Scheme 3.47*).[188] Thus, the nucleophilic addition of methyl magnesium bromide to ketone **471** afforded carbinol **473** in 80% yield. Next, carbinol **473** was transformed into derivative **474,** in 94% yield, by catalytic hydrogenation with palladium on carbon in the presence of stoichiometric amount of acetic acid.



Scheme 3.155. Formation of naphthol 474 from naphthol 471 in 2 steps: nucleophilic addition and elimination / reduction

[187] F. Mazzini, P. Salvadori, *Synthesis* **2005**, *15*, 2479-2481.
[188] S. Burmaoglu, R. Altundas, H. Seçen, *ARKIVOC* **2008**, *14*, 269-273

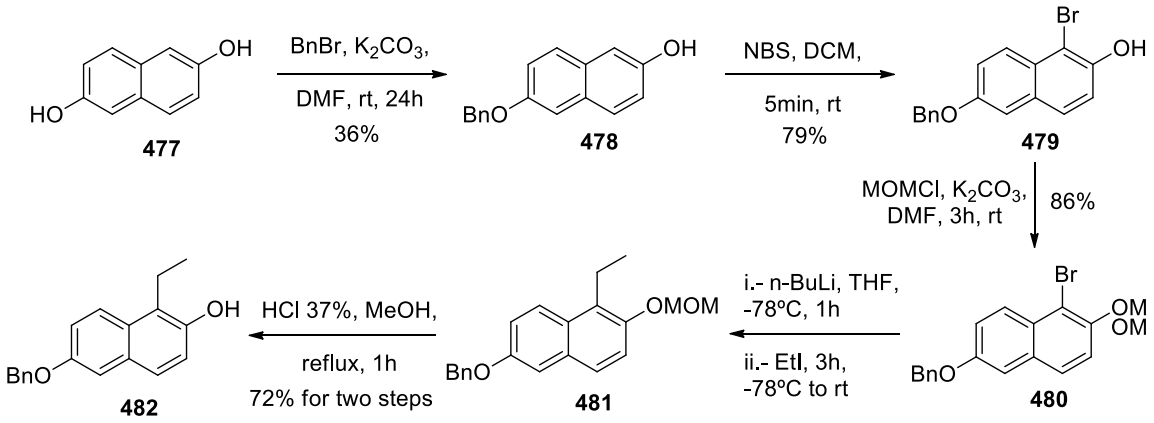
1-Aryl substituted 2-naphthols **476** were synthesized, using a reported procedure, by Suzuki-Miyaura cross-coupling between 1-bromonaphthalen-2-ol **475** and the corresponding phenylboronic acid[175a] or naphthalen-1-yl boronic acid in the presence of tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) and potassium carbonate, in moderate yields (*Scheme 3.48*).[175]



*Scheme 3.156. A Suzuki-Miyaura cross-coupling to form naphthols **476***

The last 2-naphthol derivative synthesized was 6-(benzyloxy)-1-ethylnaphthalen-2-ol (**482**) starting from naphthalene-2,6-diol (**477**), in five reaction steps, with 18% overall yield (*Scheme 3.49*). The synthetic sequence started with the mono-protection of commercially available naphthalene-2,6-diol (**477**) following a reported procedure,[189] using benzyl bromide and potassium carbonate in DMF to afford mono-benzylated derivative **478** in moderate 36% yield. Then, bromation of **478** at the C_1 position was effected with NBS in DCM giving rise to 6-(benzyloxy)-1-bromonaphthalen-2-ol (**479**) in 79% yield after 5 min of reaction. The next step consisted in the protection of the free naphthol by reaction with chloromethyl methyl ether in DMF to generate the OMOM derivative **480** in 86% yield. The treatment of **480** with *n*-butyl lithium in THF at -78 ºC followed by addition of ethyl iodide afforded the ethyl substituted derivative **481** which was used in the next step without further purification. Finally, the OMOM protecting group was removed by an acid hydrolysis, using concentrated hydrochloric acid in refluxing methanol to afford the desired 6-(benzyloxy)-1-ethylnaphthalen-2-ol (**482**) in 72% yield for the two last steps.[190]

[189] Z. He, G. Ye, W. Jiang, *Chem. Eur. J.* **2015**, *21*, 3005-3012.
[190] a) Y. Zhang, Y. Liao, X. Liu, X. Xu, L. Lin, X. Feng, *Chem. Sci.* **2017**, *8*, 6645-6649. b) T. Oguma, T. Katsuki, *J. Am. Chem. Soc.* **2012**, *134*, 20017-20020.

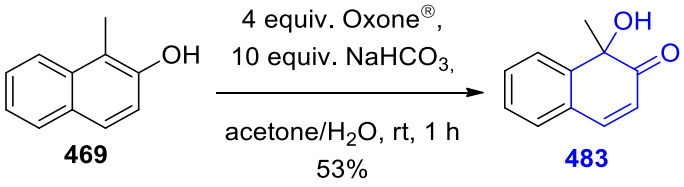


*Scheme 3.157. Synthesis of substituted naphthol **482** from naphthalene-2,6-diol (**477**) in 5 steps*

We synthesized 6-(benzyloxy)-1-ethylnaphthalen-2-ol (**482**) because it could be used in the total synthesis of lacinilene D.

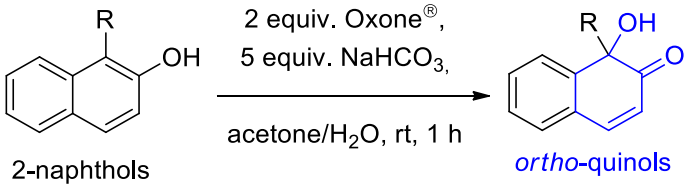
3.2.3.6. Oxidative dearomatization of 1-substituted-2-naphthols with dimethyldioxirane

The reaction of 1-methylnaphthalen-2-ol (**469**) under our standard oxidative dearomatization conditions (4 equiv. of Oxone® and 10 equiv. of $NaHCO_3$, after 1 hour of addition/reaction at rt), gave rise exclusively to 1-hydroxy-1-methylnaphthalen-2(1H)-one (**483**), in 53% yield (*Scheme 3.51*). Monitoring the reaction by TLC showed us that naphthol **469** was consumed in only 30 min after the addition of Oxone®, that is, there as an excess of reagents.



*Scheme 3.158. Oxidative dearomatization of 1-methyl-naphthalen-2-ol (**469**) with Oxone® / $NaHCO_3$ / acetone*

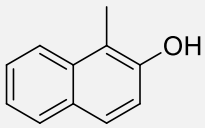
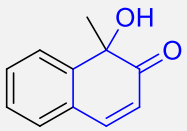
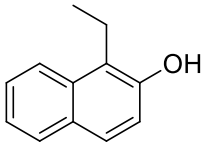
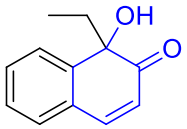
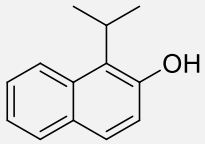
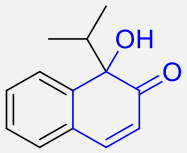
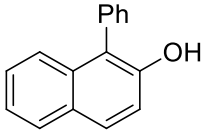
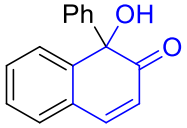
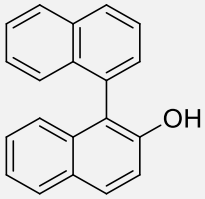
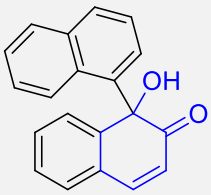
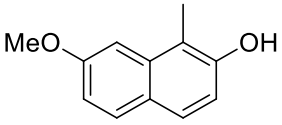
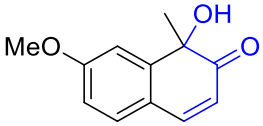
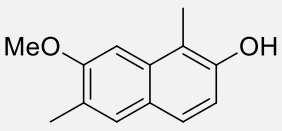
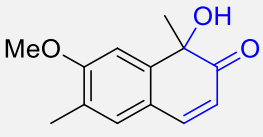
Then, we carried out the same reaction using less equivalents of Oxone® (2 equiv.) and $NaHCO_3$ (5 equiv.). Under these conditions, *ortho*-quinol **483** was obtained in a higher 80% yield (*Table 3.11*, *entry 1*). We applied these conditions to differently substituted 2-naphthols in a satisfactory way. In all cases, the final product obtained was always the corresponding *ortho*-quinols in good to excellent yields (60-99%) (*Table 3.11*).

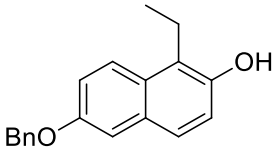
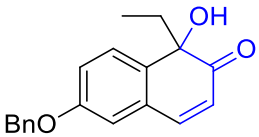
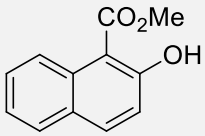
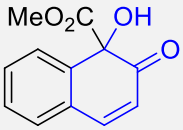


2-naphthols

ortho-quinols

R = functional group

Entry	Phenol	Final products	Yield (%)[b]
1	 **469**	 **483**	80
2	 **472**	 **484**	83
3[a]	 **474**	 **485**	79
4	 **476a**	 **486**	99
5	 **476b**	 **487**	79
6	 **488**	 **489**	85
7	 **490**	 **491**	60

8	 482	 492	82
9	 493	 494	76

a: The oxidative dearomatizacion reaction had to carry out in the dark; b: Isolated yield

Table 3.21. Oxidative dearomatization of 1-substituted-2-naphthols with Oxone® / $NaHCO_3$ / acetone

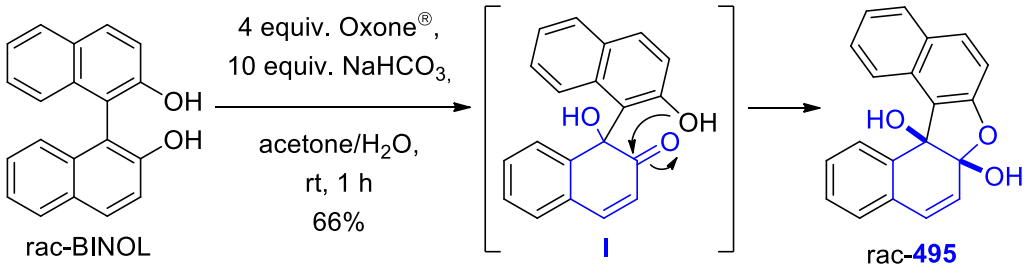
Thus, under these conditions, 1-ethyl-1-hydroxynaphthalen-2(1H)-one (**484**) could be isolated in 83% yield from 1-ethylnaphthalen-2-ol (**472**) (*Table 3.11*, *entry 2*). The oxidative dearomatization of 1-isopropylnaphthalen-2-ol (**474**) into 1-hydroxy-1-isopropylnaphthalen-2(1H)-one (**485**) in 79% yield, had to be performed in the dark, because in the literature it was described that naphthol **474** reacts with air when it is exposed to light (*Table 3.11*, *entry 3*).[191]. 1-phenylnaphthalen-2-ol (**476a**) and [1,1'-binaphthalen]-2-ol (**476b**) were oxidized to their corresponding *ortho*-quinols, 1-hydroxy-1-phenylnaphthalen-2(1H)-one (**486**) in 99% yield and 1-hydroxy-[1,1'-binaphthalen]-2(1H)-one (**487**) in 79% yield, respectively (*Table 3.11*, *entries 4* and *5*). The oxidative dearomatization of 7-methoxy-1-methylnaphthalen-2-ol (**488**), 7-methoxy-1,6-dimethylnaphthalen-2-ol (**490**) and 6-(benzyloxy)-1-ethylnaphthalen-2-ol (**482**) also gave the corresponding *ortho*-quinols in good yields, 1-hydroxy-7-methoxy-1-methylnaphthalen-2(1H)-one (**489**), 1-hydroxy-7-methoxy-1,6-dimethylnaphthalen-2(1H)-one (**491**) and 6-(benzyloxy)-1-ethyl-1-hydroxynaphthalen-2(1H)-one (**492**), respectively (*Table 3.11*, *entries 6*,*7* and *8*).

All synthesized *ortho*-quinols were relatively stable, unless methyl 1-hydroxy-2-oxo-1,2-dihydronaphthalene-1-carboxylate (**494**). Although this compound decomposed during flash chromatographic purification, it was possible to isolate pure *ortho*-quinol **494** in 76 % yield through a quick purification with a short-pad column using ethyl acetate as eluent (*Table 3.11*, *entry 9*).

We also wanted to study the reactivity of a more complex 2-naphthol under our oxidative dearomatization conditions. We chose 1,1'-bi-2-naphthol (*rac*-BINOL), which possess two naphthol rings susceptible to suffer an oxidative dearomatization process. In this case, the reaction should be performed with 4 equiv. of Oxone® and 10 equiv. of $NaHCO_3$. After 1 hour of

[191] J. Carnduff, D. G. Leppard, ***J. Chem. Soc., Perkin Trans. 1*** **1976**, ***0***, 2570-2573.

addition at rt, the reaction was completed. Under these conditions, the pentacyclic hemiacetal rac-**495**, was obtained in 66% yield, as the sole product (*Scheme 3.52*).



Scheme 3.159. Oxidative dearomatization of rac-BINOL with Oxone® / $NaHCO_3$ / acetone

We believed that pentacyclic hemiacetal rac-**495** derived from intermediate *ortho*-quinol **I**, initially formed after oxidative dearomatization of rac-BINOL with DMDO. Next, intermediate **I** could evolve to pentacyclic hemiacetal rac-**495** in the basic medium by an intramolecular nucleophilic addition of the phenolic OH to the carbonyl group.

The *cis*-diol structure of rac-**495** was determined by its spectroscopic data and the NOESY correlations observed between the protons of hydroxyl groups at C_{6a} and C_{13c} (*Figure 3.18*).

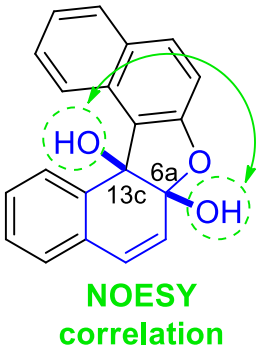


Figure 3.87. NOESY correlations

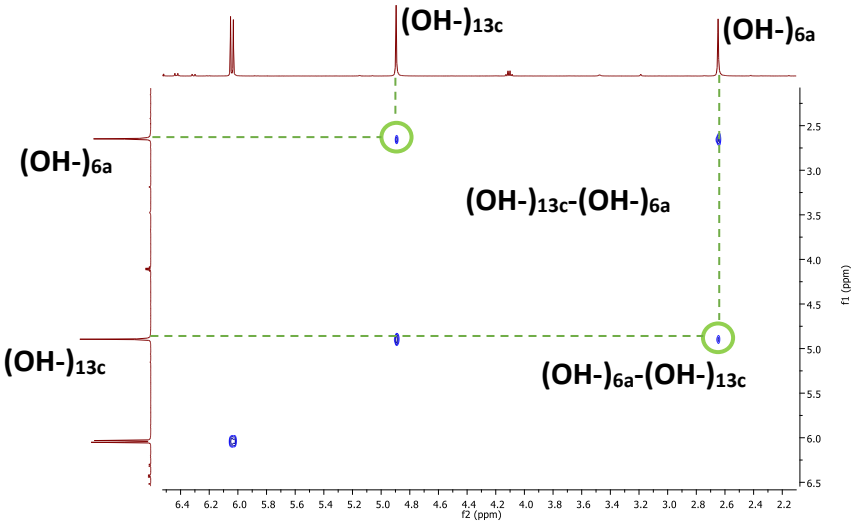
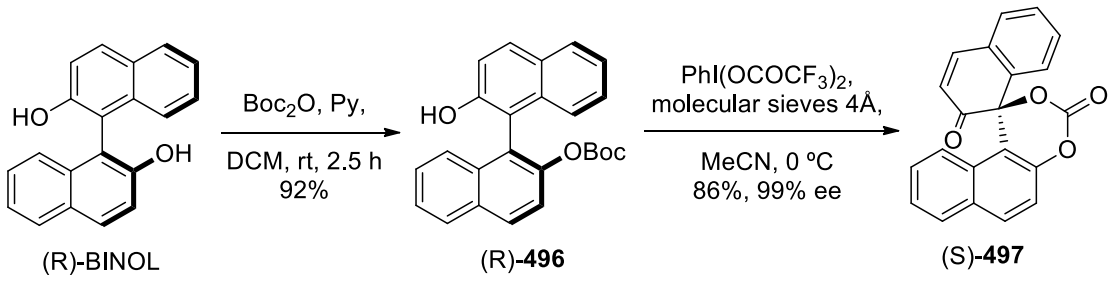


Figure 3.88. NOESY experiments of (6aR,13cS*)-6a,13c-dihydrodinaphtho[2,1-b:1',2'-d]furan-6a,13c-diol (**495**)*

3.2.3.7. Asymmetric oxidative dearomatization of axial chiral 1-naphthyl-2-naphthols with dimethyldioxirane

Axially chiral compounds have been widely used in asymmetric synthesis as chiral ligands and as key skeletons in organic catalysis.[192] In the literature, there are described numerous synthetic strategies towards a great variety of axially chiral compounds in an easy and efficient manner.[193] However, the use of these compounds in other transformations, such as chirality transfer reactions, has been less studied.

In 2011, Matsumoto and coworkers described the formation of intermediate masked *ortho*-quinol **497** in their studies to build biaryl molecules.[194] Firstly, (*R*)-BINOL was treated with di-*tert*-butyl dicarbonate (Boc_2O) and pyridine in DCM to give mono-Boc- (*R*)-BINOL **496,** in 92% yield. Then, (*R*)-**496** was transformed into masked *ortho*-quniol **497** in good yield and with 99% enantiomeric excess, using [bis(trifluoroacetoxy)iodo]benzene ($(CF_3CO_2)_2IPh$) in the presence of 4Å molecular sieves in acetonitrile (*Scheme 3.53*). Thus, Matsumoto described an efficient axial-to-central chirality conversion, from (*R*)-BINOL into masked *ortho*-quinol (*S*)-**497** by an oxidative dearomatization process.

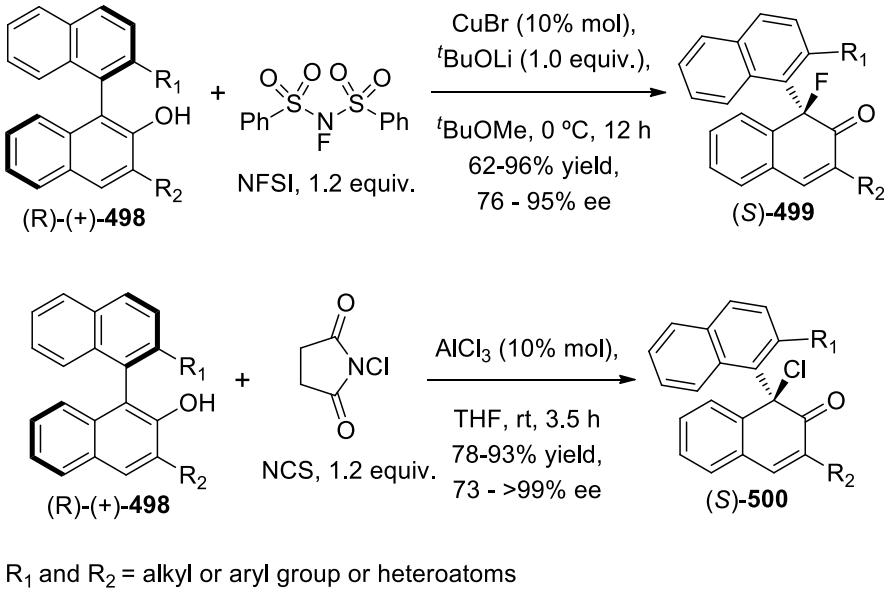


*Scheme 3.160. Asymmetric synthesis of masked ortho-quinol **497** from axial chiral (R)-BINOL*

More recently, Wang reported an asymmetric dearomative halogenation of 1-naphthyl-2-naphthols, with axial chirality, by a simple axial-to-central chirality transfer using commercially available halogenation reagents such as *N*-fluorobenzenesulfonimide (NFSI) and *N*-chlorosuccinimide (NCS) (*Scheme 3.54*).[195] Different axially chiral naphthols were submitted to this

[192] a) D. Parmar, E. Sugiono, S. Raja and M. Rueping, *Chem. Rev.* **2014**, *114*, 9047-9153. b) M. C. Kozlowski, B. J. Morgan, E. C. Linton, *Chem. Soc. Rev.* **2009**, *38*, 3193-3207.
[193] a) Y.-H. Chen, D.-J. Cheng, J. Zhang, Y. Wang, X.-Y. Liu, B. Tan, *J. Am. Chem. Soc.* **2015**, *137*, 15062-15065. b) J. Feng, B. Li, Y. He, Z. Gu, *Angew. Chem. Int. Ed.* **2016**, *55*, 2186-2190. c) V. S. Raut, M. Jean, N. Vanthuyne, C. Roussel, T. Constantieux, C. Bressy, X. Bugaut, D. Bonne, J. Rodriguez, *J. Am. Chem. Soc.* **2017**, *139*, 2140-2143.
[194] Y. Koyama, H. Kataoka, K. Suzuki, T. Matsumoto, *Chem. Asian J.* **2011**, *6*, 355-358.
[195] P. Wang, J. Wang, L. Wang, D. Li, K. Wang, Y. Liu, H. Zhu, X. Liu, D. Yang, R. Wang, *Adv. Synth. Catal.* **2018**, *360*, 401-405.

asymmetric halogenative dearomatization reaction to achieve the corresponding fluorinated and chlorinated dearomatized products in good yields and good enanioselectivities, under mild conditions.

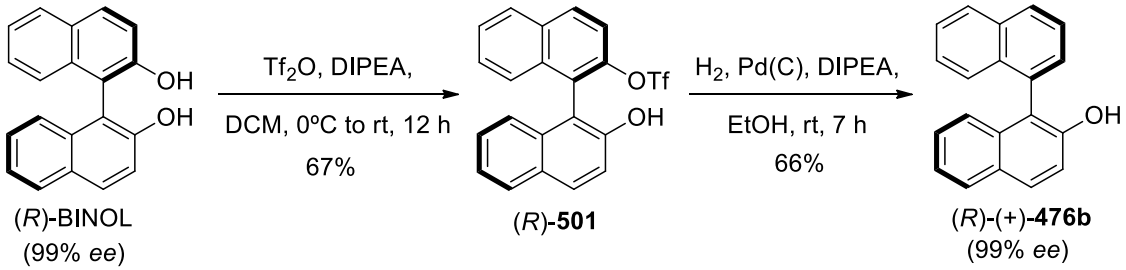


Scheme 3.161.- Asymmetric dearomative halogenation of axial chiral 1-naphthyl-2-naphthols

Taking into account these references, we had in mind to evaluate our oxidative dearomatization method with Oxone® / acetone in basic medium, as the source of dimethyldioxirane, on enantiomerically pure 1-naphthyl-2-naphthols with axial chirality to test if the axial-to-central chirality conversion could efficiently occur. As *rac*-[1,1'-binaphthalen]-2-ol **476a** and *rac*-BINOL were already oxidative dearomatized to their corresponding *rac-ortho*-quinol **487** and pentacyclic hemiketal *rac*- **495**, we decided to use in this study their optically pure enantiomers, (*R*)- [1,1'-binaphthalen]-2-ol, (*R*)-BINOL and (*S*)-BINOL, in order to evaluate the possible axial-to-central chirality transfer.

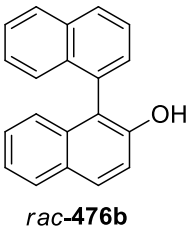
(*R*)-[1,1'-binaphthalen]-2-ol [(+)-**476b**] was not commercially available, so we had to synthesized it from (*R*)-BINOL in two steps, following a reported procedure (*Scheme 3.55*).[196] Thus, (*R*)-BINOL was mono-protected as triflate (*R*)-**501** in 67% yield, using trifluoromethanesulfonic anhydride (Tf_2O) and N,N-diisopropylethylamine (DIPEA) in DCM. A reductive elimination of the triflate group, in the presence of H_2, Pd(C) and DIPEA, afforded compound (*R*)-(+)-**476b** with axial chirality, in 66% yield, with 99% *ee*.

[196] a) V. H. G. Rohde, M. F. Müller, M. Oestreich, *Organometallics* **2015**, *34*, 3358-3373. b) Y.-N. Ma, H.-Y. Zhang, S.-. Yang, *Org. Lett.* **2015**, *17*, 2034-2037.

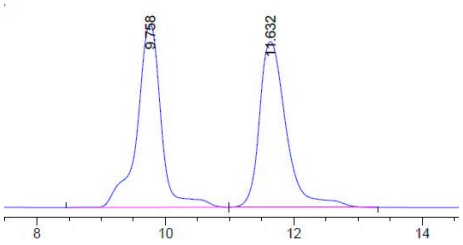


*Scheme 3.162.- Synthesis of (R)-1-naphthyl-2-naphthol (**476b**) from (R)-BINOL*

The enantiomeric excess of (*R*)-(+)-**476b** was determined by chiral HPLC using a Daicel Chiralpak IB column (Figure 10). The separation conditions of the corresponding enantiomers were determined from *rac*-**476b**, using a mixture of *n*-hexane/2-propanol in a ratio of 80/20 as eluent and a flow rate of 0.5 mL/min. Under these conditions (λ: 254 nm), the enantiomers appeared at retention times of 9.76 min and 11.63 min, respectively (*Figure 3.20*).

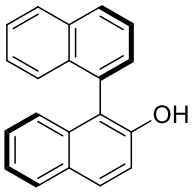


rac-**476b**

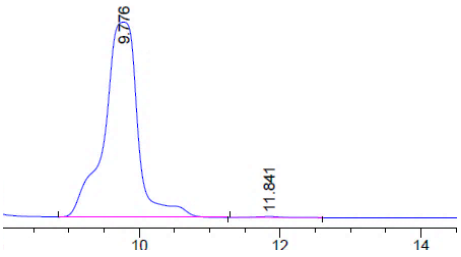


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.758	BV	0.3928	4.05956e4	1543.55066	50.0758
2	11.632	VB	0.4444	4.04727e4	1395.39001	49.9242

*Figure 3.89. Chiral HPLC chromatogram of rac-**476b***



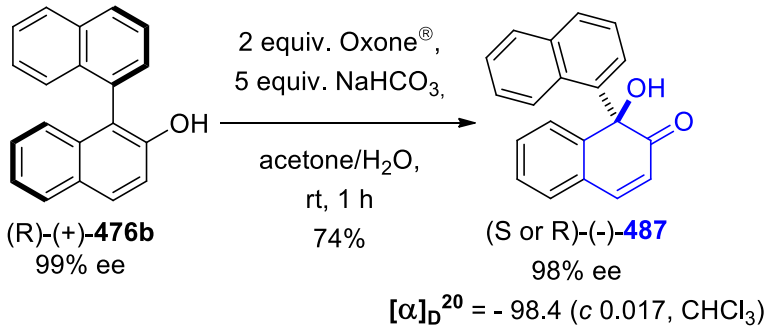
(R)-(+)-**476b**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.776	VB	0.4994	7.62628e4	2284.65723	99.5107
2	11.841	BB	0.4644	374.95456	12.48319	0.4893

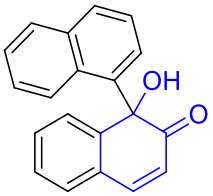
*Figure 3.90. Chiral HPLC chromatogram of (R)-**476b** (99% ee)*

The oxidative dearomatization process of (*R*)-(+)-**476b,** using 2 equiv. of Oxone® and 5 equiv. of $NaHCO_3$ in a mixture of acetone / Milli-Q water for 1 hour at rt, gave rise to the *ortho*-quinol (*S* or *R*)-(-)-**487**, in 74% yield (*Scheme 3.56*). Compound (*S* or *R*)-(-)-**487**, with central chirality, showed a specific rotation value of $[\alpha]_D^{20}$ = - 98.4 (*c* 0.017, $CHCl_3$) with a 98% of enantiomeric excess. This result indicated a complete and efficient chirality transfer from the chiral axis present in the enantiopure 1-naphthyl-2-naphthol (*R*)-(+)-**476b** to the stereogenic center of *ortho*-quinol (*R* ó *S*)-(-)-**487**, which is obtained with an excellent optical purity. The absolute configuration of compound (-)-**487** is not known yet.

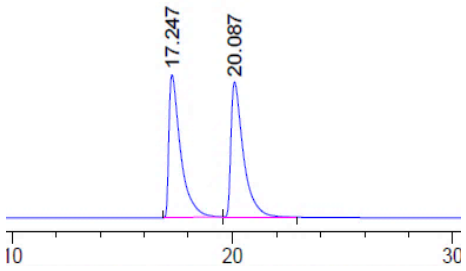


*Scheme 3.163. Oxidative dearomatization of (R)-(+)-**476b** with Oxone® / $NaHCO_3$ / acetone*

The enantiomeric excess of *ortho*-quinol (*S* or R)-(-)-**487** was determined by chiral HPLC using a Daicel Chiralpak IB column (Figure 11). The separation conditions of the corresponding enantiomers were determined from *rac*-**487**, using a mixture of *n*-hexane/2-propanol in a ratio of 80/20 as eluent and a flow rate of 0.6 mL/min. Under these conditions (λ: 254 nm), the enantiomers appeared at retention times of 17.25 min and 20.09 min, respectively (*Figure 3.22*).

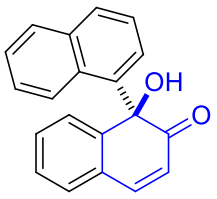


rac-**487**

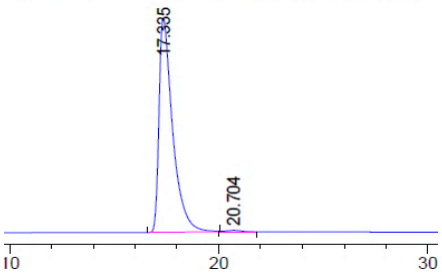


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.247	BV	0.5437	5.47873e4	1467.19666	49.9362
2	20.087	VB	0.5832	5.49274e4	1389.36841	50.0638

*Figure 3.91. HPLC chromatogram of rac-**487***



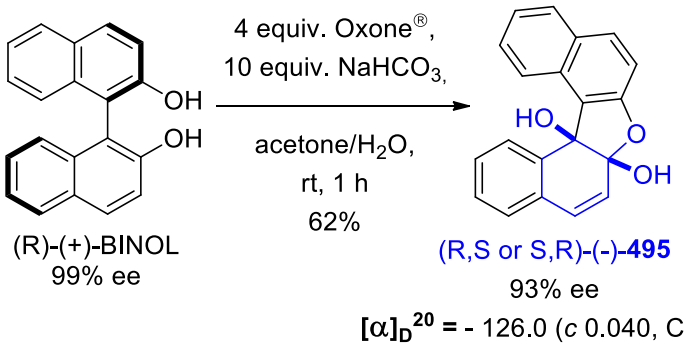
(S or R)-(-)-**487**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.335	BB	0.6701	7.94353e4	1748.17566	98.9998
2	20.704	BB	0.7996	802.50488	14.50196	1.0002

*Figure 3.92. HPLC chromatogram of (S or R)-(-)-**487***

Next, we carried out the oxidative dearomatization of commercially available (*R*)-(+)-BINOL using 4 equiv. of Oxone® and 10 equiv. of $NaHCO_3$ in a mixture of acetone / Milli-Q water for 1 hour at rt. Under these conditions, the pentacyclic hemiketal (R,S or S,R)-(-)-**495**, possessing central chirality and two stereogenic centers, was obtained in 62% yield, showing a specific rotation value of $[\alpha]_D^{20}$ = -126.0 (*c* 0.040, $CHCl_3$) with a 93% of enantiomeric excess (*Scheme 3.57*).

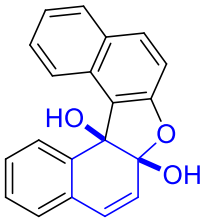


(R)-(+)-BINOL
99% ee

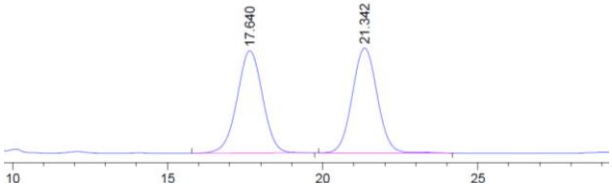
(R,S or S,R)-(-)-**495**
93% ee
$[\alpha]_D^{20}$ = - 126.0 (*c* 0.040, $CHCl_3$)

Scheme 3.164. Oxidative dearomatization of (R)-(+)-BINOL with Oxone® / $NaHCO_3$ / acetone

The optical purity of pentacyclic hemiketal (R,S or S,R)-(-)-**495** (Figure 3.14) was determined by chiral HPLC using a Daicel Chiralpak IC. The separation conditions of the corresponding enantiomers were determined from *rac*-**495** using a mixture of *n*-hexane/2-propanol in a ratio of 90/10 as eluent with a flow rate of 1.0 mL/min. Under these conditions the enantiomers appeared at retention times of 17.64 min and 21.34 min, respectively (*Figure 3.24*).

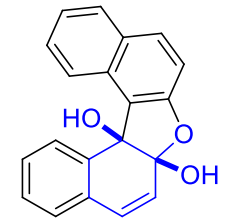


rac-**495**

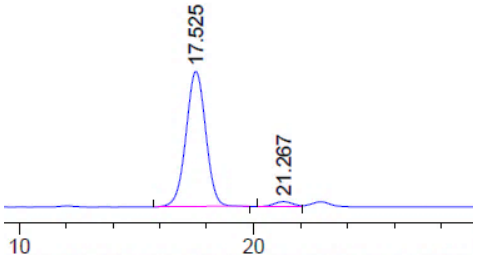


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.640	BB	0.8594	1.63713e4	288.75858	50.3286
2	21.343	BB	0.8576	1.61575e4	294.73434	49.6714

*Figure 3.93. HPLC chromatogram of rac-**495***



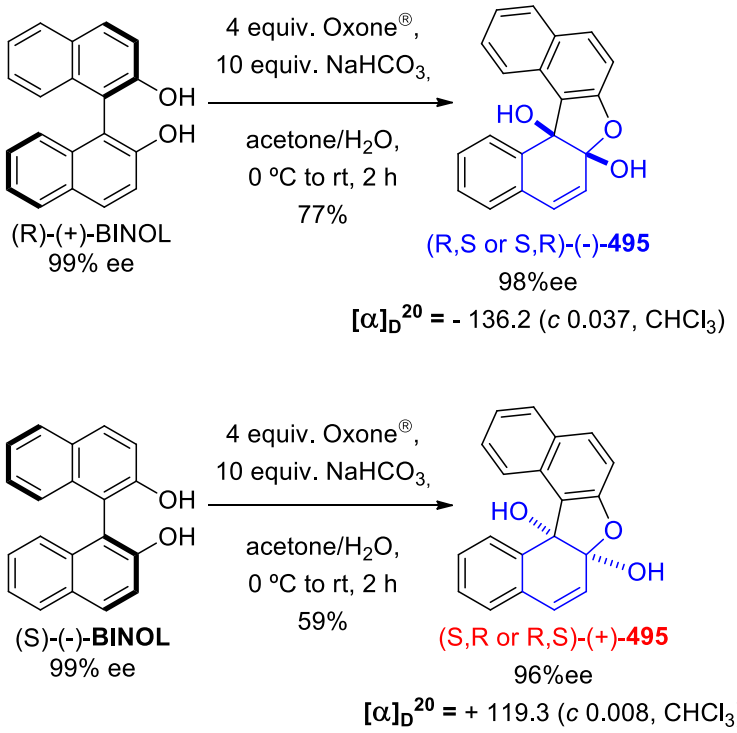
(R,S or S,R)-(-)-**495**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.525	BB	0.9027	1.22881e4	212.46950	96.6776
2	21.270	BV	0.7996	422.28763	7.72742	3.3224

*Figure 3.94. HPLC chromatogram of (R,S or S,R)-**495***

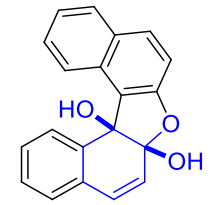
In order to improve the 93% of enantiomeric excess obtained for (R,S or S,R)-(-)-**495**, we realized the Oxone® addition on (*R*)-BINOL X at low temperature (0 ºC) and found that the enantiomeric excess of the final product (R,S or S,R)-(-)-**495** {$\mathbf{[\alpha]_D^{20}}$ **=** -136.2 (*c* 0.037, $CHCl_3$)} was increased from 93% to 98% *ee*. In addition, the yield of the reaction was also improved from 62% to 77% (*Scheme 3.58*).



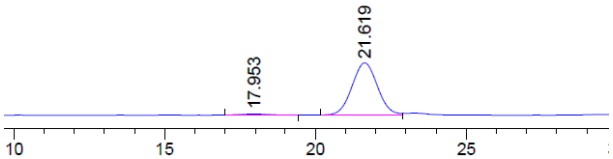
Scheme 3.165. Oxidative dearomatization of (R)-(+)-BINOL and (S)-(-)-BINOL with Oxone® / $NaHCO_3$ / acetone

Finally, when the oxidative dearomatization was carried out on commercially available (*S*)-BINOL using 4 equiv. of Oxone® and 10 equiv. of $NaHCO_3$ in a mixture of acetone / Milli-Q water for 1 hour at 0 ºC and 1 hour at rt, the corresponding enantiomer (S,R or R,S)-(+)-**495**, {**$[\alpha]_D^{20}$** = +119.3 (*c* 0.008, $CHCl_3$)}, was obtained in 59% yield and 96% enantiomeric excess.

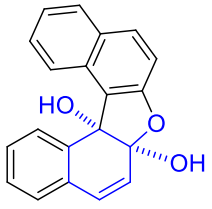
The optical purity of hemiketal pentacyclic derivatives (R,S or S,R)-(-)-**495** and (S,R or R,S)-(+)-**495** was determined by chiral HPLC under the experimental conditions established previously (*Figure 3.25*).



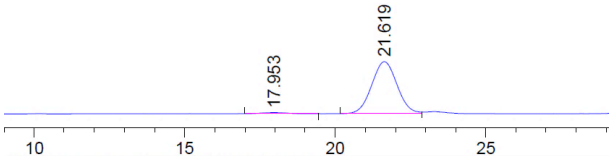
(R,S or S,R)-(-)-**495**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.061	BB	0.8916	1.43679e4	250.33305	98.9384
2	21.836	BB	0.6402	154.16002	3.15421	1.0616



(S,R or R,S)-(+)-**495**



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.953	BB	0.8479	676.46094	11.30786	2.1504
2	21.619	BV	0.9264	3.07817e4	524.70642	97.8496

*Figure 3.95. HPLC spectrum of (-)-**495** and (+)-**495***

At this moment, we do not know the absolute configuration of pentacyclic hemiketals (R,S or S,R)-(-)-**495** and (S,R or R,S)-(+)-**495**. Nevertheless, the results described herein indicated that an efficient axial-to-central chirality transfer from (R)- or (S)-BINOL, with axial chirality, has been occurred leading to the final pentacyclic hemiketals, showing central chirality and possessing two sterogenic centers. We should note that the application of our oxidative dearomatization conditions afforded excellent enantioselectivities under mild conditions.

3.2.3.7.1. Chiroptical properties of the oxygenated dearomatized compounds synthesized.

A detailed analysis of the enantioenriched structures obtained previously, suggested the possibility of further applications in asymmetric synthesis of target structures and / or asymmetric catalysis. In particular, the pentacyclic hemiketal (-)-**495**, having a stereogenic 1,2-diol moiety, could form cyclic structures leading to chiral Lewis acids or Brønsted acids,[197] by reaction with boronic acids or phosphoric acid derivatives, that could be further used in asymmetric catalysis. The interest of the possible applications led us to evaluate the chiroptical properties of compounds (-)-**487**, (-)-**495** and (+)-**495**.

The UV / vis and circular dichroism spectra of naphthyl substituted *ortho*-quinol (-)-**487**, registered in chloroform, are shown in *Figures 3.26* and *3.27*. As can be seen, the UV / vis spectrum shows intense absorption bands at λ_{max1}: 286 nm (ε_1: 13814 $Lmol^{-1}cm^{-1}$), λ_{max2}: 294 nm (ε_2: 13944 $Lmol^{-1}cm^{-1}$) and λ_{max3}: 322 nm (ε_3: 14830 $Lmol^{-1}cm^{-1}$). The bands appearing at 286 nm and 294 nm correspond to the electronic transitions $\pi \rightarrow \pi^*$ of the aromatic rings. The later is red

[197] a) Comprehensive Asymmetric Catalysis; E. N. Jacobsen, A. Pfaltz, H. Yamamoto, Ed. Springer: Heidelberg, 1999; (b) Lewis Acids in Organic Synthesis; H. Yamamoto, Ed.; Wiley: New York, NY, 2000.

shifted due to the conjugation of the aromatic aryl ring with the enone moiety. In turn, the band at longer wavelength 322 nm could be due to the overlap of the n → π* transition of the enone with those of the extended aromatic, although the contribution of the later to the intensity must be very low.

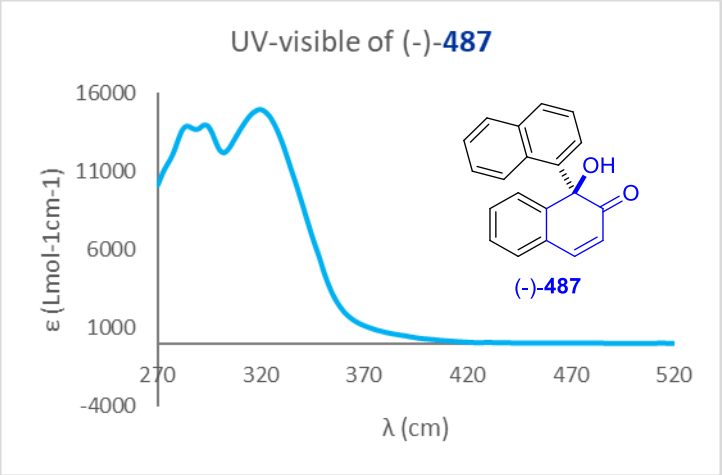


*Figure 3.96. Optical absorption spectra recorded in chloroform in quartz cuvettes (1 cm path). (-)-1-hydroxy-[1,1'-binaphthalen]-2(1H)-one (**487**) (c: 3.91 x 10^{-5} M). λ_{max1}: 286 nm (ε_1: 13814 $Lmol^{-1}cm^{-1}$), λ_{max2}: 294 nm (ε_2: 13944 $Lmol^{-1}cm^{-1}$) and λ_{max3}: 322 nm (ε_3: 14830 $Lmol^{-1}cm^{-1}$).*

The circular dichroism spectrum depicted in *Figure 3.27* evidenced a strong positive Cotton effect at $\lambda_{max} \approx 294$ nm which evidenced some chirality in the aromatic system. This could be explained considering that the molecule is rigid and shows an axial chiral, since the CD absorption of enantiopure BINOL itself shows a characteristic Cotton effect signal at around 240 nm[198]. The overall chirality of this structure is also responsible of the appearance of the less intense Cotton negative effects between 300 and 420 nm, due to the electronic transitions of the extended conjugated chiral system.

[198] I. Hanazaki and H. Akimoto, *J. Am. Chem. Soc.* **1972**, *94*, 4102-4106

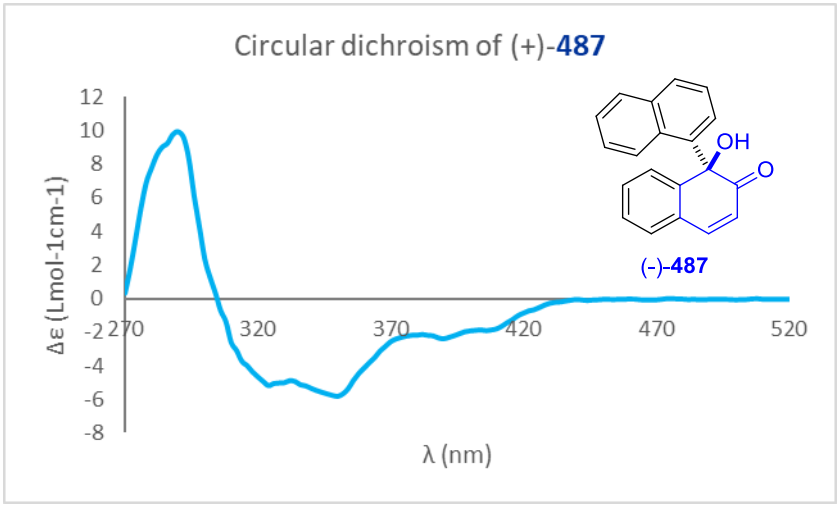


*Figure 3.97. Circular dichroism spectra recorded in chloroform in quartz cuvettes (1 cm path). (-)-1-hydroxy-[1,1'-binaphthalen]-2(1H)-one (**487**) (c: 3.91 x 10^{-5} M).*

The UV / vis and circular dichroism spectra of the hemiketal pentacyclic diol (-)-**495** registered in chloroform, are shown in *Figures 3.28* and *3.29*. As can be seen, the UV / vis spectrum shows an absorption band at λ_{max} >260 nm, whose extinction coefficient was not determined, an intense band at λ_{max1}: 284 nm (ε_1: 10248 $Lmol^{-1}cm^{-1}$) and a third less intense λ_{max2}: 344 nm (ε_2: 4979 $Lmol^{-1}cm^{-1}$). The electronic transitions $\pi \rightarrow \pi^*$ of the aromatic rings must be responsible of the higher energy absorptions λ >260 nm and λ>284 nm, whereas the less intense band at λ_{max2}: 344 nm could be assigned to a change transfer band of the bridged oxygen ether to the aromatic ring.

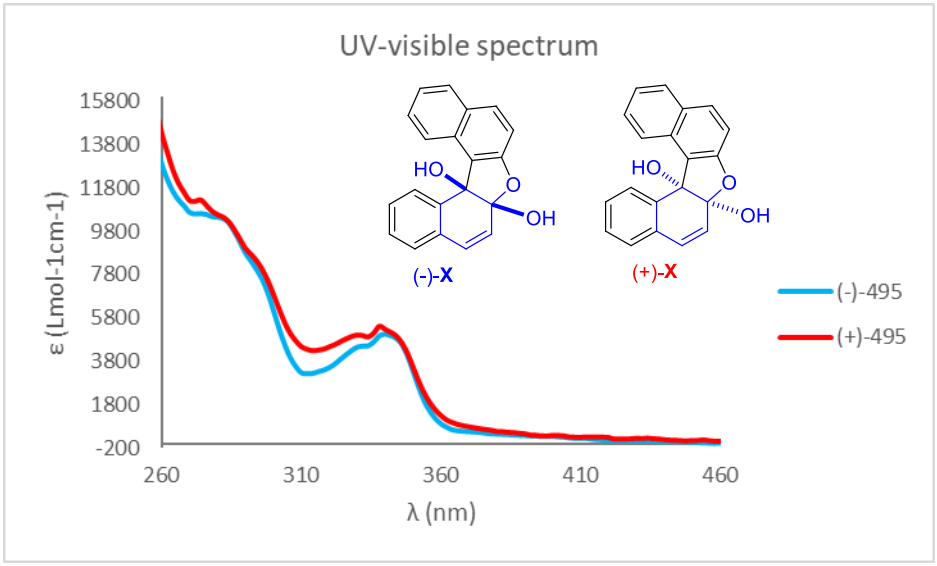


*Figure 3.98. Optical absorption spectra recorded in chloroform in quartz cuvettes (1 cm path). (-)-6a,13c-dihydrodinaphtho[2,1-b:1',2'-d]furan-6a,13c-diol (**495**) (c: 1.41 x 10^{-5} M, blue line) and (+)-6a,13c-dihydrodinaphtho[2,1-b:1',2'-d]furan-6a,13c-diol (**495**) (c: 1.06 x 10^{-5} M, red line). λ_{max1}: 284 nm (ε_1: 10248 $Lmol^{-1}cm^{-1}$) and λ_{max2}: 344 nm (ε_2: 4979 $Lmol^{-1}cm^{-1}$).*

The circular dichroism spectrum of (-)-**495**, shown in *Figure 3.29* displayed an intense positive Cotton effect at $\lambda_{max} \approx 270$ nm that must be due also to a transfer of chirality of the overall system to the aromatic rings thus suggesting the presence of a folded helically chiral structure The less intense bands at $\lambda_{max} \approx 310$ and the broad one between λ 310 and 360 nm could again be assigned to a chiral charge transfer from the oxygen. On the other hand, the circular dichroism spectrum of the enantiomer (+)-**495** is its mirror image (*Figure 3.29*).

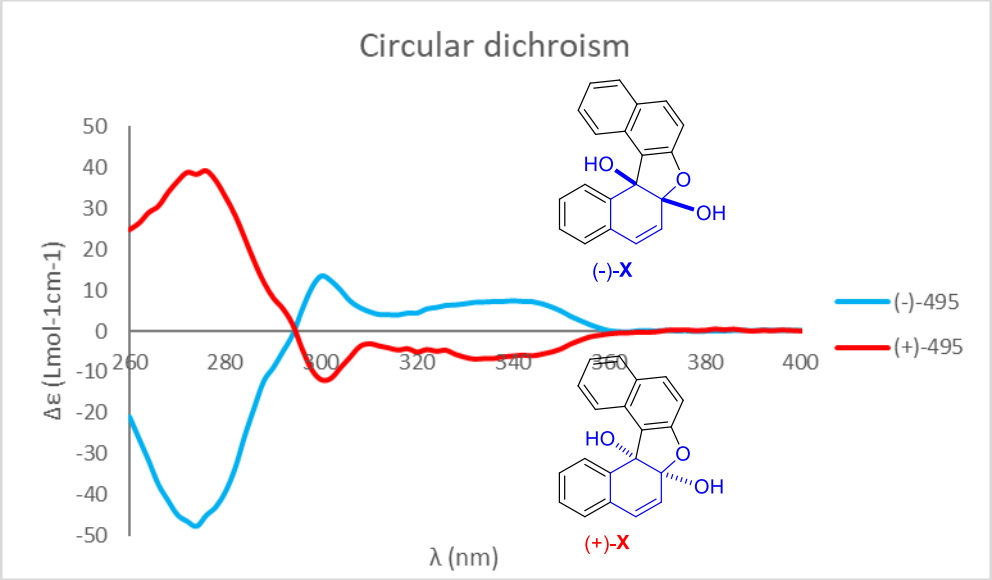
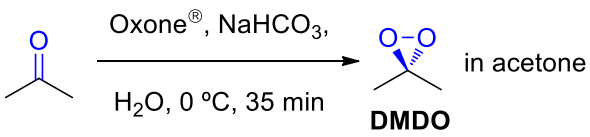


*Figure 3.99. Circular dichroism spectra recorded in chloroform in quartz cuvettes (1 cm path). (-)-6a,13c-dihydrodinaphtho[2,1-b:1',2'-d]furan-6a,13c-diol (**495**) (c: 1.41 x 10^{-5} M, blue line) and (+)-6a,13c-dihydrodinaphtho[2,1-b:1',2'-d]furan-6a,13c-diol (**495**) (c: 1.06 x 10^{-5} M, red line).*

3.2.4. Mechanistic studies

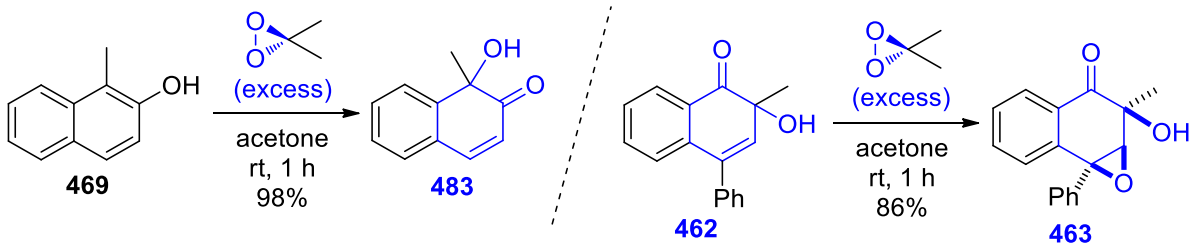
Some experiments were carried out to confirm the formation of dimethyldioxirane in the medium and to propose a mechanism for the oxidative dearomatization method of phenols and naphthols under our experimental conditions. To prove that DMDO was the oxidizing agent involved in our oxidative dearomatization process and in the further epoxidation of the γ,δ conjugated double bond, we chose stable model substrates, which could only generate a sole stable final product. These substrates were 1-methylnaphthalen-2-ol (**469**) and 2-hydroxy-2-methyl-4-phenylnaphthalen-1(2H)-one (**462**). The mechanistic experiments consisted in reacting these substrates with isolated DMDO and confirmed the formation of the corresponding oxidation products, 1-hydroxy-1-methylnaphthalen-2(1H)-one (**483**) and (1aR*,2S*,7bS*)-2-hydroxy-2-methyl-7b-phenyl-1a,2-dihydronaphtho[1,2-b]oxiren-3(7bH)-one (**463**).

The synthesis and isolation of a solution of DMDO in acetone was performed following a reported procedure from the reaction of Oxone® with acetone in a basic medium (*Scheme 1.7*). [199]



Scheme 1.7. Synthesis of dimethyldioxirane from acetone using Oxone®

Thus, the reaction of 1-methylnaphthalen-2-ol (**469**) with an excess of DMDO in acetone gave rise to the expected product *ortho*-quinol **483**, in an excellent 98% yield, while epoxy *ortho*-quinol **463** was obtained in 86% yield, when 2-hydroxy-2-methyl-4-phenylnaphthalen-1(2H)-one (**462**) was treated with the isolated solution of DMDO in acetone (*Scheme 3.58*).

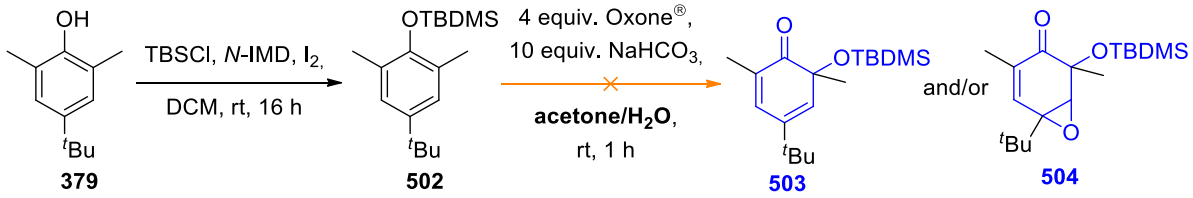


*Scheme 3.166. Oxidative dearomatization reaction od naphthol **469** and epoxidation of ortho-quinol **462** with isolated DMDO*

These experiments demonstrated that dimethyldioxirane was the final reactive species producing in both processes, in the oxidative dearomatization and the epoxidation.

Moreover, we verified if our oxidative dearomatization reaction required the presence of the free OH of phenols or naphthols to be successful (*Scheme 3.59*). To achieve this goal, the OH group of phenol **379** was protected as the corresponding silyl ether **502**, following a reported procedure[200] and submitted to our oxidative dearomatization conditions. When compound **502** was treated with 4 equiv. of Oxone® and 10 equiv. of $NaHCO_3$ in acetone / Milli-Q water at rt, the starting material remained unchanged and we didn't observe the formation of any oxidative dearomatization product (**503** and/or **504**).

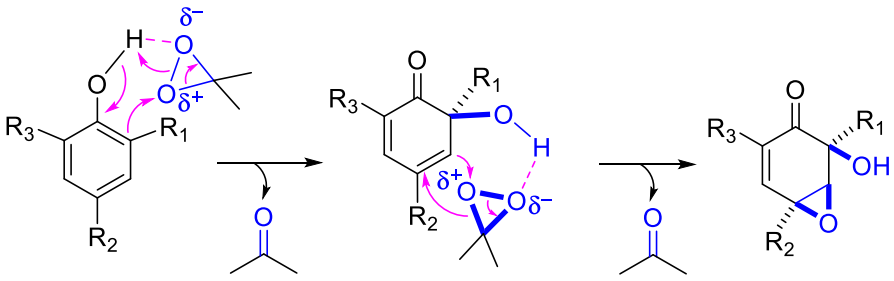
[199] D. F. Taber, P. W. DeMatteo, R. A. Hassan, *Org. Synth.* **2013**, *90*, 350-357
[200] M. Jereb, *Tetrahedron* **2012**, *68*, 3861-3867.



Scheme 3.167. Mechanistic experiment with protected hydroxy group as silyl ether

In view of these results, we could state that, under our reaction conditions, DMDO was formed in situ and was the responsible for the oxidative dearomatization of the different phenols and naphthols into the corresponding dearomatized oxidation products. In addition, DMDO was also the oxidizing agent responsible for the epoxidation of the conjugated γ,δ-double bond of the initially formed *ortho*-quinols. Moreover, it is evident that for the oxidative dearomatization process took place using our reaction conditions, the OH group of the phenol of naphthol must be free.

With these data in mind and taking into account the precedent work, we could suggest a mechanism of action of the DMDO as responsible both of the oxidative dearomatization at the *ortho* position to the OH group and the epoxidation of the conjugated double bond on the initially formed *ortho*-quinol (*Scheme 3.60*).



Scheme 3.168. Mechanistic proposal for de oxidative dearomatization of phenols with DMDO

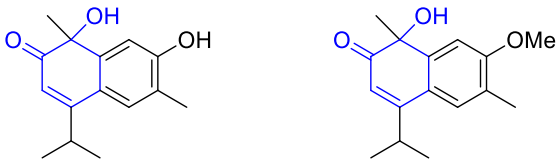
The possible mechanism could start from the previous coordination of the DMDO species to the –OH free group of phenols and naphthols, favoring the oxidation of the more accessible *ortho* position. Next, the electrophilic oxygen of the dimethyldioxirane would suffer the nucleophilic attack of the ortho aromatic carbon. The electron movement represented would give a stable cyclic six-membered transition state, leading to the formation of the carbonyl group with liberation of acetone and the formation of the corresponding *ortho*-quinol.

Once formed the initial *ortho*-quinol, a second molecule of DMDO, could coordinated with the hydroxyl group must favor the epoxidation of the conjugated double bond closer to the OH

group and by the same face occupied by the hydroxyl group. This mechanism explains the formation of only one of the possible diastereoisomers of the corresponding epoxy *ortho*-quinol, syn to the hydroxy group. The mechanism proposed the epoxidation is similar to that described in the literature through a cyclic six-membered transition state in which the double bond would act as the nucleophile and dimethyldioxirane as the electrophile.

3.2.5. Application of the oxidative dearomatization with dimethyldioxirane to the total synthesis of Lacinilene C methyl ether (30)

Lacinilene C (**505**) and lacinilene C methyl ether (**30**) (*Figure 3.30*), belong to a group of phytoalexines isolated from the cotton plant *Gossypium hirsutum*, that have been used in the growth inhibition of bacterial pathogens such as *Xanthomonas campestris* or *malvacearum*. Moreover, lacinilene C ME is associated with byssinosis or "brown lung disease".



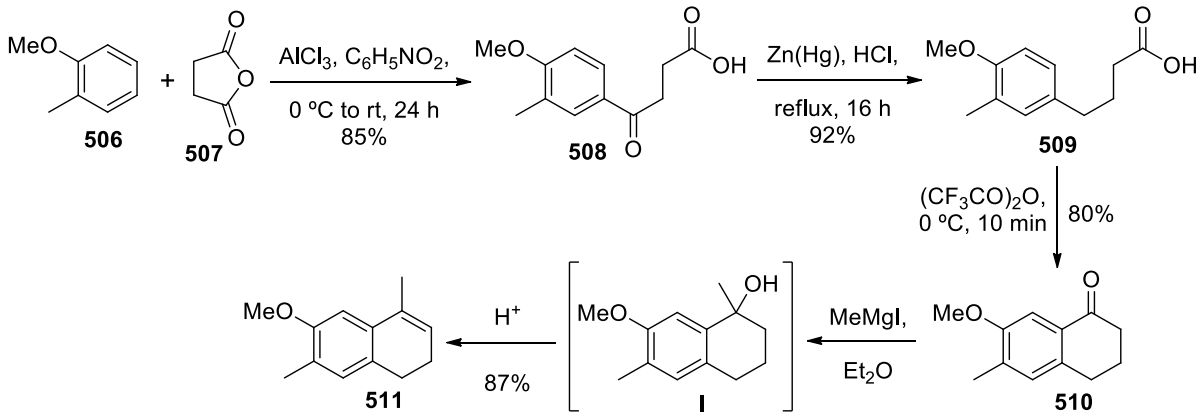
Lacinilene C (**505**) Lacinilene C ME (**30**)

*Figure 3.100. Structure of some lacinilene derivatives: lacinilene C (**505**) and lacinilene C ME (**30**)*

The first total synthesis of lacinilene C ME (**30**) was carried out by Krohn and Zimmermann in 1998. Krohn used an oxygenation strategy based on the use of a zirconium catalyst and TBHP for the oxidative dearomatization key step.

The synthesis of lacinilene C ME (**30**) started from 6-methoxy-4,7-dimethyl-1,2-dihydronaphthalene (**511**), which was obtained from 1-methoxy-2-methylbenzene (**506**) through a procedure described by Ayyangar in four reaction steps (*Scheme 3.61*).[201] First, a Friedel-Crafts acylation of **506** with succinic anhydride **507** using aluminum trichloride in nitrobenzene led to the keto acid **508** in 85% yield. The ketone was reduced under Clemmensen´s conditions to give the butyric acid derivative **509**, which was treated with trifluoroacetic anhydride suffering an intramolecular acylation to afford the tetralone **510** in high yield. Finally, the reaction between **510** and methyl magnesium iodide generated the corresponding carbinol **I**, which evolved to the dihydronaphthalene **511** in 87% yield by dehydration when the carbinol **I** was treated with acid.

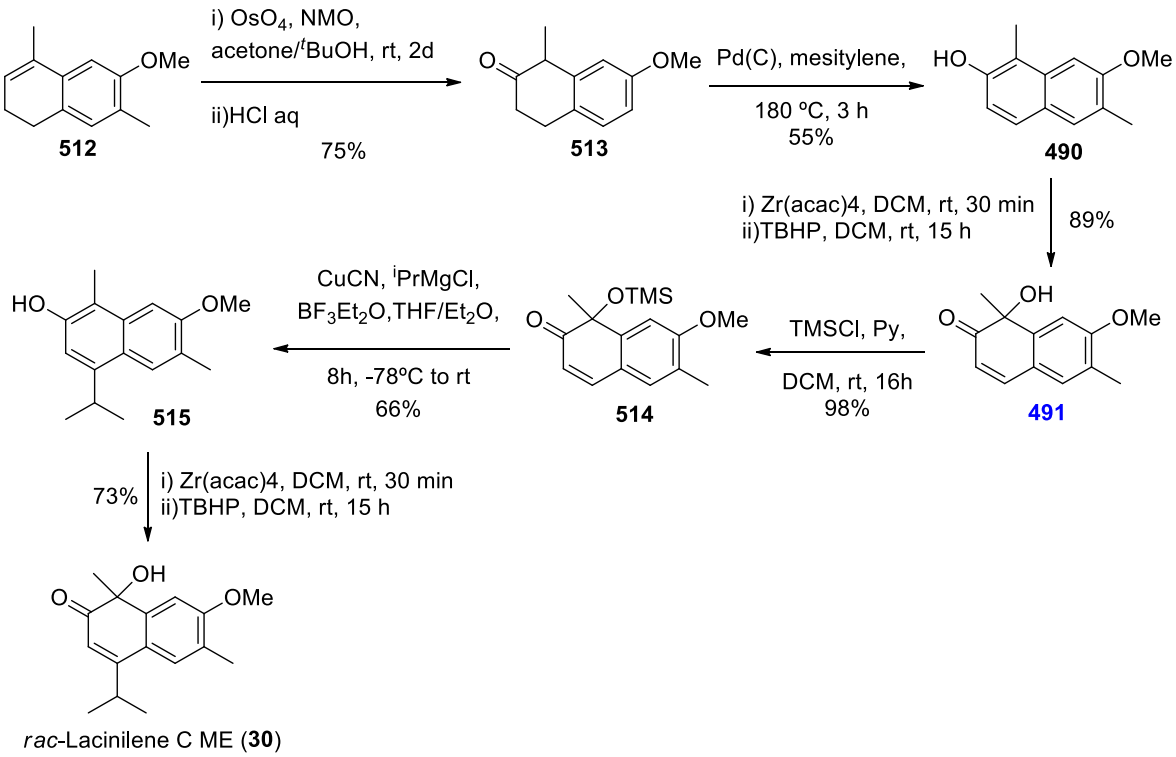
[201] P. K. Zubaidha, S. P. Chavan, U. S. Racherla, N. R. Ayyangar, *Tetrahedron* **1991**, *47*, 5759-5768



*Scheme 3.169. Synthesis of dihydronaphthalene **511** reported by Ayyangar and coworkers.*

Krohn and Zimmermann described the total synthesis of the racemic natural product lacinilene C ME (**30**) in 9% overall yield through ten reaction steps (*Scheme 3.62*).[202] Dihydronaphthalene **512** was oxidized with osmium tetroxide and of *N*-methylmorpholine *N*-oxide (NMO) to give the corresponding *cis*-diol, which was transformed to 2-tetralone **513** by treatment with hydrochloric acid. Next, 2-tetralone **513** was heated in the presence of palladium on charcoal to give 7-methoxy-1,6-dimethylnaphthalen-2-ol (**490**) in moderate yield by a thermal dehydrogenation. The oxidative dearomatization of **490** was carried out with *tert*-butyl hydroperoxide (TBHP) and the zirconium tetraacetylacetonate catalyst in DCM, affording the intermediate **491** in high yield. Then, the hydroxyl group of **491** was protected in 98% yield as trimethylsilyl ether **514**, using TMSCl in pyridine. Silyl ether **514** was transformed into the isopropyl substituted nahpthol **515** in moderate yield by an alkylation procedure using copper(I) cyanide, isopropyl magnesium chloride and boron trifluoride etherate at -78 ºC. Finally, the racemic natural product lacinilene C ME (**30**) was obtained in good yield following another oxidative dearomatization step, using the same conditions as before (TBHP and the zirconium tetraacetylacetonate catalyst in DCM).

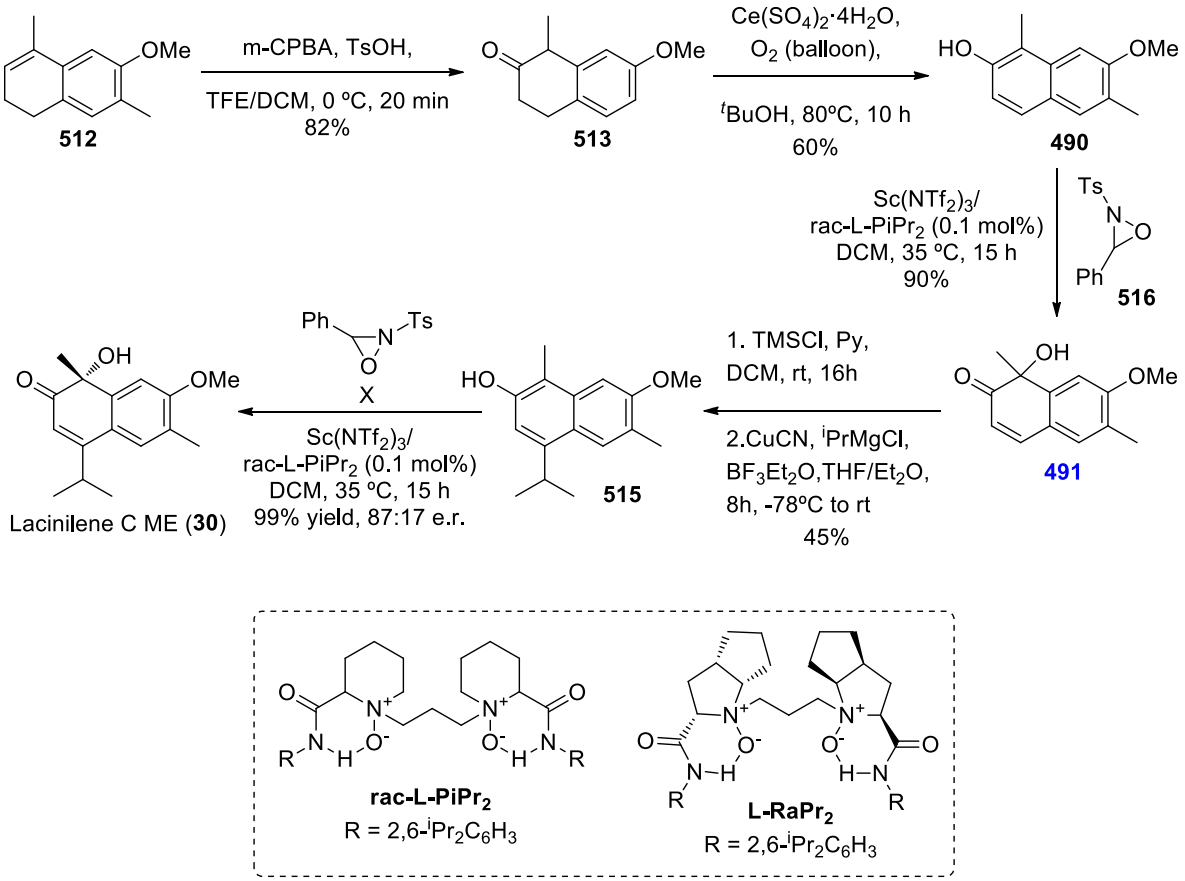
[202] K. Krohn, G. Zimmermann, *J. Org. Chem.* **1998**, *63,* 4140-4142.



*Scheme 3.170. Total synthesis of lacinilene C ME (**30**) described by Krohn and Zimmermann*

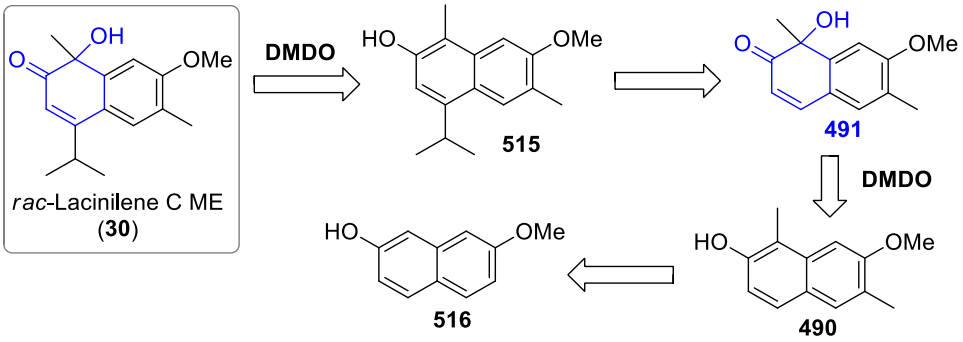
Feng and coworkers carried out in 2017 the study of the total synthesis of chiral natural product lacinilene C ME (**30**) from a racemic starting material in 11% overall yield through ten reaction steps (*Scheme 3.63*).[203] Starting from dihydronaphthalene **512**, oxidation with *m*-CPBA in the presence of TsOH gave 2-tetralone **513** with good yield. This tetralone was treated with cerium(IV) sulfate tetrahydrate under oxygen atmosphere to aromatize the ring, affording naphthol **490** in moderate yield. Naphthol **490** was submitted to an oxidative dearomatization key step using the oxaziridine **516** in the presence of catalytic amount of scandium(III) trifluoromethanesulfonimide [$Sc(NTf_2)_3$] and the racemic ligand L-$PiPr_2$, to afford intermediate **491** in high yield. Then, naphthol **515** was obtained in 45% overall yield from **491** through the same synthetic sequence reported by Krohn, protection of hydroxyl group with TMSCl and 1,4-addition / aromatization using copper(I) cyanide, isopropyl magnesium chloride and boron trifluoride etherate at -78 ºC.[202] Finally, the asymmetric oxidative dearomatization of naphthol **515** in the presence of oxaziridine X, catalytic amount of scandium (III) triflate and chiral ligand L-$RaPr_2$, afforded chiral lacinilene C ME (**30**) in quantitative yield with 83:17 e.r.

[203] Y. Zhang, Y. Liao, X. Liu, X. Xu, L. Lin, X. Feng, *Chem. Sci.* **2017**, *8*, 6645-6649.



*Scheme 3.171. Total chiral synthesis of lacinilene C ME (**30**) described by Feng and coworkers.*

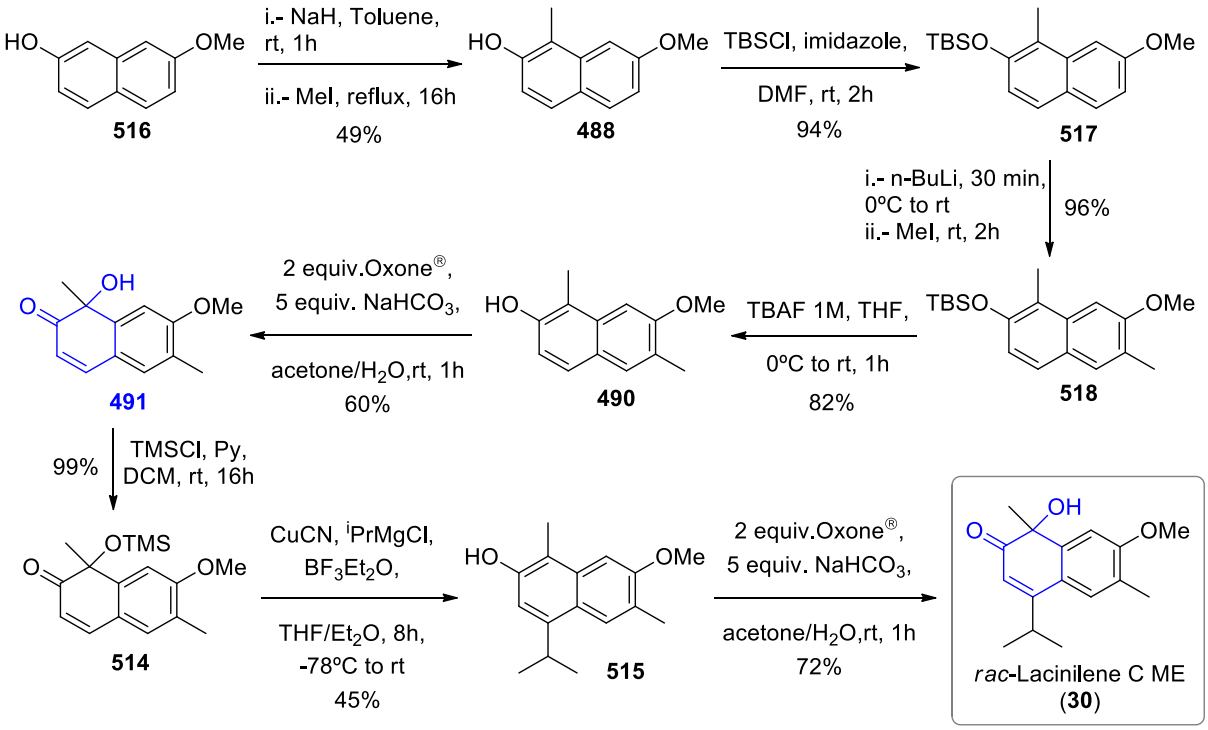
Taking into account these references and our previous work, we decided to carry out the total synthesis of racemic natural product lacinilene C methyl ether (**30**), applying our oxidative dearomatization method using the system Oxone® / $NaHCO_3$ / acetone, as the source of DMDO. Thus, as shown in the retrosynthetic scheme (*Scheme 3.64*), *rac*-lacinilene C ME (**30**) could be accessed from 4-isopropyl-7-methoxy-1,6-dimethylnaphthalen-2-ol (**515**) by DMDO-mediated *ortho*-oxidation. In turn, the starting phenol **515** would derive from 1-hydroxy-7-methoxy-1,6-dimethylnaphthalen-2(1H)-one (**491**), through a synthetic sequence already described. This *ortho*-quinol **491** could be formed again by applying our oxidative dearomatization with DMDO on 7-methoxy-1,6-dimethylnaphthalen-2-ol (**490**), which would be prepared from commercially available 7-methoxynaphthalen-2-ol (**516**), through alkylation and protection / deprotection steps.



*Scheme 3.172. Retrosynthetic scheme of Lacinilene C ME (**30**)*

Thus, the synthetic sequence towards racemic natural product Lacinilene C methyl ether (**30**) started with the treatment of 7-methoxynaphthalen-2-ol (**516**) with sodium hydride followed by the addition of methyl iodide to introduce a methyl group at C_1 position in moderate yield, as described in the literature.[204] The protection of hydroxyl group of **488** with TBSCl and imidazole in DMF at rt[205] gave the silyl ether **517** in 94% yield. The next step involved the introduction of methyl group at C_6 position. Firstly, this alkylation was carried out using *n*-BuLi at -78 ºC, to form the corresponding *ortho*-lithiated compound, which reacted with methyl iodide, added at -78 ºC.[206] However, starting material **517** remained unchanged, so increasing the temperature of the reaction to 0 ºC, *tert*-butyl((7-methoxy-1,6-dimethylnaphthalen-2-yl)oxy)dimethylsilane (**518**) could be achieved in high yield. Then, the removal of silyl ether group using tetra-*n*-butylammonium fluoride (TBAF) in THF at rt, afforded naphthol **490** in high yield. Next, we applied our oxidative dearomatization conditions (2 equiv. of Oxone® and 5 equiv. of $NaHCO_3$ in a mixture of acetone / Milli-Q water for 1 hour at rt), affording intermediate **491** in 60% yield. We synthesized naphthol **515** from **491** in 45% overall yield, employing the same synthetic sequence described by krohn[202] and by Feng[203] (protection of hydroxyl group with TMSCl and 1,4-addition / aromatization using copper(I) cyanide, isopropyl magnesium chloride and boron trifluoride etherate at -78 ºC). Finally, *rac*-lacinilene C methyl ether (**30**) was obtained in 72% yield from naphthol **515**, by appliying our oxidative dearomatization conditions (2 equiv. of Oxone® and 5 equiv. of $NaHCO_3$ in a mixture of acetone / Milli-Q water for 1 hour at rt) (*Scheme 3.65*)

[204] C. Grandclaudon, P. Y. Toullec, *Eur. J. Org. Chem.* **2016**, *2*, 260–264.
[205] T. Kaku, N. Matsunaga, A. Ojida, T. Tanaka, T. Hara, M. Yamaoka, M. Kusaka, A. Tasaka, *Bioorg. Med. Chem.* **2011**, *19*, 1751-1770.
[206] T. Oguma, T. Katsuki, *J. Am. Chem. Soc.* **2012**, *134*, 20017-20020.



*Scheme 3.173. Total synthesis of rac-Lacinilene C methyl ether (**30**) using our system Oxone® / $NaHCO_3$ / acetone.*

Thus, we have described the shortest total synthesis of *rac*-lacinilene C ME (**30**) described up to date (8 steps in 7% overall yield). In addition, the reaction times are shorter in most steps and all the reagents used are commercially available and cheap. Our total synthesis do not need a previously synthesis of complex ligands or complex reagents. This total synthesis sequence is more environmentally friendly than the other described total synthesis, because it avoids the use of highly toxic compounds such as OsO_4 and do not generate toxic metal waste such as Pd and Zn(Hg).

3.3. Experimental part

3.3.1. General Information

General Experimental Procedures. All starting materials were purchased from commercial sources (Merck, TCI, Alpha Aesar and Fluorochem) and used without further purification. Solvents used for reactions, extractions and purifications were reagent grade and used as received from Carlo Erba. When necessary, solvents were dried under standard conditions. The use of water Type I (ultrapure Milli-Q water), with a resistivity >18 (μΩ·cm), was

specified. Reactions were monitored by thin layer chromathography (TLC) using TLC silicagel coated aluminium plates 60 F_{254} (Merck) and visualized by ultraviolet light lamp (254 nm) and by staining with phosphomolybdic acid followed by heating. Column chromatography was performed with silicagel 60 (0.040-0.063 mm), packed with the corresponding eluent and run under positive air pressure. The experimental conditions for the reactions are indicated in each case.

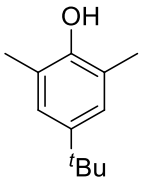
Instrumentation. ^{1}H-NMR and ^{13}C-NMR spectra were performed on Bruker, Avance 300 (300 MHz for ^{1}H and 75 MHz for ^{13}C). Chemical shifts are expressed in ppm using the residual non deuterated solvent as internal standard ($CDCl_3$ from Carlo Erba, ^{1}H-NMR: δ 7.26 ppm, ^{13}C-NMR: δ 77.16 ppm). The abbreviations used for the multiplicities are: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), td (triplet of doublets), tt (triplet of triplets) and m (multiplet); and the coupling constants (*J*) are reported in Hertz (Hz). High Resolution Mass Spectrometry (HRMS) was carried out by Servicio Interdepartamental de Investigación (SIdI) of Universidad Autónoma de Madrid. Melting points were performed on a BÜCHI B-540 capillary melting point apparatus and are uncorrected. Enantiomeric excesses were measured in a HPLC Agilent technologies, 1200 series. The addition of aqueous solution of Oxone® was added using a syringe pump Chemyx Fusion 100. Specific rotations were determined at rt on a Perkin Elmer 241 MC polarimeter with sodium lamp (λ: 589 nm) in a 10 cm glass tube.

3.3.2. Experimental Procedures and Product Characterization

3.3.2.1. Synthesis of precursors

3.3.2.1.1. Phenol derivatives

4-(*tert*-Butyl)-2,6-dimethylphenol (379)[207]



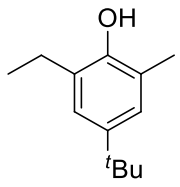
379 was synthesized followed a reported method described in the literature.[207] 2,6-dimethylphenol (**378**) (300 mg, 2.4 mmol) and *tert*-butanol (182.0 mg, 2.4 mmol) were dissolved in trifluoroacetic acid, TFA (3 mL) and the mixture was stirred 16 hours at rt. The reaction was quenched with water and extracted with DCM. The combined organic layers were washed with water and a $NaHCO_3$ saturated aqueous solution, dried over $MgSO_4$ anhydrous and concentrated

[207] U. Svanholm, V. D. Parker, *J. Chem. Soc., Perkin Trans 1* **1973**, 562-566

to dryness under reduced pressure. The desired product 4-(*tert*-butyl)-2,6-dimethylphenol (**379**) was obtained in 89% yield (394.2 mg, 2.21 mmol), as a beige solid, and used without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (s, 2H), 4.45 (s, 1H), 2.25 (s, 6H), 1.28 (s, 9H).

4-(*tert*-Butyl)-2-ethyl-6-methylphenol (381)



2-ethyl-6-methylphenol (**380**) (99.5 mg, 0.73 mmol) and *tert*-butanol (54.4 mg, 0.73 mmol) were dissolved in TFA (0.9 mL) and the mixture was stirred 16 hours at rt. The reaction was quenched with water and extracted with DCM. The combined organic layers were washed with water and a $NaHCO_3$ saturated solution, dried over $MgSO_4$ anhydrous and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 20/1) to give 4-(*tert*-butyl)-2,6-dimethylphenol (**381**) in 91% yield (127.3 mg, 0.66 mmol), as a white solid.

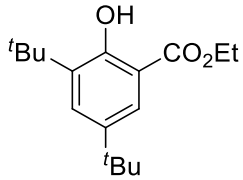
mp: 25.0 – 27.0 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (s, 2H), 4.40 (br, 1H), 2.67 (q, *J* = 7.6 Hz, 2H), 2.29 (s, 3H), 1.33 (s, 9H), 1.29 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5, 143.1, 128.8, 125.5, 123.9, 122.6, 34.0, 31.7, 23.6, 16.2, 14.3.

HRMS (EI): calculated for $C_{13}H_{20}O$ ($[M]^+$) 192.1514, found 192.1513.

Ethyl 3,5-di-tert-butyl-2-hydroxybenzoate (383)[208]



Ethyl 2-hydroxybenzoate (**382**) (0.3 mL, 2.04 mmol) and *tert*-butyl alcohol (378.0 mg, 5.10 mmol) were dissolved in MeOH (0.1 mL) and cooled to 0 ºC. Then, H_2SO_4 conc. (0.7 mL) was added to the

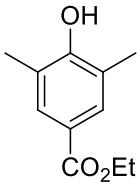
[208] Commercially available by Alfa Chemistry

solution at 0 ºC and the reaction mixture was stirred for 5 hours at rt. Next, the reaction was quenched with water and the layers were separated. The aqueous layer was extracted with DCM (x3) and the combined organic layers were dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 100/1) to give ethyl 3,5-di-tert-butyl-2-hydroxybenzoate (**383**) in 38% yield (215.2 mg, 0.77 mmol), as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 11.55 (s, 1H), 7.80 (d, *J* = 2.5 Hz, 1H), 7.60 (d, *J* = 2.5 Hz, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 1.51 – 1.46 (m, 12H), 1.39 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.4, 159.2, 140.3, 137.2, 130.3, 123.6, 111.6, 61.3, 35.2, 34.3, 31.5, 29.5, 14.4.

Ethyl 4-hydroxy-3,5-dimethylbenzoate (385)[209]

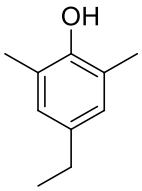


385 was synthesized followed a reported method described in the literature.[209] To a solution of 4-hydroxy-3,5-dimethylbenzoic acid (**384**) (100.0 mg, 0.60 mmol) in EtOH (1.2 mL), 4 drops of H_2SO_4 were added and stirred 16 hours at reflux. The reaction was quenched with water and extracted with EtOAc (x3). The crude was dried over Na_2SO_4, concentrated to dryness under reduced pressure and purified by flash chromatography (heptane/EtOAc 9/1) to give **385** in 95% yield (110.7 mg, 0.57 mmol), as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 2H), 4.98 (s, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.28 (s, 6H), 1.38 (t, *J* = 7.1 Hz, 3H).

[209] J. Deng, N. Li, H. Liu, Z. Zuo, O. W. Liew, W. Xu, G. Chen, X. Tong, W. Tang, J. Zhu,J. Zuo, H. Jiang, C.-G. Yang, J. Li, W. Zhu, *J. Med. Chem.* **2012**, *55*, 6278-6293.

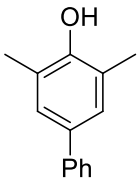
4-Ethyl-2,6-dimethylphenol (387)[210]



To a suspension of zinc (1.0 g, 15.83 mmol) and $HgCl_2$ (106.0 mg, 0.39 mmol) in water (1.8 mL), HCl 37% (40 µL) was added and the mixture was stirred 5 min. After that, toluene (1.4 mL), HCl 37% (1.5 mL) and 1-(4-hydroxy-3,5-dimethylphenyl)ethanone (**386**) (402.2 mg, 2.45 mmol) were successively added,and the mixture was stirred 16 h at 110 ºC. The reaction was cooled to rt, the phases were separated and the aqueous phase was extracted with EtOAc (x3). The organic phases were dried over Na_2SO_4 anhydrous and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 20/1) to give 4-ethyl-2,6-dimethylphenol (**387**) in 61% yield (223.2 mg, 1.48 mmol), as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (s, 2H), 4.47 (s, 1H), 2.53 (q, *J* = 7.6 Hz, 2H), 2.24 (s, 6H), 1.21 (t, *J* = 7.6 Hz, 3H).

3,5-Dimethyl-[1,1'-biphenyl]-4-ol (389)[211]



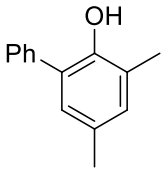
389 was synthesized followed a reported method described in the literature.[211] In a dried sealed tube, 4-bromo-2,6-dimethylphenol (**388**) (100.4 mg, 0.50 mmol), phenylboronic acid (121.0 mg, 0.99 mmol), K_2CO_3 (276.4 mg, 2.00 mmol) and $Pd(PPh_3)_4$ (23.1 mg, 5% mol) were dissolved in a mixture of deoxygenated toluene (6.2 mL), ethanol (0.2 mL) and water (0.1 mL). The mixture was stirred 16 h at 90 ºC and, then, cooled to rt. The organic layer was separated and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude was purified by flash

[210] D. Sarkar, M. K. Ghosh, N. Rout, P. Kuila, *New J. Chem.* **2017**, *41*, 3715-3718.
[211] P. H. Bos, M. T. Antalek, J. A. Porco Jr., C. R. J. Stephenson, *J. Am. Chem. Soc.* **2013**, *135*, 17978-17982.

chromatography (heptane/EtOAc : 40/1) to give 3,5-dimethyl-[1,1'-biphenyl]-4-ol (**389**) in 75% yield (73.6 mg, 0.37 mmol), as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 – 7.55 (m, 2H), 7.47 – 7.40 (m, 2H), 7.36 – 7.29 (m, 1H), 7.26 (s, 2H), 4.68 (s, 1H), 2.34 (s, 6H).

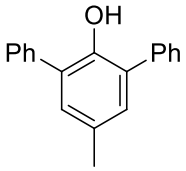
3,5-Dimethyl-[1,1'-biphenyl]-2-ol (391)[212]



In a dried sealed tube, 2-bromo-4,6-dimethylphenol (**390**) (105.2 mg, 0.52 mmol), phenylboronic acid (121.0 mg, 0.99 mmol), K_2CO_3 (276.4 mg, 2.00 mmol) and $Pd(PPh_3)_4$ (23.1 mg, 5% mol) were dissolved in a mixture of deoxygenated toluene (6.2 mL), ethanol (0.2 mL) and water (0.1 mL). The mixture was stirred 20 h at 90 ºC and, then, cooled to rt. The organic layer was separated and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 40/1) to give 3,5-dimethyl-[1,1'-biphenyl]-2-ol (**391**) in >99% yield (103.0 mg, 0.52 mmol), as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 – 7.45 (m, 4H), 7.45 – 7.37 (m, 1H), 6.99 (s, 1H), 6.92 (s, 1H), 5.11 (s, *J* = 3.0 Hz, 1H), 2.32 (s, 3H), 2.31 (s, 3H).

5'-Methyl-[1,1':3',1''-terphenyl]-2'-ol (393)[213]



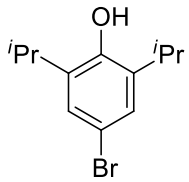
In a dried sealed tube, 2,6-dibromo-4-methylphenol (**392**) (102.0 mg, 0.46 mmol), phenylboronic acid (218.6 mg, 1.79 mmol), K_2CO_3 (742.9 mg, 5.38 mmol) and $Pd(PPh_3)_4$ (26 mg, 5 mol%) were

[212] D. H. R. Barton, N. Yadav-Bhatnagar, J.-C. Blazejewski, B. Charpiot, J.-P. Finet, D. J. Lester, W. B. Motherwell, M. T. Barros-Papoula, S. P. Stanforth, *J. Chem. Soc., Perkin Trans 1* **1985**, 2657-2665.
[213] A. P. Krysina, T. B. Khlebnikovab, B. M. Khlebnikovb, L. M. Pokrovskiia, V. G. Vasil'ev, *Russ. J. Chem.* **2009**, *79*, 1156-1162.

dissolved in a mixture of deoxygenated toluene (5.6 mL), ethanol (0.17 mL) and water (0.08 mL). The mixture was stirred 16 hours at 90 ºC and, then, cooled to rt. The organic layer was separated and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 40/1) to give 5'-methyl-[1,1':3',1''-terphenyl]-2'-ol (**393**) in 33% yield (39.7 mg, 0.15 mmol), as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.59 – 7.52 (m, 4H), 7.51 – 7.44 (m, 4H), 7.42 – 7.34 (m, 2H), 7.10 (s, 2H), 5.25 (s, 1H), 2.37 (s, 3H).

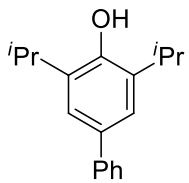
4-Bromo-2,6-diisopropylphenol (395)[214]



395 was synthesized followed a reported method described in the literature.[214] To a solution of 2,6-diisopropylphenol (**394**) (0.52 mL, 2.8 mL) in CH_3CN (4.0 mL), NBS (549.1 mg, 3.10 mmol) was added. The reaction was stirred 12 hours at reflux and the solvent was eliminated under reduced pressure. The crude reaction was extracted with EtOAc (x3), washed with brine, dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 10/1) to give 4-bromo-2,6-diisopropylphenol (**395**) in 87% yield (624.9 mg, 2.44 mmol), as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (s, 2H), 4.75 (s, 1H), 3.19 – 3.03 (m, 2H), 1.26 (s, 6H), 1.24 (s, 6H).

3,5-Diisopropyl-[1,1'-biphenyl]-4-ol (396)



In a dried sealed tube, 4-bromo-2,6-diisopropylphenol (**395**) (198.4 mg, 0.77 mmol), phenylboronic acid (190.4 mg, 1.56 mmol), K_2CO_3 (426.0 mg, 3.08 mmol) and $Pd(PPh_3)_4$ (43.8 mg,

[214] T. Jähnert, M. D. Hager, U. S. Schubert, *Macromol. Rapid Commun.* **2016**, *37*, 725−730.

5% mol) were dissolved in a mixture of deoxygenated toluene (7.7 mL), ethanol (0.9 mL) and water (1.7 mL). The mixture was stirred 16 hours at 90 ºC and, then, cooled to rt. The organic layer was separated and the aqueous layer extracted with EtOAc (x3). The combined organic layers were dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 40/1) to give 3,5-diisopropyl-[1,1'-biphenyl]-4-ol (**396**) in 62% yield (122.2 mg, 0.48 mmol), as a white solid.

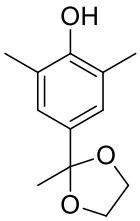
mp: 64.3 – 65.1 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, *J* = 7.9 Hz, 2H), 7.47 – 7.40 (m, 2H), 7.35 – 7.31 (m, 1H), 7.30 (s, 2H), 4.84 (s, 1H), 3.30 – 3.15 (m, 2H), 1.36 (s, 6H), 1.34 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8, 142.1, 134.1, 133.9, 128.7, 127.1, 126.6, 122.6, 27.5, 22.9.

HRMS (ESI): calculated for $C_{18}H_{22}ONa$ ($[M+Na]^+$) 277.1562, found 277.1575.

2,6-dimethyl-4-(2-methyl-1,3-dioxolan-2-yl)phenol (414)



To a mixture of 1-(4-hydroxy-3,5-dimethylphenyl)ethanone (**386**) (200.5 mg, 1.22 mmol), ethylene glycol (0.14 mL, 2.55 mmol) and $Ce(OTf)_3$ (42.9 mg, 6% mol) in hexane (2.5 mL), $HC(O\textit{i}\text{-}Pr)_3$ (0.55 mL, 2.47 mmol) was added at rt under inert atmosphere. The reaction was stirred 2 h and quenched with Et_3N and a saturated solution of $NaHCO_3$. The crude reaction was extracted with EtOAc (x3), washed with brine, dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane containing 0.1% Et_3N/EtOAc : 8/1) to give **414** in 80% yield (204.6 mg, 0.98 mmol), as a white solid.

mp: 92.4 – 93.7 ºC

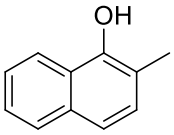
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (s, 2H), 5.03 (s, 1H), 4.07 – 3.99 (m, 2H), 3.85 – 3.78 (m, 2H), 2.26 (s, 6H), 1.66 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0, 134.8, 125.6, 122.9, 109.0, 64.4, 27.7, 16.1.

HRMS (ESI): calculated for $C_{12}H_{17}O_3$ ($[M+H]^+$) 209.1172, found 209.1161.

3.3.2.1.2. Naphthol derivatives

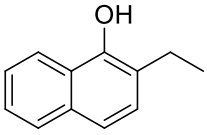
2-Methylnaphthalen-1-ol (428)[215]



428 was synthesized followed a reported method described in the literature.[227] Ethyl chloroformate (EtO_2CCl, 8.3 ml, 87.4 mmol) was added at 0 ºC to a solution of 1-hydroxy-2-naphthoic acid (**427**) (5 g, 26.5 mmol) and Et_3N (12.1 ml, 87.7 mmol) in THF (220 mL). The reaction mixture was stirred at 0 ºC for 3 h and the resulting white precipitate was filtered off and washed with THF. The combined filtrates were concentrated to dryness under reduced pressure and re-dissolved in THF (15 mL). Then, a solution of sodium borohydride ($NaBH_4$, 10.84 g, 286.5mmol) in H_2O (15 mL) was carefully added at 0 ºC to the crude solution and the mixture was stirred at 0 ºC for 3 h. After that, the temperature of the reaction was risen to rt and stirred an additional hour at rt. The reaction was quenched with an aqueous solution of HCl 1M and THF was evaporated under reduced pressure. The aqueous layer was extracted with EtOAc (x3) and the organic layer was dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 9/1) to give 2-methylnaphthalen-1-ol (**428**) in 73% yield (2.10 g, 13.3 mmol), as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.12 (d, *J* = 7.7 Hz, 1H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.51 – 7.42 (m, 2H), 7.39 (d, *J* = 8.5 Hz, 1H), 7.26 (s, 1H), 5.06 (s, 1H), 2.42 (s, 3H).

2-Ethylnaphthalen-1-ol (430)[216]



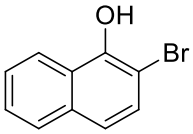
To a solution of 1-(1-hydroxynaphthalen-2-yl)ethanone (**429**) (105.7 mg, 0.57 mmol) in THF (0.41 mL), ethyl chloroformate (56.3 µL, 0.59 mmol) and Et_3N (82.0 µL, 0.59 mmol) were added at 0 ºC. The reaction was stirred 30 min at rt and filtered. To the filtrate, $NaBH_4$ (40.8 mg, 1.08 mmol) was

[215] F. Mazzini, P. Salvadori, *Synthesis* **2005**, *15*, 2479-2481.
[216] C. Grandclaudon, P. Y. Toullec, *Eur. J. Org. Chem.* **2016**, *2*, 260–264.

added and the reaction was stirred at rt for 1 h and quenched with water. The mixture was extracted with EtOAc (x3) and the organic layer was dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 40/1) to give 2-ethylnaphthalen-1-ol (**430**) in 70% yield (68.9 mg, 0.40 mmol), as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, *J* = 7.8 Hz, 1H), 7.81 – 7.76 (m, 1H), 7.51 – 7.40 (m, 3H), 7.28 (d, *J* = 8.5 Hz, 1H), 5.13 (s, 1H), 2.79 (q, *J* = 7.6 Hz, 2H), 1.32 (t, *J* = 7.6 Hz, 3H).

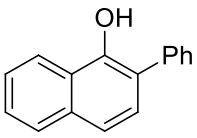
2-Bromonaphthalen-1-ol (432)[217]



432 was synthesized followed a reported method described in the literature.[217] A solution of NBS (307.9 mg, 1.73 mmol) in DCM (5.6 mL) was added slowly to a stirred solution of naphthalen-1-ol (**431**) (250.0 mg, 1.73 mmol) and *i*-Pr_2NH (24 µL, 10% mol) in DCM (3.5 mL) at rt. The reaction mixture was stirred 23 hours at reflux and, then, was quenched with and aqueous solution of H_2SO_4 2M. The mixture was extracted with DCM (x3) and the organic layer was dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 40/1) to afford 2-bromonaphthalen-1-ol (**432**) in 51% yield (199.2 mg, 0.89 mmol), as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.33 – 8.25 (m, 1H), 7.82 – 7.75 (m, 1H), 7.58 – 7.52 (m, 2H), 7.49 (d, *J* = 8.8 Hz, 1H), 7.32 (d, *J* = 8.8 Hz, 1H), 6.03 (s, 1H).

2-Phenylnaphthalen-1-ol (433)[218]



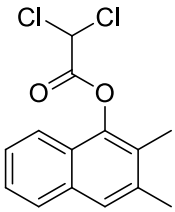
In a dried sealed tube, 1-bromonaphthalen-2-ol (**432**) (96.9 mg, 0.43 mmol), phenylboronic acid (109.03 mg, 0.90 mmol), K_2CO_3 (130.6 mg, 0.94 mmol) and $Pd(PPh_3)_4$ (26.0 mg, 0.02 mg) were

[217] K. Fuchibe, T. Morikawa, K. Shigeno, T. Fujita, J. Ichikawa, *Org. Lett.* **2015**, *17*, 1126-1129.
[218] H.-Y. Yin, X.-L. Lin, S.-W. Li, L.-X. Shao, *Org. Biomol. Chem.* **2015**, *13*, 9012-9021.

dissolved in a mixture of deoxygenated toluene (4.5 mL), ethanol (0.9 mL) and water (1.0 mL). The mixture was stirred 20 h at 90 ºC and, then, cooled to rt. The organic layer was separated and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 40/1) to give 1-phenylnaphthalen-2-ol (**433**) in 37% yield (35.4 mg, 0.16 mmol), as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.37 – 8.30 (m, 1H), 7.89 – 7.83 (m, 1H), 7.59 – 7.44 (m, 8H), 7.39 (d, *J* = 8.4 Hz, 1H), 5.87 (s, 1H).

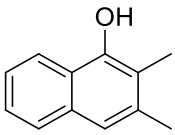
2,3-Dimethylnaphthalen-1-yl 2,2-dichloroacetate (436)[219]



436 was synthesized followed a reported method described in the literature.[219] To a solution of lead tetraacetate ($Pb(OAc)_4$, 1.1 g, 2.60 mmol) and dichloroacetic acid (1.1 mL, 13.45 mmol) in $CHCl_3$ (8.0 mL), a solution of 2,3-dimethylnaphthalene (**435**) (496.0 mg, 3.17 mmol) in $CHCl_3$ (2.1 mL) was added at 0 ºC with a rapid stirring. The reaction mixture was stirred 16 hours at rt and filtered to remove the precipitate (lead dioxide). The solid was washed with $CHCl_3$ and the organic solution was washed with water. The organic layer was dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 20/1) and recrystallized from heptane to give **435** in 28% yield (252.6 mg, 0.89 mmol), as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.87 – 7.76 (m, 2H), 7.61 (s, 1H), 7.55 – 7.44 (m, 2H), 6.37 (s, 1H), 2.47 (s, 3H), 2.29 (s, 3H).

2,3-Dimethylnaphthalen-1-ol (437)[219]

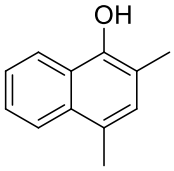


[219] H Greenland, J. T. Pinhey, S Sternhell, *Aust. J. Chem.* **1987**, *40*, 325-331.

437 was synthesized followed a reported method described in the literature.[219] To a solution of **436** (125.1 mg, 0.44 mmol) in EtOH (9 mL), a deoxygenated aqueous solution of NaOH 3M (4.8 mL, 14.40 mmol) was added at 0 ºC under inert atmosphere and the reaction was stirred 1 hour at rt. The reaction was extracted with DCM (x3), dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 20/1) to give 2,3-dimethylnaphthalen-1-ol (**437**) in 79% yield (60.0 mg, 0.35 mmol), as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.09 – 8.01 (m, 1H), 7.75 – 7.68 (m, 1H), 7.46 – 7.39 (m, 2H), 7.29 (s, 1H), 5.13 (s, 1H), 2.45 (s, 3H), 2.33 (s, 3H).

2,4-Dimethylnaphthalen-1-ol (446)[220]

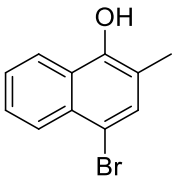


446 was synthesized followed a reported method described in the literature.[220] Methyllithium (MeLi 1.6 M in Et_2O, 5 mL, 8.00 mmol) was added to a solution of 1,4-naphthoquinone (**445**) (500.9 mg, 3.17 mmol) in THF (64 mL) at -78 ºC under inert atmosphere. The reaction mixture was stirred for 1 h, while the reaction temperature was rising to rt. Then, the reaction mixture was cooled to -78 ºC, acidified with an aqueous solution of H_2SO_4 2M (75 mL) and stirred 1 hour at rt. The mixture was concentrated under reduced pressure and extracted with DCM (x3). The organic layer was dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 40/1) to afford 2,4-dimethyl-1-naphthol (**446**) in 52% yield (285.6 mg, 1.66 mmol), as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.94 (d, *J* = 9.4 Hz, 2H), 7.52 (t, *J* = 8.1 Hz, 1H), 7.40 (t, *J* = 8.1 Hz, 1H), 6.93 (s, 1H), 4.88 (s, 1H), 2.64 (s, 3H), 2.52 (s, 3H).

[220] C. T. Wigal, J. D. McKinley, J. Coyle, D. J. Porter, D. E. Lehman, *J. Org. Chem.* **1995**, *60*, 8421-8423.

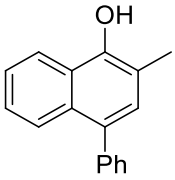
4-Bromo-2-methylnaphthalen-1-ol (447)[221]



447 was synthesized followed a reported method described in the literature.[221] *N*-bromosuccinimide (1.4 g, 10.7 mmol) was added in four portions to a stirred solution of 2-methylnaphthalen-1-ol (**428**) (1.7 g, 10.7 mmol) in dry acetonitrile (8.9 mL) at rt. The reaction mixture was stirred for 30 min and, then, quenched with water. The organic layer was separated and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 10/1) to give 4-bromo-2-methylnaphthalen-1-ol (**447**) in 55% yield (1.40 g, 5.9 mmol), as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.19 – 8.09 (m, 2H), 7.59 – 7.49 (m, 3H), 5.05 (s, 1H), 2.40 (s, 3H).

2-Methyl-4-phenylnaphthalen-1-ol (448a)[222]

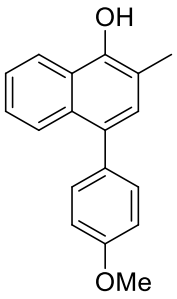


In a dried sealed tube, 4-bromo-2-methylnaphthalen-1-ol (**428**) (148.6 mg, 0.63 mmol), phenylboronic acid (156.1 mg, 1.28 mmol), K_2CO_3 (353.8 mg, 2.56 mmol) and $Pd(PPh_3)_4$ (37.0 mg, 5% mol) were dissolved in a mixture of deoxygenated toluene (6.4 mL), ethanol (1.3 mL) and water (1.4 mL). The mixture was stirred 16 h at 90 ºC and, then, cooled to rt. The organic layer was separated and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 20/1) to give 2-methyl-4-phenylnaphthalen-1-ol (**448a**) in 61% yield (90.1 mg, 0.38 mmol), as a white solid.

[221] S. Companys, P. A. Peixoto, C. Bosset, S. Chassaing, K. Miqueu, J.-M. Sotiropoulos, L. Pouysegu, S. Quideau, *Chem. Eur. J.* **2017**, *23*, 13309-13313.
[222] *D. Zhou, X. Yu, J. Zhang,W. Wang, H. Xie, Org. Lett.* **2018**, *20*, 174–177.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.25 (d, *J* = 8.3 Hz, 1H), 7.89 (d, *J* = 8.4 Hz, 1H), 7.56 – 7.39 (m, 7H), 7.25 (s, 1H), 5.16 (s, 1H), 2.47 (s, 3H).

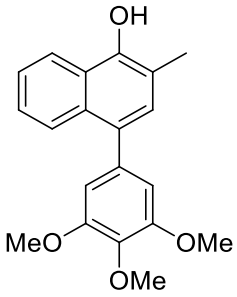
4-(4-Methoxyphenyl)-2-methylnaphthalen-1-ol (448b)[222]



In a dried sealed tube, 4-bromo-2-methylnaphthalen-1-ol (**428**) (148.6 mg, 0.63 mmol), (4-methoxyphenyl)boronic acid (194.6 mg, 1.28 mmol), K_2CO_3 (353.8 mg, 2.56 mmol) and $Pd(PPh_3)_4$ (37.0 mg, 5% mol) were dissolved in a mixture of deoxygenated toluene (6.4 mL), ethanol (1.3 mL) and water (1.4 mL). The mixture was stirred 16 h at 90 ºC and, then, cooled to rt. The organic layer was separated and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 20/1 to 9/1) to give 4-(4-methoxyphenyl)-2-methylnaphthalen-1-ol (**448b**) in 71% yield (117.0 mg, 0.44 mmol), as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.21 (d, *J* = 8.3 Hz, 1H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.44 – 7.36 (m, 3H), 7.20 (s, 1H), 7.02 (d, *J* = 8.2 Hz, 2H), 5.12 (s, 1H), 3.90 (s, 3H), 2.45 (s, 3H).

2-Methyl-4-(3,4,5-trimethoxyphenyl)naphthalen-1-ol (448c)



In a dried sealed tube, 4-bromo-2-methylnaphthalen-1-ol (**428**) (198.9 mg, 0.84 mmol), (3,4,5-trimethoxyphenyl)boronic acid (362.5 mg, 1.71 mmol), K_2CO_3 (469.9 mg, 3.40 mmol) and $Pd(PPh_3)_4$ (49.1 mg, 5% mol) were dissolved in a mixture of deoxygenated toluene (8.5 mL),

ethanol (1.7 mL) and water (1.9 mL). The mixture was stirred 16 h at 90 ºC and, then, cooled to rt. The organic layer was separated and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 5/1) to give 2-methyl-4-(3,4,5-trimethoxyphenyl)naphthalen-1-ol (**448c**) in 72% yield (196.6 mg, 0.61 mmol), as a pale brown solid.

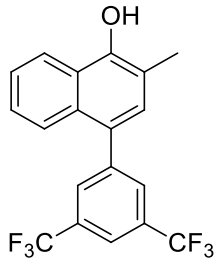
mp: 132.9-133.6

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.28 (d, *J* = 8.2 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.45 (dt, *J* = 15.0, 6.7 Hz, 2H), 6.73 (s, 2H), 5.86 (s, 1H), 4.00 (s, 3H), 3.88 (s, 6H), 2.46 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 152.9, 148.5, 136.9, 136.6, 132.5, 131.2, 129.9, 125.8, 125.5, 125.1, 124.7, 121.5, 116.3, 107.4, 61.0, 56.1, 15.6.

HRMS (APCI): calculated for $C_{10}H_{20}O_4$ ($[M]^+$) 324.1344, found 324.1356.

4-(3,5-Bis(trifluoromethyl)phenyl)-2-methylnaphthalen-1-ol (448d)



In a dried sealed tube, 4-bromo-2-methylnaphthalen-1-ol (**428**) (199.5 mg, 0.84 mmol), (3,5-bis(trifluoromethyl)phenyl)boronic acid (440.4 mg, 1.71 mmol), K_2CO_3 (469.9 mg, 3.40 mmol) and $Pd(PPh_3)_4$ (49.1 mg, 5% mol) were dissolved in a mixture of deoxygenated toluene (8.5 mL), ethanol (1.7 mL) and water (1.9 mL). The mixture was stirred 16 h at 90 ºC and, then, cooled to rt. The organic layer was separated and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 20/1) to give 4-(3,5-bis(trifluoromethyl)phenyl)-2-methylnaphthalen-1-ol (**448d**) in 79% yield (244.8 mg, 0.66 mmol), as a white solid.

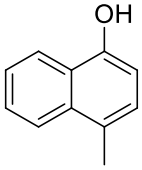
mp: 154.6 – 155.4 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.27 (d, *J* = 8.3 Hz, 1H), 7.95 (s, 3H), 7.68 (d, *J* = 8.3 Hz, 1H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.4 Hz, 1H), 7.24 (s, 1H), 5.29 (s, 1H), 2.48 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 149.5, 143.1, 132.0, 131.6, 130.9, 130.8, 130.4 (q, $J_{C\text{-}F}$ = 3.3 Hz, CF_3), 129.5, 126.6, 125.9, 125.4, 124.8, 124.6, 121.8, 120.9 (q, $J_{C\text{-}F}$ = 3.9 Hz, CF_3), 115.9, 15.7.

HRMS (APCI): calculated for $C_{19}H_{12}F_6O$ ($[M]^+$) 370.0772, found 370.0787.

4-Methylnaphthalen-1-ol (450)[223]

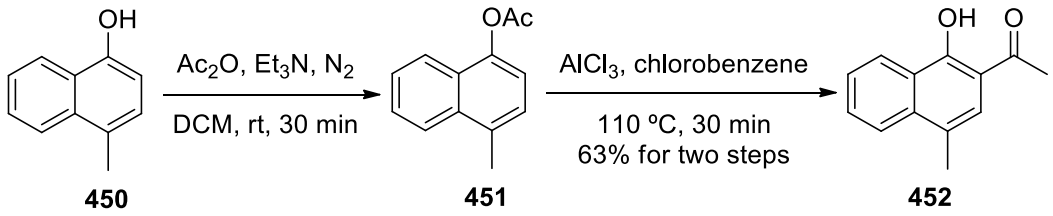


450 was synthesized followed a reported method described in the literature.[223] To a solution of 4-methyl-1-naphthaldehyde (**449**) (1.0 g, 5.90 mmol) in DCM (98.0 mL), *m*-CPBA (3.0 g, 17.60 mmol) was added and the reaction was stirred at rt for 16 h. The reaction was quenched with an aqueous solution of $Na_2S_2O_3$ 10% (39.0 mL) and extracted with DCM (x3). The organic layer was dried over $MgSO_4$ and concentrated to dryness under reduced pressure, to afford a yellow solid. To a solution of this solid in acetone (98.0 mL), an aqueous solution of HCl 10% (29.5 mL) was added and stirred at reflux for 4 h. The reaction was quenched with a mixture of ice/water and extracted with DCM (x3). The organic layer was dried over $MgSO_4$, concentrated to dryness under reduced pressure and purified by flash chromatography (heptane/EtOAc : 20/1) to give 4-methylnaphthalen-1-ol (**450**) in 61% yield (569.5 mg, 3.60 mmol), as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.32 – 8.24 (m, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.64 – 7.51 (m, 2H), 7.16 (d, *J* = 7.5 Hz, 1H), 6.73 (d, *J* = 7.5 Hz, 1H), 5.30 (s, 1H), 2.66 (s, 3H).

[223] Tetsuya Takeya, Hirohisa Doi, Tokutaro Ogata, Tsuyoshi Otsuka, Iwao Okamoto, Eiichi Kotani, *Tetrahedron* **2004**, *60*, 6295-6310.

1-(1-Hydroxy-4-methylnaphthalen-2-yl)ethanone (452)[224]



450 **451** **452**

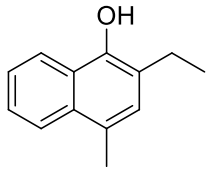
4-Methylnaphthalen-1-yl acetate (**451**):[225] To a solution of 4-methylnaphthalen-1-ol (**450**) (594.9 mg, 3.76 mmol) in DCM (37.0 mL), Et_3N (1.30 mL, 9.26 mmol) and Ac_2O (0.43 mL, 4.50 mmol) were added and the reaction was stirred 30 min at rt under inert atmosphere. The reaction was quenched with an aqueous solution of HCl 1M and extracted with DCM (x3). The organic layer was dried over $MgSO_4$ and concentrated to dryness under reduced pressure to give **451**, as a white solid, which was used in the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.07 – 8.01 (m, 1H), 7.98 – 7.90 (m, 1H), 7.64 – 7.54 (m, 2H), 7.34 (d, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 2.71 (s, 3H), 2.49 (s, 3H).

1-(1-Hydroxy-4-methylnaphthalen-2-yl)ethanone (**452**):[224] To a solution of 4-methylnaphthalen-1-yl acetate in chlorobenzene (**451**) (15.0 mL), $AlCl_3$ (1.5 g, 11.28 mmol) was added slowly and the reaction was stirred 30 min at 110 ºC. The reaction was quenched with an aqueous solution of HCl 1M and extracted with DCM (x3). The organic layer was dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 20/1) to give 1-(1-hydroxy-4-methylnaphthalen-2-yl)ethanone (**452**) in 63% yield (475.7 mg, 2.38 mmol), as a yellow solid.

^{1}H NMR (300 MHz, CDCl3) δ: 13.87 (s, 1H), 8.50 (d, *J* = 8.3 Hz, 1H), 7.87 (d, *J* = 8.3 Hz, 1H), 7.67 (t, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.42 (s, 1H), 2.67 (s, 3H), 2.57 (s, 3H).

2-Ethyl-4-methylnaphthalen-1-ol (453)[226]

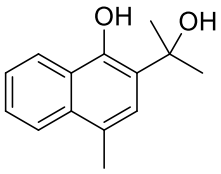


[224] T. Matsuda, Y. Nishida, K. Yamanaka, Y. Sakurai, *Tetrahedron* **2015**, *71*, 869-874.
[225] S. Sankararaman, J. K. Kochi, *J. Chem. Soc., Perkin Trans. 2* **1991**, 1-12.
[226] *Wiadomosci Chemiczne* **1995**, *49*, 761-763

To a suspension of zinc (318.4 mg, 4.90 mmol) and $HgCl_2$ (32.6 mg, 0.12 mmol) in water (0.56 mL), HCl 37% (20.0 µL) was added and the mixture was stirred 5 min. After that, toluene (0.42 mL), HCl 37% (0.48 mL) and 1-(1-hydroxy-4-methylnaphthalen-2-yl)ethanone (**452**) (147.7 mg, 0.75 mmol) was successively added to the mixture and the reaction was stirred for 16 h at 110 ºC. The reaction was cooled to rt, the phases were separated and the aqueous phase extracted with EtOAc (x3). The organic phase was dried over Na_2SO_4 anhydrous and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 40/1) to give 1-ethylnaphthalen-2-ol (**453**) in 79% yield (108.0 mg, 0.56 mmol), as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.21 – 8.14 (m, 1H), 7.97 – 7.91 (m, 1H), 7.56 – 7.48 (m, 2H), 7.13 (s, 1H), 5.02 (s, 1H), 2.77 (q, *J* = 7.6 Hz, 2H), 2.64 (s, 3H), 1.33 (t, *J* = 7.6 Hz, 3H).

2-(2-Hydroxypropan-2-yl)-4-methylnaphthalen-1-ol (454)



To a solution of 1-(1-hydroxy-4-methylnaphthalen-2-yl)ethanone (**452**) (99.8 mg, 0.50 mmol) in dry THF (1.0 mL), MeMgBr (3M in Et_2O, 0.67 mL, 2.0 mmol) was added dropwise under inert atmosphere. The reaction was stirred at reflux for 3 h, cooled in an ice/water bath and carefully quenched with a saturated aqueous solution of NH_4Cl. The mixture was extracted with EtOAc (x3) and the organic layer was dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography using neutral silica (heptane/EtOAc : 20/1) to give 1-(2-hydroxypropan-2-yl)naphthalen-2-ol (**454**) in 92% yield (98.9 mg, 0.46 mmol), as a pale brown solid.

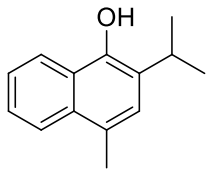
mp: 55.5 – 57.4 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.77 (s, 1H), 8.35 (d, *J* = 7.8 Hz, 1H), 7.89 (dd, *J* = 6.8, 1.6 Hz, 1H), 7.58 – 7.46 (m, 2H), 6.99 (s, 1H), 2.70 (s, 1H), 2.60 (s, 3H), 1.70 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 149.3, 132.7, 126.2, 125.8, 125.0, 124.7, 123.9, 123.8, 122.9, 122.8, 76.8, 30.7, 19.1.

HRMS (ESI): calculated for $C_{14}H_{16}O_2Na$ ($[M+Na]^+$) 239.1042, found 239.1048.

2-Isopropyl-4-methylnaphthalen-1-ol (455)



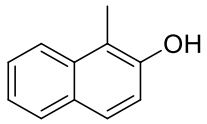
Triethyl silane (0.18 mL, 1.14 mmol) was added to a solution of 2-(2-hydroxypropan-2-yl)-4-methylnaphthalen-1-ol (**454**) (24.7 mg, 0.11 mmol) in DCM (0.54 mL) at rt under inert atmosphere. Then, trifluoroacetic acid (87µL, 1.14 mmol) was added to the mixture and the reaction was stirred for 40 min. Next, the solvent was removed under reduced pressure and the crude was dissolved in DCM and washed with an aqueous saturated solution of sodium bicarbonate, and water. The organic layer was dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography in a neutral silica (heptane/EtOAc : 10/1) to afford 2-isopropyl-4-methylnaphthalen-1-ol (**455**) in 63% yield (14.4 mg, 0.07 mmol), as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.20 – 8.12 (m, 1H), 7.96 – 7.88 (m, 1H), 7.54 – 7.46 (m, 2H), 7.19 (s, 1H), 5.08 (s, 1H), 3.37 – 3.26 (m, 1H), 2.63 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.6, 131.9, 126.7, 125.4, 125.2, 124.9, 124.7, 124.3, 121.7, 27.1, 23.0, 19.2.

HRMS (ESI): calculated for $C_{14}H_{16}O$ ($[M+H]^+$) 221.0936, found 221.0937.

1-Methylnaphthalen-2-ol (470)[227]



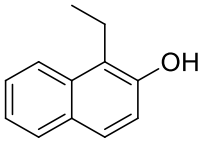
470 was synthesized followed a reported method described in the literature.[227] Ethyl chloroformate (EtO_2CCl, 1.3 mL, 13.82 mmol) was added at 0 ºC to a solution of 2-hydroxy-1-naphthoic acid (**469**) (1.0 g, 5.31 mmol) and Et_3N (1.9 mL, 13.82 mmol) in THF (33 mL). The reaction mixture was stirred for 3 hours at 0 ºC and the resulting white precipitate was filtered off and washed with THF. The combined filtrates were concentrated to dryness under reduced pressure and re-dissolved in THF (33 mL). Then, a solution of sodium borohydride ($NaBH_4$, 1.6 g, 42.48 mmol) in H_2O (33 mL) was carefully added at 0 ºC to the crude solution and the mixture was

[227] F. Mazzini, P. Salvadori, *Synthesis* **2005**, *15*, 2479-2481.

stirred 3 hours at 0 ºC. After that, the temperate of the reaction was risen to rt and stirred an additional hour at rt. The reaction was quenched with an aqueous solution of HCl 1M and THF was evaporated under reduced pressure. The aqueous layer was extracted with EtOAc (x3) and the organic layer was dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 9/1) to give 1-methylnaphthalen-2-ol (**470**) in 56% yield (477.4 mg, 3.02 mmol), as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.92 (d, *J* = 8.5 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.63 (d, *J* = 8.8 Hz, 1H), 7.50 (ddd, *J* = 8.4, 6.8, 1.4 Hz, 1H), 7.34 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 1H), 4.81 (s, 1H), 2.54 (s, 3H).

1-Ethylnaphthalen-2-ol (472)[228]

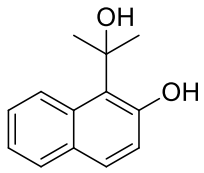


472 was synthesized followed a reported method described in the literature.[228] To a suspension of zinc (456.4 mg, 6.98 mmol) and $HgCl_2$ (46.5 mg, 0.17 mmol) in water (0.8 mL), HCl 37% (20 µL) was added and the mixture was stirred 5 min. After that, toluene (0.6 mL), HCl 37% (0.7 mL) and 1-(2-hydroxynaphthalen-1-yl)ethanone (**471**) (200.4 mg, 1.07 mmol) were successively added and the mixture was stirred for 16 h at 110 ºC. The reaction was cooled to rt, the phases were separated and the aqueous phase was extracted with EtOAc (x3). The organic phases were dried over Na_2SO_4 anhydrous and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 20/1) to give 1-ethylnaphthalen-2-ol (**472**) in 87% yield (161.0 mg, 0.93 mmol), as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.97 (d, *J* = 8.6 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.07 (d, *J* = 8.8 Hz, 1H), 4.92 (bs, 1H), 3.09 (q, *J* = 7.6 Hz, 2H), 1.31 (t, *J* = 7.6 Hz, 3H).

[228] Patent, WO2012/101244, 2012 A1.

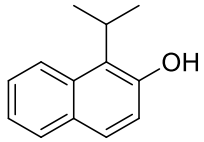
1-(2-Hydroxypropan-2-yl)naphthalen-2-ol (473)[229]



To a solution of 2-hydroxy-1-naphthaldehyde (**472**) (199.6 mg, 1.07 mmol) in dry THF (2.1 mL), MeMgBr (3M in Et_2O, 0.87 mL, 7.52 mmol) was added dropwise under inert atmosphere. The reaction was stirred 3 hours at reflux, cooled in an ice/water bath and quenched with an aqueous solution of NH_4Cl saturated, carefully. The mixture was extracted with EtOAc (x3) and the organic layer was dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography in a neutral silica (heptane/EtOAc : 9/1) to give 1-(2-hydroxypropan-2-yl)naphthalen-2-ol (**473**) in 80% yield (173.9 mg, 0.86 mmol), as a white solid.

^{1}H NMR (300 MHz, $CHCl_3$) δ: 7.92 (d, *J* = 8.7 Hz, 1H), 7.78 – 7.73 (m, 1H), 7.65 (d, *J* = 8.8 Hz, 1H), 7.46 – 7.39 (m, 1H), 7.32 – 7.26 (m, 1H), 7.09 (d, *J* = 8.8 Hz, 1H), 2.03 (s, 5H).

1-Isopropylnaphthalen-2-ol (474)[230]

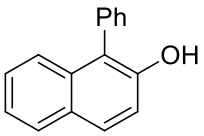


To a solution of 1-(2-hydroxypropan-2-yl)naphthalen-2-ol (**473**) (135.2 mg, 0.67 mmol) in MeOH (9.6 mL), 10% Pd/C (13.6 mg, 10% w) and acetic acid (38 µL, 067 mmol) were added at rt. The mixture was saturated with H_2 and stirred under 1 atm. of H_2 (a balloon) for 16 hours at rt. Then, the crude was filter through a short-pad column in the dark (heptane/EtOAc : 9/1) to give 1-isopropylnaphthalen-2-ol (**474**) in 94% yield (117.6 mg, 0.63 mmol), as an unstable colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.12 (d, *J* = 8.7 Hz, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 7.6 Hz, 1H), 6.98 (d, *J* = 8.7 Hz, 1H), 4.82 (s, 1H), 3.98 – 3.86 (m, 1H), 1.54 (s, 3H), 1.51 (s, 3H).

[229] J. Carnduff, P. A. Brady, *J. Chem. Res. (S)* **1977**, *9*, 235
[230] R. Yadav, A. Sakthivel, *New J. Chem.* **2016**, *40*, 2886-2894

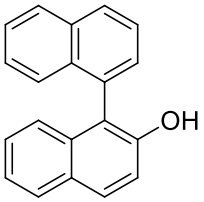
1-Phenylnaphthalen-2-ol (476a)[231]



476a was synthesized followed a reported method described in the literature.[231] In a dried sealed tube, 1-bromonaphthalen-2-ol (**475**) (104.1 mg, 0.47 mmol), phenylboronic acid (109.3 mg, 0.89 mmol), K_2CO_3 (130.6 mg, 0.94 mmol) and $Pd(PPh_3)_4$ (26.0 mg, 0.02 mg) were dissolved in a mixture of deoxygenated toluene (4.5 mL), ethanol (0.9 mL) and water (1.0 mL). The mixture was stirred 20 h at 90 ºC and, then, cooled to rt. The organic layer was separated and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 20/1) to give 1-phenylnaphthalen-2-ol (**476a**) in 69% yield (70.9 mg, 0.32 mmol), as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.88 – 7.81 (m, 2H), 7.65 – 7.58 (m, 2H), 7.56 – 7.49 (m, 1H), 7.48 – 7.42 (m, 3H), 7.40 – 7.33 (m, 2H), 7.30 (d, *J* = 8.9 Hz, 1H), 5.19 (br, 1H).

[1,1'-binaphthalen]-2-ol (476b)[232]



In a dried sealed tube, 1-bromonaphthalen-2-ol (**475**) (100 mg, 0.45 mmol), naphthalen-1-ylboronic acid (154.2 mg, 0.90 mmol), K_2CO_3 (130.6 mg, 0.94 mmol) and $Pd(PPh_3)_4$ (26.0 mg, 0.02 mg) were dissolved in a mixture of deoxygenated toluene (4.5 mL), ethanol (0.9 mL) and water (1.0 mL). The mixture was stirred 20 h at 90 ºC and, then, cooled to rt. The organic layer was separated and the aqueous layer was extracted with EtOAc (x3). The combined organic layers were dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 40/1) to give [1,1'-binaphthalen]-2-ol (**476b**) in 41% yield (69.7 mg, 0.26 mmol), as a white solid.

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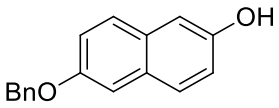
[231] I. Khan, S. R. Chidipudi, H. W. Lam, *Chem. Commun.* **2015**, *51*, 2613-2616.
[232] H. Kajita, A. Togni, *ChemistrySelect* **2017**, *2*, 1117- 1121

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.04 (d, *J* = 8.2 Hz, 2H), 7.99 (d, *J* = 8.3 Hz, 2H), 7.91 (d, *J* = 8.9 Hz, 2H), 7.87 (d, *J* = 7.9 Hz, 2H), 7.67 (dd, *J* = 8.2, 7.0 Hz, 2H), 7.58 – 7.50 (m, 4H), 7.42 – 7.30 (m, 8H), 7.28 – 7.21 (m, 3H), 7.10 (d, *J* = 8.4 Hz, 2H), 4.91 (s, 2H).

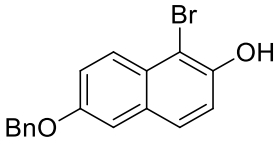
6-(Benzyloxy)naphthalen-2-ol (478)[233]



478 was synthesized followed a reported method described in the literature.[233] To a solution of naphthalene-2,6-diol (**477**) (1.0 g, 6.25 mmol) and K_2CO_3 (718.6 mg, 5.20 mmol) in DMF (3.9 mL), BnBr (0.62 mL, 5.22 mmol) was added at 0 ºC. The reaction was stirred 24 hours at rt, quenched with water and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 9/1) to give 6-(benzyloxy)naphthalen-2-ol (**478**) in 36% yield (477.4 mg, 1.91 mmol), as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.62 (t, *J* = 8.7 Hz, 2H), 7.51 – 7.47 (m, 2H), 7.44 – 7.31 (m, 3H), 7.23 – 7.18 (m, 2H), 7.12 – 7.05 (m, 2H), 5.15 (s, 2H), 4.72 (s, 1H).

6-(Benzyloxy)-1-bromonaphthalen-2-ol (479)



To a solution of 6-(benzyloxy)naphthalen-2-ol (**478**) (101.2 mg, 0.40 mmol) in DCM (2.0 mL), NBS (71.1 mg, 0.40 mmol) was added. The reaction was stirred 5 min at rt, quenched with water and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 10/1) to give 6-(benzyloxy)-1-bromonaphthalen-2-ol (**479**) in 79% yield (104.7 mg, 0.32 mmol), as a white solid.

mp: 107.6 – 108.4 ºC

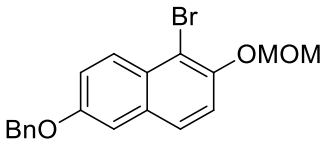
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.96 (d, *J* = 9.2 Hz, 1H), 7.61 (d, *J* = 8.9 Hz, 1H), 7.52 – 7.47 (m, 2H), 7.45 – 7.30 (m, 5H), 7.23 (d, *J* = 8.9 Hz, 1H), 7.20 (d, *J* = 2.5 Hz, 1H), 5.74 (s, 1H), 5.17 (s, 2H).

[233] Z. He, G. Ye, W. Jiang, *Chem. Eur. J.* **2015**, *21*, 3005-3012.

^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.7, 149.1, 136.8, 130.6, 128.8, 128.2, 128.1, 127.8, 127.7, 127.1, 120.6, 117.6, 108.1, 106.4, 70.3.

HRMS (EI): calculated for $C_{17}H_{13}O_2Br$ ([M]$^+$) 328.0099, found 328.0099.

6-(Benzyloxy)-1-bromo-2-(methoxymethoxy)naphthalene (480)



To a solution of 6-(benzyloxy)-1-bromonaphthalen-2-ol (**479**) (487.9 mg, 1.48 mmol) and K_2CO_3 (819,5 mg, 5.93 mmol) in DMF (2.5 mL), MOMCl (0.17 mL, 2.22 mmol) was added at 0 ºC under inert atmosphere. The reaction was stirred 3 hours at rt, quenched with water and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 10/1) to give **480** in 86% yield (474.8 mg, 1.27 mmol), as a white solid.

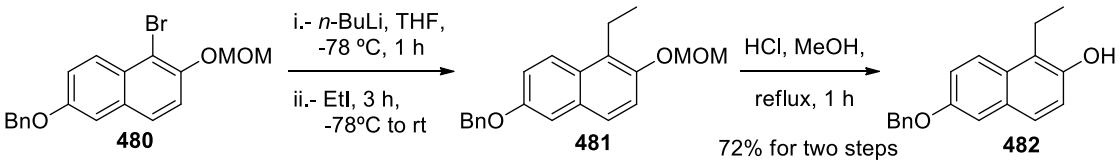
mp: 89.1 – 92.0 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.16 (d, *J* = 9.3 Hz, 1H), 7.65 (d, *J* = 9.0 Hz, 1H), 7.49 (d, *J* = 7.0 Hz, 2H), 7.45 – 7.29 (m, 5H), 7.19 (d, *J* = 2.5 Hz, 1H), 5.32 (s, 2H), 5.18 (s, 2H), 3.58 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.2, 150.4, 136.8, 131.6, 128.7, 128.6, 128.3, 128.2, 127.6, 127.6, 120.7, 118.0, 111.0, 107.5, 96.0, 70.2, 56.6.

HRMS (EI): calculated for $C_{19}H_{17}O_3Br$ ([M]$^+$) 372.0361, found 372.0374.

6-(Benzyloxy)-1-ethylnaphthalen-2-ol (482)



6-(Benzyloxy)-1-ethyl-2-(methoxymethoxy)naphthalene (**481**): In a dry flask **480** (99.8 mg, 0.27 mmol) was dissolved in dry THF (0.9 mL) and cooled to -78 ºC. *n*-BuLi (29.7 µL, 0.32 mmol) was added dropwise to the solution at -78 ºC and the reaction was stirred 1 h at -78 ºC, observing a change of color in the reaction from colorless to yellow. Then, EtI (67.4 µL, 0.67 mmol) was

added dropwise to the mixture at -78 ºC and the reaction was stirred at rt for 3 h. The reaction was quenched with an aqueous saturated solution of NH_4Cl and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated to dryness under reduced pressure to give **481** as a colorless oil, which was used in the next step without further purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.96 (d, *J* = 9.3 Hz, 1H), 7.61 (d, *J* = 9.0 Hz, 1H), 7.56 – 7.50 (m, 3H), 7.48 – 7.34 (m, 3H), 7.30 (dd, *J* = 9.3, 2.7 Hz, 1H), 7.23 (d, *J* = 2.7 Hz, 1H), 5.30 (s, *J* = 1.8 Hz, 2H), 5.19 (s, *J* = 2.7 Hz, 2H), 3.58 (s, 3H), 3.16 (q, *J* = 7.5 Hz, 2H), 1.31 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.3, 150.5, 137.2, 131.1, 128.7, 128.3, 128.1, 127.7, 127.4, 126.1, 125.2, 119.3, 117.3, 108.0, 95.6, 70.1, 56.2, 18.7, 14.9.

HRMS (EI): calculated for $C_{21}H_{22}O_3$ ($[M]^+$) 322.1569, found 322.1566.

6-(Benzyloxy)-1-ethylnaphthalen-2-ol (**482**): **481** was dissolved in MeOH (0.54 mL) and 4 drops of HCl 37% were added to the solution. The reaction was stirred 1 hour at reflux, cooled to rt and quenched with water. The mixture was extracted with EtOAc and the organic layer was dried over $MgSO_4$ and concentrated to dryness under reduced pressure The crude was purified by flash chromatography (heptane/EtOAc : 20/1) to give 6-(benzyloxy)-1-ethylnaphthalen-2-ol in (**482**) 72% yield for the two steps (53.4 mg, 0.19 mmol), as a white solid.

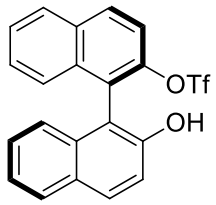
mp: 115.7 – 117.2 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.87 (d, *J* = 9.3 Hz, 1H), 7.53 – 7.47 (m, 3H), 7.44 – 7.30 (m, 3H), 7.28 – 7.23 (m, 1H), 7.19 (d, *J* = 2.6 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 1H), 5.16 (s, 2H), 4.66 (s, 1H), 3.04 (q, *J* = 7.6 Hz, 2H), 1.28 (t, *J* = 7.6 Hz, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 154.9, 148.7, 137.2, 130.5, 128.7, 128.4, 128.1, 127.7, 126.3, 124.6, 122.3, 119.4, 118.3, 108.5, 70.2, 18.5, 14.4.

HRMS (EI): calculated for $C_{19}H_{18}O_2$ ($[M]^+$) 278.1307, found 278.1307.

(*R*)-2'-Hydroxy-[1,1'-binaphthalen]-2-yl trifluoromethanesulfonate (501)[234]

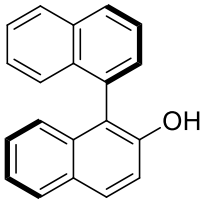


[234] V. H. G. Rohde, M. F. Müller, M. Oestreich, *Organometallics* **2015**, *34*, 3358-3373.

(*R*)-**501** was synthesized followed a reported method described in the literature.[234] To a solution of (*R*)-(+)-1,1'-bi-2-naphthol (50.6 mg, 0.18 mmol) in DCM (1.0 mL), a solution of DIPEA (29.4 µL, 0.18 mmol) in DCM (0.3 mL) and a solution of Tf_2O (30.5 µL, 0.18 mmol) in DCM (0.3 mL) were added slowly at 0 ºC at the same time under inert atmosphere. The reaction was stirred 12 hours at rt and quenched with a 10% aqueous solution of HCl. Then, the mixture was extracted with DCM (x3) and the organic layer was washed with an aqueous saturated solution of $NaHCO_3$ and with an aqueous saturated solution of NaCl. The organic phase was dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 9/1) to give (*R*)-**501** in 67% yield (49.5 mg, 0.12 mmol), as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.89 – 7.82 (m, 2H), 7.66 – 7.57 (m, 2H), 7.57 – 7.42 (m, 4H), 7.41 – 7.34 (m, 2H), 7.32 (d, *J* = 8.9 Hz, 1H), 5.21 (s, 1H).

(*R*)-[1,1'-binaphthalen]-2-ol (476b)[235]

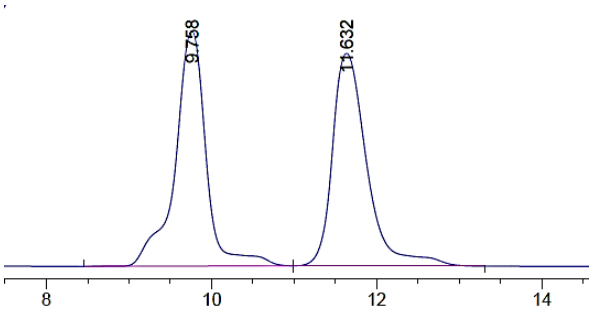


(*R*)-**476b** was synthesized followed a reported method described in the literature.[235] A mixture of (*R*)-**501** (82.4 mg, 0.20 mmol), 10% Pd/C (21 mg, 0.20 mmol) and DIPEA (69.7 µL, 0.40 mmol) were dissolved in EtOH (0.91 mL). The suspension was saturated with H_2 gas and stirred 7 hours at rt under H_2 gas (1 atm, a balloon). The reaction was filtered through Celite® plug and the Celite® was washed with EtOAc. The crude was concentrated to dryness under reduced pressure and purified by flash chromatography (heptane/EtOAc : 20:1) to give (*R*)-[1,1'-binaphthalen]-2-ol (**476b**) in 66% yield (35.1 mg, 0.13 mmol), as a white solid.

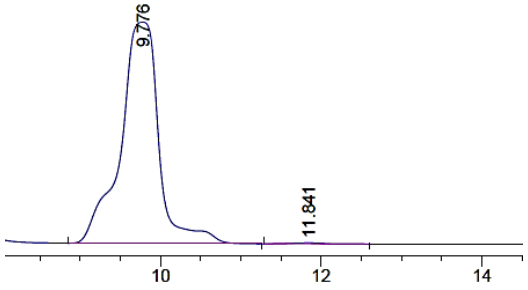
^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.04 (d, *J* = 8.2 Hz, 2H), 7.99 (d, *J* = 8.3 Hz, 2H), 7.91 (d, *J* = 8.9 Hz, 2H), 7.87 (d, *J* = 7.9 Hz, 2H), 7.67 (dd, *J* = 8.2, 7.0 Hz, 2H), 7.58 – 7.50 (m, 4H), 7.43 – 7.30 (m, 8H), 7.28 – 7.21 (m, 3H), 7.10 (d, *J* = 8.4 Hz, 2H), 4.91 (s, 2H).

HPLC: *Daicel Chiralpak* IB, *n*-hexane / 2-propanol: 80/20, flow rate: 0.5 mL/min, λ: 254 nm, t_R (major): 9.78 min, t_R (minor): 11.84 min., T: 25 °C, 99% ee.

[235] Y.-N. Ma, H.-Y. Zhang, S.-. Yang, *Org. Lett.* **2015**, *17*, 2034-2037.



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.758	BV	0.3928	4.05956e4	1543.55066	50.0758
2	11.632	VB	0.4444	4.04727e4	1395.39001	49.9242



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.776	VB	0.4994	7.62628e4	2284.65723	99.5107
2	11.841	BB	0.4644	374.95456	12.48319	0.4893

3.3.2.2. Oxidative dearomatization with Oxone/$NaHCO_3$/acetone as a source of dimethyldioxirane (DMDO)

Method A: General procedure for the oxidative dearomatization at room temperature.

$NaHCO_3$ and the corresponding phenol or naphtol derivative were dissolved in acetone (0.1 M) and Milli-Q water (0.1 M). A solution of Oxone® in Milli-Q water was added dropwise to the mixture at rt for 1 h, using a syringe pump (*Figure 3.X*). After that, the crude mixture was extracted with DCM (x3), dried over $MgSO_4$ and concentrated to dryness, under reduced pressure. The residue was purified by flash chromatography (the specific conditions are indicated in each case) to give the desired product.

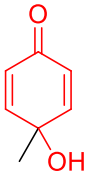
Method B: General procedure for the oxidative dearomatization at 0 ºC.

$NaHCO_3$ and the corresponding phenol or naphtol derivative were dissolved in acetone (0.1 M) and Milli-Q water (0.1 M). A solution of Oxone® in Milli-Q water was added dropwise to the mixture at 0 ºC for 1h, using a syringe pump (*Figure 3.X*), and stirred at rt for an additional hour. After that, the crude mixture was extracted with DCM (x3), dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The residue was purified by flash chromatography (the specific conditions are indicated in each case) to give the desired product.

Figure 3.101. Addition of an aqueous solution of Oxone® to the reaction mixture, using a syringe pump.

3.3.2.2.1. Oxidative dearomatization of phenol derivatives

4-Hydroxy-4-methylcyclohexa-2,5-dienone (366)[236]



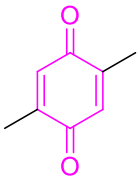
para-Cresol (**364**) (22.9 mg, 0.21 mmol) and $NaHCO_3$ (310.8 mg, 3.70 mmol) were dissolved in acetone (3.6 mL) and Milli-Q water (3.6 mL). An aqueous solution of Oxone® (454.8 mg, 1.50 mmol) in Milli-Q water (3.6 mL) was added dropwise to the mixture for 1h at rt, using a syringe pump (*Figure 3.31*). After that, the crude was extracted with DCM (x3), dried over $MgSO_4$ and

[236] M. González-López, A. Urbano, M. C. Carreño, *Angew Chem Int Ed* **2006**, *45*, 2737–2741

concentrated to dryness under reduced pressure. The residue was purified by flash chromatography (heptane/EtOAc : 2/1) to give *para*-quinol **366** in 19% yield (5.0 mg, 0.04 mmol), as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.88 (d, *J* = 10.1 Hz, 2H), 6.14 (d, *J* = 10.1 Hz, 2H), 2.01 (s, 1H), 1.49 (s, 3H).

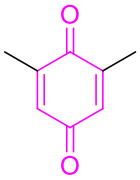
2,5-Dimethylcyclohexa-2,5-diene-1,4-dione (370)[237]



2,5-Dimethylphenol (**369**) (40.2 mg, 0.33 mmol) and $NaHCO_3$ (277.2 mg, 3.30 mmol) were dissolved in acetone (6.6 mL) and Milli-Q water (6.6 mL). An aqueous solution of Oxone® (405.7 mg, 1.32 mmol) in Milli-Q water (6.6 mL) was added dropwise to the mixture for 30 min at 0 ºC, using a syringe pump (*Figure 3.31*), and stirred for additional 45 min at rt. After that, the crude was extracted with DCM (x3), dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The residue was purified by flash chromatography (heptane/EtOAc : 40/1) to afford quinone **370** in 32% yield (14.3 mg, 0.11 mmol), as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.59 – 6.56 (m, 1H), 2.01 (s, 3H).

2,6-Dimethylcyclohexa-2,5-diene-1,4-dione (372)[237]



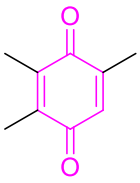
2,6-Dimethylphenol (**371**) (40.6 mg, 0.33 mmol) and $NaHCO_3$ (277.2 mg, 3.30 mmol) were dissolved in acetone (6.6 mL) and Milli-Q water (6.6 mL). An aqueous solution of Oxone® (405.7 mg, 1.32 mmol) in Milli-Q water (6.6 mL) was added dropwise to the mixture for 30 min at 0 ºC, using a syringe pump, and stirred for additional 45 min at rt. After that, the crude was extracted with DCM (x3), dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The

[237] Y. Lin, B. Li, Z. Feng, Y. A. Kim, M. Endo, D. S. Su, *ACS Catal.* **2015**, *5*, 5921-5926.

residue was purified by flash chromatography (heptane/EtOAc : 40/1) to give quinone **372** in 39% yield (17.5 mg, 0.13 mmol), as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.55 (s, 1H), 2.05 (d, *J* = 1.4 Hz, 3H).

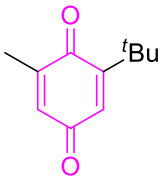
2,3,5-Trimethylcyclohexa-2,5-diene-1,4-dione (374)[237]



2,3,6-Trimethylphenol (**373**) (40.7 mg, 0.29 mmol) and $NaHCO_3$ (235.2 mg, 2.80 mmol) were dissolved in acetone (5.6 mL) and Milli-Q water (5.6 mL). An aqueous solution of Oxone® (343.1 mg, 1.12 mmol) in Milli-Q water (5.6 mL) was added dropwise to the mixture for 30 min at 0 ºC, using a syringe pump, and stirred for additional 45 min at rt. After that, the crude was extracted with DCM (x3), dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The residue was purified by flash chromatography (heptane/EtOAc : 40/1) to give quinone **374** in 43% yield (17.9 mg, 0.12 mmol), as a yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.54 (s, 1H), 2.02 (s, 6H), 2.00 (s, 3H).

2-(*tert*-Butyl)-6-methylcyclohexa-2,5-diene-1,4-dione (376)[238]



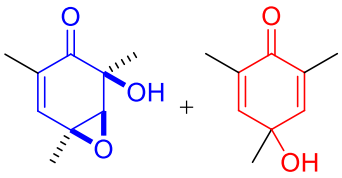
2-*tert*-Butyl-6-methylphenol (**375**) (41 µL, 0.24 mmol) and $NaHCO_3$ (201.6 mg, 2.40 mmol) were dissolved in acetone (4.8 mL) and Milli-Q water (4.8 mL). An aqueous solution of Oxone® (295.1 mg, 0.96 mmol) in Milli-Q water (4.8 mL) was added dropwise to the mixture for 30 min at 0 ºC, using a syringe pump, and stirred for additional 45 min at rt. After that, the crude was extracted with DCM (x3), dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The

[238] R. Bernini, E. Mincione, M. Barontini, G. Fabrizi, M. Pasqualetti, S. Tempesta, *Tetrahedron* **2006**, *62*, 7733-7737.

residue was purified by flash chromatography (heptane/EtOAc 40/1) to afford quinone **376** in 35% yield (15.1 mg, 0.09 mmol), as a yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.53 (s, 2H), 2.04 (d, *J* = 0.9 Hz, 3H), 1.27 (s, 9H).

(1*R,2*S**,6*S**)-2-Hydroxy-2,4,6-trimethyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (377)[239] and 4-hydroxy-2,4,6-trimethylcyclohexa-2,5-dienone (342)[236]**



Following **Method B**, epoxy *ortho*-quinol **377** (27.7 mg, 0.16 mmol, 55% yield, white solid) and *para*-quinol **342** (10.7 mg, 0.07 mmol, 23% yield, white solid) were obtained from 2,4,6-trimethylphenol (**341**) (40.0 mg, 0.29 mmol) and $NaHCO_3$ (189.0 mg, 2.25 mmol), and a solution of Oxone® (279.8 mg, 0.90 mmol) in Milli-Q water (6.0 mL). The crude mixture was purified by flash chromatography (DCM/ether : 40/1).

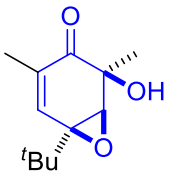
(1*R**,2*S**,6*S**)-2-Hydroxy-2,4,6-trimethyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (**377**):[239]

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.72 – 6.65 (m, 1H), 3.65 (s, 1H), 3.48 (s, 1H), 1.85 (d, *J* = 1.6 Hz, 3H), 1.56 (s, 3H), 1.32 (s, 3H).

4-Hydroxy-2,4,6-trimethylcyclohexa-2,5-dienone (**342**):[236]

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.62 (s, 2H), 1.86 (s, 6H), 1.43 (s, 3H).

(1R*,2S*,6R*)-6-(*tert*-Butyl)-2-hydroxy-2,4-dimethyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (397)



Following **Method A**, epoxy *ortho*-quinol **397** was obtained in 66% yield (30.3 mg, 0.14 mmol), as a colorless oil, from 4-(*tert*-butyl)-2,6-dimethylphenol (**379**) (40.0 mg, 0.22 mmol), $NaHCO_3$ (184.8

[239] S. Quideau, G. Lyvinec, M. Marguerit, K. Bathany, A. Ozanne-Beaudenon, T. Buffeteau, D. Cavagnat, A. Chénedé, *Angew. Chem. Int. Ed.* **2009**, *48*, 4605-4609.

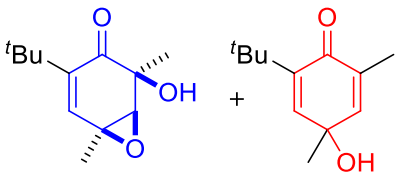
mg, 2.20 mmol) and a solution of Oxone® (275.9 mg, 0.90 mmol) in Milli-Q water (4.4 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 5/1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.98 – 6.94 (m, 1H), 3.67 (d, *J* = 0.8 Hz, 1H), 3.66 (s, 1H), 1.89 (d, *J* = 1.5 Hz, 3H), 1.30 (s, 3H), 1.04 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 199.9, 141.8, 136.6, 74.6, 62.7, 59.4, 32.1, 25.5, 25.0, 16.1.

HRMS (ESI): calculated for $C_{12}H_{18}O_3Na$ ([M+Na]$^+$) 233.1148, found 233.1146.

(1*R,2*S**,6*S**)-4-(*tert*-Butyl)-2-hydroxy-2,6-dimethyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (399) and 2-(*tert*-butyl)-4-hydroxy-4,6-dimethylcyclohexa-2,5-dienone (400)[240]**



Following **Method B**, epoxy *ortho*-quinol **399** (45.1 mg, 0.21 mmol, 46% yield, colorless oil) and *para*-quinol **400** (40.6 mg, 0.21 mmol, 45% yield, white solid) were obtained from 2-(*tert*-butyl)-4,6-dimethylphenol (**398**) (86.1 mg, 0.48 mmol), $NaHCO_3$ (304.1 mg, 3.62 mmol) and a solution of Oxone® (446.6 mg, 1.45 mmol) in Milli-Q water (9.7 mL). The crude mixture was purified by flash chromatography (DCM/EtOAc : 20/1).

(1*R**,2S*,6*S**)-4-(*tert*-Butyl)-2-hydroxy-2,6-dimethyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (**399**):

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.55 (s, 1H), 3.92 (s, 1H), 3.46 (s, 1H), 1.59 (s, 3H), 1.28 (s, 3H), 1.17 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 200.0, 148.3, 140.1, 76.0, 62.3, 54.5, 34.8, 29.0, 23.8, 21.3.

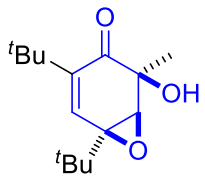
HRMS (ESI): calculated for $C_{12}H_{18}O_3Na$ ([M+Na]$^+$) 233.1154, found 233.1148.

2-(*tert*-Butyl)-4-hydroxy-4,6-dimethylcyclohexa-2,5-dienone (**400**):[240]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.62 (d, 1H), 6.57 (m, 1H), 1.85 (d, 3H), 1.43 (s, 3H), 1.22 (s, 9H).

[240] Y.-F. Liang, K. Wu, Z. Liu, X. Wang, Y. Liang, *Sci China Chem* **2015**, *58*, 1334-1339

(1*R,2*S**,6*R**)-4,6-Di-*tert*-butyl-2-hydroxy-2-methyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (402)**



Following **Method A**, epoxy *ortho*-quinol **402** was obtained in 67% yield (15.3 mg, 0.06 mmol), as a white solid, from 2,4-di-*tert*-butyl-6-methylphenol (**401**) (19.8 mg, 0.09 mmol), $NaHCO_3$ (114.7 mg, 1.36 mmol) and a solution of Oxone® (167.8 mg, 0.55 mmol) in Milli-Q water (0.9 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 20/1).

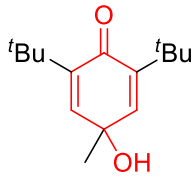
mp: 83.7 – 85.3 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 – 6.83 (m, 1H), 3.93 (s, 1H), 3.62 (d, *J* = 0.7 Hz, 1H), 1.25 (s, 3H), 1.20 (s, 9H), 1.04 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 200.4, 148.6, 137.6, 75.7, 62.6, 59.1, 35.1, 32.5, 29.1, 25.7, 24.0.

HRMS (ESI): calculated for $C_{15}H_{24}O_3Na$ ($[M+Na]^+$) 275.1617, found 275.1629.

2,6-Di-*tert*-butyl-4-hydroxy-4-methylcyclohexa-2,5-dienone (358)[240]



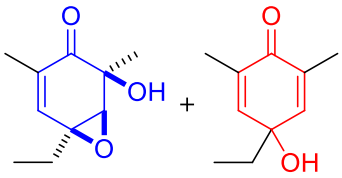
Using acetone. Following **Method A**, *para*-quinol **358** was obtained in 56% yield (24.5 mg, 0.10 mmol), as a white solid, from 2,6-(di-*tert*-butyl)-4-methylphenol (**357**) (40.0 mg, 0.18 mmol), $NaHCO_3$ (302.4 mg, 3.6 mmol) and a solution of Oxone® (446.4 mg, 1.44 mmol) in Milli-Q water (3.6 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 20/1).

Using 1,1,1-trifluoroacetone. 2,6-(Di-*tert*-butyl)-4-methylphenol (**357**) (40.0 mg, 0.18 mmol), $NaHCO_3$ (302.4 mg, 3.6 mmol) and 1,1,1-trifluoroacetone (0.17 mL, 1.7 mmol) were dissolved in acetonitrile (3.6 mL) and Milli-Q water (3.6 mL). A solution of Oxone® (446.4 mg, 1.44 mmol) in Milli-Q water (3.6 mL) was added dropwise to the mixture for 1h at rt, using a syringe pump (*Figure 3.31*). After that, the crude mixture was extracted with DCM (x3), dried over $MgSO_4$ and concentrated to dryness under reduced pressure. The residue was purified by flash

chromatography (heptane/EtOAc : 20/1) to give *para*-quinol **358** in 80% yield (34.5 mg, 0.15mmol), as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.55 (s, 2H), 1.89 (s, 1H), 1.40 (s, 3H), 1.21 (s, 18H).

(1*R,2*S**,6*S**)-6-Ethyl-2-hydroxy-2,4-dimethyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (403) and 4-ethyl-4-hydroxy-2,6-dimethylcyclohexa-2,5-dienone (404)**



Following **Method B**, epoxy *ortho*-quinol **403** (15.6 mg, 0.09 mmol, 64% yield, white solid) and *para*-quinol **404** (2.7 mg, 0.02 mmol, 12% yield, white solid) were obtained from 4-ethyl-2,6-dimethylphenol (**387**) (20.1 mg, 0.13 mmol), $NaHCO_3$ (109.2 mg, 1.30 mmol) and a solution of Oxone® (163.7 mg, 0.53 mmol) in Milli-Q water (1.3 mL). The crude mixture was purified by flash chromatography (DCM/EtOAc : 40/1).

(1*R**,2*S**,6*S**)-6-Ethyl-2-hydroxy-2,4-dimethyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (**403**):

mp: 64.6 – 65.3 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.76 – 6.70 (m, 1H), 3.65 (s, 1H), 3.49 (s, 1H), 2.00 – 1.88 (m, 2H), 1.87 (d, *J* = 1.6 Hz, 3H), 1.77 – 1.61 (m, 1H), 1.31 (s, 3H), 1.04 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 199.8, 143.3, 136.9, 74.9, 61.4, 58.2, 27.3, 25.0, 15.9, 9.3.

HRMS (ESI): calculated for $C_{10}H_{14}O_3Na$ ($[M+Na]^+$) 205.0835, found 205.0829.

4-Ethyl-4-hydroxy-2,6-dimethylcyclohexa-2,5-dienone (**404**):

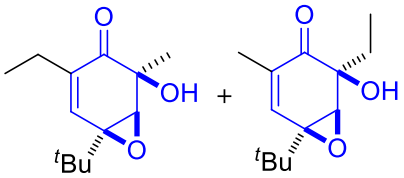
mp: 68.5 – 69.7 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54 (s, 3H), 1.89 (s, 9H), 1.75 (q, *J* = 7.5 Hz, 4H), 1.64 (s, 1H), 0.83 (t, *J* = 7.5 Hz, 5H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 187.0, 146.1, 135.1, 70.5, 33.2, 16.0, 8.3.

HRMS (ESI): calculated for $C_{10}H_{14}O_2Na$ ($[M+Na]^+$) 189.0886, found 189.0892.

(1*R,2*S**,6*R**)-6-(*tert*-Butyl)-4-ethyl-2-hydroxy-2-methyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (405) and (1*R**,2*S**,6*R**)-6-(*tert*-butyl)-2-ethyl-2-hydroxy-4-methyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (406)**



Following **Method A**, epoxy *ortho*-quinol **405** (20.6 mg, 0.09 mmol, 43% yield, white solid) and epoxy *ortho*-quinol **406** (24.4 mg, 0.11 mmol, 51% yield, colorless oil) were obtained from 4-(*tert*-butyl)-2-ethyl-6-methylphenol (**380**) (40.7 mg, 0.21 mmol), $NaHCO_3$ (220.5 mg, 2.62 mmol) and a solution of Oxone® (322.7 mg, 1.05 mmol) in Milli-Q water (2.1 mL). The crude mixture was purified by flash chromatography using neutral silica (heptane/EtOAc : 20/1 to 9/1).

(1*R**,2*S**,6*R**)-6-(*tert*-Butyl)-4-ethyl-2-hydroxy-2-methyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (**405**):

mp: 50.0 – 51.3 ºC

^{1}H NMR (300 MHz, CDCl3) δ 6.90 – 6.86 (m, 1H), 3.69 (s, 1H), 3.66 (d, J = 0.7 Hz, 1H), 2.42 – 2.19 (m, 2H), 1.28 (s, 3H), 1.04 (s, 9H), 1.04 (t, J = 7.4 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 199.8, 142.4, 139.9, 74.9, 62.7, 59.4, 32.3, 25.6, 24.8, 23.2, 12.5.

HRMS (ESI): calculated for $C_{13}H_{21}O_3$ ($[M+H]^+$) 225.1485, found 225.1478.

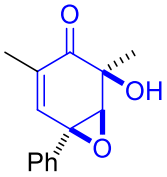
(1*R**,2*S**,6*R**)-6-(*tert*-Butyl)-2-ethyl-2-hydroxy-4-methyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (**406**):

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.93 (s, 1H), 3.67 (s, 2H), 1.87 (d, *J* = 1.3 Hz, 3H), 1.75 (dq, *J* = 15.0, 7.5 Hz, 1H), 1.49 (dq, *J* = 14.7, 7.5 Hz, 1H), 1.03 (s, 9H), 0.83 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 199.7, 141.7, 137.1, 77.7, 62.8, 59.0, 32.2, 31.0, 25.6, 16.0, 7.2.

HRMS (ESI): calculated for $C_{13}H_{20}O_3Na$ ($[M+Na]^+$) 247.1304, found 247.1297.

(1*R,2*S**,6*R**)-2-Hydroxy-2,4-dimethyl-6-phenyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (408)**



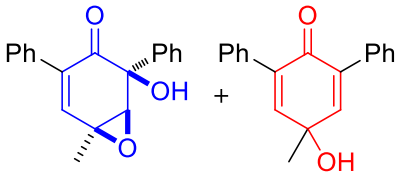
Following **Method A**, epoxy *ortho*-quinol **408** was obtained in 70% yield (16.1 mg, 0.07 mmol), as a colorless oil, from 3,5-dimethyl-[1,1'-biphenyl]-4-ol (**389**) (19.9 mg, 0.10 mmol), $NaHCO_3$ (84.0 mg, 1.00 mmol) and a solution of Oxone® (124.0 mg, 0.40 mmol) in Milli-Q water (1.0 mL). The crude mixture was purified by flash chromatography (heptane:EtOAc : 9:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 – 7.36 (m, 5H), 7.10 – 7.07 (m, 1H), 3.71 (s, 1H), 3.61 (d, *J* = 0.6 Hz, 1H), 1.97 (d, *J* = 1.6 Hz, 3H), 1.39 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 199.3, 142.9, 137.7, 137.6, 129.0, 128.6, 125.5, 74.7, 65.3, 57.6, 25.0, 16.2.

HRMS (ESI): calculated for $C_{14}H_{14}O_3Na$ ($[M+Na]^+$) 253.0835, found 253.0839.

(1*R,2*S**,6*S**)-2-Hydroxy-6-methyl-2,4-diphenyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (409) and 5'-hydroxy-5'-methyl-[1,1':3',1''-terphenyl]-2'(5'H)-one (410)[241]**



Following **Method B**, epoxy *ortho*-quinol **409** (3.7 mg, 0.01 mmol, 24% yield, white solid) and *para*-quinol **410** (7.0 mg, 0.02 mmol, 47% yield, white solid) were obtained from 5'-methyl-[1,1':3',1''-terphenyl]-2'-ol (**393**) (13.9 mg, 0.05 mmol), $NaHCO_3$ (53.4 mg, 0.64 mmol) and a solution of Oxone® (97.7 mg, 0.32 mmol) in Milli-Q water (0.5 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 4/1).

(1*R**,2*S**,6*S**)-2-Hydroxy-6-methyl-2,4-diphenyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (**409**):

mp: 111.4 – 113.2 ºC

[241] M. P. Hartshorn, R. J. Martyn, W. T. Robinson, K. H. Sutton, J. Vaughan, J. M. White, *Aust. J. Chem.* **1985**, *38*, 1613-1630.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.53 – 7.49 (m, 2H), 7.43 – 7.27 (m, 7H), 7.10 – 7.05 (m, 3H), 4.62 (s, 1H), 3.87 (s, 1H), 1.82 (s, 3H).

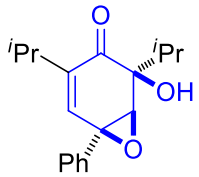
^{13}C NMR (75 MHz, $CDCl_3$) δ: 195.7, 143.8, 140.5, 137.3, 134.2, 129.2, 129.1, 129.0, 128.6, 127.9, 126.0, 79.6, 63.5, 55.7, 21.1.

HRMS (EI): calculated for $C_{19}H_{16}O_3$ ($[M]^+$) 292.1099, found 292.1086.

5'-Hydroxy-5'-methyl-[1,1':3',1''-terphenyl]-2'(5'H)-one (**410**):

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.47 – 7.34 (m, 10H), 6.98 (s, 2H), 1.65 (s, 3H), 1.64 (s, 1H).

(1*R,2*S**,6*R**)-2-Hydroxy-2,4-diisopropyl-6-phenyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (411)**



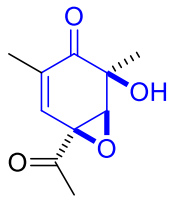
Following **Method A**, epoxy *ortho*-quinol **411** was obtained in 39% yield (8.7 mg, 0.03 mmol), as a colorless oil, from 3,5-diisopropyl-[1,1'-biphenyl]-4-ol (**396**) (20.0 mg, 0.08 mmol), $NaHCO_3$ (66.4 mg, 0.79 mmol) and a solution of Oxone® (96.7 mg, 0.31 mmol) in Milli-Q water (0.8 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 9/1).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.45 – 7.37 (m, 5H), 6.96 – 6.94 (m, 1H), 3.78 (s, 1H), 3.66 (d, *J* = 0.8 Hz, 1H), 2.94 (double of quintet, *J* = 6.9, 1.3 Hz, 1H), 1.99 (quintet, *J* = 6.9 Hz, 1H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.09 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 199.4, 148.6, 140.0, 138.1, 129.0, 128.5, 125.4, 79.5, 64.3, 57.9, 35.1, 28.3, 22.1, 21.1, 17.2, 16.7.

HRMS (ESI): calculated for $C_{18}H_{23}O_3$ ($[M+H]^+$) 287.1641, found 287.1647.

(1*R,2*S**,6*S**)-6-Acetyl-2-hydroxy-2,4-dimethyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (412)**



Following **Method B**, epoxy *ortho*-quinol **412** was obtained in 22% yield (9.9 mg, 0.05 mmol), as a white solid, from 4'-hydroxy-3',5'-dimethylacetophenone (**386**) (40.0 mg, 0.24 mmol), $NaHCO_3$ (151.2 mg, 1.80 mmol) and a solution of Oxone® (217.9 mg, 0.71 mmol) in Milli-Q water (4.8 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 5/1).

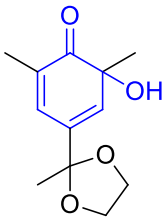
mp: 106.8 – 108.6 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.21 – 7.18 (m, 1H), 3.92 (d, *J* = 0.8 Hz, 1H), 2.15 (s, 3H), 1.92 (d, *J* = 1.6 Hz, 3H), 1.31 (s, 3H).

^{13}C NMR (75 MHz, DMSO) δ 203.7, 198.8, 137.6, 136.5, 74.7, 60.5, 59.1, 24.7, 23.2, 16.0.

HRMS (ESI): calculated for $C_{10}H_{12}O_4Na$ ([M+Na]$^+$) 219.0627, found 219.0631.

6-Hydroxy-2,6-dimethyl-4-(2-methyl-1,3-dioxolan-2-yl)cyclohexa-2,4-dienone (415)



Following **Method B**, *ortho*-quinol **415** was obtained in 64% yield (13.8 mg, 0.06 mmol), as a yellow solid, from **414** (20.0 mg, 0.10 mmol), $NaHCO_3$ (42.0 mg, 0.50 mmol) and a solution of Oxone® (61.5 mg, 0.20 mmol) in Milli-Q water (1.0 mL). The crude mixture was purified by flash chromatography using neutral silica (heptane/EtOAc : 60/1).

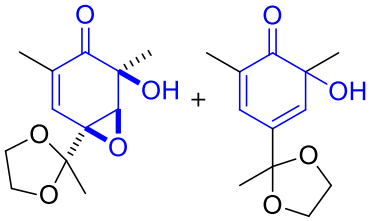
mp: 62.4 – 64.5 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 – 6.82 (m, 1H), 6.47 (d, *J* = 2.3 Hz, 1H), 4.03 – 3.98 (m, 2H), 3.88 – 3.81 (m, 2H), 3.23 (s, 1H), 1.94 (d, *J* = 1.4 Hz, 3H), 1.52 (s, 3H), 1.36 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 206.5, 137.8, 136.1, 133.9, 132.4, 107.4, 75.7, 64.8, 64.7, 29.2, 24.7, 15.3.

HRMS (ESI): calculated for $C_{12}H_{16}O_4Na$ ([M+Na]$^+$) 247.0940, found 247.0948.

(1*R,2*S**,6*S**)-2-Hydroxy-2,4-dimethyl-6-(2-methyl-1,3-dioxolan-2-yl)-7-oxabicyclo[4.1.0]hept-4-en-3-one (416) and 6-hydroxy-2,6-dimethyl-4-(2-methyl-1,3-dioxolan-2-yl)cyclohexa-2,4-dienone (415)**



Following **Method A**, epoxy *ortho*-quinol **416** (11.6 mg, 0.05 mmol, 48% yield, white solid) and *ortho*-quinol **415** (6.0 mg, 0.03 mmol, 27% yield, yellow solid) were obtained from **414** (20.9 mg, 0.10 mmol), $NaHCO_3$ (161.3 mg, 1.92 mmol) and a solution of Oxone® (236.1 mg, 0.77 mmol) in Milli-Q water (1.3 mL). The crude mixture was purified by flash chromatography using neutral silica (DCM/EtOAc : 80/1).

(1*R**,2*S**,6*S**)-2-Hydroxy-2,4-dimethyl-6-(2-methyl-1,3-dioxolan-2-yl)-7-oxabicyclo[4.1.0]hept-4-en-3-one (**416**):

mp: 94.0 – 95.6 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (s, 1H), 4.07 – 3.94 (m, 4H), 3.72 (s, 1H), 3.64 (s, 1H), 1.90 (d, *J* = 1.5 Hz, 3H), 1.47 (s, 3H), 1.31 (s, 3H).

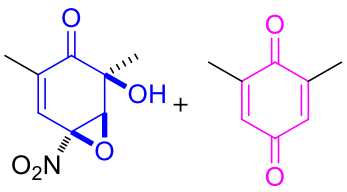
^{13}C NMR (75 MHz, $CDCl_3$) δ 199.6, 139.9, 137.7, 106.2, 74.6, 66.5, 65.7, 60.3, 58.4, 25.0, 22.8, 16.1.

HRMS (ESI): calculated for $C_{12}H_{16}O_5Na$ ($[M+Na]^+$) 263.0889, found 263.0894.

6-Hydroxy-2,6-dimethyl-4-(2-methyl-1,3-dioxolan-2-yl)cyclohexa-2,4-dienone (**415**):

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 – 6.82 (m, 1H), 6.47 (d, *J* = 2.3 Hz, 1H), 4.03 – 3.98 (m, 2H), 3.88 – 3.81 (m, 2H), 3.23 (s, 1H), 1.94 (d, *J* = 1.4 Hz, 3H), 1.52 (s, 3H), 1.36 (s, 3H).

(1*R,2*S**,6*S**)-2-Hydroxy-2,4-dimethyl-6-nitro-7-oxabicyclo[4.1.0]hept-4-en-3-one (418) and 2,6-dimethylcyclohexa-2,5-diene-1,4-dione (372)[237]**



Following **Method B**, epoxy *ortho*-quinol **418** (21.6 mg, 0.11 mmol, 44% yield, white solid) and quinone **372** (3.0 mg, 0.02 mmol, 9% yield, yellow solid) were obtained from 2,6-dimethyl-4-nitrophenol (**417**) (40.0 mg, 0.24 mmol), $NaHCO_3$ (151.2 mg, 1.80 mmol) and a solution of Oxone® (220.7 mg, 0.72 mmol) in Milli-Q water (2.4 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 4/1).

(1*R**,2*S**,6*S**)-2-Hydroxy-2,4-dimethyl-6-nitro-7-oxabicyclo[4.1.0]hept-4-en-3-one (**418**):

mp: 121.0 – 122.7 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 – 7.41 (m, 1H), 4.26 (s, 1H), 3.64 (s, 1H), 2.02 (d, *J* = 1.5 Hz, 3H), 1.39 (s, 3H).

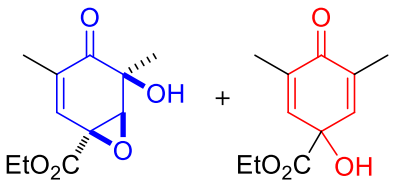
^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 139.4, 131.1, 81.1, 74.2, 61.2, 24.5, 16.3.

HRMS (ESI): calculated for $C_8H_9NO_5Na$ ([M+Na]$^+$) 222.0372, found 222.0381.

2,6-Dimethylcyclohexa-2,5-diene-1,4-dione (**372**):[237]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.55 (s, 1H), 2.05 (d, *J* = 1.4 Hz, 3H).

(1*S,5*S**,6*R**)-Ethyl-5-hydroxy-3,5-dimethyl-4-oxo-7-oxabicyclo[4.1.0]hept-2-ene-1-carboxylate (419) and ethyl 1-hydroxy-3,5-dimethyl-4-oxocyclohexa-2,5-dienecarboxylate (420)**



Following **Method B**, epoxy *ortho*-quinol **419** (8.1 mg, 0.03 mmol, 34% yield, colorless oil) and *para*-quinol **420** (6.6 mg, 0.03 mmol, 30% yield, colorless oil) were obtained from ethyl 4-hydroxy-3,5-dimethylbenzoate (**385**) (20.5 mg, 0.10 mmol), $NaHCO_3$ (86.5 mg, 1.03 mmol) and a solution of

Oxone® (126.6 mg, 0.41 mmol) in Milli-Q water (1.0 mL). The crude mixture was purified by flash chromatography (DCM to DCM/EtOAc : 100/1).

(1*S**,5*S**,6*R**)-Ethyl-5-hydroxy-3,5-dimethyl-4-oxo-7-oxabicyclo[4.1.0]hept-2-ene-1-carboxylate (**419**):

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 – 7.24 (m, 1H), 4.35 – 4.23 (m, 2H), 4.00 (s, 1H), 3.68 (s, 1H), 1.93 (d, *J* = 1.5 Hz, 3H), 1.34 (s, 3H), 1.33 (t, *J* = 7.10, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9, 167.6, 137.7, 136.8, 74.6, 62.8, 61.3, 53.6, 24.7, 16.1, 14.2.

HRMS (ESI): calculated for $C_{11}H_{14}O_5Na$ ([M+Na]$^+$) 249.0733, found 249.0742.

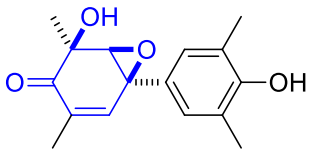
Ethyl 1-hydroxy-3,5-dimethyl-4-oxocyclohexa-2,5-dienecarboxylate (**420**):

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.45 (s, 2H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 1H), 1.92 (s, 6H), 1.23 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 186.5, 172.4, 140.1, 137.0, 71.7, 63.7, 16.0, 14.1.

HRMS (ESI): calculated for $C_{11}H_{14}O_4Na$ ([M+Na]$^+$) 233.0784, found 233.0788.

(1*R,2*S**,6*R**)-2-Hydroxy-6-(4-hydroxy-3,5-dimethylphenyl)-2,4-dimethyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (422)**



Following **Method A**, epoxy *ortho*-quinol **422** was obtained in 62% yield (14.0 mg, 0.05 mmol), as a colorless oil, from 3,3',5,5'-tetramethyl-[1,1'-biphenyl]-4,4'-diol (**421**) (20.0 mg, 0.08 mmol), $NaHCO_3$ (68.9 mg, 0.82 mmol) and a solution of Oxone® (101.5 mg, 0.33 mmol) in Milli-Q water (0.8 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 1/2).

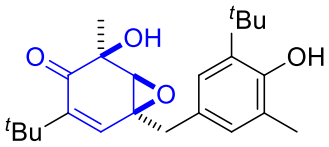
mp: 185.1 – 187.7 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.63 (s, 1H), 7.50 (s, 2H), 5.03 (d, *J* = 1.5 Hz, 1H), 4.12 (s, 1H), 3.12 (s, 1H), 2.11 (s, *J* = 1.4 Hz, 6H), 2.10 (s, 3H), 1.30 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 201.3, 187.3, 139.2, 139.1, 137.8, 135.8, 135.7, 134.7, 131.0, 129.3, 77.3, 73.2, 24.1, 17.1, 17.0, 16.8.

HRMS (EI): calculated for $C_{16}H_{18}O_4$ ([M]$^+$) 274.1205, found 274.1199.

(1*R,2*S**,6*S**)-4-(*tert*-butyl)-6-(3-(*tert*-butyl)-4-hydroxy-5-methylbenzyl)-2-hydroxy-2-methyl-7-oxabicyclo[4.1.0]hept-4-en-3-one (424)**

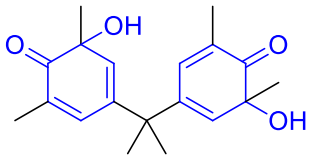


Following **Method A**, epoxy *ortho*-quinol **424** was obtained in v39% yield (8.5 mg, 0.02 mmol), as a colorless oil, from 4,4'-methylenebis(2-(*tert*-butyl)-6-methylphenol) (**423**) (20.0 mg, 0.06 mmol), $NaHCO_3$ (100.8 mg, 1.20 mmol) and a solution of Oxone® (147.5 mg, 0.48 mmol) in Milli-Q water (1.2 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 5/1).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.98 (d, *J* = 2.0 Hz, 1H), 6.88 (d, *J* = 1.9 Hz, 1H), 6.64 (s, 1H), 4.73 (s, 1H), 3.93 (s, 1H), 3.50 (s, 1H), 3.08 (d, *J* = 14.6 Hz, 1H), 2.91 (d, *J* = 14.6 Hz, 1H), 2.24 (s, 3H), 1.40 (s, 9H), 1.21 (s, 3H), 1.12 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 200.2, 151.9, 148.3, 139.1, 136.0, 129.6, 126.8, 126.2, 123.5, 75.9, 61.2, 57.5, 40.3, 34.9, 34.7, 29.9, 29.0, 23.8, 16.2.

4,4'-(Propane-2,2-diyl)bis(6-hydroxy-2,6-dimethylcyclohexa-2,4-dienone) (426)



Following **Method A**, *bis ortho*-quinol **426** was obtained in 43% yield (19.2 mg, 0.06 mmol), as a pale yellow solid, from 4,4'-(propane-2,2-diyl)bis(2,6-dimethylphenol) (**425**) (40.2 mg, 0.14 mmol), $NaHCO_3$ (118.4 mg, 1.41 mmol) and a solution of Oxone® (172.9 mg, 0.56 mmol) in Milli-Q water (1.4 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 3/1).

mp: 108.7 – 110.6 ºC

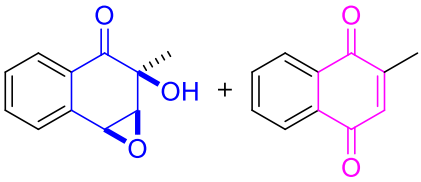
^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.51 (s, 1H), 6.28 (s, 1H), 3.30 (s, 1H), 1.88 (s, 3H), 1.39 (d, *J* = 1.2 Hz, 3H), 1.30 (t, *J* = 2.9 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 206.3, 206.3, 139.0, 137.4, 137.3, 135.3, 132.4, 132.3, 76.0, 75.9, 41.4, 41.3, 29.5, 25.8, 25.4, 15.3.

HRMS (ESI): calculated for $C_{19}H_{24}O_4Na$ ([M+Na]$^+$) 339.1566, found 339.1569.

3.3.2.2.2. Oxidative dearomatization of naphthol derivatives

(1a*S,2*S**,7b*S**)-2-Hydroxy-2-methyl-1a,2-dihydronaphtho[1,2-b]oxiren-3(7b*H*)-one (438)[239] and 2-methyl naphthalene-1,4-dione (439)[237]**



Following **Method B**, epoxy *ortho*-quinol **438** (12.1 mg, 0.06 mmol, 50% yield, colorless oil) and quinone **439** (8.4 mg, 0.05 mmol, 34% yield, yellow solid) were obtained from 2-methyl-1-naphthol (**428**) (20.0 mg, 0.13 mmol), $NaHCO_3$ (136.9 mg, 1.63 mmol) and a solution of Oxone® (194.3 mg, 0.63 mmol) in Milli-Q water (2.6 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 4/1).

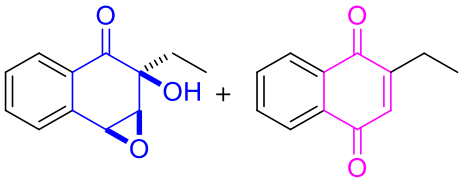
(1a*S**,2*S**,7b*S**)-2-Hydroxy-2-methyl-1a,2-dihydronaphtho[1,2-b]oxiren-3(7bH)-one (**438**):

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.91 (d, *J* = 7.4 Hz, 1H), 7.66 – 7.58 (m, 2H), 7.55 – 7.47 (m, 1H), 4.12 (d, *J* = 3.9 Hz, 1H), 3.90 (d, *J* = 4.1 Hz, 1H), 3.88 (s, 1H), 1.33 (s, 3H).

2-Methyl naphthalene-1,4-dione (**439**):

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.14 – 8.04 (m, 2H), 7.76 – 7.70 (m, 2H), 6.85 (q, *J* = 1.5 Hz, 1H), 2.20 (d, *J* = 1.5 Hz, 3H).

(1a*S,2*S**,7b*S**)-2-Ethyl-2-hydroxy-1a,2-dihydronaphtho[1,2-b]oxiren-3(7b*H*)-one (440) and 2-ethyl naphthalene-1,4-dione (441)[242]**



Following **Method B**, epoxy *ortho*-quinol **440** (10.7 mg, 0.05 mmol, 46% yield, colorless oil) and quinone **441** (9.7 mg, 0.06 mmol, 54% yield, yellow solid) were obtained from 2-ethylnaphthalen-1-ol (**430**) (19.6 mg, 0.11 mmol), $NaHCO_3$ (75.6 mg, 0.90 mmol) and a solution of Oxone® (107.1 mg, 0.35 mmol) in Milli-Q water (1.2 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 4/1).

(1a*S**,2*S**,7b*S**)-2-Ethyl-2-hydroxy-1a,2-dihydronaphtho[1,2-b]oxiren-3(7b*H*)-one (**440**):

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, *J* = 7.8 Hz, 1H), 7.65 – 7.58 (m, 2H), 7.55 – 7.46 (m, 1H), 4.12 (d, *J* = 4.1 Hz, 1H), 3.90 (s, 1H), 3.90 (d, *J* = 4.0 Hz, 2H), 1.80 (qd, *J* = 15.0, 7.5 Hz, 1H), 1.46 (dq, *J* = 14.8, 7.5 Hz, 1H), 0.82 (t, *J* = 7.5 Hz, 3H).

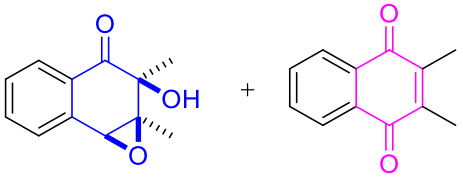
^{13}C NMR (75 MHz, $CDCl_3$) δ 198.7, 138.9, 134.0, 131.1, 129.8, 128.0, 78.2, 56.7, 53.1, 30.0, 6.9.

HRMS (ESI): calculated for $C_{12}H_{12}O_3Na$ ($[M+Na]^+$) 227.0678, found 227.0674.

2-Ethyl naphthalene-1,4-dione (**441**):

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.13 – 8.02 (m, 2H), 7.76 – 7.69 (m, 2H), 6.79 (t, *J* = 1.6 Hz, 1H), 2.62 (qd, *J* = 7.4, 1.6 Hz, 2H), 1.21 (t, *J* = 7.4 Hz, 3H).

(1aS*,2S*,7bS*)-2-Hydroxy-1a,2-dimethyl-1a,2-dihydronaphtho[1,2-b]oxiren-3(7b*H*)-one (443) and 2,3-dimethyl naphthalene-1,4-dione (444)[242]



[242] S. I. El-Hout, H. Suzuki, S. M. El-Sheikh, H. M. A. Hassan, F. A. Harraz, I. A. Ibrahim, E. A. El-Sharkawy, S. Tsujimura, M. Holzinger, Y. Nishina, *Chem. Commun.* **2017**, *53*, 8890-8893.

Following **Method B**, epoxy *ortho*-quinol **443** (9.2 mg, 0.04 mmol, 40% yield, colorless oil) and quinone **444** (11.9 mg, 0.06 mmol, 56% yield, yellow solid) were obtained from 2,3-dimethylnaphthalen-1-ol (**437**) (19.6 mg, 0.11 mmol), $NaHCO_3$ (100.8 mg, 1.20 mmol) and a solution of Oxone® (147.5 mg, 0.48 mmol) in Milli-Q water (1.2 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 4/1).

(1a*S**,2*S**,7b*S**)-2-Hydroxy-1a,2-dimethyl-1a,2-dihydronaphtho[1,2-b]oxiren-3(7b*H*)-one (**443**):

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.86 – 7.82 (m, 1H), 7.63 – 7.53 (m, 2H), 7.52 – 7.45 (m, 1H), 3.89 (s, 2H), 1.68 (s, 3H), 1.28 (s, 3H).

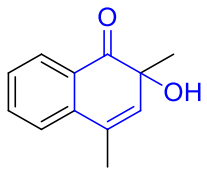
^{13}C NMR (75 MHz, $CDCl_3$) δ: 200.0, 139.1, 133.8, 130.2, 129.5, 129.3, 128.2, 61.8, 60.1, 24.9, 15.6.

HRMS (ESI): calculated for $C_{12}H_{12}O_3Na$ ([M+Na]$^+$) 227.0678, found 227.0673.

2,3-Dimethylnaphthalene-1,4-dione (**444**):[242]

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.11 – 8.04 (m, 1H), 7.72 – 7.65 (m, 1H), 2.17 (s, 3H).

2-Hydroxy-2,4-dimethylnaphthalen-1(2*H*)-one (456)



Following **Method A**, *ortho*-quinol **456** was obtained in 63% yield (13.7 mg, 0.07 mmol), as a white solid, from 2,4-dimethylnaphthalen-1-ol (**445**) (19.8 mg, 0.11 mmol), $NaHCO_3$ (48.7 mg, 0.58 mmol) and a solution of Oxone® (71.3 mg, 0.23 mmol) in Milli-Q water 2.3 mL). The crude mixture was purified by flash chromatography column (heptane/EtOAc : 9/1).

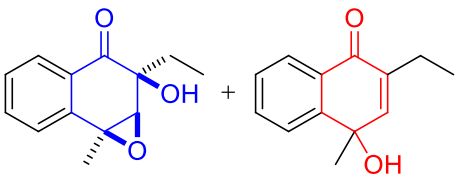
mp: 104.0 – 105.0 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.73 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.52 (d, *J* = 8.6 Hz, 1H), 7.46 (td, *J* = 7.5, 1.3 Hz, 1H), 7.36 (td, *J* = 7.6, 1.4 Hz, 1H), 6.13 (d, *J* = 1.0 Hz, 1H), 3.73 (s, 1H), 2.38 (d, *J* = 1.2 Hz, 3H), 1.54 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 204.5, 154.0, 145.0, 130.6, 129.7, 127.7, 125.7, 125.6, 122.0, 77.0, 33.5, 20.6.

HRMS (ESI): calculated for $C_{12}H_{12}O_2Na$ ([M+Na]$^+$) 211.0735, found 211.0728.

(1a*R,2*S**,7b*S**)-2-Ethyl-2-hydroxy-7b-methyl-1a,2-dihydronaphtho[1,2-b]oxiren-3(7b*H*)-one (457) and 2-ethyl-4-hydroxy-4-methylnaphthalen-1(4*H*)-one (458)**



Following **Method B**, epoxy *ortho*-quinol **457** (14.4 mg, 0.07 mmol, 62% yield, white solid) and *para*-quinol **458** (4.5 mg, 0.02 mmol, 21% yield, white solid) were obtained from 2-ethyl-4-methylnaphthalen-1-ol (**453**) (19.9 mg, 0.11 mmol), $NaHCO_3$ (46.2 mg, 0.55 mmol) and a solution of Oxone® (66.0 mg, 0.21 mmol) in Milli-Q water (1.1 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 5/1).

(1a*R**,2*S**,7b*S**)-2-Ethyl-2-hydroxy-7b-methyl-1a,2-dihydronaphtho[1,2-b]oxiren-3(7b*H*)-one (**457**):

mp:88.3 – 89.6 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.85 (d, *J* = 7.3 Hz, 1H), 7.66 – 7.58 (m, 2H), 7.52 – 7.44 (m, 1H), 3.89 (s, 1H), 3.69 (s, 1H), 1.87 (s, 3H), 1.84 – 1.74 (m, 1H), 1.52 – 1.39 (m, 1H), 0.80 (t, *J* = 7.5 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 199.3, 141.4, 133.8, 130.9, 129.2, 128.1, 127.4, 78.1, 64.0, 56.9, 30.1, 18.9, 7.0.

HRMS (ESI): calculated for $C_{13}H_{14}O_3Na$ ([M+Na]$^+$) 241.0835, found 241.0842.

2-Ethyl-4-hydroxy-4-methylnaphthalen-1(4*H*)-one (**458**):

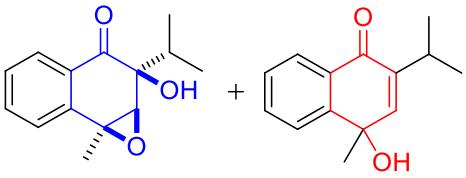
mp: 86.7 – 88.0 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.08 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.76 (dd, *J* = 7.9, 0.4 Hz, 1H), 7.60 (td, *J* = 7.6, 1.3 Hz, 1H), 7.42 (td, *J* = 7.8, 1.0 Hz, 1H), 6.74 (t, *J* = 1.2 Hz, 1H), 2.42 (qd, *J* = 7.4, 1.2 Hz, 2H), 1.63 (s, 3H), 1.13 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 184.7, 147.3, 146.9, 138.9, 133.1, 129.7, 128.2, 126.9, 126.2, 68.4, 31.0, 22.4, 12.6.

HRMS (ESI): calculated for $C_{13}H_{14}O_2Na$ ([M+Na]$^+$) 225.0886, found 225.0891.

(1a*R,2*S**,7b*S**)-2-Hydroxy-2-isopropyl-7b-methyl-1a,2-dihydronaphtho[1,2-b]oxiren-3(7b*H*)-one (459) and 4-hydroxy-2-isopropyl-4-methylnaphthalen-1(4*H*)-one (460)**



Following **Method B**, epoxy *ortho*-quinol **459** (4.9 mg, 0.02 mmol, 29% yield, yellow oil) and *para*-quinol **460** (2.7 mg, 0.01 mmol, 17% yield, yellow oil) were obtained from 2-isopropyl-4-methylnaphthalen-1-ol (**455**) (14.4 mg, 0.07 mmol), $NaHCO_3$ (30.2 mg, 0.36 mmol) and a solution of Oxone® (44.2 mg, 0.14 mmol) in Milli-Q water (0.7 mL). The crude mixture was purified by flash chromatography (DCM/EtOAc : 100/1).

(1a*R**,2*S**,7b*S**)-2-Hydroxy-2-isopropyl-7b-methyl-1a,2-dihydronaphtho[1,2-b]oxiren-3(7b*H*)-one (**459**):

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.83 – 7.79 (m, 1H), 7.64 – 7.60 (m, 2H), 7.50 – 7.43 (m, 1H), 3.78 (s, 1H), 1.87 (s, 3H), 1.83 – 1.74 (d, *J* = 7.0 Hz, 1H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.69 (d, *J* = 6.9 Hz, 3H).

HRMS (ESI): calculated for $C_{14}H_{16}O_3Na$ ([M+Na]$^+$) 255.0991, found 55.0988.

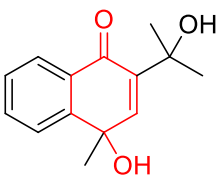
4-Hydroxy-2-isopropyl-4-methylnaphthalen-1(4*H*)-one (**460**):

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.11 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.77 (d, *J* = 7.9 Hz, 1H), 7.61 (td, *J* = 7.6, 1.4 Hz, 1H), 7.43 (td, *J* = 7.8, 1.2 Hz, 1H), 6.73 (d, *J* = 1.0 Hz, 1H), 3.12 (qd, *J* = 7.0, 1.0 Hz, 1H), 2.08 (s, 1H), 1.63 (s, 3H), 1.16 (d, *J* = 6.9 Hz, 3H), 1.11 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 184.2, 147.1, 145.4, 143.3, 133.0, 129.9, 128.2, 127.0, 126.1, 68.4, 31.2, 26.5, 22.0, 21.9.

HRMS (ESI): calculated for $C_{14}H_{16}O_2Na$ ([M+Na]$^+$) 239.1042, found 239.1052.

4-Hydroxy-2-(2-hydroxypropan-2-yl)-4-methylnaphthalen-1(4*H*)-one (461)



Following **Method A**, *para*-quinol **461** was obtained in 46% yield (9.7 mg, 0.04 mmol), as a white solid, from 2-(2-hydroxypropan-2-yl)-4-methylnaphthalen-1-ol (**454**) (19.6 mg, 0.09 mmol), $NaHCO_3$ (77.7 mg, 0.92 mmol) and a solution of Oxone® (113.7 mg, 0.37 mmol) in Milli-Q water (0.9 mL). The crude mixture was purified by flash chromatography (heptane EtOAc : 2/1 to 1/1).

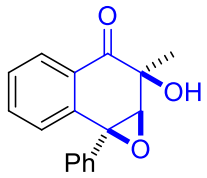
mp: 131.3-132.4 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.08 (d, *J* = 7.9 Hz, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.64 (td, *J* = 7.6, 1.3 Hz, 1H), 7.46 (td, *J* = 7.5, 1.2 Hz, 1H), 6.95 (s, 1H), 4.46 (s, 1H), 2.44 (s, 1H), 1.63 (s, 3H), 1.52 (d, *J* = 6.3 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 186.2, 147.4, 147.3, 140.8, 133.7, 129.8, 128.3, 127.1, 126.1, 72.1, 68.2, 31.0, 29.3, 28.9.

HRMS (ESI): calculated for $C_{14}H_{16}O_3Na$ ([M+Na]$^+$) 255.0991, found 255.0997.

(1aR*,2S*,7bS*)-2-Hydroxy-2-methyl-7b-phenyl-1a,2-dihydronaphtho[1,2-b]oxiren-3(7b*H*)-one (463)



Following **Method A**, epoxy *ortho*-quinol **463** was obtained in 95% yield (21.2 mg, 0.08 mmol), as a white solid, from 2-methyl-4-phenylnaphthalen-1-ol (**448a**) (19.7 mg, 0.08 mmol), $NaHCO_3$ (71.4 mg, 0.85 mmol) and a solution of Oxone® (105.0 mg, 0.34 mmol) in Milli-Q water (0.8 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 9/1).

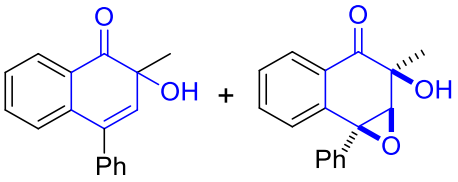
mp: 97.4-98.8 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.02 – 7.95 (m, 1H), 7.51 – 7.43 (m, 7H), 7.18 – 7.11 (m, 1H), 3.94 (s, 1H), 3.79 (s, 1H), 1.49 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 199.3, 141.3, 135.7, 133.8, 130.7, 130.3, 129.4, 128.7, 127.7, 74.9, 64.8, 62.0, 24.7.

HRMS (ESI): calculated for $C_{17}H_{14}O_3Na$ ([M+Na]$^+$) 289.0835, found 289.0844.

2-Hydroxy-2-methyl-4-phenylnaphthalen-1(2*H*)-one (462) and (1a*R,2*S**,7b*S**)-2-hydroxy-2-methyl-7b-phenyl-1a,2-dihydronaphtho[1,2-b]oxiren-3(7b*H*)-one (463)**



Following **Method A**, *ortho*-quinol **462** (6.6 mg, 0.03 mmol, 30% yield, colorless oil) and epoxy *ortho*-quinol **463** (11.8 mg, 0.04 mmol, 51% yield, white solid) were obtained from 2-methyl-4-phenylnaphthalen-1-ol (**448a**) (20.4 mg, 0.09 mmol), $NaHCO_3$ (33.6 mg, 0.40 mmol) and a solution of Oxone® (52.5 mg, 0.17 mmol) in Milli-Q water (0.8 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 9/1).

2-Hydroxy-2-methyl-4-phenylnaphthalen-1(2*H*)-one (**462**):

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.04 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.53 (td, *J* = 7.7, 1.5 Hz, 1H), 7.46 – 7.37 (m, 4H), 7.37 – 7.32 (m, 2H), 7.13 (d, *J* = 7.8 Hz, 1H), 6.25 (s, 1H), 3.49 (s, 1H), 1.55 (s, 3H).

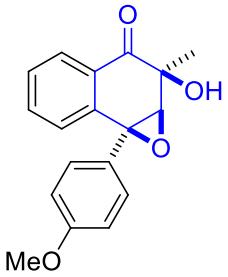
^{13}C NMR (75 MHz, $CDCl_3$) δ: 204.4, 138.5, 138.4, 136.3, 135.6, 135.0, 129.1, 128.7, 128.6, 128.3, 128.1, 127.6, 127.1, 75.9, 28.7.

HRMS (ESI): calculated for $C_{17}H_{14}O_2Na$ ($[M+Na]^+$) 273.0886, found 273.0893.

(1a*R**,2*S**,7b*S**)-2-Hydroxy-2-methyl-7b-phenyl-1a,2-dihydronaphtho[1,2-b]oxiren-3(7b*H*)-one (**463**):

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.02 – 7.95 (m, 1H), 7.51 – 7.43 (m, 7H), 7.18 – 7.11 (m, 1H), 3.94 (s, 1H), 3.79 (s, 1H), 1.49 (s, 3H).

(1a*R,2*S**,7b*S**)-2-Hydroxy-7b-(4-methoxyphenyl)-2-methyl-1a,2-dihydronaphtho[1,2-b]oxiren-3(7b*H*)-one (465)**



Following **Method A**, epoxy *ortho*-quinol **465** was obtained in 76% yield (17.1 mg, 0.06 mmol), as a white solid, from 4-(4-methoxyphenyl)-2-methylnaphthalen-1-ol (**448b**) (20.1 mg, 0.08 mmol), $NaHCO_3$ (63.8 mg, 0.76 mmol) and a solution of Oxone® (93.0 mg, 0.30 mmol) in -Q water (0.8 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 4/1).

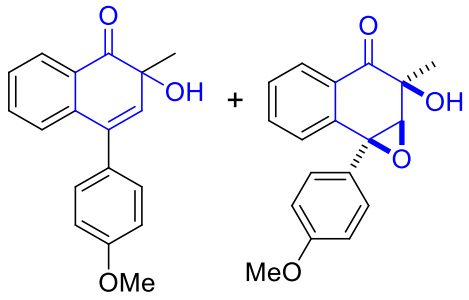
mp: 12.0 – 128.7 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.00 – 7.93 (m, 1H), 7.51 – 7.44 (m, 2H), 7.40 (d, *J* = 7.8 Hz, 2H), 7.19 – 7.13 (m, 1H), 6.98 (d, *J* = 8.9 Hz, 2H), 3.96 (s, 1H), 3.86 (s, 3H), 3.77 (s, 1H), 1.48 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 199.4, 159.8, 141.6, 133.8, 130.5, 130.2, 129.3, 129.0, 128.6, 127.7, 114.1, 74.9, 64.8, 61.7, 55.5, 24.6.

HRMS (ESI): calculated for $C_{18}H_{16}O_4Na$ ([M+Na]$^+$) 319.0940, found 319.0936.

2-Hydroxy-4-(4-methoxyphenyl)-2-methylnaphthalen-1(2*H*)-one (464) and (1a*R,2*S**,7b*S**)-2-hydroxy-7b-(4-methoxyphenyl)-2-methyl-1a,2-dihydronaphtho[1,2-b]oxiren-3(7b*H*)-one (465)**



Following **Method A**, *ortho*-quinol **464** (3.4 mg, 0.01 mmol, 17% yield, colorless oil) and epoxy *ortho*-quinol **465** (13.9 mg, 0.05 mmol, 66% yield, white solid) were obtained from 4-(4-methoxyphenyl)-2-methylnaphthalen-1-ol (**448b**) (18.8 mg, 0.07 mmol), $NaHCO_3$ (30.2 mg, 0.36 mmol) and a solution of Oxone® (44.2 mg, 0.14 mmol) in Milli-Q water (0.7 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 5/1).

2-Hydroxy-4-(4-methoxyphenyl)-2-methylnaphthalen-1(2*H*)-one (**464**):

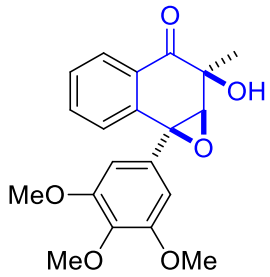
^{1}H NMR (300 MHz, CDCl3) δ: 8.02 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.53 (td, *J* = 7.6, 1.5 Hz, 1H), 7.38 (td, *J* = 7.5, 1.0 Hz, 1H), 7.27 (d, *J* = 8.7 Hz, 3H), 7.15 (d, *J* = 8.0 Hz, 1H), 6.96 (d, *J* = 8.7 Hz, 2H), 6.21 (s, 1H), 3.86 (s, 3H), 3.48 (s, 1H), 1.53 (s, 3H).

HRMS (ESI): calculated for $C_{18}H_{16}O_3Na$ ([M+Na]$^+$) 303.0991, found 303.0994.

(1a*R**,2*S**,7b*S**)-2-hydroxy-7b-(4-methoxyphenyl)-2-methyl-1a,2-dihydronaphtho[1,2-b]oxiren-3(7b*H*)-one (**465**):

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.00 – 7.93 (m, 1H), 7.51 – 7.44 (m, 2H), 7.40 (d, *J* = 7.8 Hz, 2H), 7.19 – 7.13 (m, 1H), 6.98 (d, *J* = 8.9 Hz, 2H), 3.96 (s, 1H), 3.86 (s, 3H), 3.77 (s, 1H), 1.48 (s, 3H).

(1a*R,2*S**,7b*S**)-2-Hydroxy-2-methyl-7b-(3,4,5-trimethoxyphenyl)-1a,2-dihydronaphtho[1,2-b]oxiren-3(7b*H*)-one (466)**



Following **Method A**, epoxy *ortho*-quinol **466** was obtained in 25% yield (5.6 mg, 0.02 mmol), as a pale yellow solid, from 2-methyl-4-(3,4,5-trimethoxyphenyl)naphthalen-1-ol (**448c**) (20.0 mg, 0.06 mmol), $NaHCO_3$ (52.1 mg, 0.62 mmol) and a solution of Oxone® (75.8 mg, 0.25 mmol) in Milli-Q water (0.6 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 2/1).

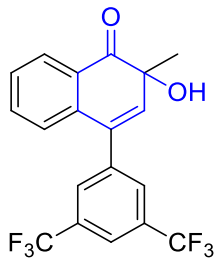
mp: 124.4-126.0 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.02 – 7.96 (m, 1H), 7.56 – 7.46 (m, 2H), 7.29 – 7.23 (m, 1H), 3.91 (s, 3H), 3.90 (s, 1H), 3.87 (s, 6H), 3.79 (s, 1H), 1.50 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 199.0, 141.0, 138.1, 133.7, 131.0, 130.5, 130.1, 129.3, 128.6, 104.5, 74.6, 65.0, 61.9, 60.9, 56.3, 24.6.

HRMS (ESI): calculated for $C_{20}H_{20}O_6Na$ ([M+Na]$^+$) 379.1152, found 379.1134.

4-[3,5-Bis(trifluoromethyl)phenyl]-2-hydroxy-2-methylnaphthalen-1(2*H*)-one (467)



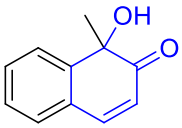
Following **Method A**, *ortho*-quinol **467** was obtained in 57% yield (11.8 mg, 0.03 mmol), as a brown oil, from 4-(3,5-bis(trifluoromethyl)phenyl)-2-methylnaphthalen-1-ol (**448d**) (20.0 mg, 0.05 mmol), $NaHCO_3$ (22.7 mg, 0.27 mmol) and a solution of Oxone® (33.2 mg, 0.11 mmol) in Milli-Q water (0.6 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 9/1).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.09 (d, *J* = 7.6 Hz, 1H), 7.94 (s, 1H), 7.82 (s, 2H), 7.59 (td, *J* = 7.6, 1.0 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.34 (s, 1H), 3.51 (s, 1H), 1.58 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 203.4, 140.7, 137.8, 136.9, 135.4, 134.1, 132.5, 132.1, 129.3 (q, J_{C-F} = 3.5 Hz), 129.2, 128.5, 128.1, 126.2, 125.1, 122.2 (q, J_{C-F} = 3.7 Hz), 121.5, 75.8, 28.6.

HRMS (ESI): calculated for $C_{19}H_{12}O_2F_6Na$ ($[M+Na]^+$) 409.0633, found 409.0627.

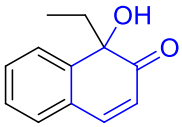
1-Hydroxy-1-methylnaphthalen-2(1*H*)-one(483)[243]



Following **Method A**, *ortho*-quinol **483** was obtained in 80% yield (17.6 mg, 0.10 mmol), as a colorless oil from 1-methylnaphthalen-2-ol (**469**) (20.0 mg, 0.13 mmol), $NaHCO_3$ (53.0 mg, 0.63 mmol) and a solution of Oxone® (78.0 mg, 0.25 mmol) in Milli-Q water (2.5 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 20/1).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.72 (d, *J* = 7.8 Hz, 1H), 7.48 – 7.41 (m, 2H), 7.36 – 7.28 (m, 2H), 6.20 (d, *J* = 9.9 Hz, 1H), 3.69 (s, 1H), 1.55 (s, 3H).

1-Ethyl-1-hydroxynaphthalen-2(1*H*)-one (484)[243]

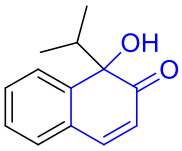


Following **Method A**, *ortho*-quinol **484** was obtained in 83% yield (17.9 mg, 0.09 mmol), as a white solid, from 1-ethylnaphthalen-2-ol (**472**) (19.7 mg, 0.11 mmol), $NaHCO_3$ (50.4 mg, 0.60 mmol) and a solution of Oxone® (71.4 mg, 0.23 mmol) in Milli-Q water (1.2 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 9/1).

[243] Y. Zhang, Y. Liao, X. Liu, X. Xu, L. Lin, X. Feng, *Chem. Sci.* **2017**, *8*, 6645-6649.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.65 (d, *J* = 7.7 Hz, 1H), 7.46 – 7.37 (m, 2H), 7.35 – 7.27 (m, 2H), 6.17 (d, *J* = 9.9 Hz, 1H), 3.74 (s, 1H), 1.89 – 1.74 (m, 2H), 0.82 (t, *J* = 7.4 Hz, 3H).

1-Hydroxy-1-isopropylnaphthalen-2(1*H*)-one (485)[244]



Following **Method A**, *ortho*-quinol **485** was obtained in 79% yield (17.1 mg, 0.08 mmol), as a white solid, from 1-isopropylnaphthalen-2-ol (**474**) (20.0 mg, 0.11 mmol), $NaHCO_3$ (45.1 mg, 0.54 mmol) and a solution of Oxone® (66.0 mg, 0.21 mmol) in Milli-Q water (1.1 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 20/1).

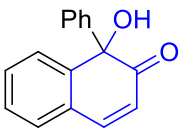
mp: 73.1 – 75.0 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.60 (d, *J* = 7.6 Hz, 1H), 7.44 – 7.26 (m, 4H), 6.13 (d, *J* = 9.9 Hz, 1H), 3.76 (s, 1H), 2.09 – 0.83 (m, 1H), 0.84 (d, *J* = 6.9 Hz, 3H), 0.82 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 206.4, 145.8, 143.6, 129.7, 129.4, 129.1, 127.6, 127.1, 123.1, 82.4, 40.6, 17.6, 16.8.

HRMS (ESI): calculated for $C_{13}H_{14}O_2Na$ ($[M+Na]^+$) 225.0886, found 225.0879.

1-Hydroxy-1-phenylnaphthalen-2(1*H*)-one (486)



Following **Method A**, *ortho*-quinol **486** was obtained in 99% yield (21.0 mg, 0.09 mmol), as a white solid, from 1-phenylnaphthalen-2-ol (**476a**) (19.9 mg, 0.10 mmol), $NaHCO_3$ (42.0 mg, 0.50 mmol) and a solution of Oxone® (55.8 mg, 0.20 mmol) in Milli-Q water (0.9 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 9/1).

mp: 115.2 – 115.8 ºC.

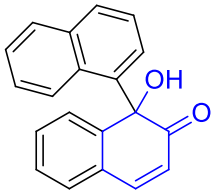
[244] J. Carnduff, D. G. Leppard, *J. Chem. Soc., Perkin Trans. 1* **1976**, *0*, 2570-2573.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.65 – 7.61 (m, 3H), 7.48 – 7.46 (m, 2H), 7.46 – 7.41 (m, 5H), 7.40 – 7.35 (m, 6H), 7.24 (s, 15H), 6.15 (d, *J* = 9.9 Hz, 3H), 4.63 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 202.5, 146.4, 143.6, 141.3, 131.0, 129.7, 129.3, 128.7, 128.5, 128.3, 127.8, 125.7, 123.0, 80.4.

HRMS (ESI): calculated for $C_{16}H_{12}O_2Na$ ([M+Na]$^+$) 259.0729, found 259.0720.

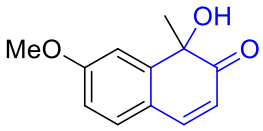
1-Hydroxy-[1,1'-binaphthalen]-2(1*H*)-one (487)[245]



Following **Method A**, *ortho*-quinol **487** was obtained in 79% yield (16.0 mg, 0.06 mmol), as a white solid, from [1,1'-binaphthalen]-2-ol (**476b**) (19.0 mg, 0.07 mmol), $NaHCO_3$ (31.1 mg, 0.37 mmol) and a solution of Oxone® (45.5 mg, 0.15 mmol) in Milli-Q water (0.7 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 3/1).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.01 (d, *J* = 7.2 Hz, 1H), 7.84 (t, *J* = 8.7 Hz, 2H), 7.64 (d, *J* = 9.9 Hz, 1H), 7.59 – 7.52 (m, 1H), 7.46 (d, *J* = 7.4 Hz, 1H), 7.37 (td, *J* = 8.7, 3.9 Hz, 3H), 7.30 – 7.27 (m, 1H), 7.26 – 7.23 (m, 1H), 7.23 – 7.19 (m, 1H), 6.38 (d, *J* = 9.9 Hz, 1H), 3.22 (s, 1H).

1-Hydroxy-7-methoxy-1-methylnaphthalen-2(1*H*)-one (489) [243]

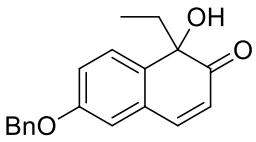


Following **Method A**, *ortho*-quinol **489** was obtained in 85% yield (18.5 mg, 0.09 mmol), as a yellow solid, from 7-methoxy-1-methylnaphthalen-2-ol (**488**) (20.1 mg, 0.11 mmol), $NaHCO_3$ (44.5 mg, 0.53 mmol) and a solution of Oxone® (65.4 mg, 0.21 mmol) in Milli-Q water (1.1 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 9/1)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39 (d, *J* = 9.8 Hz, 2H), 7.25 (d, *J* = 3.3 Hz, 2H), 7.21 (s, 1H), 6.82 (dd, *J* = 8.4, 2.6 Hz, 2H), 6.07 (d, *J* = 9.8 Hz, 2H), 3.87 (s, 6H), 3.78 (s, 2H), 1.54 (s, 6H).

[245] S. Duan, Y. Xu, X. Zhang, X. Fan, *Chem. Commun.* **2016**, *52*, 10529-10532.

6-(Benzyloxy)-1-ethyl-1-hydroxynaphthalen-2(1*H*)-one (492)



Following **Method A**, *ortho*-quinol **492** was obtained in 82% yield (8.4 mg, 0.03 mmol), as a pale yellow solid, from 6-(benzyloxy)-1-ethylnaphthalen-2-ol (**482**) (9.7 mg, 0.03 mmol), $NaHCO_3$ (16.8 mg, 0.20 mmol) and a solution of Oxone® (22.1 mg, 0.08 mmol) in Milli-Q water (0.4 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 9/1).

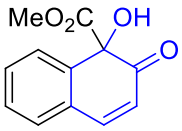
mp: 81.7 – 83.0 ºC

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.55 (d, *J* = 8.5 Hz, 1H), 7.46 – 7.30 (m, 6H), 7.03 (dd, *J* = 8.5, 2.6 Hz, 1H), 6.89 (d, *J* = 2.6 Hz, 1H), 6.17 (d, *J* = 9.9 Hz, 1H), 5.09 (s, 2H), 3.66 (s, 1H), 1.87 – 1.71 (m, 2H), 0.81 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 205.6, 158.4, 145.8, 136.7, 136.6, 130.2, 128.8, 128.3, 127.6, 127.5, 123.6, 116.3, 115.8, 79.9, 70.4, 38.6, 8.2.

HRMS (EI): calculated for $C_{19}H_{18}O_3$ ($[M]^+$) 294.1262, found 294.1256.

Methyl 1-hydroxy-2-oxo-1,2-dihydronaphthalene-1-carboxylate (494)[246]

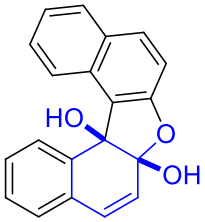


Following **Method A**, *ortho*-quinol **494** was obtained in 76% yield (16.1 mg, 0.07 mmol), as a brown solid, from methyl 2-hydroxy-1-naphthoate (**493**) (19.6 mg, 0.10 mmol), $NaHCO_3$ (42.0 mg, 0.50 mmol) and a solution of Oxone® (61.5 mg, 0.20 mmol) in Milli-Q water (1.0 mL). The crude mixture was quickly passed through a short-pad of silica gel (EtOAc).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.62 (dd, *J* = 7.0, 1.3 Hz, 1H), 7.51 (d, *J* = 10.0 Hz, 1H), 7.47 – 7.38 (m, 2H), 7.38 – 7.32 (m, 1H), 6.22 (d, *J* = 10.0 Hz, 1H), 4.53 (s, 1H), 3.65 (s, 3H).

[246] M. Uyanik, T. Mutsuga, K. Ishihara, *Angew. Chem. Int. Ed.* **2017**, *56*, 3956-3960

(6a*R,13c*S**)-6a,13c-Dihydrodinaphtho[2,1-b:1',2'-d]furan-6a,13c-diol (495)**



Following **Method A**, *cis*-diol (6a*R**,13c*S**)-**495** was obtained in 66% yield (14.0 mg, 0.05 mmol), as a pale brown solid, from 1,1'-bi-2-naphthol (20.1 mg, 0.07 mmol), $NaHCO_3$ (58.8 mg, 0.70 mmol) and a solution of Oxone® (85.9 mg, 0.28 mmol) in Milli-Q water (0.7 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 5/1).

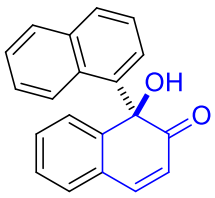
mp: 67.4 – 69.0 ºC

^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.23 (d, *J* = 7.7 Hz, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.78 (t, *J* = 8.8 Hz, 2H), 7.42 (td, *J* = 7.6, 1.3 Hz, 1H), 7.38 – 7.26 (m, 3H), 7.13 (t, *J* = 7.3 Hz, 2H), 6.60 (d, *J* = 9.8 Hz, 1H), 6.04 (d, *J* = 9.8 Hz, 1H), 4.90 (s, 1H), 2.65 (s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.5, 134.8, 132.8, 131.4, 131.1, 131.0, 130.5, 129.4, 129.2, 128.7, 128.5, 127.9, 127.5, 125.1, 123.5, 121.6, 120.5, 113.0, 107.7, 81.2.

HRMS (ESI): calculated for $C_{20}H_{14}O_3Na$ ($[M+Na]^+$) 325.0835, found 325.0829.

(-)-(*S* or *R*)-1-Hydroxy-[1,1'-binaphthalen]-2(1*H*)-one (487)

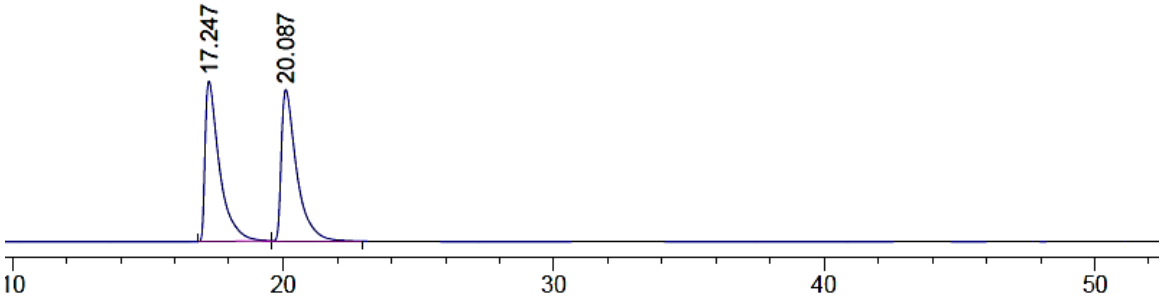


Following **Method A**, *ortho*-quinol (-)-**487** was obtained in 74% yield (15.9 mg, 0.05 mmol), as a white solid, from (*R*)-(+)-[1,1'-binaphthalen]-2-ol (**476b**) (20.0 mg, 0.07 mmol), $NaHCO_3$ (31.1 mg, 0.37 mmol) and a solution of Oxone® (45.5 mg, 0.15 mmol) in Milli-Q water (0.8 mL). The crude mixture was purified by flash chromatography column (heptane/EtOAc : 3/1).

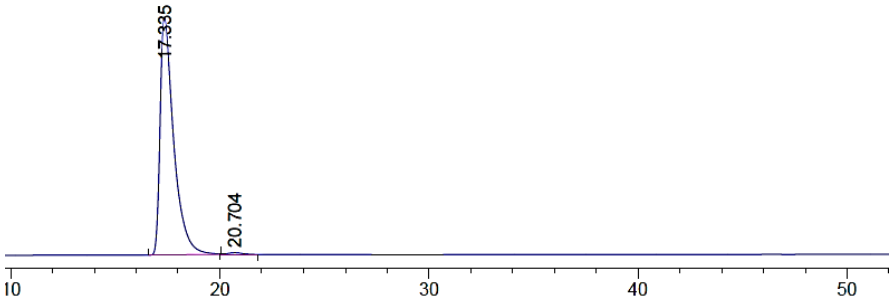
^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.01 (d, *J* = 7.2 Hz, 1H), 7.84 (t, *J* = 8.7 Hz, 2H), 7.64 (d, *J* = 9.9 Hz, 1H), 7.59 – 7.52 (m, 1H), 7.46 (d, *J* = 7.4 Hz, 1H), 7.37 (td, *J* = 8.7, 3.9 Hz, 3H), 7.30 – 7.27 (m, 1H), 7.26 – 7.23 (m, 1H), 7.23 – 7.19 (m, 1H), 6.38 (d, *J* = 9.9 Hz, 1H), 3.22 (s, 1H).

$[\alpha]_D^{20}$ = –98.37 (*c* = 0.017, $CHCl_3$).

HPLC: *Daicel Chiralpak* IB, *n*-hexane/2-propanol: 80/20, flow rate: 0.6 mL/min, λ: 254 nm, t_R (major): 17.34 min, t_R (minor): 20.70 min., T: 25 °C, 98% *ee*.

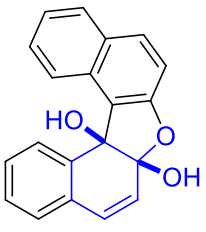


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.247	BV	0.5437	5.47873e4	1467.19666	49.9362
2	20.087	VB	0.5832	5.49274e4	1389.36841	50.0638



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.335	BB	0.6701	7.94353e4	1748.17566	98.9998
2	20.704	BB	0.7996	802.50488	14.50196	1.0002

(-)-(6a*R*,13c*S* or 6a*S*,13c*R*)-6a,13c-dihydrodinaphtho[2,1-b:1',2'-d]furan-6a,13c-diol (495)



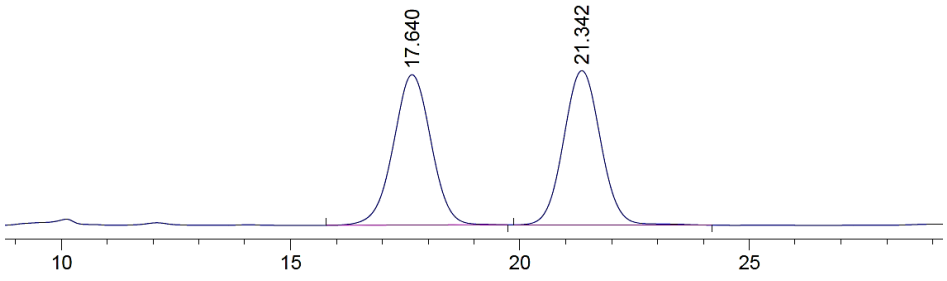
Following **Method B**, *cis*-diol (-)-**495** was obtained in 77% yield (16.6 mg, 0.06 mmol), as a pale brown solid, from (*R*)-(+)-1,1'-bi-2-naphthol (20.5 mg, 0,07 mmol), $NaHCO_3$ (58.8 mg, 0.70 mmol)

and a solution of Oxone® (85.9 mg, 0.28 mmol) in Milli-Q water (0.7 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 5/1).

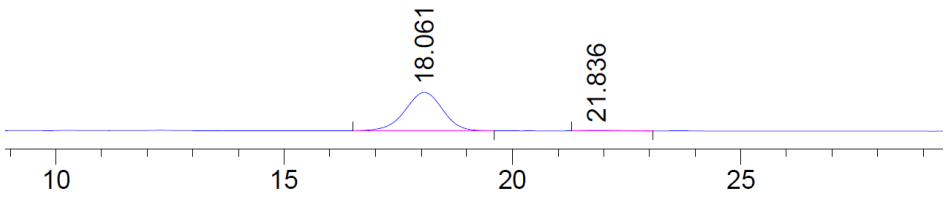
^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.23 (d, *J* = 7.7 Hz, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.78 (t, *J* = 8.8 Hz, 2H), 7.42 (td, *J* = 7.6, 1.3 Hz, 1H), 7.38 – 7.26 (m, 3H), 7.13 (t, *J* = 7.3 Hz, 2H), 6.60 (d, *J* = 9.8 Hz, 1H), 6.04 (d, *J* = 9.8 Hz, 1H), 4.90 (s, 1H), 2.65 (s, 1H).

$[\alpha]_D^{20}$ = - 136.22 (*c* = 0.037, $CHCl_3$).

HPLC: *Daicel Chiralpak* IC, *n*-hexane/2-propanol: 90/10, flow rate: 1.0 mL/min, λ: 254 nm, t_R (major): 18.06 min, t_R (minor): 21.84 min., T: 25 °C, 98% *ee*.

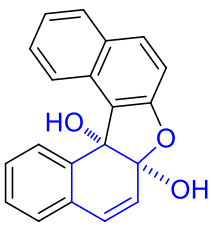


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.640	BB	0.8594	1.63713e4	288.75858	50.3286
2	21.343	BB	0.8576	1.61575e4	294.73434	49.6714



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.061	BB	0.8916	1.43679e4	250.33305	98.9384
2	21.836	BB	0.6402	154.16002	3.15421	1.0616

(+)-(6a*S*,13c*R* or 6a*R*,13c*S*)-6a,13c-dihydrodinaphtho[2,1-b:1',2'-d]furan-6a,13c-diol (495)

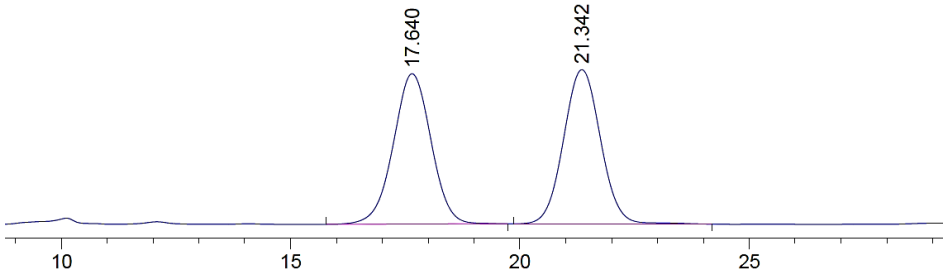


Following **Method B**, *cis*-diol (+)-**495** was obtained in 59% yield (12.3 mg, 0.04 mmol), as a brown solid, from (*S*)-(-)-1,1'-bi-2-naphthol (19.8 mg, 0,07 mmol), $NaHCO_3$ (58.8 mg, 0.70 mmol) and a solution of Oxone® (85.9 mg, 0.28 mmol) in Milli-Q water (0.7 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 5/1).

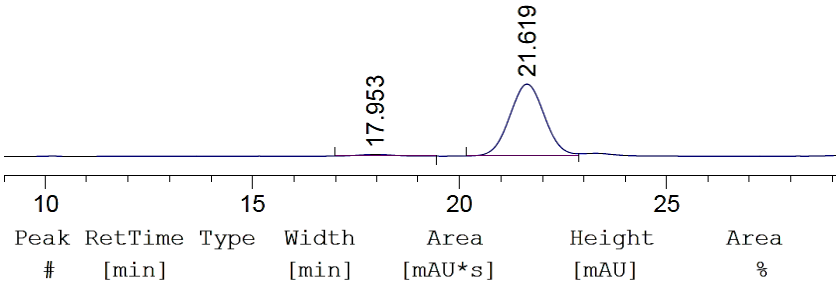
^{1}H NMR (500 MHz, $CDCl_3$) δ: 8.23 (d, *J* = 7.7 Hz, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.78 (t, *J* = 8.8 Hz, 2H), 7.42 (td, *J* = 7.6, 1.3 Hz, 1H), 7.38 – 7.26 (m, 3H), 7.13 (t, *J* = 7.3 Hz, 2H), 6.60 (d, *J* = 9.8 Hz, 1H), 6.04 (d, *J* = 9.8 Hz, 1H), 4.90 (s, 1H), 2.65 (s, 1H).

$[\alpha]_D^{20}$ = +119.32 (*c* = 0.008, $CHCl_3$).

HPLC: *Daicel Chiralpak* IC, *n*-hexane/2-propanol: 90/10, flow rate: 1.0 mL/min, λ: 254 nm, t_R (minor): 17.95 min, t_R (major): 21.62 min., T: 25 °C, 96% *ee*.



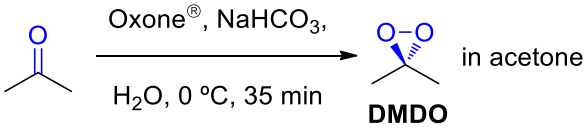
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.640	BB	0.8594	1.63713e4	288.75858	50.3286
2	21.343	BB	0.8576	1.61575e4	294.73434	49.6714



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	17.953	BB	0.8479	676.46094	11.30786	2.1504
2	21.619	BV	0.9264	3.07817e4	524.70642	97.8496

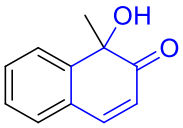
3.3.2.2.3. Mechanistic studies

Formation and isolation of dimethyldioxirane (DMDO)[247]



DMDO was synthesized followed a reported method described in the literature.[199] $NaHCO_3$ (12.0 g, 0.14 mol), Milli-Q water (10 mL) and acetone (15 mL) was mixed in a 250 mL round flask, chilled in an ice/water bath and stirred 20 min at 0 ºC. Then, Oxone® (12.5 g, 0.04 mol) was added to the mixture in one portion and stirred vigorously for 15 min at 0 ºC. Next, Milli-Q water was added to the reaction mixture and the stir bar was removed. The reaction flask was attached to a rotary evaporator with a bump bulb, which was chilled in a dry ice/acetone bath. The flask was rotated moderately with a pressure of 200 mmHg for 15 min and, then, the bath temperature was raised 40 ºC. When the bath reached 40 ºC, the distillation was stopped and a pale yellow acetone solution of DMDO (6 mL) was collected in the bump bulb. The DMDO solution was dried over Na_2SO_4 and filtered. To know the final concentration of the obtained acetone solution of DMDO is necessary to make a titration.

1-Hydroxy-1-methylnaphthalen-2(1*H*)-one(483)[248]

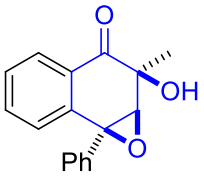


Using an isolated acetone solution of DMDO. 1-methylnaphthalen-2-ol (**469**) (19.4 mg, 0.12 mmol) was dissolved in the acetone solution of DMDO (3 mL) and stirred at rt for 1 hour. Then, the crude mixture was concentrated to dryness under reduced pressure and purified by flash chromatography (heptane/EtOAc : 20/1) to give *ortho*-quinol **483** in 98% yield (21.0 mg, 0.12 mmol), as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.72 (d, *J* = 7.8 Hz, 1H), 7.48 – 7.41 (m, 2H), 7.36 – 7.28 (m, 2H), 6.20 (d, *J* = 9.9 Hz, 1H), 3.69 (s, 1H), 1.55 (s, 3H).

[247] D. F. Taber, P. W. DeMatteo, R. A. Hassan, *Org. Synth.* **2013**, *90*, 350-357
[248] Y. Zhang, Y. Liao, X. Liu, X. Xu, L. Lin, X. Feng, *Chem. Sci.* **2017**, *8*, 6645-6649.

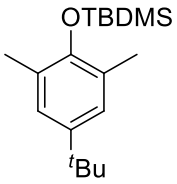
(1aR*,2S*,7bS*)-2-Hydroxy-2-methyl-7b-phenyl-1a,2-dihydronaphtho[1,2-b]oxiren-3(7b*H*)-one (463)



Using an isolated acetone solution of DMDO. *ortho*-Quinol **462** (13.8 mg, 0.06 mmol) was dissolved in the acetone solution of DMDO (3 mL) and stirred at rt for 1 hour. Then, the crude mixture was concentrated to dryness under reduced pressure and purified by flash chromatography (heptane/EtOAc : 9/1) to afford epoxy *ortho*-quinol **463** in 86% yield (12.7 mg, 0.05 mmol), as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.02 – 7.95 (m, 1H), 7.51 – 7.43 (m, 7H), 7.18 – 7.11 (m, 1H), 3.94 (s, 1H), 3.79 (s, 1H), 1.49 (s, 3H).

***tert*-Butyl(4-(*tert*-butyl)-2,6-dimethylphenoxy)dimethylsilane (502)**



To a solution of 4-(*tert*-butyl)-2,6-dimethylphenol (**379**) (102.2 mg, 0.57 mmol), *N*-methylimidazole (0.14 mL, 1.68 mmol) and iodine (213.6 mg, 1.68 mmol) in dry DCM (1.7 mL), TBDMSCl (92.8 mg, 0.66 mmol) was added and the reaction was stirred 16 hours at rt. The reaction was concentrated to dryness under reduced pressure, and the crude dissolved in EtOAc and washed with an aqueous saturated solution of $Na_2S_2O_3$. The organic layer was dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 40/1) to give **502** in 49% yield (83.1 mg, 0.28 mmol), as a white solid.

mp: 48.4 – 49.3 ºC

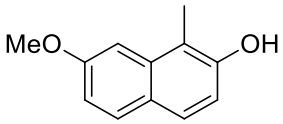
^{1}H NMR (300 MHz, $CDCl_3$) δ 6.97 (s, 2H), 2.21 (s, 6H), 1.28 (s, 9H), 1.04 (s, 9H), 0.19 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8, 143.8, 127.8, 125.8, 34.0, 31.7, 26.3, 18.9, 18.2, -2.7.

HRMS (ESI): calculated for $C_{18}H_{33}OSi$ ($[M+H]^+$) 293.2295, found 293.2288.

3.3.2.3. Total Synthesis of Lacinilene C methyl ether (30)

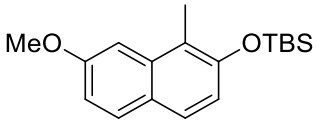
7-Methoxy-1-methylnaphthalen-2-ol (488)[216]



488 was synthesized followed a reported method described in the literature.[216] To a solution of 7-methoxynaphthalen-2-ol (**516**) (1.0 g, 5.77 mmol) in dry toluene (6.9 mL), NaH (60% mineral oil, 153.2 mg, 6.38 mmol) was added in three parts at 0 ºC under inert atmosphere and the reaction was stirred at rt for 2 h. Then, MeI (1.8 mL, 28.91 mmol) was added to the mixture and the reaction was stirred at 110 ºC for 16 h. The reaction was cooled to rt, quenched with an aqueous saturated solution of NH_4Cl and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 9/1) to give 7-methoxy-1-methylnaphthalen-2-ol (**488**) in 49% yield (523.7 mg, 2.78 mmol), as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.67 (d, *J* = 8.9 Hz, 1H), 7.55 (d, *J* = 8.7 Hz, 1H), 7.16 (d, *J* = 2.4 Hz, 1H), 7.01 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 1H), 4.79 (s, 1H), 3.95 (s, 3H), 2.49 (s, 3H).

***tert*-Butyl[(7-methoxy-1-methylnaphthalen-2-yl)oxy]dimethylsilane (517)**



TBDMSCl (353.1 mg, 2.34 mmol) was added to a solution of 7-methoxy-1-methylnaphthalen-2-ol (**488**) (403.9 mg, 2.15 mmol) and imidazole (217.2 mg, 3.20 mmol) in dry DMF (2.0 mL) at 0 ºC under inert atmosphere. The reaction was stirred at rt for 2 h and quenched with water. The mixture was extracted with EtOAc (x3), dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 80/1) to give **517** in 94% yield (607.8 mg, 2.01 mmol), as a white solid.

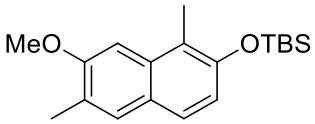
mp: 50.2 – 51.4 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.67 (d, *J* = 8.9 Hz, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 7.16 (d, *J* = 2.4 Hz, 1H), 7.02 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 1H), 3.94 (s, 3H), 2.48 (s, 3H), 1.06 (s, 9H), 0.23 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.1, 151.3, 135.5, 129.9, 126.6, 124.9, 120.1, 118.6, 115.7, 102.6, 55.2, 26.0, 18.5, 11.8, -3.9.

HRMS (ESI): calculated for $C_{18}H_{27}O_2Si$ ($[M+H]^+$) 303.1774, found 303.1785.

***tert*-Butyl[(7-methoxy-1,6-dimethylnaphthalen-2-yl)oxy]dimethylsilane (518)**



In a dry flask, **517** (49.5 mg, 0.16 mmol) was dissolved in dry THF (0.7 mL) and cooled at 0 ºC in an ice / water bath. Then, *n*-BuLi (16.8 µL, 0.18 mmol) was added dropwise to the solution at 0 ºC and the reaction was stirred 30 min at rt, observing a change of color in the reaction from colorless to red or orange. Then, MeI (20.5 µL, 0.33 mmol) was added dropwise to the mixture at 0 ºC and the reaction was stirred at rt for 2 h. The reaction was quenched with an aqueous saturated solution of NH_4Cl and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 100/1) to give **518** in 96% yield (49.5 mg, 0.16 mmol), as a white solid.

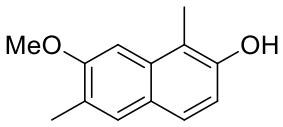
mp: 74.9 – 75.8 ºC.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.51 (s, 1H), 7.47 (d, *J* = 8.8 Hz, 1H), 7.09 (s, 1H), 6.93 (d, *J* = 8.7 Hz, 1H), 3.98 (s, 3H), 2.51 (s, 3H), 2.36 (s, 3H), 1.09 (s, 9H), 0.25 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.3, 150.5, 134.1, 129.4, 125.8, 125.6, 124.7, 119.9, 118.5, 100.9, 77.6, 77.2, 76.7, 55.3, 26.0, 18.5, 16.6, 11.9, -3.9.

HRMS (EI): calculated for $C_{19}H_{28}O_2Si$ ($[M]^+$) 316.1859, found 316.1852.

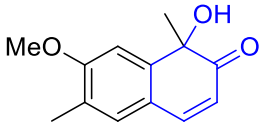
7-Methoxy-1,6-dimethylnaphthalen-2-ol (490)[243]



To a solution of **518** (36.4 mg, 0.11 mmol) in dry THF (0.24 mL), tetrabutylammonium fluoride (TBAF 1M in THF, 0.26 mL, 0.26 mmol) was added at 0 ºC under inert atmosphere and the reaction was stirred for 1 hour at rt. The reaction was quenched with water and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 8/1) to give 7-methoxy-1,6-dimethylnaphthalen-2-ol (**490**) in 82% yield (19.1 mg, 0.09 mmol), as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.49 (s, 1H)7.47 (d, *J* = 8.9 Hz, 2H), 7.07 (s, 1H), 6.89 (d, *J* = 8.7 Hz, 1H), 4.70 (s, 1H), 3.96 (s, 3H), 2.49 (s, 3H), 2.33 (s, 3H).

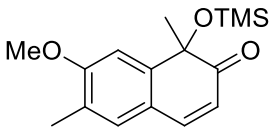
1-Hydroxy-7-methoxy-1,6-dimethylnaphthalen-2(1*H*)-one (491)[243]



Following **Method A**, *ortho*-quinol **491** was obtained in 60% yield (26.1 mg, 0.12 mmol), as a yellow solid, from 7-methoxy-1,6-dimethylnaphthalen-2-ol (**490**) (40.1 mg, 0.20 mmol), $NaHCO_3$ (84.0 mg, 1.00 mmol) and a solution of Oxone® (69.8 mg, 0.40 mmol) in Milli-Q water (2.0 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 9/1).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36 (d, *J* = 9.8 Hz, 1H), 7.17 (s, 1H), 7.07 (s, 1H), 6.05 (d, *J* = 9.8 Hz, 1H), 3.92 (s, 3H), 3.76 (s, 1H), 2.21 (s, 3H), 1.54 (s, 3H).

7-Methoxy-1,6-dimethyl-1-((trimethylsilyl)oxy)naphthalen-2(1*H*)-one (514)[249]

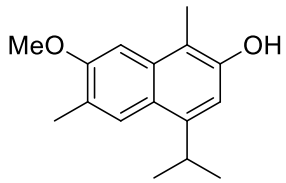


[249] Y. Zhang, Y. Liao, X. Liu, X. Xu, L. Lin, X. Feng, *Chem. Sci.* **2017**, *8*, 6645-6649.

514 was synthesized followed a reported method described in the literature.[243] TMSCl (23.0 µL, 0.18 mmol) was added to a solution of **491** (28.4 mg, 0.13 mmol) and pyridine (12.1 µL, 0.15 mmol) in dry DCM (0.56 mL) at 0 ºC under inert atmosphere. The reaction was stirred for 16 hours at rt and quenched with water. The mixture was extracted with EtOAc (x3), dried over Na_2SO_4 and concentrated to dryness under reduced pressure to afforf **514** in 99% yield (37.3 mg, 0.13 mmol), as a white solid, which was used in the next step without purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.29 (d, *J* = 9.8 Hz, 1H), 7.15 (s, 1H), 7.05 (s, 1H), 6.01 (d, *J* = 9.8 Hz, 1H), 3.90 (s, 3H), 2.21 (s, 3H), 1.51 (s, 3H), 0.08 – 0.03 (m, 9H).

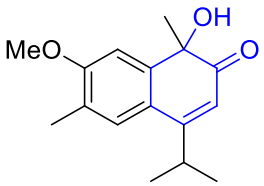
4-Isopropyl-7-methoxy-1,6-dimethylnaphthalen-2-ol (515)[249]



515 was synthesized followed a reported method described in the literature.[243] To a suspension of copper (I) cyanide (CuCN, 25.0 mg, 0.28 mmol) in a mixture of dry THF (0.21 mL) and dry Et_2O (0.21 mL), isopropyl magnesium chloride (^{i}PrMgCl 2.0 M in THF, 0.28 mL, 0.56 mmol), boron trifluoride etherate (BF_3OEt_2, 0.14 mL) and **514** (20.3 mg, 0.07 mmol) were successively added at -78 ºC under inert atmosphere. The reaction was stirred for 8 hours while it was allowed to reach rt, quenched with an aqueous saturated solution of NH_4Cl and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated to dryness under reduced pressure. The crude was purified by flash chromatography (heptane/EtOAc : 10/1) to give 4-isopropyl-7-methoxy-1,6-dimethylnaphthalen-2-ol (**515**) in 45% yield (9.1 mg, 0.04 mmol), as a white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.78 (s, 1H), 7.10 (s, 1H), 6.84 (s, 1H), 4.73 (s, 1H), 3.96 (s, 3H), 3.72 – 3.60 (m, 1H), 2.47 (s, 3H), 2.38 (s, 3H), 1.37 (s, 3H), 1.34 (s, 3H).

Lacinilene C methyl ether (30)[250]



Following **Method A**, Lacinilene C methyl ether (**30**) was obtained in 72% yield (3.0 mg, 0.01 mmol), as a yellow solid, from 4-isopropyl-7-methoxy-1,6-dimethylnaphthalen-2-ol (**515**) (3.9 mg, 0.02 mmol), $NaHCO_3$ (8.4 mg, 0.10 mmol) and a solution of Oxone® (10.0 mg, 0.03 mmol) in Milli-Q water (0.2 mL). The crude mixture was purified by flash chromatography (heptane/EtOAc : 4/1).

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35 (s, 1H), 7.21 (s, 1H), 6.02 (s, 1H), 3.92 (s, 3H), 3.28 – 3.17 (m, 1H), 2.24 (s, 3H), 1.53 (s, 3H), 1.28 (d, *J* = 5.1 Hz, 3H), 1.26 (d, *J* = 5.2 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ: 205.7, 164.40, 159.6, 145.7, 127.8, 125.5, 121.0, 114.9, 107.4, 77.0, 55.8, 34.2, 29.3, 22.4, 22.1, 16.4.

HRMS (EI): calculated for $C_{16}H_{20}O_3$ ($[M]^+$) 260.1412, found 260.1401.

[250] Y. Zhang, Y. Liao, X. Liu, X. Xu, L. Lin, X. Feng, *Chem. Sci.* **2017**, *8*, 6645-6649.

Chapter 4

Conclusion

The development of this PhD thesis allows establishing the following conclusions:

Chapter 2. Oxidative dearomatization of angular tetracyclic phenols: Synthesis of *oxygenated* angucyclinone derivatives.

7,12-Dimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (**22a**) and 7,8,12-trimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (**22b**) were synthesized efficiently in four reaction steps: Hauser-Kraus anulation, benzylation of phenol group at C_6, reductive methylation of quinone moieties and reductive debenzylation, in 57% and 46% overall yield, respectively. 6-Hydroxy-7,12-dimethoxy-3,4-dihydrotetraphen-1(2*H*)-one (**22c**) could be synthesized in 45% overall yield after 5 reaction steps including the same steps as before, and an additional photooxidation reaction at C_1.

7,12-Dimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (**24a**) and 7,8,12-trimethoxy-1,2,3,4-tetrahydrotetraphen-6-ol (**24b**) were isolated in 76% and 30% overall yield, respectively from the corresponding para-alkyl phenol **22**, using the optimized oxidative dearomatization conditions (Oxone® / $NaHCO_3$ / acetone) in the dark, established after optimization (*Figure 4.1*).

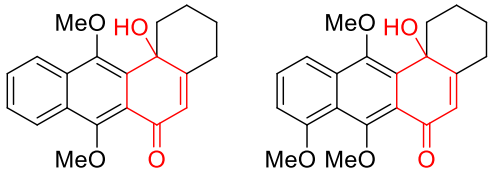


*Figure 4.102. Tetracyclic para-quinols **24a** and **24b** synthesized from tetracyclic phenols **22a** and **22b***

During the development of this Thesis, we discovered that tetracyclic phenols **22** could act as a photosensitizer promoting their own oxidative dearomatizaton. This photooxidation occurred under mild conditions and, in comparison with other oxidative methods, is more environmentally friendly and inexpensive, only light and air were used, not addition of metal catalysts, photosensitizers or external oxidants are requiered. The oxidation into the corresponding *para*-peroxy quinols **23a** and **23b**, quinones **196** and **198** and bisperoxy bisketal **197** (*Figure 4.2*) took place using the oxygen of the air as the oxidant.

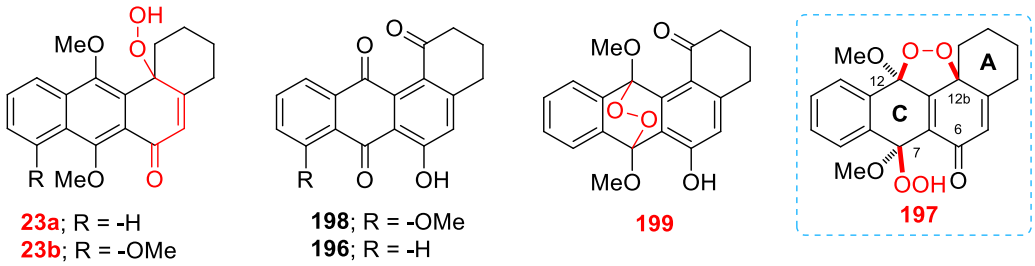


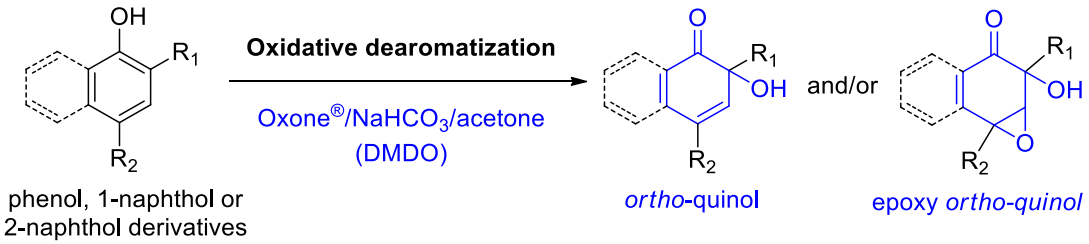
Figure 4.103. Tetracyclic oxidized products formed by irradiation of the corresponding phenol precursors under air.

The different degrees of oxidation of the final products could be controlled choosing the solvent employed during the irradiation process. Also, the selectivity in the ring oxidation was dependent on the substituent existent in the tetracyclic precursors whose influence on the electron density of the different rings, is essential in the selectivity: always the most electron-rich ring was oxidized. Thus, the irradiation of phenol **22a** and **22b** in acetone gave the corresponding *para*-peroxy quinols **23a** and **23b**, while the irradiation of phenol **22c** in acetone afforded the endoperoxide **199**. Also, the irradiation of a chloroform solution of phenols **22b** and **22c** generated the corresponding tetracyclic quinones **198** and **196**, but the irradiation of phenol **22a** in chloroform afforded a new unexpected compound, the bisperoxi bisketal **197** with a masked anthraquinone structure. The structure of bisperoxide **197** is the result of a double oxidative dearomatization process by the incorporation of two molecules of oxygen into the tetracyclic structure of phenol **22a**, in a very selective manner.

The biological studies of bisperoxy bisketal **197** were carried out on three different established human cell lines, larynx Hep-2, breast MDA-MB and cervix HeLa cells. The results indicated a significant anticancer activity, even better than the one displayed by doxorubicin, an anticancer agent currently used for the treatment of different types of cancer in patients.

Chapter 3. Synthesis of *ortho*-quinols by oxidative dearomatization of phenols using the system Oxone® / $NaHCO_3$ / acetone as the source of dimethyldioxirane

The system Oxone® / $NaHCO_3$ / acetone, as a source of dimethyldioxirane (DMDO), promoted the oxidative dearomatization of differently substitued phenols and naphthols affording the epoxy *ortho*-quinols, as the major compounds, together with the corresponding *para*-quinols or quinone, depending on the substituent existent at para position (*Scheme 4.1*).

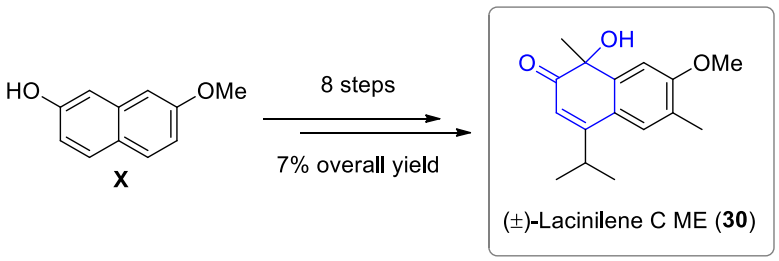


Scheme 4.174. Oxidative dearomatization products of the reaction of ortho substituted phenols / naphthols.

This oxidative dearomatization process is very simple, easy to carried out, not dangerous because the DMDO was formed and consumed in the reaction medium and, the reagents used (Oxone® and $NaHCO_3$) are commercially available and cheap. The method is very sensitive to steric effects, bulky groups such as *tert*-butyl, completely blocked the oxidation on the occupied.

An axial-to-center chirality transfer from enantiopure binaphthols with axial chirality to the resulting ortho-quinols having central chirality occurred during the process in excellent enantiomeric excess

This oxidative dearomatization methodology was applied to the total synthesis of natural product lacinilene C methyl ether (**30**) as the key step to introduce a hydroxyl group an ortho position.



*Scheme 4.175. Total synthesis of lacinilene C methyl ether (**30**)*

Conclusiones

Del trabajo realizado descrito en esta Tesis Doctoral, se pueden establecer las siguientes conclusiones, según los capítulos:

Capítulo 2. Desaromatización oxidante de fenoles tetracíclicos angulares: Síntesis de derivados oxigenados de anguciclinonas.

Se sintetizaron los *para*-alquil fenoles 7,12-dimetoxi-1,2,3,4-tetrahidrotetrafen-6-ol (**22a**) y 7,8,12-trimetoxi-1,2,3,4-tetrahidrotetrafen-6-ol (**22b**) de forma eficiente en cuatro pasos de reacción: una anulación de Hauser-Kraus, bencilación del grupo fenólico en C6, una reducción / metilación de la quinona y una desbencilación en condiciones reductoras, con redimientos globales de 57% y 46%, respectivamente. 6-Hidroxi-7,12-dimetoxi-3,4-dihidrotetrafen-1(2*H*)-ona (**22c**) se obtuvo con un rendimiento global de 45% en 5 pasos de reacción, siguiendo la misma secuencia sintética descrita antes, pero incluyendo una etapa de fotooxidación en C_1.

Los *para*-quinoles 7,12-dimetoxi-1,2,3,4-tetrahidrotetrafen-6-ol (**24a**) y 7,8,12-trimetoxi-1,2,3,4-tetrahidrotetrafen-6-ol (**24b**) se aislaron con unos rendimientos globales del 76% y 30%, respectivamente desde el correspondiente para-alquil fenol 22, usando un método de desaromatización oxidante optimizado (Oxono® / $NaHCO_3$ / acetona en la oscuridad) (*Figura 4.1*).

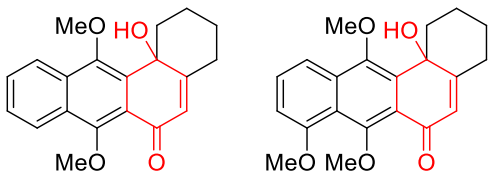


*Figura 4.1. para-Quinoles tetracíclicos **24a** y **24b** sintetizados a partir de los fenoles tetracíclicos **22a** y **22b***

Durante el desarrollo de esta Tesis, descubrimos que los fenoles tetracíclicos **22** eran sensibles a la luz, evolucionando hacia sus productos de desaromatización oxidante. Estos fenoles **22** actuarían como auto-fotosensilizadores durante este proceso de fotoxidación, que tuvo lugar bajo condiciones suaves y de forma sostenible, en comparación con otros métodos de oxidación. Es un método barato de oxidación, ya que sólo requirió de una fuente de luz y de aire. La obtención de los correspondientes productos de oxidación; *para*-peroxi quinoles **23a** y **23b**, quinonas **196** y **198** y bisperoxi bisacetal **197** (*Figura 4.2*), tuvo lugar usando oxígeno del aire como agente oxidante.

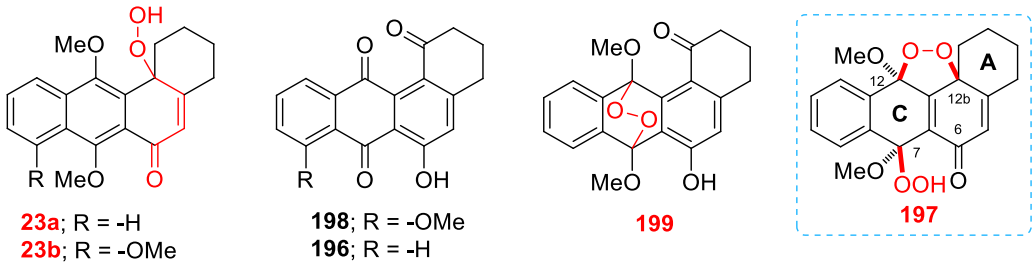


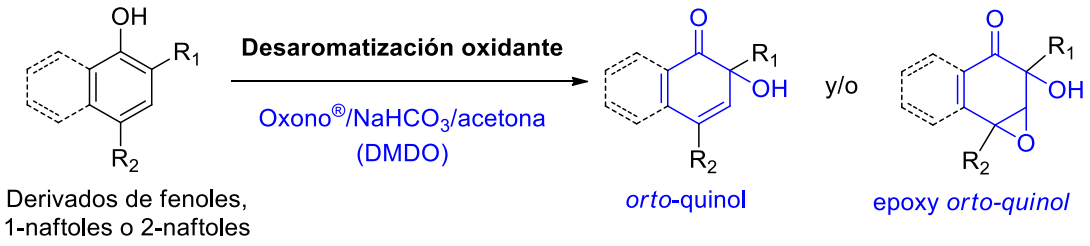
*Figura 4.104. Productos de oxidación tetracíclicos sintetizados al irradiar los correspondientes para-alquil fenoles tetracíclicos **22** al aire.*

Dependiendo del disolvente empleado, se pudo controlar los diferentes grados de oxidación de los productos obtenidos durante la irradiación. También, se observó que el anillo a oxidarse dependía de la densidad electrónica de los distintos sustituyentes de la molécula, por lo que siempre se oxidaba el anillo más rico en electrones. Por lo tanto, al irradiar una disolución en acetona de los fenoles **22a** y **22b**, se obtuvieron los correspondientes *para*-peroxy quinoles **23a** y **23b**, mientras que la irradiación del fenol **22c** en acetona generó el endoperoxido **199**. Por otro lado, la irradiación de los fenoles **22b** y **22c** en cloroformo dio lugar a las correspondientes quinonas tetracíclicas **198** y **196** y, sin embargo, la irradiación de **22a** en cloroformo generó un nuevo compuesto de forma inesperada, el bisperoxi bisacetal **197**. La estructura de este nuevo compuesto **197** es el resultado de un proceso de doble desaromatización oxidante a través de la incorporación de dos moléculas de oxígeno a la estructura tetracíclica del fenol **22a**, de forma diastereoselectiva.

se estudiaron las propiedades anticancerígenas del bisperoxi bisacetal **197** en tres líneas celulares: laringe Hep-2, MDA-MB de mama y células HeLa de cuello uterino. Los resultados obtenidos indicaron la alta capacidad del bisperóxido **197** para inducir mortalidad en las diferentes líneas celulares cancerígenas, incluso mejores que los que presenta la doxorrubicina, un agente anticancerígeno actualmente utilizado para el tratamiento de diferentes tipos de cáncer en pacientes.

Capítulo 3. Síntesis de orto-quinoles mediante desaromatización oxidante de fenoles usando el sistema Oxono® / $NaHCO_3$ / acetona como fuente de dimetildioxirano

El sistema Oxono® / $NaHCO_3$ / acetona, como fuente de dimetildioxirano (DMDO), provocó la desaromatización oxidante de fenoles y naftoles diferentemente sustituidos, generándose en la mayoría de los casos los correspondientes epoxi *orto*-quinoles, como producto mayoritario, junto con los correspondientes *para*-quinoles o quinonas (*Esquema 4.1*).

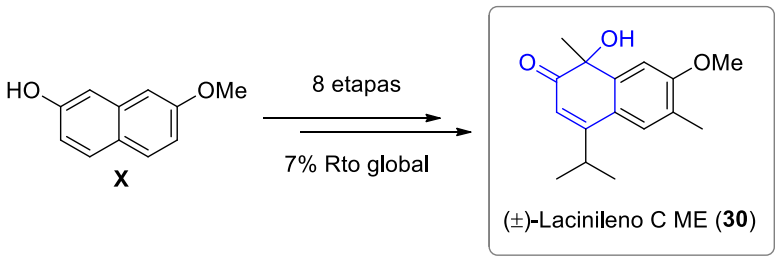


Esquema 4.176. Productos dela reacción de desaromatización oxidante de fenoles / naftoles orto sustituidos

Este proceso de desaromatización oxidante es muy simple y fácil de realizar experimentalmente. No es un proceso peligroso porque el DMDO se genera en el propio medio de reacción y se consume a la vez. Además, los reactivos usados (Oxono® and $NaHCO_3$) son comerciales y baratos. Este método es muy sensible a los efectos estéricos, ya que grupos voluminosos como el *terc*-butilo, bloquean completamente la posición que ocupan.

Al utilizar esta metodología de desaromatización oxidante en binaftoles enantiopuros con quiralidad axial, se observó una completa transferencia de quiralidad axial a quiralidad central ya que se obtuvieron los correspondientes *orto*-quinoles con quiralidad central con excelentes excesos enantioméricos.

Por último, se usó este método como etapa clave en la síntesis total del producto natural lacinileno C metil éter, en la introducción de un grupo hidroxilo en la posición orto.



*Esquema 4.177. Síntesis total del lacinilene C metil éter (**30**)*

Resumen

La desaromatización oxidante de compuestos aromáticos da lugar a productos muy interesantes desde el punto de vista sintético. En el caso de los fenoles, este proceso puede derivar en varias especies oxidadas, como quinonas, acetales de quinona, y derivados de quinoles, incluyendo *para*-hidroperóxidos, dependiendo de los grupos funcionales y las posiciones que estos ocupen (*Figura 1*).[1, 2, 3, 4] Como consecuencia, el control de estos procesos oxidativos resulta fundamental para su posible aplicación en la síntesis de un producto determinado.

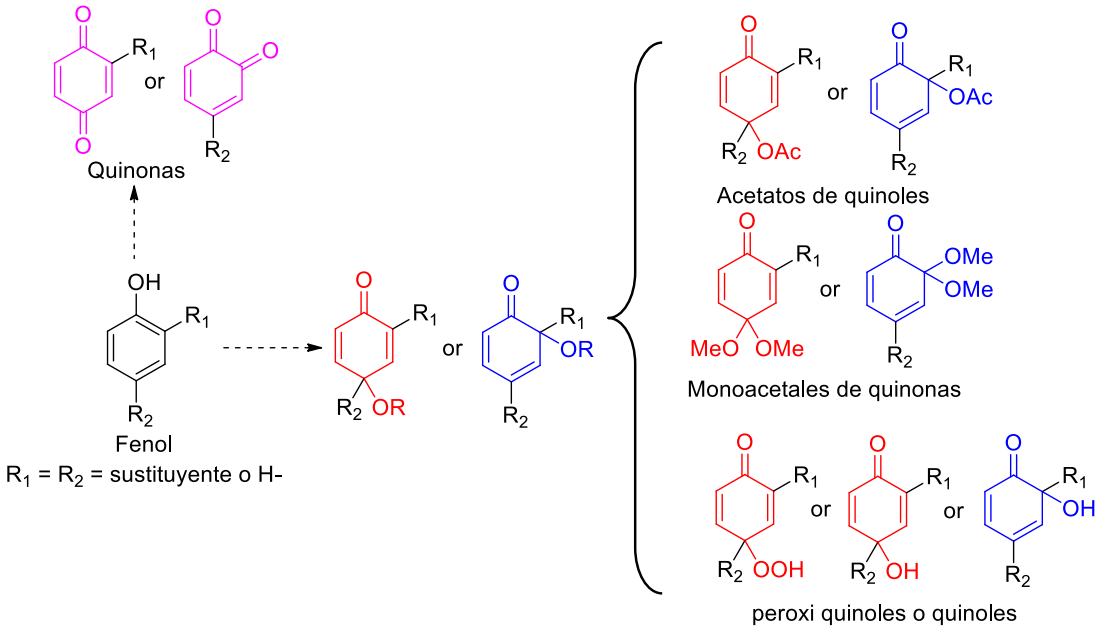


Figura 2. Posibles derivados resultantes de la desaromatización oxidante de fenoles diferentemente sustituidos

En concreto la transformación de los fenoles en quinoles, puede dar lugar a tres tipos distintos de sistemas: 4-alquil-4-hidroperoxi-2,5-ciclohexadienonas (*para*-peroxi quinoles), 4-alquil-4-hidroxi-2,5-ciclohexadienonas (*para*-quinoles) y 6-alquil-6-hidroxi-2,4-ciclohexadienonas (*orto*-quinoles). Estas estructuras se encuentran presentes en muchos productos naturales, así como en moléculas más complejas con importantes propiedades terapéuticas.[5]

1

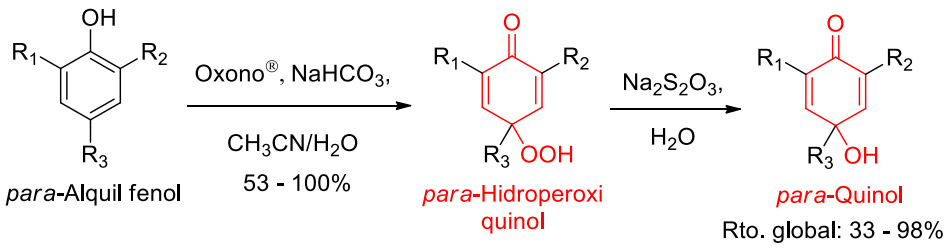
2 a) S. Quideau, L. Pouysegu, P. A. Peixoto, D. Deffieux, *Top Curr Chem* **2016**, *373*, 25. b) S. P. Roche, J. A. Porco Jr., *Angew. Chem. Int. Ed.* **2011**, *50*, 4068.

3 D. Magdziak, S. J. Meek, T. R. R. Pettus, *Chem. Rev.* **2004,** *104,* 1383.

4 a) Q. Ding, Y. Ye, R. Fan, *Synthesis* **2013**, *45*, 1-16; b) C.-X. Zhuo, W. Zhang, S.-L. You, *Angew. Chem. Int. Ed.* **2012**, *51*, 12662-12686; c) S. P. Roche, J. A. Porco Jr., *Angew. Chem. Int. Ed.* **2011**, *50*, 4068-4093.

5 J. E. Baldwin, R. M. Adlington, V. W.-W. Sham, R. Marquez, P. G. Bulger, Tetrahedron **2005**, *61*, 2353-2363. For recent examples, see: a) L. Pan, J. Dong, D. Xie, Y. Li, Q. Liu, *Adv. Synth. Catal.* **2018**, *360*, 958-964; b) N.

En el año 2006, nuestro grupo de investigación desarrolló una reacción de desaromatización oxidante simple y selectiva de *para*-alquil fenoles usando Oxono® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) y bicarbonato sódico ($NaHCO_3$) en una mezcla de acetonitrilo / H_2O (*Esquema 1*).[6] El Oxono® en un medio básico acuoso descompone formando oxígeno singlete ($^1O_2$), que resultó ser la especie oxidante que reaccionó con varios fenoles *para*-alquil sustituidos a través de una cicloadición [4+2] para generar los correspondientes *para*-peroxi quinoles. Tras una etapa de reducción, estos *para*-peroxi quinoles se pudieron transformar en los correspondientes *para*-quinoles con buenos rendimientos.



Esquema 1. Desaromatización oxidante de para-alquil fenoles con el sistema Oxono® / $NaHCO_3$

Esta nueva metodología pudo ser aplicada con éxito en la síntesis de varios productos naturales, como la rengiolona, la cochinchinenona o la cefalosporolida G.[7]

Teniendo en cuenta los buenos resultados obtenidos, se decidió aplicar esta reacción de desaromatización oxidante en la síntesis de un grupo de productos naturales, anguciclinonas con hidroxilos angulares, que presentan importantes propiedades biológicas. Las agluconas de esta familia de compuestos se caracterizan estructuralmente por poseer un esqueleto tetracíclico angular de tipo benz[*a*]antraquinona, con un grupo metilo en la posición C_3 y grupos oxigenados en las posiciones C_1, C_3 y C_8 y se diferencian en los distintos grados de insaturación y oxidación del resto de la molécula (*Figura 2*).[8] Dentro de esta familia, existe un subgrupo que posee uno o dos grupos hidroxilos angulares en las posiciones C_{4a} y / o C_{12b}, como en la aquayamicina (**11**).[9] La importancia de este grupo de anguciclinonas oxigenadas radica en sus importantes actividades terapéuticas. Su síntesis total sigue suponiendo un reto sintético hoy en día, que no está bien

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J. Green, C. A. Connolly, K. P. W. Rietdijk, G. S. Nichol, F. Duarte, A. L. Lawrence, *Angew. Chem. Int. Ed.* **2018**, *57*, 6198-6202; c) J.-J. Xing, Y.-N. Gao, M. Shi, *Adv. Synth. Catal.* **2018**, *360*, 1-9.

[6] M. C. Carreño, M. González-López, A. Urbano, *Angew. Chem.Int. Ed.* **2006**, *45*, 2737-2741.

[7] a) S. Barradas, G. Hernández-Torres, A. Urbano, M. C. Carreño, *Org. Lett.* **2012**, *14*, 5952-5955; b) S. Barradas, A. Urbano, M. Carmen Carreño, *Chem. Eur. J.* **2009**, *15*, 9286-9289.

[8] a) M. K. Kharel, P. Pahari, M. D. Shepherd, N. Tibrewal, S. E. Nybo, K. A. Shaaban, J. Rohr, *Nat. Prod. Rep.* **2012**, *29*, 264−325; b) K. Krohn, J. Rohr, *Top. Curr. Chem.* **1997**,*188*, 127-195; c) J. Rohr, R. Thiericke, *Nat. Prod. Rep.* **1992**, *9*, 103-137.

[9] S. I. Elshahawi, K. A. Shaaban, M. K. Kharel, J. S. Thorson, ***Chem. Soc. Rev.*** **2015**, ***44***, 7591-7697

resuelto. Los pocos ejemplos descritos utilizan un acoplamiento intramolecular para generar una estructura de pinacol de forma diatereoselectiva, una ciclación mediada por SmI_2 de un derivado dicarbonílico o una adición intramolecular de un anión derivado de una cianhidrina, como etapas clave para instalar los grupos hidroxilos en las posiciones C_{4a} y C_{12b}.[10]

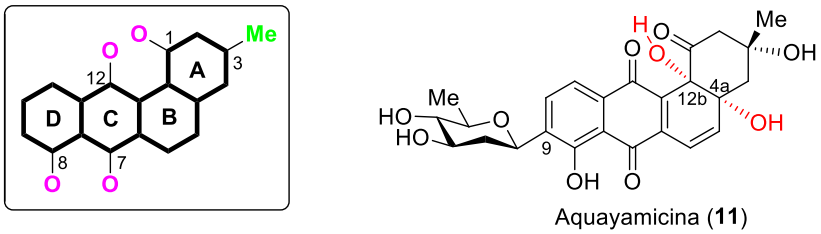
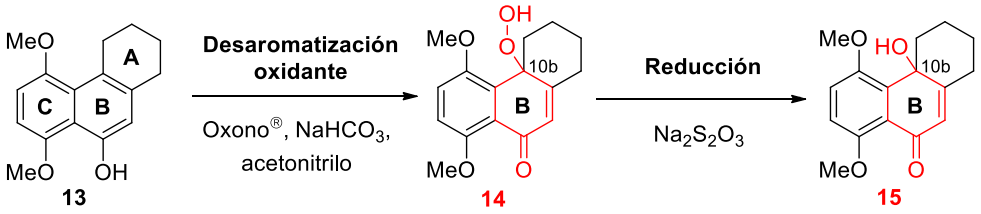


Figura 3. Características estructurales comunes de las anguciclinonas. Aquayamicina: ejemplo de anguciclinona con hidroxilos angulares.

La posible aplicación de la metodología de desaromatización oxidante utilizando Oxono® a la síntesis de estos productos naturales, se inició en nuestro grupo sobre un sustrato modelo, el *para*-alquil fenol tricíclico **13**.[11] La desaromatización oxidante del fenol **13** con el sistema Oxono® / $NaHCO_3$ en acetonitrilo condujo de forma selectiva al *para*-peroxi quinol tricíclico **14**, cuya reducción con tiosulfato sódico generó al *para*-quinol **15**, que ya posee uno de los hidroxilos angulares presentes en las anguciclicnonas. Este *para*-quinol tricíclico **15** se transformó de forma divergente y selectiva en seis derivados tricíclicos oxigenados similares a varias anguciclinonas naturales.



Esquema 2. Desaromatización oxidante de sustratos modelo con estructuras angulares de tipo ABC

Teniendo en cuenta este resultado, se planteó como primer objetivo de este trabajo el estudio dirigido a la síntesis total de anguciclinonas con oxígenos angulares, aplicando el sistema Oxono® / $NaHCO_3$ sobre sustratos modelo tetracíclicos. Así, la primera parte de esta Tesis

[10] a) S. Kusumi, H. Nakayama, T. Kobayashi, H. Kuriki, Y. Matsumoto, D. Takahashi, K. Toshima, *Chem. Eur. J*, **2016**, 22, 18733-18736; b) H. R. Khatri, H. Nguyen, J. K. Dunaway, J. Zhu, *Chem. Eur. J*. **2015**, *21*, 13553-13557; c) T. Matsumoto, H. Yamaguchi, M. Tanabe, Y. Yasui, K. Suzuki, *Tetrahedron Lett*. **2000**, 8393-8396; d) K. Krohn, P. Frese, U. Florke, *Chem. Eur. J.,* **2000**, *6*, 3887-3896; e) G. A. Kraus, Z. Wan, *Tetrahedron Lett.* **1997**, *38*, 6509-6512.

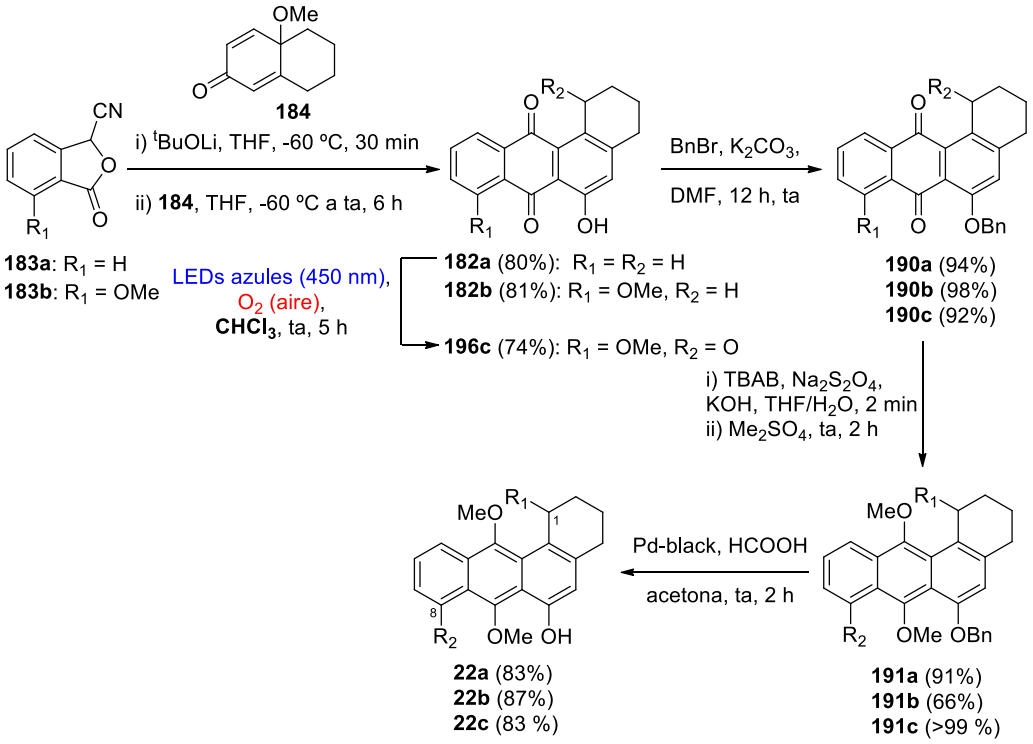
[11] S. Vila-Gisbert, A. Urbano, M. C. Carreño, *Chem. Commun*. **2013**, *49*, 3561-3563.

Doctoral se enfocó hacia este estudio sintético. Durante la realización de este estudio, se observaron distintos resultados de gran interés, que dieron lugar a las investigaciones desarrolladas en la segunda parte de esta Tesis Doctoral. Así, los resultados obtenidos que se presentan en esta Memoria, están recogidos en los siguientes capítulos:

Capítulo 2. Desaromatización oxidante de fenoles tetracíclicos angulares: Síntesis de derivados oxigenados de anguciclinonas.

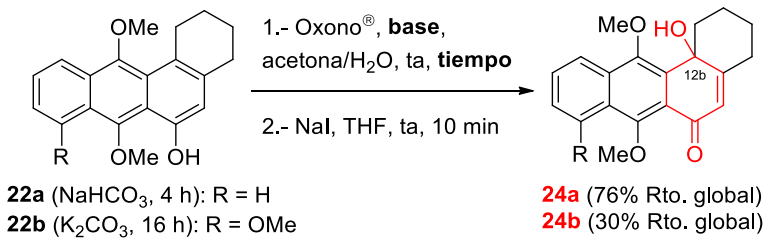
Para extender los resultados previamente obtenidos en el estudio de los modelos tricíclicos, dirigidos a la síntesis de las anguciclinonas naturales con hidroxilos angulares, se planteó el estudio de desaromatización oxidante con el sistema Oxono® / $NaHCO_3$ sobre fenoles *para*-alquil sustituidos con estructura tetracíclica angular, los cuales tuvieron que ser previamente sintetizados Los sustratos elegidos se encuentran indicados en el *Esquema 3*. Se trata de derivados del 7,12-dimetoxi-1,2,3,4-tetrahidrotetrafen-6-ol (**22a**), sin ningún sustituyente en los anillos A y D, el fenol **22b**, que presenta un grupo metoxilo en la posición C_8, y el derivado **22c**, con un grupo carbonilo en C_1. Los fenoles **22a** y **22b** fueron sintetizados en cuatro pasos de reacción con unos rendimientos globales de 57% y 46%, respectivemante, a través de la secuencia de reacciones que se muestran el *Esquema 3*. El esqueleto tetracíclico angular se construyó mediante una anulación de Hauser-Kraus entre la ciclohexenona **184** y una cianoftalida **183a** / **183b**. La protección ortogonal del grupo fenol como bencilo y posterior reducción y metilación de la quinona, dio lugar al derivado tetracíclico **191a** / **191b**. Por último, la desbencilación con el sistema HCOOH, Pd-black, acetona, generó el fenol tetracíclico **22a** / **22b**. Por otro lado, la síntesis del fenol **22c** incluyó una etapa de fotooxidación de la posición C_1 en presencia de oxígeno, entre la anulación de Hauser-Kraus y la bencilación (*Esquema 3*). Este proceso de fotooxidación ya había sido descrito por Kronh.[12]

[12] a) R. Karmakar, D. Mal, *J. Org. Chem.* **2012**, *77*, 10235-10248; b) K. Krohn, M. H. Sohrab, U. Florke, *Tetrahedron*: *Asymmetry* **2004**, *15*, 713-718; c) K. Krohn, F. Ballwanz, W. Baltus, *Liebigs. Ann. Chem*. **1993**, 911–913.



*Esquema 3. Síntesis de para-alquil fenoles **22** con esqueleto tetracíclico angular*

Una vez sintetizados los *para*-alquil fenoles tetracíclicos **22**, se inició el estudio de la reacción con Oxono® sobre el sustrato más sencillo **22a**. Después de una optimización de las condiciones de reacción, se logró sintetizar el *para*-quinol tetracíclico **24a** de forma selectiva y con un rendimiento global del 76%, tras dos etapas de reacción (*Esquema 4*), consistentes en el tratamiento con 8 equivalentes de Oxono® y 24 equivalentes de $NaHCO_3$ en acetona, seguido de una reducción con NaI en THF.



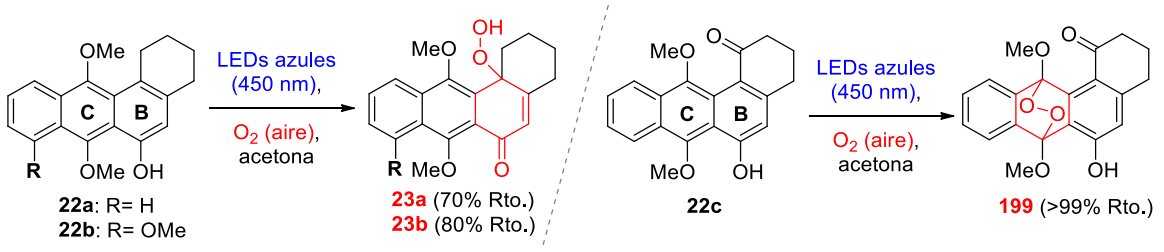
*Esquema 4. Desaromatización oxidante de los fenoles **22a** y **22b** con Oxono®*

Estas condiciones de desaromatización oxidante se aplicaron sobre los sustratos fenólicos **22b** y **22c**. La reacción del sustrato **22b** requirió la utilización de carbonato potásico como base, pudiéndose aislar el *para*-quinol tetracíclico **24b** con un rendimiento global del 30%, tras las dos etapas de reacción. Sin embargo, el fenol **22c** no reaccionó en presencia de Oxono®, en ninguna

de las condiciones ensayadas. El grupo carbonilo atractor de electrones situado en la posición C_1 disminuye la reactividad del anillo B dificultando su oxidación.

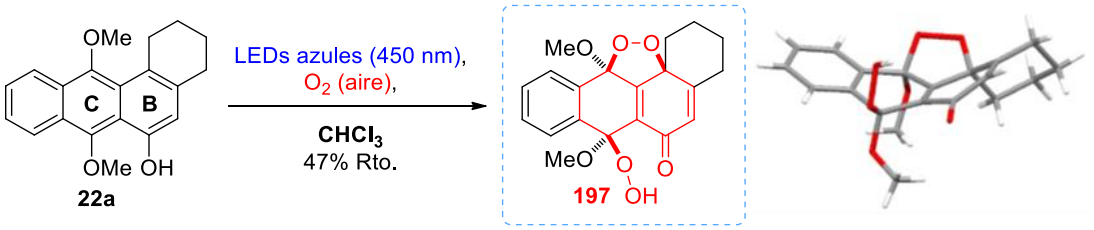
Durante el desarrollo de la síntesis de los fenoles tetracíclicos **22**, se observó que el 7,12-dimetoxi-1,2,3,4-tetrahidrotetrahen-6-ol (**22a**) era sensible a la luz y al aire. Esta observación condicionaba los rendimientos obtenidos que sólo resultaron útiles trabajando en la oscuridad. La fotooxidación de derivados de anguciclinonas había sido descrita en la bibliografía para la oxidación de la posición C_1 de este tipo de compuestos al ser irradiados con luz solar en presencia de oxígeno.[12] Teniendo en cuenta este antecedente y los rendimientos variables obtenidos en la síntesis de los fenoles tetracíclicos, se decidió investigar en profundidad el proceso de fotooxidación de los sustratos **22**. Así, se pudo establecer que el fenol **22a** se oxidaba a una mezcla del *para*-peroxi quinol **23a** y *para*-quinol **24a**, en presencia de luz ambiental y aire.

Así, la reacción de fotooxidación del fenol **22a** se estudió bajo la acción de diferentes fuentes lumínicas (lámpara de sobremesa, luz solar, luz roja, lámpara UV y LEDs azules y verdes) y distintos disolventes (cloroformo y acetona) y expuestos al aire, usando unas condiciones similares a las descritas por Kronh.[12] Los mejores resultados se obtuvieron usando los LEDs azules. Así, los fenoles **22a** y **22b** se transformaron en sus correspondientes productos de desaromatización oxidante *para*-peroxi quinoles **23a** y **23b** de forma selectiva, al ser irradiados con LEDs azules en acetona y al aire (*Esquema 5*). Al irradiar el fenol **22c** bajo estas mismas condiciones de fotooxidación se aisló el endoperóxido **199**, producto de oxidación del anillo más rico en electrones, que en este caso es el anillo C.



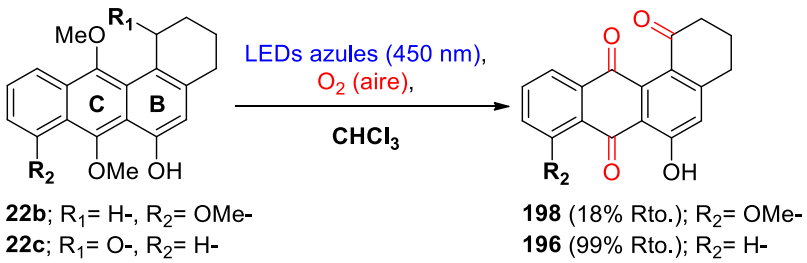
Esquema 5. Fotooxidación de los fenoles 22 irradiando con LEDs azules en acetona

Por otro lado, la irradiación con LEDs azules de una disolución en cloroformo del fenol **22a** generó, de forma inesperada un producto de doble oxidación, el *bis*-peroxi *bis*-acetal **197** con un rendimiento moderado (*Esquema 6*). La estructura de este nuevo compuesto fue determinada en base a sus datos espectroscópicos y corroborada por difracción de rayos-X. En este *bis*-peroxi *bis*-acetal de quinona **197** se habían incorporado dos moléculas de oxígeno y se habían generado tres nuevos centros estereogénicos de una forma diastereoselectiva.



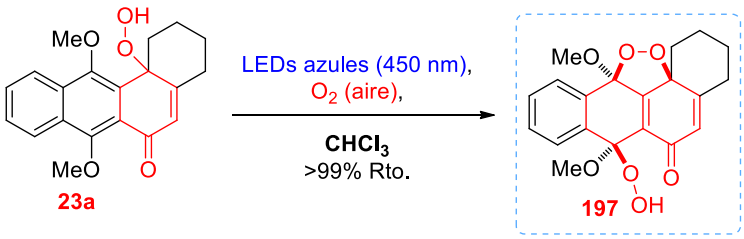
*Esquema 6. Formación del bis-peroxi bis-acetal **197** al irradiar el fenol **22a** con LEDs azules en cloroformo*

Por otra parte, la irradiación de los fenoles **22b** y **22c** con LEDs azules en cloroformo y al aire generó las correspondientes quinonas **198** y **196** con rendimientos aislados de 18% y 99%, respectivamente, tal y como muestra el *Esquema 7*.



*Esquema 7. Irradiación de los fenoles **22b** y **22c** con LEDs azules en cloroformo*

También, se comprobó que el *para*-peroxi quinol **23a** era el intermedio sintético en la formación del bisperoxi bisacetal **197**, ya que cuando **23a** se irradió con LEDs azules en cloroformo y al aire, se generó el bisperoxi bisacetal **197** de forma cuantitativa (*Esquema 8*).



*Esquema 8. Irradiación del para-peroxi quinol **23a** con LEDs azules en cloroformo*

Debido a las características estructurales que presenta del bisperoxi bisacetal **197**, con dos fragmentos peroxídicos, se estudiaron sus propiedades anticancerígenas en tres líneas celulares: laringe Hep-2, MDA-MB de mama y células HeLa de cuello uterino. Estos estudios in vitro fueron llevados a cabo por las doctoras Silvia Lucena y Ángeles Juarranz del Departamento de Biología, Facultad de Ciencias, Universidad Autónoma de Madrid. Los estudios realizados indicaron la alta capacidad del bisperóxido **197** para inducir mortalidad en las diferentes líneas celulares cancerígenas. Los resultados obtenidos fueron incluso mejores que los que presenta la

doxorrubicina, un agente anticancerígeno actualmente utilizado para el tratamiento de diferentes tipos de cáncer en pacientes.

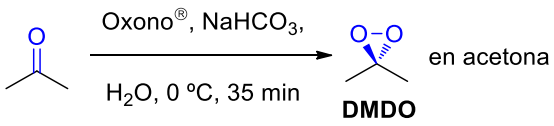
También se realizaron varios ensayos mecanísticos con el fin de elucidar el proceso de fotooxidación en la formación del bisperoxi bisacetal **197**. Se llevaron a cabo diferentes pruebas en las que se utilizó cloroformo deuterado, que acelera las reacciones del oxígeno singlete, DABCO, un inhibidor de oxígeno singlete y TEMPO, un inhibidor de radicales, con el fin de evaluar la participación del oxígeno singlete así como de procesos radicalarios en el mecanismo. A la vista de los resultados obtenidos se pudo proponer un mecanismo para la doble oxidación que consta de dos etapas. En la primera de ellas, se produce la formación de oxígeno singlete al irradiar el fenol **22a**, que puede actuar como autofotosensibilizador. El oxígeno singlete formado reacciona con el fenol **22a** a través de una cicloadición [4+2], dando lugar a un endoperóxido intermedio que evoluciona espontáneamente al *para*-hidroperóxido derivado del quinol **23a**. La segunda etapa implica la formación de oxígeno singlete además de un mecanismo radicalario, que se inhibe en presencia de TEMPO. El grupo hidroperóxido del *para*-peroxi quinol **23a** dirige el ataque del oxígeno singlete, produciéndose por la misma cara y originando únicamente uno de los posibles diatereoisómeros en la formación del bisperoxi bisacetal **197**.

Capítulo 3. Síntesis de orto-quinoles mediante desaromatización oxidante de fenoles usando el sistema Oxono® / $NaHCO_3$ / acetona como fuente de dimetildioxirano

La optimización de las condiciones de desaromatización oxidante con Oxono® que fue necesario hacer para lograr los mejores resultados con los fenoles tetracíclicos **22**, puso de manifiesto que el uso de la acetona en lugar de acetonitrilo como disolvente, permitía acceder directamente a los *para*-quinoles, disminuyendo la proporción relativa de *para*-peroxi quinol inicialmente observada. Así, cuando el fenol tetracíclico **22a** se trató con el sistema Oxono® / $NaHCO_3$ / acetona, se obtuvo una mezcla de los correspondiente *para*-peroxi quinol **23a** y *para*-quinol **24a**, en una proporción 57:43 versus la obtenida en acetonitrilo 77:23. Esta observación hacía pensar en la existencia de un proceso competitivo de oxidación diferente al de actuación del oxígeno singlete, debido a la presencia de la acetona. Como es sabido, la acetona puede ser oxidada en presencia de Oxono® en un medio básico originando dimetildioxirano (DMDO),[13] que es un nuevo agente de oxidación electrófilo. Como se muestra en el *Esquema 9*, el DMDO es el

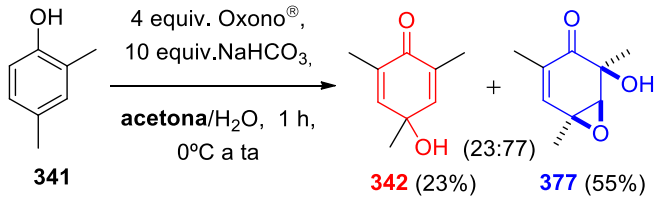
[13] a) H. Hussain, I. R. Green, I. Ahmed, *Chem. Rev.* **2013**, *113*, 3329-3371; b) P. Kachasakul, S. Assabumrungrat, P. Praserthdam, U. Pancharoen, *Chem. Eng. J.* **2003**, *92*, 131-139; c) N. Hashimoto, A. Kanda, *Org. Process. Res. Dev.* **2002**, *6,* 405-406.

peróxido cíclico derivado de la acetona que podría actuar como un agente oxidante en presencia de fenoles ricos en electrones. [14]



Esquema 9. Síntesis de dimetildioxirano (DMDO) usando Oxono®

Con el fin de investigar el comportamiento de fenoles diferentemente sustituidos en presencia de este agente oxidante, se llevó a cabo un estudio sobre distintos sustratos modelo. Así se puso de manifiesto que los fenoles 2,4,6-trisustituidos podían originar los productos de oxidación en la posición, de forma selectiva. Así la desaromatización oxidante del 2,4,6-trimetilfenol (**341**), con sustituyentes metilo en posición orto respecto del OH-, daba lugar, mayoritariamente, al derivado epoxidado **377** del correspondiente orto-quinol, usando un exceso del sistema Oxono® / $NaHCO_3$ / acetona, frente al *para*-quinol **342** (*Esquema 10*).



*Esquema 10. Desaromatización oxidante del 2,4,6-trimetil fenol (**341**) con exceso de Oxono® / $NaHCO_3$ / acetona*

Con el fin de evaluar la generalidad de la reacción de formación de los derivados de orto-quinol a partir de fenoles 2,4,6-trisustituidos con el sistema Oxono® / $NaHCO_3$ / acetona, se realizó la reacción sobre sustratos con sustituyentes de diferente tamaño y naturaleza electrónica, tanto electroatractores y electrodonadores. La *Figura 3* muestra un resumen de los orto-quinoles y los epoxi orto-quinoles que se sintetizaron en este estudio. De los resultados obtenidos, se puede concluir que esta reacción de desaromatización oxidante es sensible a efectos estéricos, ya que grupos voluminosos como el *terc*-butilo, impiden la oxidación de la posición que ocupan. Por otra parte, los fenoles con sustituyentes que pueden actuar como grupos salientes o que reaccionan con el Oxono®, como el grupo carbonilo, dieron reacciones secundarias, en este caso una reacción de Baeyer-Villiger, generando otros productos de oxidación, como quinonas.

[14] a) A. Altamura, C. Fusco, L. D'Accolti, R. Mello, T. Prencipe, R. Curci, *Tetrahedron Lett.* **1991**, *132*, 5445-5448, b) J. K. Crandall, M. Zucco, R. S. Kirsch, D. M. Coppert, *Tetrahedron Lett.* **1991**, 132, 5441-5441.

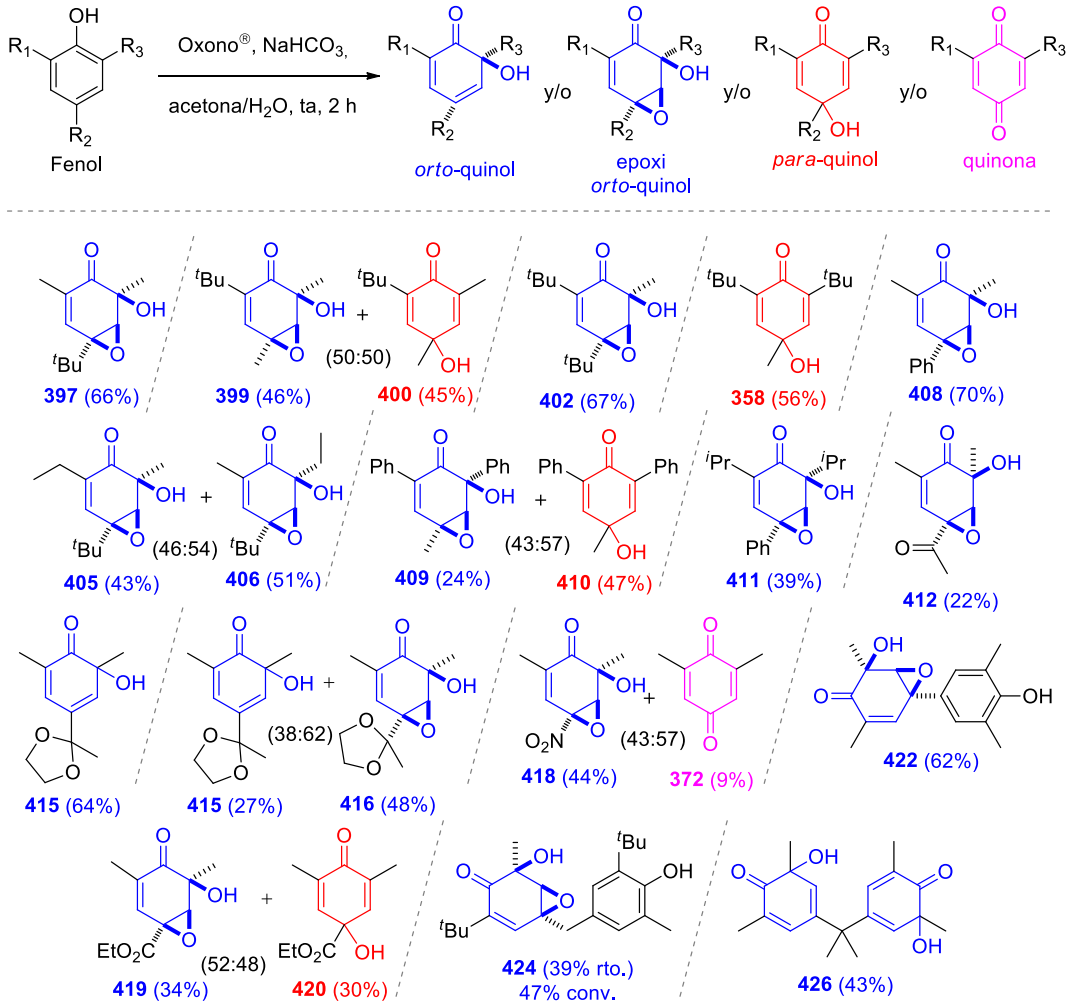


Figura 4. Resumen de los resultados obtenidos con distintos fenoles 2,4,6-trisustituidos

También se estudió la reactividad de derivados de 1- y 2-naftol con el sistema Oxono® / $NaHCO_3$ / acetona. Su comportamiento es similar. La desaromatización oxidante de 2-alquil-1-naftoles generó los correspondientes epoxi orto-quinoles, observándose como producto secundario las correspondientes quinonas, resultantes de la oxidación de la posición C_4 libre (*Figura 4*).

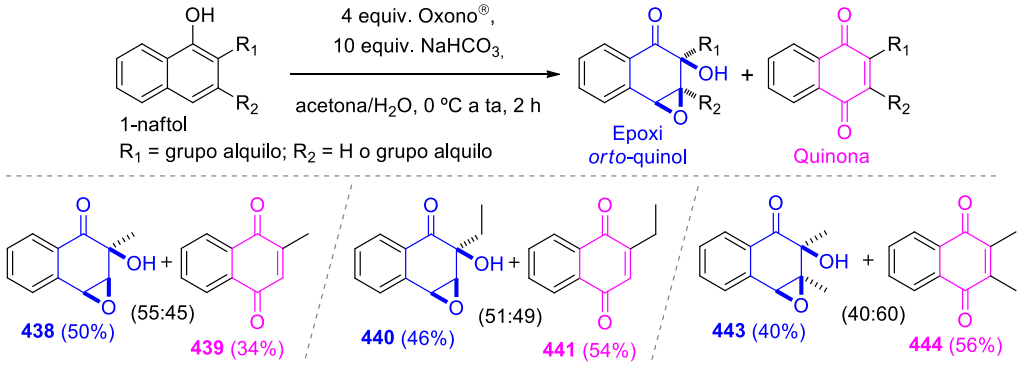


Figura 5. Desaromatización oxidante de 2-alquil-1-naftoles

Por otra parte, la desaromatización oxidante de 2,4-dialquil-1-naftoles puede generar mezcla de orto-quinoles y de los correspondientes epóxidos o con los productos de oxidación en la posición para, para-quinoles (*Figura 5*). Cuando la posición C_2 está ocupada por un grupo voluminoso, como el etilo o el *iso*-propilo, que bloquea parciamente esta posición, se pudieron aislar los correspondientes *para*-quinoles junto con los *orto*-quinoles. También, se detectaron los *orto*-quinoles junto con sus epóxidos al introducir un grupo fenilo en la posición C_4 y, dependiendo de los sustituyentes del grupo fenilo, se observaron variaciones en las proporciones de los productos obtenidos.

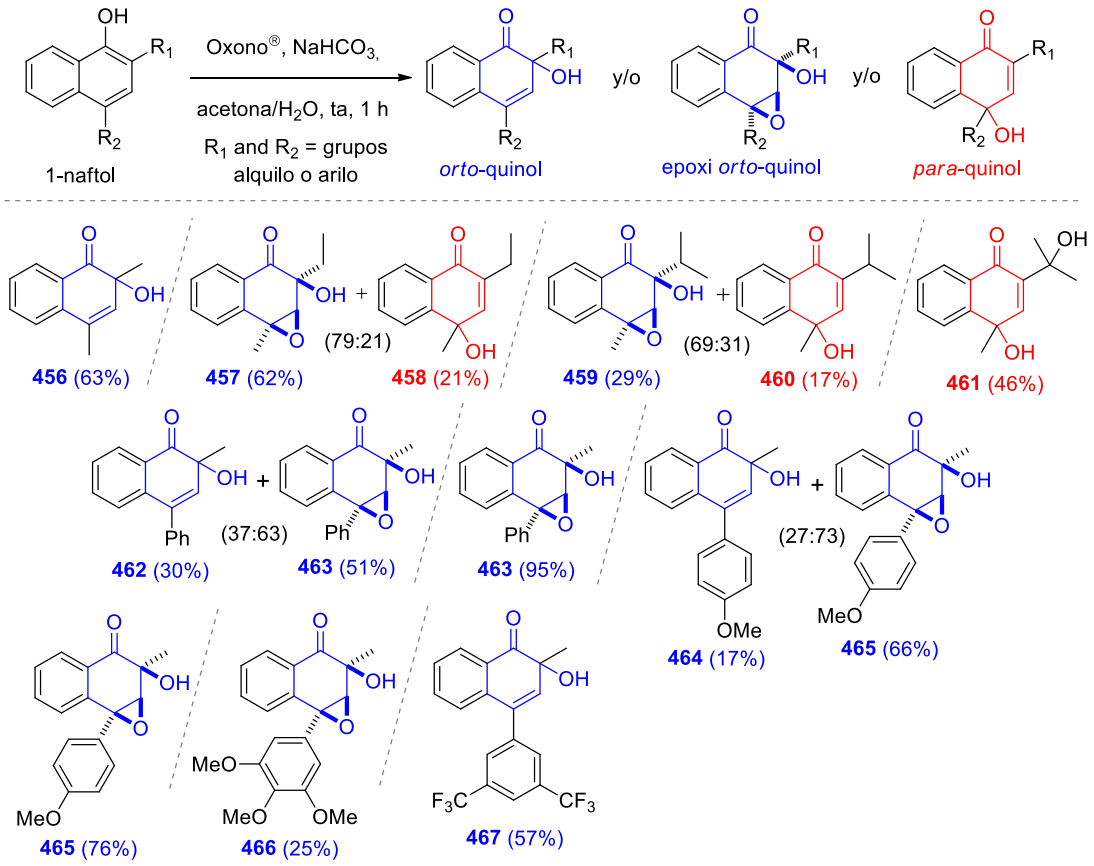


Figura 6. Desaromatización oxidante de 2,4-dialquil-1-naftoles

Por otro lado, la desaromatización oxidante de 1-alquil-2-naftoles solo generó orto-quinoles, excepto el BINOL racémico, que dió lugar al producto de condensación *rac*-**495**, un hemiacetal cíclico con una estructura de tipo furanosa (*Figura 6*).

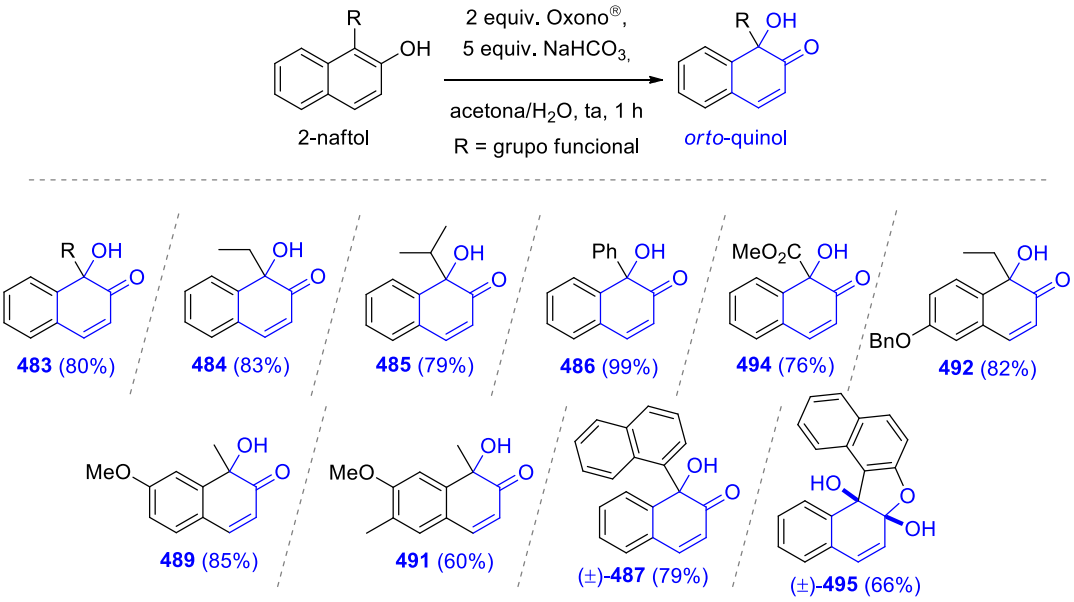


Figura 7. Desaromatización oxidante de 2-naftoles 1-sustituidos

La desaromatización oxidante de 1-naftil-2-naftoles enantiopuros con quiralidad axial condujo a los correspondientes productos oxidados con quiralidad central con excelentes excesos enantioméricos (98-96% ee), produciéndose una transferencia de quiralidad axial a quiralidad central (*Esquema 7*).

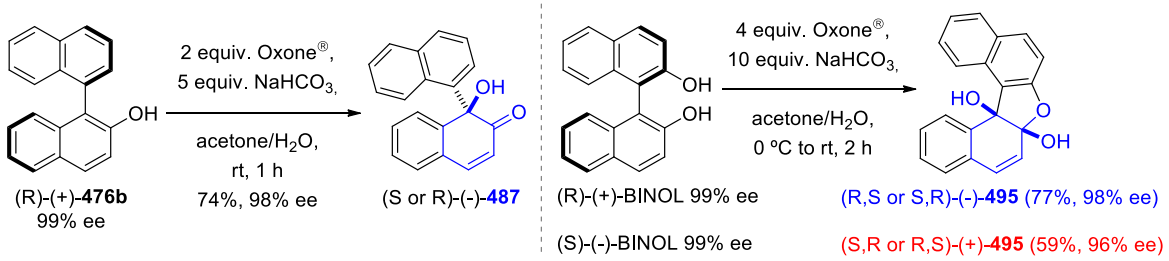


Figura 8. Desaromatización oxidante de binaftoles enantiopuros con quiralidad axial

En la última parte de esta Tesis Doctoral, aplicó la metodología de síntesis de *orto*-quinoles encontrada (Oxono® / $NaHCO_3$ / acetona) a la síntesis total de un producto natural, el lacinileno C metil éter (**30**) (*Figura 8*). Este producto natural **30** fue sintetizado en ocho pasos de reacción a partir del reactivo comercial 7-metoxi-2-naftol (**516**) y utilizando la desaromatización oxidante como etapa clave en la introducción del grupo hidroxilo en la posición orto del naftol **515**.

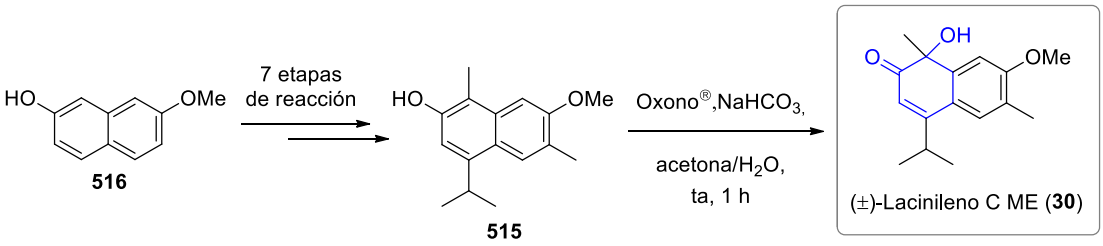


Figura 9. Síntesis del lacinileno C metil éter