

Supporting information for

Cu^I-Catalyzed Asymmetric [3+2] Cycloaddition of Azomethine Ylides with Cyclobutenones

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1. General methods

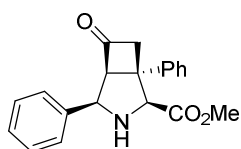
All air- and moisture-sensitive manipulations were carried out in anhydrous solvents and under argon. Toluene, tetrahydrofuran and acetonitrile were dried over the *PureSolv MD* purification system. Melting points were taken in open-end capillary tubes. Reactions were monitored by thin-layer chromatography carried out on 0.25 mm silica gel plates (230-400 mesh). Flash column chromatographies were performed using silica gel (230-400 mesh). NMR spectra were recorded on 300 or 500 MHz instrument and calibrated using residual non-deuterated solvent (CDCl_3 or benzene- d_6) as internal reference ($\delta_H=7.26$ ppm, $\delta_C=77.2$ ppm for CDCl_3 and $\delta_H=7.16$ ppm, $\delta_C=128.5$ ppm for benzene- d_6). HRMS spectra were recorded on a TOF mass spectrometer with electrospray ionization (ES) as the ionization source. The chromatograms of the racemic and enantiomerically enriched cycloadducts were obtained by HPLC or SFC. Arylcyclobutenones **2a**, **2b**, **2c**, **2d**, and **2e** were prepared following the procedure reported in the literature.¹ α -Iminoesters were prepared by condensation of methyl glycinate hydrochloride and the corresponding aldehydes.² Due to their lability, all α -iminoesters once isolated were immediately used in the 1,3-dipolar cycloaddition without further purification.

1. Sugimoto, K.; Hayashi, R.; Nemoto, H.; Toyooka, N.; Matsuyama, Y. *Org. Lett.*, **2012**, *14*, 3510.

2. a) Cabrera, S.; Arrayás, R. G.; Carretero, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 16394; b) Nájera, C.; Sansano, J. M. *Curr. Org. Chem.* **2003**, *7*, 1105; c) Cooper, D. M.; Grigg, R.; Hargreaves, S.; Kennewell, P.; Redpath, J. *Tetrahedron* **1995**, *51*, 7791.

2. Typical procedure for the asymmetric 1,3-dipolar cycloaddition.

(1*S*, 3*R*, 3*aS*, 5*aR*)-Methyl-3,5*a*-diphenyl-4-(oxo)heptahydrocyclobuta[*c*]pyrrole-1-carboxylate (*endo*-**3a**).



To a solution of $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{PF}_6$ (19.3 mg, 0.052 mmol) and (*R*)-Fesulphos (28.6 mg, 0.062 mmol) in toluene (8 mL), under nitrogen atmosphere, at 0 °C, a solution of α -iminoester **1a** (368.2 mg, 2.08 mmol) in toluene (6.24 mL), KO^tBu (1M in THF) (208 μ l, 0.208 mmol) and a solution of 3-phenylcyclobutenone **2a** (150 mg, 1.04 mmol) in toluene (6 mL) were successively added. After 24h at 0 °C, the mixture was diluted with 50 mL of CH_2Cl_2 and filtered through a plug of celite®. The solvent was evaporated under reduced pressure and the residue was purified by silica gel flash chromatography (cyclohexane/EtOAc 6:1) to afford the cycloadduct *endo*-**3a** (282.5 mg, 84%, colorless oil).

$[\alpha]_{\text{D}}^{20}$: +35.8 (c=0.22, CHCl_3), 90% *ee*.

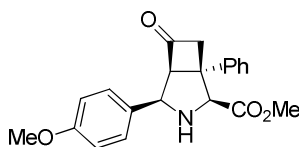
SFC: The enantiomeric excess was determined by SFC using a Chiralpak-ID-3 column [CO_2/MeOH from 95:5 to 60:40 in 8 min, 2.0 mL/min ($\lambda = 230.4$ nm)]: $t_{\text{R}} = 2.584$ min (1*R*, 3*S*, 3*aR*, 5*aS*)-**3a** and 3.072 min (1*S*, 3*R*, 3*aS*, 5*aR*)-**3a**.

¹H-NMR (300 MHz, CDCl_3): δ 7.46 – 7.30 (m, 10H), 4.73 (d, $J = 7.3$ Hz, 1H), 4.21 (s, 1H), 3.92 (ddd, $J = 7.2, 3.9, 2.1$ Hz, 1H), 3.73 (s, 3H), 3.53 (dd, $J = 18.4, 2.1$ Hz, 1H), 3.43 (dd, $J = 18.4, 3.9$ Hz, 1H).

¹³C-NMR (75 MHz, CDCl_3): δ 205.1, 170.7, 142.2, 136.6, 128.7, 128.5, 128.2, 127.4, 127.3, 127.2, 71.3, 65.0, 56.9, 53.6, 52.2, 47.6.

HRMS (ESI⁺): calcd for $\text{C}_{20}\text{H}_{20}\text{NO}_3$, 322.1443; found, 322.1425 ($[\text{M}+\text{H}]$, 100).

(1*S*, 3*R*, 3*aS*, 5*aR*)-Methyl-5*a*-phenyl-3-(4-methoxyphenyl)-4-(oxo)heptahydrocyclobuta[*c*]pyrrole-1-carboxylate (*endo*-**3b**).



Following the typical procedure, the reaction of 3-phenylcyclobutenone **2a** (14.4mg, 0.1 mmol) and **1b** (41.4 mg, 0.2 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane/EtOAc 6:1), the cycloadduct *endo*-**3b** (26.9 mg, 77%, yellow oil).

$[\alpha]_{\text{D}}^{20}$: +44.8 (c=0.22, CHCl_3), 98% *ee*.

HPLC: The enantiomeric excess was determined by HPLC using a Daicel Chiralpak IB

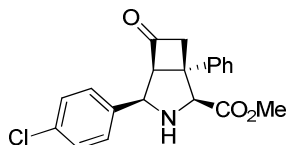
column, *n*-hexane/isopropanol 95:5, flow rate 0.7 mL/min ($\lambda = 230.16$ nm): $t_R = 81.2$ min (1*R*, 3*S*, 3*aR*, 5*aS*)-**3b** and 103.1 min (1*S*, 3*R*, 3*aS*, 5*aR*)-**3b**.

¹H-NMR (300 MHz, CDCl₃): δ 7.46-7.28 (m, 7H), 6.89 (d, $J = 8.5$ Hz, 2H), 4.69 (d, $J = 7.2$ Hz, 1H), 4.20 (s, 1H), 3.91-3.83 (m, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 3.57-3.48 (m, 1H), 3.42 (dd, $J = 18.4, 3.8$ Hz, 1H).

¹³C-NMR (75 MHz, CDCl₃): δ 206.7, 170.9, 159.4, 142.4, 129.0, 128.7, 128.4, 127.5, 127.2, 113.9, 71.4, 64.7, 55.4, 53.6, 52.1, 47.7.

HRMS (ESI⁺): calcd for C₂₁H₂₂NO₄, 352.1549; found, 352.1536 ([M+H], 100).

(1*S*, 3*R*, 3*aS*, 5*aR*)-Methyl-5*a*-phenyl-3-(4-chlorophenyl)-4(oxo)heptahydrocyclobuta[c]pyrrole-1-carboxylate (*endo*-3c**).**



Following the typical procedure, the reaction of 3-phenylcyclobutenone **2a** (14.4mg, 0.1 mmol) and **1c** (42.3 mg, 0.2 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane/EtOAc 6:1), the cycloadduct *endo*-**3c** (26.9 mg, 84%, white solid).

M.p.: 134-136 °C.

$[\alpha]_D^{20}$: +26.2 ($c=0.22$, CHCl₃), 81% *ee*.

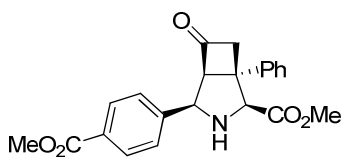
HPLC: The enantiomeric excess was determined by HPLC using a Daicel Chiralpak IB column, *n*-hexane/isopropanol 95:5, flow rate 0.7 mL/min ($\lambda = 230.16$ nm): $t_R = 53.0$ min (1*R*, 3*S*, 3*aR*, 5*aS*)-**3c** and 61.1 min (1*S*, 3*R*, 3*aS*, 5*aR*)-**3c**.

¹H-NMR (300 MHz, CDCl₃): δ 7.44 – 7.30 (m, 9H), 4.70 (d, $J = 7.1$ Hz, 1H), 4.20 (s, 1H), 3.90 – 3.85 (m, 1H), 3.73 (s, 3H), 3.56-3.48 (m, 1H), 3.48-3.39 (m, 1H), 2.75 (bs, 1H).

¹³C-NMR (75 MHz, CDCl₃): δ 205.7, 170.9, 159.4, 142.3, 128.9, 128.7, 128.3, 127.4, 127.1, 113.8, 71.3, 64.7, 55.3, 53.5, 52.1, 47.6.

HRMS (ESI⁺): calcd for C₂₀H₁₉NO₃Cl, 356.1053; found, 356.1052 ([M+H], 100).

(1*S*, 3*R*, 3*aS*, 5*aR*)-Methyl-5*a*-phenyl-3-(4-methoxycarbonyl)phenyl-4(oxo)heptahydrocyclobuta[c]pyrrole-1-carboxylate (*endo*-3d**).**



Following the typical procedure, the reaction of 3-phenylcyclobutenone **2a** (14.4mg, 0.1 mmol) and **1d** (47.0 mg, 0.2 mmol) afforded, after purification by silica

gel flash chromatography (cyclohexane/EtOAc 6:1), the cycloadduct *endo*-**3d** (27.7 mg, 73%, yellow solid).

M.p.: 142-144 °C.

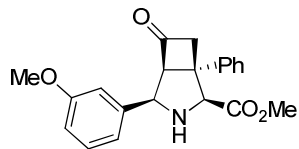
$[\alpha]_D^{20}$: +19.3 (c=0.22, CHCl₃), 85% *ee*.

HPLC: The enantiomeric excess was determined by HPLC using a Daicel Chiralpak IB column, *n*-hexane/isopropanol 95:5, flow rate 0.7 mL/min (λ = 230.16 nm): t_R = 32.8 min (1*R*, 3*S*, 3*aR*, 5*aS*)-**3d** and 35.6 min (1*S*, 3*R*, 3*aS*, 5*aR*)-**3d**.

¹H-NMR (300 MHz, CDCl₃): δ 7.91 (d, J = 8.9 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 7.30 – 7.26 (m, 4H), 7.13 (s, 1H), 4.65 (d, J = 7.0 Hz, 1H), 4.09 (s, 1H), 3.85-3.80 (m, 1H), 3.79 (s, 3H), 3.61 (s, 3H), 3.45-3.36 (m, 1H), 3.32 (dd, J = 18.6, 3.3 Hz, 1H), 2.66 (bs, 1H). **¹³C-NMR** (75 MHz, CDCl₃): δ 206.1, 170.7, 166.9, 142.4, 142.2, 129.8, 129.7, 128.7, 127.4, 127.3, 127.1, 76.0, 71.3, 64.5, 53.8, 52.18, 52.16, 47.4.

HRMS (ESI+): calcd for C₂₂H₂₂NO₅, 380.1498; found, 380.1498 ([M+H], 100).

(1*S*, 3*R*, 3*aS*, 5*aR*)-Methyl-5*a*-phenyl-3-(3-methoxyphenyl)-4(oxo)heptahydrocyclobuta[c]-pyrrole-1-carboxylate (*endo*-3e**).**



Following the typical procedure, the reaction of 3-phenylcyclobutenone **2a** (14.4mg, 0.1 mmol) and **1e** (41.4 mg, 0.2 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane/EtOAc 6:1), the cycloadduct *endo*-**3e** (27.1 mg, 72%, yellow oil).

$[\alpha]_D^{20}$: +48.6 (c=0.22, CHCl₃), 85% *ee*.

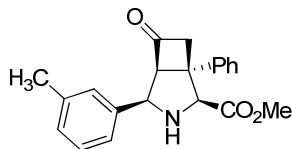
HPLC: The enantiomeric excess was determined by HPLC using a Daicel Chiralpak IB column, *n*-hexane/isopropanol 95:5, flow rate 0.7 mL/min (λ = 210.8 nm): t_R = 142.5 min (1*S*, 3*R*, 3*aS*, 5*aR*)-**3e** and 215.8 min (1*R*, 3*S*, 3*aR*, 5*aS*)-**3e**.

¹H-NMR (300 MHz, CDCl₃): δ 7.45-7.38 (m, 4H), 7.36-7.24 (m, 2H), 7.04-6.96 (m, 2H), 6.88-6.81 (m, 1H), 4.70 (d, J = 7.1 Hz, 1H), 4.19 (s, 1H), 3.93 – 3.86 (m, 1H), 3.82 (s, 3H), 3.73 (s, 3H), 3.59-3.48 (m, 1H), 3.42 (dd, J = 18.5, 3.7 Hz, 1H), 2.77 (bs, 1H).

¹³C-NMR (75 MHz, CDCl₃): δ 205.3, 170.8, 159.7, 142.3, 138.7, 129.4, 128.7, 127.4, 127.2, 119.4, 113.5, 112.8, 76.6, 71.3, 64.9, 55.3, 53.6, 52.1, 47.5.

HRMS (ESI+): calcd for C₂₁H₂₂NO₄, 352.1549; found, 352.1542 ([M+H], 100).

(1*S*, 3*R*, 3*aS*, 5*aR*)-Methyl-5*a*-phenyl-3-(3-methylphenyl)-4-(oxo)heptahydrocyclobuta[*c*]pyrrole-1-carboxylate (*endo*-3f**).**



Following the typical procedure, the reaction of 3-phenylcyclobutenone **2a** (14.4mg, 0.1 mmol) and **1f** (38.2 mg, 0.2 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane/EtOAc 6:1), the cycloadduct *endo*-**3f** (27.9 mg, 84%, colorless oil).

$[\alpha]_D^{20}$: +74.4 (c=0.22, CHCl₃), 86% *ee*.

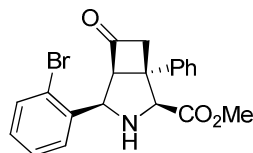
SFC: The enantiomeric excess was determined by SFC using a Chiralpak ID-3 column [CO₂/MeOH 95:5 in 60 min, flow rate 2.0 mL/min (λ = 210.4 nm)]: t_R = 4.996 min (1*R*, 3*S*, 3*aR*, 5*aS*)-**3f** and 8.527 min (1*S*, 3*R*, 3*aS*, 5*aR*)-**3f**.

¹H-NMR (300 MHz, CDCl₃): δ 7.21-7.16 (m, 1H), 7.15-7.04 (m, 7H), 7.00 –6.95 (m, 1H), 4.55 (d, J = 7.2 Hz, 1H), 4.05 (s, 1H), 3.78-3.73 (m, 1H), 3.59 (s, 3H), 3.38 (dd, J = 18.5, 1.9 Hz, 1H), 3.28 (dd, J = 18.5, 3.9 Hz, 1H), 2.61 (bs, 1H), 2.22 (s, 3H).

¹³C-NMR (75 MHz, CDCl₃): δ 205.4, 170.9, 142.3, 138.0, 136.9, 128.9, 128.7, 128.3, 127.7, 127.4, 127.2, 124.2, 71.4, 65.0, 53.6, 52.1, 47.6, 29.8, 21.6.

HRMS (ESI⁺): calcd for C₂₁H₂₂NO₃, 336.1594; found, 336.1600 ([M+H], 100).

(1*S*, 3*R*, 3*aS*, 5*aR*)-Methyl-5*a*-phenyl-3-(2-bromophenyl)-4-(oxo)heptahydrocyclobuta[*c*]pyrrole-1-carboxylate (*endo*-3g**).**



Following the typical procedure, the reaction of 3-phenylcyclobutenone **2a** (14.4mg, 0.1 mmol) and **1g** (51.2 mg, 0.2 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane/EtOAc 6:1), the cycloadduct *endo*-**3g** (30.0 mg, 72%, white solid).

M.p.: 150-152 °C.

$[\alpha]_D^{20}$: +70.2 (c=0.22, CHCl₃), 92% *ee*.

SFC: The enantiomeric excess was determined by SFC using a Chiralpak-ID-3 column [CO₂/MeOH from 95:5 to 60:40 in 8 min, 2.0 mL/min (λ = 230.4 nm)]: t_R = 2.411 min (1*R*, 3*S*, 3*aR*, 5*aS*)-**3g** and 2.866 min (1*S*, 3*R*, 3*aS*, 5*aR*)-**3g**.

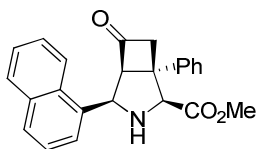
¹H-NMR (300 MHz, CDCl₃): δ 7.68 (dd, J = 7.9, 1.6 Hz, 1H), 7.57 (dd, J = 7.9, 1.6 Hz, 1H), 7.49-7.43 (m, 4H), 7.37 – 7.28 (m, 2H), 7.18 (td, J = 7.7, 1.7 Hz, 1H), 4.98 (d, J =

6.8 Hz, 1H), 4.21 (s, 1H), 4.18 (ddd, $J = 6.8, 3.4, 1.9$ Hz, 1H), 3.74 (s, 3H), 3.52 (dd, $J = 18.4, 1.9$ Hz, 1H), 3.43 (dd, $J = 18.4, 3.4$ Hz, 1H), 2.62 (bs, 1H).

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 205.5, 170.9, 142.6, 136.5, 132.7, 129.5, 128.7, 128.6, 127.6, 127.2, 123.2, 73.1, 70.8, 63.6, 54.0, 52.1, 46.9.

HRMS (ESI+): calcd for $\text{C}_{20}\text{H}_{19}\text{NO}_3\text{Br}$, 400.0548; found, 400.0518 ($[\text{M}+\text{H}]$, 100).

(1*S*, 3*R*, 3*aS*, 5*aR*)-Methyl-5*a*-phenyl-3-(1-naphthyl)-4-(oxo)heptahydrocyclobuta[c]pyrrole-1-carboxylate (*endo*-3h**).**



Following the typical procedure, the reaction of 3-phenylcyclobutenone **2a** (14.4mg, 0.1 mmol) and **1h** (45.4 mg, 0.2 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane/EtOAc 6:1), the cycloadduct *endo*-**3h** (33.4 mg, 90%, white solid).

M.p.: 108-110 °C.

$[\alpha]_{\text{D}}^{20}$: +23.4 ($c=0.22$, CHCl_3), 97% *ee*.

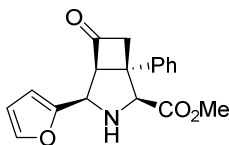
SFC: The enantiomeric excess was determined by SFC using a Chiralpak-ID-3 column [CO_2/MeOH from 95:5 to 60:40 in 8 min, 2.0 mL/min ($\lambda = 230.4$ nm)]: $t_{\text{R}} = 3.597$ min (1*R*, 3*S*, 3*aR*, 5*aS*)-**3h** and 4.319 (min) (1*S*, 3*R*, 3*aS*, 5*aR*)-**3h**.

$^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 8.01-7.81 (m, 5H), 7.58-7.35 (m, 7H), 7.45-7.34 (m, 7H), 5.43 (d, $J = 6.9$ Hz, 1H), 4.34 (s, 1H), 4.20-4.14 (m, 1H), 3.77 (s, 3H), 3.57 (dd, $J = 18.4, 2.5$ Hz, 1H), 3.44 (dd, $J = 18.4, 3.9$ Hz, 1H).

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3): δ 205.1, 171.0, 142.6, 133.8, 132.7, 130.9, 129.5, 128.8, 128.5, 127.6, 127.3, 126.4, 125.7, 125.6, 124.0, 122.2, 74.9, 70.9, 60.8, 54.0, 52.2, 47.3.

HRMS (ESI+): calcd for $\text{C}_{24}\text{H}_{22}\text{NO}_3$, 372.1600; found, 372.1609 ($[\text{M}+\text{H}]$, 100).

(1*S*, 3*R*, 3*aS*, 5*aR*)-Methyl-5*a*-phenyl-3-(furan-2-yl)-4-(oxo)heptahydrocyclobuta[c]pyrrole-1-carboxylate (*endo*-3i**).**



Following the typical procedure, the reaction of 3-phenylcyclobutenone **2a** (14.4mg, 0.1 mmol) and **1i** (33.4 mg, 0.2 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane/EtOAc 6:1), the cycloadduct *endo*-**3i** (24.9 mg, 80%, yellow oil).

$[\alpha]_{\text{D}}^{20}$: +18.1 ($c=0.22$, CHCl_3), 88% *ee*.

HPLC: The enantiomeric excess was determined by HPLC using a Daicel Chiralpak IB

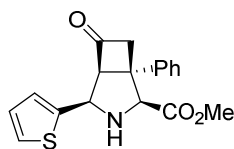
column, *n*-hexane/isopropanol 95:5, flow rate 0.7 mL/min ($\lambda = 210.8$ nm): $t_R = 44.2$ min (1*S*, 3*R*, 3*aS*, 5*aR*)-**3i** and 57.8 min (1*R*, 3*S*, 3*aR*, 5*aS*)-**3i**.

¹H-NMR (300 MHz, CDCl₃): δ 7.43-7.33 (m, 6H), 6.47-6.34 (m, 2H), 4.74 (d, $J = 7.3$ Hz, 1H), 4.13 (s, 1H), 4.00-3.90 (m, 1H), 3.72 (s, 3H), 3.57-3.47 (m, 1H), 3.47-3.38 (m, 1H), 1.71 (bs, 1H).

¹³C-NMR (75 MHz, CDCl₃): δ 204.4, 170.6, 150.3, 142.5, 141.8, 128.8, 127.3, 110.6, 107.8, 71.5, 59.1, 53.2, 52.3, 48.4, 29.8.

HRMS (ESI⁺): calcd for C₁₈H₁₈NO₄, 312.1236; found, 312.1232 ([M+H], 100).

(1*S*, 3*R*, 3*aS*, 5*aR*)-Methyl-5*a*-phenyl-3-(thiophen-2-yl)-4(oxo)heptahydrocyclobuta[c]pyrrole-1-carboxylate (*endo*-3j**).**



Following the typical procedure, the reaction of 3-phenylcyclobutenone **2a** (14.4mg, 0.1 mmol) and **1j** (36.6 mg, 0.2 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane/EtOAc 6:1), the cycloadduct *endo*-**3j** (24.5 mg, 75%, yellow oil).

$[\alpha]_D^{20}$: +51.0 (c=0.22, CHCl₃), 80% *ee*.

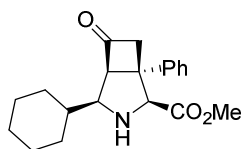
SFC: The enantiomeric excess was determined by SFC using a Chiralpak-IC column [CO₂/MeOH from 95:5 to 60:40 in 8 min, 2.0 mL/min ($\lambda = 230.4$ nm)]: $t_R = 4.578$ min (1*S*, 3*R*, 3*aS*, 5*aR*)-**3j** and 6.07 min (1*R*, 3*S*, 3*aR*, 5*aS*)-**3j**.

¹H-NMR (300 MHz, CDCl₃): δ 7.33-7.27 (m, 2H), 7.25-7.17 (m, 2H), 7.16-7.12 (m, 2H), 7.02 (d, $J = 3.6$ Hz, 1H), 6.89 (dd, $J = 5.0, 3.6$ Hz, 1H), 4.85 (d, $J = 7.2$ Hz, 1H), 4.06 (s, 1H), 3.82 (ddd, $J = 7.1, 3.7, 1.6$ Hz, 1H), 3.60 (s, 3H), 3.41 (dd, $J = 18.6, 1.6$ Hz, 1H), 3.32 (dd, $J = 18.6, 3.7$ Hz, 1H), 2.82 (bs, 1H).

¹³C-NMR (75 MHz, CDCl₃): δ 204.8, 170.5, 142.0, 140.2, 128.9, 128.8, 127.4, 127.3, 127.0, 126.0, 125.3, 125.0, 71.4, 61.1, 53.6, 52.2, 48.2, 29.9.

HRMS (ESI⁺): calcd for C₁₈H₁₈NO₃S, 328.1007; found, 328.0991 ([M+H], 100).

(1*S*, 3*S*, 3*aS*, 5*aR*)-Methyl-3-cyclohexyl-5*a*-phenyl-4(oxo)heptahydrocyclobuta[c]pyrrole-1-carboxylate (*endo*-3k**).**



Following the typical procedure, the reaction of 3-phenylcyclobutenone **2a** (14.4mg, 0.1 mmol) and **1k** (36.6 mg, 0.2 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane/EtOAc 6:1), the cycloadduct *endo*-**3k** (20.9 mg, 64%,

colorless oil).

$[\alpha]_D^{20}$: +60.1 (c=0.22, CHCl₃), 72% *ee*.

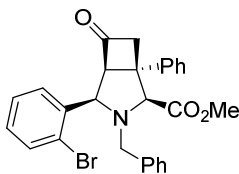
HPLC: The enantiomeric excess was determined by HPLC using a Daicel Chiralpak IA column, *n*-hexane/isopropanol 95:5, flow rate 0.7 mL/min (λ = 210.8 nm): t_R = 19.7 min (1*R*, 3*R*, 3*aR*, 5*aS*)-**3k** and 21.8 min (1*S*, 3*S*, 3*aS*, 5*aR*)-**3k**.

¹H-NMR (300 MHz, CDCl₃): δ 7.42-7.35 (m, 2H), 7.32-7.27 (m, 3H), 4.00 (s, 1H), 3.81 (ddd, J = 7.3, 3.3, 1.4 Hz, 1H), 3.68 (s, 3H), 3.42-3.34 (m, 1H), 3.30 (dd, J = 18.6, 1.4 Hz, 1H), 3.20 (dd, J = 9.9, 7.1 Hz, 1H), 2.33 (bs, 1H), 2.07-1.93 (m, 2H), 1.77-1.63 (m, 3H), 1.39-1.00 (m, 6H).

¹³C-NMR (75 MHz, CDCl₃): δ 207.0, 171.2, 142.7, 128.7, 127.2, 127.1, 75.2, 71.9, 68.2, 52.9, 52.1, 48.0, 39.8, 31.6, 30.8, 26.4, 25.8, 25.7.

HRMS (ESI+): calcd for C₂₀H₂₆NO₃, 328.1913; found, 328.1907 ([M+H], 100).

(1*S*, 3*R*, 3*aS*, 5*aR*)-Methyl-5*a*-phenyl-3-(2-bromophenyl)-2-N-(benzyl)-4-(oxo)-heptahydro-cyclobuta[c]pyrrole-1-carboxylate (N-benzyl derivative of *endo*-3g**).**



To a solution of *endo*-**3g** (116.1 mg, 0.36 mmol) in THF (15.0 mL) at room temperature, was added successively K₂CO₃ (80 mg, 0.58 mmol) and benzyl bromide (56 μ L, 0.47 mmol). The mixture

was stirred at 40 °C for 12 h and then was cooled to room temperature. After that, water was added (10.0 mL) and the aqueous phase was extracted with CH₂Cl₂ (3 x 8 mL). The resulting organic phase was washed with brine (2 x 8 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (cyclohexane-EtOAc 3:1), to afford the N-benzyl derivative (142.8 mg, 95%, white solid).

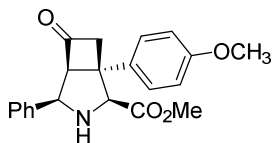
M.p.: 158-160 °C.

¹H-NMR (300 MHz, CDCl₃): δ 7.71 (dd, J = 7.8, 1.5 Hz, 1H), 7.66-7.60 (m, 1H), 7.46-7.33 (m, 3H), 7.32-7.25 (m, 4H), 7.24-7.15 (m, 3H), 6.98 (dd, J = 7.0, 2.6 Hz, 1H), 4.45 (d, J = 7.7 Hz, 1H), 4.05-3.97 (m, 2H), 3.94 (d, J = 14.4 Hz, 1H), 3.70 (d, J = 14.4 Hz, 1H), 3.60 (s, 3H), 3.59 (s, 1H), 3.26 (dd, J = 18.8, 5.3 Hz, 1H).

¹³C-NMR (75 MHz, CDCl₃): δ 205.0, 170.9, 142.0, 134.8, 133.2, 133.0, 130.5, 130.1, 129.6, 128.8, 128.4, 127.8, 127.7, 127.3, 127.1, 124.1, 74.4, 71.8, 67.2, 53.9, 53.8, 51.9, 46.7.

HRMS (ESI+): calcd for C₂₇H₂₅BrNO₃, 490.1018; found, 490.1442 ([M+H], 100).

(1*S*, 3*R*, 3*aS*, 5*aR*)-Methyl-3-phenyl-5a-(4-methoxyphenyl)-4-(oxo)heptahydrocyclo-buta[*c*]pyrrole-1-carboxylate (*endo*-3l**).**



Following the typical procedure, the reaction of 3-(4-methoxyphenyl)cyclobutenone **2b** (17.4 mg, 0.1 mmol) and **1a** (35.4 mg, 0.2 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane/EtOAc 6:1), the cycloadduct *endo*-**3l** (28.1 mg, 80%, white solid).

M.p.: 134-136 °C.

$[\alpha]_D^{20}$: +22.7 (c=0.22, CHCl₃), 90% *ee*.

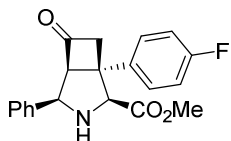
SFC: The enantiomeric excess was determined by SFC using a Chiralpak-IC column [CO₂/MeOH from 95:5 to 60:40 in 8 min, 2.0 mL/min (λ = 230.4 nm)]: t_R = 5.1 min (1*S*, 3*R*, 3*aS*, 5*aR*)-**3l** and 6.085 min (1*R*, 3*S*, 3*aR*, 5*aS*)-**3l**.

¹H-NMR (300 MHz, CDCl₃): δ 7.45-7.29 (m, 7H), 6.97-6.92 (m, 2H), 4.71 (d, J = 7.3 Hz, 1H), 4.17 (s, 1H), 3.90-3.86 (m, 1H), 3.84 (s, 3H), 3.74 (s, 3H), 3.50 (dd, J = 18.4, 2.3 Hz, 1H), 3.38 (dd, J = 18.4, 4.2 Hz, 1H).

¹³C-NMR (75 MHz, CDCl₃): δ 205.4, 170.9, 158.6, 137.0, 134.1, 128.5, 128.4, 128.0, 127.0, 114.0, 71.3, 64.8, 55.3, 53.6, 53.4, 52.0, 47.0.

HRMS (ESI⁺): calcd for C₂₁H₂₁NO₄, 352.1549; found, 352.1538 ([M+H], 100).

(1*S*, 3*R*, 3*aS*, 5*aR*)-Methyl-3-phenyl-5a-(4-fluorophenyl)-4-(oxo)heptahydrocyclo-buta[*c*]pyrrole-1-carboxylate (*endo*-3m**).**



Following the typical procedure, the reaction of 3-(4-fluorophenyl)cyclobutenone **2c** (16.2 mg, 0.1 mmol) and **1a** (35.4 mg, 0.2 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane/EtOAc 6:1), the cycloadduct *endo*-**3m** (24.4 mg, 72%, yellow solid).

M.p.: 150-152 °C.

$[\alpha]_D^{20}$: +12.6 (c=0.22, CHCl₃), 90% *ee*.

SFC: The enantiomeric excess was determined by SFC using a Chiralpak-IC column [CO₂/MeOH from 95:5 to 60:40 in 8 min, 2.0 mL/min (λ = 210.4 nm)]: t_R = 3.989 min (1*S*, 3*R*, 3*aS*, 5*aR*)-**3m** and 4.917 min (1*R*, 3*S*, 3*aR*, 5*aS*)-**3m**.

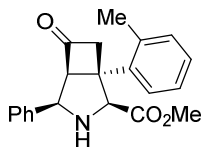
¹H-NMR (300 MHz, CDCl₃): δ 7.43-7.31 (m, 7H), 7.10 (t, *J* = 8.6 Hz, 2H), 4.71 (d, *J* = 7.3 Hz, 1H), 4.16 (s, 1H), 3.87 (ddd, *J* = 7.3, 4.3, 2.5 Hz, 1H), 3.74 (s, 3H), 3.53 (dd, *J* = 18.4, 2.5 Hz, 1H), 3.38 (dd, *J* = 18.4, 4.3 Hz, 1H).

¹³C-NMR (75 MHz, CDCl₃): δ 205.0, 170.8, 162.0 (d, *J* = 246.6 Hz), 138.1 (d, *J* = 3.3 Hz), 137.0, 129.2 (d, *J* = 8.1 Hz), 128.5, 128.2, 127.1, 115.6 (d, *J* = 21.5 Hz), 76.5, 71.4, 65.0, 53.9, 52.2, 47.1.

¹⁹F-NMR (75 MHz, CDCl₃): δ -115.4.

HRMS (ESI+): calcd for C₂₀H₁₈FNO₃, 340.1349; found, 340.1356 ([M+H], 100).

(1*S*, 3*R*, 3*aS*, 5*aR*)-Methyl-3-phenyl-5*a*-(2-methylphenyl)-4-(oxo)heptahydrocyclobuta[*c*]pyrrole-1-carboxylate (*endo*-3n**).**



Following the typical procedure, the reaction of 3-(2-methylphenyl)cyclobutenone **2d** (15.8 mg, 0.1 mmol) and **1a** (35.4 mg, 0.2 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane/EtOAc 6:1), the cycloadduct *endo*-**3n** (23.1 mg, 69%, white solid).

M.p.: 172-174 °C.

[α]_D²⁰: +33.0 (c=0.22, CHCl₃), 92% *ee*.

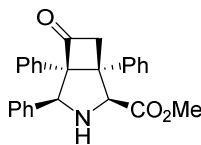
SFC: The enantiomeric excess was determined by SFC using a Chiralpak-IC column [CO₂/MeOH from 95:5 to 60:40 in 8 min, 2.0 mL/min (λ = 210.4 nm)]: *t_R* = 4.564 min (1*S*, 3*R*, 3*aS*, 5*aR*)-**3n** and 5.654 min (1*R*, 3*S*, 3*aR*, 5*aS*)-**3n**.

¹H-NMR (300 MHz, CDCl₃): δ 7.37-7.13 (m, 9H), 4.77 (d, *J* = 7.1 Hz, 1H), 4.10 (s, 1H), 4.06-3.98 (m, 1H), 3.63-3.54 (m, 4H), 3.37 (dd, *J* = 18.4, 4.5 Hz, 1H), 2.31 (s, 3H).

¹³C-NMR (75 MHz, CDCl₃): δ 206.1, 171.4, 139.0, 137.0, 136.0, 132.3, 129.3, 128.5, 128.1, 127.7, 127.1, 126.4, 75.0, 70.0, 64.4, 53.8, 52.1, 49.2, 21.4.

HRMS (ESI+): calcd for C₂₁H₂₁NO₃, 336.1600; found, 336.1586 ([M+H], 100).

(1*S*, 3*S*, 3*aS*, 5*aS*)-Methyl-3,3*a*,5*a*-triphenyl-4-(oxo)heptahydrocyclobuta[*c*]pyrrole-1-carboxylate (*endo*-3o**).**



Following the typical procedure, the reaction of 2,3-diphenylcyclobutenone **2e** (22.0 mg, 0.1 mmol) and **1a** (35.4 mg, 0.2 mmol) afforded, after purification by silica gel flash chromatography (cyclohexane/EtOAc 6:1), the cycloadduct *endo*-**3o** (22.3 mg, 64%, white solid).

M.p.: 152-154 °C.

$[\alpha]_D^{20}$: +30.3 (c=0.22, CHCl₃), 84% *ee*.

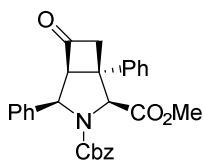
SFC: The enantiomeric excess was determined by SFC using a Chiralpak-IC column [CO₂/MeOH from 95:5 to 60:40 in 8 min, 2.0 mL/min (λ = 210.4 nm)]: t_R = 4.475 min (1*S*, 3*S*, 3*aS*, 5*aS*)-**3o** and 4.745 min (1*R*, 3*R*, 3*aR*, 5*aR*)-**3o**.

¹H-NMR (300 MHz, Benzene-*d*₆): δ 7.12-7.06 (m, 3H), 7.04-6.84 (m, 12H), 4.51 (s, 1H), 4.13 (s, 1H), 3.90 (d, J = 18.9 Hz, 1H), 3.30 (s, 3H), 3.22 (d, J = 18.9 Hz, 1H).

¹³C-NMR (75 MHz, CDCl₃): δ 207.8, 171.2, 139.9, 136.3, 135.8, 128.3, 128.1, 128.0 (bs), 127.9, 127.8, 127.2, 126.9, 126.6, 86.6, 73.3, 65.7, 55.1, 52.8, 52.5.

HRMS (ESI+): calcd for C₂₆H₂₃NO₃, 398.1756; found, 398.1751 ([M+H], 100).

(1*S*, 3*R*, 3*aS*, 5*aR*)-Methyl-3, 5*a*-diphenyl-2-N-(benzyloxycarbonyl)-4-(oxo)-heptahydrocyclobuta[c]pyrrole-1-carboxylate (*endo*-7).



To a solution of *endo*-**3a** (125 mg, 0.39 mmol) in THF (16.0 mL) at room temperature, K₂CO₃ (95.8 mg, 0.69 mmol) and benzyl chloroformate (66 μ L, 0.46 mmol) were successively added. The reaction was stirred at room temperature for 12 hours and the mixture was quenched with H₂O (10.0 mL). Then the aqueous phase was extracted with CH₂Cl₂ (3 x 8 mL) and the resulting organic phase was washed with brine (20 mL), dried over MgSO₄ and concentrated under reduce pressure. The residue was purified by silica gel flash chromatography (CH₂Cl₂/TBME (*tert*-butyl methyl ether) 80:1) to afford the compound *endo*-**7** (158 mg, 89%, orange solid).

M.p.: 168-170 °C.

$[\alpha]_D^{20}$: +41.7 (c=0.22, CHCl₃), 90 % *ee*.

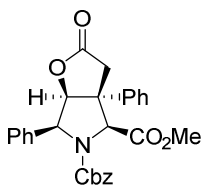
SFC: The enantiomeric excess was determined by SFC using a Chiralpak-IC column [CO₂/MeOH from 95:5 to 60:40 in 8 min, 2.0 mL/min (λ = 210.4 nm)]: t_R = 4.475 min (1*R*, 3*S*, 3*aR*, 5*aS*)-**7** and 5.682 min (1*S*, 3*R*, 3*aS*, 5*aR*)-**7**.

¹H-NMR (300 MHz, CDCl₃): δ 7.51 (d, J = 7.4 Hz, 2H), 7.46 – 7.27 (m, 9H), 7.21 – 7.13 (m, 2H), 6.93-6.84 (m, 2H), 5.44 (d, J = 10.5 Hz, 1H), 4.96 (s, 2H), 4.83 (s, 1H), 4.27 (ddd, J = 10.5, 5.2, 2.4 Hz, 1H), 3.75 (s, 3H), 3.60 (dd, J = 18.1, 2.4 Hz, 1H), 3.27 (dd, J = 18.1, 5.2 Hz, 1H).

¹³C-NMR (75 MHz, CDCl₃): δ 200.6, 170.9, 155.1, 142.6, 138.2, 135.7, 129.2, 128.7, 128.4, 128.0, 127.8, 127.7, 127.6, 126.3, 126.2, 75.0, 72.2, 67.8, 65.6, 55.3, 52.6, 48.2.

HRMS (ESI+): calcd for C₂₈H₂₆NO₅, 456.1811; found, 456.1808 ([M+H], 100).

5-Benzyl 4-methyl (3*aR*, 4*S*, 6*S*, 6*aS*)-2-oxo-3*a*,6-diphenylhexahydro-5*H*-furo[2,3-*c*]pyrrole-4,5-dicarboxylate (*endo*-8).



To a solution of *endo*-7 (80.0 mg, 0.18 mmol) in CH₂Cl₂ (5.0 mL) at 0 °C *m*-chloroperbenzoic acid (≤ 77 % purity, 151.9 mg, 0.88 mmol) was added. The mixture was stirred at room temperature for 24 h and CH₂Cl₂ (5.0 mL) and a solution of saturated Na₂SO₃ (5.0 mL) were added. The organic phase was sequentially washed with a saturated solution of NaHCO₃ (5 x 10 mL), H₂O (2 x 10 mL) and brine (2 x 10 mL), dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (cyclohexane-EtOAc 4:1), to afford the lactone *endo*-8 (59.7 mg, 72 %, white solid).

M.p.: 178-180 °C.

[α]_D²⁰: + 22.4 (c=0.22, CHCl₃), 90 % *ee*.

SFC: The enantiomeric excess was determined by SFC using a Chiralpak-ID column [CO₂/MeOH from 95:5 to 60:40 in 8 min, 2.0 mL/min ($\lambda = 210.4$ nm)]: *t*_R = 5.390 min (3*aS*, 4*R*, 6*R*, 6*aR*)-8 and 5.615 min (3*aR*, 4*S*, 6*S*, 6*aS*)-8.

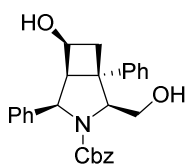
¹H-NMR (300 MHz, CDCl₃): δ 7.65 – 7.57 (m, 2H), 7.49 – 7.29 (m, 10H), 7.25-7.18 (m, 3H), 5.46 (d, *J* = 5.9 Hz, 1H), 5.26 (d, *J* = 5.9 Hz, 1H), 5.01 (d, *J* = 10.4 Hz, 2H), 4.97 (s, 1H), 3.86 (s, 3H), 3.18 (d, *J* = 18.0 Hz, 1H), 2.90 (d, *J* = 18.0 Hz, 1H).

¹³C-NMR (75 MHz, CDCl₃): δ 172.5, 170.5, 141.0, 135.7, 135.6, 129.8, 128.5, 128.4, 128.3, 128.1, 128.0, 127.8, 127.5, 125.3, 88.1, 70.0, 67.9, 66.0, 56.3, 53.0, 39.1.

HRMS (ESI⁺): calcd for C₂₈H₂₆NO₆, 472.1760; found, 472.1774 ([M+H], 100).

IR (KBr, cm⁻¹): 1708, 1755, 1794.

(1*S*, 3*R*, 3*aS*, 4*S*, 5*aR*)-4-hydroxy-1-hydroxymethyl-3, 5*a*-diphenyl-2-N-(benzyloxycarbonyl)-heptahydrocyclobuta[c]pyrrole (*endo*-9).



To a solution of *endo*-7 (134.4 mg, 0.295 mmol) in THF (1.5 mL) a 1 M solution of lithium aluminum hydride in THF (0.885 mL, 0.885 mmol) was added dropwise at -78 °C. The mixture was stirred at -78 °C for 4 h and then warmed to room temperature and stirred for 12 hours until completion. Ethyl acetate (3.5 mL) was added, the mixture was stirred for

one hour and a saturated solution of aqueous ammonium chloride (5 mL) was added. The organic phase was separated, washed with water (10 mL) and brine (10 mL), dried with MgSO₄, filtered and evaporated at reduced pressure. After purification by flash chromatography (cyclohexane/EtOAc 3:1) diol *endo-9* was obtained as white solid (112.7 mg, 89%).

M.p.: 172-174 °C.

$[\alpha]_D^{20}$: + 36.5 (c=0.22, CHCl₃), 90 % *ee*.

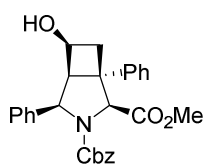
SFC: The enantiomeric excess was determined by SFC using a Chiralpak-IC column [CO₂/MeOH from 95:5 to 60:40 in 8 min, 2.0 mL/min (λ = 210.4 nm)]: t_R = 6.484 min (1*S*, 3*R*, 3*aS*, 4*S*, 5*aR*)-**9** and 7.726 min (1*R*, 3*S*, 3*aR*, 4*R*, 5*aS*)-**9**.

¹H-NMR (300 MHz, Benzene-*d*₆): δ 7.25 (d, J = 7.4 Hz, 2H), 7.13-7.04 (m, 5H), 7.02-6.92 (m, 6H), 6.73-6.66 (m, 2H), 5.28 (d, J = 10.4 Hz, 1H), 4.93 (d, J = 12.6 Hz, 1H), 4.82 (d, J = 12.6 Hz, 1H), 4.24 (dd, J = 11.7, 6.3 Hz, 1H), 4.13 (dd, J = 11.7, 3.0 Hz, 1H), 4.08 (dd, J = 6.3, 3.0 Hz, 1H), 3.80 (q, J = 7.8 Hz, 1H), 3.08 (ddd, J = 10.4, 6.8, 3.9 Hz, 1H), 2.80 (d, J = 8.7 Hz, 1H), 2.41 (ddd, J = 12.1, 8.0, 3.9 Hz, 1H), 2.29 (dd, J = 12.1, 8.0 Hz, 1H).

¹³C-NMR (75 MHz, CDCl₃): δ 157.9, 143.7, 140.2, 135.7, 129.3, 129.0, 128.4, 128.0, 127.9, 127.5, 127.1, 126.3, 126.2, 73.6, 68.0, 65.3, 65.2, 63.9, 55.5, 50.4, 37.2.

HRMS (ESI+): calcd for C₂₇H₂₅NO₄, 430.2018 and 452.1838; found, 430.2012 ([M+H], 17), 452.1812 ([M+Na], 100).

(1*S*, 3*R*, 3*aS*, 4*S*, 5*aR*)-Methyl-3, 5*a*-diphenyl-2-*N*-(benzyloxycarbonyl)-4-hydroxy-heptahydrocyclobuta[*c*]pyrrole-1-carboxylate (*endo-10*).



To a solution of *endo-7* (150.0 mg, 0.329 mmol) in MeOH (5.0 mL) at room temperature NaBH₄ (18.7 mg, 0.49 mmol) was added and the mixture was stirred for 2 h. Then a saturated solution of NH₄Cl (5.0 mL) was added and the resulting aqueous phase was extracted with CH₂Cl₂ (3 x 5 mL). The organic phase was washed successively with a saturated solution of NaHCO₃ (2 x 5 mL), H₂O (2 x 5 mL) and brine (5.0 mL). The resulting organic solution was dried with MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (cyclohexane/EtOAc 1:1), to afford the alcohol *endo-10* (98.7 mg, 65%, white solid).

M.p.: 154-156 °C.

$[\alpha]_D^{20}$: + 57.8 (c=0.22, CHCl₃), 90 % *ee*.

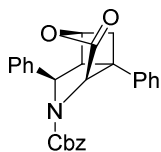
SFC: The enantiomeric excess was determined by SFC using a Chiralpak-IA column [CO₂/MeOH from 95:5 to 60:40 in 8 min, 2.0 mL/min ($\lambda = 210.4$ nm)]: $t_R = 5.281$ min (1*R*, 3*S*, 3*aR*, 4*R*, 5*aS*)-**10** and 6.656 min (1*S*, 3*R*, 3*aS*, 4*S*, 5*aR*)-**10**.

¹H-NMR (300 MHz, C₆D₆): δ 7.85 (d, $J=7.5$ Hz, 2H), 7.53-7.22 (m, 11H), 7.10-6.93 (m, 2H), 5.75 (d, $J = 10.3$ Hz, 1H), 5.07 (s, 2H), 4.56 (s, 1H), 4.10-3.95 (m, 1H), 3.92 – 3.82 (m, 1H), 3.79 (s, 3H), 2.87– 2.65 (m, 2H), 1.16 (d, $J = 11.4$ Hz, 1H).

¹³C-NMR (75 MHz, CDCl₃): δ 171.1, 155.1, 143.0, 139.7, 136.0, 129.2, 128.9, 128.4, 128.0, 127.9, 127.5, 127.3, 126.9, 126.3, 72.1, 67.6, 65.2, 64.6, 56.9, 52.3, 50.3, 39.2.

HRMS (ESI+): calcd for C₂₈H₂₈NO₅, 458.1967; found, 458.1922 ([M+H], 100).

(1*R*, 3*S*, 6*S*, 8*R*, 9*S*)-Benzyl-5-oxo-1,8-diphenyl-4-oxa-7-azatricycle[4.3.0.0^{3,9}]-nonane-7-carboxylate (*endo*-11**).**



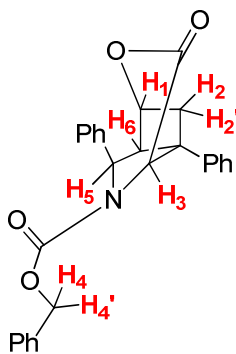
To a solution of PPh₃AuCl (3.25 mg, 0.0066 mmol) and AgOTf (1.69 mg, 0.0066 mmol) in toluene (1.0 mL) at room temperature a suspension of alcohol *endo*-**10** (30.0 mg, 0.066 mmol) in toluene (1.5 mL) was added. Then, the mixture was stirred at 110 °C for 30 minutes and Et₃N (0.1 mL), AcOEt (5.0 mL) and H₂O (5.0 mL) were successively added. The aqueous phase was extracted with CH₂Cl₂ (3 x 3mL) and the resulting organic phase was washed with H₂O (2 x 5 mL) and brine (2 x 5mL), dried over MgSO₄ and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (cyclohexane/EtOAc 4:1), to afford the lactone **11** (27.8 mg, 99%, white solid).

M.p.: 148-150 °C.

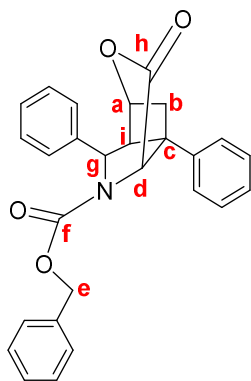
[α]_D²⁰: + 48.2 (c=0.22, CHCl₃), 90 % *ee*.

SFC: The enantiomeric excess was determined by SFC using a Chiralpak-IC column [CO₂/MeOH from 95:5 to 60:40 in 8 min, 2.0 mL/min ($\lambda = 240.4$ nm)]: $t_R = 5.315$ min (1*R*, 3*S*, 6*S*, 8*R*, 9*S*)-**11** and 6.424 min (1*S*, 3*R*, 6*R*, 8*S*, 9*R*)-**11**

¹H-NMR, COSY (300 MHz, CDCl₃, 1:0.63 mixture of rotamers. The asterisk * denotes the signal of the minor rotamer): δ 7.40-7.13 (m, 15 H), 5.63 (d, $J=6.5$ Hz, 1H, H₅), 5.51* (d, $J=6.3$ Hz, 1H, H₅), 5.42* (d, $J=1.5$ Hz, 1H, H₃), 5.30 (d, $J=1.4$ Hz, 1H, H₃), 5.29* (d, $J=12.5$ Hz, 2H, H₄/H_{4'}), 5.09 (d, $J=12.5$ Hz, 2H, H₄/H_{4'}), 4.72 (t, $J=4.1$ Hz, 1H, H₁), 4.69* (t, $J= 4.2$ Hz, 1 H, H₁), 3.68 (m, 1H, H₆), 3.61* (m, 1H, H₆), 2.59 (dd, $J= 12.0, 4.2$ Hz, H₂/H_{2'}), 2.40 (dd, $J=11.9,$



4.7 Hz, 1H, H₂/H₂'.



¹³C-NMR, DEPT-135, HMQC, HMBC (75 MHz, CDCl₃, 1:0.63 mixture of rotamers. The asterisk * denotes the signal of the minor rotamer):³ δ 166.8 (1C, C_h), 154.3 (1C, C_f), 154.1* (1C, C_f), 139.3 (1C, CH_{ar}), 139.1* (1C, CH_{ar}), 137.0* (1C, CH_{ar}), 136.2 (1C, CH_{ar}), 135.8 (1C, CH_{ar}), 135.7* (1C, CH_{ar}), 129.2 (3C, CH, CH_{ar}), 128.7 (CH_{ar}), 128.6* (CH_{ar}), 128.5 (2C, CH_{ar}), 128.3* (CH_{ar}), 127.9* (CH_{ar}), 127.6*, 127.5* (2C, CH, CH_{ar}), 127.3 (2C, CH, CH_{ar}), 125.3* (CH_{ar}), 125.24* (CH_{ar}), 125.3 (2C, CH, CH_{ar}), 125.0* (2C, CH, CH_{ar}), 75.74* (1C, CH, C_a), 75.7 (1C, CH, C_a), 69.45 (1C, CH, C_d), 68.9* (1C, CH, C_d), 67.7 (1C, CH₂, C_e), 67.6* (1C, CH₂, C_e), 62.3* (1C, CH, C_g), 62.2 (1C, CH, C_g), 60.3 (1C, CH, C_i), 56.5* (1C, CH, C_i), 55.1 (1C, C_c), 54.5* (1C, C_c), 36.3 (1C, CH₂, C_b), 36.4* (1C, CH₂, C_b).

HRMS (ESI⁺): calcd for C₂₇H₂₄NO₄, 426.1705; found, 426.1532 ([M+H], 100).

3. Preparation of racemic products for HPLC analysis.

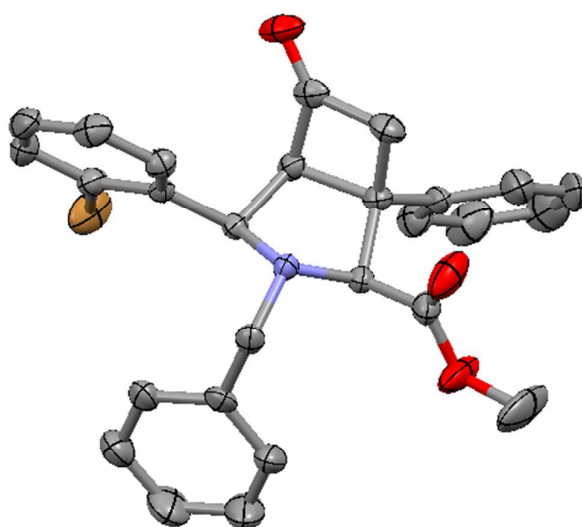
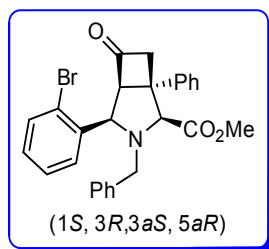
The racemic pyrrolidines were prepared according to the general procedure, but using (±)-Binap as ligand. The samples for HPLC analysis were dissolved in isopropyl alcohol for the determination of enantiomeric excess in the case of HPLC and dichloromethane for SFC, and used as quickly as possible to minimize the formation of decomposition products.

4. Regiochemical and stereochemical assignment

The relative and absolute configuration of *endo*-**3g** was unequivocally established by X-ray crystal structure analysis of its N-benzyl derivative.

CCDC 1828413 contains the supplementary crystallographic data. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via <https://www.ccdc.cam.ac.uk>

3. Some aromatic carbons could not be assigned from the collected spectroscopic data due to the complexity of the spectrum around 125.0-140.0 ppm. These signals are indicated as CH_{ar}.

Figure S1: X-Ray Structure of the N-benzyl derivative of *endo*-**3g****Table S1.** Crystal data of **7** (Hydrogen atoms removed for clarity).

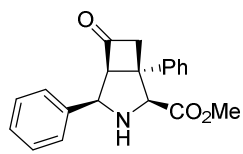
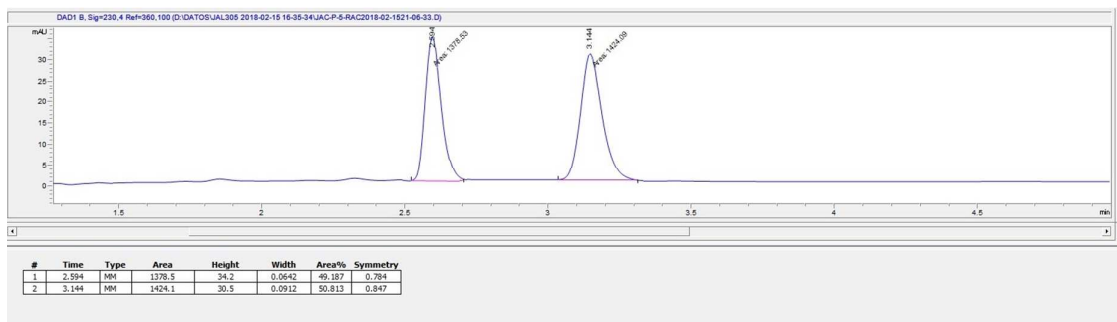
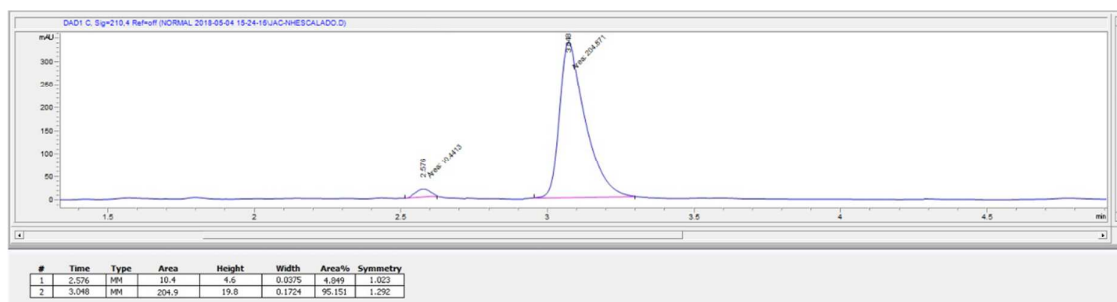
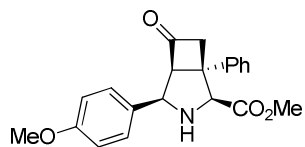
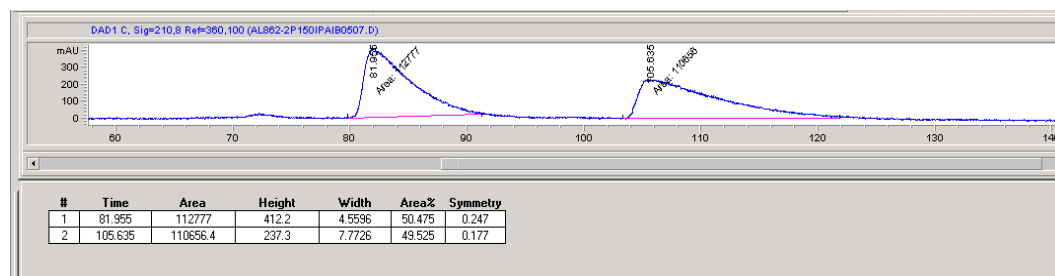
Chemical formula	C ₂₇ H ₂₄ BrNO ₃	
Formula weight	490.38 g/mol	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal size	0.076 x 0.191 x 0.427 mm	
Crystal habit	clear colourless prismatic	
Crystal system	orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 7.3574(3) Å	α = 90°
	b = 17.3491(9) Å	β = 90°
	c = 18.2869(9) Å	γ = 90°
Volume	2334.22(19) Å ³	
Z	4	
Density (calculated)	1.395 g/cm ³	

Absorption coefficient	1.789 mm ⁻¹
F(000)	1008

Table S2. Data collection and structure refinement

Diffractometer	Bruker APEX-II CCD
Theta range for data collection	2.23 to 25.35°
Index ranges	-7 ≤ h ≤ 8, -20 ≤ k ≤ 20, -22 ≤ l ≤ 2
Reflections collected	21048
Independent reflections	4274 [R(int) = 0.0597]
Coverage of independent reflections	100.0%
Absorption correction	multi-scan
Max. and min. transmission	0.8760 and 0.5150
Structure solution technique	direct methods
Structure solution program	SHELXS-97 (Sheldrick 2008)
Refinement method	Full-matrix least-squares on F ²
Refinement program	SHELXL-2014/7 (Sheldrick, 2014)
Function minimized	Σ w(F _o ² - F _c ²) ²
Data / restraints / parameters	4274 / 0 / 290
Goodness-of-fit on F²	1.012
Final R indices	3399 data; R1 = 0.0361, I > 2σ(I) wR2 = 0.0684 all data R1 = 0.0561, wR2 = 0.0746
Weighting scheme	w = 1/[σ ² (F _o ²) + (0.0313P) ² + 0.3686P] where P = (F _o ² + 2F _c ²)/3
Absolute structure parameter	-0.0(0)
Largest diff. peak and hole	0.294 and -0.349 eÅ ⁻³
R.M.S. deviation from mean	0.051 eÅ ⁻³

5. HPLC charts.

*endo-3a*Figure S2: (\pm)-*endo-3a*Figure S3: (+)-*endo-3a*; 90% *ee**endo-3b*Figure S4: (\pm)-*endo-3b*

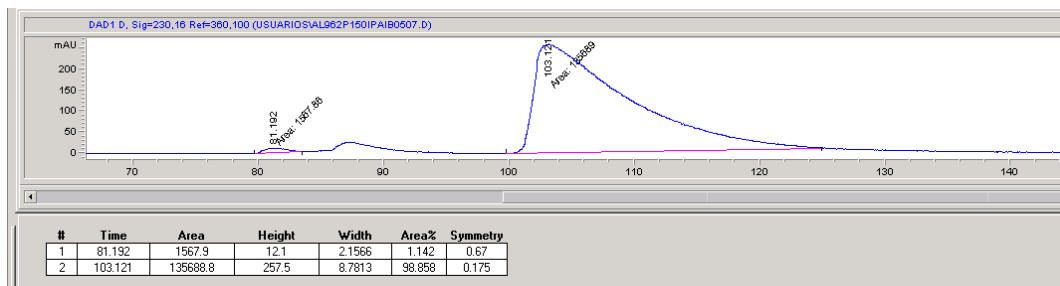


Figure S5: (+)-endo-3b; 98% ee

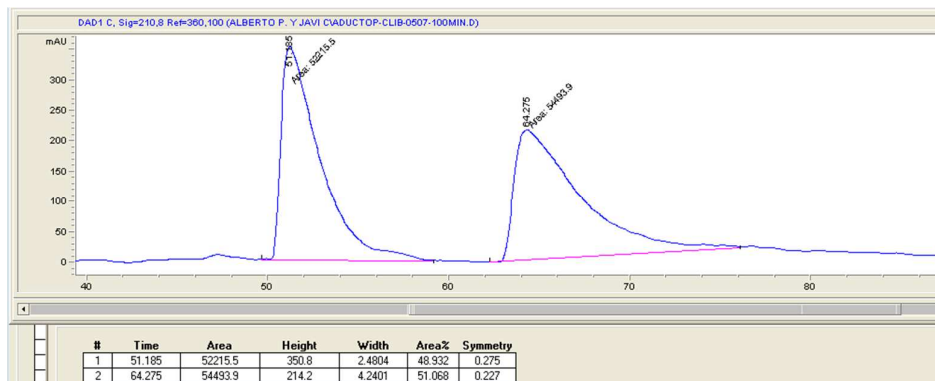
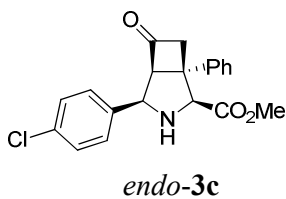


Figure S6: (±)-endo-3c

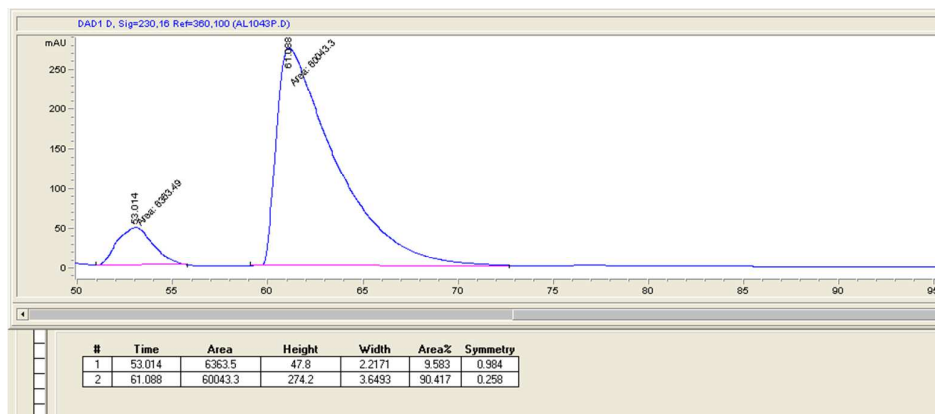
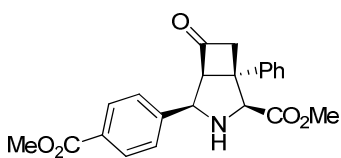
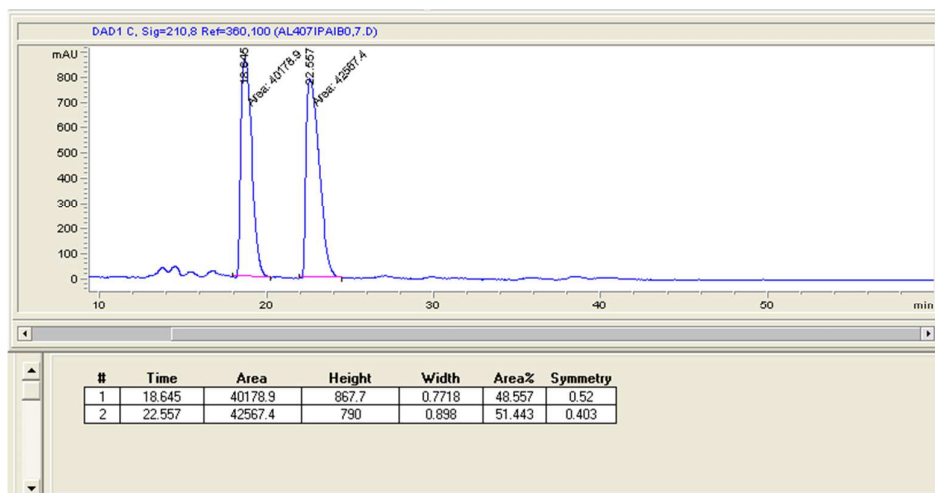
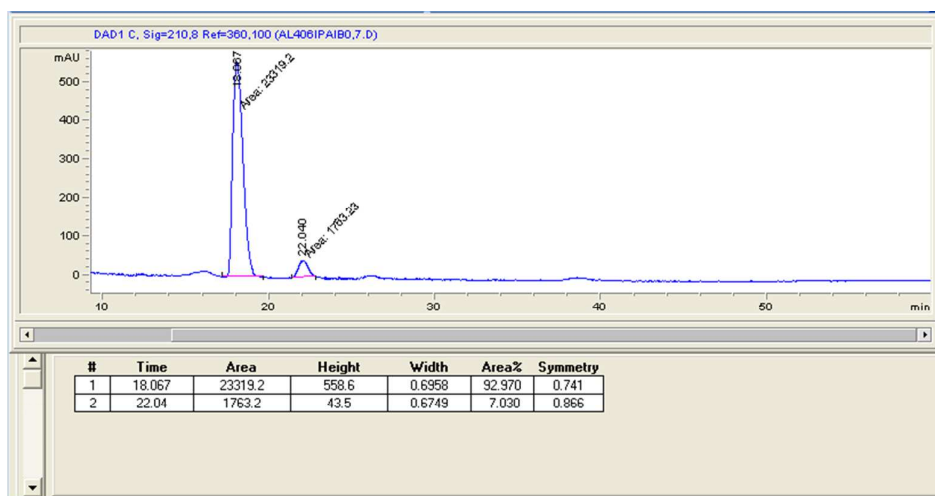
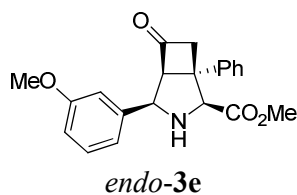


Figure S7: (+)-endo-3c; 81% ee



endo-3dFigure S8: (±)-*endo-3d*Figure S9: (+)-*endo-3d*; 85% *ee*

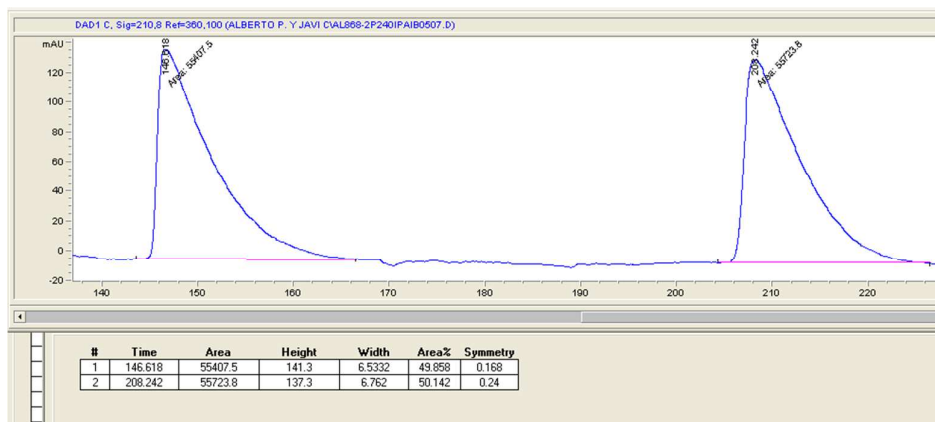


Figure S10: (±)-endo-3e

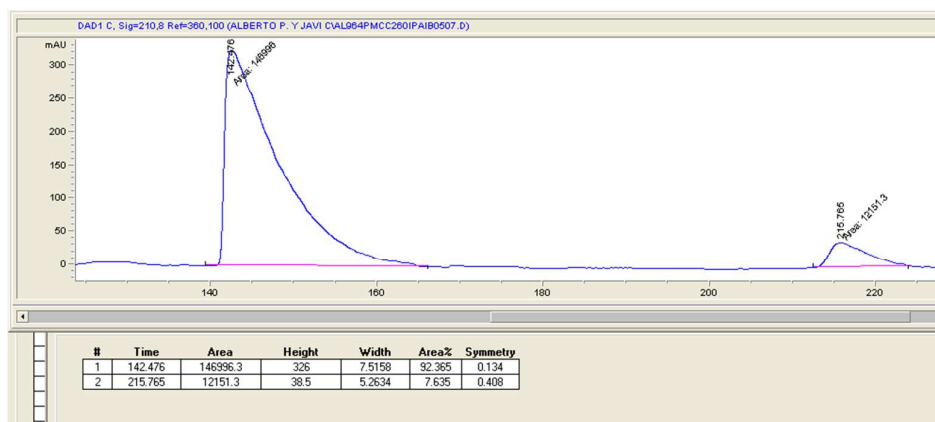
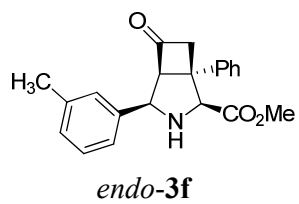


Figure S11: (+)-endo-3e; 85% ee



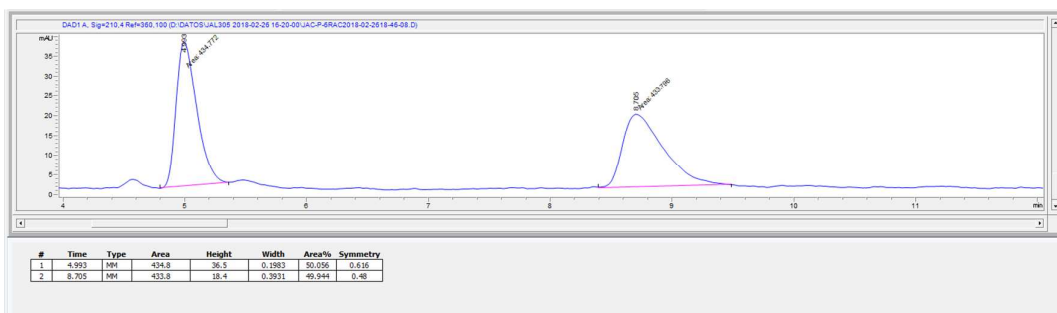


Figure S12: (±)-endo-3f

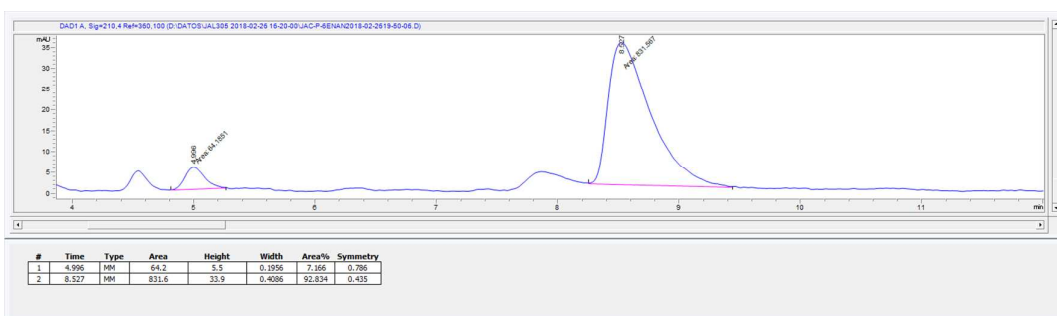


Figure S13: (+)-endo-3f; 86% ee

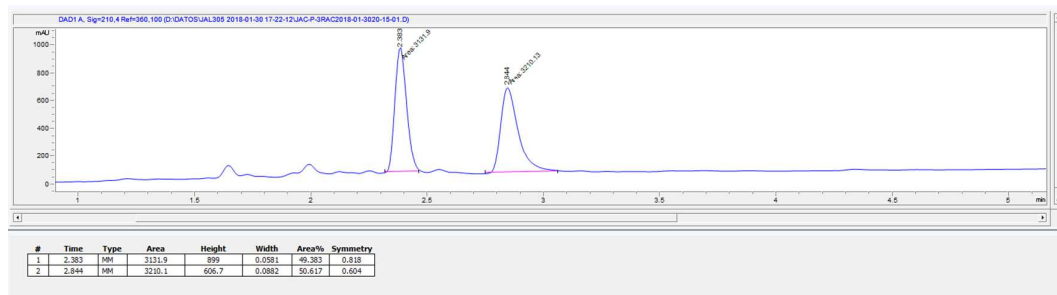
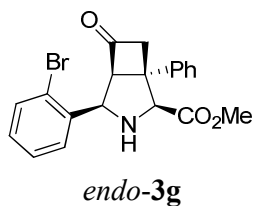


Figure S14: (±)-endo-3g

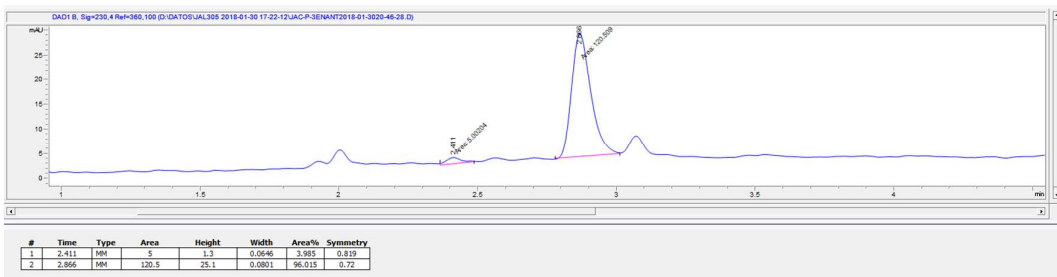


Figure S15: (+)-endo-3g; 92% ee

S24

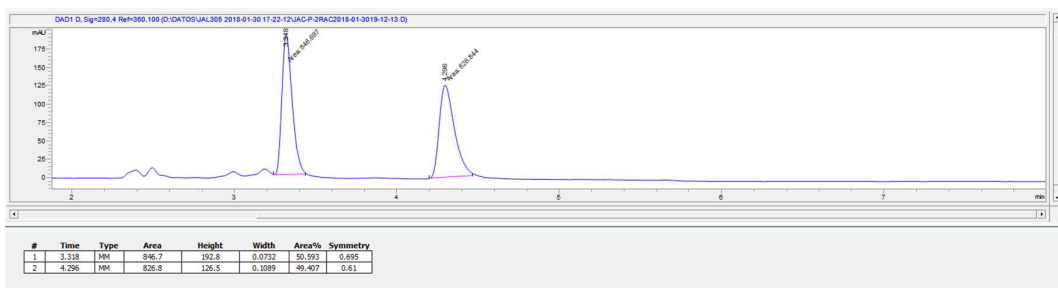
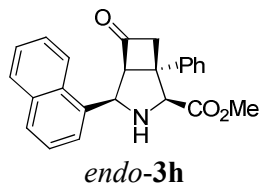


Figure S16: (±)-*endo-3h*

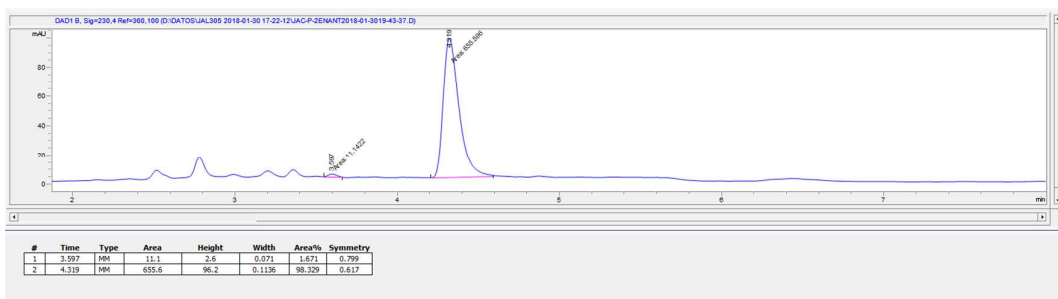
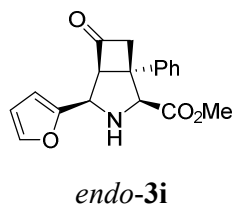


Figure S17: (+)-*endo-3h*; 97% ee



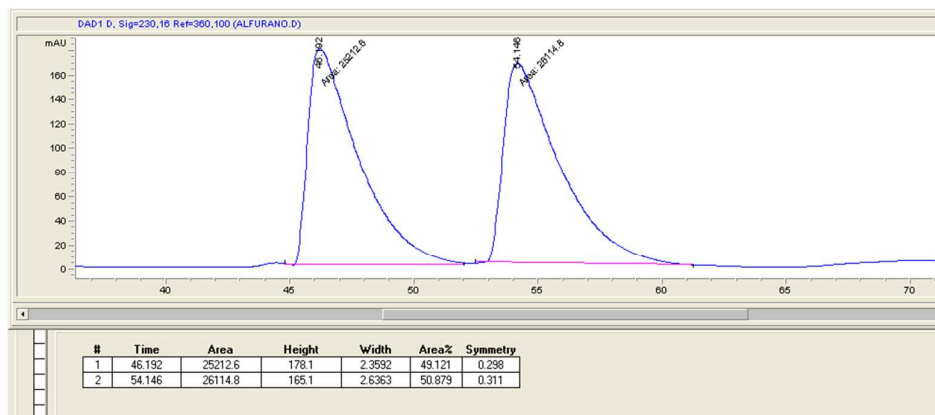
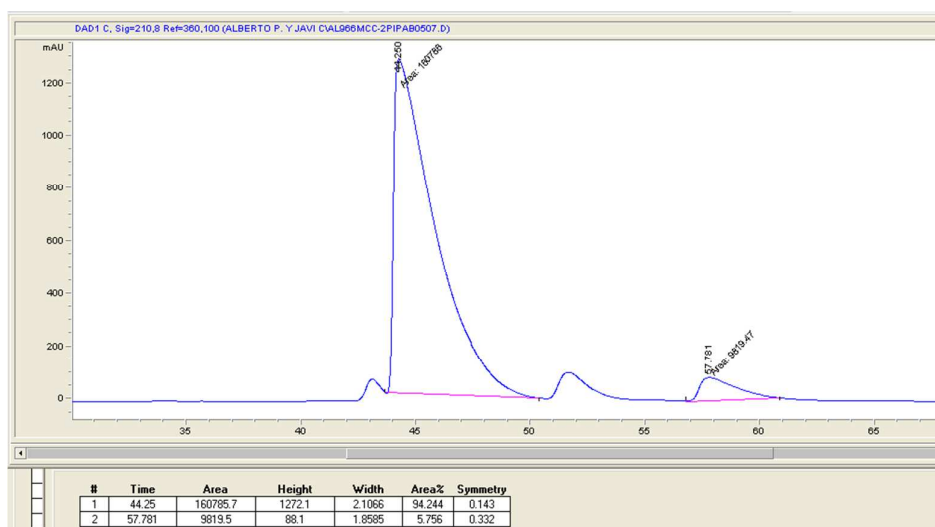
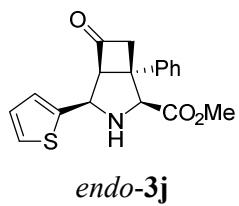
Figure S18: (\pm)-endo-3i

Figure S19: (+)-endo-3i; 88% ee



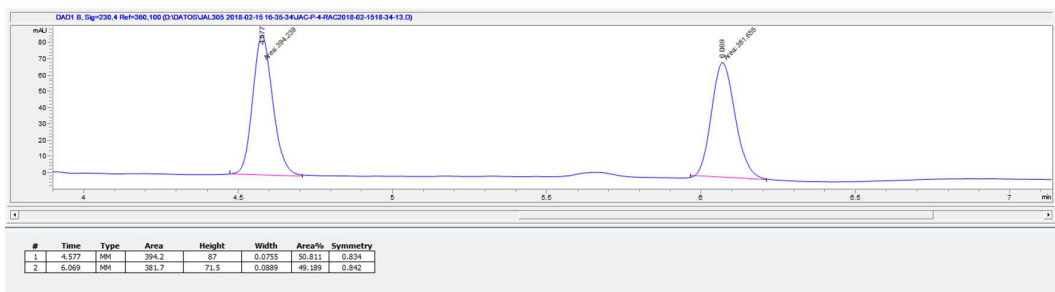


Figure S20: (±)-endo-3j

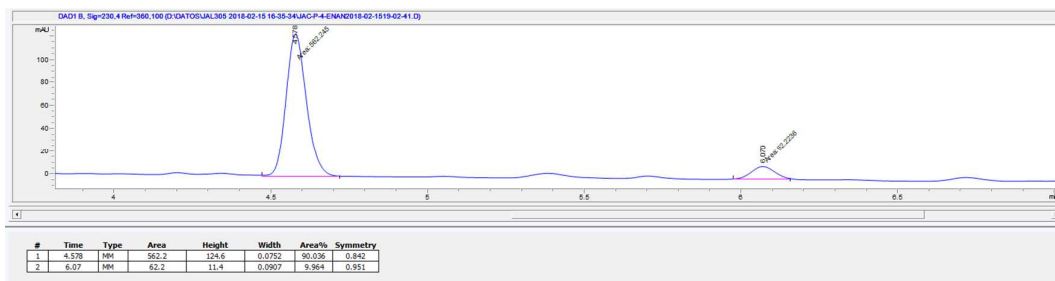


Figure S21: (+)-endo-3j; 80% ee

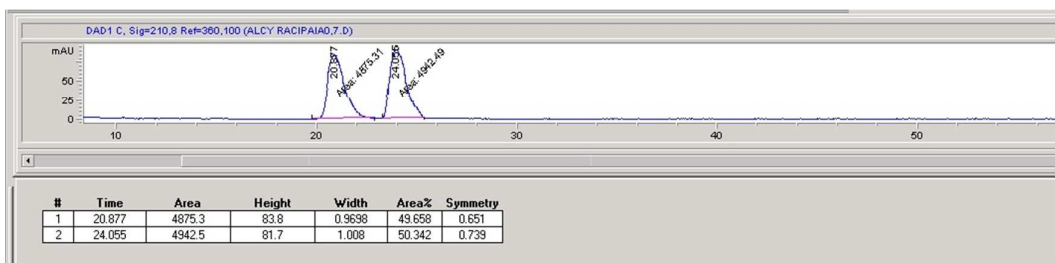
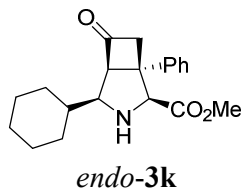


Figure S22: (±)-endo-3k

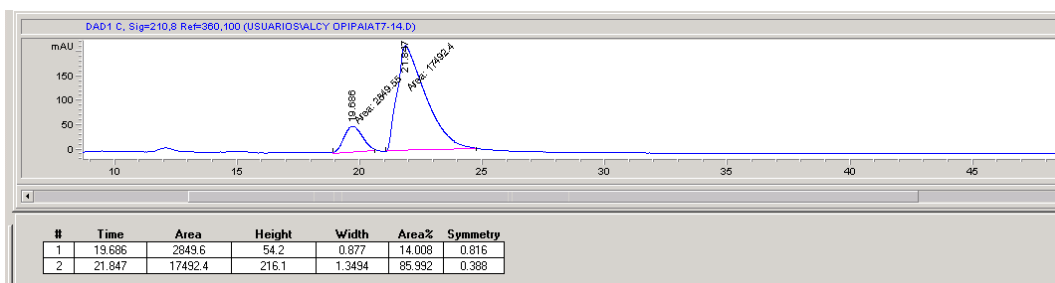
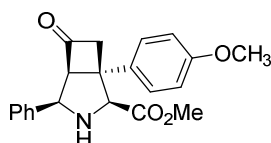
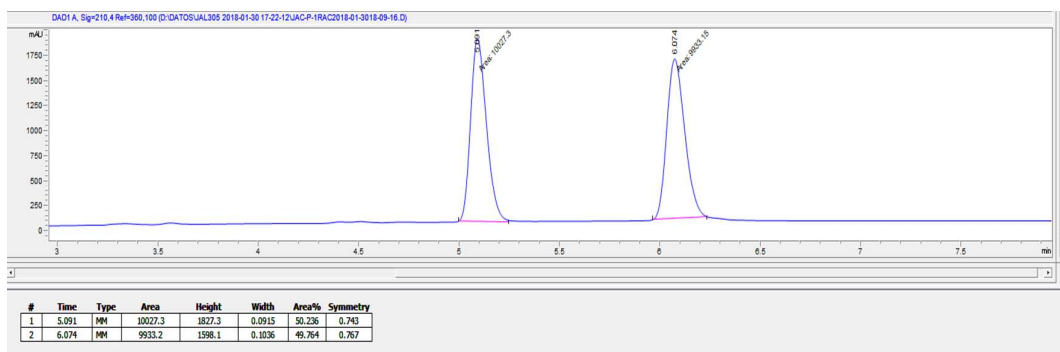
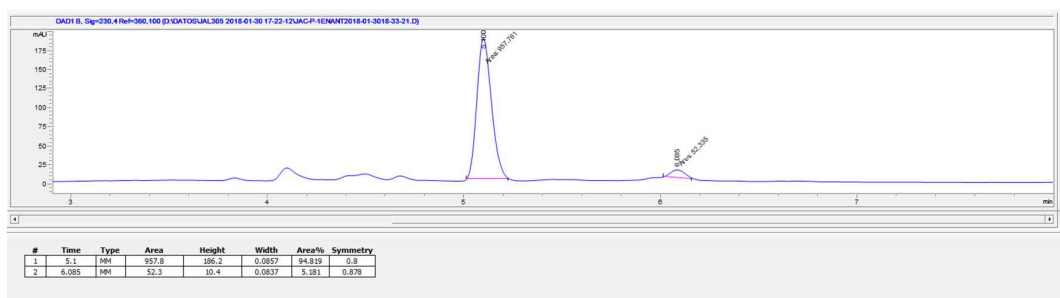
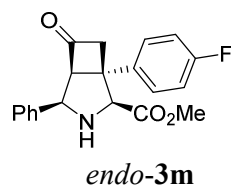


Figure S23: (+)-endo-3k; 72% ee



endo-3lFigure S24: (\pm)-*endo-3l*Figure S25: (+)-*endo-3l*; 90% *ee*

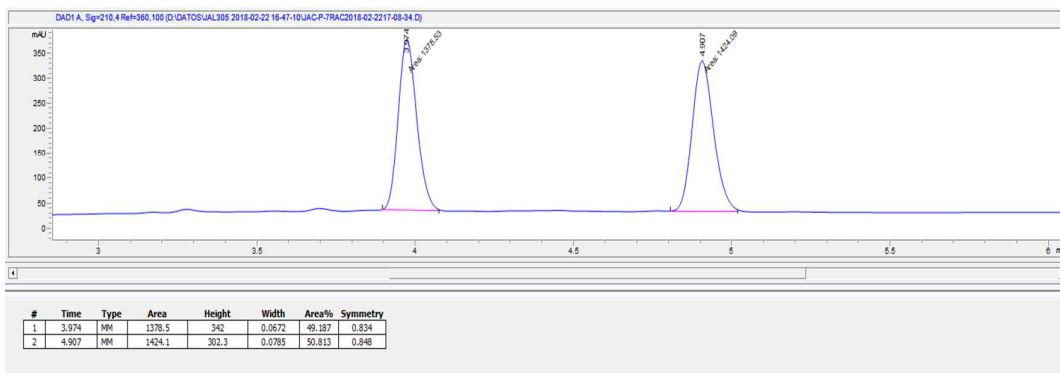


Figure S26: (±)-endo-3m

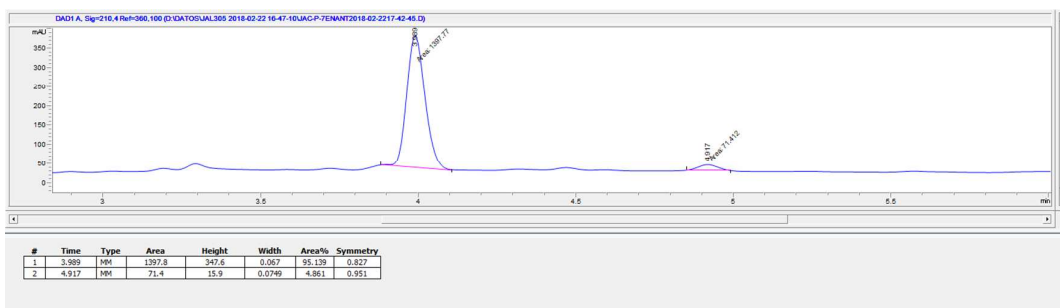


Figure S27: (+)-endo-3m; 90% ee

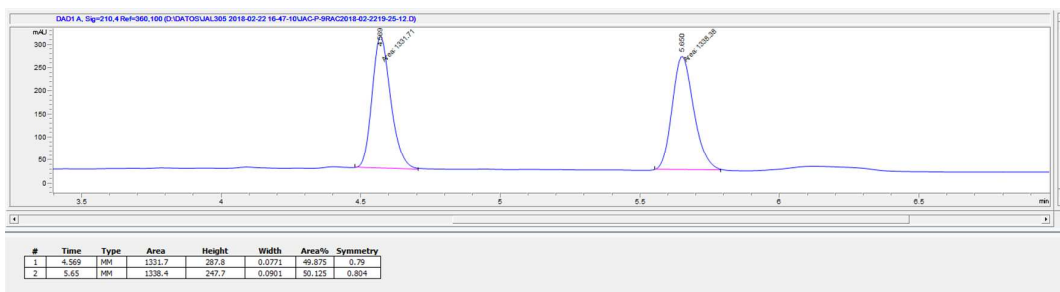
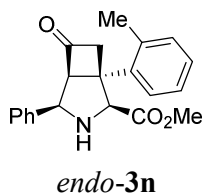


Figure S28: (±)-endo-3n

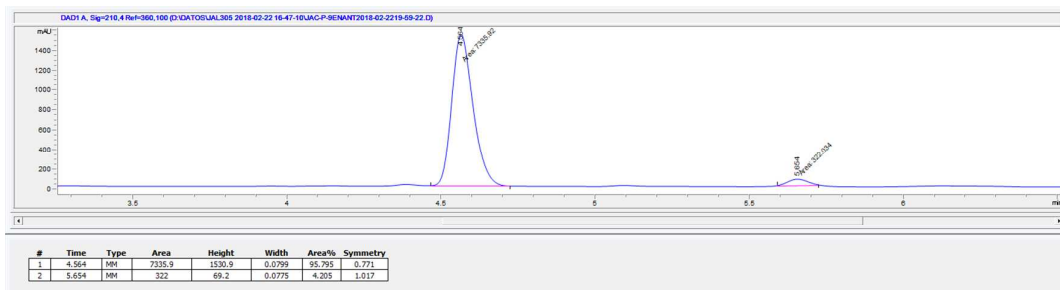


Figure S29: (+)-endo-3n; 92% ee

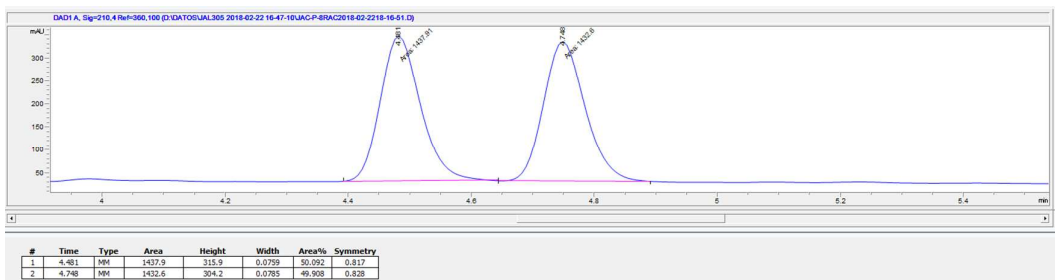
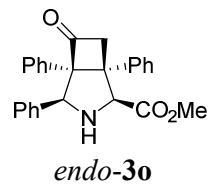


Figure S30: (±)-endo-3o

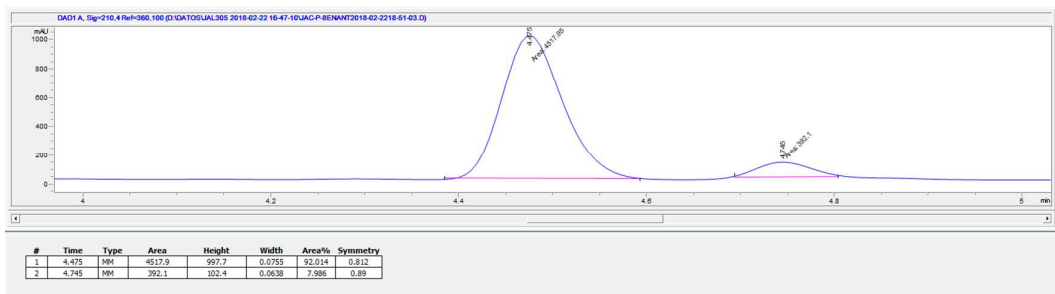


Figure S31: (+)-endo-3o; 84% ee

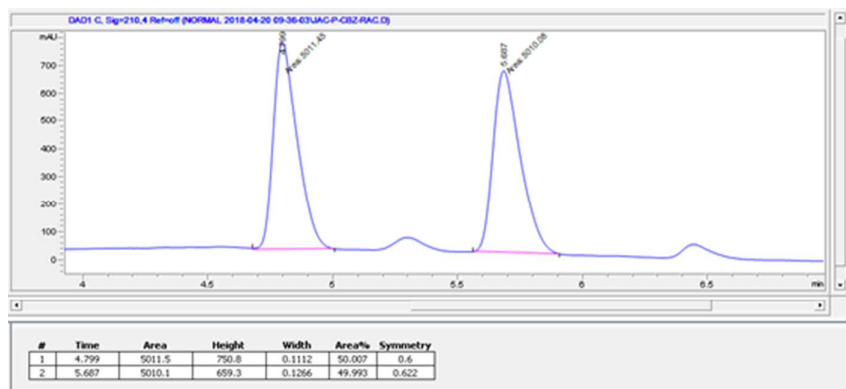
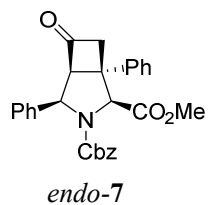


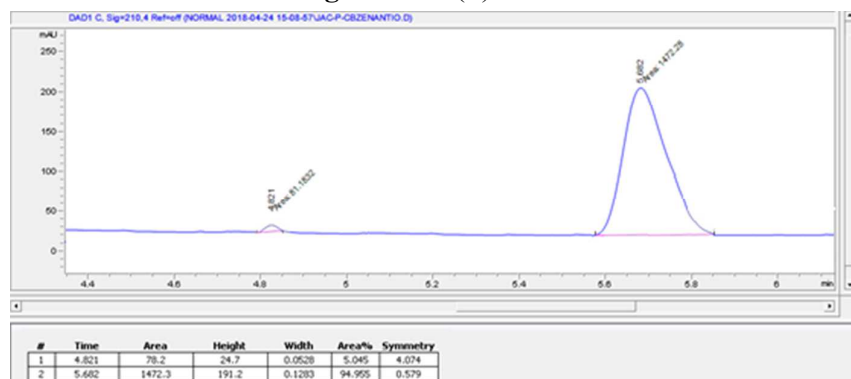
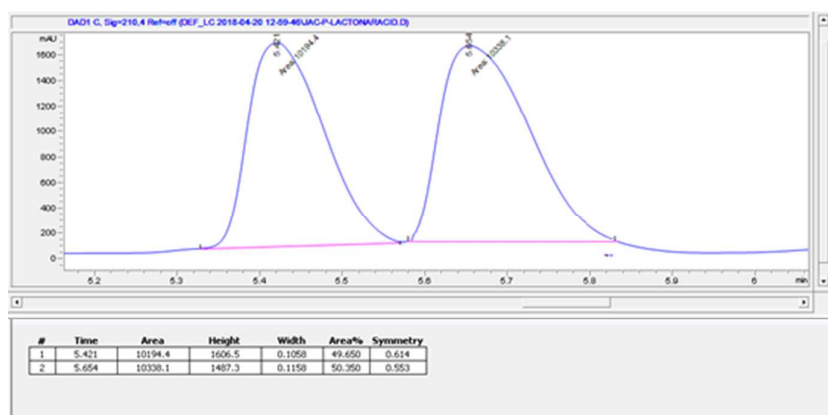
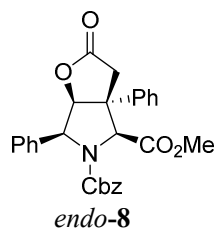
Figure S32: (\pm)-endo-7

Figure S33: (+)-endo-7, 90 % ee

Figure S34: (\pm)-endo-8

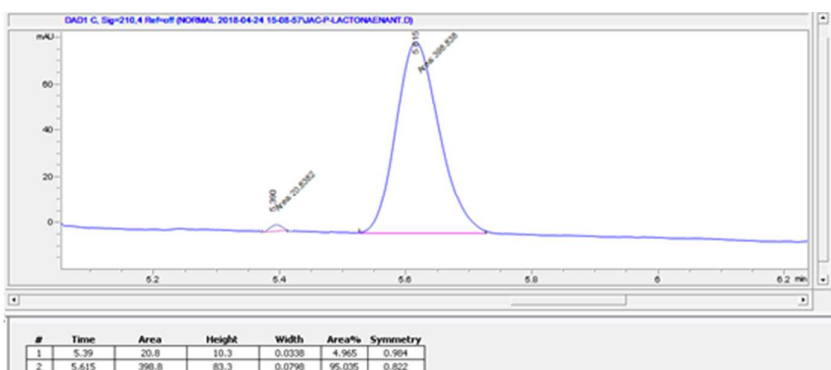
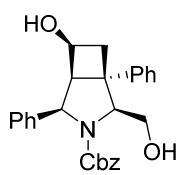


Figure S35: (+)-endo-8, 90 % ee



endo-9

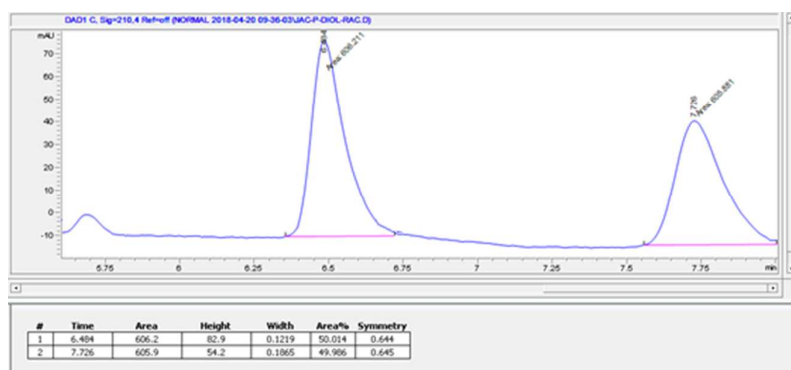


Figure S36: (±)-endo-9

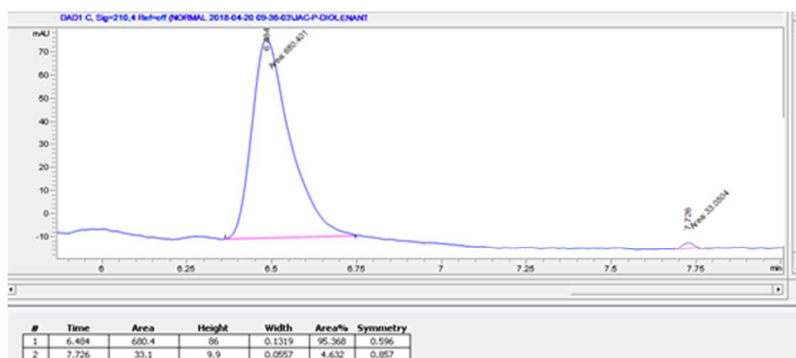


Figure S37: (+)-endo-9, 90 % ee

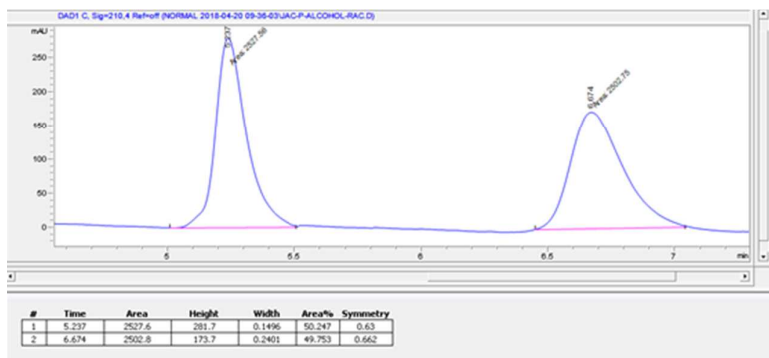
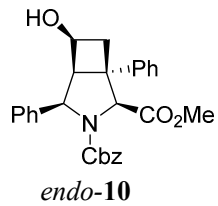
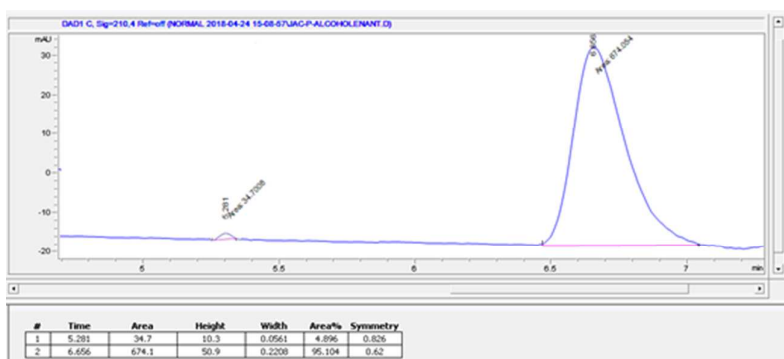
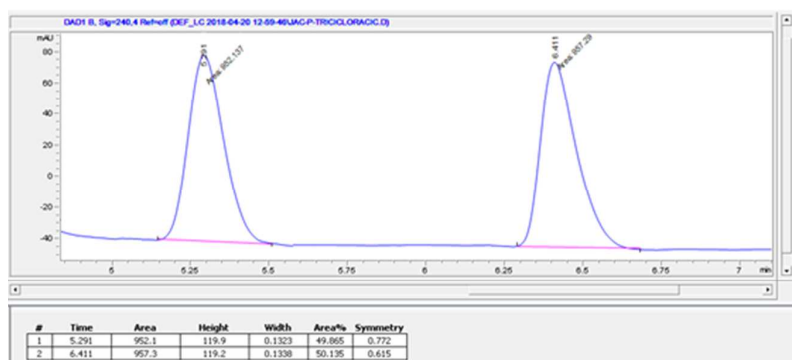
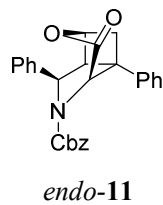
Figure S38: (\pm)-*endo*-10Figure S39: (+)-*endo*-10, 90 % ee

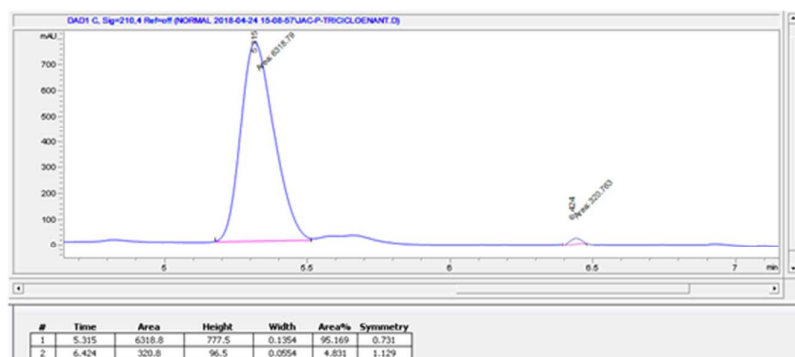
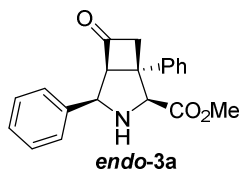
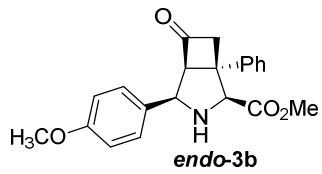
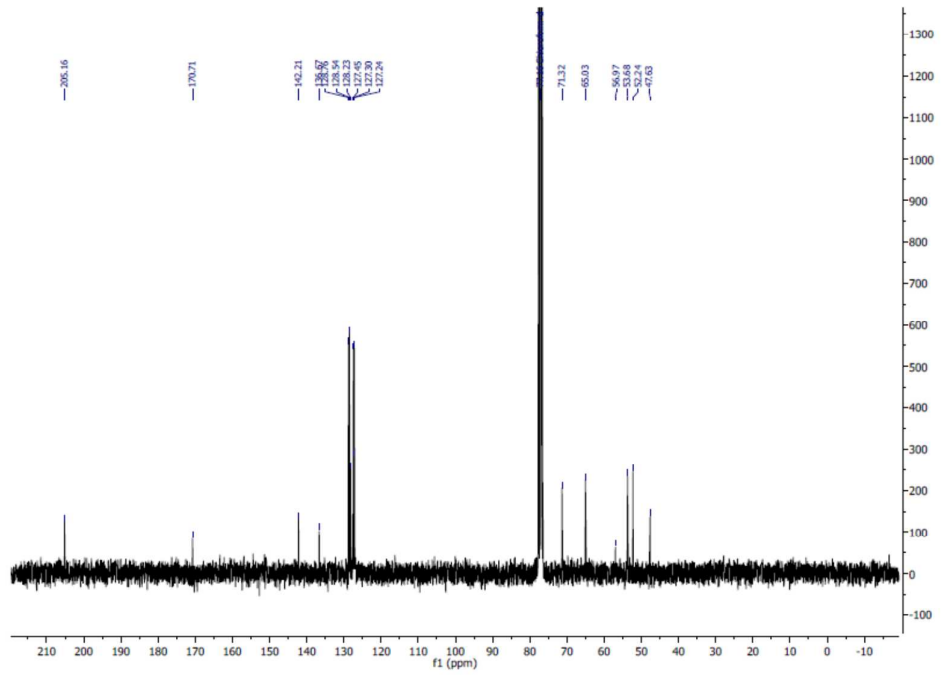
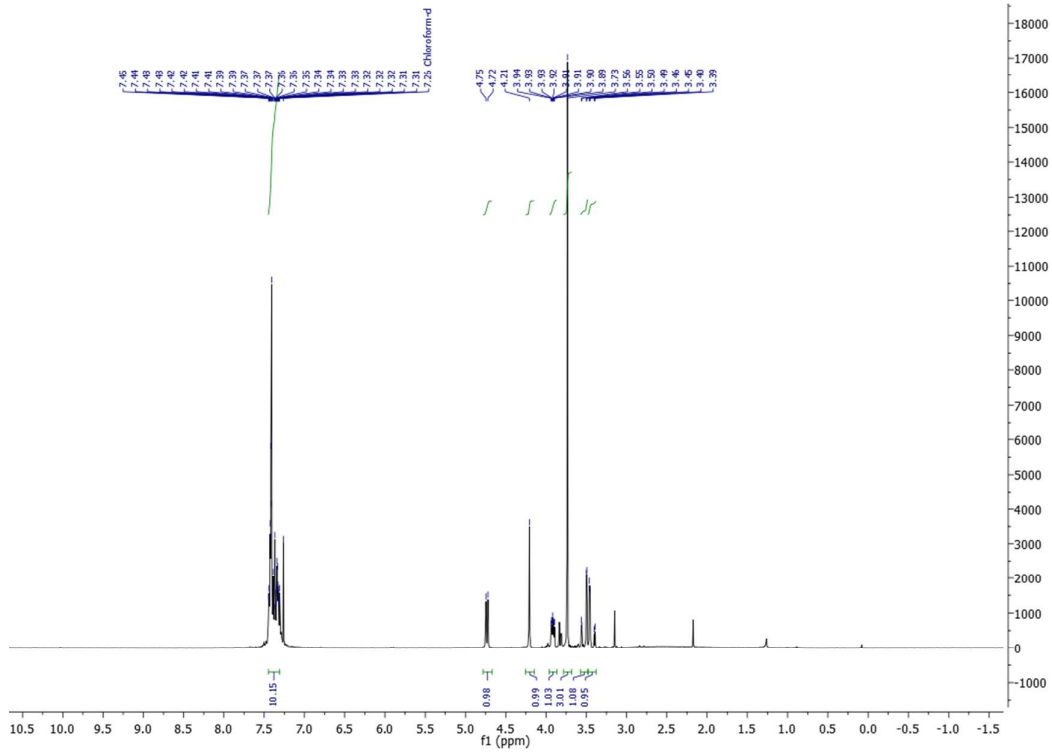
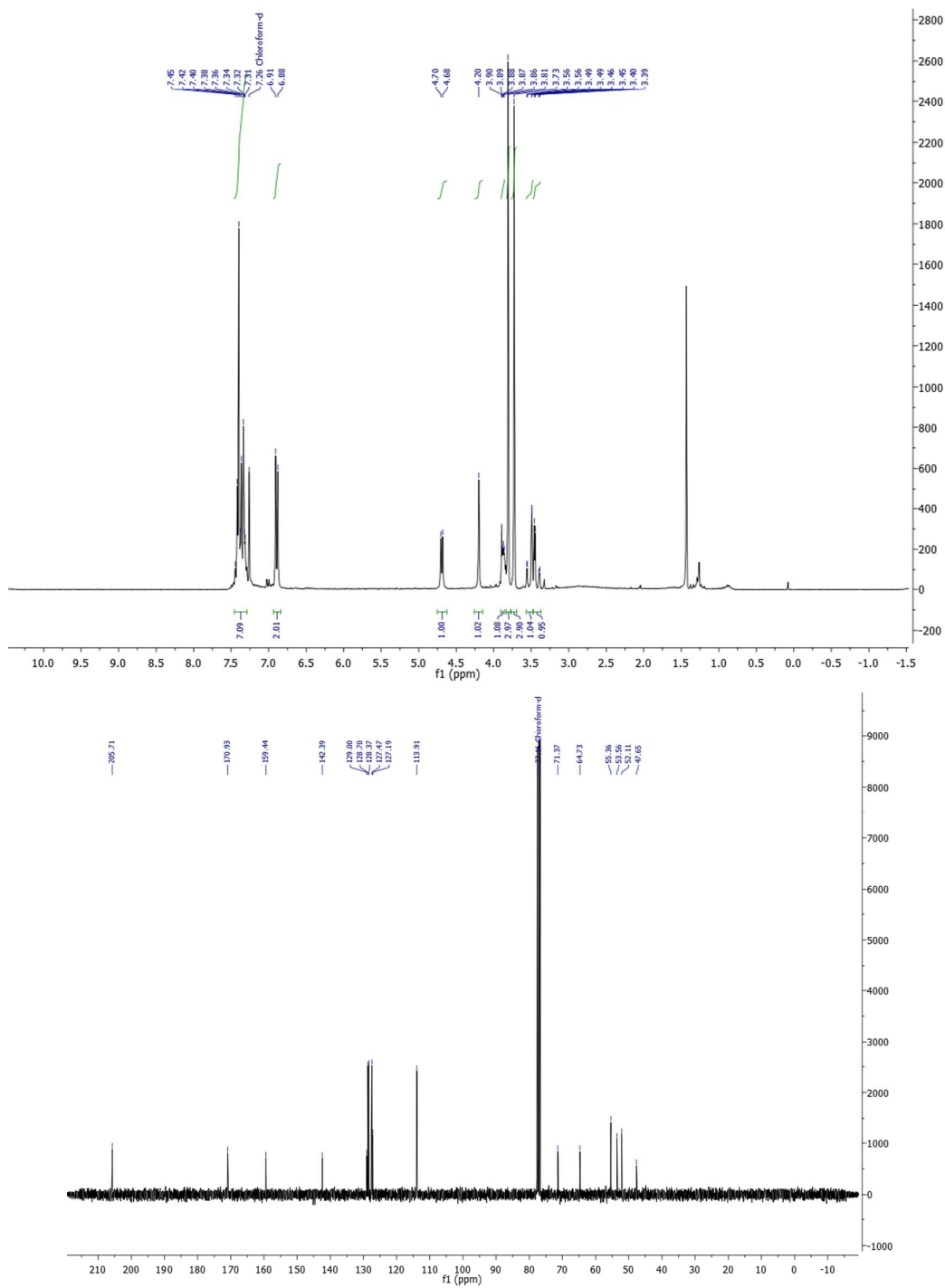
Figure S40: (\pm)-endo-11

Figure S41: (+)-endo-11, 90 % ee

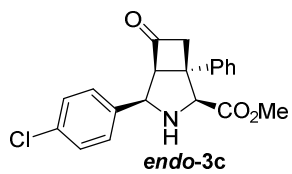
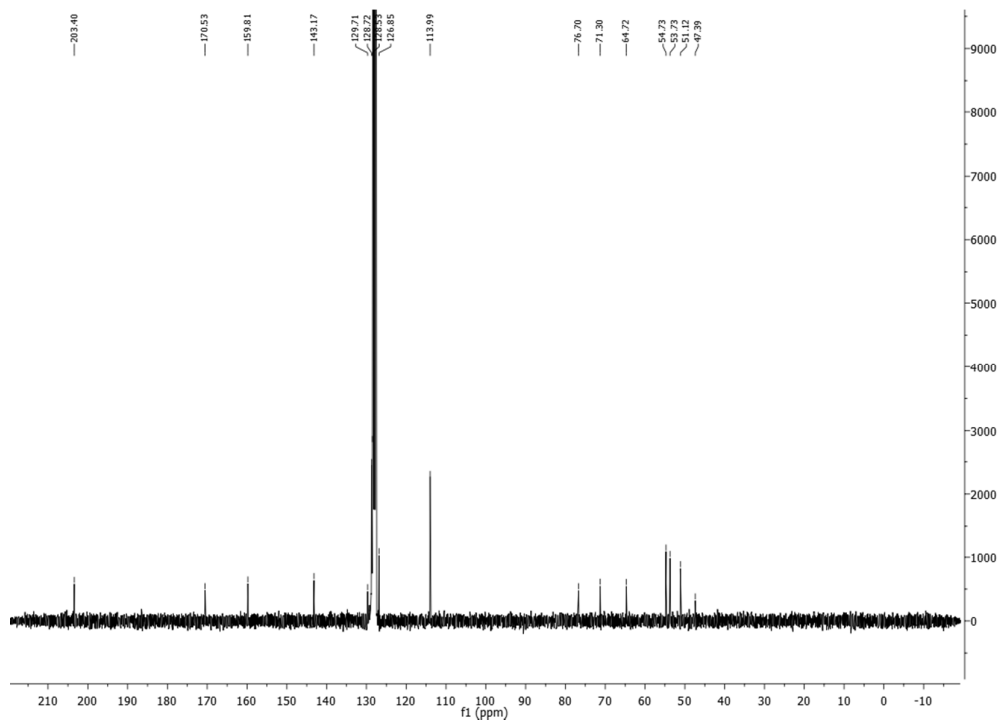
6. NMR spectra collection

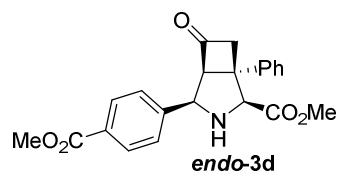
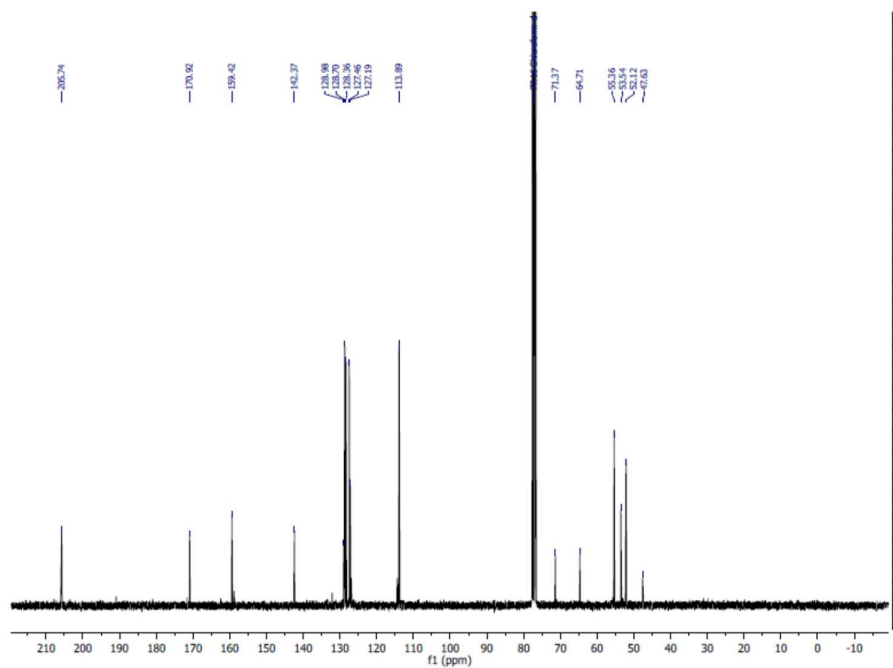
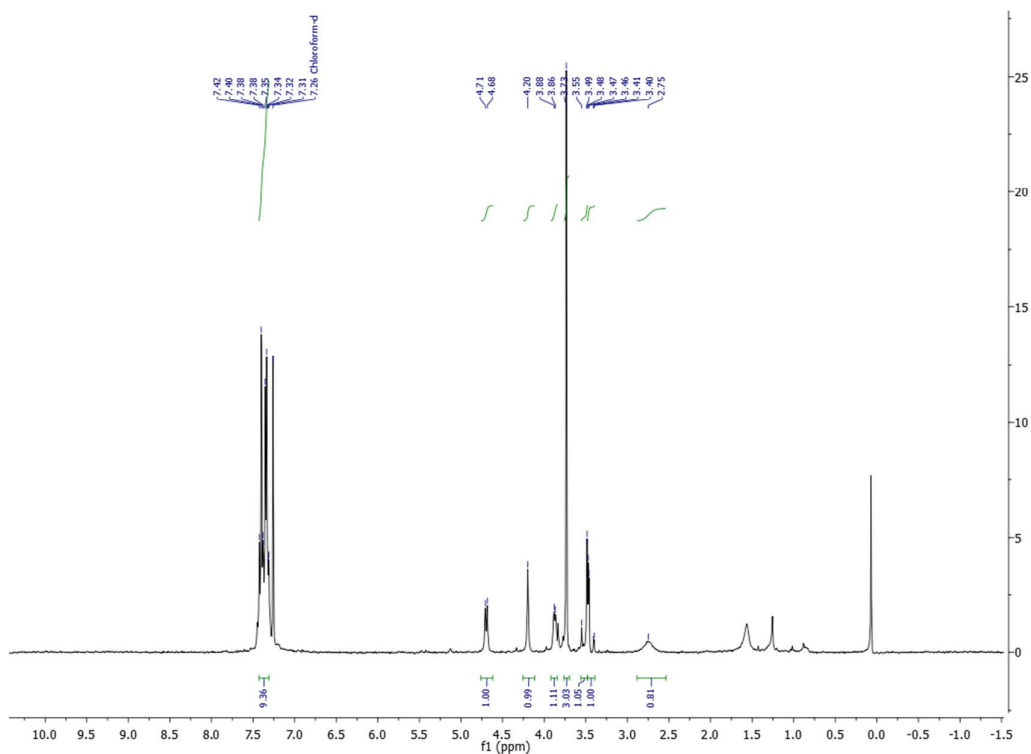


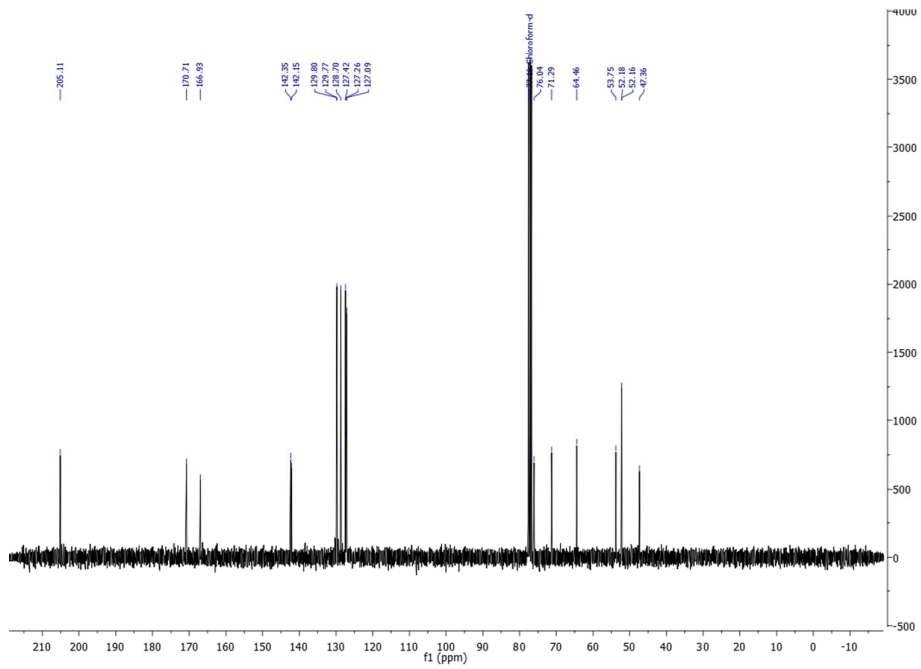
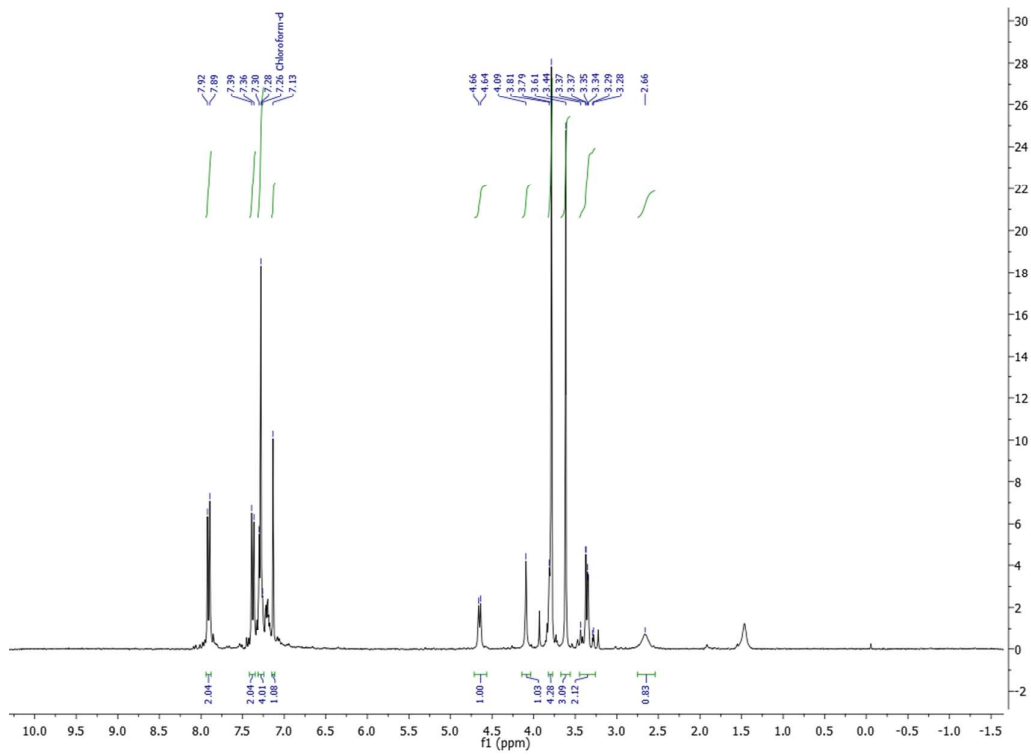




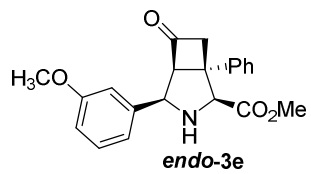
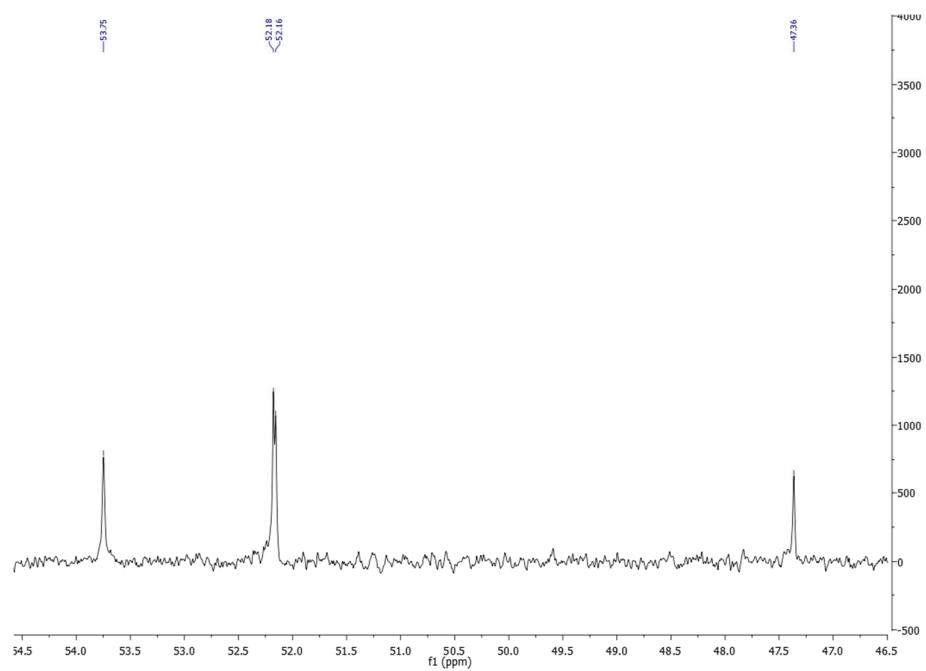
The existence of seven aliphatic carbons in compound *endo-3b* was determined by recording the ¹³C-NMR in benzene-*d*₆.

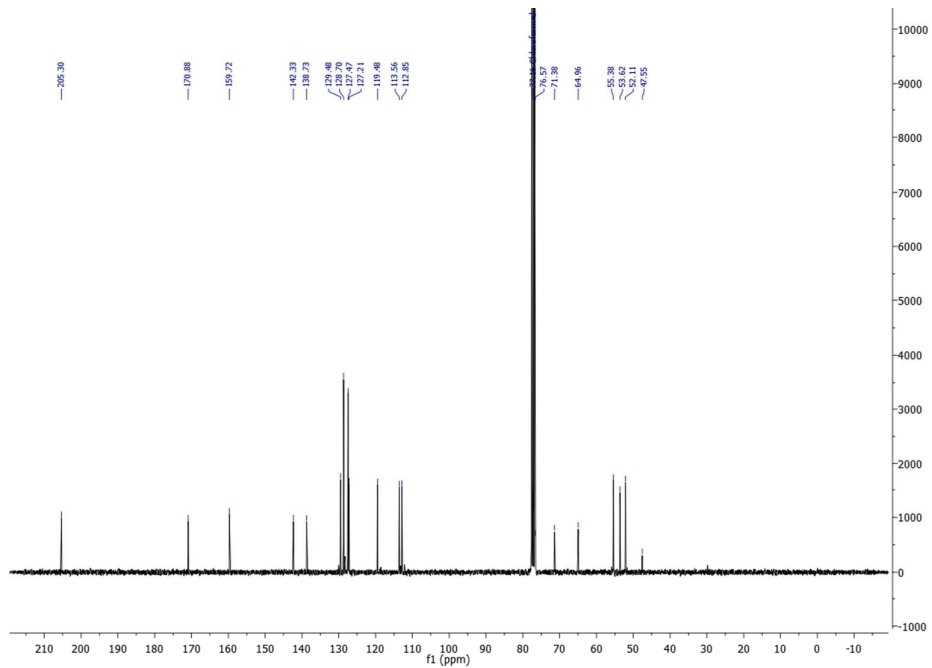
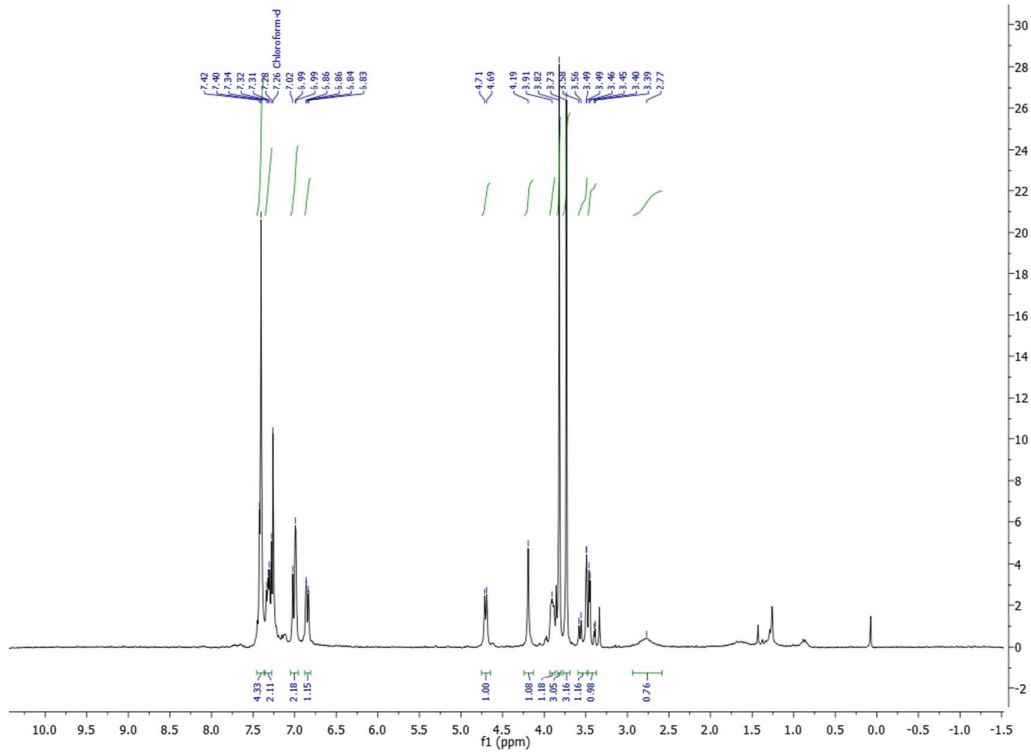




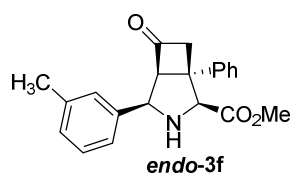
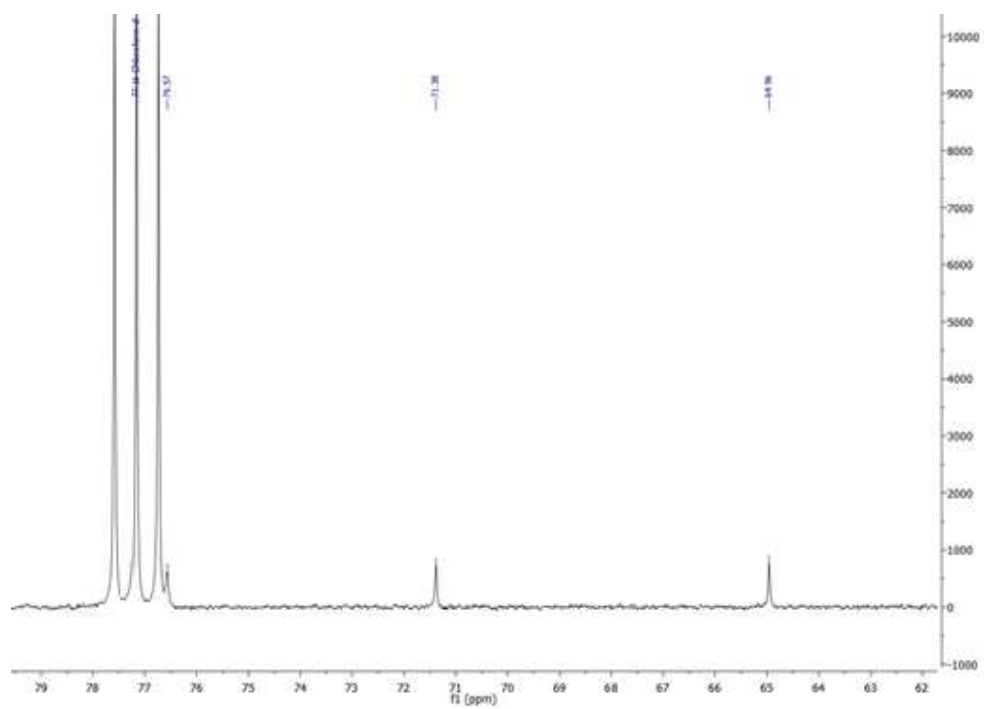


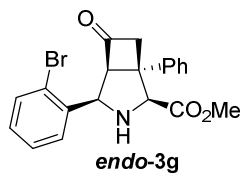
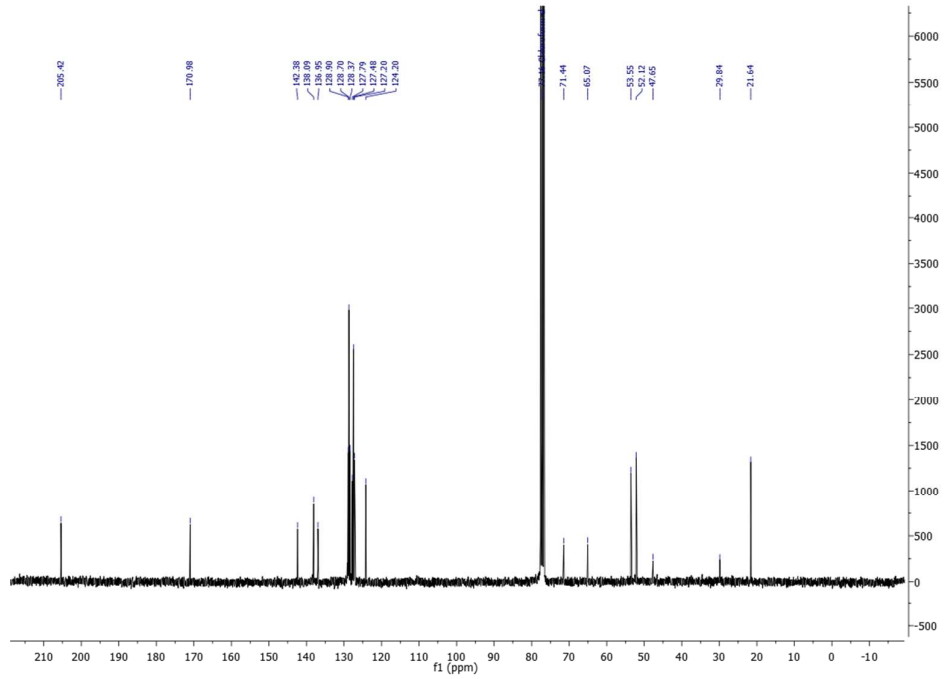
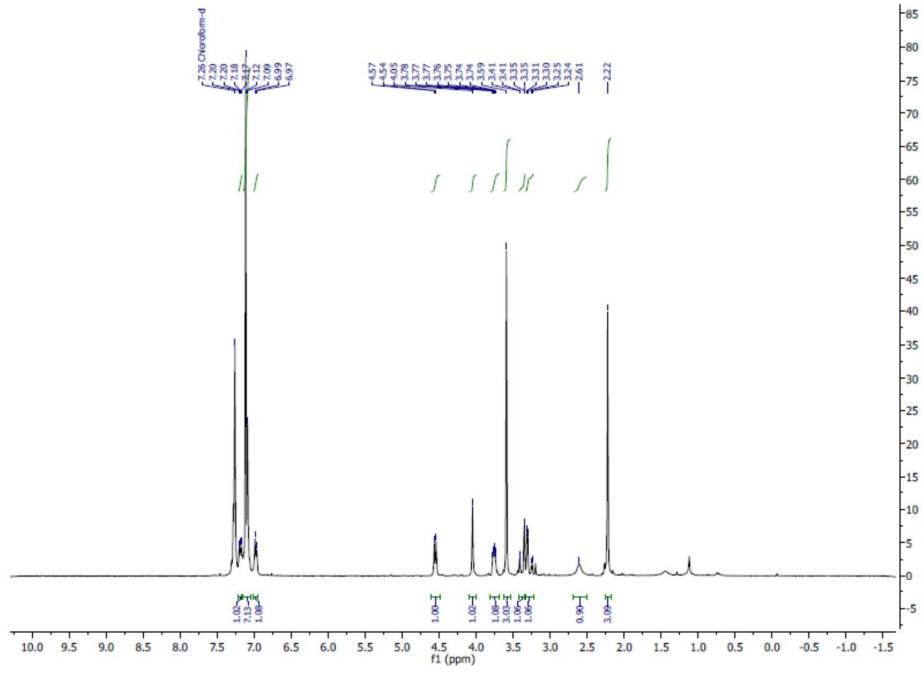
Scaling up in the region between 47.0-54.5 ppm:

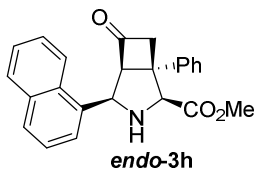
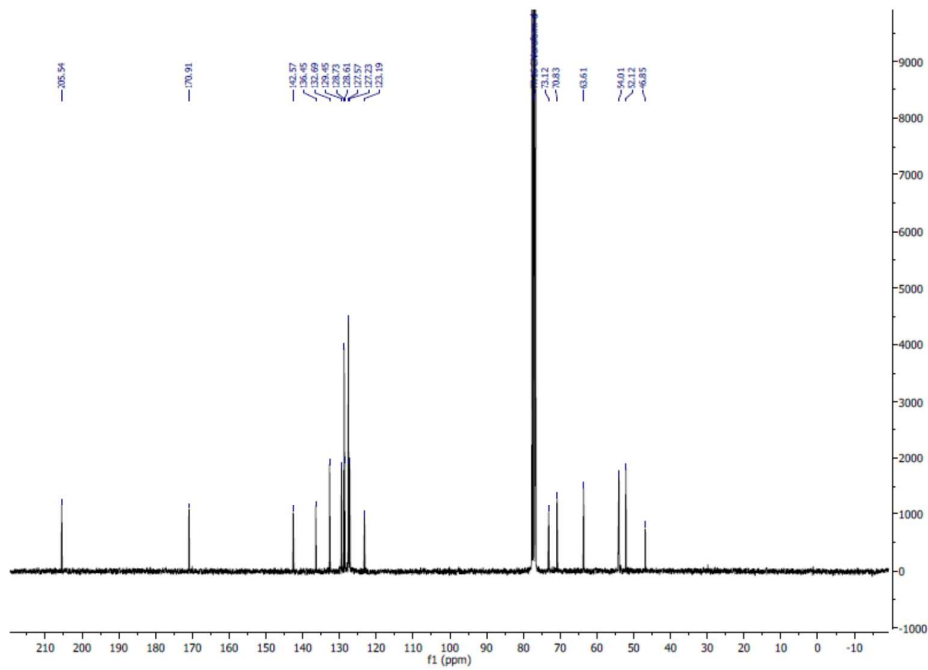
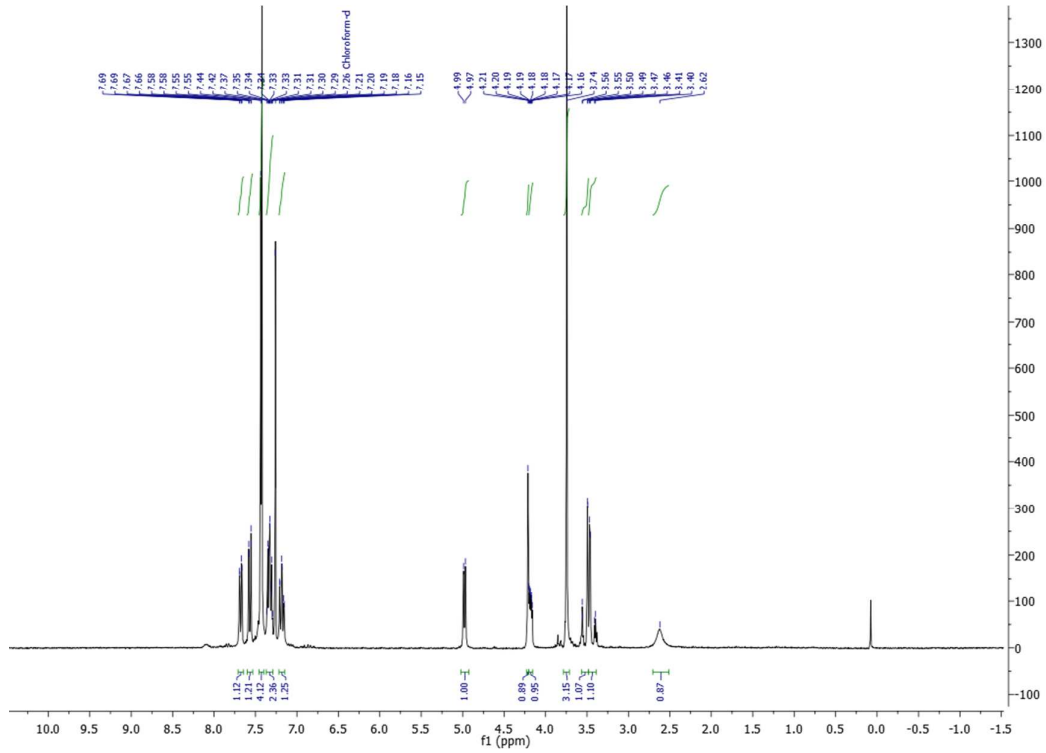


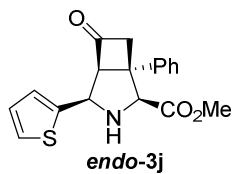
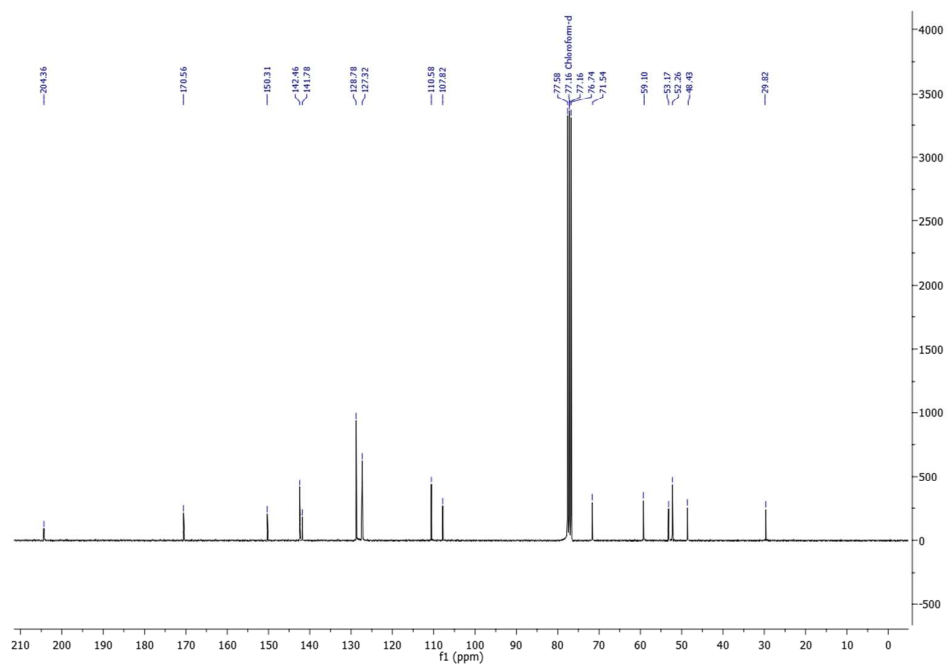
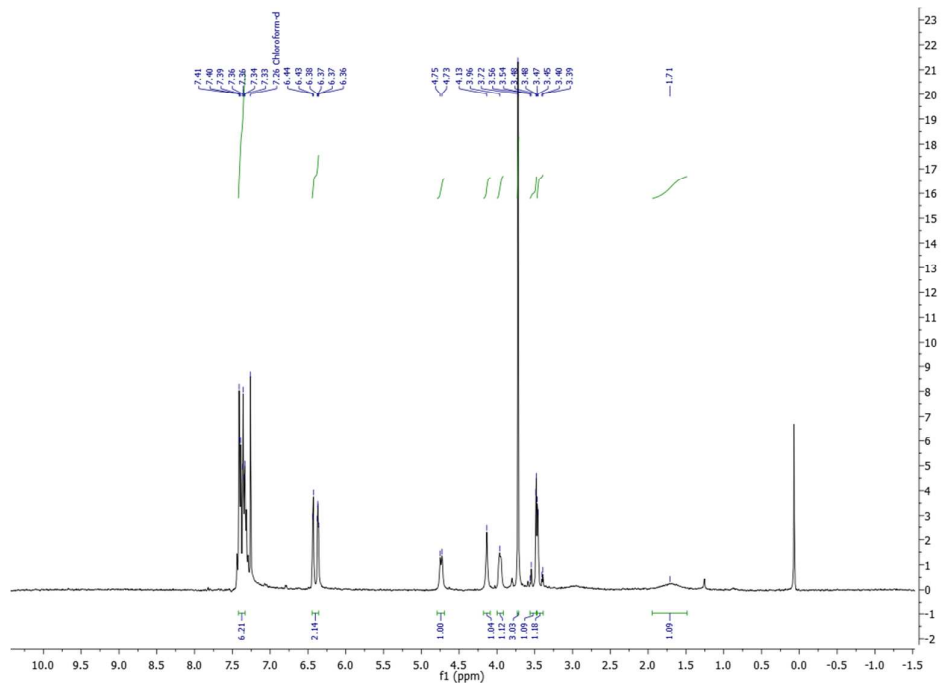


Scaling up in the region 62.0-79.0 ppm

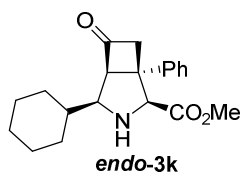
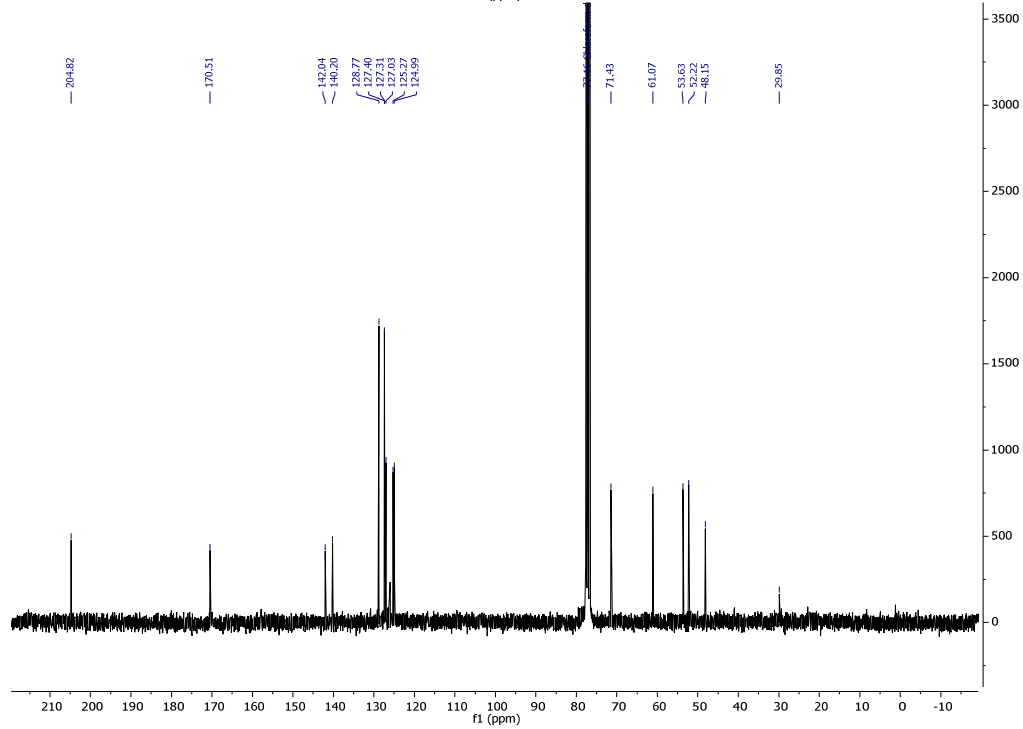
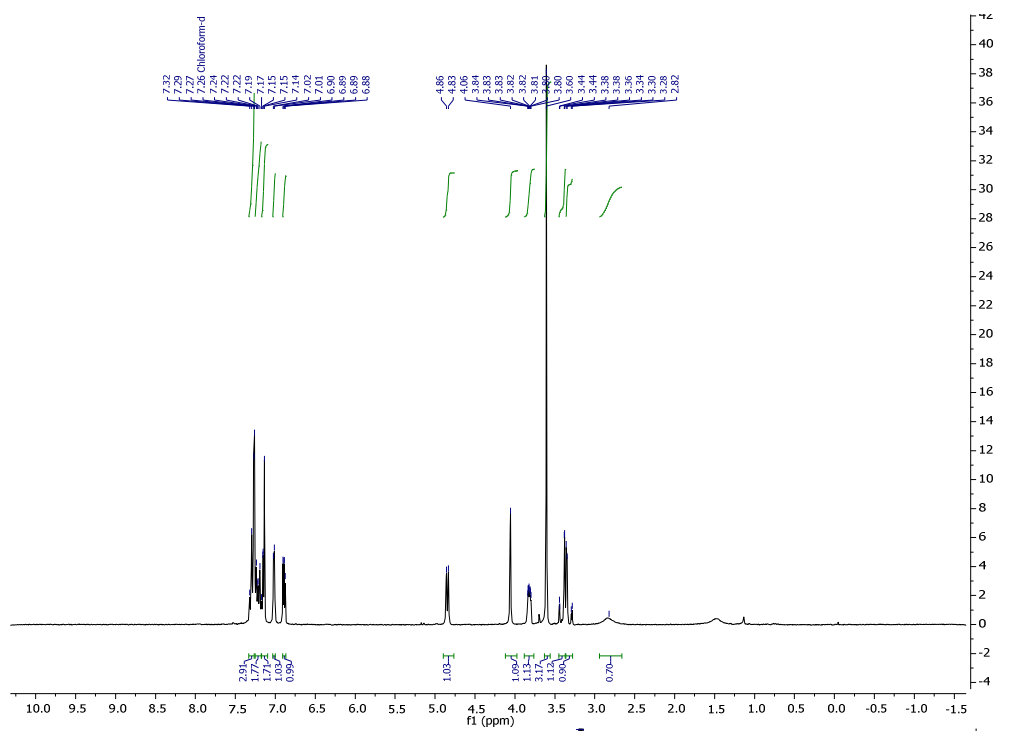


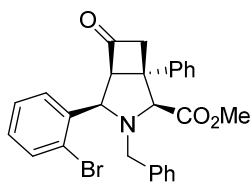
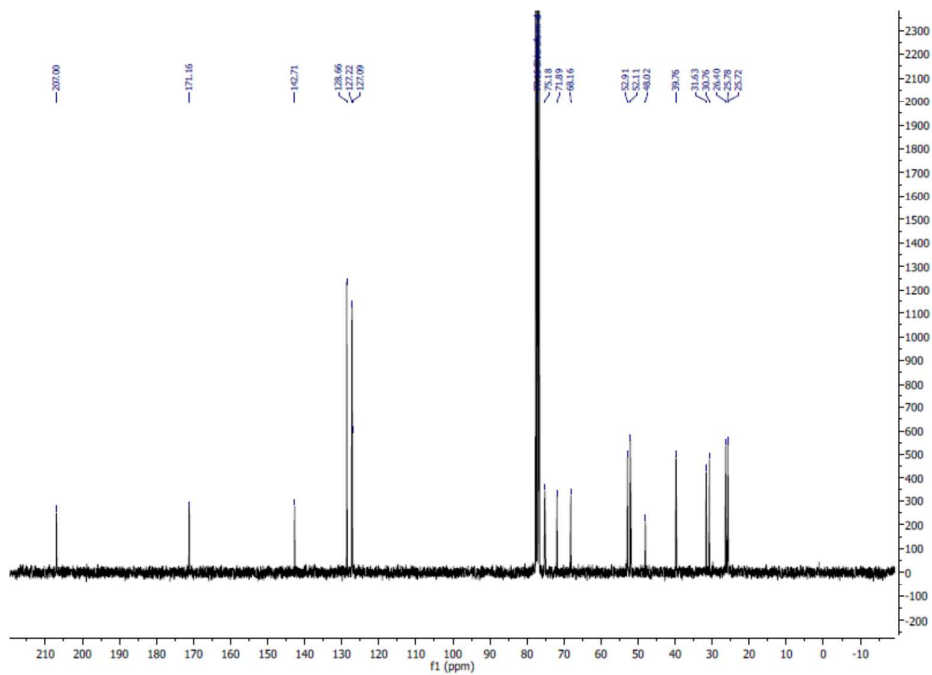
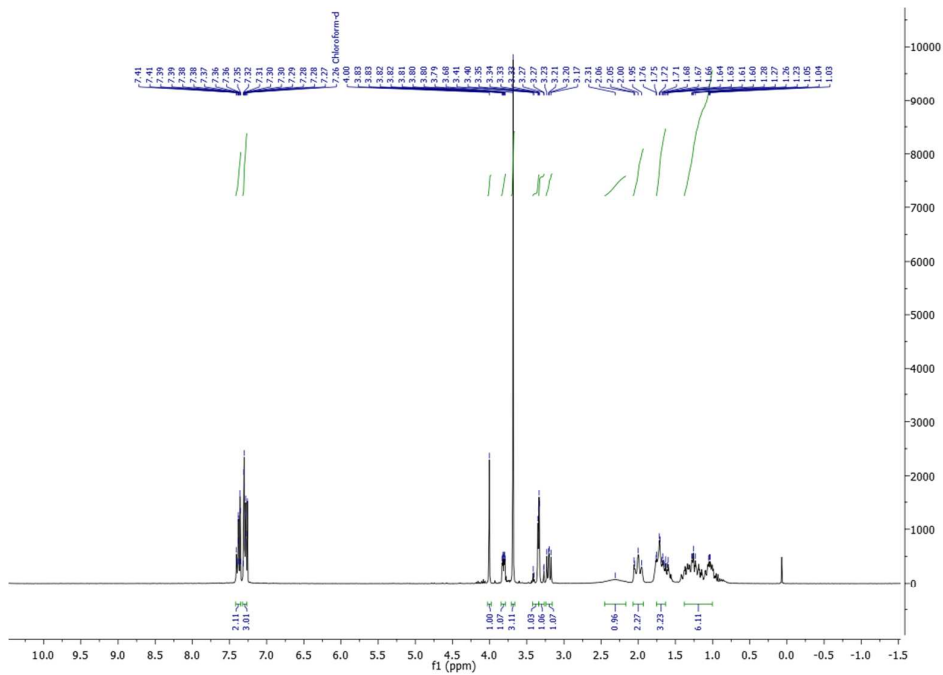


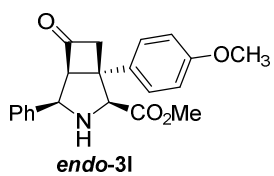
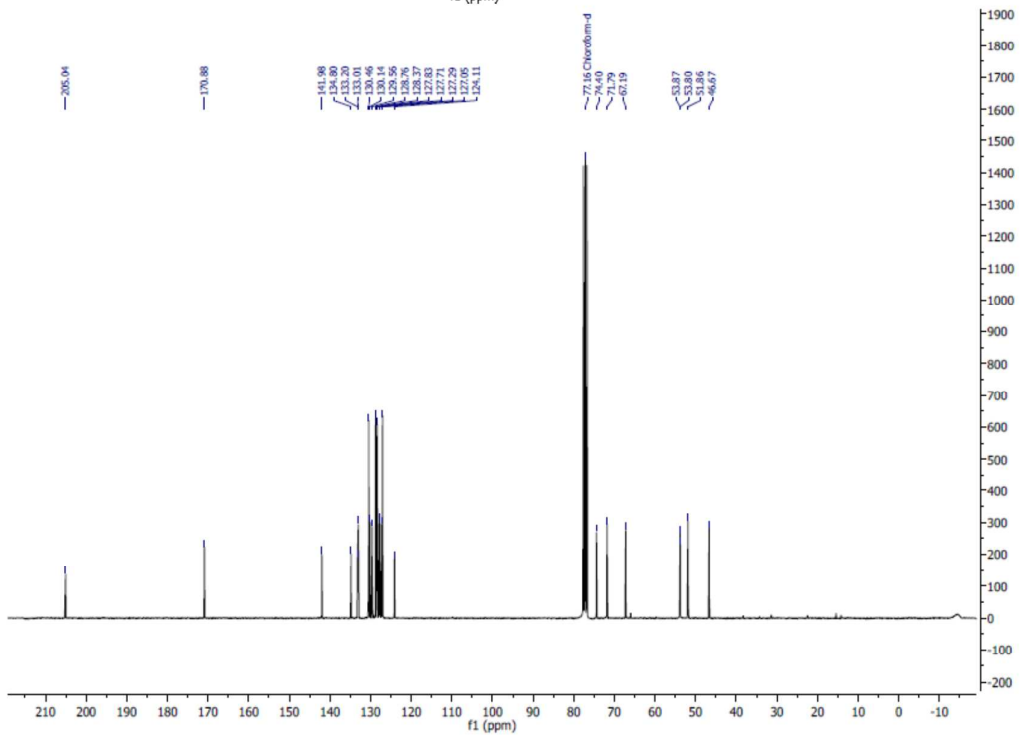
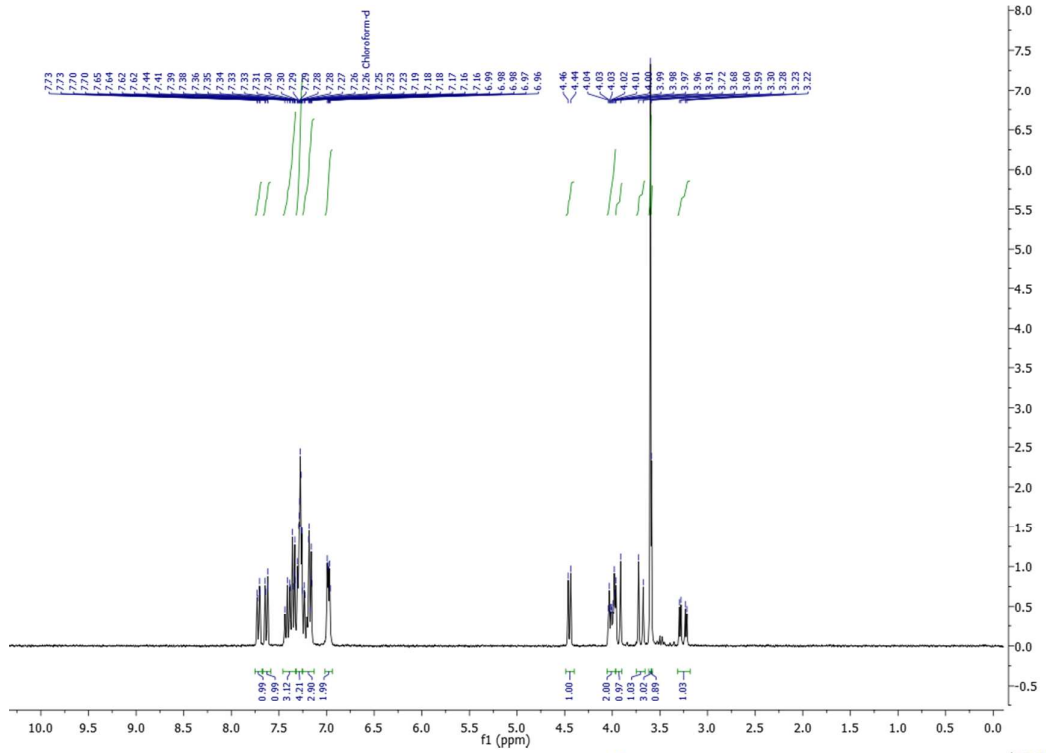


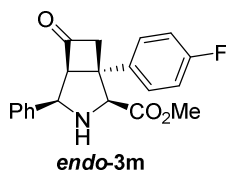
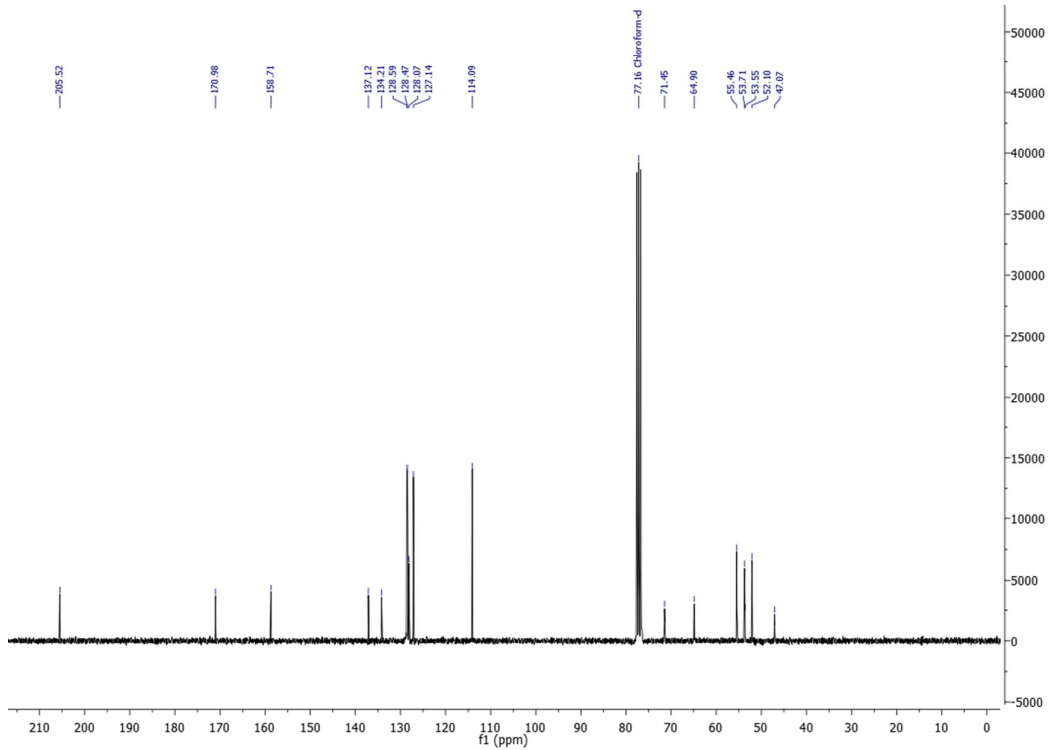
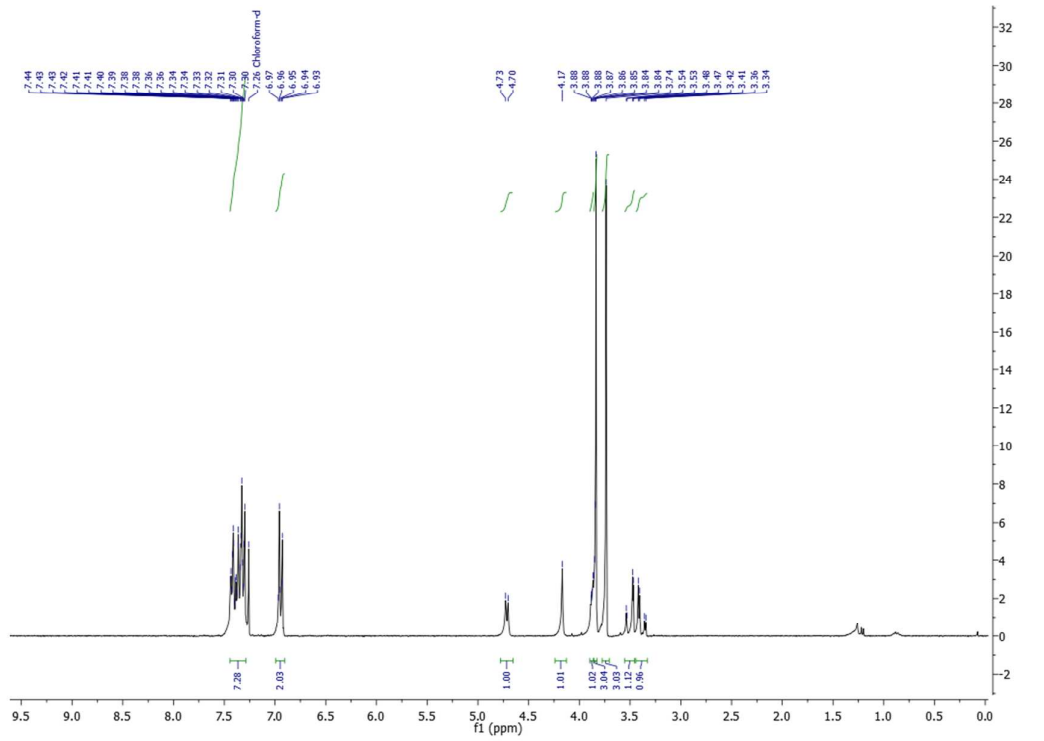


S46

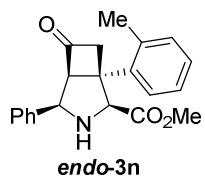
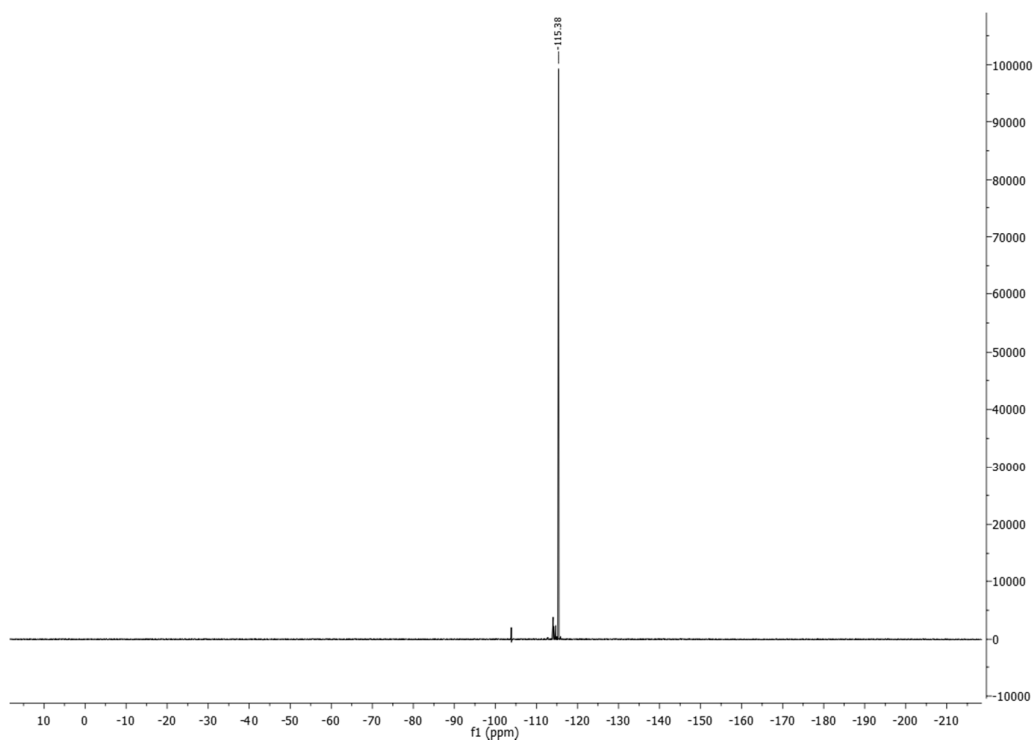


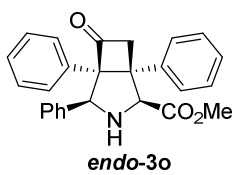
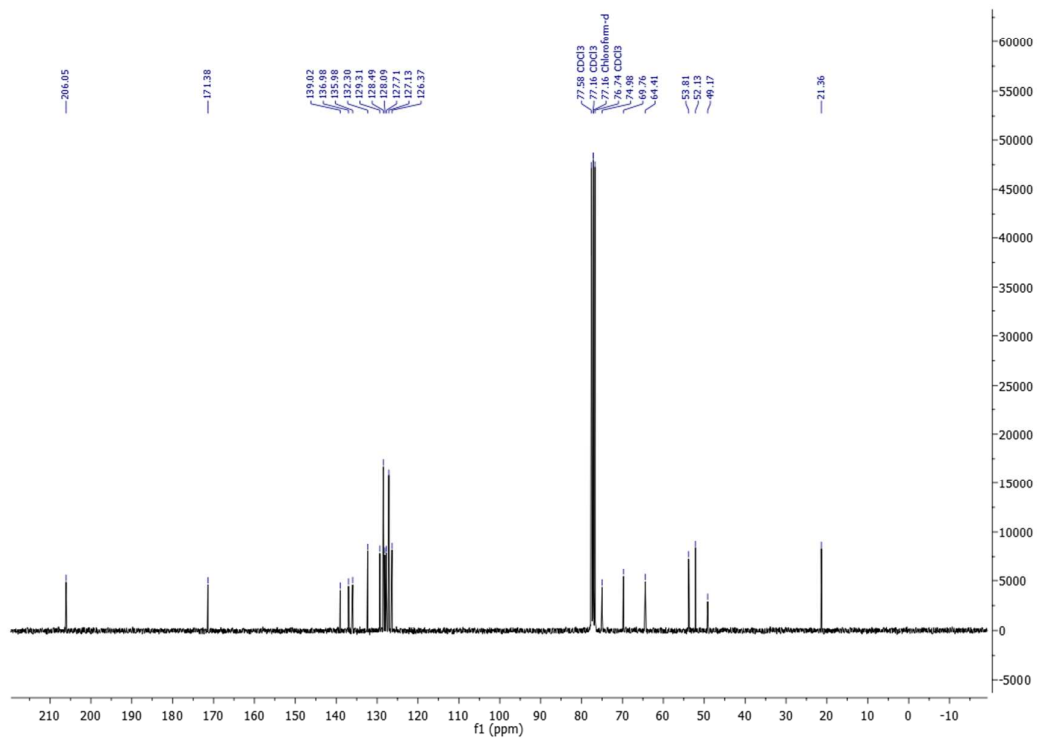
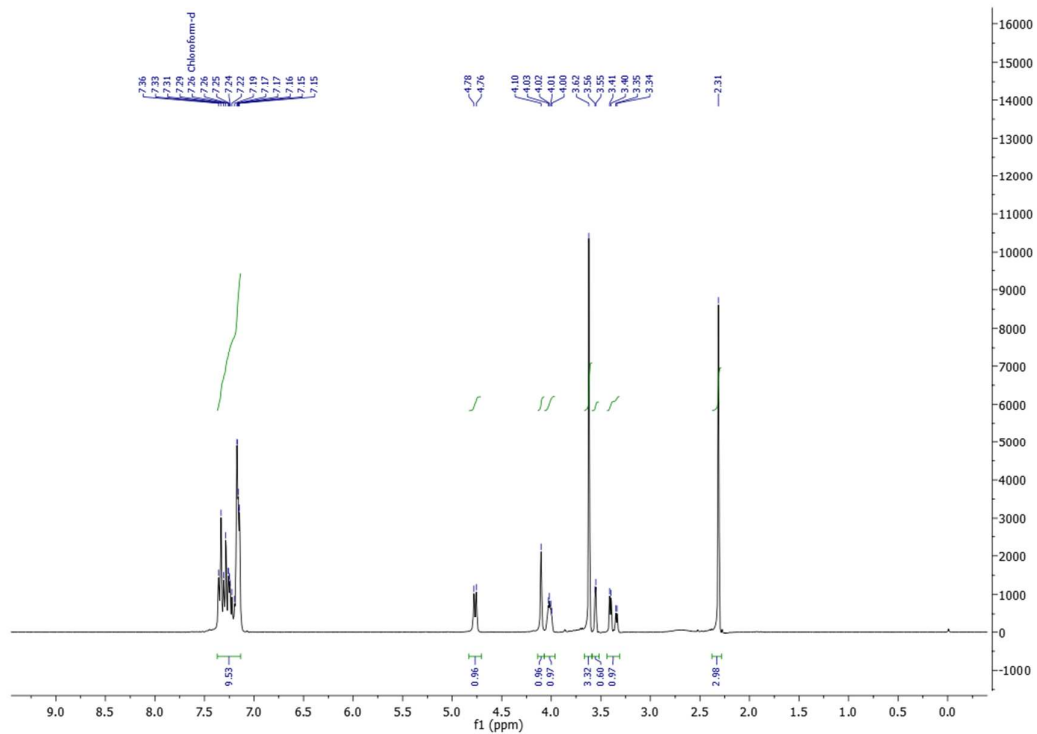


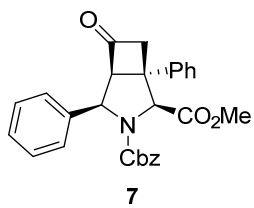
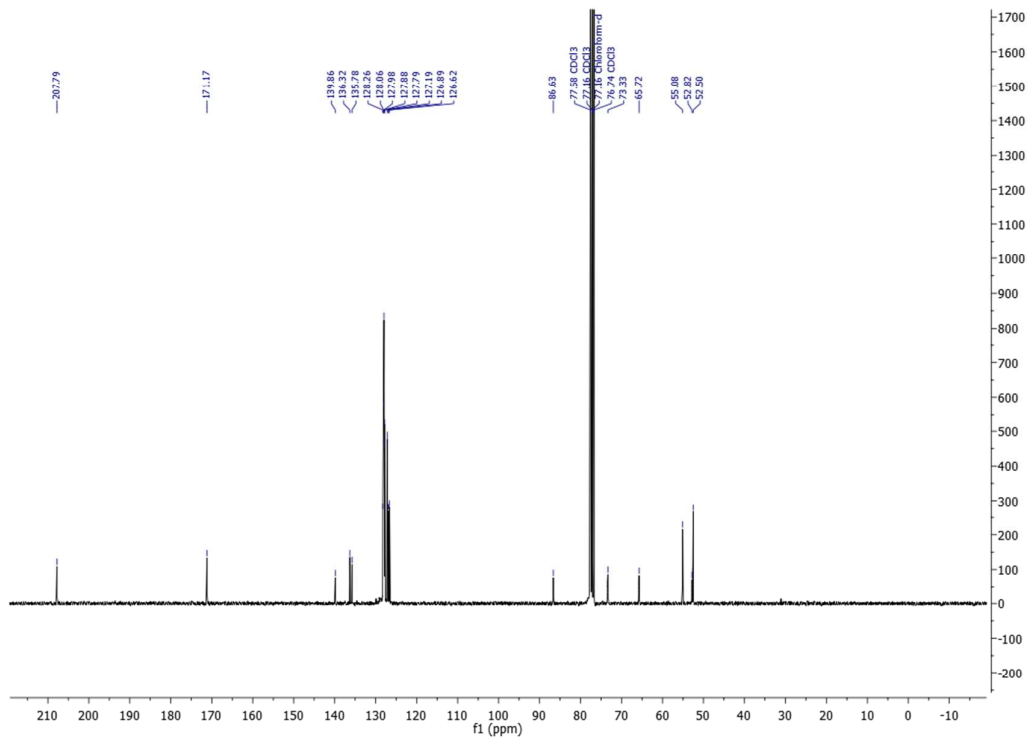
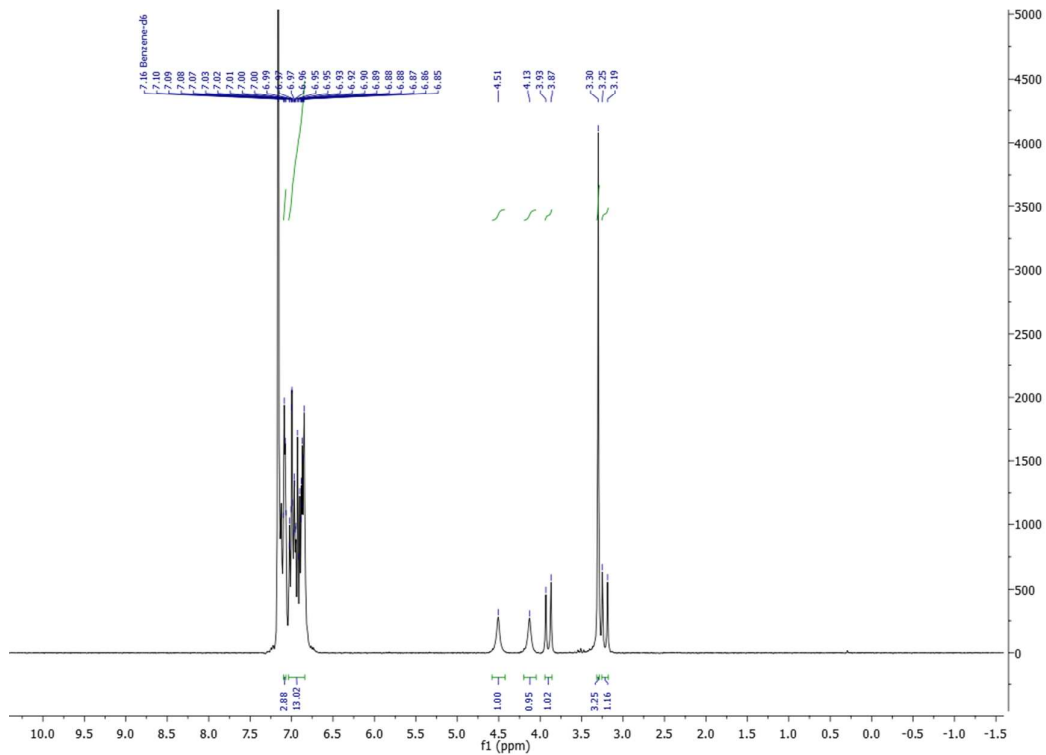


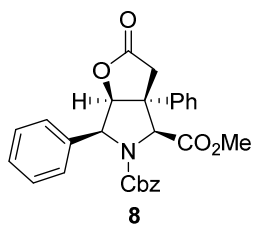
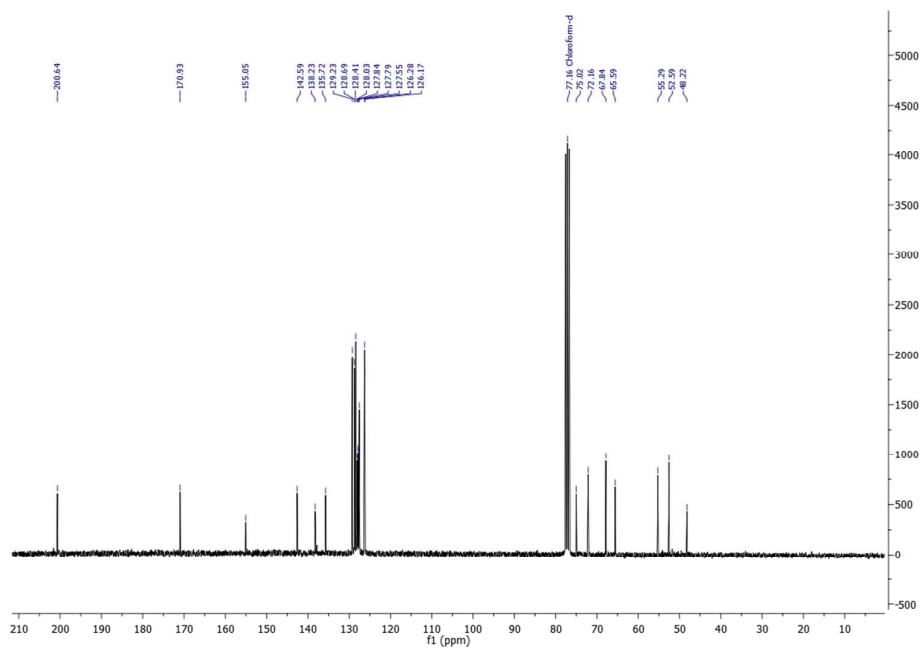
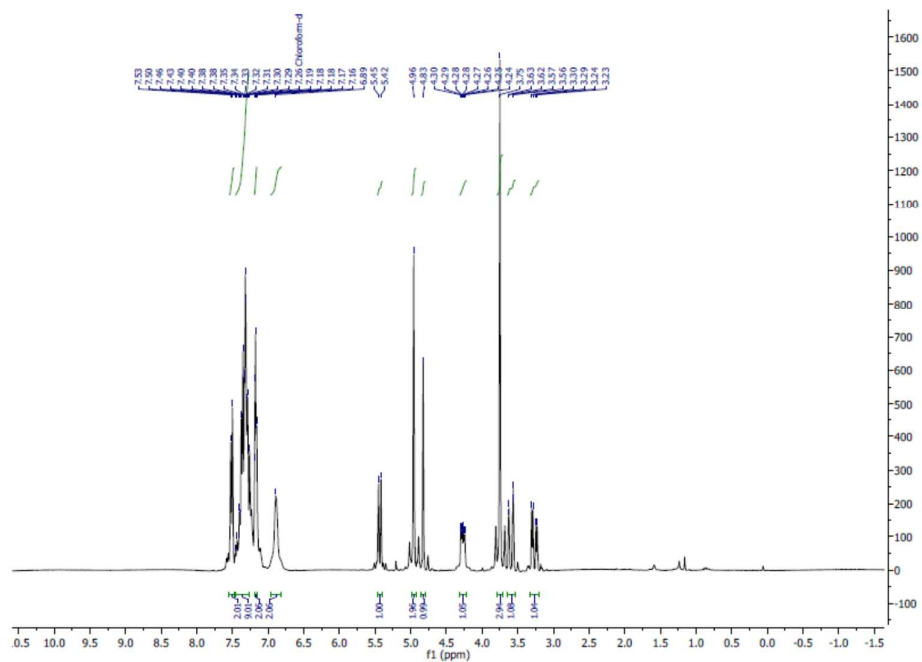


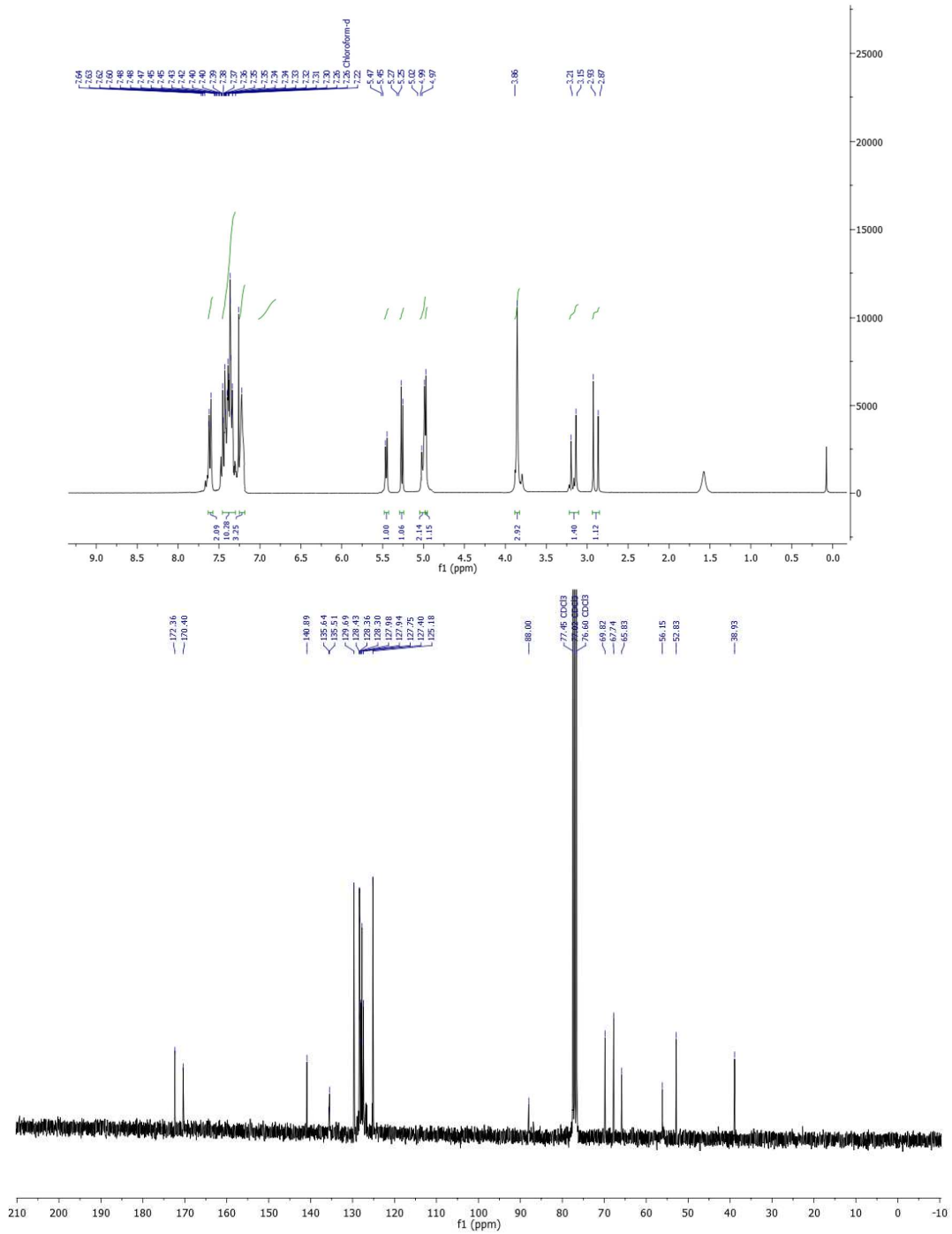
S51

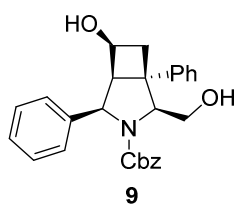
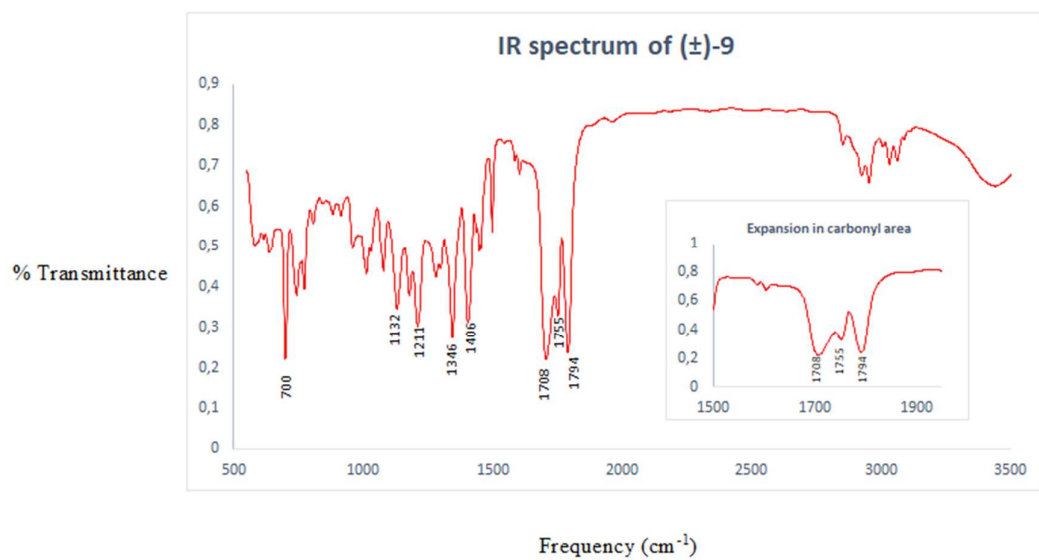


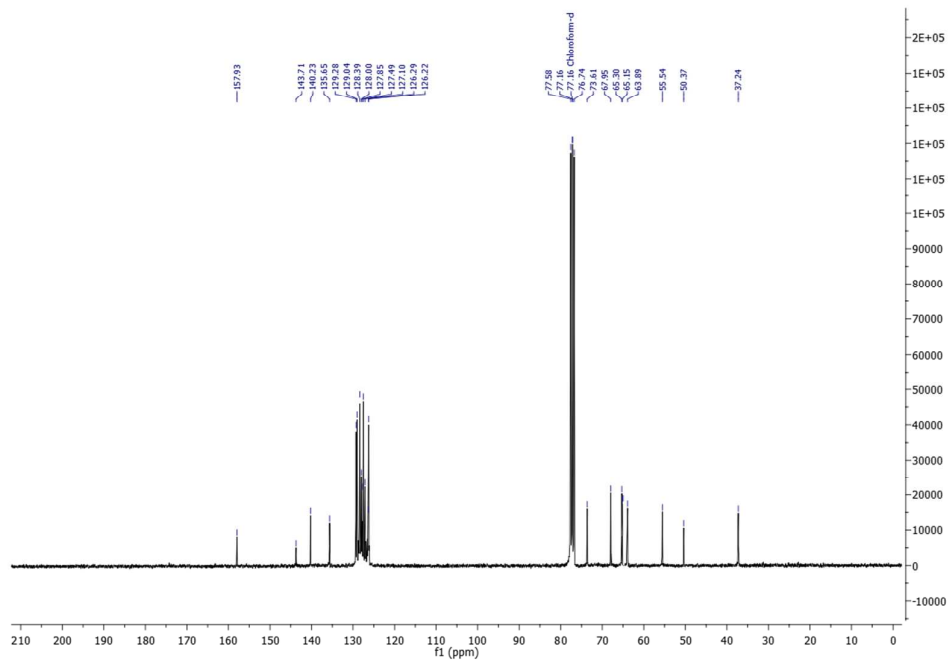
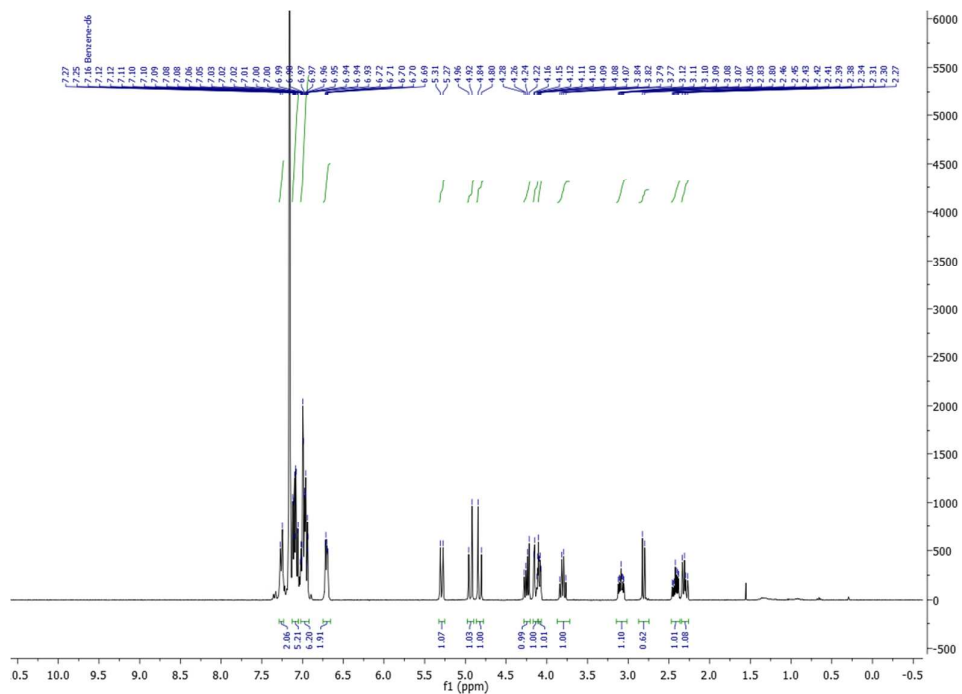




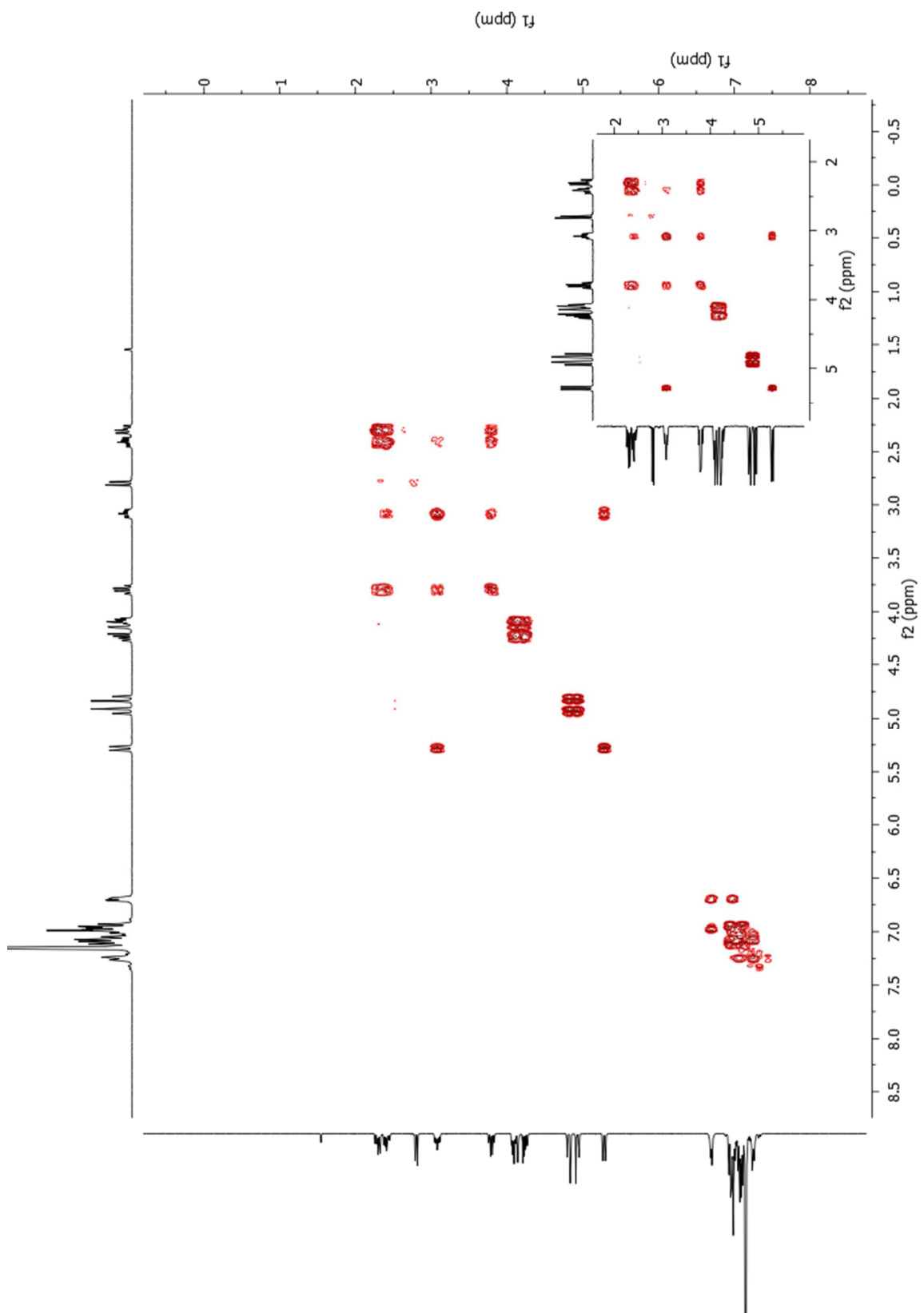




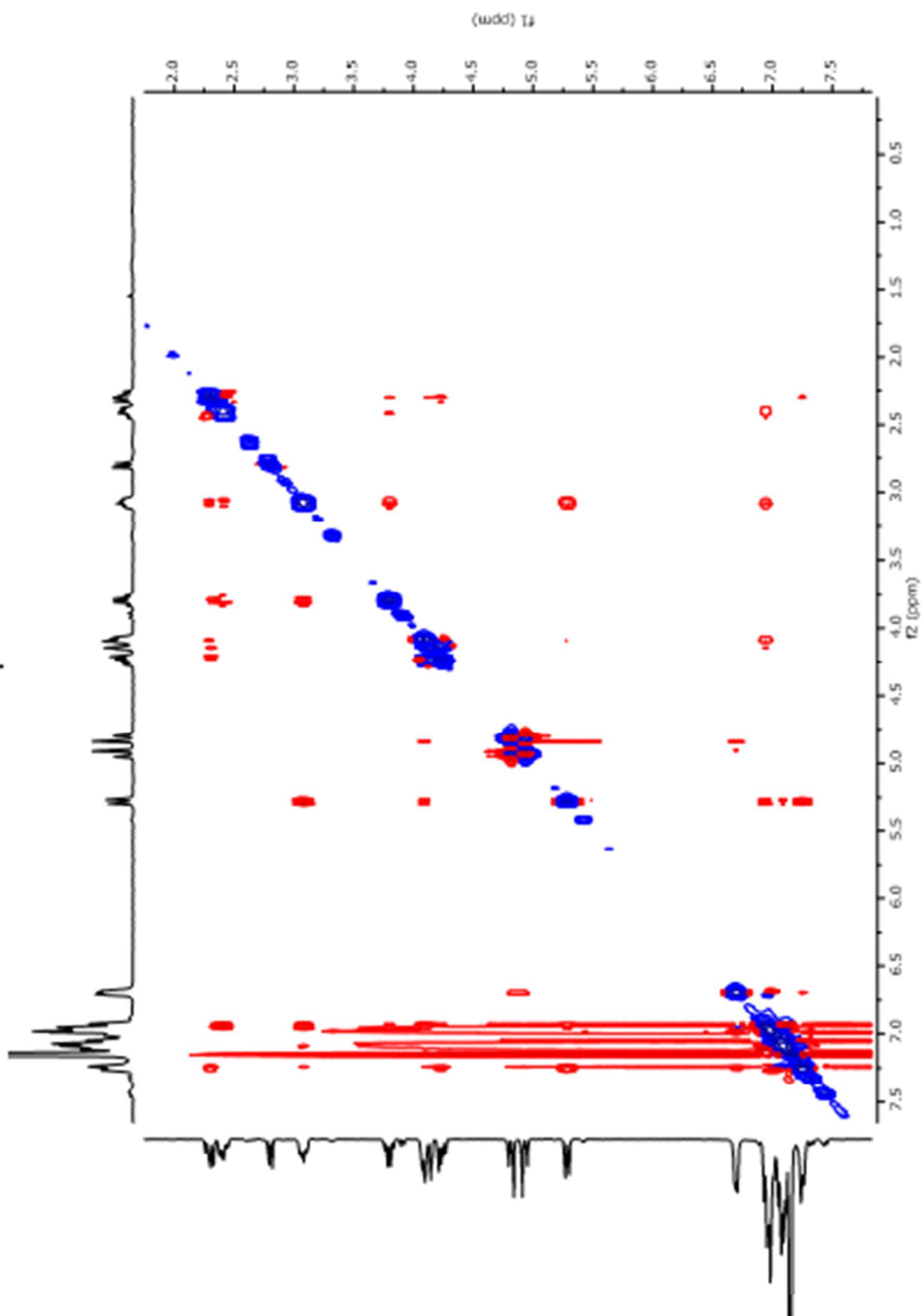


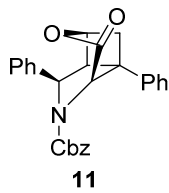
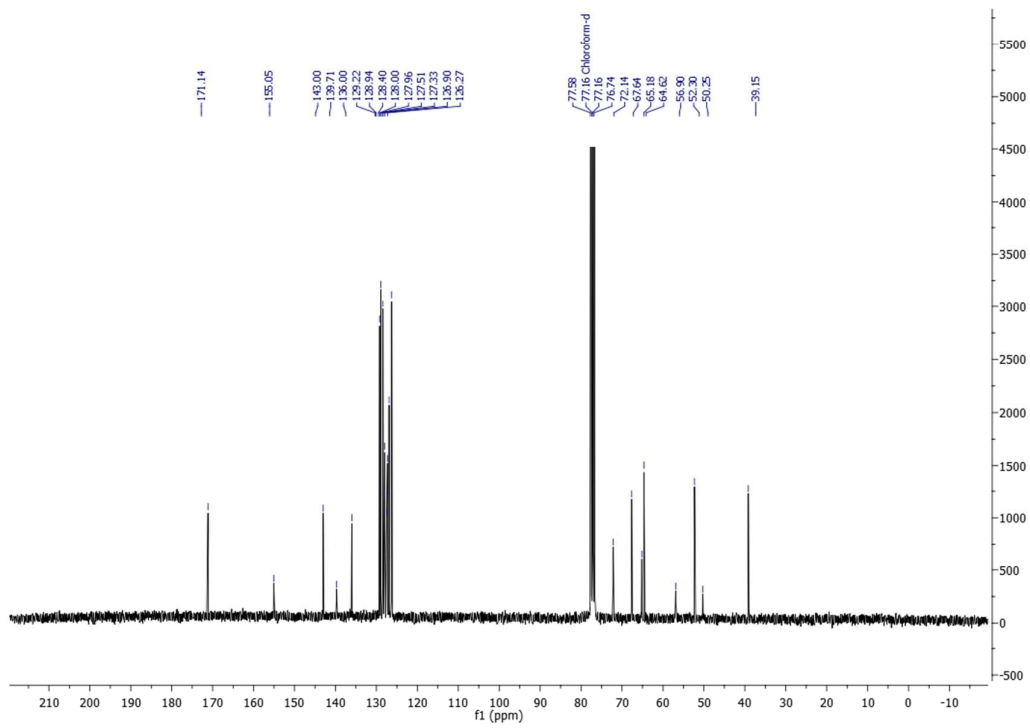
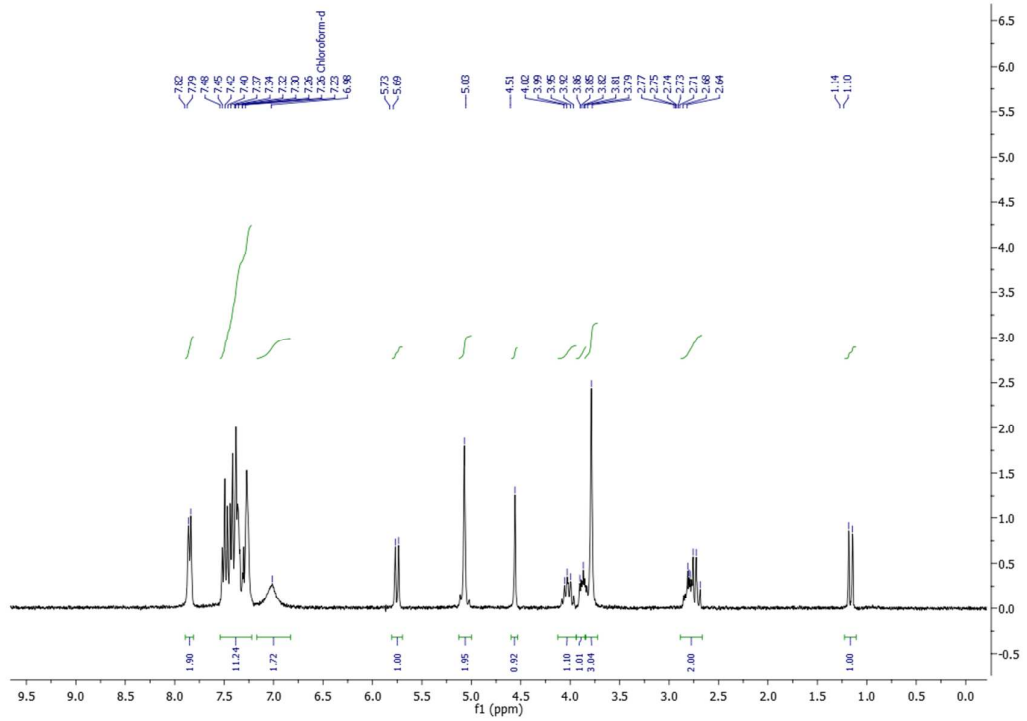


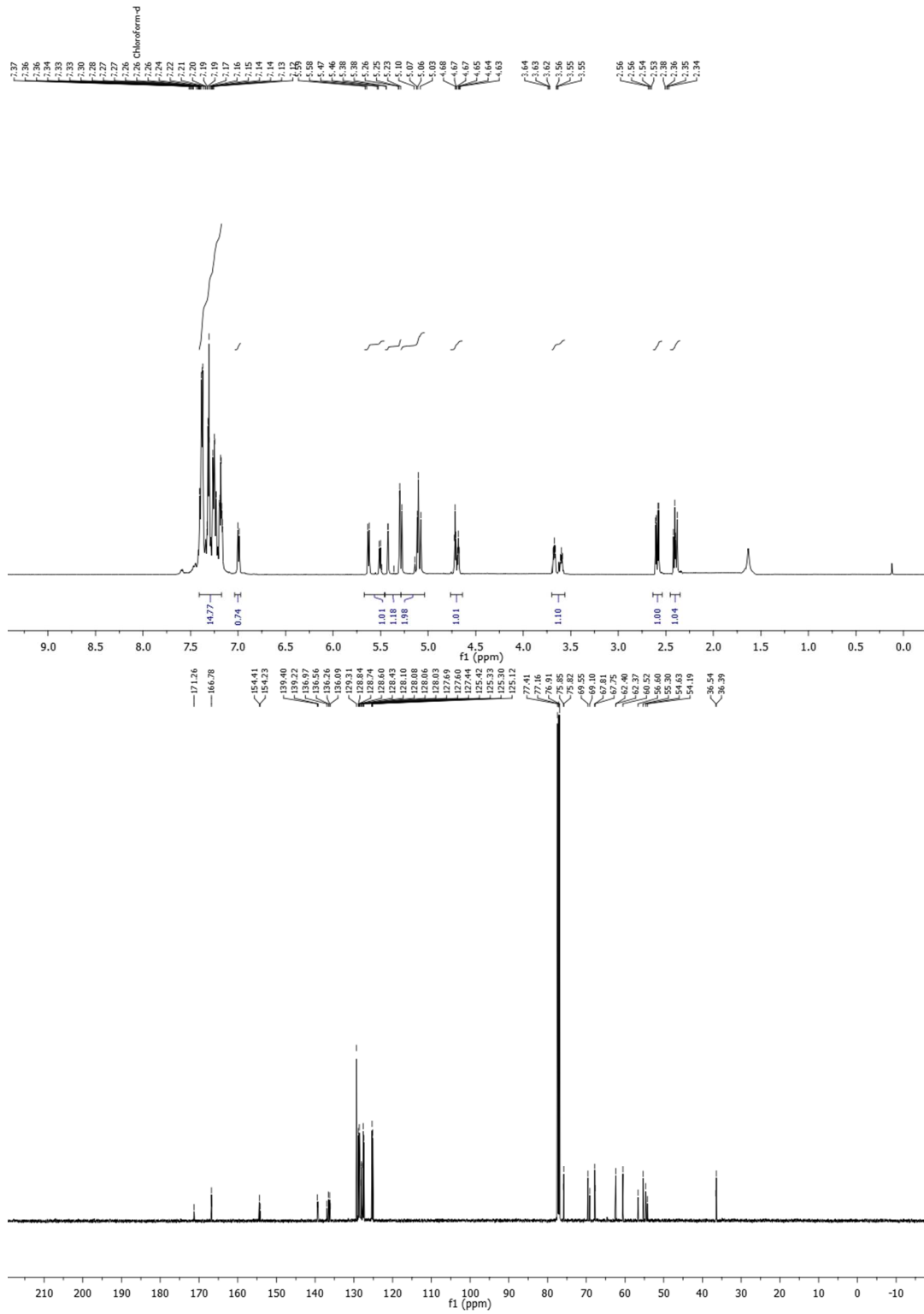
COSY spectrum:



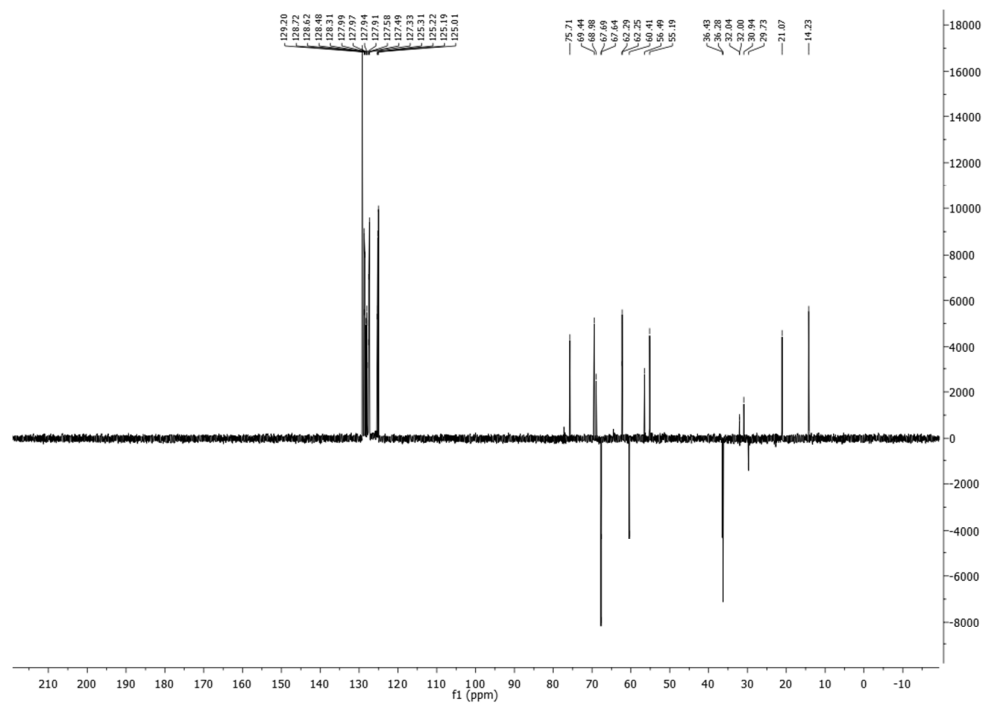
NOESY spectrum:



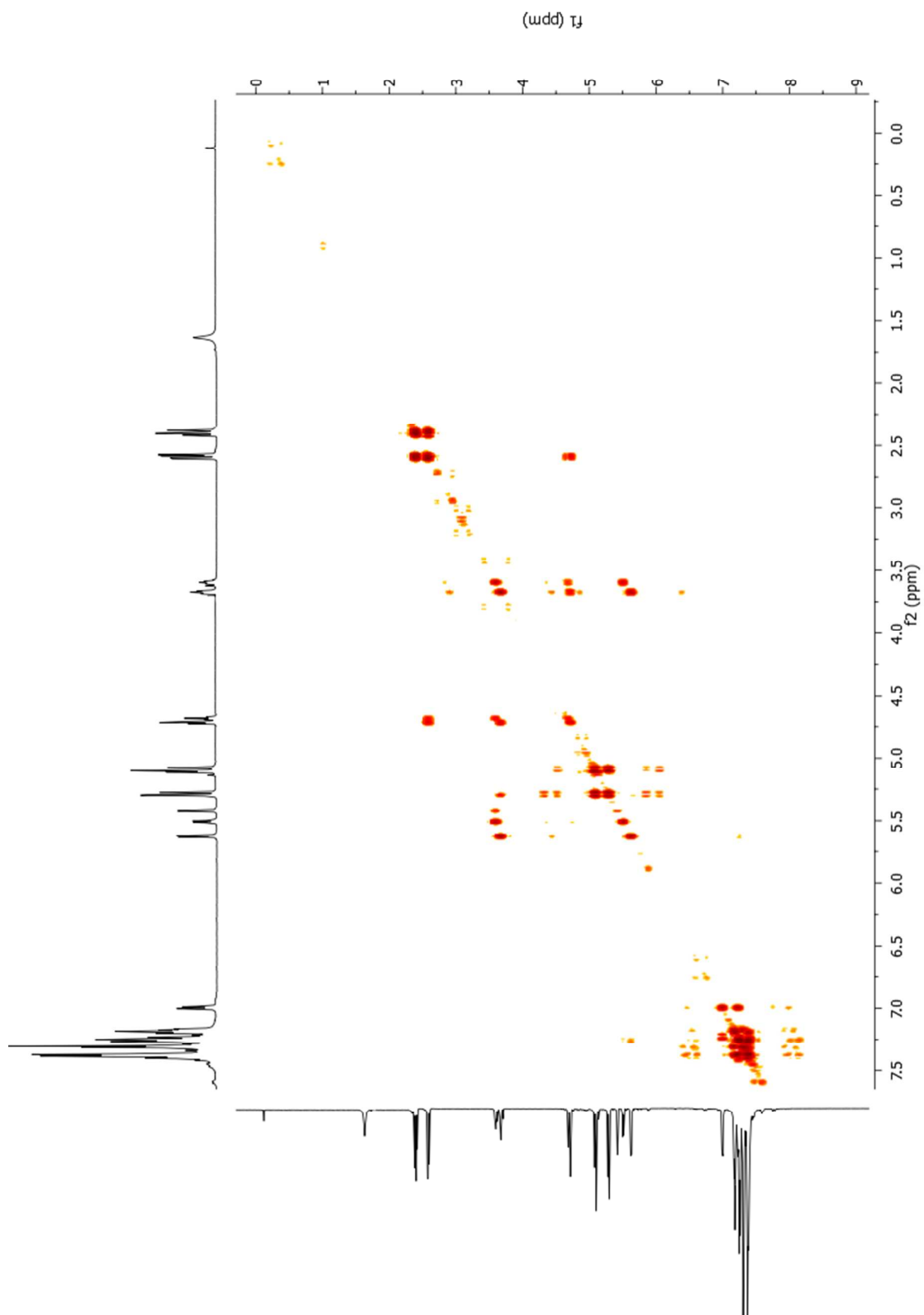




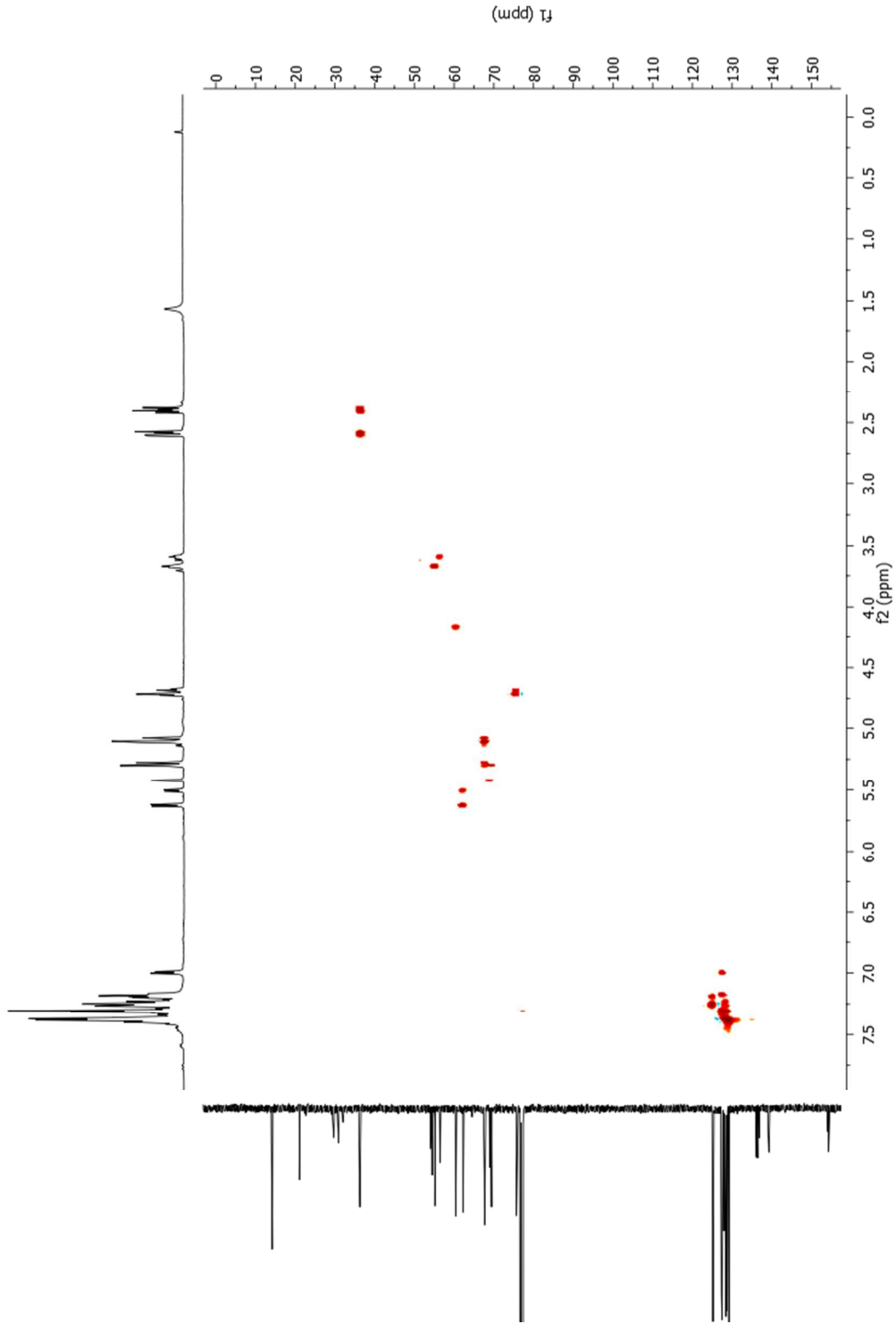
DEPT 135 spectrum:



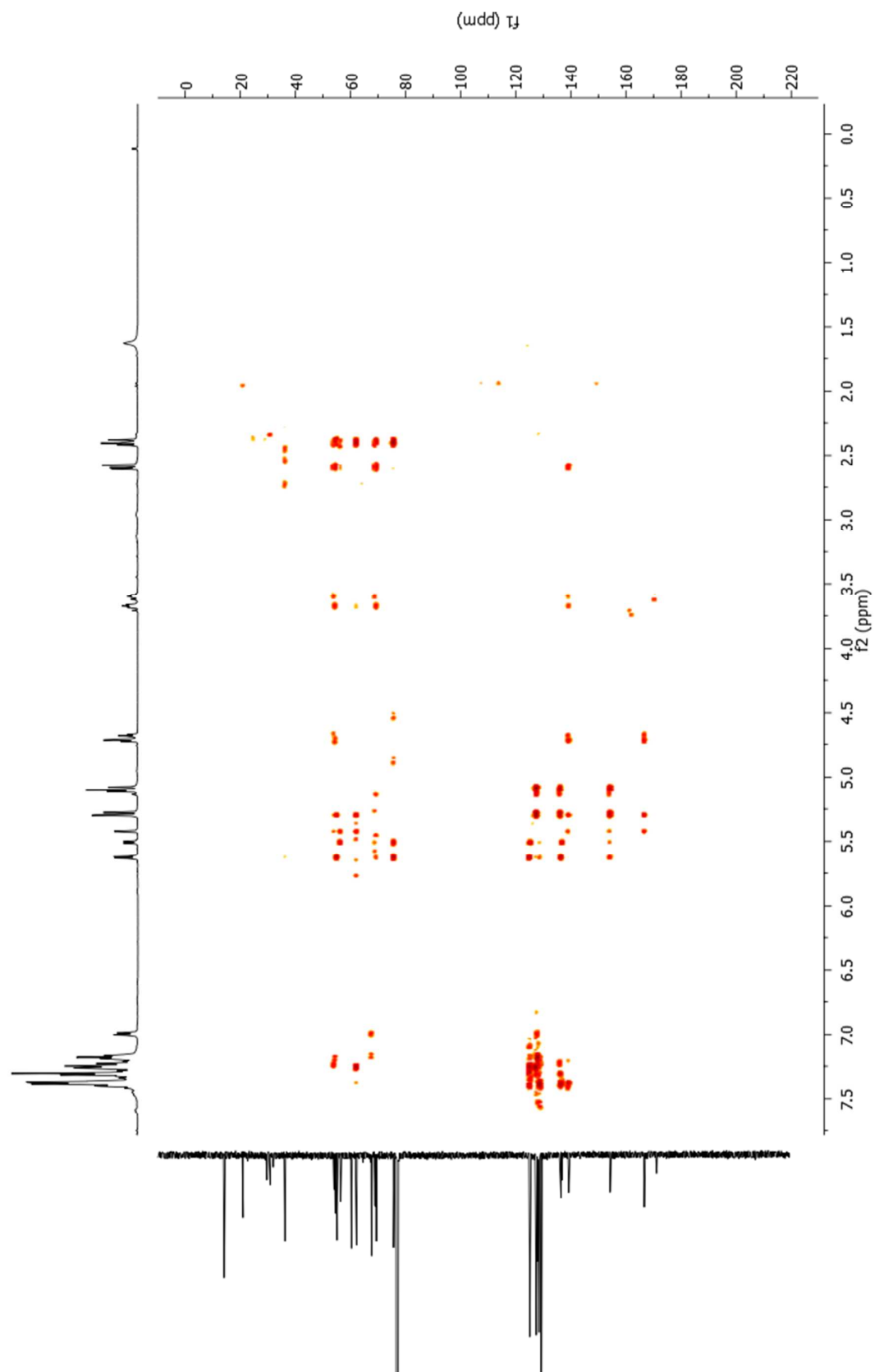
COSY spectrum:



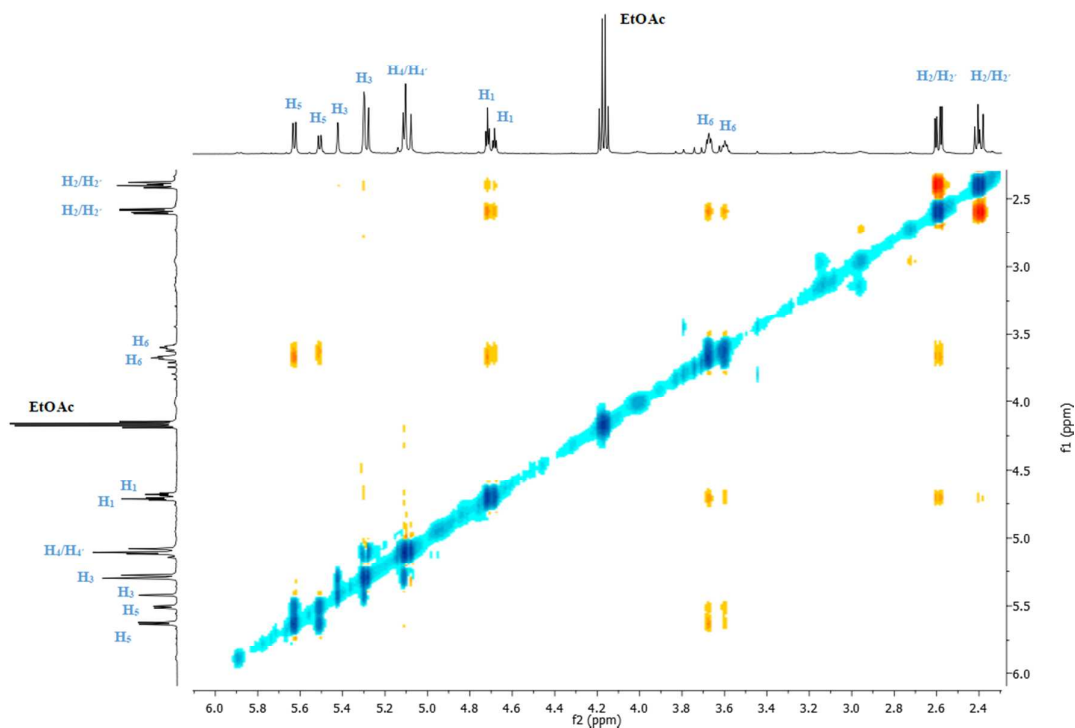
HMQC spectrum:



HMBC spectrum:



The existence of an equilibrium between rotamers was evidenced qualitatively from the performance of a 2D NOESY experiment of compound **12** in CDCl_3 (see below). In addition to the signals corresponding to the nuclear Overhauser effect (nOe, indicated in yellow) strong peaks of cross between protons in equivalent equilibrium of a pair of rotamers were detected (peaks EXSY, indicated in blue). These two types of signals easily differentiate between them in the spectrum since they appear in different phases (positive peaks NOE, in yellow, negative peaks EXSY, in blue).⁴



4. For other examples of the use of this technique for the discrimination between rotamers, see: Rayyan, S.; Fossen, T.; Solheim Nateland, H.; Andersen, M. *Phytochem. Anal.*, **2005**, *16*, 334 and references cited therein.