Supporting Information

for

En-route to 3-Spiroindolizines Containing Isoindole Ring Through Intramolecular Arylation of Spiro-*N*-Acyliminium Species: A new Family of Potent Farnesyltransferase Inhibitors

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I. General remarks

Solvents (CH_2Cl_2, CH_3CN) were distilled prior to use, taking precaution to exclude moisture by refluxing over CaH_2. All reactions were performed under argon inert atmosphere. All glass apparatus was oven dried and cooled under vacuum before use.

Thin layer chromatography (TLC) was performed on pre-coated sheets of silica gel 60 with fluorescent indicator UV_{254} (Merck). Detection was accomplished by irradiation with a UV lamp and by an ethanolic solution of *p*-anisaldehyde. Chromatographic separations were achieved on silica gel columns (Kieselgel 60, 40–63 μm, Merck) typically using a cyclohexane/ethyl acetate eluent system. In all cases, distilled solvents were used as eluents for column chromatography.

Melting points were determined on a Stuart Scientific SMP 10 analyzer and are uncorrected.

The infrared spectra (IR) were recorded on a Perkin-Elmer FT-IR Paragon 1000 spectrometer.

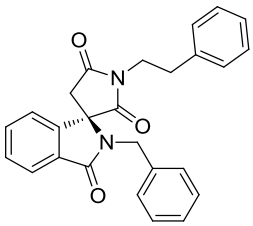
^1H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance™ 300 MHz spectrometer. Chemical shifts are reported in parts per million (δ).

Mass spectra (GC-MS) were obtained on a ThermoFinnigan Automass III spectrometer coupled with a gas chromatograph Trace GC 2000. High resolution mass spectra (HRMS) were measured on a Agilent 6530 Q-Tof MS system.

II. General procedure for the preparation of spirosuccinimides (±)-10a-c

To a solution of *N*-alkylated isoindolin-1-one **5** (0.01 mol) in 100 mL of CH_3CN anhydrous were added potassium carbonate (0.015 mol, 2.07 g) and bromoacetamide **9** (0.015 mol) under dry argon atmosphere. The mixture was then refluxed for 24 h. The solution was cooled at room temperature and filtered through a plug of celite. After removal of solvents under reduced pressure, the crude was analysed by ^1H NMR spectroscopy then purified by flash chromatography on silica gel column using a mixture of cyclohexane/AcOEt (4/1) as eluent.

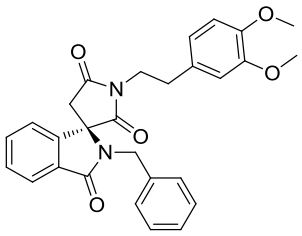
(±)-2-Benzyl-1'-phenethylspiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (10a)



Spirosuccinimide (±)-10a: This product was isolated as a white solid in 75% yield after crystallization from anhydrous ethanol; R_f (cyclohexane/AcOEt: 3/2) = 0.5; Mp = 150-152 °C; IR (ATR) 1694.83, 1670.92 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.78 (d, *J* = 18.0 Hz, 1H, CH_2), 2.88 (d, *J* = 18.0 Hz, 1H,CH_2), 2.94-3.05 (m, 2H, CH_2), 3.76-3.94 (m, 2H, CH_2), 4.20 (d, *J* = 16.0 Hz, 1H, CH_2), 5.05 (d, *J* = 16 Hz, 1H, CH_2), 6.78 (d, *J* = 7.0 Hz, 1H, H_{aro}), 7.21-7.36 (m, 10H, H_{aro}), 7.43-7.57 (m, 2H, H_{aro}), 7.92-7.95 (m, 1H, H_{aro}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.8 (CH_2), 37.3 (CH_2), 40.0 (CH_2), 44.2 (CH_2), 68.3 (C^q), 119.9 (CH_{aro}), 124.4 (CH_{aro}), 127.0 (CH_{aro}), 128.1 (3 x CH_{aro}), 128.7 (2 x CH_{aro}), 128.9 (4 x CH_{aro}), 129.8 (CH_{aro}), 130.8(C^q_{aro}), 132.8 (CH_{aro}), 135.8 (C^q_{aro}),

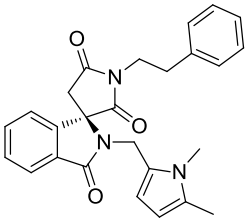
136.9 (C^q_{aro}), 144.0 (C^q_{aro}), 168.6 (C=O), 172.8 (C=O), 173.6 (C=O) ppm. HRMS (+ESI) calculated for $C_{26}H_{23}N_2O_3[M+H]^+$: 411.1664, found: 411.1722.

(±)-2-Benzyl-1'-(3,4-dimethoxyphenethyl)spiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (10b)



Spirosuccinimide (±)-10b: This product was isolated as a white solid in 66% yield after crystallization from anhydrous ethanol; R_f (cyclohexane/AcOEt: 2/3) = 0.42; Mp = 155-157 °C; IR (ATR) 1719.36, 1698.63 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.72 (d, *J* = 18 Hz, 1H, CH_2), 2.85 (d, *J* = 18 Hz, 1H, CH_2), 2.90-2.98 (m, 2H, CH_2), 3.77 (s, 3H, OCH_3), 3.75-3.81 (m, 2H, CH_2), 3.86 (s, 3H, OCH_3), 4.15 (d, *J* = 16 Hz, 1H, CH_2), 5.06 (d, *J* = 16 Hz, 1H, CH_2), 6.62-6.82 (m, 4H, H_{aro}), 7.16-7.40 (m, 5H, H_{aro}), 7.48-7.55 (m, 2H, H_{aro}), 7.89 (d, *J* = 6.8 Hz, 1H, H_{aro}) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 32.2 (CH_2), 37.3 (CH_2), 39.8 (CH_2), 44.3 (CH_2), 55.9 (OCH_3), 56.0 (OCH_3), 68.4 (C^q), 111.2 (CH_{aro}), 111.9 (CH_{aro}), 119.9 (CH_{aro}), 121.0 (CH_{aro}), 124.5 (CH_{aro}), 128.1 (2 x CH_{aro}), 128.2 (CH_{aro}), 129.0 (2 x CH_{aro}), 129.2 (C^q_{aro}), 129.9 (CH_{aro}), 130.7 (C^q_{aro}), 132.8 (CH_{aro}), 136.0 (C^q_{aro}), 144.0 (C^q_{aro}), 148.0 (C^q_{aro}), 149.1 (C^q_{aro}), 168.7 (C=O), 173.0 (C=O), 173.8 (C=O) ppm. HRMS (+ESI) calculated for $C_{28}H_{27}N_2O_5[M+H]^+$: 471.1875, found 471.1917.

(±)-2-((1,5-Dimethyl-1H-pyrrol-2-yl)methyl)-1'-phenethylspiro[isoindoline-1,3'-pyrrolidine]-2',3,5'-trione (10c)

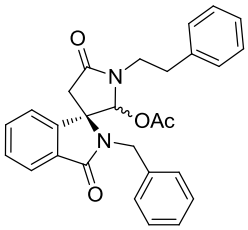


Spirosuccinimide (±)-10c: This compound was isolated as a white solid in 34% yield after crystallization from anhydrous ethanol; R_f (cyclohexane/AcOEt: 2/3) = 0.42; Mp = 146-148 °C ;IR (ATR) 1697.62 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.19 (s, 3H, CH_3), 2.83 (d, *J* = 18.0 Hz, 1H, CH_2), 2.88-2.98 (m, 2H, CH_2), 3.06 (d, *J* = 18.0 Hz, 1H, CH_2), 3.39 (s, 3H, CH_3), 3.50-3.60 (m, 1H, CH_2), 3.67-3.76 (m, 1H, CH_2), 4.41 (d, *J* = 18.0 Hz, 1H, CH_2), 5.18 (d, *J* = 18.0 Hz, 1H, CH_2), 5.72 (d, *J* = 3.0 Hz, 1H, H_{aro}), 5.84 (d, *J* = 3.0 Hz, 1H, H_{aro}), 6.54 (d, *J* = 6.0 Hz, 1H, H_{aro}), 7.18-7.21 (m, 2H, H_{aro}), 7.29-7.32 (m, 3H, H_{aro}), 7.40-7.45 (m, 1H, H_{aro}), 7.48-7.53 (m, 1H, H_{aro}), 7.87 (d, *J* = 9.0 Hz, 1H, H_{aro}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.4 (CH_3), 30.3 (CH_3), 32.8 (CH_2), 35.8 (CH_2), 36.1 (CH_2), 39.9 (CH_2), 66.8 (C^q), 105.3 (CH_{aro}), 109.2 (CH_{aro}), 119.7 (CH_{aro}), 123.6 (C^q_{aro}), 124.2 (CH_{aro}), 126.7 (CH_{aro}), 128.6 (2 x CH_{aro}), 128.8 (2 x CH_{aro}), 129.6 (CH_{aro}), 130.7 (C^q_{aro}), 131.5 (C^q_{aro}), 132.7 (CH_{aro}), 137.3 (C^q_{aro}), 144.7(C^q_{aro}), 167.8 (C=O), 172.9 (2 x C=O) ppm. HRMS (+ESI) calculated for $C_{28}H_{26}N_3NaO_3[M+Na]^+$: 450.1794, found 450.1791.

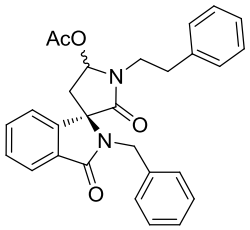
III. General procedure for the synthesis of α-acetoxy lactams (±)-6a-c (A,A') and (±)-6a-c (B,B')

To a solution of spirosuccinimide **(±)-10a-c** (2.5 mmol) in a mixture of THF/EtOH (1:1) was added sodium borohydride (10 mmol, 4 equiv.) at 0 °C then the mixture was left under stirring at room temperature for 4 h. The reaction mixture was then cooled to 0 °C and quenched by addition of 1 mL of water then acidified to pH 3 by 2M HCl solution. The mixture was extracted twice by 30 mL of dichloromethane and the organic layer was dried over $MgSO_4$ then evaporated to dryness. The oily residue was purified by flash chromatography on a silica gel column using a mixture of cyclohexane/AcOEt (4/1) as eluent. In a second step, acetic anhydride (2 equiv.) was added dropwise to a solution of the above hydroxy lactams **(±)-11a-c** (1 equiv.), NEt_3 (2 equiv.), and DMAP (0.1 equiv.) in CH_2Cl_2 (10 mL per 1 mmol of hydroxy lactam **11**). The mixture was stirred at room temperature overnight and quenched by addition of a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (20 mL), and organic layers were combined, dried over $MgSO_4$, and evaporated. The acetate derivatives **(±)-6** were then obtained after purification of the residue by flash chromatography on a silica gel column.

(±)-2-Benzyl-3,5'-dioxo-1'-phenethylspiro[isoindoline-1,3'-pyrrolidin]-2'-yl acetate (±)-6a(A,A')



6a(A) and **6a(A')**



6a(B) and **6a(B')**

Spirosuccinimide (±)-**10a** gave a mixture of two regioisomers (±)-**6a(A,A')** and (±)-**6a(B,B')** and each regioisomer was obtained as two diastereoisomers in an overall yield of 80%.

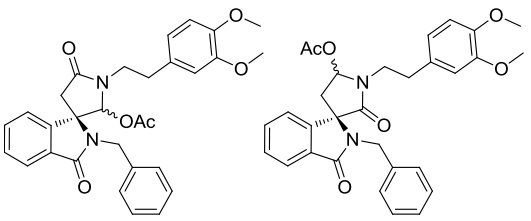
The product **(±)-6a(A)** was isolated as a white solid in 23% yield. R_f (cyclohexane/AcOEt: 2/3) = 0.56; Mp = 143-145 °C; IR (ATR) 1745.21, 1702.27 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.81 (s, 3H, CH_3), 2.38 (d, *J* = 18 Hz, 1H, CH_2), 2.83-3.01 (m, 2H, CH_2), 3.06 (d, *J* = 17 Hz, 1H, CH_2), 3.18-3.25 (m, 1H, CH_2), 4.01-4.11 (m, 1H, CH_2), 4.74 (d, *J* = 16 Hz, 1H, CH_2), 5.18 (d, *J* = 16 Hz, 1H, CH_2), 6.18 (s, 1H, CH), 6.92 (d, *J* = 8 Hz, 1H, H_{aro}), 7.14-7.28 (m, 10H, H_{aro}), 7.41-7.60 (m, 2H, H_{aro}), 7.85-7.94 (m, 1H, H_{aro}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.6 (CH_3), 33.4 (CH_2), 36.8 (CH_2), 41.8 (CH_2), 45.3 (CH_2), 65.7 (C^q), 86.5 (CH), 120.3 (CH_{aro}), 124.3 (CH_{aro}), 126.6 (2 x CH_{aro}), 126.9 (CH_{aro}), 127.4 (CH_{aro}), 128.7 (2 x CH_{aro}), 128.8 (2 x CH_{aro}), 128.9 (2 x CH_{aro}), 129.7 (CH_{aro}), 129.8 (C^q_{aro}), 133.2 (CH_{aro}), 137.6 (C^q_{aro}), 137.7 (C^q_{aro}), 147.1 (C^q_{aro}), 169.1 (C=O), 170.1 (C=O), 172.1 (C=O) ppm. HRMS (+ESI) calculated for $C_{28}H_{26}N_2NaO_4[M+Na]^+$: 477.1790, found 477.1799.

α-Acetoxylactam (±)-6a(A') was isolated as white solid in 7% yield. R_f (cyclohexane/AcOEt: 2/3) = 0.58; Mp = 151-152 °C; IR (ATR) 1754.03, 1697.69 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.89 (s, 3H, CH_3), 2.52 (d, *J* = 18.0 Hz, 1H, CH_2), 2.60-2.67 (m, 1H, CH_2), 2.72-2.82 (m, 1H, CH_2), 3.06 (d, *J* = 18.0 Hz, 1H, CH_2), 3.30-3.35 (m, 2H, CH_2), 4.52 (d, *J* = 15 Hz, 1H, CH_2), 4.60(d, *J* = 15 Hz, 1H, CH_2), 6.06 (s, 1H, CH), 7.17-7.35 (m, 9H, H_{aro}), 7.49-7.54 (m, 1H, H_{aro}), 7.56-7.64 (m, 2H, H_{aro}), 7.93-7.96 (m, 2H, H_{aro}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.8 (CH_3), 33.5 (CH_2), 39.4 (CH_2),

42.7 (CH_2), 43.3 (CH_2), 67.6 (C^q), 87.7 (CH), 123.5 (CH_{aro}), 124.3 (CH_{aro}), 126.9 (CH_{aro}), 127.4 (2 x CH_{aro}), 127.9 (CH_{aro}), 128.7 (2 x CH_{aro}), 128.8 (2 x CH_{aro}), 128.9 (2 x CH_{aro}), 129.7 (CH_{aro}), 131.7 (C^q_{aro}), 131.9 (CH_{aro}), 137.4 (C^q_{aro}), 137.9 (C^q_{aro}), 142.9 (C^q_{aro}), 168.0 (C=O), 169.0 (C=O), 172.8 (C=O) ppm. HRMS (+ESI) calculated for $C_{28}H_{26}N_2NaO_4$ $[M+Na]^+$: 477.1790, found 477.1810.

α-Acetoxylactams (±)-6a(B,B') were obtained as inseparable mixture together with products **(±)-6a(A,A')**, thus their NMR characteristics were not extracted from the spectrum because of its complexity.

(±)-2-Benzyl-1'-(3,4-dimethoxyphenethyl)-3,5'-dioxospiro[isoindoline-1,3'-pyrrolidin]-2'-yl acetate (±)-6b(A,A') and (±)-6b(B,B')



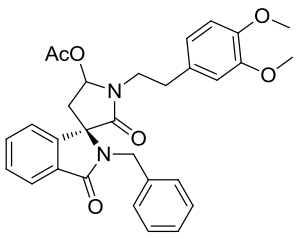
6b(A) and **6b(A')** **6b(B)** and **6b(B')**

Spirosuccinimide **(±)-10b** gave a mixture of two regioisomers (±)-**6b(A,A')** and (±)-**6b(B,B')** and each regioisomer was obtained as two diastereoisomers in an overall yield of 98%. The ^{1}H NMR characteristics of these products were extracted from the spectrum of the mixture.

Major diastereoisomer (±)-6b(A): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.75 (s, 3H, CH_3), 2.29 (d, *J* = 17.0 Hz, 1H, CH_2), 2.98 (d, *J* = 17.0 Hz, 1H, CH_2), 3.76 (s, 3H, OCH_3), 3.89-4.07 (m, 2H, CH_2), 3.81 (s, 3H, OCH_3), 4.67 (d, *J* = 16.0 Hz, 1H, CH_2), 5.14 (d, *J* = 16.0 Hz, 1H, CH_2), 6.21 (s, 1H, CH), 6.61-6.77 (m, 3H, H_{aro}), 7.03-7.55 (m, 8H, H_{aro}), 7.78-7.87 (m, 1H, H_{aro}) ppm.

Minor diastereoisomer (±)-6b(A'): ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.81 (s, 3H, CH_3), 2.44 (d, *J* = 18.0 Hz, 1H, CH_2), 2.58-2.63 (m, 1H, CH_2), 2.97 (d, *J* = 18.0 Hz, 1H, CH_2), 3.22 (t, *J* = 8.0 Hz, 2H, CH_2), 3.76 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.93-4.07 (m, 1H, CH_2), 4.49 (s, 2H, CH_2), 5.99 (s, 1H, CH), 6.61-6.77 (m, 3H, H_{aro}), 7.03-7.55 (m, 8H, H_{aro}), 7.78-7.87 (m, 1H, H_{aro}) ppm.

(±)-2-Benzyl-1'-(3,4-dimethoxyphenethyl)-2',3-dioxospiro[isoindoline-1,3'-pyrrolidin]-5'-yl acetate (±)-6b(B,B')



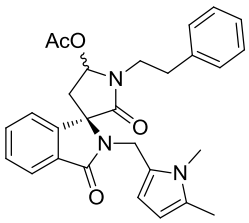
The ^{1}H NMR characteristics of these products were extracted from the spectrum of the mixture.

Major diastereoisomer (±)-6b(B): ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.04 (d, *J* = 15.0 Hz, 1H, CH_2), 2.12 (s, 3H, CH_3), 2.16 (dd, *J* = 3.0, 15.0 Hz, 1H, CH_2), 3.06-3.15 (m, 2H, CH_2), 3.50 (d, *J* = 16.2 Hz, 1H, CH_2), 3.77 (s, 3H, OCH_3), 3.89-4.07 (m, 2H, CH_2), 3.80 (s, 3H, OCH_3), 5.11 (d, *J* = 16.2 Hz,

1H, CH_2), 6.13 (s, 1H, CH), 6.61-6.77 (m, 3H, H_{aro}), 7.03-7.55 (m, 8H, H_{aro}), 7.78-7.87 (m, 1H, H_{aro}) ppm.

Minor diastereoisomer (±)-6b(B'): ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.02 (s, 3H, CH_3), 2.52-2.91 (m, 2H, CH_2), 3.26-3.37 (m, 2H, CH_2), 3.63 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 3.88-4.07 (m, 2H, CH_2), 4.22 (d, *J* = 16.1 Hz, 1H, CH_2), 5.09 (d, *J* = 16.6 Hz, 1H, CH_2), 6.22 (dd, *J* = 2.4, 7.0 Hz, 1H, CH), 6.29 (d, 1H, *J* = 7.43 Hz, 1H, H_{aro}), 6.61-6.77 (m, 2H, H_{aro}), 7.03-7.55 (m, 8H, H_{aro}), 7.78-7.87 (m, 1H, H_{aro}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) of **(±)-6b(A,A')** and **(±)-6b(B,B')**. The ^{13}C NMR characteristics of these products were given from the spectrum of the mixture: δ 20.5 (CH_3), 20.7 (CH_3), 21.0 (CH_3), 21.3 (CH_3), 32.2 (CH_2), 32.7 (2 x CH_2), 33.0 (CH_2), 34.7 (CH_2), 35.3 (CH_2), 36.7 (CH_2), 39.4 (CH_2), 41.1 (CH_2), 41.4 (CH_2), 42.3 (CH_2), 42.6 (CH_2), 43.2 (CH_2), 44.0 (CH_2), 44.1 (CH_2), 45.2 (CH_2), 55.8 (2 x OCH_3), 55.9 (2 x OCH_3), 56.0 (2 x OCH_3), 56.1 (2 x OCH_3), 65.5 (C^q), 67.5 (C^q), 69.5 (C^q), 70.0 (C^q), 79.9 (CH), 80.0 (CH), 86.3 (CH), 87.6 (CH), 111.2 (2 x CH_{aro}), 111.4 (3 x CH_{aro}), 111.5 (CH_{aro}), 111.6 (CH_{aro}), 111.7 (CH_{aro}), 111.9 (CH_{aro}), 120.1 (CH_{aro}), 120.3 (CH_{aro}), 120.5 (CH_{aro}), 120.7 (CH_{aro}), 121.5 (CH_{aro}), 123.5 (CH_{aro}), 123.9 (CH_{aro}), 124.0 (CH_{aro}), 124.1 (CH_{aro}), 124.2 (CH_{aro}), 126.4 (2 x CH_{aro}), 127.3 (3 x CH_{aro}), 127.4 (3 x CH_{aro}), 127.5 (CH_{aro}), 127.6 (CH_{aro}), 127.7 (CH_{aro}), 127.8 (CH_{aro}), 128.4 (2 x CH_{aro}), 128.7 (2 x CH_{aro}), 128.8 (3 x CH_{aro}), 129.1 (CH_{aro}), 129.2 (CH_{aro}), 129.5 (CH_{aro}), 129.6 (CH_{aro}), 129.7 (C^q_{aro}), 129.8 (C^q_{aro}), 130.0 (C^q_{aro}), 130.2 (C^q_{aro}), 131.0 (C^q_{aro}), 131.1 (C^q_{aro}), 131.6 (C^q_{aro}), 131.8 (CH_{aro}), 132.3 (CH_{aro}), 133.0 (CH_{aro}), 137.3 (2 x C^q_{aro}), 137.5 (C^q_{aro}), 142.8 (C^q_{aro}), 145.0 (C^q_{aro}), 145.9 (C^q_{aro}), 146.9 (C^q_{aro}), 147.0 (2 x C^q_{aro}), 147.8 (C^q_{aro}), 147.9 (C^q_{aro}), 148.0 (C^q_{aro}), 148.1 (C^q_{aro}), 149.0 (C^q_{aro}), 149.1 (C^q_{aro}), 149.2 (C^q_{aro}), 149.3 (C^q_{aro}), 169.0 (2 x C=O), 169.1 (C=O), 169.2 (C=O), 170.0 (C=O), 170.2 (C=O), 170.3 (2 x C=O), 171.1 (C=O), 172.1 (2 x C=O), 172.7 (C=O) ppm; HRMS (+ESI) calculated for $C_{30}H_{30}N_2NaO_6$ $[M+Na]^+$: 537.2002, found 537.2011.

(±)-2-((1,5-Dimethyl-1H-pyrrol-2-yl)methyl)-2',3-dioxo-1'-phenethylspiro[isoindoline-1,3'-pyrrolidin]-5'-yl acetate (±)-6c(B,B')



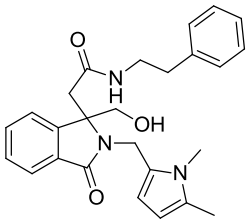
This product was obtained as a mixture of inseparable two diastereoisomers, R_f (cyclohexane/AcOEt: 2/3) = 0.48, IR (ATR): 1660.60 cm^{-1}. The NMR characteristics of these products were extracted from the spectrum of the mixture.

Major diastereoisomer (±)-6c(B): ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.12-2.24 (m, 1H, CH_2), 2.15 (s, 3H, CH_3), 2.20 (s, 3H, CH_3), 2.76 (dd, *J* = 7.0, 15.0 Hz, 1H, CH_2), 2.82-2.91 (m, 2H, CH_2), 3.31-3.41 (m, 1H, CH_2), 3.45 (s, 3H, CH_3), 3.35-3.65 (m, 1H, CH_2), 4.75 (d, *J* = 16.0 Hz, 1H, CH_2), 4.83 (d, *J* = 16.0 Hz, 1H, CH_2), 5.75-5.77 (m, 1H, H_{aro}), 5.81-5.83 (m, 1H, H_{aro}), 6.25 (d, *J* = 6.6 Hz, 1H, CH), 7.23-7.37 (m, 5H, H_{aro}), 7.48-7.61 (m, 3H, H_{aro}), 7.87-7.91 (m, 1H, H_{aro}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.4 (CH_3), 21.3 (CH_3), 30.4 (CH_3), 33.7 (CH_2), 33.8 (CH_2), 36.1 (CH_2), 43.9 (CH_2), 68.5 (C^q), 81.2 (CH), 105.2 (CH_{aro}), 108.7 (CH_{aro}), 121.2 (CH_{aro}), 123.9 (CH_{aro}), 124.6 (C^q_{aro}), 126.7

(CH_{aro}), 128.6 (2 x CH_{aro}), 128.8 (2 x CH_{aro}), 129.1 (CH_{aro}), 130.8 (C^q_{aro}), 131.0 (C^q_{aro}), 132.4 (CH_{aro}), 136.1 (C^q_{aro}), 146.1 (C^q_{aro}), 168.6 (C=O), 170.3 (2 x C=O) ppm.

Minor diastereoisomer (±)-6c(B'): ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.19 (s, 3H, CH_3), 2.24 (s, 3H, CH_3), 2.35 (dd, *J* = 3.6, 15.0 Hz, 1H, CH_2), 2.65 (dd, *J* = 7.1, 15.0 Hz, 1H, CH_2), 2.92-3.02 (m, 2H, CH_2), 3.22-3.28 (m, 1H, CH_2), 3.46 (s, 3H, CH_3), 3.85-3.95 (m, 1H, CH_2), 4.71 (d, *J* = 16.0 Hz, 1H, CH_2), 4.91 (d, *J* = 16.0 Hz, 1H, CH_2), 5.74-5.77 (m, 1H, H_{aro}), 6.00-6.02 (m, 1H, H_{aro}), 6.32 (dd, *J* = 3.6, 7.1 Hz, 1H, CH), 6.39-6.41 (m, 1H, H_{aro}), 7.23-7.37 (m, 5H, H_{aro}), 7.39-7.48 (m, 2H, H_{aro}), 7.80-7.83 (m, 1H, H_{aro}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.5 (CH_3), 21.1 (CH_3), 30.5 (CH_3), 32.9 (CH_2), 34.6 (CH_2), 36.0 (CH_2), 41.2 (CH_2), 68.8 (C^q), 80.0 (CH), 104.5 (CH_{aro}), 109.7 (CH_{aro}), 119.8 (CH_{aro}), 123.9 (CH_{aro}), 124.7 (C^q_{aro}), 126.8 (CH_{aro}), 128.7 (2 x CH_{aro}), 128.8 (2 x CH_{aro}), 129.0 (CH_{aro}), 130.5 (C^q_{aro}), 131.0 (C^q_{aro}), 132.5 (CH_{aro}), 137.7 (C^q_{aro}), 146.6 (C^q_{aro}), 168.3 (C=O), 169.0 (C=O), 170.3 (C=O) ppm. HRMS (+ESI) calculated for $C_{28}H_{30}N_3O_4[M+H]^+$: 472.2236, found 472.2237.

(±)-2-(2-((1,5-Dimethyl-1H-pyrrol-2-yl)methyl)-1-(hydroxymethyl)-3-oxoisoindolin-1-yl)-*N*-phenethylacetamide (±)-12c

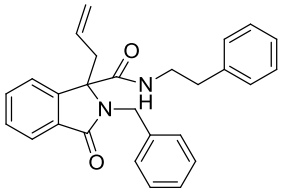


Compound (±)-12c: This product was isolated as a white solid in 34% yield after crystallization from anhydrous ethanol; R_f (cyclohexane/AcOEt: 2/3) = 0.22; Mp = 155-157 °C ; IR (ATR): 1670.98, 1649.51 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.18 (s, 3H, CH_3), 2.48 (d, *J* = 14.0 Hz, 1H, CH_2), 2.56-2.62 (m, 2H, CH_2), 2.88 (d, *J* = 14.0 Hz, 1H, CH_2), 3.13-3.23 (m, 1H, CH_2), 3.31-3.41 (m, 1H, CH_2), 3.49 (s, 3H, CH_3), 3.80 (d, *J* = 12.0 Hz, 1H, CH_2), 3.85 (d, *J* = 12.0 Hz, 1H, CH_2), 4.80 (d, *J* = 16.0 Hz, 1H, CH_2), 4.91 (d, *J* = 16.0 Hz, 1H, CH_2), 5.16-5.21 (m, 1H, OH), 5.80 (d, *J* = 3.0 Hz, 1H, H_{aro}), 6.08 (d, *J* = 3.0 Hz, 1H, H_{aro}), 7.06-7.08 (m, 2H, H_{aro}), 7.22-7.56 (m, 6H, H_{aro}), 7.82 (d, *J* = 7.0 Hz, 1H, H_{aro}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 12.6 (CH_3), 30.7 (CH_3), 35.7 (CH_2), 35.9 (CH_2), 40.62 (2 x CH_2), 66.7 (CH_2), 66.5 (C^q), 105.6 (CH_{aro}), 108.5 (CH_{aro}), 122.1 (CH_{aro}), 123.1 (CH_{aro}), 126.5 (CH_{aro}), 127.3 (C^q_{aro}), 128.5 (2 x CH_{aro}), 128.6 (2 x CH_{aro}), 128.8 (CH_{aro}), 130.4 (C^q_{aro}), 131.4 (C^q_{aro}), 131.9 (CH_{aro}), 138.4 (C^q_{aro}), 146.1 (C^q_{aro}), 168.3 (C=O), 168.4 (C=O) ppm**.** HRMS (+ESI) calculated for $C_{26}H_{29}N_3NaO_3[M+Na]^+$: 454.2107, found 454.2104.

IV. General Procedure for the Peptide Coupling

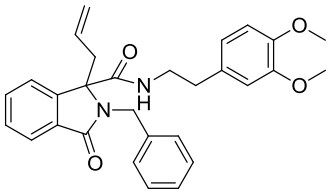
To a solution of carboxylic acid (**±)-17** (5 mmol, 1.53 g) along with the appropriate amine (5 mmol), HOBt (5 mmol, 0.67 g), and NEt_3 (5 mmol, 0.70 mL) in dry $CHCl_3$ (50 mL) was added a solution of EDCI.HCl (5 mmol, 0.96 g) in $CHCl_3$ (50 mL). The reaction mixture was stirred at room temperature under argon atmosphere overnight. After the reaction was completed (TLC), the solution was washed with 1N $NaHCO_3$ solution, 10% citric acid solution then saturated NaCl solution. The organic layer was dried and concentrated under reduced pressure. The obtained solid crude was recrystallized in anhydrous EtOH to afford the product as a white solid in 87 to 99 % yield.

(±)-1-Allyl-*N*-benzyl-3-oxo-*N*-phenethylisoindoline-1-carboxamide (±)-19a



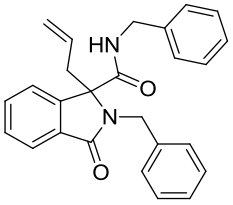
Starting from the phenyl ethylamine, this product was isolated as white solid in 87% yield; R_f (cyclohexane/AcOEt: 2/3) = 0.77; Mp = 158-160 °C; IR (ATR): 1679.18, 1665.12 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.36 (t, *J* = 7.0 Hz, 2H, CH_2), 2.70-2.86 (m, 1H, CH_2), 2.96-3.07 (m, 1H, CH_2), 3.18-3.37 (m, 2H, CH_2), 4.41 (d, *J* = 15 Hz, 1H, CH_2), 4.79-4.86 (m, 4H, CH_2), 5.58 (s broad, 1H, NH),6.79-6.81 (m, 2H, H_{aro}), 7.15-7.61 (m, 11H, H_{aro}), 7.74 (d, *J* = 7.0 Hz, 1H, H_{aro}) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 34.8 (CH_2), 36.7 (CH_2), 40.7 (CH_2), 44.6 (CH_2), 72.5 (C^q), 120.0 (CH_2=), 122.1 ($CH_=$), 123.9 (CH_{aro}), 126.5 (CH_{aro}), 127.8 (CH_{aro}), 128.5 (2 x CH_{aro}), 128.6 (2 x CH_{aro}), 128.8 (2 x CH_{aro}), 129.0 (3 x CH_{aro}), 130.3 (CH_{aro}), 130.6 (C^q_{aro}), 132.6 (CH_{aro}), 137.6 (C^q_{aro}), 138.3 (C^q_{aro}), 145.2 (C^q_{aro}), 168.9 (C=O), 169.9 (C=O) ppm**.** HRMS (+ESI) calculated for $C_{27}H_{27}N_2O_2$ $[M+H]^+$:411.2073, found 411.2068.

(±)-1-Allyl-*N*-benzyl-*N*-(3,4-dimethoxyphenethyl)-3-oxoisoindoline-1-carboxamide (±)-19b



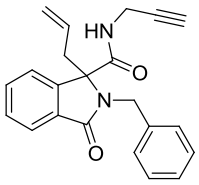
This product was isolated as white solid in 99% yield; R_f (cyclohexane/AcOEt: 3/2) = 0.37; Mp = 143-144 °C; IR (ATR): 1677.33, 1663.69 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.19 (t, *J* = 7.0 Hz, 2H, CH_2), 2.66-2.77 (m, 1H, CH_2), 3.02-3.09 (m, 1H, CH_2), 3.13-3.24 (m, 1H, CH_2), 3.28-3.35 (m, 1H, CH_2), 3.80 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.33 (d, *J* = 15 Hz, 1H, CH_2), 4.80-4.91 (m, 3H, CH_2), 4.94 (d, *J* = 15.0 Hz, 1H, CH_2), 5.20 (s broad, 1H, NH), 6.27 (dd, *J* = 2.0, 7.0 Hz, 1H, H_{aro}), 6.40 (d, *J* = 2.0 Hz, 1H, H_{aro}), 6.63 (d, *J* = 7.0 Hz, 1H, H_{aro}), 7.30-7.35 (m, 3H, H_{aro}), 7.44-7.60 (m, 5H, H_{aro}), 7.87 (dd, *J* = 2.0, 7.0 Hz, 1H, H_{aro}) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 34.3 (CH_2), 36.7 (CH_2), 40.6 (CH_2), 44.5 (CH_2), 55.7 (OCH_3), 55.9 (OCH_3), 72.3 (C^q), 111.1 (CH_{aro}), 111.4 (CH_{aro}), 120.0 (CH_2=), 120.4 (CH=),122.0 (CH_{aro}), 123.9 (CH_{aro}), 127.8 (CH_{aro}), 128.8 (2 x CH_{aro}), 129.0 (3 x CH_{aro}), 130.1 (CH_{aro}), 130.5 (2 x C^q_{aro}), 132.5 (CH_{aro}), 137.5 (C^q_{aro}), 145.1 (C^q_{aro}), 147.6 (C^q_{aro}), 148.8 (C^q_{aro}), 168.8 (C=O), 169.8 (C=O) ppm. HRMS (+ESI) calculated for $C_{29}H_{31}N_2O_4[M+H]^+$:471.2284, found 471.2281.

(±)-1-Allyl-*N*,*N*-dibenzyl-3-oxoisoindoline-1-carboxamide (±)-19e



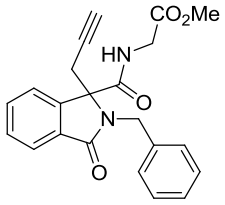
Starting from the benzylamine, this product was isolated as white solid in 97% yield; R_f (cyclohexane/AcOEt: 3/2) = 0.57; Mp = 194-195 °C; IR (KBr): 1690.41, 1660.58 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.02-3.13 (m, 1H, CH_2), 3.30-3.40 (m, 1H, CH_2), 3.62 (dd, *J* = 5.0, 15.0 Hz, 1H, CH_2), 4.20 (dd, *J* = 7.0, 15.0 Hz, 1H, CH_2), 4.43 (d, *J* = 15.0 Hz, 1H, CH_2), 4.79-4.86 (m, 3H, CH_2), 4.94 (d, *J* = 15.0 Hz, 1H, CH_2), 5.83 (s broad, 1H, NH), 6.74-6.79 (m, 2H, H_{aro}), 7.12-7.18 (m, 3H, H_{aro}), 7.25-7.28 (m, 3H, H_{aro}), 7.44-7.54 (m, 5H, H_{aro}), 7.73 (d, *J* = 7.0 Hz, 1H, H_{aro}) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 36.8 (CH_2), 43.6 (CH_2), 44.9 (CH_2), 72.7 (C^q), 120.1 (CH_2=), 122.1 (CH=), 124.0 (CH_{aro}), 127.4 (2 x CH_{aro}), 128.0 (CH_{aro}), 128.5 (2 x CH_{aro}), 128.9 (2 x CH_{aro}), 129.2 (2 x CH_{aro}), 130.2 (2 x CH_{aro}), 130.6 (C^q_{aro}), 132.6 (2 x CH_{aro}), 137.3 (C^q_{aro}), 137.4 (C^q_{aro}), 145.2 (C^q_{aro}), 169.1 (C=O), 170.1 (C=O) ppm. HRMS (+ESI) calculated for $C_{26}H_{25}N_2O_2$ $[M+H]^+$: 397.1871, found 397.1869.

(±)-1-Allyl-*N*-benzyl-3-oxo-*N*-(prop-2-yn-1-yl)isoindoline-1-carboxamide (±)-19f



Starting from propargylamine, this product was isolated as white solid in 97% yield ; R_f (cyclohexane/AcOEt: 3/2) = 0.57; Mp = 152-154 °C; IR (ATR): 1665.48 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.02 (t, *J* = 2.0 Hz, 1H, CH_2), 3.00-3.10 (m, 1H, CH_2), 3.25-3.37 (m, 2H, CH_2), 3.60-3.73 (m, 1H, CH_2), 4.41 (d, *J* = 15.0 Hz, 1H, CH_2), 4.82-4.84 (m, 3H, CH=CH_2), 5.00 (d, *J* = 15.0 Hz, 1H, CH_2), 5.58 (s broad, 1H, NH), 7.30-7.38 (m, 3H, H_{aro}), 7.43-7.62 (m, 5H, H_{aro}), 7.81 (d, *J*= 7.0 Hz, 1H, H_{aro}) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 29.4 (CH_2), 36.7 (CH_2), 44.9 (CH_2), 71.5 (C^q), 72.5 (C^q), 78.8 (CH), 120.0 (CH_2=), 122.0 (CH=), 123.8 (CH_{aro}), 127.9 (CH_{aro}), 128.8 (2 x CH_{aro}), 129.0 (CH_{aro}), 129.2 (2 x CH_{aro}), 130.0 (CH_{aro}), 130.5 (C^q_{aro}), 132.6 (CH_{aro}), 137.1 (C^q_{aro}), 144.7 (C^q_{aro}), 169.0 (C=O), 170.0 (C=O) ppm. HRMS (+ESI) calculated for $C_{22}H_{21}N_2O_2$ $[M+H]^+$: 345.1558, found 345.1566.

Methyl 2-(2-benzyl-3-oxo-1-(prop-2-yn-1-yl)isoindoline-1-carboxamido)acetate (±)-20



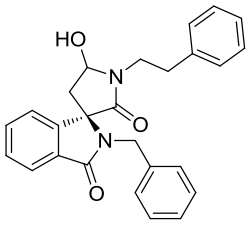
This product was isolated from reaction between (±)-**18** and glycine methyl ester hydrochloride as a white solid in 75% yield after crystallization from anhydrous ethanol; R_f (cyclohexan/AcOEt: 3/2)= 0.5; Mp= 219-220 °C; IR (ATR) 1749.90, 1668.64 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.66 (t, *J* = 2.6 Hz, 1H, CH), 3.11 (dd, *J* = 2.6, 17.5 Hz, 1H, CH_2), 3.38 (dd, *J* = 2.6, 17.5 Hz, 1H, CH_2), 3.39 (d, *J* = 17.7 Hz, 1H, CH_2), 3.63 (s, 3H, CH_3), 3.71 (dd, *J* = 5.8, 17.7 Hz, 1H, CH_2), 4.60 (d, *J* = 15.2 Hz, 1H, CH_2), 5.04 (d, *J* = 15.2 Hz, 1H, CH_2), 6.18 (t, *J* = 5.8 Hz, 1H, NH), 7.25-7.33 (m, 3H, H_{aro}), 7.45-7.62 (m, 5H, H_{aro}), 7.82 (d, *J* = 7.4 Hz, 1H, H_{aro}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.4 (CH_3), 41.1 (CH_2), 44.5 (CH_2), 52.2 (CH_2), 70.8 (C^q), 72.1 (C^q), 77.2 (CH), 121.7 (CH_{aro}), 123.9 (CH_{aro}), 127.7 (CH_{aro}), 128.6 (2 x CH_{aro}), 129.0 (2 x CH_{aro}), 129.5 (CH_{aro}), 130.9 (C^q_{aro}), 132.7

(CH_{aro}), 136.8 (C^q_{aro}), 144.2 (C^q_{aro}), 168.5 (C=O), 169.0 (C=O), 169.8 (C=O) ppm. HRMS (+ESI) calculated for $C_{22}H_{20}N_2O_4[M+H]^+$: 377.1457, found: 377.1521.

V. General Procedure for the Preparation of Spiro-hydroxy lactams (±)-11a,b,e,f(B,B') and (±)-22

OsO_4 (4%, w/w solution in water, 0.76 mL, 0.12 mmol) was added to a solution of **19a,b,e,f** or **17g**[2] (2 mmol) in 40 mL of THF/H_2O (3/1), under argon atmosphere. The reaction mixture was stirred at room temperature for 20 min then $NaIO_4$ (6 mmol, 1.28 g) was slowly added. After 2 to 3 h of stirring, water (30 mL) was added and the mixture was extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ then evaporated to dryness. The oil residue was purified by flash chromatography on silica gel column using the mixture cyclohexane/AcOEt (4/1) as the eluent.

***N*-Benzyl-5'-hydroxy-*N*'-phenethylspiro[isoindoline-1,3'-pyrrolidine]-2',3-dione (±)-11a(B,B')**



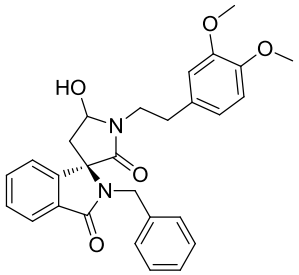
This products was obtained as a mixture of inseparable two diastereoisomers in 55:45 ratio, and were isolated as white solid in 54% global yield; R_f (cyclohexane/AcOEt: 3/2) = 0.25.

Major diastereoisomer (±)-11a(B): The NMR characteristics of this product were extracted from the spectrum of the mixture; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.98-2.15 (m, 1H, CH_2), 2.39-2.54 (m, 1H, CH_2), 2.77-3.00 (m, 2H, CH_2), 3.36-3.46 (m, 1H, CH_2), 3.61-3.68 (m, 1H, CH_2), 3.75 (d, *J* = 16 Hz, 1H, CH_2), 4.81(d, *J* = 16.0 Hz, 1H, CH_2), 5.25 (t, *J* = 5.0 Hz, 1H, CH), 6.93 (d, *J* = 5.0 Hz,1H, OH), 7.15-7.34 (m, 10H, H_{aro}), 7.50-7.75 (m, 3H, H_{aro}), 7.83 (d, *J* = 8Hz, 1H, H_{aro}) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 32.6 (CH_2), 36.2 (CH_2), 41.2 (CH_2), 43.0 (CH_2), 70.7 (C^q), 77.9 (CH), 122.7 (CH_{aro}), 126.3 (CH_{aro}), 126.9 (2 x CH_{aro}), 127.1 (2 x CH_{aro}), 128.4 (4 x CH_{aro}), 128.7 (3 x CH_{aro}), 130.6 (C^q_{aro}), 132.4 (CH_{aro}), 137.6 (C^q_{aro}), 138.7 (C^q_{aro}), 146.1 (C^q_{aro}), 168.3 (C=O), 169.3 (C=O).

Minor diastereoisomer (±)-11a(B'): The NMR characteristics of this product were extracted from the spectrum of the mixture; ^{1}H NMR (200 MHz, DMSO-d_6): δ 1.98-2.15 (m, 1H, CH_2), 2.68 (dd, *J* = 6.5, 14.3 Hz, 1H, CH_2), 2.77-3.00 (m, 2H, CH_2), 3.36-3.46 (m, 1H, CH_2), 3.61-3.68 (m, 1H, CH_2), 4.24 (d, *J* = 16.0 Hz, 1H, CH_2), 4.89 (d, *J* = 16.0 Hz, 1H, CH_2), 5.44-5.53 (m, 1H, CH), 6.76 (d, *J* = 6.5 Hz, 1H, OH), 6.96-7.00 (m, 1H, H_{aro}), 7.15-7.34 (m, 10H, H_{aro}), 7.50-7.86 (m, 3H, H_{aro}) ppm. ^{13}C NMR (50 MHz, DMSO-d_6): δ 32.5 (CH_2), 37.3 (CH_2), 40.5 (CH_2), 43.2 (CH_2), 70.5 (C^q), 78.0 (CH), 122.6 (CH_{aro}), 126.8 (2 x CH_{aro}), 127.0 (2 x CH_{aro}), 128.2 (CH_{aro}), 128.4 (3 x CH_{aro}), 128.6 (3 x CH_{aro}), 128.8 (CH_{aro}), 130.7 (C^q_{aro}), 132.4 (CH_{aro}), 137.8 (C^q_{aro}), 138.6 (C^q_{aro}), 146.3 (C^q_{aro}), 168.0 (C=O), 169.3 (C=O) ppm. HRMS (+ESI) calculated for $C_{26}H_{25}N_2O_3$ $[M+H]^+$: 413.1820, found 413.1831.

[2] Rammah, M. M.; Othman, M.; Ciamala, K.; Knorr, M.; Strohmann, C.; Rammah, M. B. *Heterocycles* **2009**, *78*, 2787–2798.

***N*-Benzyl-*N*'-(3,4-dimethoxyphenethyl)-5'-hydroxyspiro[isoindoline-1,3'-pyrrolidine]-2',3-dione (±)-11b(B)**

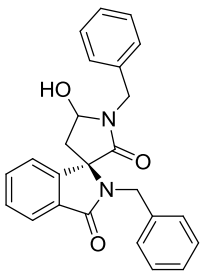


This product was obtained as a mixture of inseparable two diastereoisomers in 50:50 ratio and 57% yield.

Major diastereoisomer (±)-11b(B): The NMR characteristics of this product were extracted from the spectrum of the mixture; R_f (cyclohexane/AcOEt: 2/3) = 0.27; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.03-2.12 (m, 2H, CH_2), 2.40 (dd, *J* = 6.5, 14.4 Hz, 1H, CH_2), 2.73-2.92 (m, 2H, CH_2), 3.36-3.43 (m, 1H, CH_2), 3.66 (d, *J* = 16.4 Hz, 1H, CH_2), 3.71 (s, 3H, OCH_3), 3.73 (s, 3H, OCH_3), 4.81 (d, *J* = 16.4 Hz, 1H, CH_2), 5.26 (t, *J* = 5.4Hz, 1H, CH), 6.75-6.90 (m, 3H, H_{aro}), 6.94 (d, *J* = 4.6 Hz, 1H, OH), 7.13-7.15 (m, 2H, H_{aro}), 7.24-7.33 (m, 2H, H_{aro}), 7.44-7.58 (m, 2H, H_{aro}), 7.63-7.75 (m, 2H, H_{aro}), 7.84 (d, *J*= 7.6 Hz, 1H,H_{aro}) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 32.6 (CH_2), 36.7 (CH_2), 41.4 (CH_2), 43.5 (CH_2), 55.8 (OCH_3), 55.9 (OCH_3), 71.2 (C^q), 78.3 (CH), 112.2 (CH_{aro}), 112.8 (CH_{aro}), 121.0 (CH_{aro}), 123.1 (CH_{aro}), 127.3 (3 x CH_{aro}), 127.4 (CH_{aro}), 128.4 (2 x CH_{aro}), 129.3 (CH_{aro}), 131.1(CH_{aro}), 131.3 (C^q_{aro}), 132.8 (C^q_{aro}), 138.1 (C^q_{aro}), 146.5 (C^q_{aro}), 147.8 (C^q_{aro}), 149.1 (C^q_{aro}), 168.8 (C=O), 169.7 (C=O) ppm.

Minor diastereoisomer (±)-11b(B'): The NMR characteristics of this product were extracted from the spectrum of the mixture; R_f (cyclohexane/AcOEt: 2/3) = 0.27; ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.03-2.12 (m, 2H, CH_2), 2.67 (dd, *J* = 6.5, 14.3 Hz, 1H, CH_2), 2.73-2.92 (m, 2H, CH_2), 3.36-3.43 (m, 1H, CH_2), 3.64 (s, 3H, OCH_3), 3.69-3.72 (m, 1H, CH_2), 3.74 (s, 3H, OCH_3), 4.22 (d, *J* = 16.3 Hz, 1H, CH_2), 4.91 (d, *J* = 16.3 Hz, 1H, CH_2), 5.45-5.51 (m, 1H, CH), 6.75-6.90 (m, 4H, 3H_{aro}+ OH), 7.24-7.33 (m, 7H, H_{aro}), 7.44-7.58 (m, 1H, H_{aro}), 7.63-7.75 (m, 1H, H_{aro}) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 32.3 (CH_2), 37.7 (CH_2), 40.7 (CH_2), 43.7 (CH_2), 55.8 (OCH_3), 56.0 (OCH_3), 71.1 (C^q), 78.2 (CH), 112.3 (CH_{aro}), 112.8 (CH_{aro}), 121.1 (CH_{aro}), 121.6 (CH_{aro}), 123.1 (2 x CH_{aro}), 127.5 (3 x CH_{aro}), 128.7 (2 x CH_{aro}), 129.2 (CH_{aro}), 131.2 (C^q_{aro}), 132.6 (C^q_{aro}), 138.3 (C^q_{aro}), 146.7 (C^q_{aro}), 147.9 (C^q_{aro}), 149.2 (C^q_{aro}), 168.5 (C=O), 168.6 (C=O) ppm. HRMS (+ESI) calculated for $C_{28}H_{29}N_2O_5$ $[M+H]^+$: 473.2032, found 473.2041.

***N,N'*-Dibenzyl-5'-hydroxy-spiro[isoindoline-1,3'-pyrrolidine]-2',3-dione (±)-11e(B,B')**

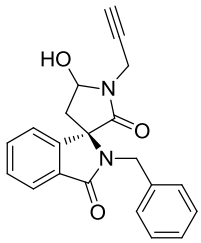


This product was isolated as a mixture of inseparable two diastereoisomers in 53:47 ratio and 74% yield. IR (ATR) 1669.40 cm^{-1}. The NMR characteristics of these products were extracted from the spectra of the mixture; R_f (cyclohexane/AcOEt: 2/3) = 0.36.

Major diastereoisomer (±)-11e(B): ^{1}H NMR ($CDCl_3$): δ 2.09 (d, *J* = 14.8 Hz, 1H, CH_2), 2.35 (dd, *J* = 14.8, 6.7 Hz, 1H, CH_2), 3.87 (d, *J* = 16.2 Hz, 1H, CH_2), 4.21 – 4.09 (m, 1H, CH), 4.26 (d, *J* = 14.0 Hz, 1H, CH_2), 4.92 (d, *J* = 13.3 Hz, 1H, CH_2), 5.01 (d, *J* = 5.5 Hz, 1H, CH_2), 5.21 (m, 1H, OH), 7.08 (dd, *J* = 6.8, 3.0 Hz, 2H, H_{aro}), 7.41 – 7.17 (m, 7H, H_{aro}), 7.61 – 7.51 (m, 1H, H_{aro}), 7.84 (dd, *J* = 10.4, 7.3 Hz, 4H, H_{aro}).

Minor diastereoisomer (±)-11e(B') :^{1}H NMR ($CDCl_3$): δ 2.20 (dd, *J* = 14.6, 4.3 Hz, 1H, CH_2), 2.58 (dd, *J* = 14.7, 6.6 Hz, 1H, CH_2), 4.26 (d, *J* = 14.0 Hz, 1H, CH_2), 4.37 (d, *J* = 16.0 Hz, 1H, CH_2), 4.71 (d, *J* = 4.7 Hz, 1H, OH), 4.93 (d, *J* = 7.5 Hz, 1H, CH_2), 5.21-5.28 (m, 1H, CH), 5.30 (d, *J* = 16.3 Hz, 1H, CH_2), 6.92 – 6.83 (m, 1H, H_{aro}), 7.42 – 7.25 (m, 10H, H_{aro}), 7.51 – 7.41 (m, 2H, H_{aro}), 7.84 (dd, *J* = 10.4, 7.3 Hz, 1H, H_{aro}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 37.3 (CH_2), 38.29 (CH_2), 44.0 (CH_2), 44.3 (CH_2), 44.3 (CH_2), 44.6 (CH_2), 70.7 (C^q), 71.1 (C^q), 78.2 (CH), 78.3 (CH), 120.2 (CH_{aro}), 122.6 (CH_{aro}), 123.6 (CH_{aro}), 124.1 (CH_{aro}), 127.3 (2 x CH_{aro}), 127.5 (2 x CH_{aro}), 127.8 (CH_{aro}), 127.8 (CH_{aro}), 128.1 (CH_{aro}), 128.1 (CH_{aro}), 128.6 (2 x CH_{aro}), 128.6 (3 x CH_{aro}), 128.6 (3 x CH_{aro}), 128.7 (2 x CH_{aro}), 128.9 (CH_{aro}), 129.0 (2 x CH_{aro}), 129.1 (CH_{aro}), 130.7 (C^q_{aro}), 131.0 (C^q_{aro}), 132.5 (CH_{aro}), 132.6 (CH_{aro}), 135.8 (C^q_{aro}), 135.9 (C^q_{aro}), 137.2 (C^q_{aro}), 137.2 (C^q_{aro}), 145.9 (C^q_{aro}), 146.4 (C^q_{aro}), 169.2 (C=O), 169.8 (C=O), 170.2 (2 x C=O) ppm. HRMS (+ESI) calculated for $C_{25}H_{23}N_2O_3$ $[M+H]^+$: 398.1630, found 398,1641.

2-Benzyl-5'-hydroxy-*N*'-(prop-2-yn-1-yl)spiro[isoindoline-1,3'-pyrrolidine]-2',3-dione (±)-11f(B,B')



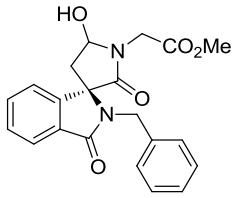
This product was obtained as a mixture of partially separable two diastereoisomers in 55:45 ratio, and were isolated as white solid in 97% global yield; R_f (cyclohexane/AcOEt: 3/2) = 0.29.

Major diastereoisomer (±)-11f(B): The NMR characteristics were extracted from the spectra of the mixture. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.26-2.32 (m, 2H, CH_2 and C≡CH), 2.67 (dd, *J* = 6.6, 14.6 Hz, 1H, CH_2), 3.84-3.98 (m, 1H, CH_2), 4.38-4.45 (m, 1H, CH_2), 4.40 (d, *J* = 16.0 Hz, 1H, CH_2), 4.93 (d, *J* = 6.3 Hz, 1H, OH), 5.13 (d, *J* = 16.0 Hz, 1H, CH_2), 5.64-5.70 (m, 1H, CH), 7.20-7.35 (m, 6H, H_{aro}), 7.45-7.60 (m, 2H, H_{aro}) 7.86-7.89 (m, 1H, H_{aro}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.8 (CH_2), 37.9 (CH_2), 44.2 (CH_2), 70.8 (C^q), 72.8 (CH), 77.0 (C^q), 78.1 (CH), 120.6 (CH_{aro}), 124.0 (CH_{aro}), 127.4 (CH_{aro}), 127.8 (2 x CH_{aro}), 128.5 (2 x CH_{aro}), 129.3 (CH_{aro}), 130.9 (C^q_{aro}), 132.7 (CH_{aro}), 137.0 (C^q_{aro}), 146.1 (C^q_{aro}), 168.9 (C=O), 169.5 (C=O) ppm.

Minor diastereoisomer (±)-11f(B'): Pure fractions of this product were obtained by flash chromatography. Mp = 112-114 °C; IR (ATR): 1712.55, 1668.35 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.14 (d, *J* = 14.9 Hz, 1H, CH_2), 2.34 (t, *J* = 2.4 Hz, 1H, CCH), 2.47 (dd, *J* = 6.7, 14.8 Hz, 1H, CH_2),

3.99 (d, *J* = 16.0 Hz, 1H, CH_2), 3.94 (dd, *J* = 2.4, 17.5 Hz, 1H, CH_2), 4.40 (dd, *J* = 2.4, 17.5 Hz, 1H, CH_2), 4.67 (d, *J* = 4.4 Hz, 1H, OH), 5.24 (d, *J* = 16.0 Hz, 1H, CH_2), 5.42 (t, *J* = 5.2 Hz, 1H, CH), 7.25-7.26 (m, 5H, H_{aro}), 7.45 (t, *J* = 7.4 Hz, 1H, H_{aro}), 7.52 (t, *J* = 7.4 Hz, 1H, H_{aro}), 7.74 (d, *J* = 7.7 Hz, 1H, H_{aro}), 7.84 (d, *J* = 7.2 Hz, 1H, H_{aro}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.3 (CH_2), 37.0 (CH_2), 44.3 (CH_2), 71.1 (C^q), 72.3 (CH), 77.3 (C^q), 78.2 (CH), 122.8 (CH_{aro}), 123.5 (CH_{aro}), 127.5 (2 x CH_{aro}), 127.7 (CH_{aro}), 128.8 (2 x CH_{aro}), 129.1 (CH_{aro}), 130.6 (C^q_{aro}), 132.8 (CH_{aro}), 137.0 (C^q_{aro}), 145.7 (C^q_{aro}), 169.7 (C=O), 170.0 (C=O) ppm. HRMS (+ESI) Calculated for $C_{21}H_{19}N_2O_3$ 346.1317 found 346.1327.

Methyl 2-((1R)-2-benzyl-5'-hydroxy-2',3-dioxospiro[isoindoline-1,3'-pyrrolidin]-1'-yl)acetate (±)-22

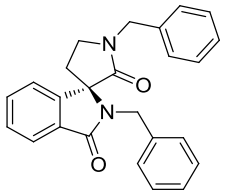


This product was isolated as a white solid in 66% yield after crystallization from anhydrous ethanol; R_f (cyclohexan/AcOEt: 2/3)= 0.32; Mp = 175-177 °C; IR (ATR) 1750.70, 1663.72 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.11 (d, *J* = 15.1 Hz, 1H, CH_2), 2.50 (dd, *J* = 6.7, 15.1 Hz, 1H, CH_2), 3.69 (s, 3H, CH_3), 3.98-4.25 (m, 3H, CH_2), 4.81 (d, *J* = 3.8 Hz, 1H, CH), 5.106-5.25 (m, 2H, CH_2 + OH), 7.16-7.35 (m, 5H, H_{aro}), 7.38-7.50 (m, 2H, H_{aro}), 7.68 (d, *J* = 7.4 Hz, 1H, H_{aro}), 7.77 (d, *J* = 7.4 Hz, 1H, H_{aro}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 37.5 (CH_2), 42.5 (CH_2), 44.1 (CH_2), 52.7 (CH_3), 70.6 (C^q), 80.01 (CH), 122.5 (CH_{aro}), 123.6 (CH_{aro}), 127.5 (CH_{aro}), 127.6 (2 x CH_{aro}), 128.7 (2 x CH_{aro}), 129.1 (CH_{aro}), 130.8 (C^q_{aro}), 132.6 (CH_{aro}), 137.6 (C^q_{aro}), 145.5 (C^q_{aro}), 169.5 (C=O), 169.7 (C=O), 170.9 (C=O) ppm. HRMS (+ESI) calculated for $C_{21}H_{20}N_2O_5[M+H]^+$: 381.1406 found: 381.1521.

VI. Procedure for the preparation of compound (±)-24

To a solution of spiro-hydroxy lactam **(±)-11e(B,B')** (mixture of two diastereoisomers) (0.75 mmol) in 7 mL of dry CH_2Cl_2 was added Et_3SiH (18.75 mmol, 3 mL) then trifluoroacetic acid (18.75 mmol, 1.4 mL). The reaction mixture was stirred at room temperature for 24 h. The solution was then diluted carefully with water (10 mL) and extracted twice with CH_2Cl_2 (20 mL). The organic layer was neutralized with a cold 10% $NaHCO_3$ aqueous solution, dried over $MgSO_4$ and evaporated in vacuo to give an oil residue which was purified by flash column chromatography on silica gel column using cyclohexane-ethyl acetate (2/3) to give polyheterocyclic compound **(±)-24**.

***N'*,*N*-Dibenzylspiro[isoindoline-1,3'-pyrrolidine]-2',3-dione (±)-24**



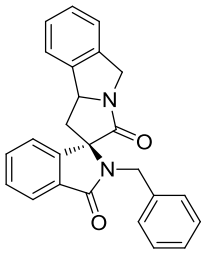
This compound was isolated as a white solid in 80% yield after crystallization from anhydrous ethanol. R_f (cyclohexane/AcOEt: 2/3) = 0.56; Mp = 148-150 °C; IR (ATR): 1695.53, 1682.59 cm^{-1};

^{1}H NMR (300 MHz, $CDCl_3$): δ 2.17-2.33 (m, 2H, CH_2), 3.21-3.31 (m, 1H, CH_2), 3.42-3.51 (m, 1H, CH_2), 4.07 (d, *J* = 16.0 Hz, 1H, CH_2), 4.47 (d, *J* = 14.0 Hz, 1H, CH_2), 4.65 (d, *J* = 14.0 Hz, 1H, CH_2), 5.38 (d, *J* = 16.0 Hz, 1H, CH_2), 7.15-7.18 (m, 1H, H_{aro}), 7.22-7.33 (m, 7H, H_{aro}), 7.39-7.43 (m, 3H, H_{aro}) 7.52-7.55 (m, 2H, H_{aro}), 7.94-7.97 (m, 1H, H_{aro}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.3 (CH_2), 43.0 (CH_2), 44.3 (CH_2), 48.0 (CH_2), 71.0 (C^q), 120.4 (CH_{aro}), 124.2 (CH_{aro}), 127.3 (CH_{aro}), 127.4 (2 x CH_{aro}), 128.2 (CH_{aro}), 128.6 (3 x CH_{aro}), 129.0 (2 x CH_{aro}), 129.1 (2 x CH_{aro}), 131.2 (C^q_{aro}), 132.3 (CH_{aro}), 135.8 (C^q_{aro}), 137.8 (C^q_{aro}), 146.4 (C^q_{aro}), 169.2 (C=O), 170.0 (C=O) ppm. HRMS (+ESI) calculated for $C_{25}H_{23}N_2O_2[M+H]^+$: 383.1760, found 383.1757.

VII. Procedure for the preparation of compound (±)-23(B,B')

To a solution of spiro-hydroxy lactam **(±)-11e(B,B')** (mixture of two diastereoisomers) (0.7 mmol) in 10 mL of dry toluene was added 1 equivalent of *p*-TSA. The reaction mixture was refluxed for 1h. After cooling at room temperature, the solution was concentrated in reduced pressure and diluted in 30 mL of dichloromethane. The organic layer was neutralized with a cold 10% $NaHCO_3$ aqueous solution, dried over $MgSO_4$ and evaporated under reduced pressure to give an oil residue which was purified by flash column chromatography on silica gel column using cyclohexane-ethyl acetate (7:3) to give polyheterocyclic compounds as following.

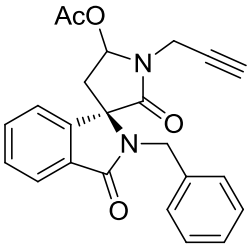
***N*-Benzyl-*N*',9*b*'-dihydrospiro[isoindoline-1,2'-pyrrolo[2,1-*a*]isoindole]-3,3'(5'*H*)-dione (±)-23(B,B')**



Compound (±)-23(B,B'): This product was obtained as single diastereoisomer and was isolated as a yellow oil in 63% yield; R_f (Cyclohexane/AcOEt : 3/2) = 0.54; IR (ATR): 1687.35, 1685.59 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.04 (d, *J* = 12.8 Hz, 1H, CH_2), 2.87 (dd, *J* = 12.7, 7.5 Hz, 1H, CH_2), 3.81 (d, *J* = 14.6 Hz, 1H, CH_2), 4.17 (d, *J* = 16.3 Hz, 1H, CH_2), 4.49 (d, *J* = 7.5 Hz, 1H, CH), 4.96 (d, *J* = 14.5 Hz, 1H, CH_2), 5.38 (d, *J* = 16.4 Hz, 1H, CH_2), 7.06 (d, *J* = 6.7 Hz, 1H, H_{aro}), 7.36 – 7.16 (m, 8H, H_{aro}), 7.45 (t, *J* = 7.3 Hz, 2H, H_{aro}), 7.56 (t, *J* = 7.1 Hz, 1H, H_{aro}), 7.84 (d, *J* = 9 Hz, 1H, H_{aro}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 41.0 (CH_2), 44.4 (CH_2), 45.6 (CH_2), 60.3 (CH), 71.4 (C^q), 122.1 (CH_{aro}), 124.1 (CH_{aro}), 128.0 (CH_{aro}), 128.0 (CH_{aro}), 128.6 (2 x CH_{aro}), 128.8 (2 x CH_{aro}), 128.9 (CH_{aro}), 129.2 (CH_{aro}), 129.4 (CH_{aro}), 130.7 (CH_{aro}), 132.2 (CH_{aro}), 132.9 (C^q_{aro}), 134.5 (C^q_{aro}), 135.3 (C^q_{aro}), 138.2 (C^q_{aro}), 142.5 (C^q_{aro}), 169.9 (C=O), 167.3 (C=O) ppm. HRMS (+ESI) Calculated for $C_{25}H_{21}N_2O_2$ $[M+H]^+$: 381.1603, found: 381.1598.

VIII. Procedure for the preparation of compound (±)-25

***N*-Benzyl-2',3-dioxo-*N*'-(prop-2-yn-1-yl)spiro[isoindoline-1,3'-pyrrolidin]-5'-yl acetate (±)-25**



This product was obtained as a mixture of inseparable two diastereoisomers in 63:37 ratio and **7**6% yield. IR (ATR): 1719.27, 1693.44 cm^{-1}.

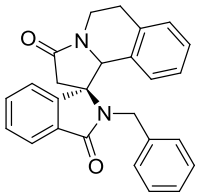
Major diastereoisomer (±)-25(B): The NMR characteristics of this product were extracted from the spectrum of the mixture*:* R_f (cyclohexane/AcOEt : 2/3) = 0.52. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.10 (s, 3H, CH_3), 2.33-2.42 (m, 1H+1H, CH_2+C≡CH), 2.93 (dd, *J* = 7.0, 15.5 Hz, 1H, CH_2), 3.91 (dd, *J* = 2.5, 17.5 Hz, 1H, CH_2), 4.37 (d, *J* = 16.1 Hz, 1H, CH_2), 4.46 (dd, *J* = 2.5, 17.5 Hz, 1H, CH_2), 5.20 (d, *J* = 16.1 Hz, 1H, CH_2), 6.60 (dd, *J* = 2.5, 6.9 Hz, 1H, CH), 7.27-7.37 (m, 6H, H_{aro}), 7.53-7.63 (m, 2H, H_{aro}) 7.93-7.95 (m, 1H, H_{aro}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.9 (CH_3), 31.3 (CH_2), 35.7 (CH_2), 44.2 (CH_2), 69.4 (C^q), 73.2 (CH), 76.4 (C^q), 79.8 (CH), 120.4 (CH_{aro}), 124.2 (CH_{aro}), 127.5 (CH_{aro}), 127.6 (2 x CH_{aro}), 128.5 (2 x CH_{aro}), 129.5 (CH_{aro}), 131.0 (C^q_{aro}), 132.7 (CH_{aro}), 137.1 (C^q_{aro}), 145.8 (C^q_{aro}), 169.0 (C=O),169.7 (C=O), 169.9 (C=O) ppm.

Minor diastereoisomer (±)-25(B'): The NMR characteristics of this product were extracted from the spectra of the mixture; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.23 (s, 3H, CH_3), 2.24 (d, 1H, *J* = 15.5 Hz, 1H, CH_2), 2.33-2.42 (m, 1H, C≡CH), 2.71 (dd, *J* = 7.0, 15.5 Hz, 1H, CH_2), 3.99 (dd, *J* = 2.5, 17.5 Hz, 1H, CH_2), 4.09 (d, *J* = 16.0 Hz, 1H, CH_2), 4.44 (dd, *J* = 2.5, 17.5 Hz, 1H, CH_2), 5.30 (d, *J* = 16.0 Hz, 1H, CH_2), 6.44 (d, *J* = 6.7 Hz, 1H, CH), 7.27-7.37 (m, 5H, H_{aro}), 7.53-7.63 (m, 3H, H_{aro}), 7.93-7.95 (m, 1H, H_{aro}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.1 (CH_3), 31.6 (CH_2), 35.0 (CH_2), 44.3 (CH_2), 69.6 (C^q), 73.1 (CH), 76.6 (C^q), 79.8 (CH), 121.5 (CH_{aro}), 124.1 (CH_{aro}), 127.8 (CH_{aro}), 127.9 (2 x CH_{aro}), 128.9 (2 x CH_{aro}), 129.4 (CH_{aro}), 131.0 (C^q_{aro}), 132.6 (CH_{aro}), 137.0 (C^q_{aro}), 145.0 (C^q_{aro}), 169.1 (C=O), 170.0 (C=O), 170.3 (C=O) ppm. HRMS (+ESI) calculated for $C_{23}H_{21}N_2O_4$ $[M+H]^+$: 388.1423, found 388.1423.

IX. General procedure for π-cationic cyclization of α-acetoxy lactams (±)-6

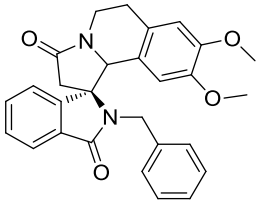
To a solution of α-acetoxy lactam **(±)-6** (pure form or mixture of two diastereoisomers or mixture of two regioisomers, 0.7 mmol) in 2 mL of acetonitrile was added 10 mol% of TMSOTf then the reaction mixture was stirred at room temperature for 24 h. The reaction mixture was then diluted carefully with water (10 mL) and extracted twice with dichloromethane (20 mL). The organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to give an oil residue which was purified by flash column chromatography on silica gel column using the mixture of cyclohexane/ethyl acetate (1:1) to give spirocyclic indolizine **(±)-7** as following.

(±)-*N*-benzyl-5',6'-dihydro-2'*H*-spiro[isoindoline-1,1'-pyrrolo[2,1-*a*]isoquinoline]-3,3'(10b'*H*)-dione ((±)-7aA)



The reaction was carried out on pure α-acetoxy lactams **(±)-6aA** or **(±)-6aA'**. In both cases the same spirocyclic indolizine **(±)-6a** was isolated as sole diastereoisomer in 80% yield: Mp = 168-169 °C, ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.42-2.51 (m, 1H, CH_2), 2.88-3.10 (m, 3H, 2 x CH_2), 3.68-3.77 (m, 1H, CH_2), 4.14 (d, *J* = 16.0 Hz, 1H, CH_2), 4.63 (s, 1H, CH), 5.13 (d, *J* = 16.0 Hz, 1H, CH_2), 6.99-7.03 (m, 1H, H_{aro}), 7.10-7.13 (m, 2H, H_{aro}), 7.17-7.30 (m, 7H, H_{aro}), 7.34-7.40 (m, 1H, H_{aro}), 7.50 (t, *J* = 7.3 Hz, 1H, H_{aro}), 7.64 (d, *J* = 7.5 Hz, 1H, H_{aro}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.2 (CH_2), 39.9 (CH_2), 41.6 (CH_2), 42.4 (CH_2), 64.1 (C^q), 64.8 (CH), 121.1 (CH_{aro}), 124.0 (CH_{aro}), 126.8 (CH_{aro}), 127.5 (CH_{aro}), 127.6 (CH_{aro}), 128.7 (2 x CH_{aro}), 128.9 (2 x CH_{aro}), 129.1 (CH_{aro}), 129.2 (CH_{aro}), 130.3 (CH_{aro}), 130.9 (C^q_{aro}), 131.3 (C^q_{aro}), 132.9 (CH_{aro}), 136.1 (C^q_{aro}), 138.3 (C^q_{aro}), 148.2 (C^q_{aro}), 168.3 (C=O), 171.3 (C=O) ppm. HRMS (+ESI) calculated for $C_{26}H_{23}N_2O_2[M+H]^+$: 395.1760, found 395.1776.

(±)-*N*-Benzyl-8',9'-dimethoxy-5',6'-dihydro-2'*H*-spiro[isoindoline-1,1'-pyrrolo[2,1-a]isoquinoline]-3,3'(10b'*H*)-dione ((±)-7bA)



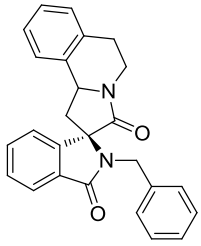
The reaction was carried out on a mixture of two regioisomers of α-acetoxy lactams **(±)-6b(A,A')** and **(±)-6b(B,B')** (ratio 60:40) and afforded the desired spirocyclic indolizine as a mixture of two regioisomers in 80:20 ratio **(±)-7bA**/**8bB** and in an overall yield of 54%. Spirocyclic indolizine **(±)-7bA** was isolated as one pure diastereoisomer: this compound was purified by fractional crystallization from dry ethanol; R_f (cyclohexane/AcOEt: 2/3)= 0.23; IR (ATR): 1692.73, 1667.41, Mp = 193-195 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.45 (d, *J* = 16.0 Hz, 1H, CH_2), 2.64-270 (m, 1H, CH_2), 2.83-3.04 (m, 2H, CH_2), 3.17 (d, *J* = 16.0 Hz, 1H, CH_2), 3.54 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 4.57-4.62 (m, 1H, CH_2), 4.97 (d, *J* = 16.0 Hz, 1H, CH_2), 5.16 (d, *J* = 16.0 Hz, 1H, CH_2), 5.24 (s, 1H, CH), 5.94 (s, 1H, H_{aro}), 6.38 (s, 1H, H_{aro}), 7.10-7.13 (m, 1H, H_{aro}), 7.24-7.39 (m, 5H, H_{aro}), 7.51-7.54 (m, 2H, H_{aro}), 7.74 (d, *J* = 7.0 Hz, 1H, H_{aro}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.2 (CH_2), 36.7 (CH_2), 39.7 (CH_2), 43.6 (CH_2), 55.6 (OCH_3), 55.8 (OCH_3), 58.9 (CH), 70.1 (C^q), 106.5 (CH_{aro}), 111.2 (CH_{aro}), 120.4 (CH_{aro}), 122.9 (C^q_{aro}), 123.5 (CH_{aro}), 125.5 (C^q_{aro}), 128.1 (CH_{aro}), 128.3 (2 x CH_{aro}), 129.0 (CH_{aro}), 129.1 (2 x CH_{aro}), 130.2 (C^q_{aro}), 132.1 (CH_{aro}), 137.0 (C^q_{aro}), 146.8 (C^q_{aro}), 147.6 (C^q_{aro}), 147.8 (C^q_{aro}), 168.9 (C=O), 169.1 (C=O) ppm. HRMS (+ESI) calculated for $C_{28}H_{27}N_2O_4[M+H]^+$: 455.1971, found 455.1968.

X. General procedure for π-cationic cyclization of α-hydroxy lactams (±)-11

A solution of spiro-hydroxy lactams **(±)-11a-b(B,B')** as a mixture of two diastereoisomers (0.7 mmol) in 2 mL trifluoroacetic acid was stirred at room temperature for 24 h. The reaction mixture was then diluted carefully with water (10 mL) and extracted twice with dichloromethane (20 mL).

The organic layer was neutralized with a cold 10% $NaHCO_3$ aqueous solution, dried over $MgSO_4$ and evaporated *in vacuo* to give an oil residue which was purified by flash column chromatography on silica gel column using cyclohexane and ethyl acetate (1:1) to give spirocyclic isoindoles **(±)-8** as following.

***N*-Benzyl-5',6'-dihydro-1'*H*-spiro[isoindoline-1,2'-pyrrolo[2,1-*a*]isoquinoline]-3,3'(10b'*H*)-dione ((±)-8a(B,B'))**

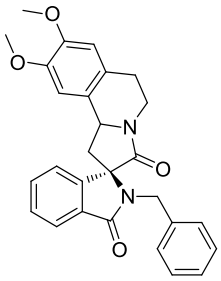


This product was obtained as separable two diastereisomers.

Major diastereoisomer (±)-8a(B): This compound was isolated by flash chromatography, Mp = 247-248 °C; IR (ATR): 1687.98 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.49 (dd, 1H, *J* = 7, 14 Hz, CH_2), 2.82-2.89 (m, 2H, CH_2), 2.98-3.14 (m, 2H, CH_2), 4.19-4.27 (m, 1H, CH_2), 4.50 (d, *J* = 16.0 Hz, 1H, CH_2), 4.75 (t, *J* = 7.0 Hz, 1H, CH), 5.17 (d, *J* = 16.0 Hz, 1H, CH_2), 6.90-6.96 (m, 2H, H_{aro}), 7.24-7.52 (m, 10H, H_{aro}), 7.93 (d, *J* = 8.0 Hz, 1H, H_{aro}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.3 (CH_2), 37.2 (CH_2), 38.2 (CH_2), 44.5 (CH_2), 53.6 (CH), 71.4 (C^q), 121.3 (CH_{aro}), 123.9 (CH_{aro}), 124.9 (CH_{aro}), 127.1 (CH_{aro}), 127.5 (CH_{aro}), 127.6 (2 x CH_{aro}), 127.7 (CH_{aro}), 128.6 (2 x CH_{aro}), 129.0 (CH_{aro}), 129.4 (CH_{aro}), 131.5(C^q_{aro}), 132.4 (CH_{aro}), 133.4 (C^q_{aro}), 136.7 (C^q_{aro}), 137.2 (C^q_{aro}), 146.3 (C^q_{aro}), 168.4 (C=O), 169.0 (C=O). HRMS (+ESI) calculated for $C_{26}H_{23}N_2O_2$ $[M+H]^+$: 395.1760, found 395.1756.

Minor diastereoisomer (±)-8a(B'): This compound was purified by fractional crystallization from dry ethanol; R_f (cyclohexane/AcOEt: 2/3) = 0.43; IR (ATR): 1687.98 cm^{-1}; Mp = 188-190 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 2.30 (dd, *J* = 8.5, 13.3 Hz, 1H, CH_2), 2.82 (dd, *J* = 7.3, 13.3 Hz, 1H, CH_2), 2.85-2.95 (m, 1H, CH_2), 3.00-3.11 (m, 1H, CH_2), 3.27-3.36 (m, 1H, CH_2), 4.08 (d, *J* = 16 Hz, 1H, CH_2), 4.33-4.40 (m, 1H, CH_2), 5.16 (t, *J* = 7.8 Hz, 1H, CH), 5.22 (d, *J* = 16 Hz, 1H, CH_2), 6.87-6.90 (m, 1H, H_{aro}), 7.09-7.14 (m, 4H, H_{aro}), 7.22-7.26 (m, 4H, H_{aro}), 7.44-7.46 (m, 3H, H_{aro}), 7.96 (d, 1H, *J*= 7.0 Hz, H_{aro}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.4 (CH_2), 36.6 (CH_2), 38.5 (CH_2), 44.5 (CH_2), 53.3 (CH), 72.0 (C^q), 120.6 (CH_{aro}), 124.2 (CH_{aro}), 124.7 (CH_{aro}), 127.2 (CH_{aro}), 127.5 (CH_{aro}), 127.8 (2 x CH_{aro}), 128.4 (2 x CH_{aro}), 129.1 (CH_{aro}), 129.2 (CH_{aro}), 131.0 (C^q_{aro}), 132.4 (CH_{aro}), 133.1 (C^q_{aro}), 136.3 (C^q_{aro}), 137.2 (C^q_{aro}), 146.0 (C^q_{aro}), 168.6 (C=O), 169.1 (C=O) ppm. HRMS (+ESI) calculated for $C_{26}H_{23}N_2O_2[M+H]^+$: 395.1760, found 395.1756.

***N*-Benzyl-8',9'-dimethoxy-5',6'-dihydro-1'*H*-spiro[isoindoline-1,2'-pyrrolo[2,1-*a*]isoquinoline]-3,3'(10b'*H*)-dione (±)-8b(B,B')**

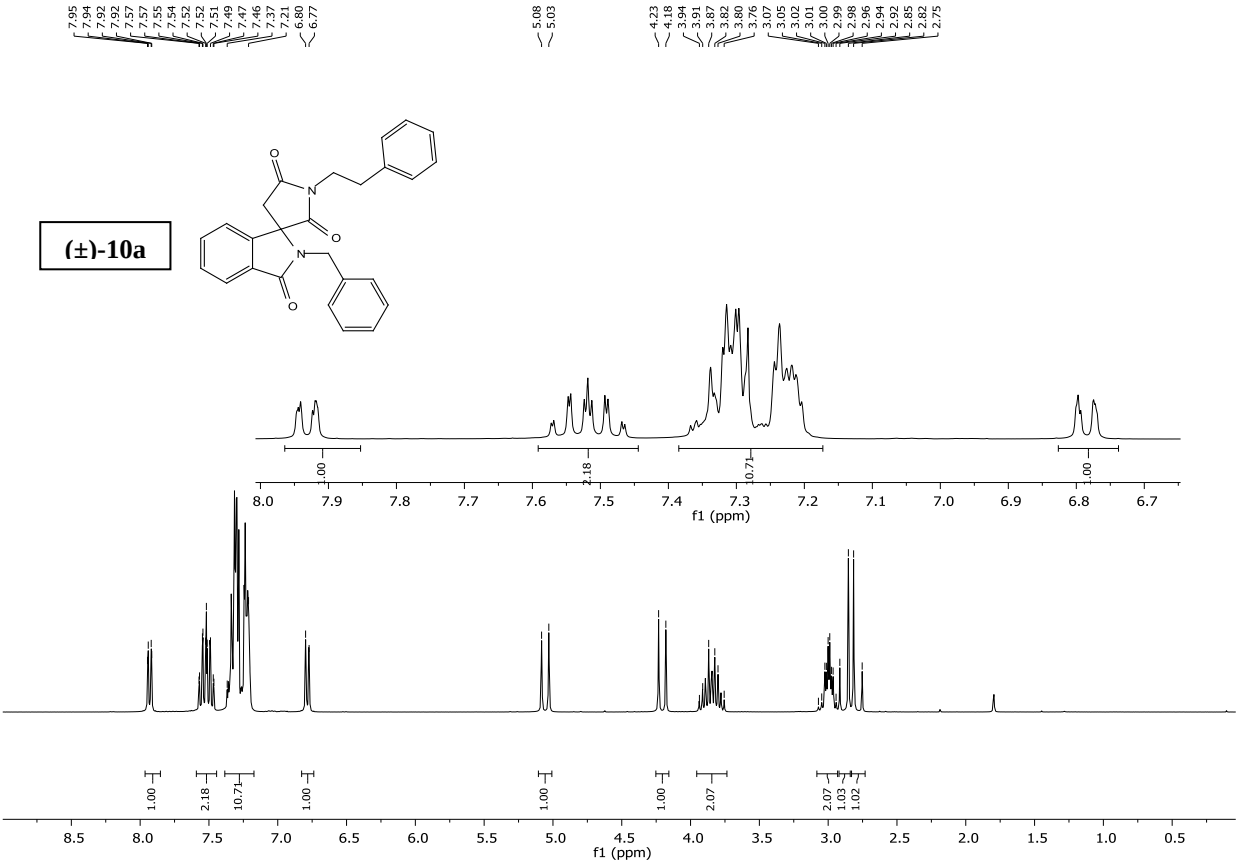


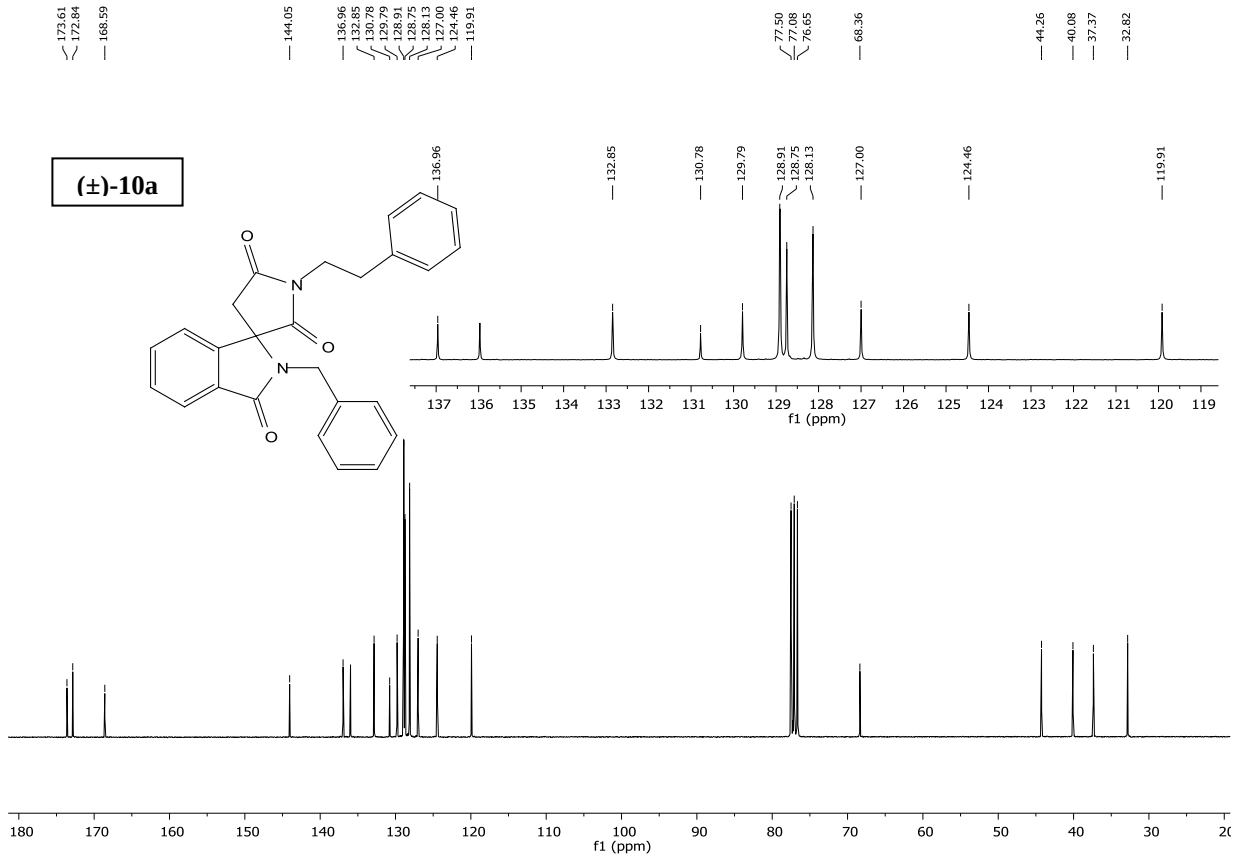
Spirocyclic indolizine **(±)-8b(B,B'):** These products were obtained as a mixture of inseparable two diastereoisomers (d.r. 75:25).

Major diastereoisomer (±)-8bB: The NMR characteristics of this product were extracted from the spectrum of the mixture; R_f (cyclohexane/AcOEt: 1/4) = 0.37; IR (ATR): 1694.71, 1681.21 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.27 (dd, *J* = 8.0, 13.0 Hz, 1H, CH_2), 2.74-2.83 (m, 2H, CH_2), 2.96-3.09 (m, 1H, CH_2), 3.22-3.31 (m, 1H, CH_2), 3.73 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.00 (d, *J* = 16.0 Hz, 1H, CH_2), 4.36-4.42 (m, 1H, CH_2), 5.08 (t, *J* = 8.0 Hz, 1H, CH), 5.26 (d, *J* = 16 Hz, 1H, CH_2), 6.27 (s, 1H, H_{aro}), 6.69 (s, 1H, H_{aro}), 7.06-7.14 (m, 4H, H_{aro}), 7.36-7.48 (m, 2H, H_{aro}), 7.51-7.62 (m, 2H, H_{aro}), 7.93-7.96 (m, 1H, H_{aro}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.9 (CH_2), 36.6 (CH_2), 38.6 (CH_2), 44.5 (CH_2), 53.1 (OCH_3), 55.9 (OCH_3), 56.0 (CH), 72.0 (C^q), 107.3 (CH_{aro}), 111.6 (CH_{aro}), 120.6 (CH_{aro}), 124.2 (CH_{aro}), 125.1 (C^q_{aro}), 127.1 (CH_{aro}), 127.6 (CH_{aro}), 127.8 (2 x CH_{aro}), 128.2 (C^q_{aro}), 128.3 (2 x CH_{aro}), 131.0 (C^q_{aro}), 132.4 (CH_{aro}), 137.3 (C^q_{aro}), 146.1 (C^q_{aro}), 148.3 (C^q_{aro}), 148.4 (C^q_{aro}), 168.5 (C=O), 169.1 (C=O) ppm.

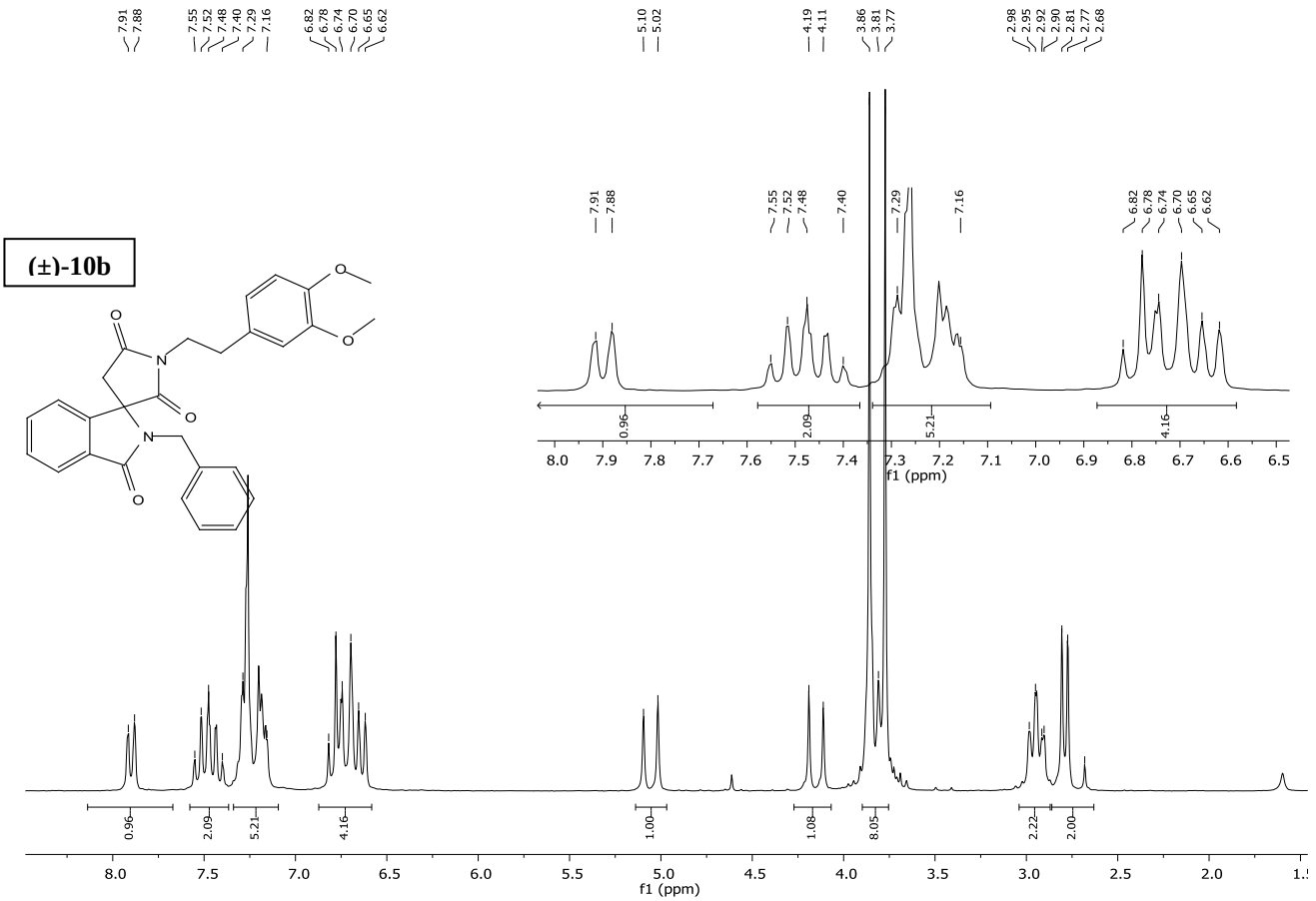
Minor diastereoisomer (±)-8bB': The NMR characteristics of this product were extracted from the spectrum of the mixture: ^1H NMR (300 MHz, $CDCl_3$): δ 2.46 (dd, *J* = 6.0, 14.0 Hz, 1H, CH_2), 2.74-2.83 (m, 2H, CH_2), 2.96-3.09 (m, 2H, CH_2), 3.80 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 4.24-4.31 (m, 1H, CH_2), 4.48 (d, *J* = 16.0 Hz, 1H, CH_2), 4.73 (t, *J* = 7.0 Hz,1H, CH), 5.16 (d, *J* = 16.0 Hz, 1H, CH_2), 6.40 (s, 1H, H_{aro}), 6.67 (s, 1H, H_{aro}), 6.85-6.88 (m, 1H, H_{aro}), 7.08-7.14 (m, 4H, H_{aro}), 7.30-7.62 (m, 3H, H_{aro}), 7.90-7.96 (m, 1H, H_{aro}) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.8 (CH_2), 37.0 (CH_2), 38.4 (CH_2), 44.5 (CH_2), 53.4 (OCH_3), 55.9 (OCH_3), 56.0 (CH), 71.4 (C^q), 107.6 (CH_{aro}), 111.8 (CH_{aro}), 121.2 (CH_{aro}), 123.9 (CH_{aro}), 125.4 (C^q_{aro}), 127.6 (CH_{aro}), 128.2 (C^q_{aro}), 128.6 (2 x CH_{aro}), 128.9 (CH_{aro}), 129.1 (2 x CH_{aro}), 131.4 (C^q_{aro}), 132.4 (CH_{aro}), 137.4 (C^q_{aro}), 146.4 (C^q_{aro}), 148.3 (2 x C^q_{aro}), 168.4 (C=O), 169.0 (C=O) ppm. HRMS (+ESI) calculated for $C_{28}H_{27}N_2O_4$ $[M+H]^+$:455.1971, found 455.1968.

XI. Copies of ^{1}H and ^{13}C NMR spectra for all new compounds

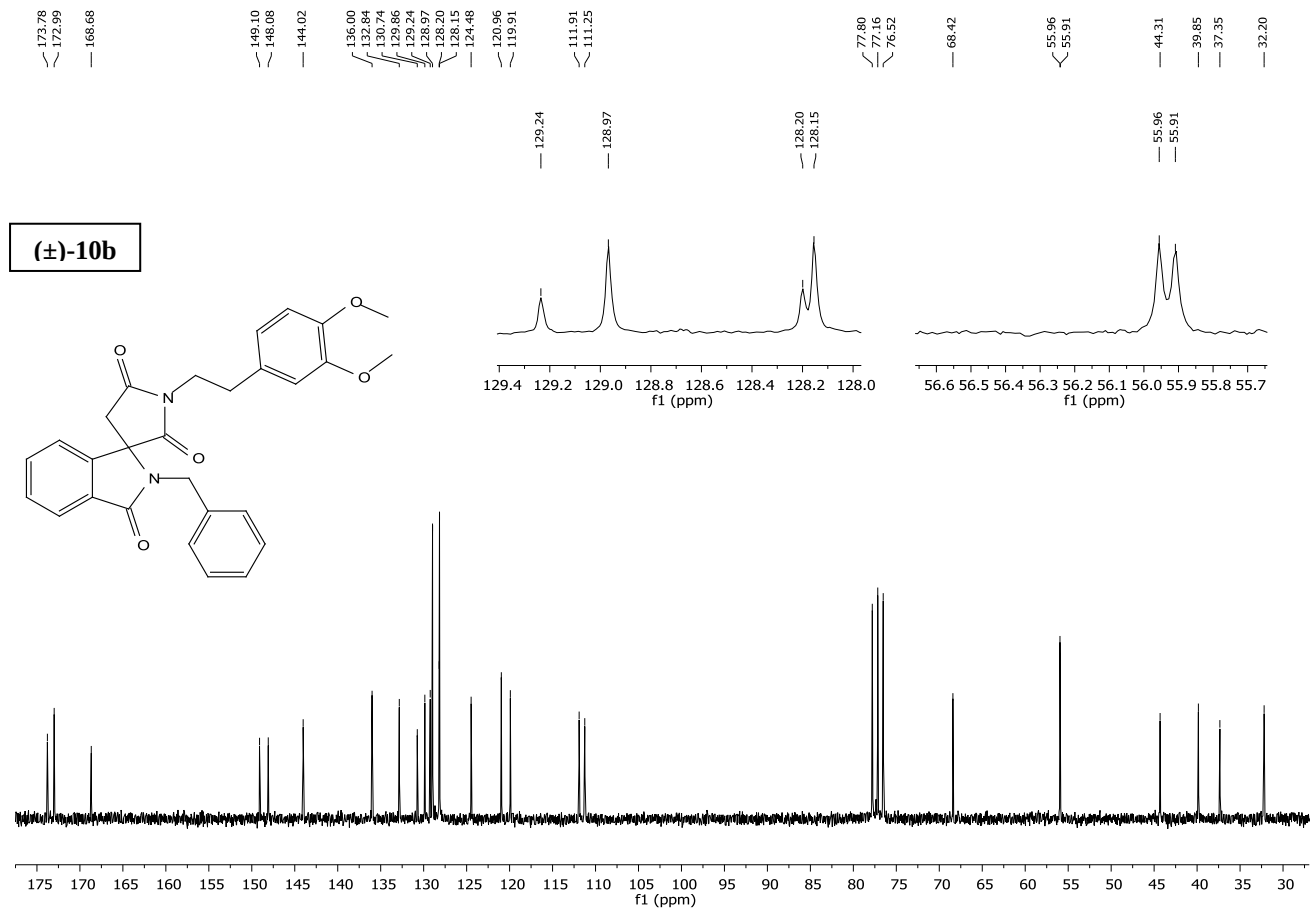


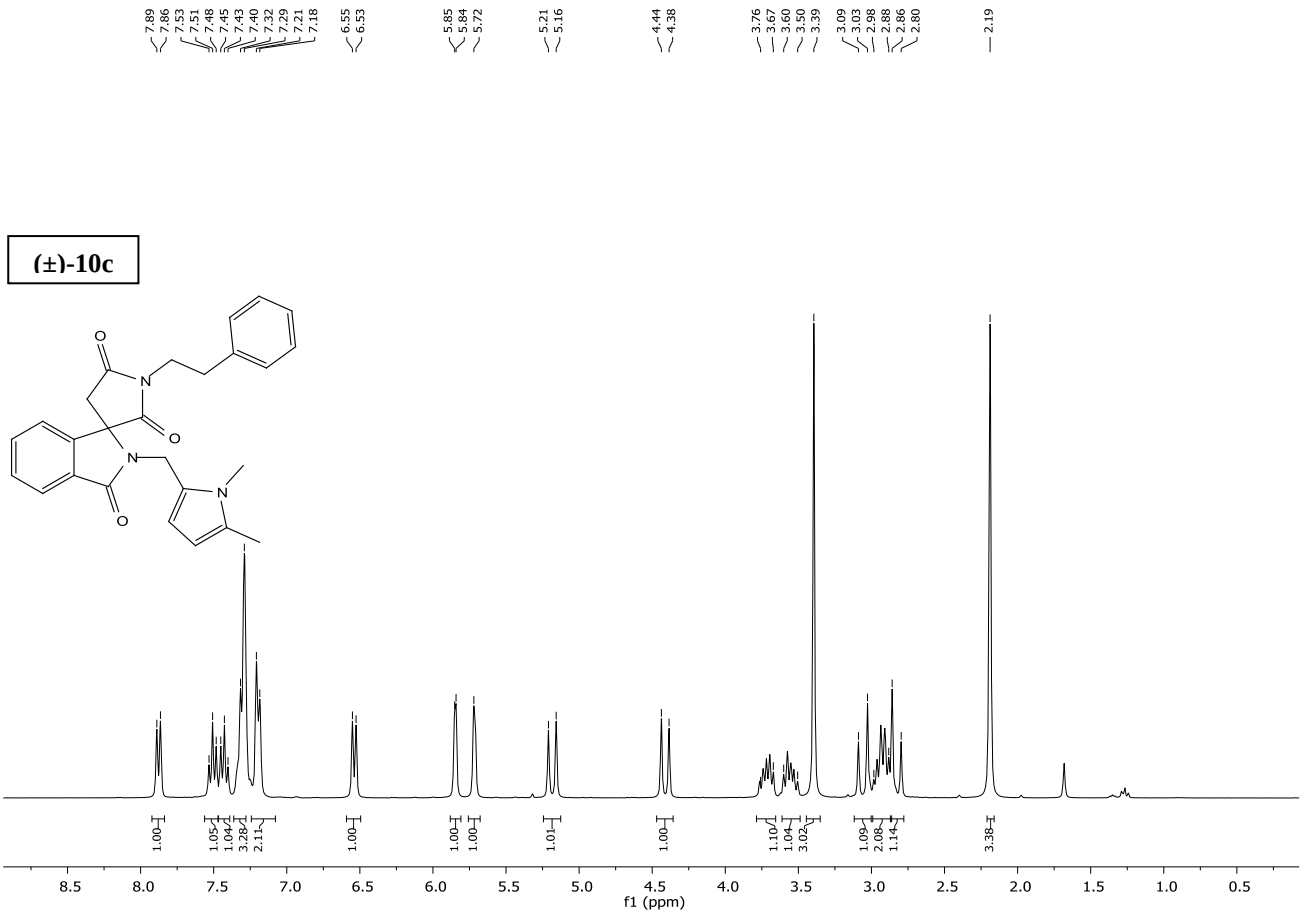


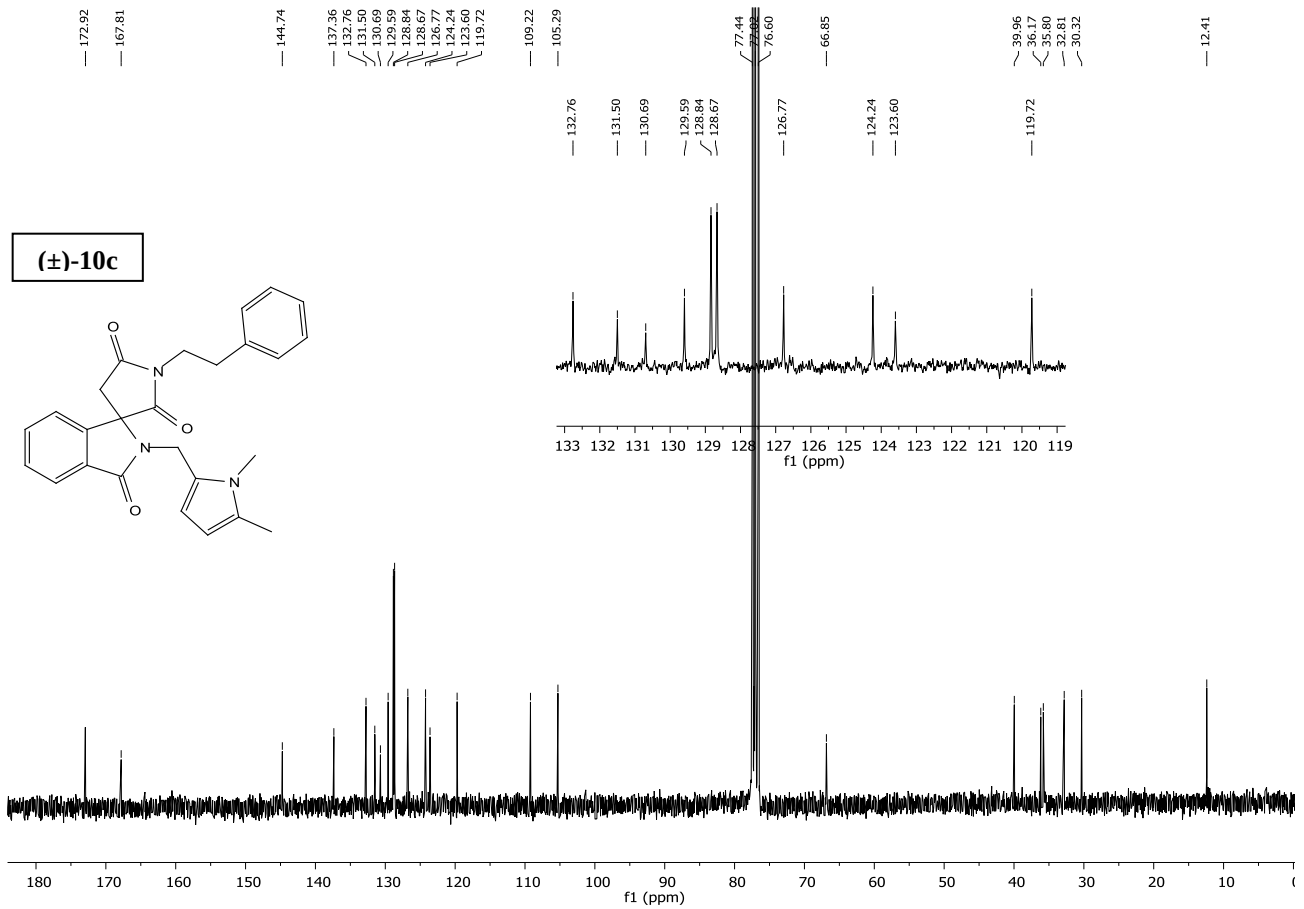
(±)-10b



(±)-10b




(±)-10c
7.89
7.86
7.53
7.51
7.48
7.45
7.43
7.40
7.32
7.29
7.21
7.18
6.55
6.53
5.85
5.84
5.72
5.21
5.16
4.44
4.38
3.76
3.67
3.60
3.50
3.39
3.09
3.03
2.98
2.88
2.86
2.80
2.19
1.00
1.05
1.04
3.28
2.11
1.00
1.00
1.00
1.01
1.00
1.10
1.04
3.02
1.09
2.08
1.14
3.38
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


(±)-10c
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167.81
144.74
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132.76
131.50
130.69
129.59
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128.67
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123.60
119.72
109.22
105.29
77.44
77.02
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36.17
35.80
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30.32
12.41
132.76
131.50
130.69
129.59
128.84
128.67
126.77
124.24
123.60
119.72
133 132 131 130 129 128 127 126 125 124 123 122 121 120 119
f1 (ppm)
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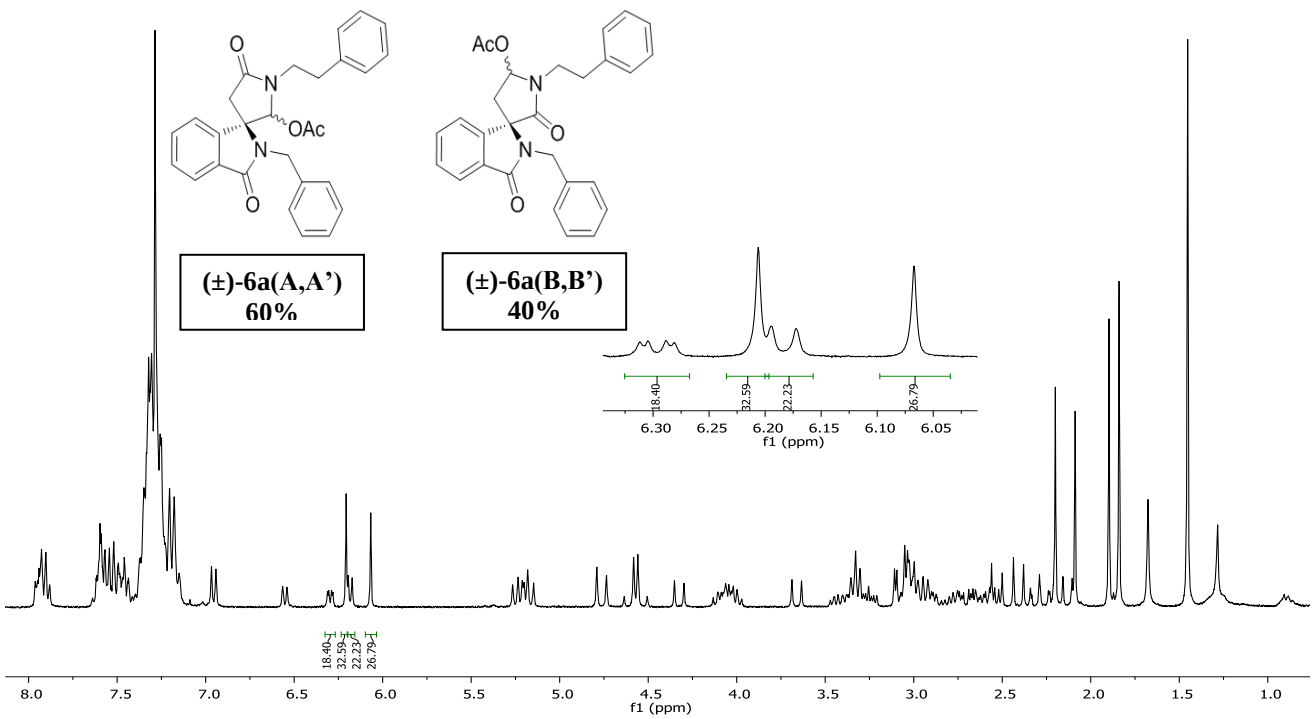
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)


(±)-6a(A,A')
60%
(±)-6a(B,B')
40%
18.40
32.59
22.23
26.79
f1 (ppm)


7.90
7.88
7.54
7.54
7.52
7.52
7.50
7.49
7.46
7.45
7.43
7.43
7.41
7.40
7.35
7.15
6.93
6.91
6.18
5.21
5.15
4.77
4.71
4.11
4.08
4.08
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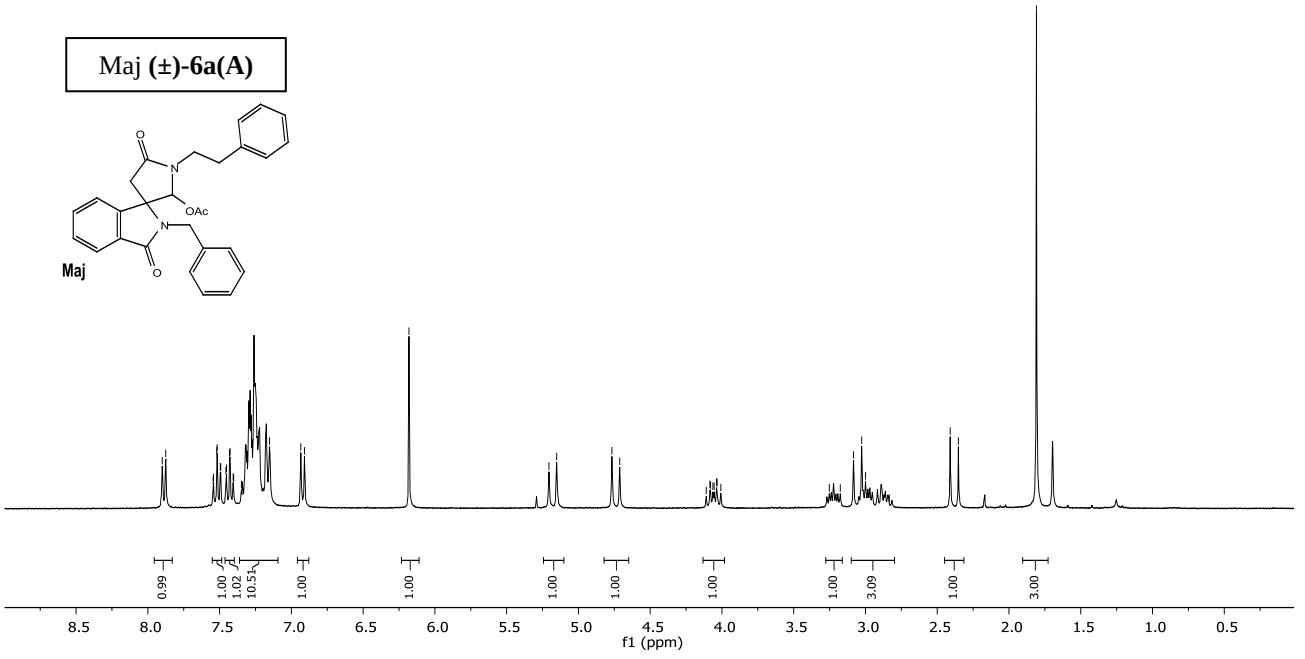
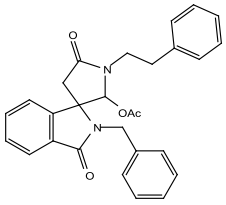
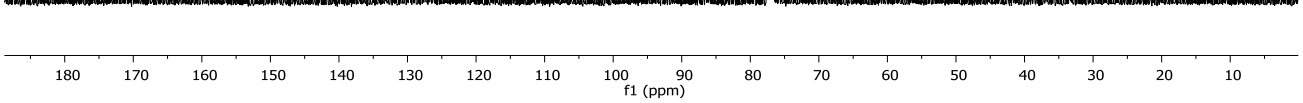
3.03
3.00
2.83
2.41
2.35
1.81

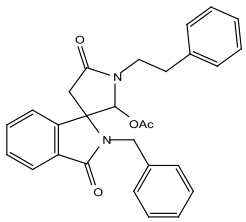

Maj (±)-6a(A)
Maj
OAc
0.99
1.00
1.02
10.51
1.00
1.00
1.00
1.00
1.00
3.09
1.00
3.00
f1 (ppm)

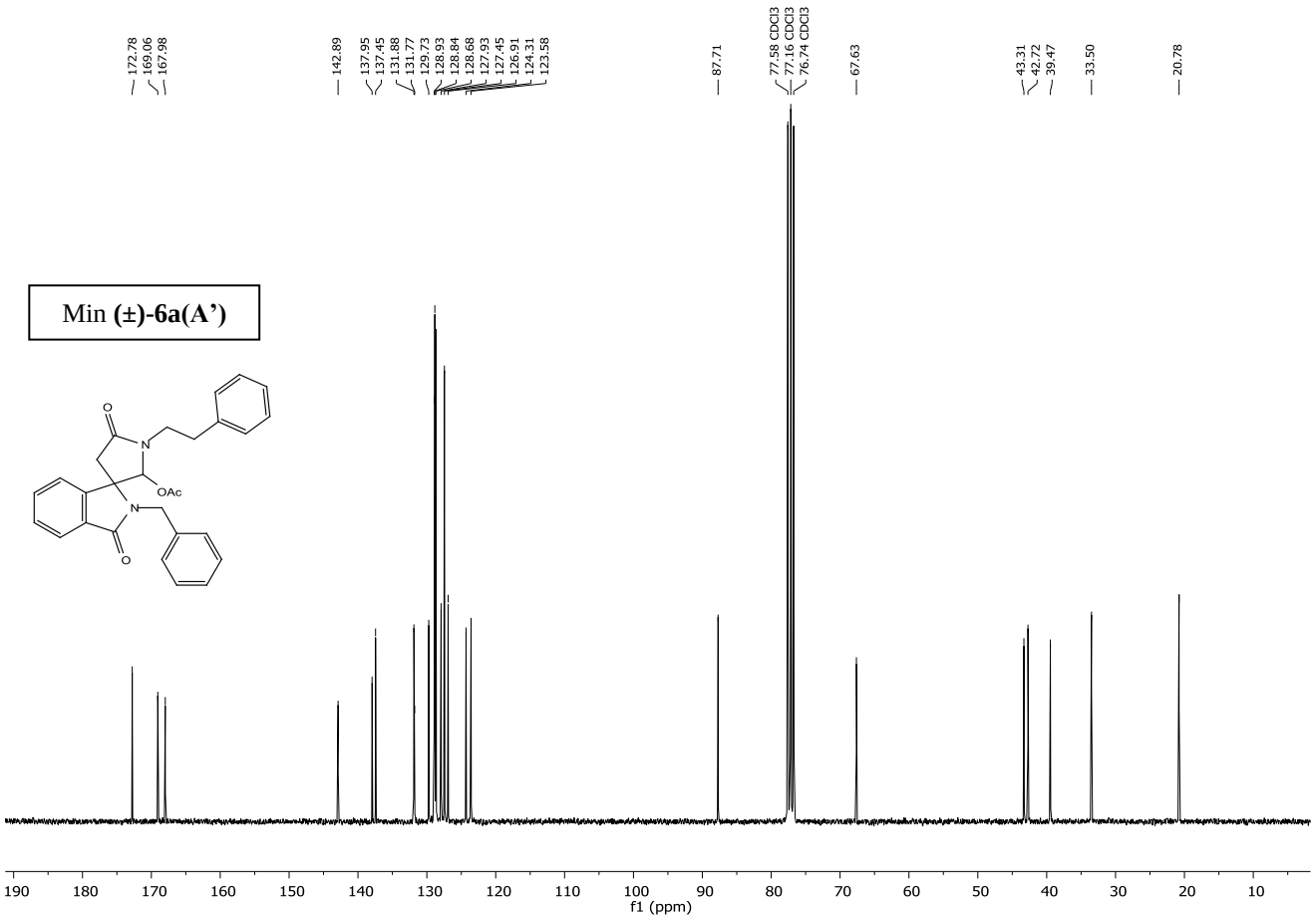
Maj **(±)-6a(A)**

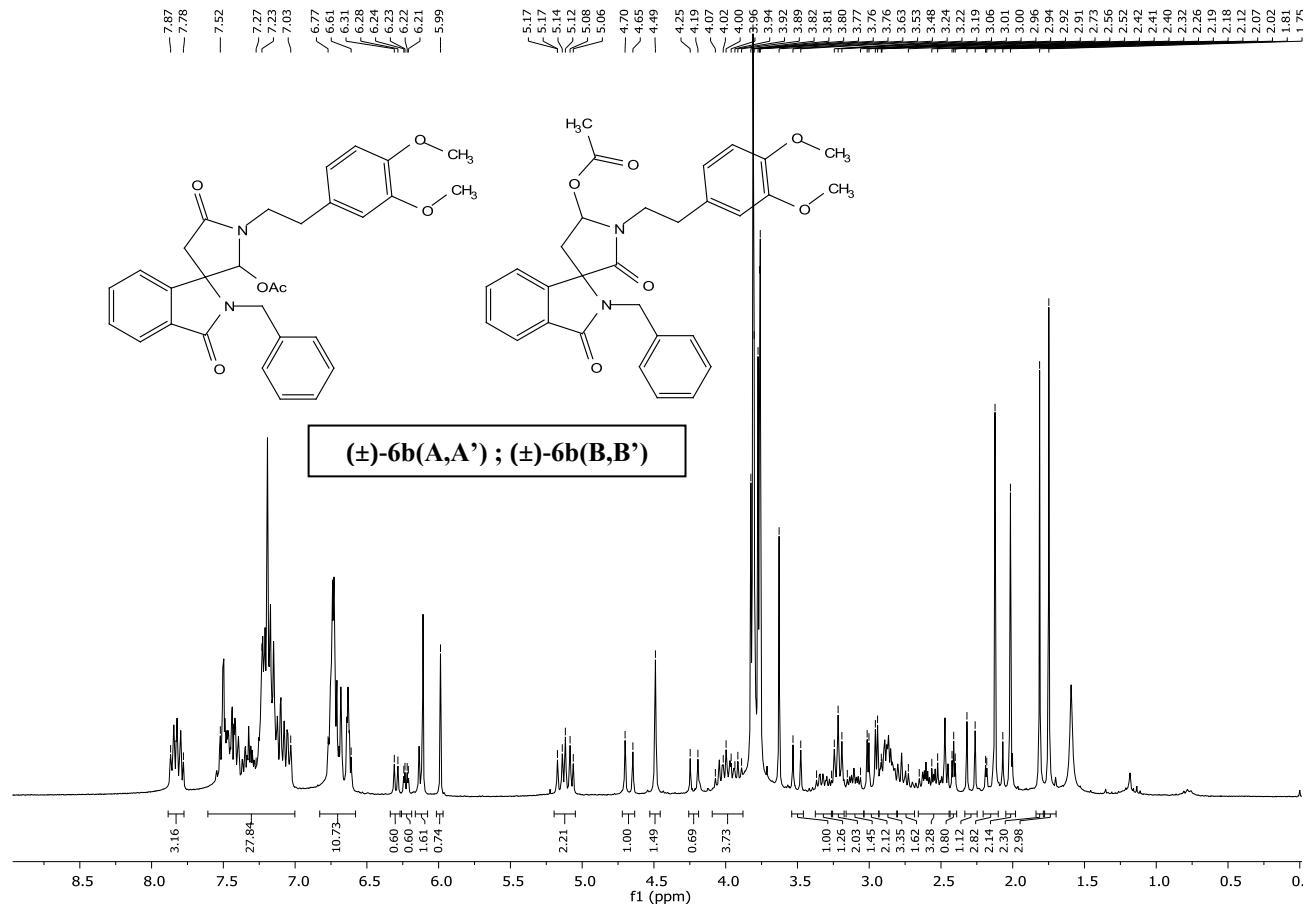


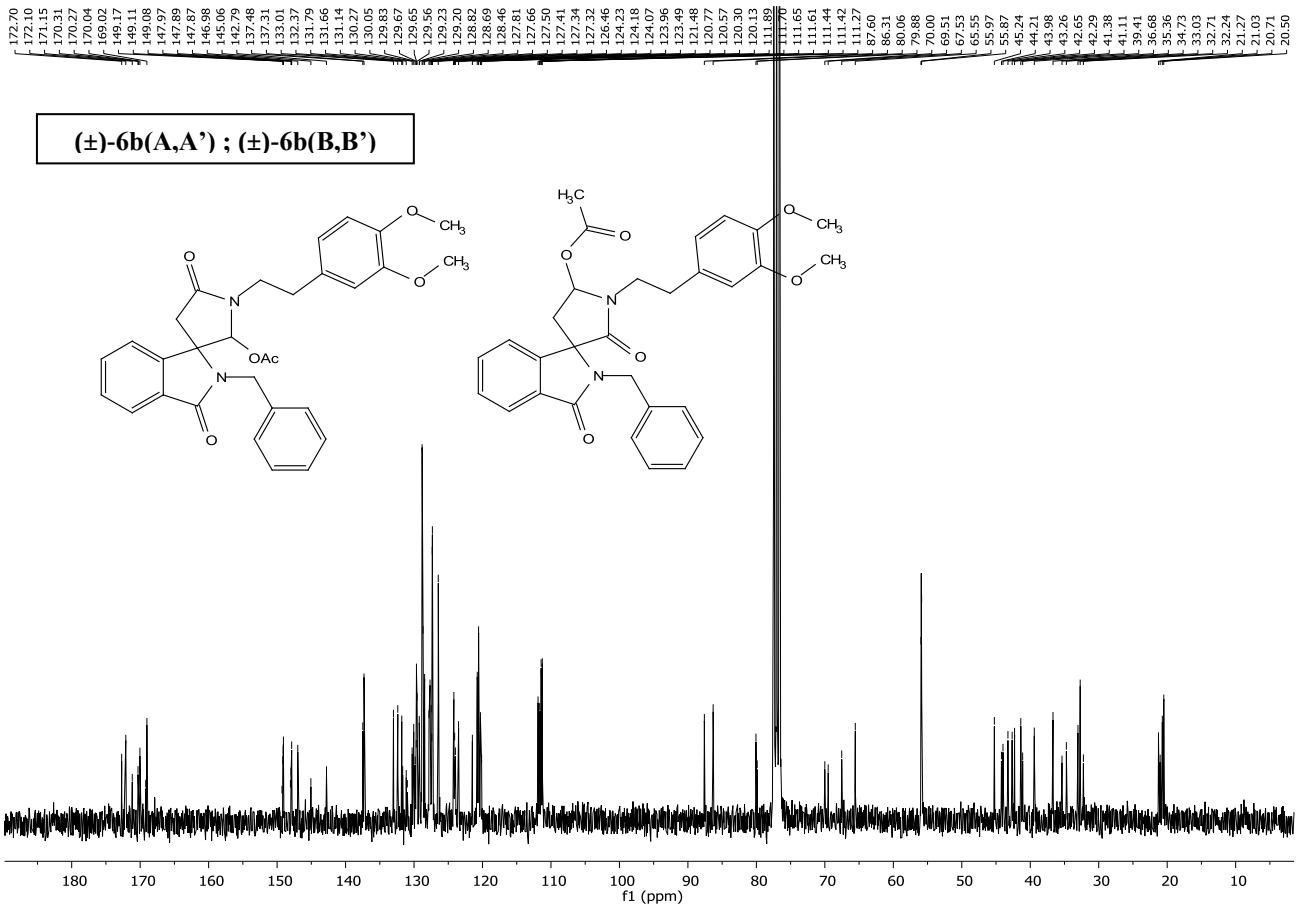


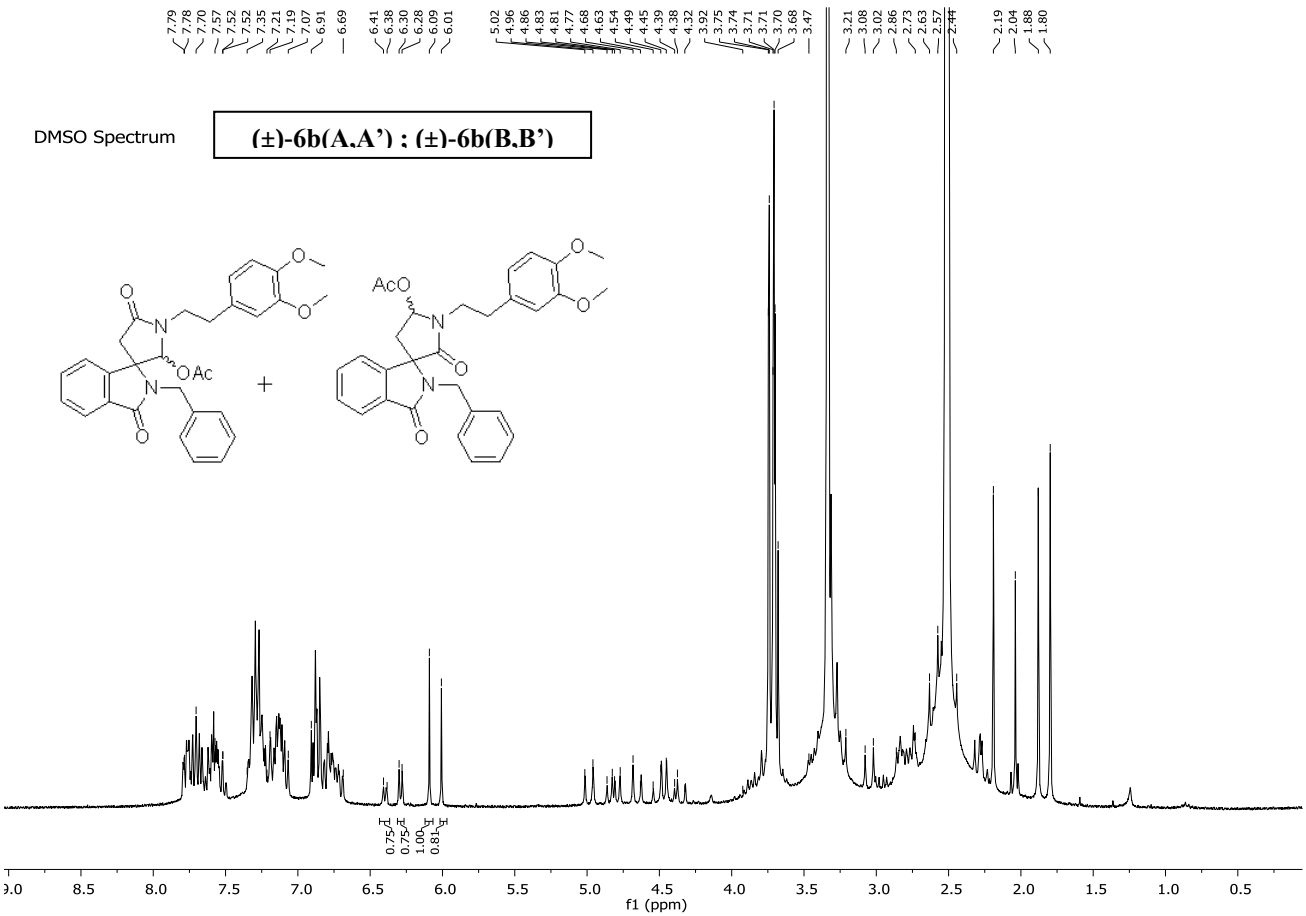
Min **(±)-6a(A')**



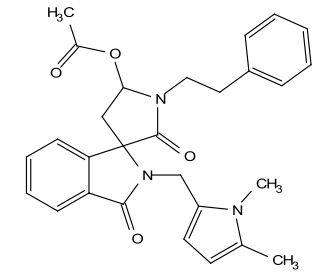

Min (±)-6a(A')
OAc
f1 (ppm)


(±)-6b(A,A') ; (±)-6b(B,B')
OAc
f1 (ppm)

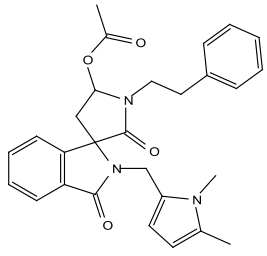

(±)-6b(A,A') ; (±)-6b(B,B')
f1 (ppm)

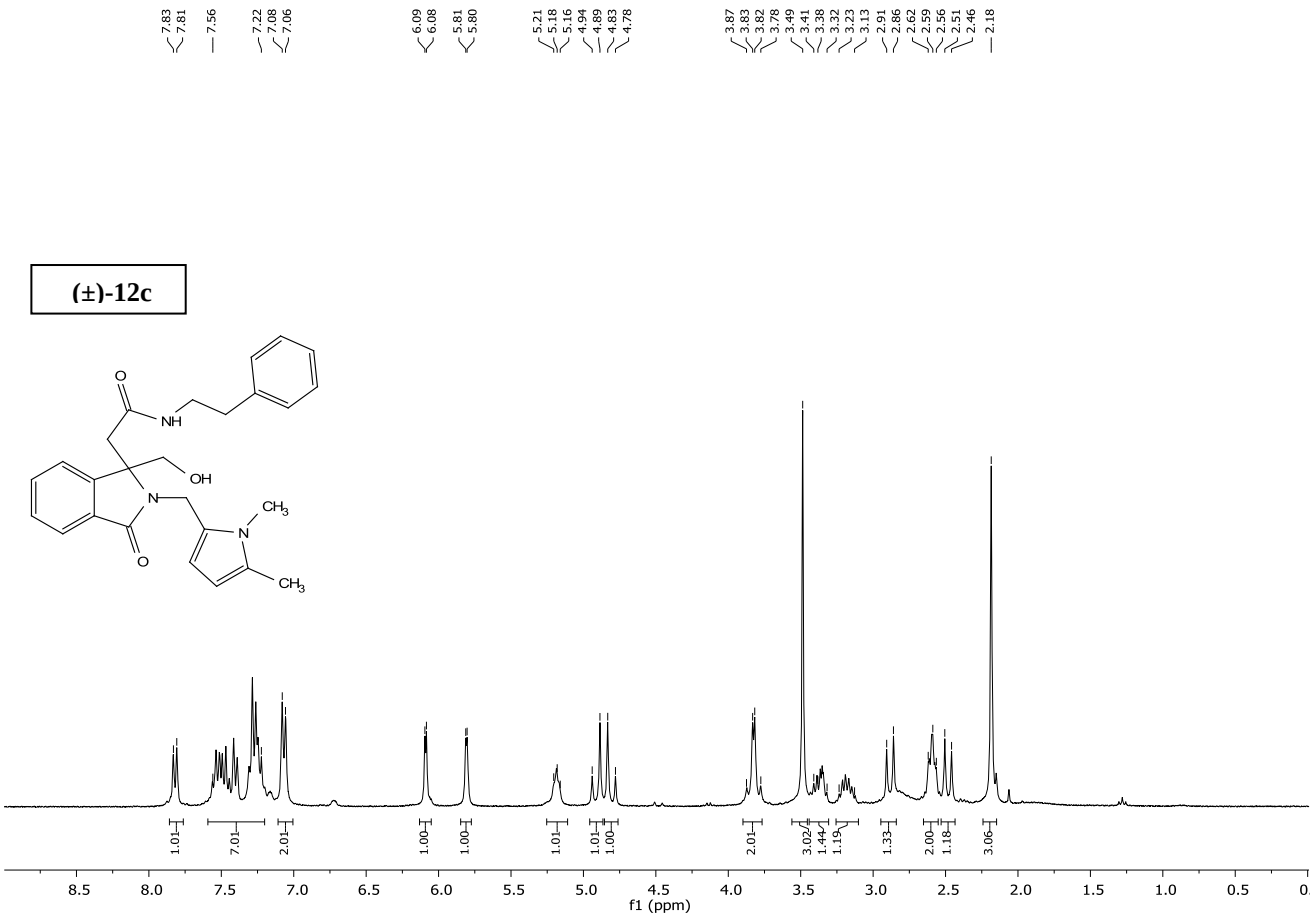

DMSO Spectrum
(±)-6b(A,A') : (±)-6b(B,B')
f1 (ppm)

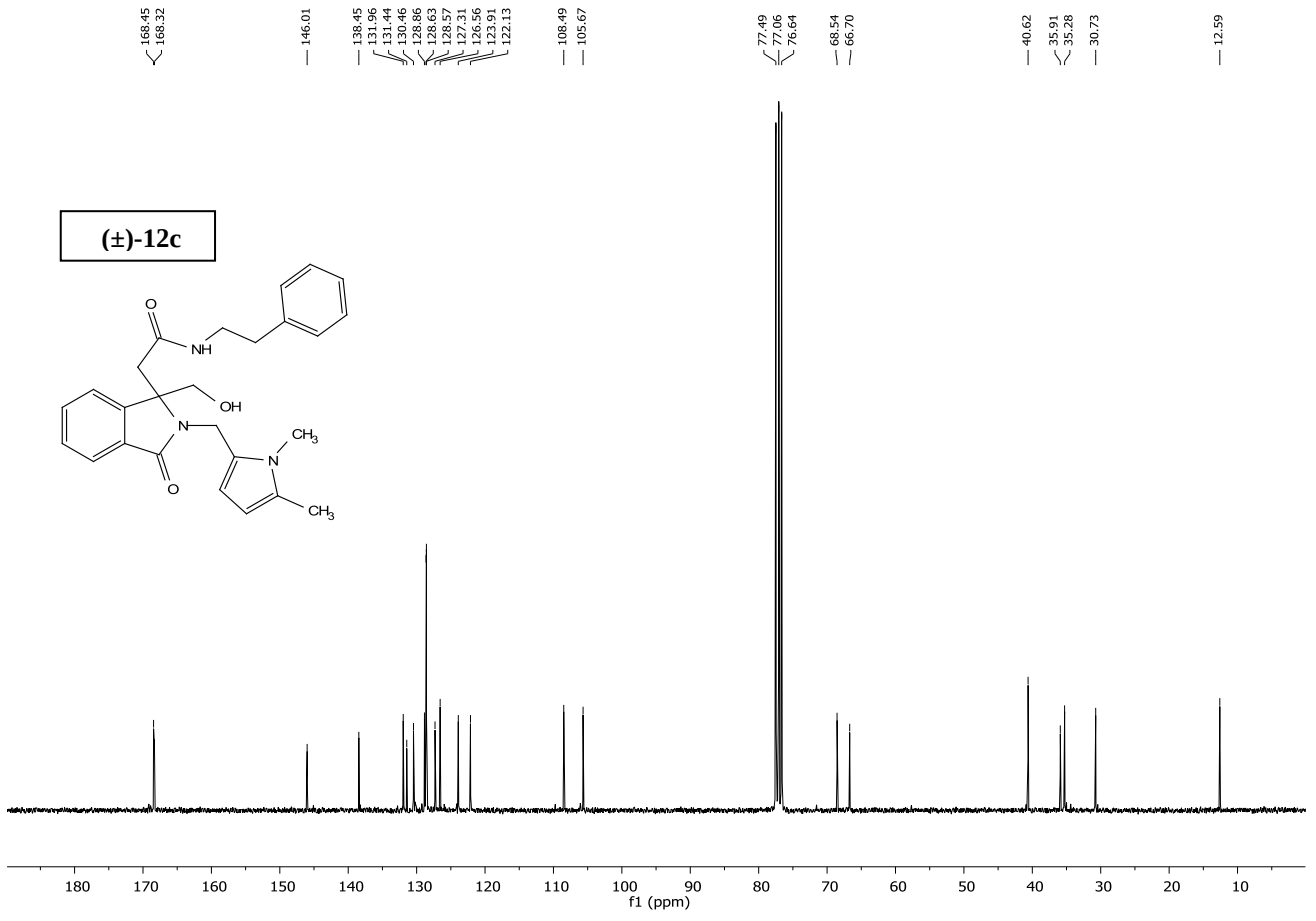
(±)-6c(B,B')



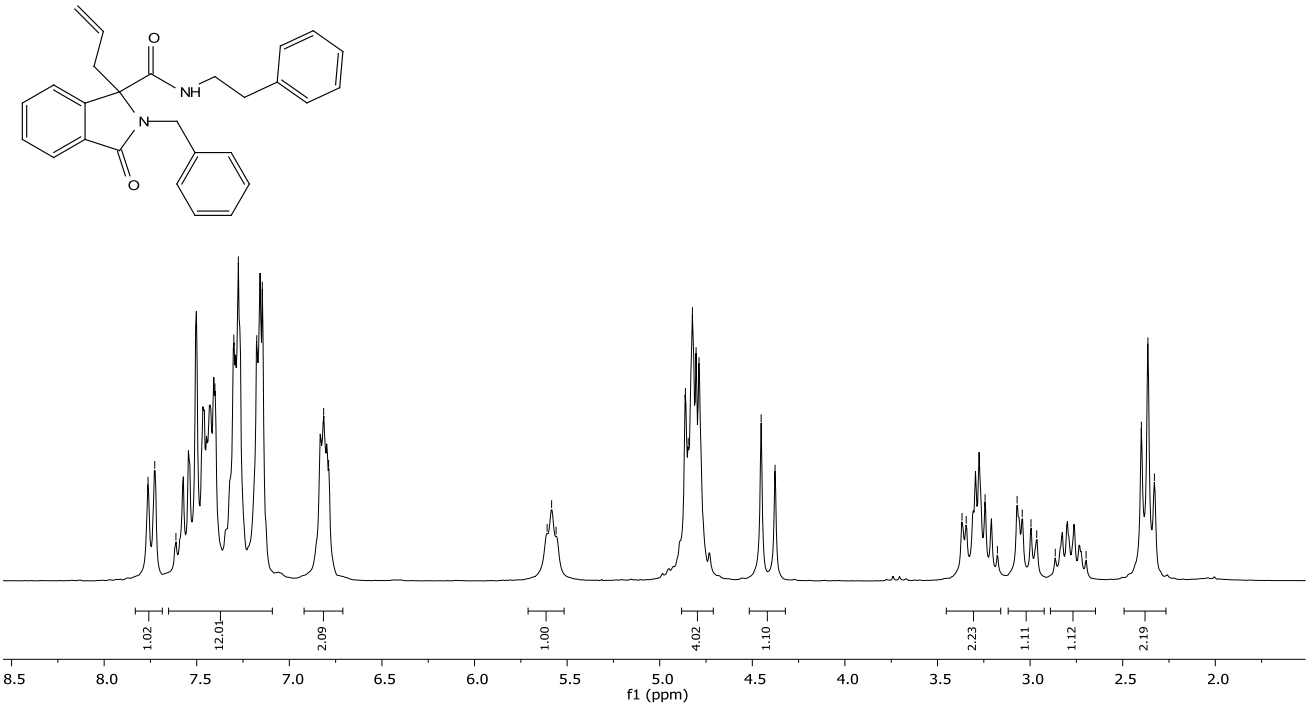
(±)-6c(B,B')

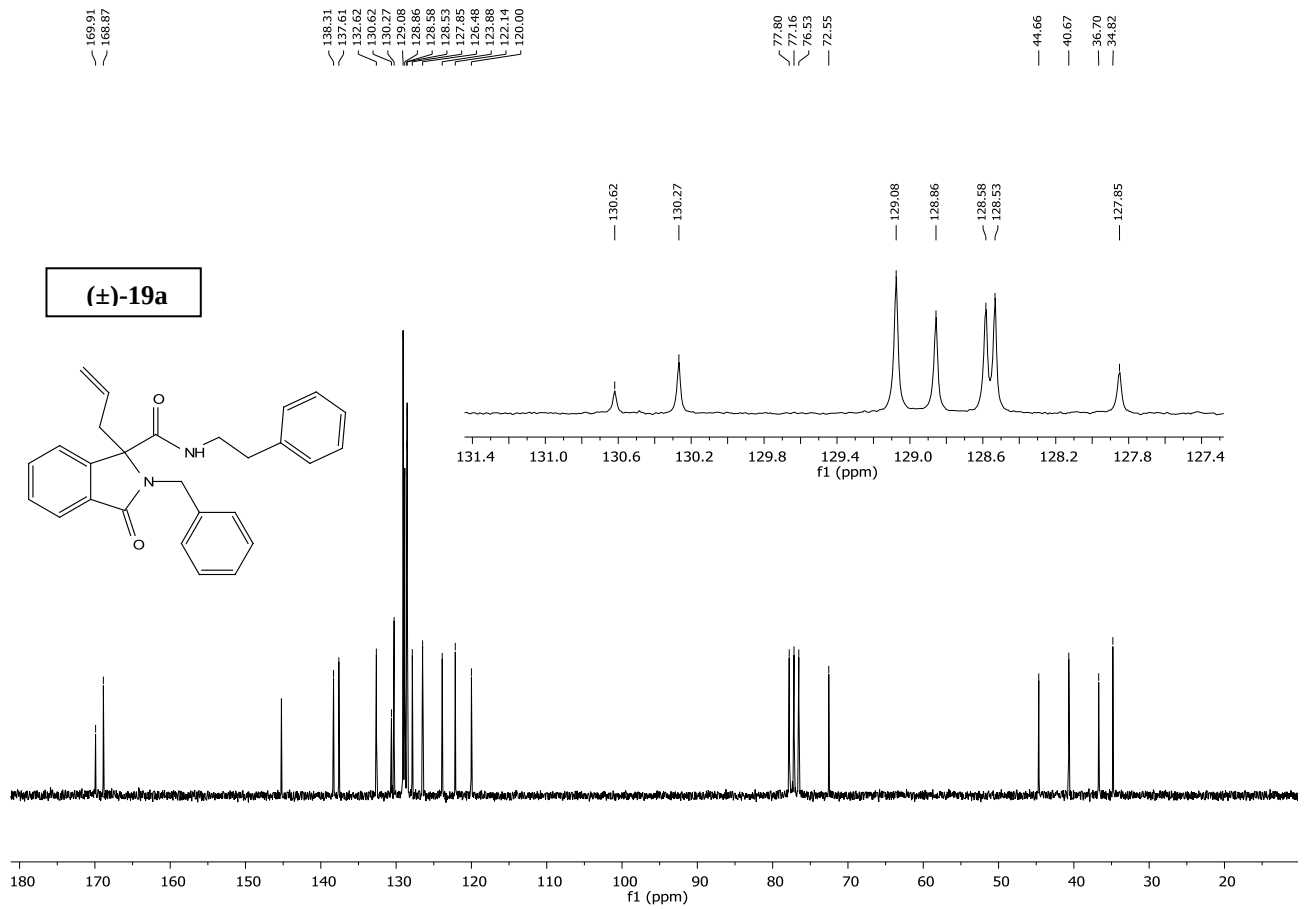



7.83
7.81
7.56
7.22
7.08
7.06
6.09
6.08
5.81
5.80
5.21
5.18
5.16
4.94
4.89
4.83
4.78
3.87
3.83
3.82
3.78
3.49
3.41
3.38
3.32
3.23
3.13
2.91
2.86
2.62
2.59
2.56
2.51
2.46
2.18
(±)-12c
O
NH
OH
N
CH3
N
O
CH3
1.01
7.01
2.01
1.00
1.00
1.01
1.01
1.00
2.01
3.02
1.44
1.19
1.33
2.00
1.18
3.06
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

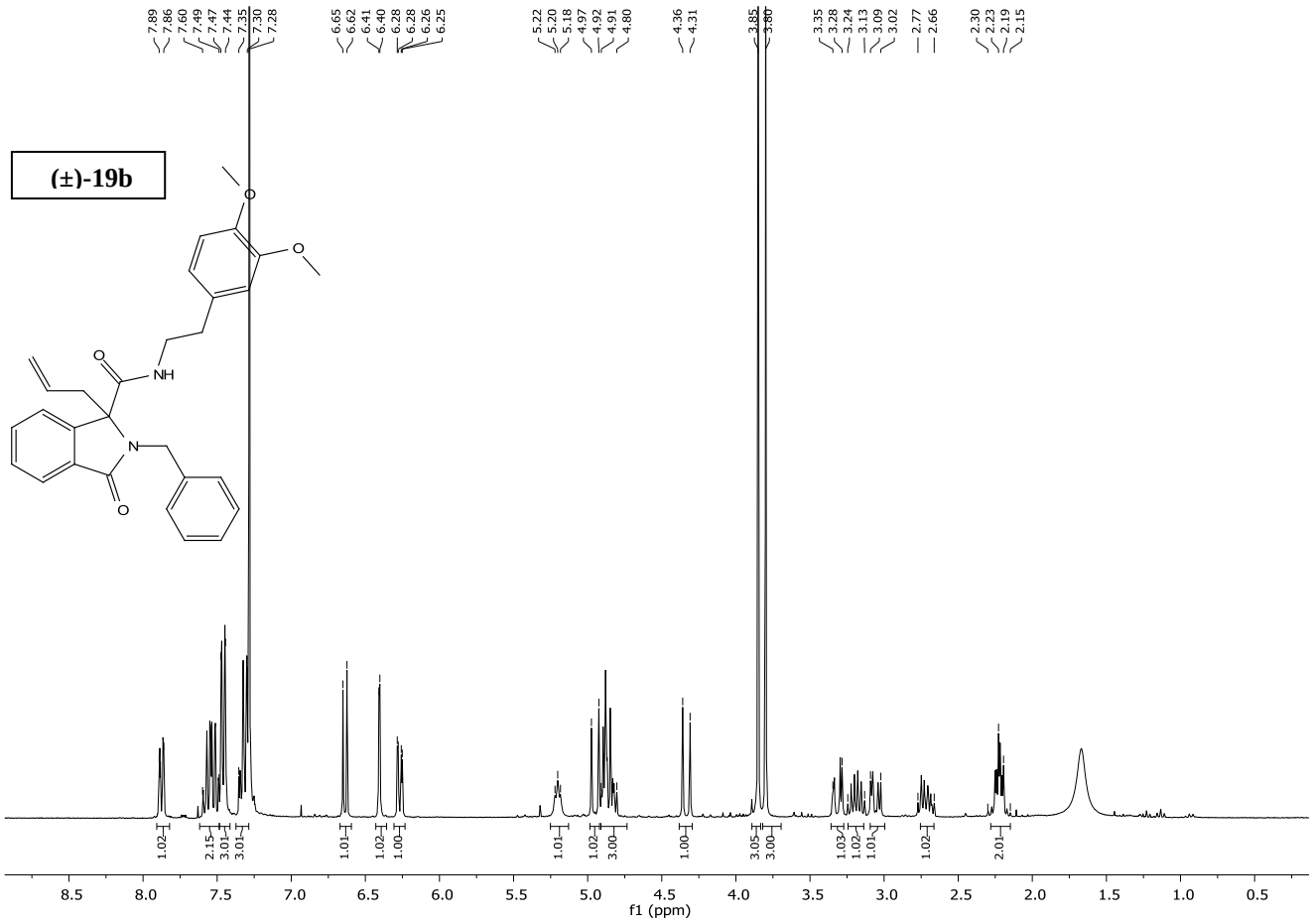

168.45
168.32
146.01
138.45
131.96
131.44
130.46
128.86
128.63
128.57
127.31
126.56
123.91
122.13
108.49
105.67
77.49
77.06
76.64
68.54
66.70
40.62
35.91
35.28
30.73
12.59
(±)-12c
O
NH
OH
N
CH3
N
O
CH3
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

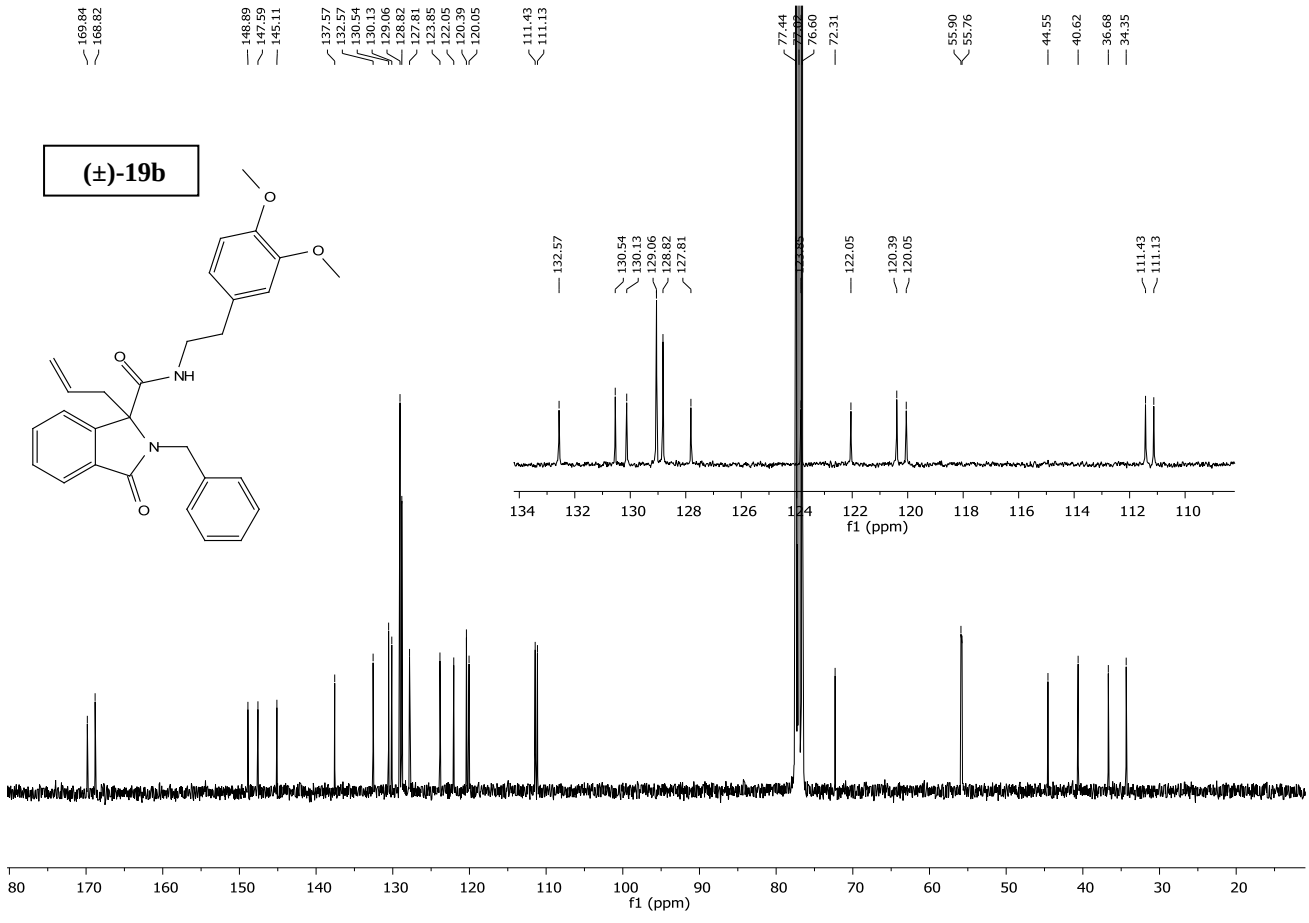
(±)-19a

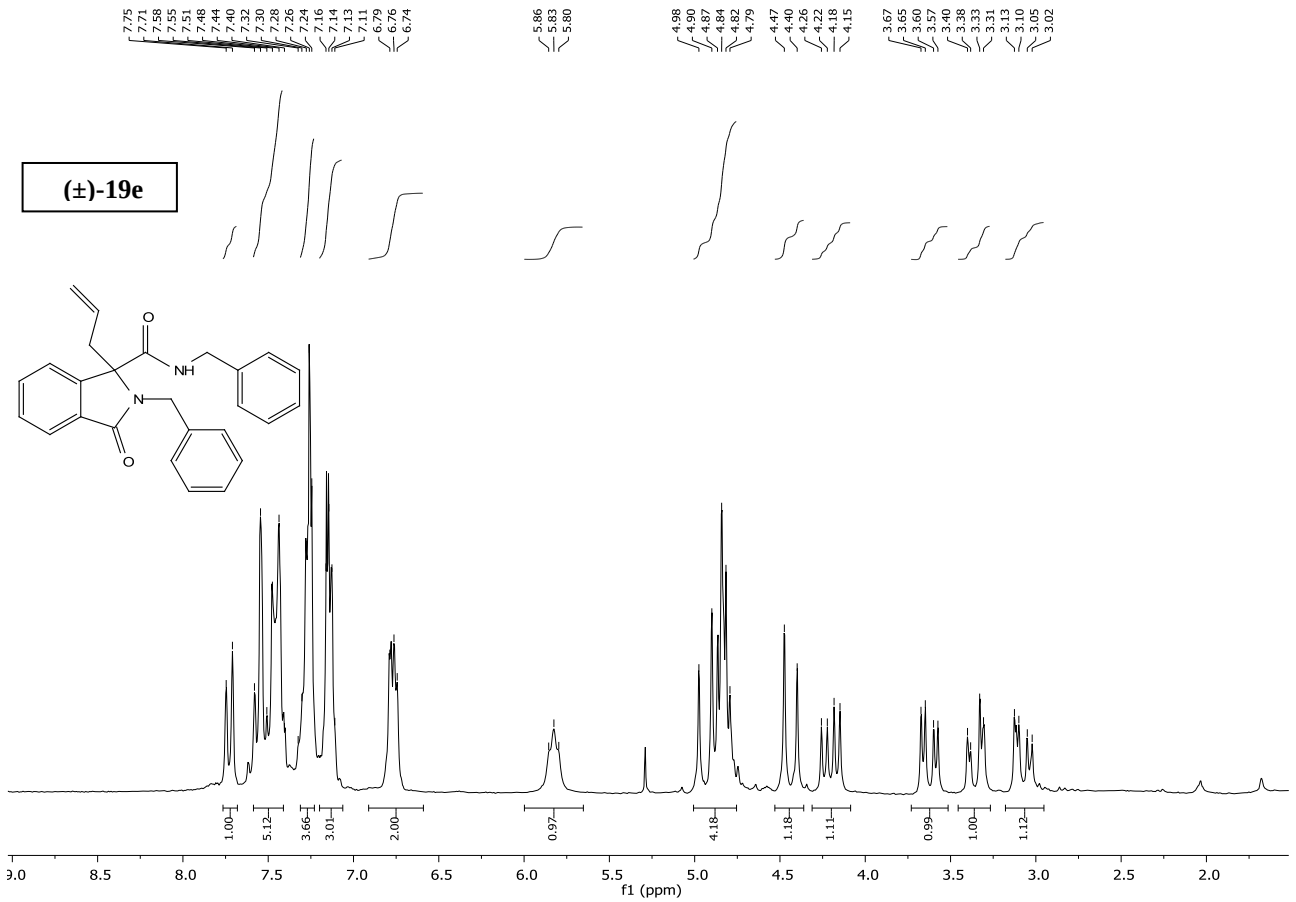

7.76
7.73
7.61
7.40
7.30
7.28
7.18
7.15
6.81
6.79
5.61
5.58
5.56
4.86
4.85
4.82
4.80
4.79
4.45
4.38
3.37
3.35
3.24
3.18
3.07
3.04
3.00
2.96
2.86
2.70
2.40
2.36
2.33
O
NH
N
O
1.02
12.01
2.09
1.00
4.02
1.10
2.23
1.11
1.12
2.19
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f1 (ppm)

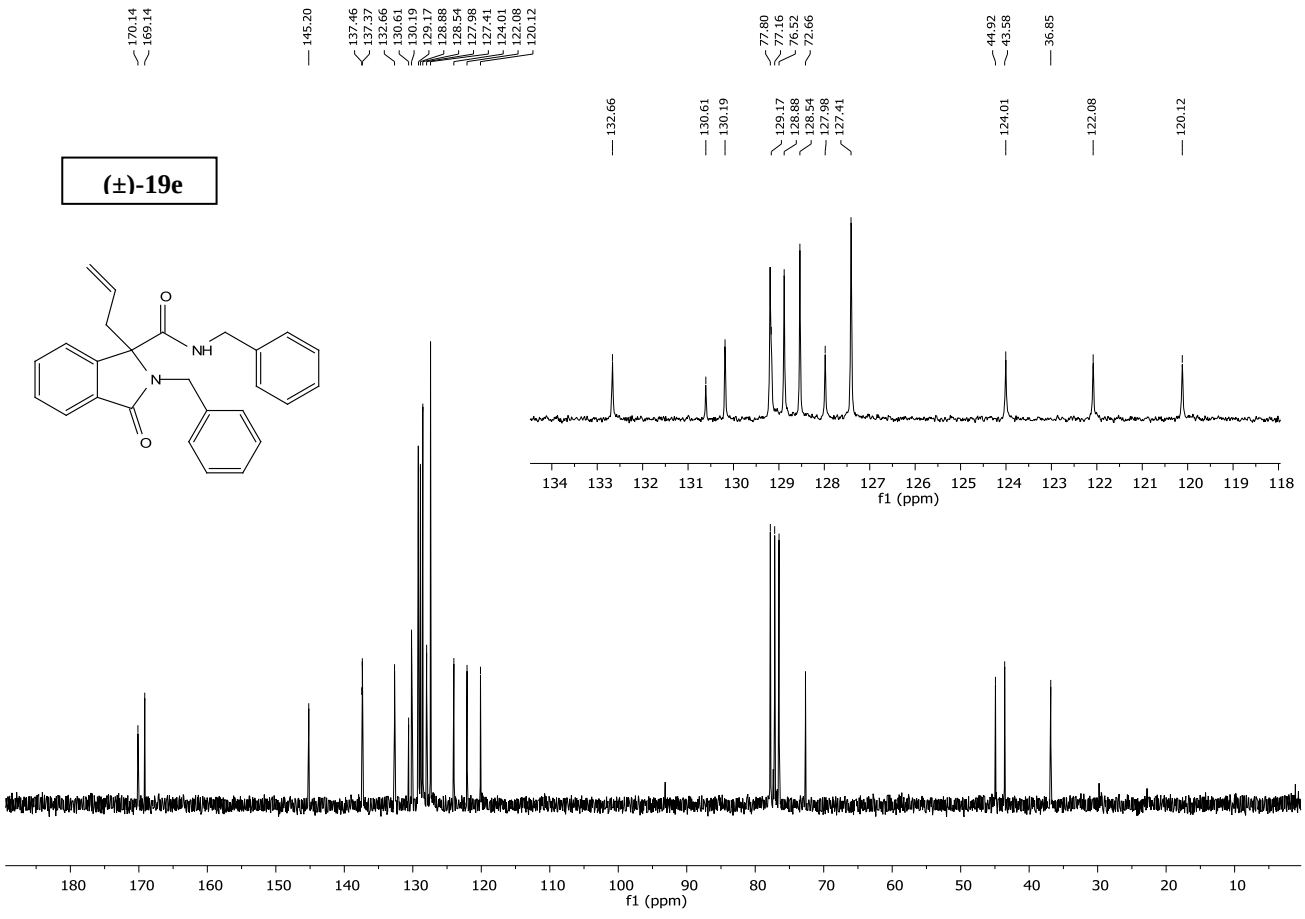

169.91
168.87
138.31
137.61
132.62
130.62
130.27
129.08
128.86
128.58
128.53
127.85
126.48
123.98
122.14
120.00
77.80
77.16
76.53
72.55
44.66
40.67
36.70
34.82
130.62
130.27
129.08
128.86
128.58
128.53
127.85
131.4
131.0
130.6
130.2
129.8
129.4
129.0
128.6
128.2
127.8
127.4
f1 (ppm)
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
f1 (ppm)

(±)-19a

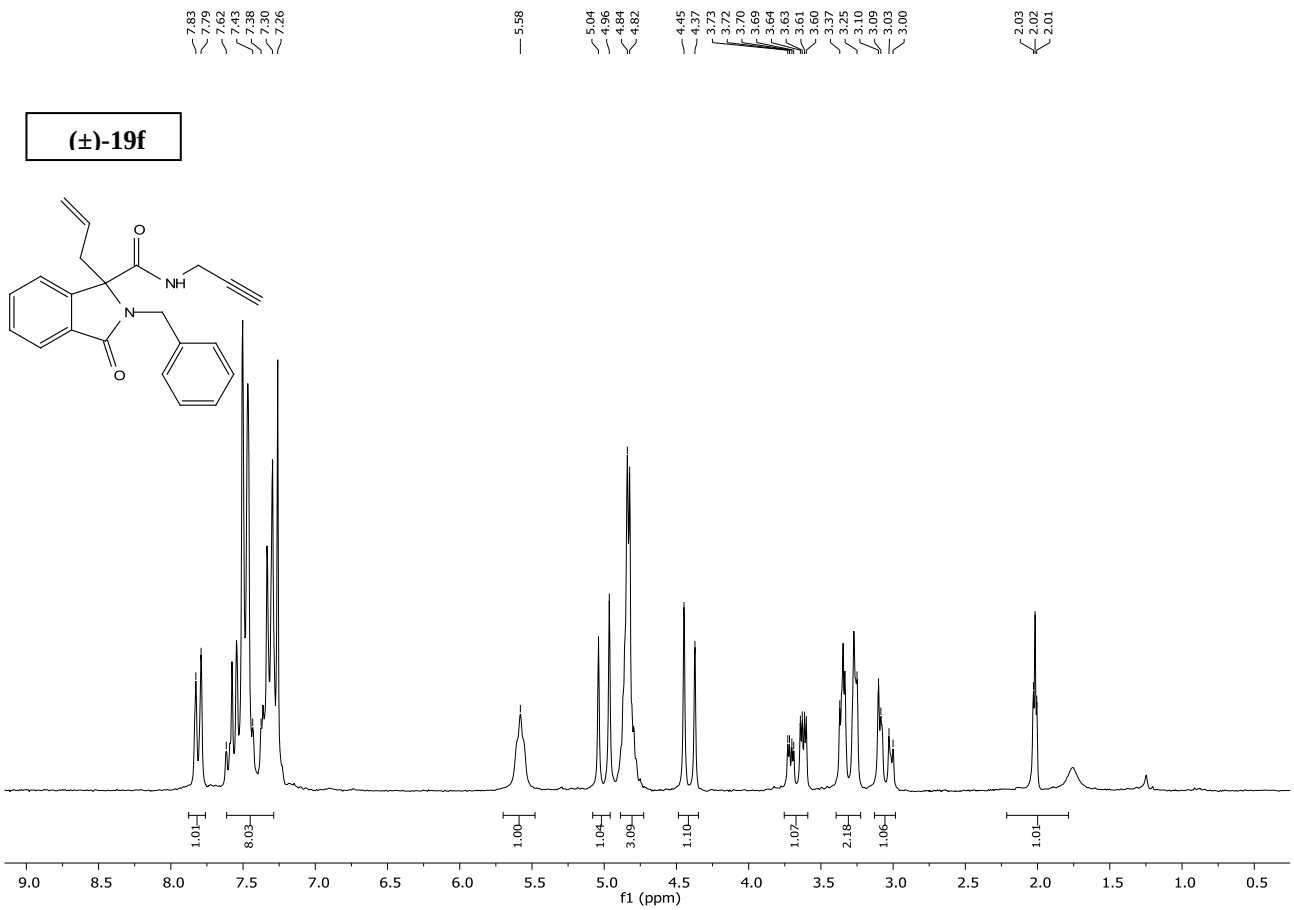

(±)-19b
7.89
7.86
7.60
7.49
7.47
7.44
7.35
7.30
7.28
6.65
6.62
6.41
6.40
6.28
6.28
6.26
6.25
5.22
5.20
5.18
4.97
4.92
4.91
4.80
4.36
4.31
3.85
3.80
3.35
3.28
3.24
3.13
3.09
3.02
2.77
2.66
2.30
2.23
2.19
2.15
1.02
2.15
3.01
3.01
1.01
1.02
1.00
1.01
1.02
3.00
1.00
3.05
3.00
1.03
1.02
1.01
1.02
2.01
f1 (ppm)


(±)-19b
169.84
168.82
148.89
147.59
145.11
137.57
132.57
130.54
130.13
129.06
128.82
127.81
123.85
122.05
120.39
120.05
111.43
111.13
77.44
77.02
76.60
72.31
55.90
55.76
44.55
40.62
36.68
34.35
f1 (ppm)

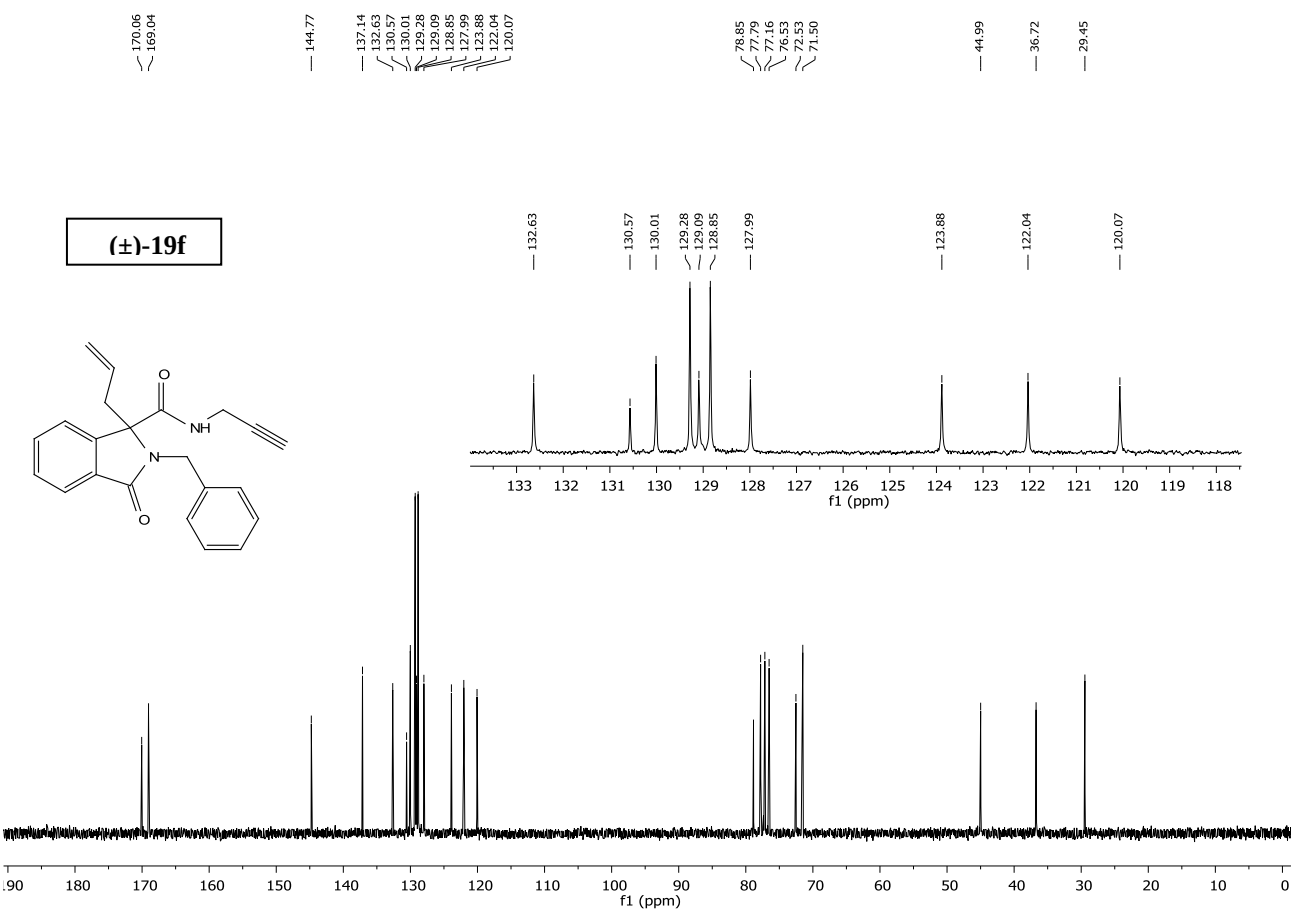

(±)-19e
7.75 7.71 7.58 7.55 7.51 7.48 7.44 7.40 7.32 7.30 7.28 7.26 7.24 7.16 7.14 7.13 7.11 6.79 6.76 6.74
5.86 5.83 5.80
4.98 4.90 4.87 4.84 4.82 4.79 4.47 4.40 4.26 4.22 4.18 4.15
3.67 3.65 3.60 3.57 3.40 3.38 3.33 3.31 3.13 3.10 3.05 3.02
O
NH
N
O
1.00 5.12 3.66 3.01 2.00 0.97 4.18 1.18 1.11 0.99 1.00 1.12
f1 (ppm)

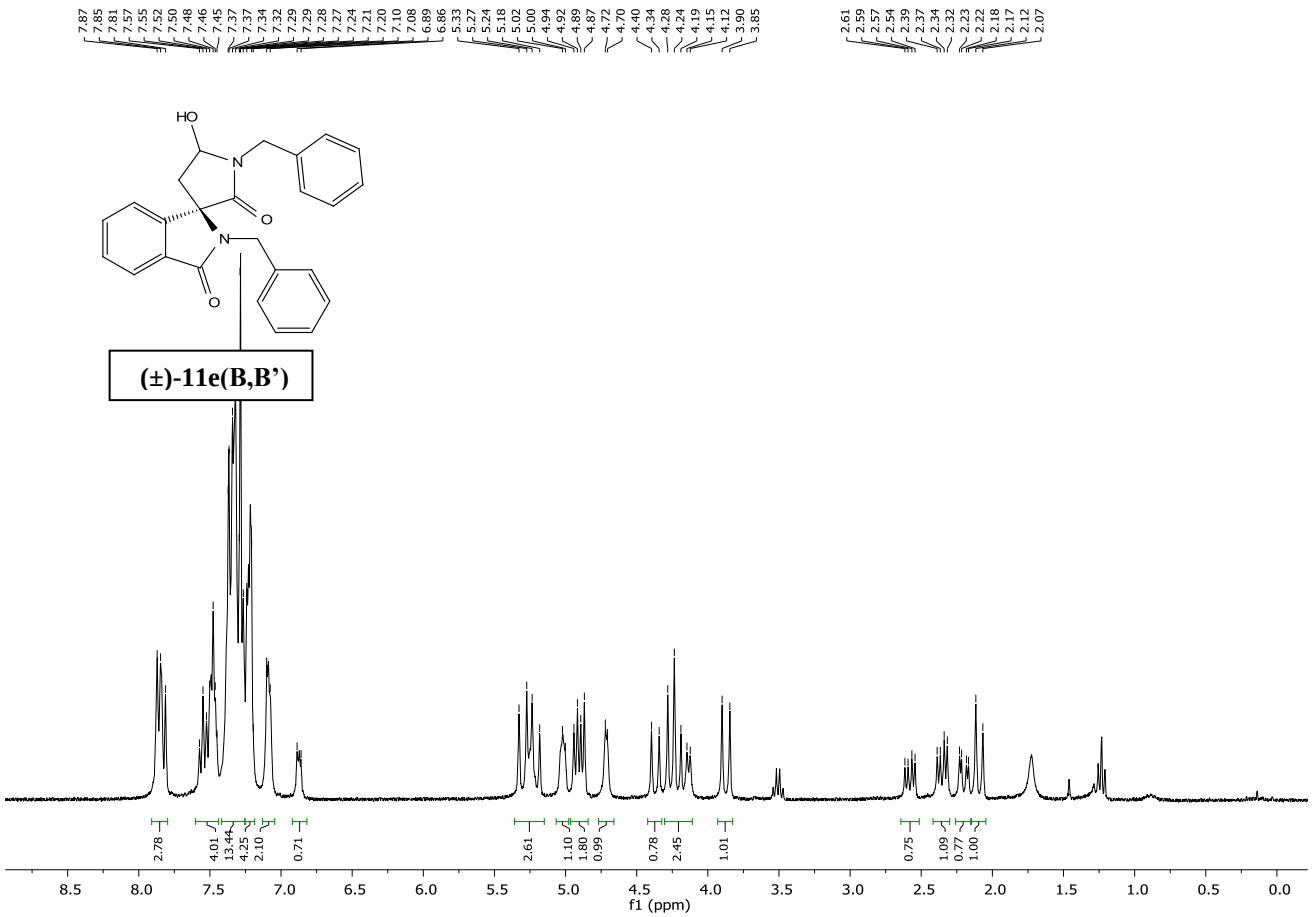

(±)-19e
170.14 169.14 145.20 137.46 137.37 132.66 130.61 130.19 129.17 128.88 128.54 127.98 127.41 124.01 122.08 120.12
77.80 77.16 76.52 72.66
44.92 43.58 36.85
O
NH
N
O
f1 (ppm)

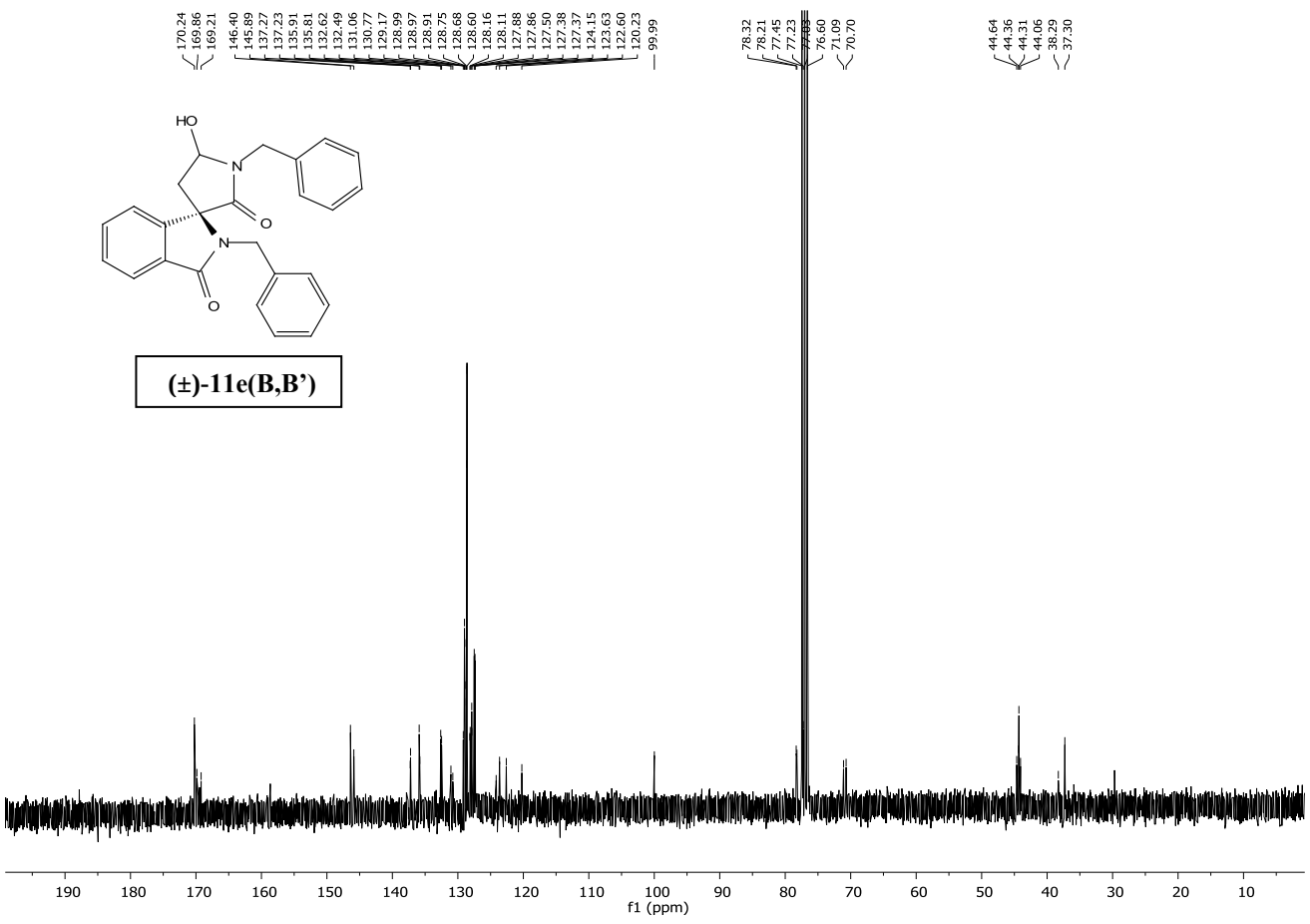
(±)-19f

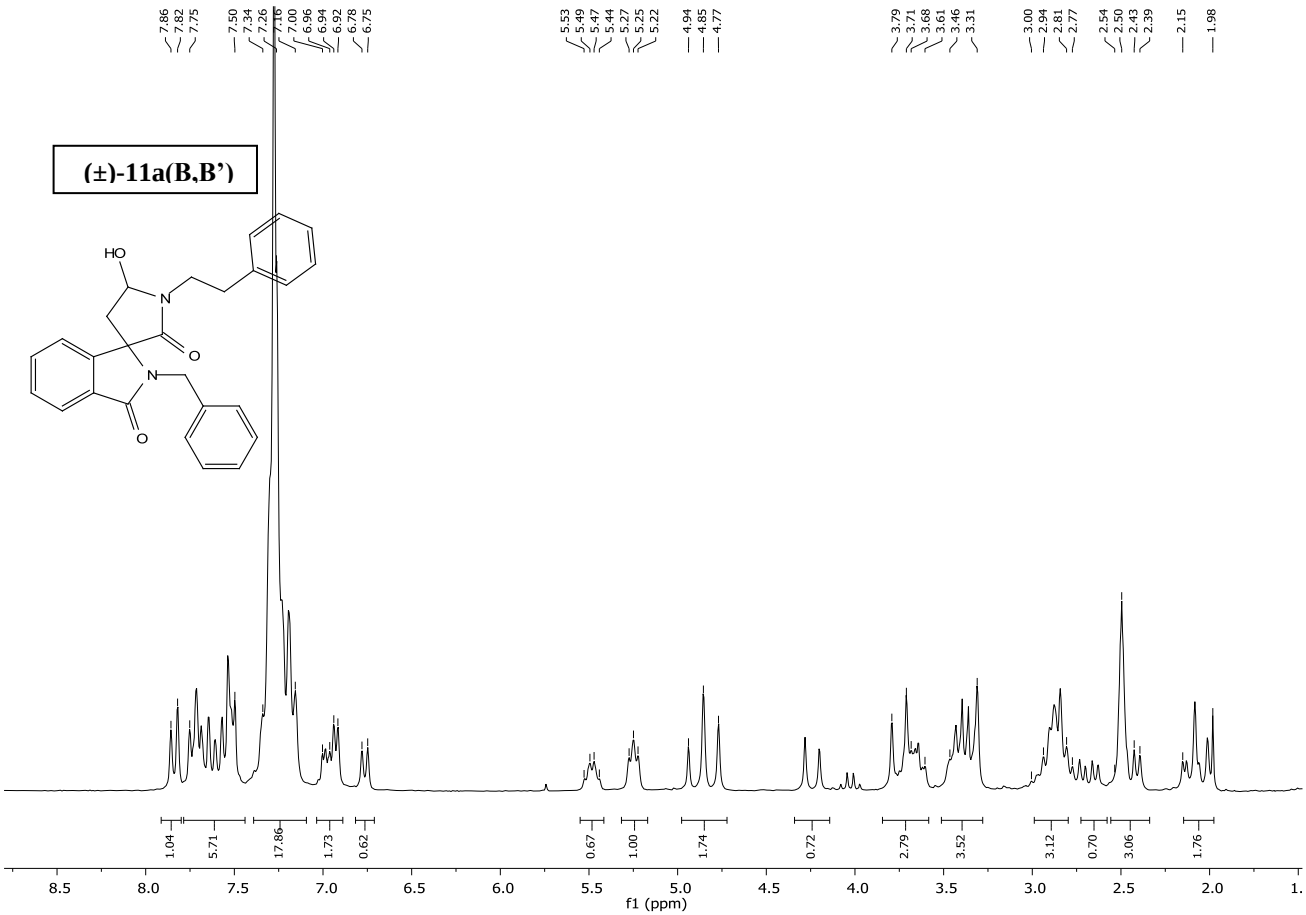

7.83
7.79
7.62
7.43
7.38
7.30
7.26
5.58
5.04
4.96
4.84
4.82
4.45
4.37
3.73
3.72
3.70
3.69
3.64
3.63
3.61
3.60
3.37
3.25
3.10
3.09
3.03
3.00
2.03
2.02
2.01
O
NH
N
O
1.01
8.03
1.00
1.04
3.09
1.10
1.07
2.18
1.06
1.01
f1 (ppm)

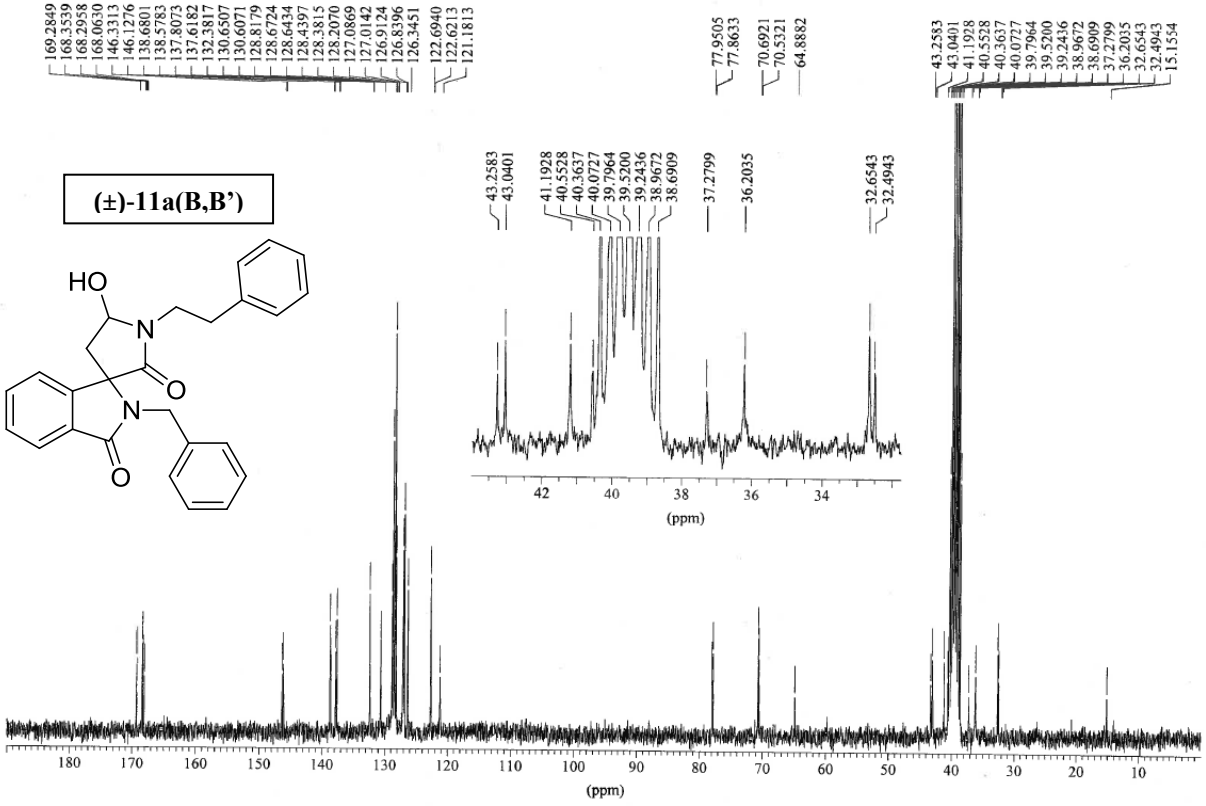
(±)-19f


170.06
169.04
144.77
137.14
132.63
130.57
130.01
129.28
129.09
128.85
127.99
123.88
122.04
120.07
78.85
77.79
77.16
76.53
72.53
71.50
44.99
36.72
29.45
O
NH
N
O
f1 (ppm)
f1 (ppm)


HO
N
O
N
O
(±)-11e(B,B')
f1 (ppm)


HO
N
O
N
O
(±)-11e(B,B')
f1 (ppm)


(±)-11a(B,B')
HO
N
O
N
O
7.86
7.82
7.75
7.50
7.34
7.26
7.16
7.00
6.96
6.94
6.92
6.78
6.75
5.53
5.49
5.47
5.44
5.27
5.25
5.22
4.94
4.85
4.77
3.79
3.71
3.68
3.61
3.46
3.31
3.00
2.94
2.81
2.77
2.54
2.50
2.43
2.39
2.15
1.98
1.04
5.71
17.86
1.73
0.62
0.67
1.00
1.74
0.72
2.79
3.52
3.12
0.70
3.06
1.76
f1 (ppm)


(±)-11a(B,B')
HO
N
O
N
O
169.2849
168.3539
168.2958
168.0630
146.3313
146.1276
138.6801
138.5783
137.8073
137.6182
132.3817
130.6507
130.6071
128.8179
128.6724
128.6434
128.4397
128.3815
128.2070
127.0869
127.0142
126.9124
126.8396
126.3451
122.6940
122.6213
121.1813
77.9505
77.8633
70.6921
70.5321
64.8882
43.2583
43.0401
41.1928
40.5528
40.3637
40.0727
39.7964
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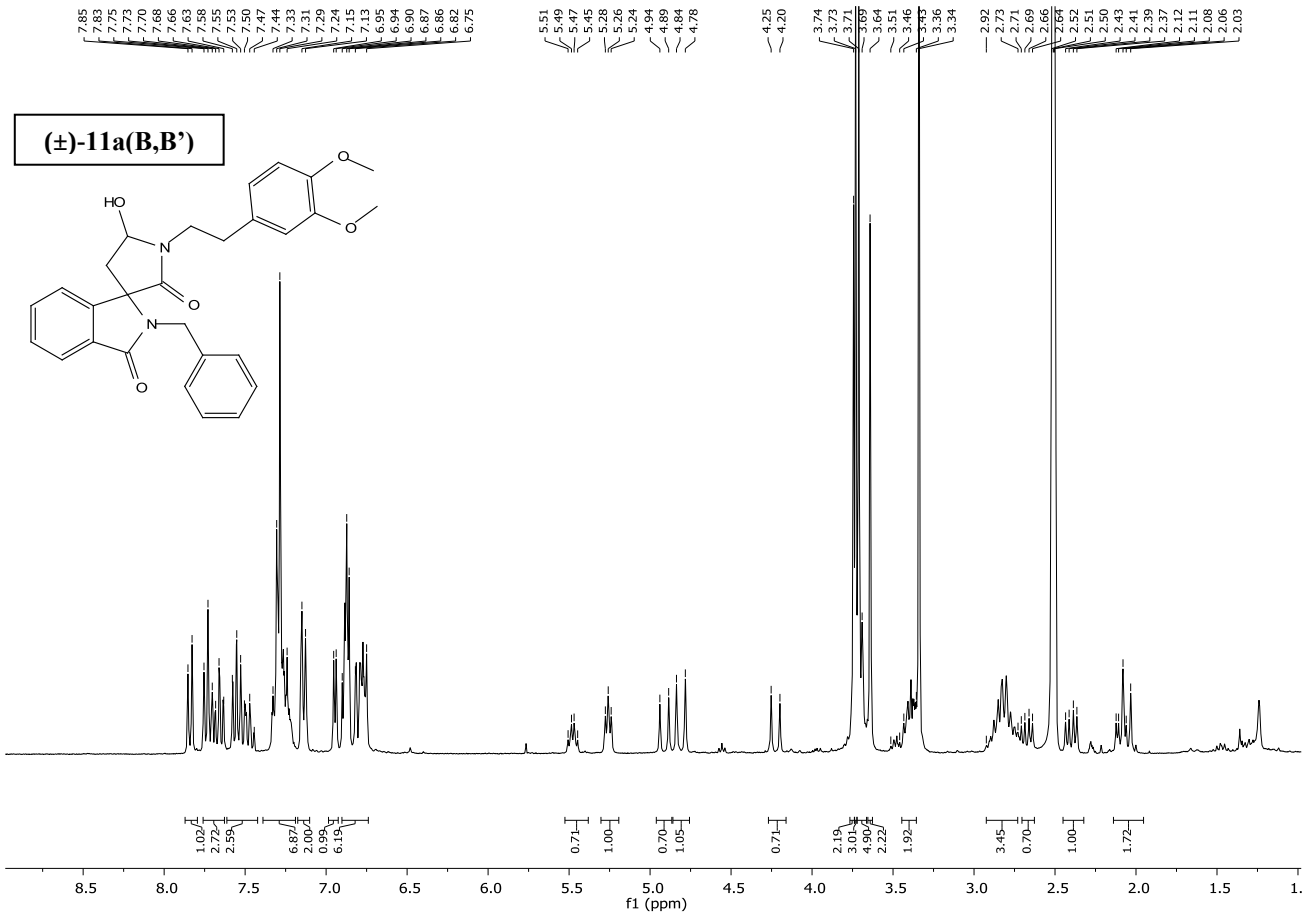
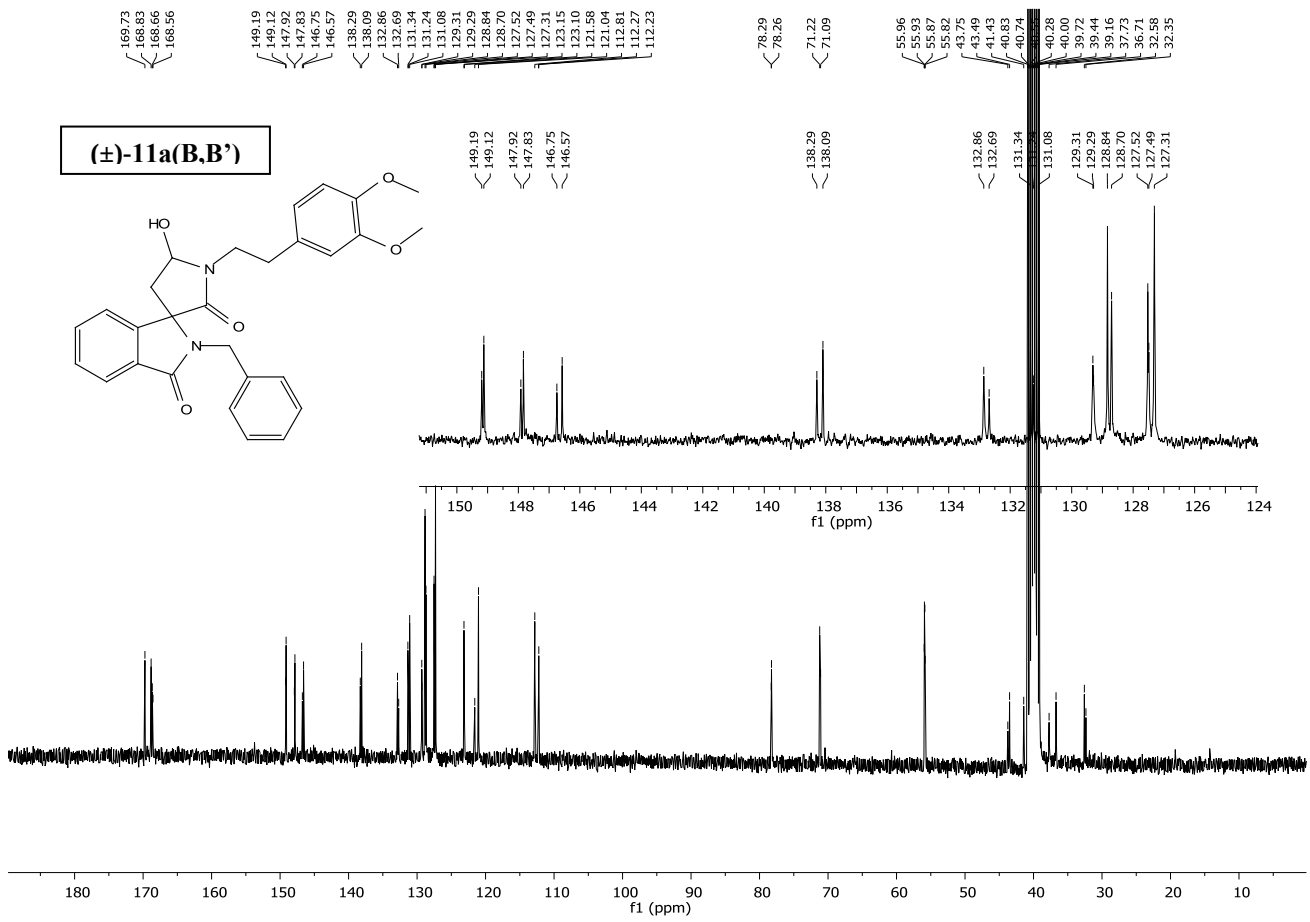
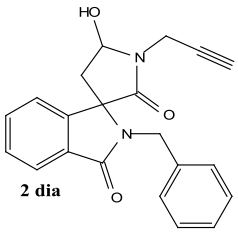
36.2035
32.6543
32.4943
15.1534
(ppm)

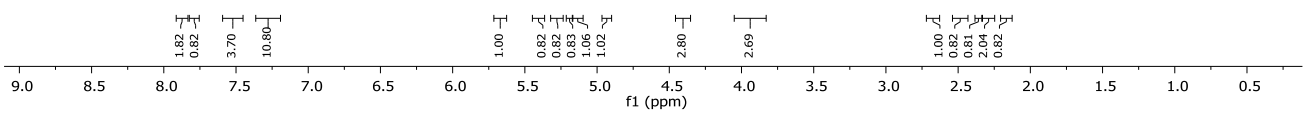

(±)-11a(B,B')
HO
O
N
O
N
O
O
f1 (ppm)


(±)-11a(B,B')
HO
O
N
O
N
O
O
f1 (ppm)
f1 (ppm)

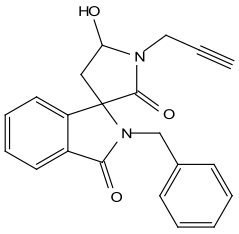
(±)-11f(B,B')

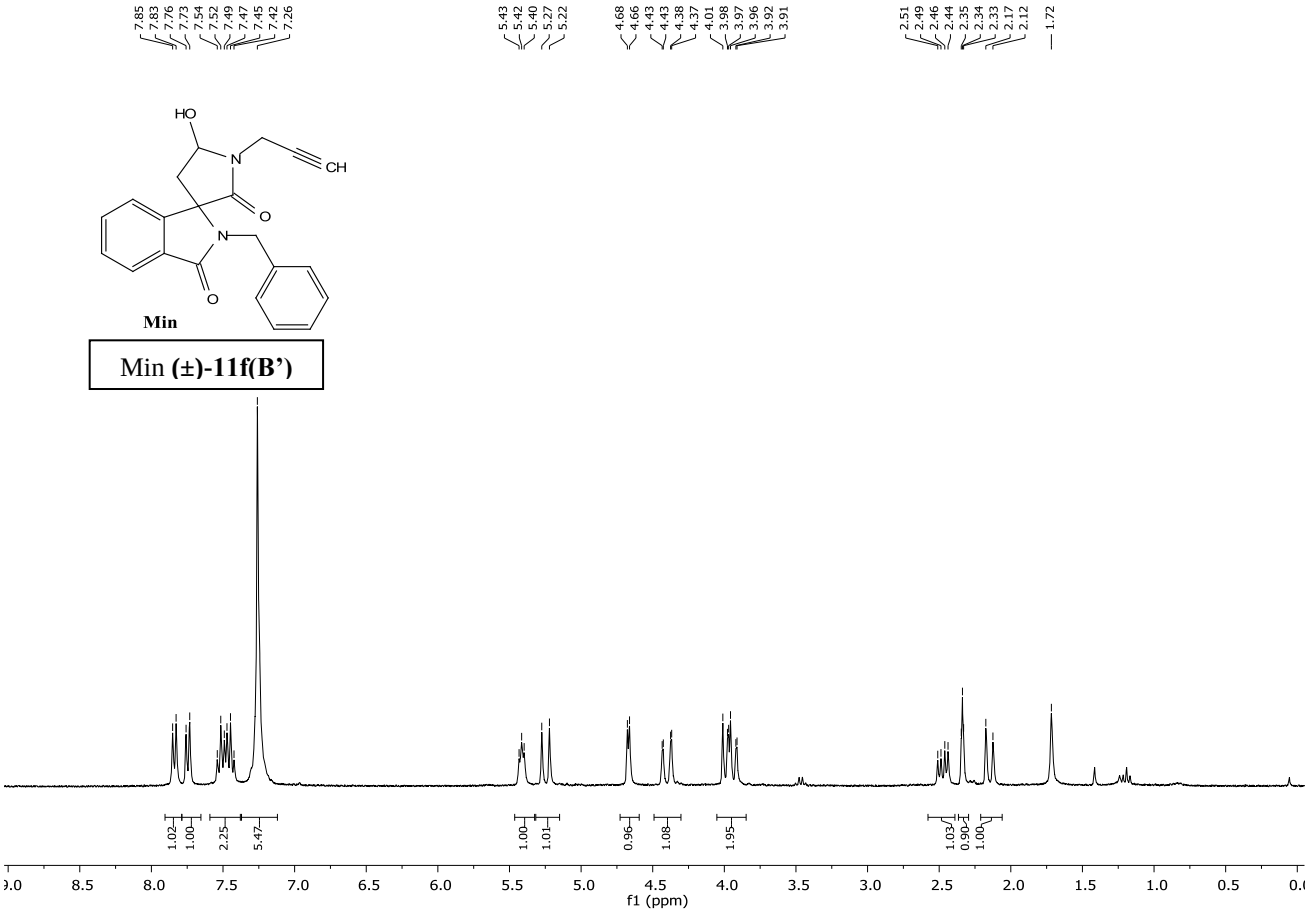


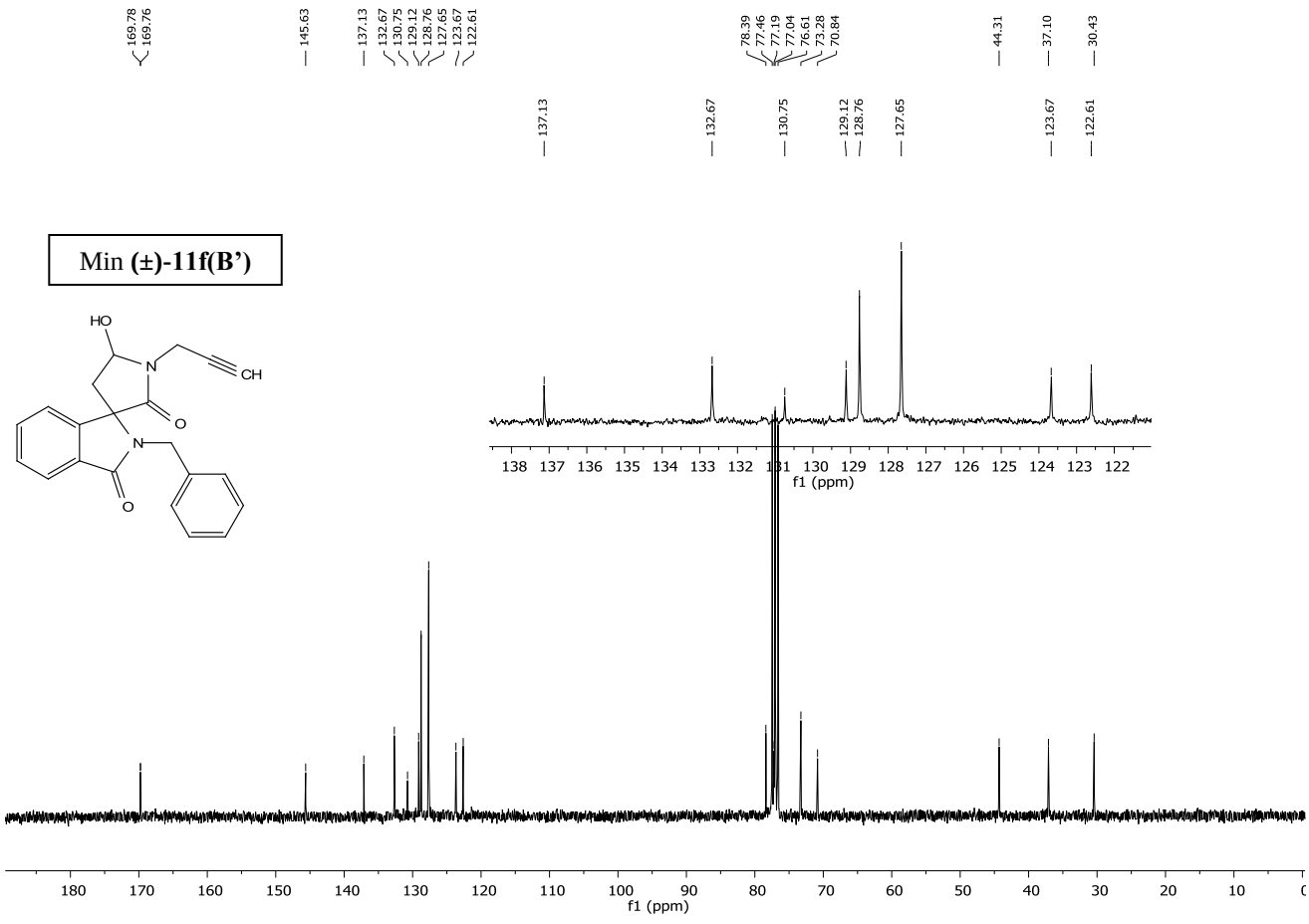
2 dia



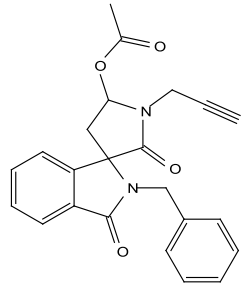
(±)-11f(B,B')




7.85
7.83
7.76
7.73
7.54
7.52
7.49
7.47
7.45
7.42
7.26
5.43
5.42
5.40
5.27
5.22
4.68
4.66
4.43
4.43
4.38
4.37
4.01
3.98
3.97
3.96
3.92
3.91
2.51
2.49
2.46
2.44
2.35
2.34
2.33
2.17
2.12
1.72
HO
N
CH
O
N
O
Min
Min (±)-11f(B')
1.02
1.00
2.25
5.47
1.00
1.01
0.96
1.08
1.95
1.03
0.90
1.00
f1 (ppm)

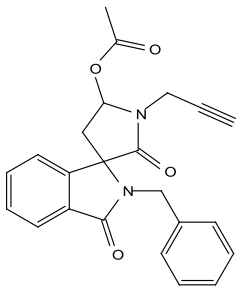

169.78
169.76
145.63
137.13
132.67
130.75
129.12
128.76
127.65
123.67
122.61
78.39
77.46
77.19
77.04
76.61
73.28
70.84
44.31
37.10
30.43
Min (±)-11f(B')
HO
N
CH
O
N
O
f1 (ppm)

(±)-25



7.95
7.93
7.63
7.53
7.37
7.27
6.62
6.61
6.59
6.59
6.45
6.43
5.33
5.28
5.23
5.18
4.50
4.49
4.48
4.47
4.44
4.43
4.42
4.41
4.40
4.34
4.12
4.07
4.03
4.02
3.97
3.96
3.95
3.94
3.89
3.88
2.98
2.95
2.92
2.90
2.76
2.73
2.70
2.68
2.42
2.39
2.33
2.27
2.23
2.22
2.10
1.60
3.83
9.27
1.00
0.58
0.60
1.00
0.60
0.62
0.98
1.01
0.60
2.53
2.40
3.00
f1 (ppm)

(±)-25



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169.90
169.75
169.13
169.00
145.79
145.03
137.14
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132.75
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131.04
131.02
129.48
129.38
128.86
128.53
127.85
127.80
127.64
127.49
124.19
124.13
121.46
120.42
79.82
77.56
77.13
76.71
76.62
76.45
73.26
73.14
69.62
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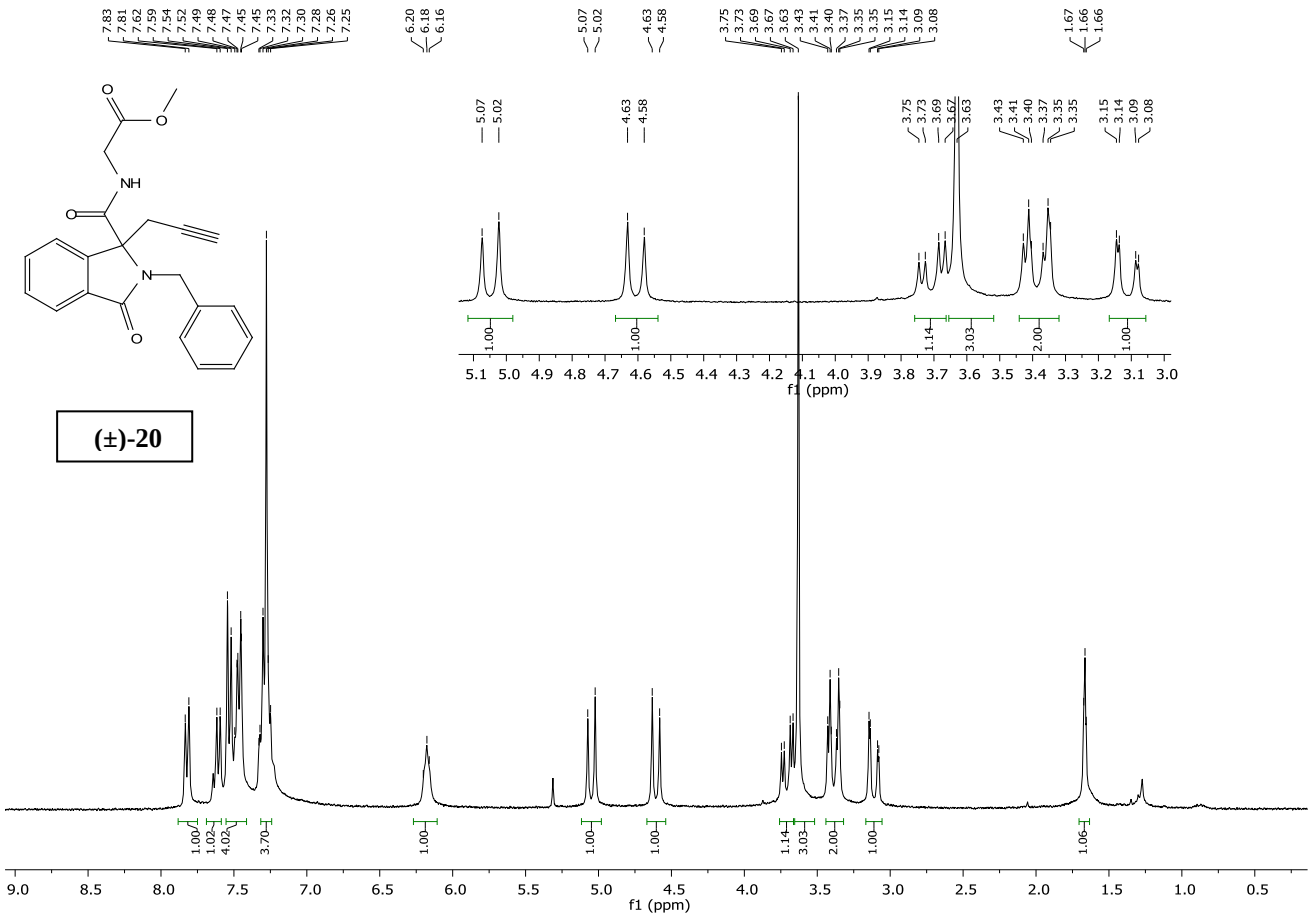
44.29
44.24
35.72
35.07
31.66
31.33
21.16
20.93
f1 (ppm)


(±)-20
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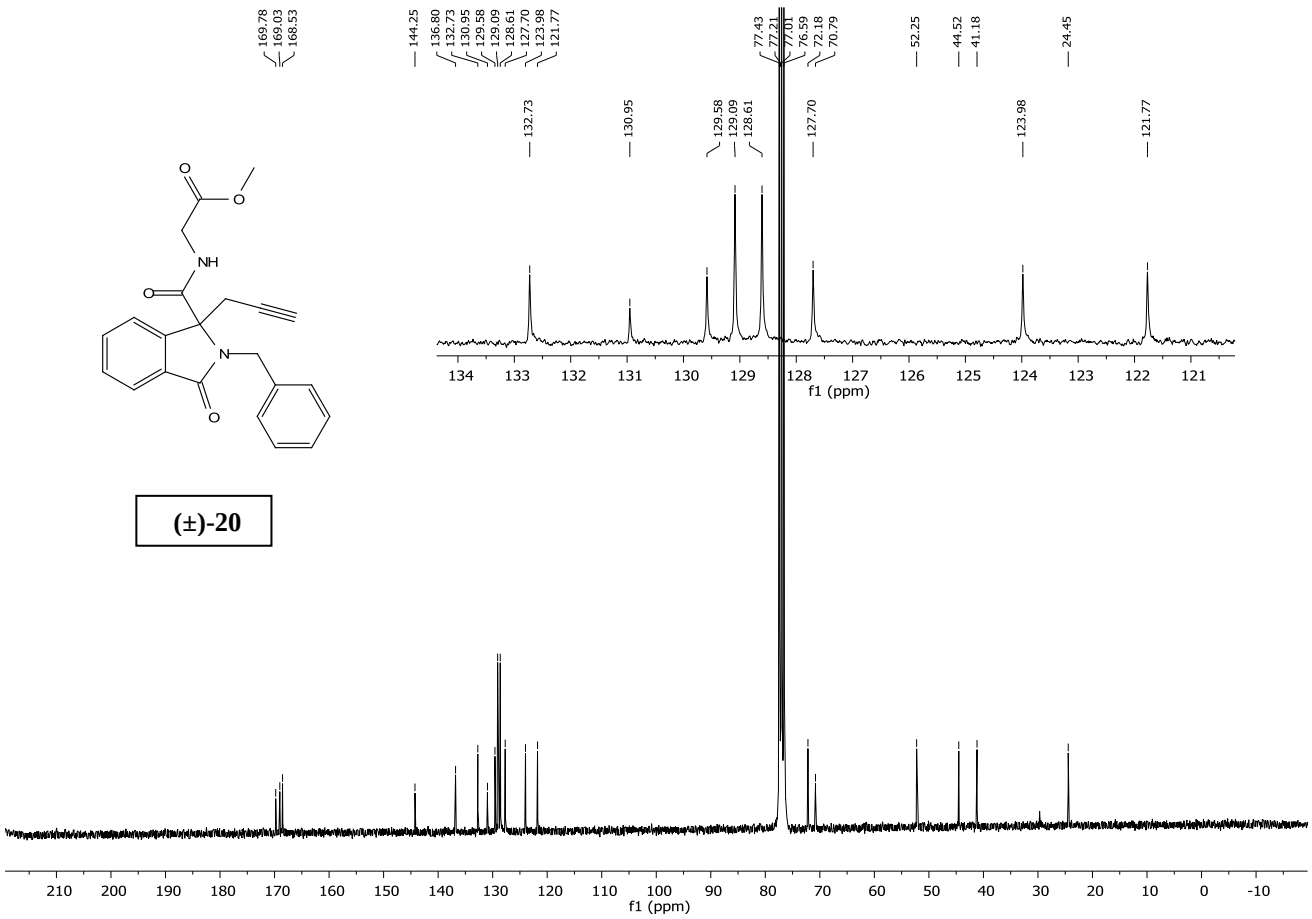
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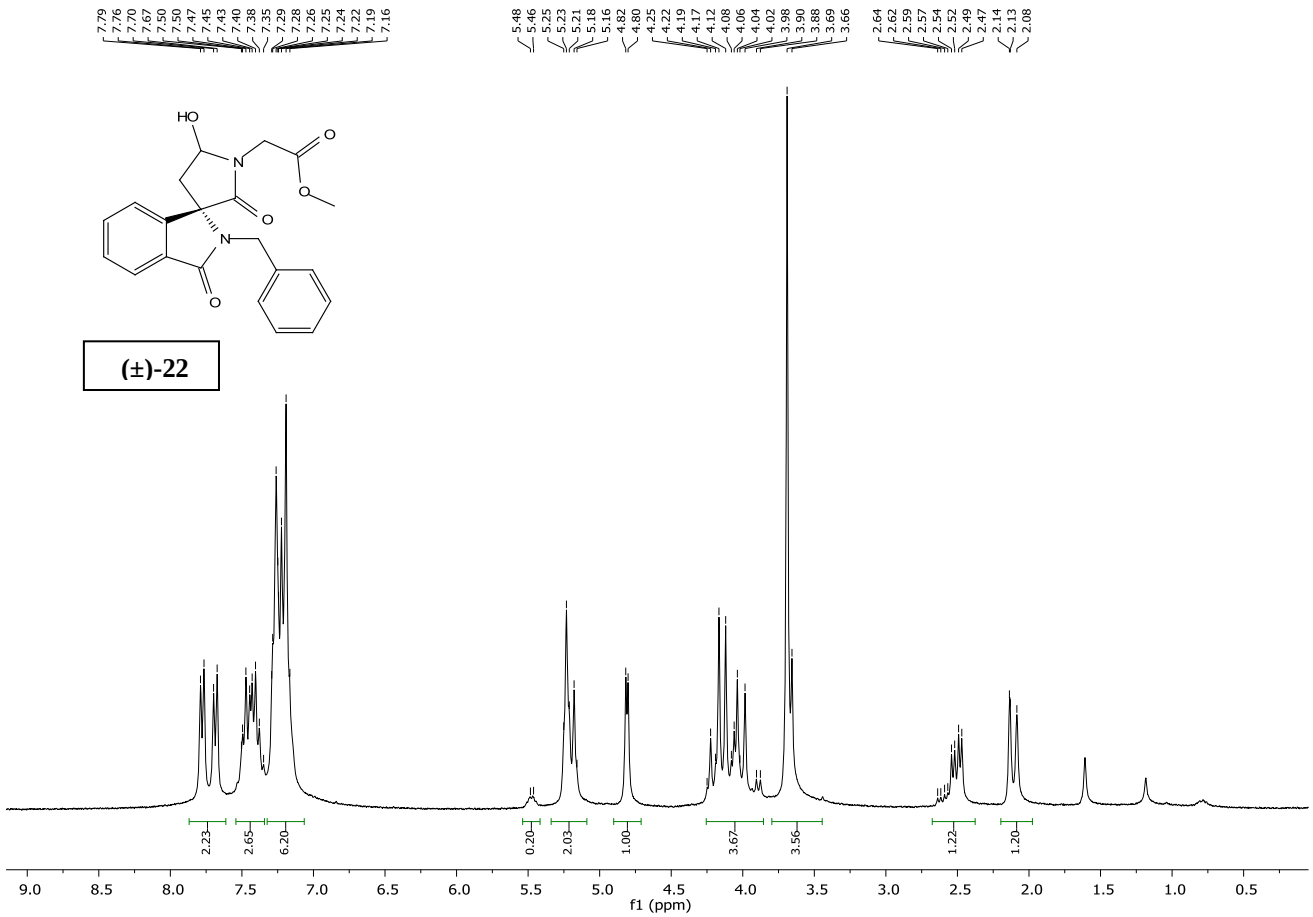
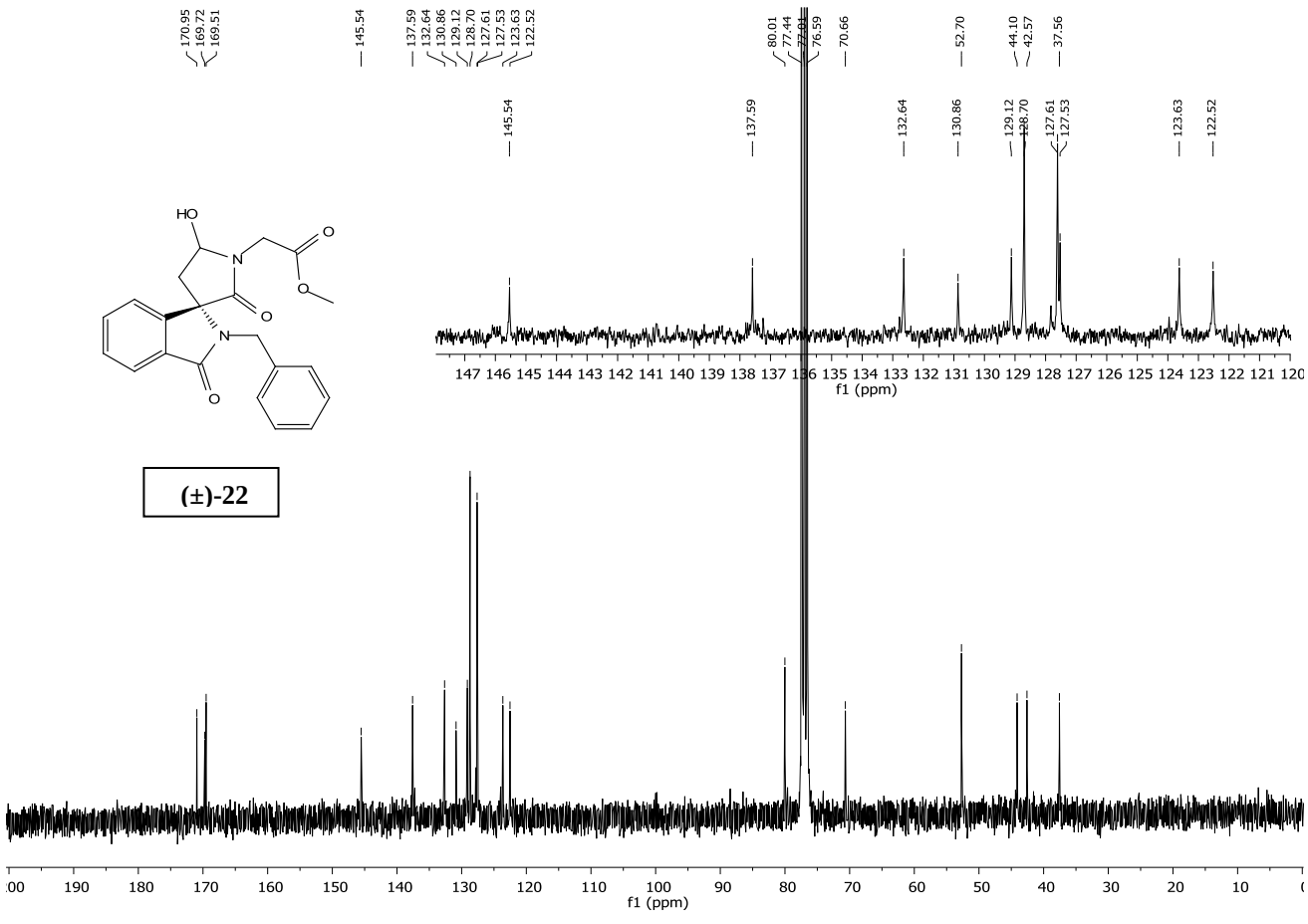
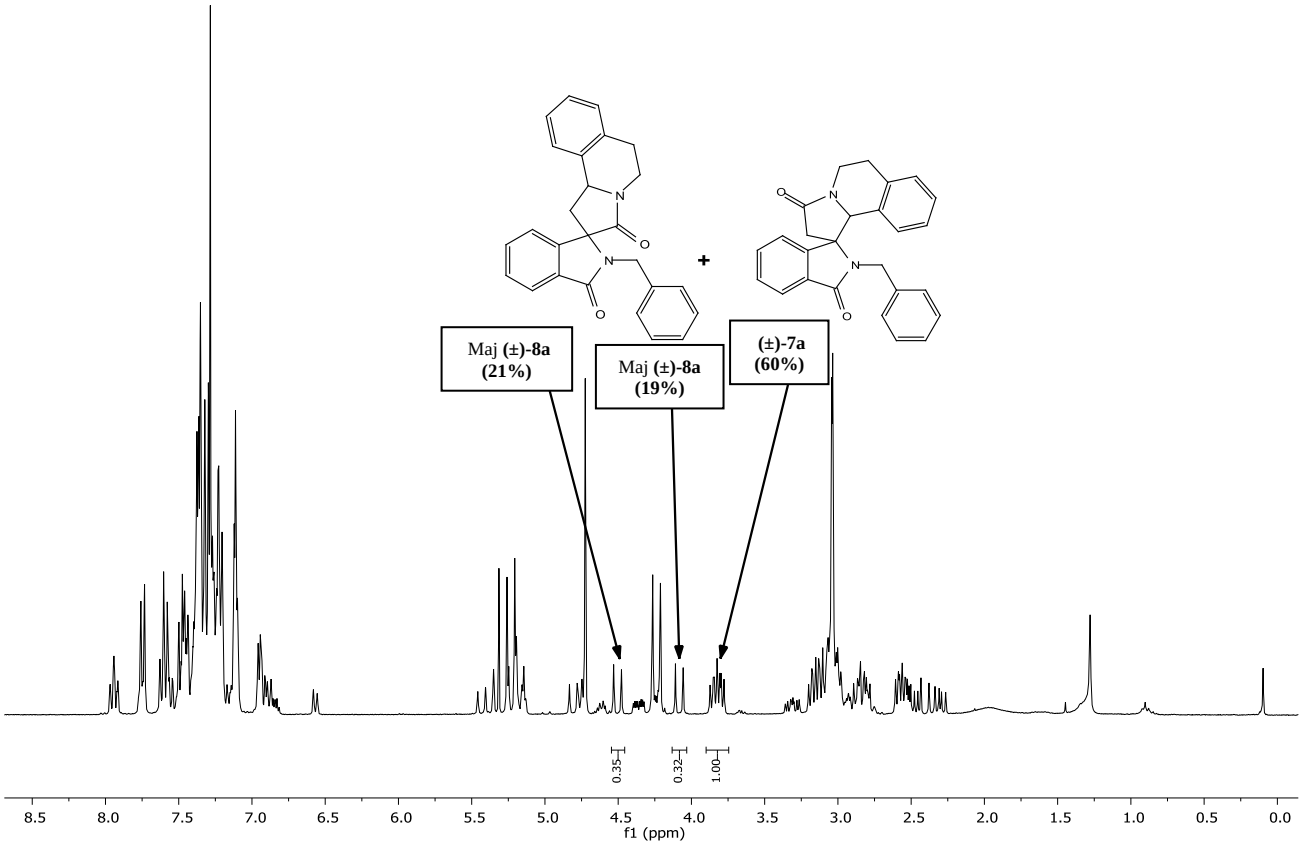
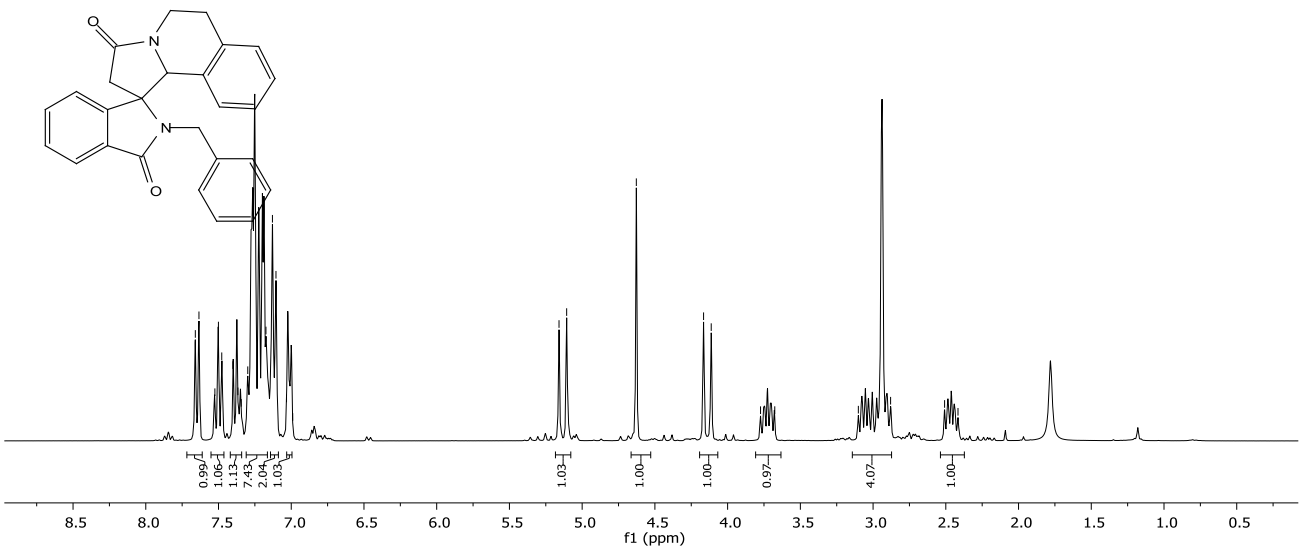

HO
O
N
O
O
N
O
(±)-22
f1 (ppm)


HO
O
N
O
O
N
O
(±)-22
f1 (ppm)

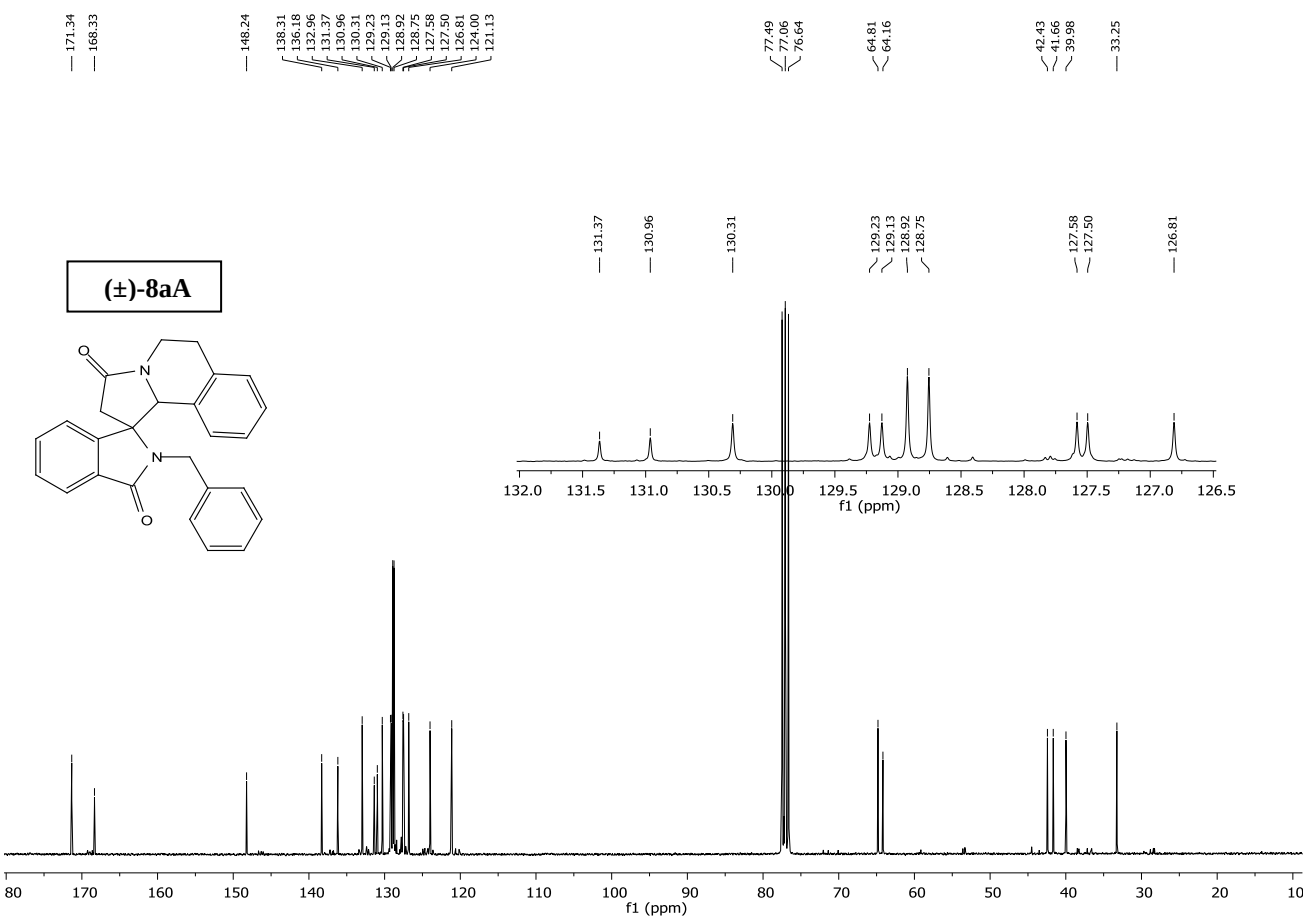


7.66 7.63 7.52 7.50 7.48 7.40 7.37 7.34 7.30 7.17 7.13 7.10 7.03 6.99 5.16 5.11 4.63 4.17 4.11 3.77 3.68 3.10 2.88 2.51 2.42

(±)-7aA



(±)-8aA


171.34
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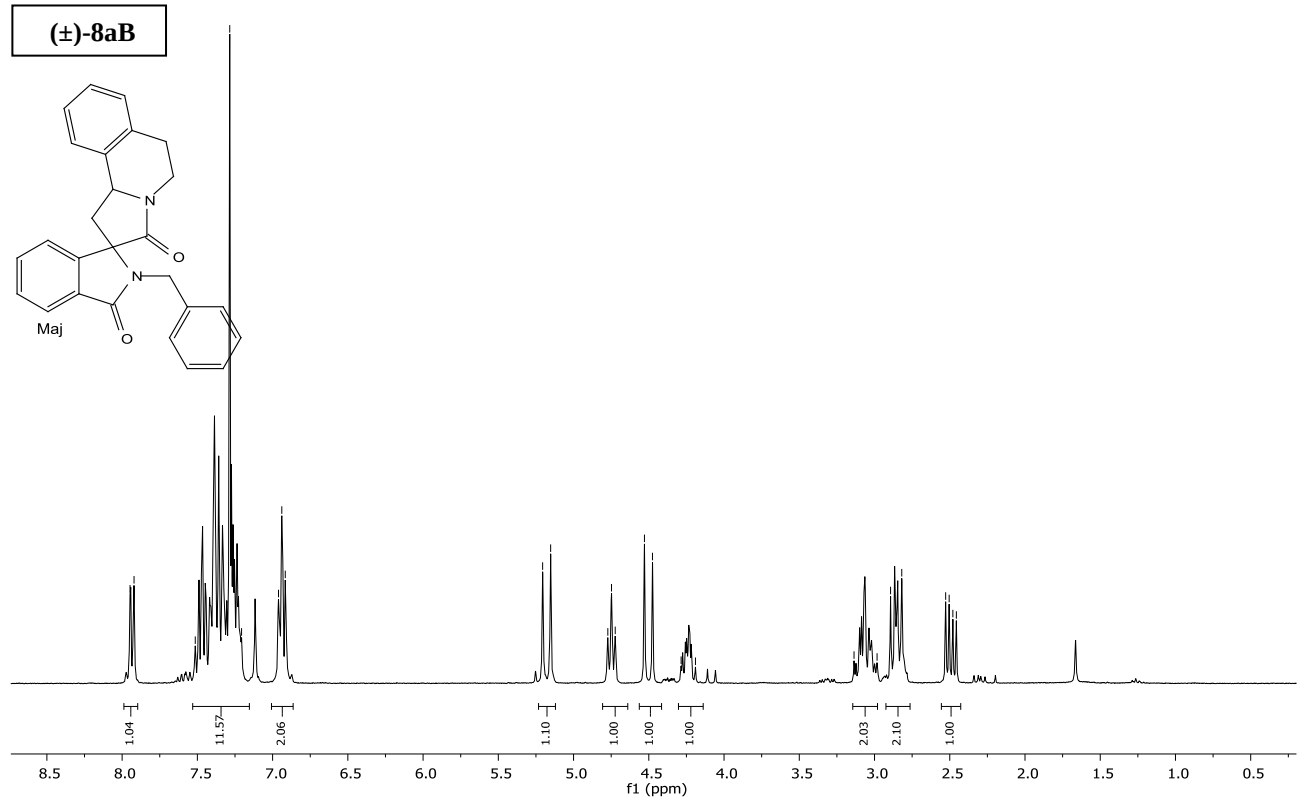
138.31
136.18
132.96
131.37
130.96
130.31
129.23
129.13
128.92
128.75
127.58
127.50
126.81
124.00
121.13
77.49
77.06
76.64
64.81
64.16
42.43
41.66
39.98
33.25
131.37
130.96
130.31
129.23
129.13
128.92
128.75
127.58
127.50
126.81
f1 (ppm)
f1 (ppm)

(±)-8aB

Maj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6.96
6.94
6.92
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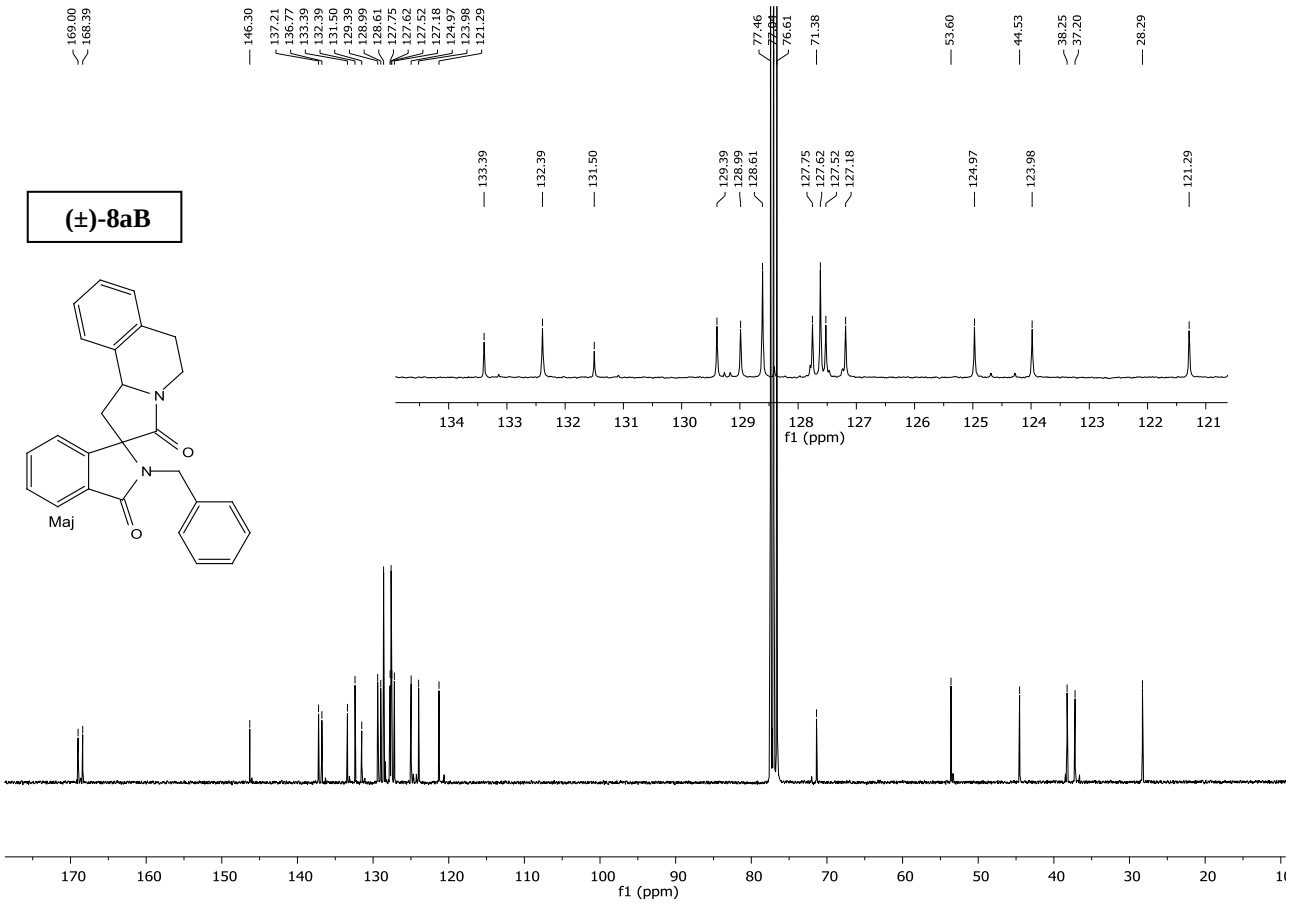
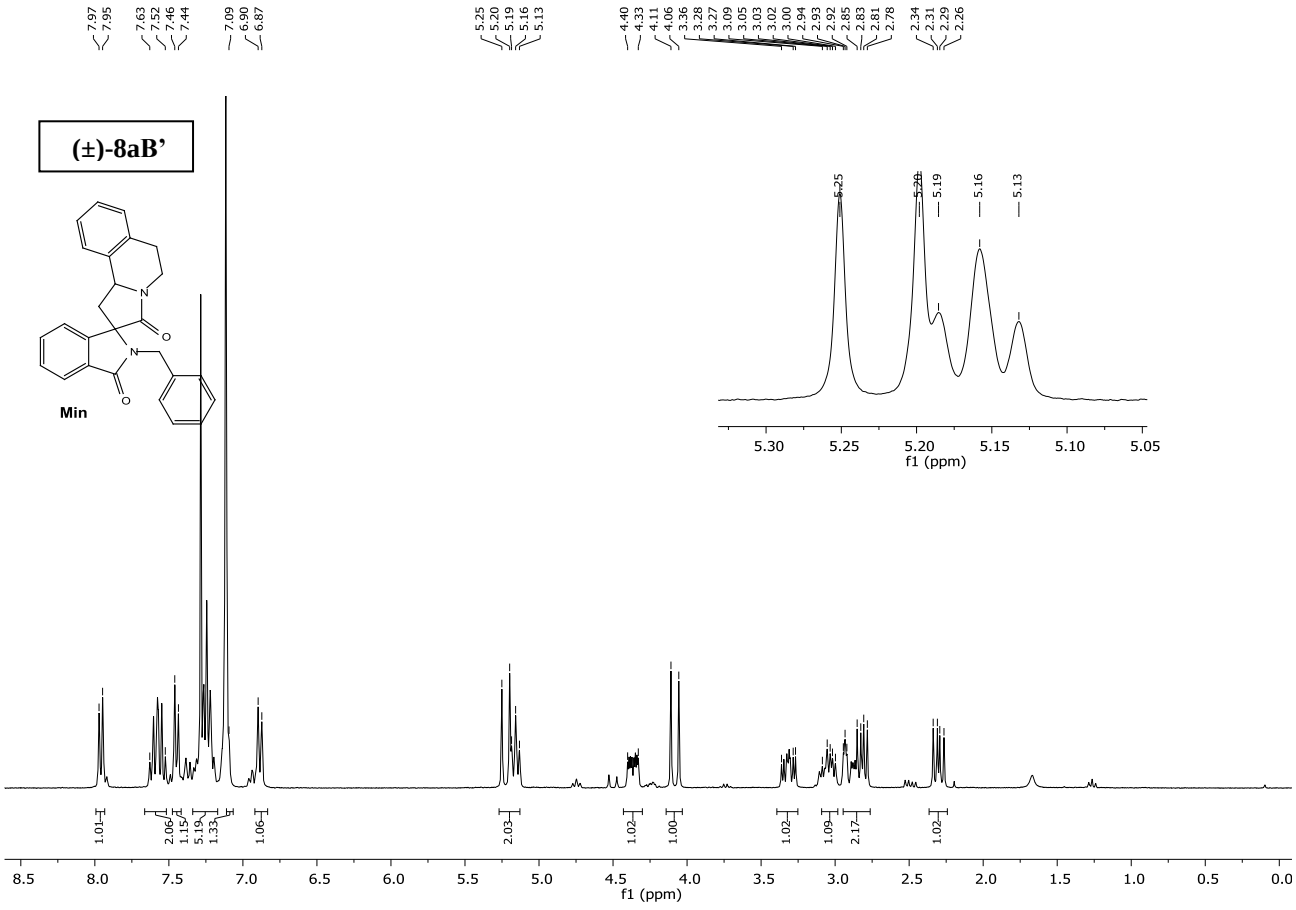
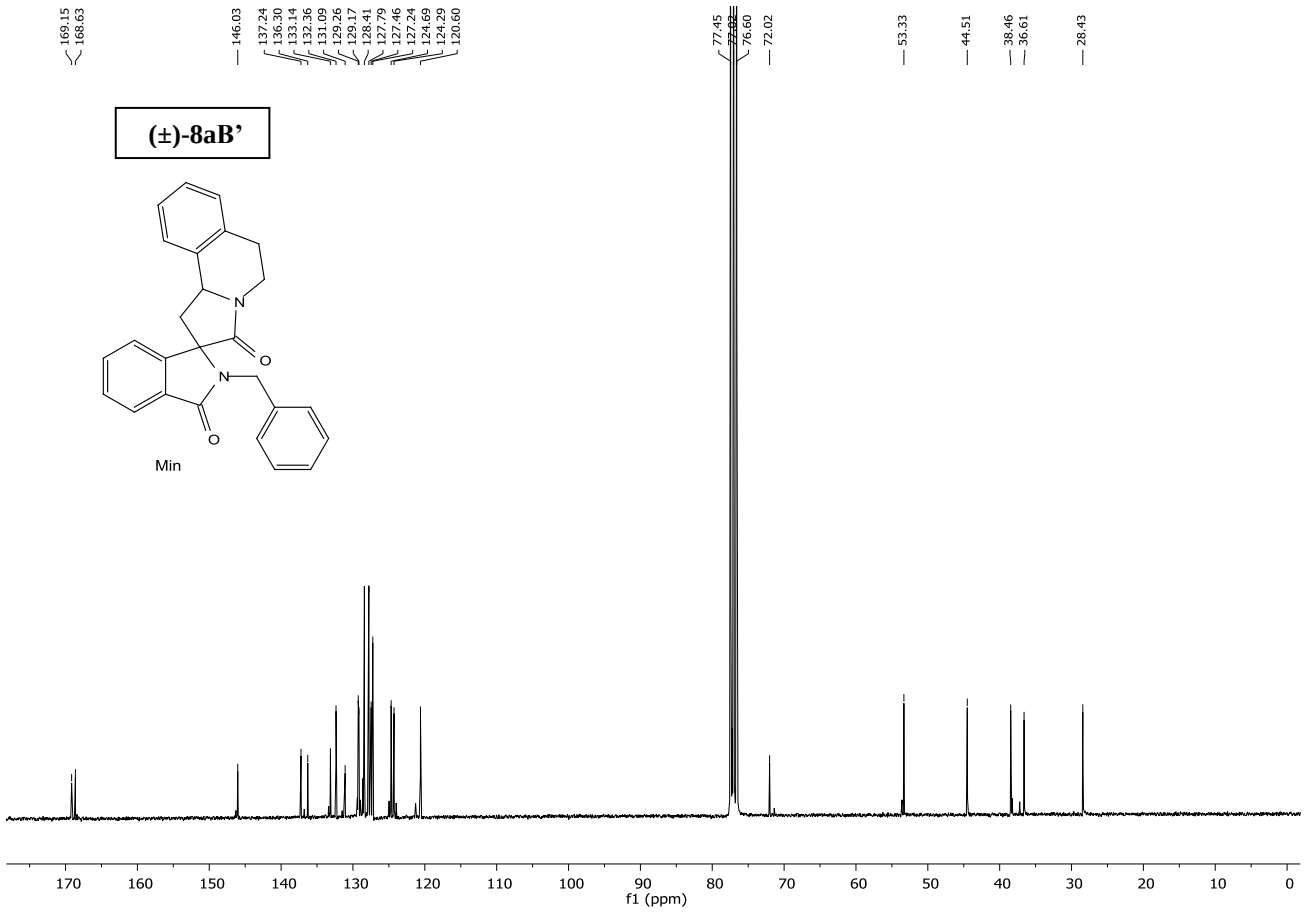
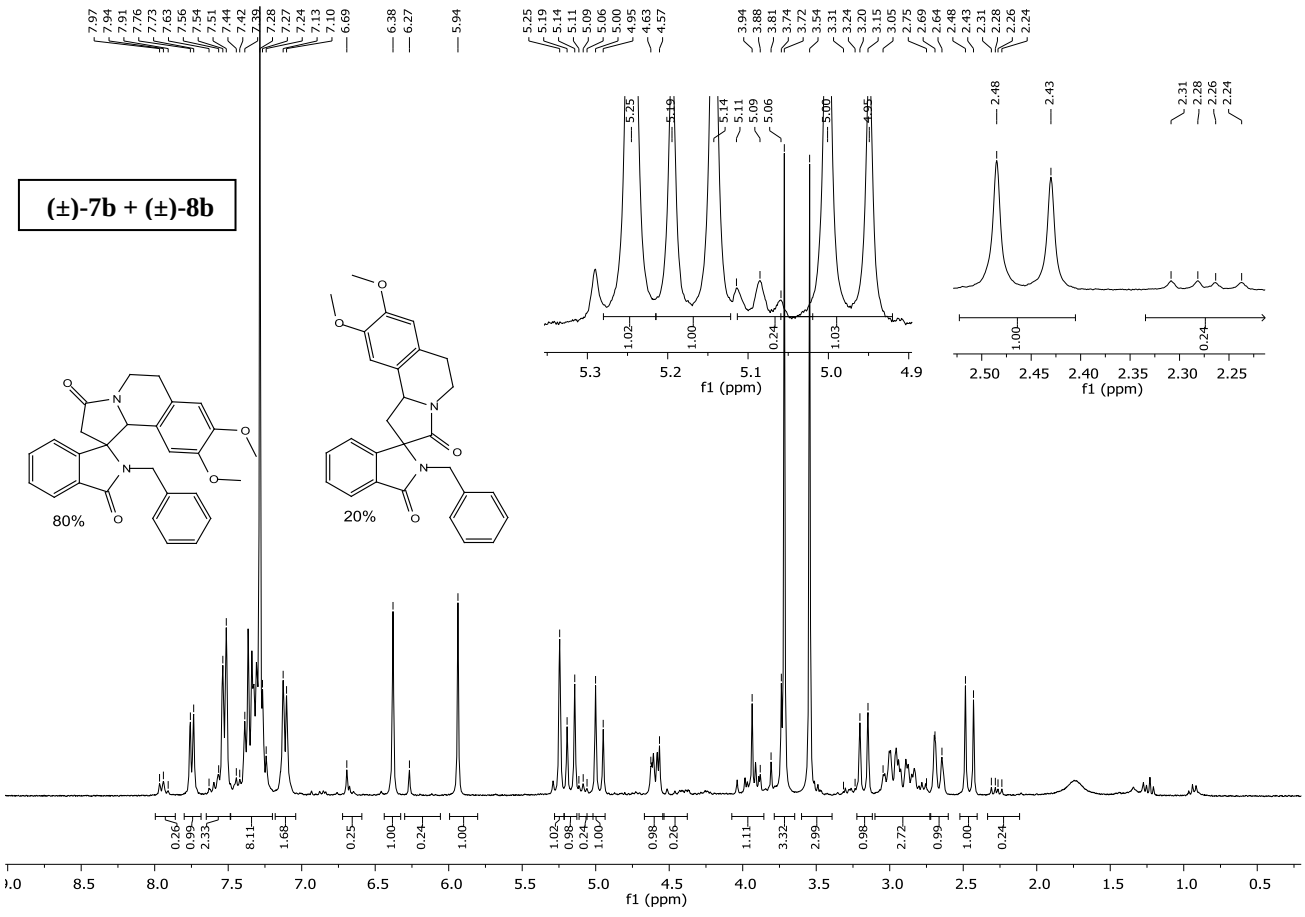
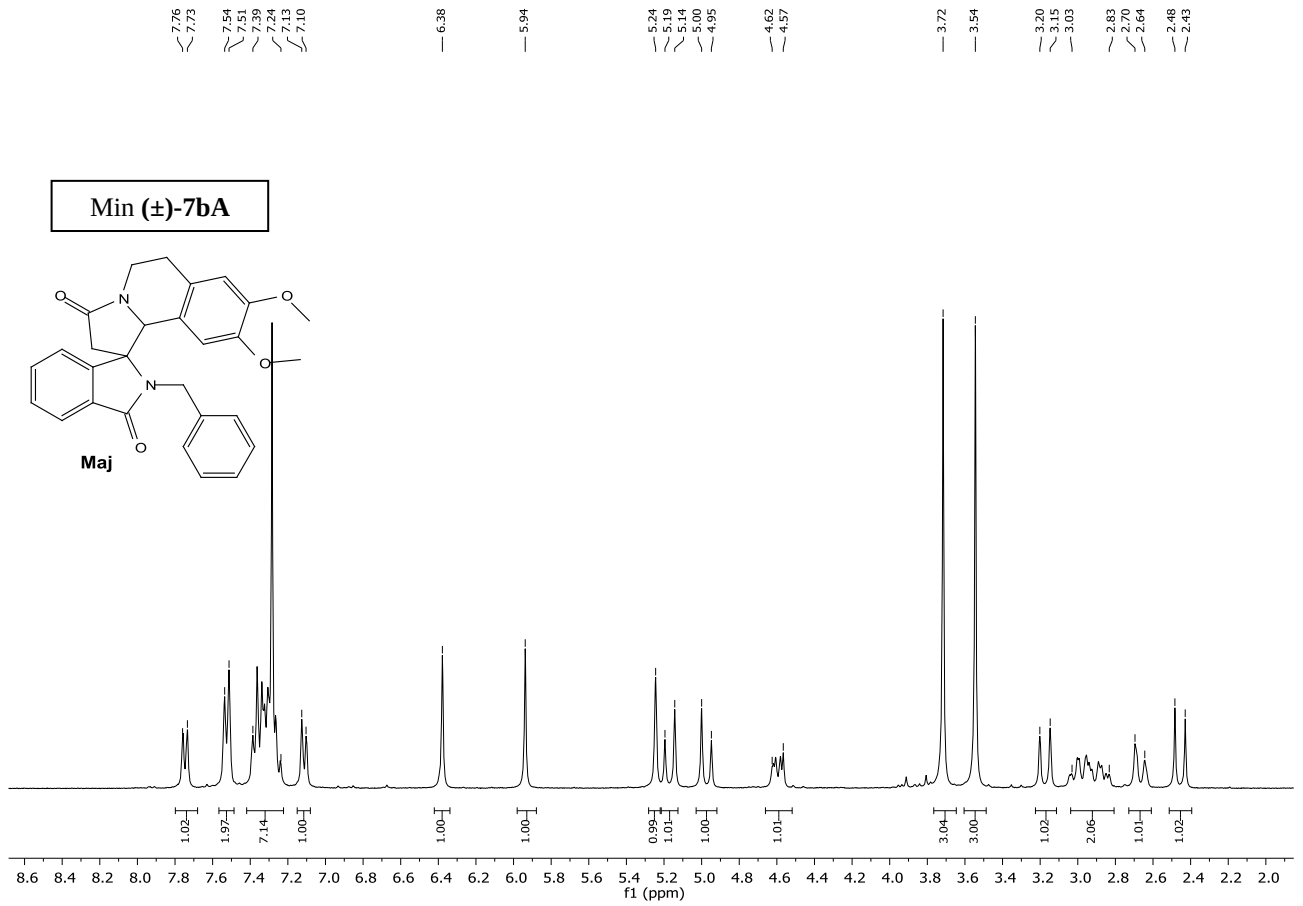
5.15
4.77
4.75
4.72
4.53
4.48
4.29
4.19
3.14
2.98
2.89
2.82
2.53
2.50
2.48
2.46
1.04
11.57
2.06
1.10
1.00
1.00
1.00
2.03
2.10
1.00
f1 (ppm)

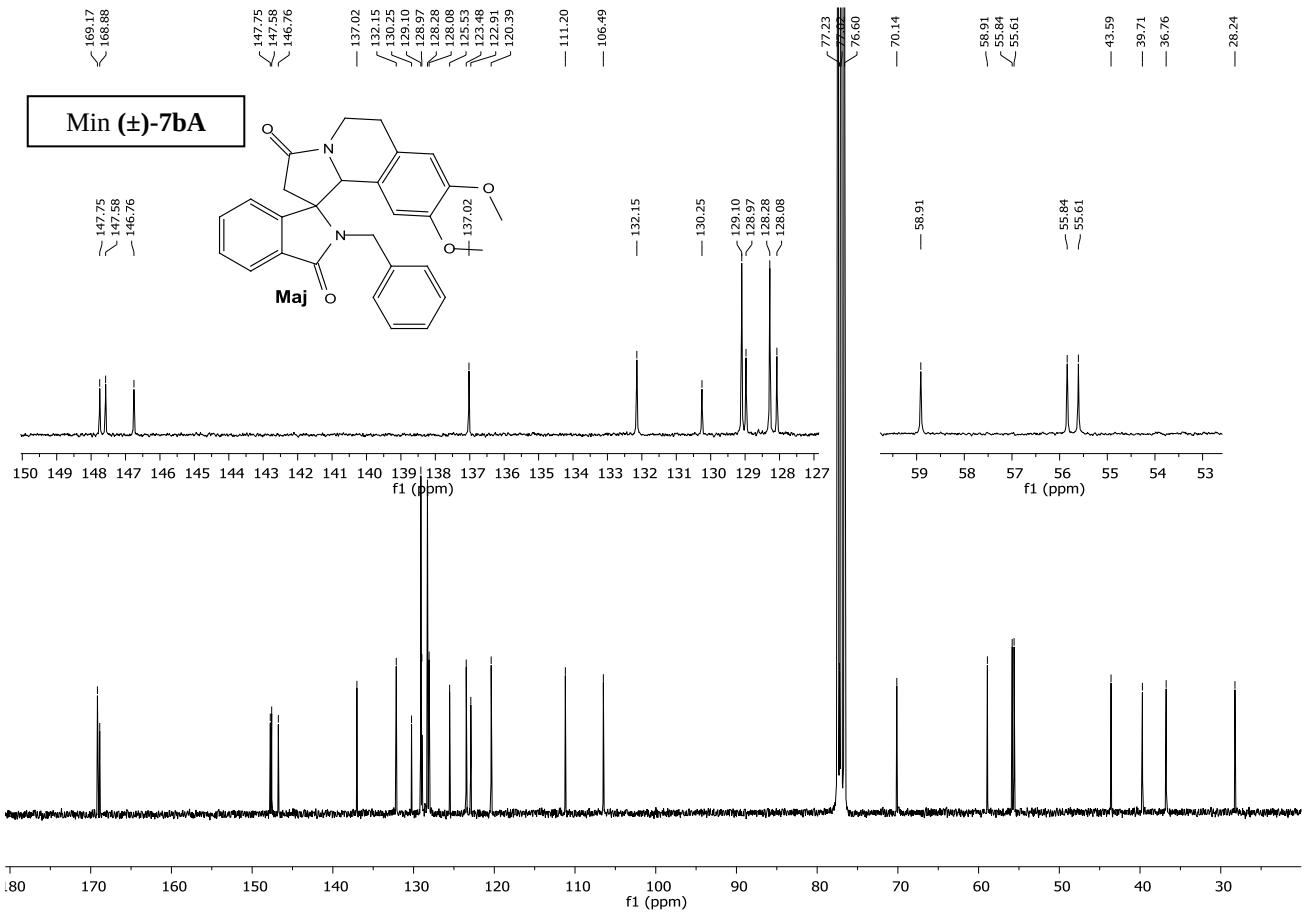

(±)-8aB
Maj
f1 (ppm)

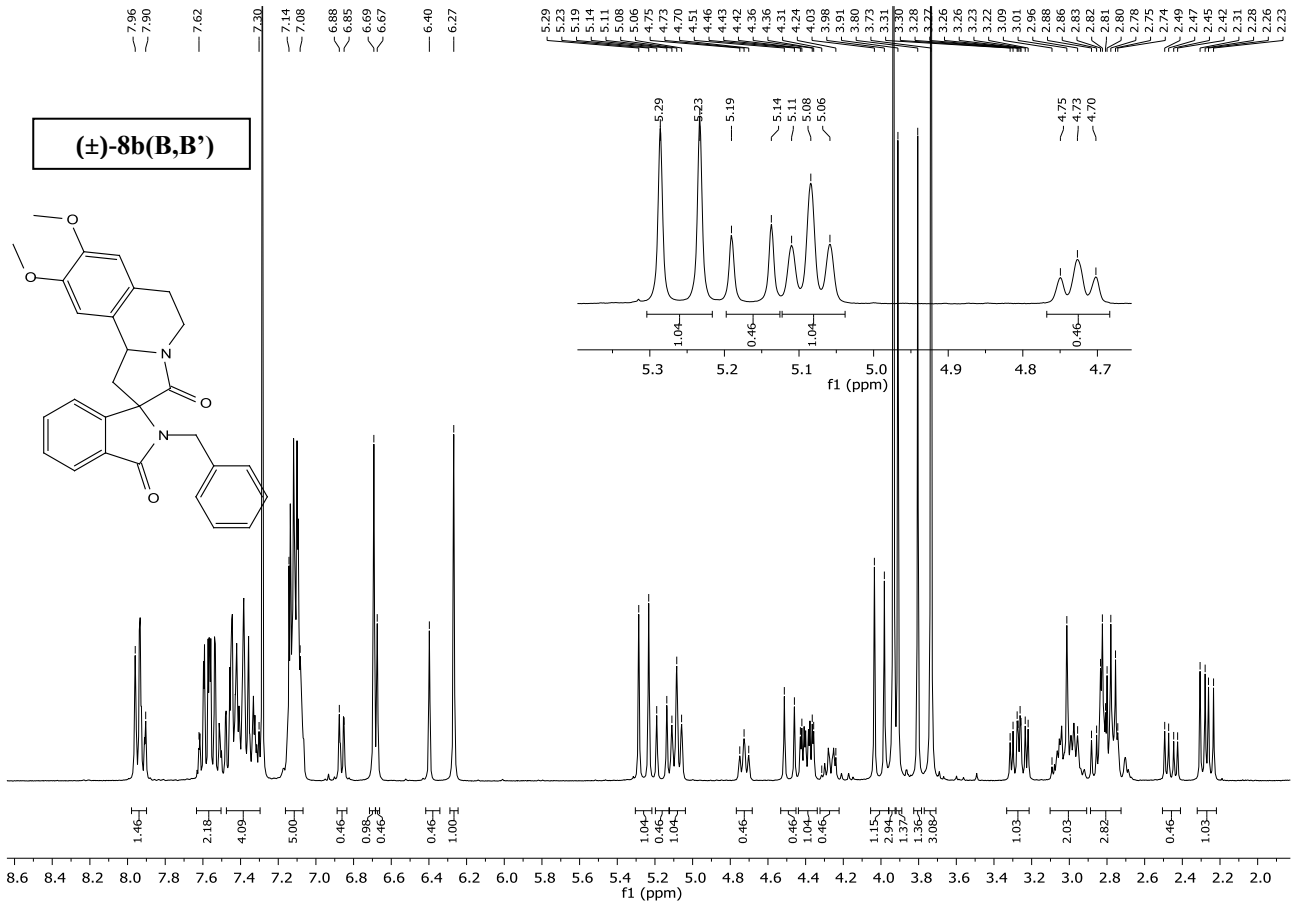

(±)-8aB'
Min
f1 (ppm)

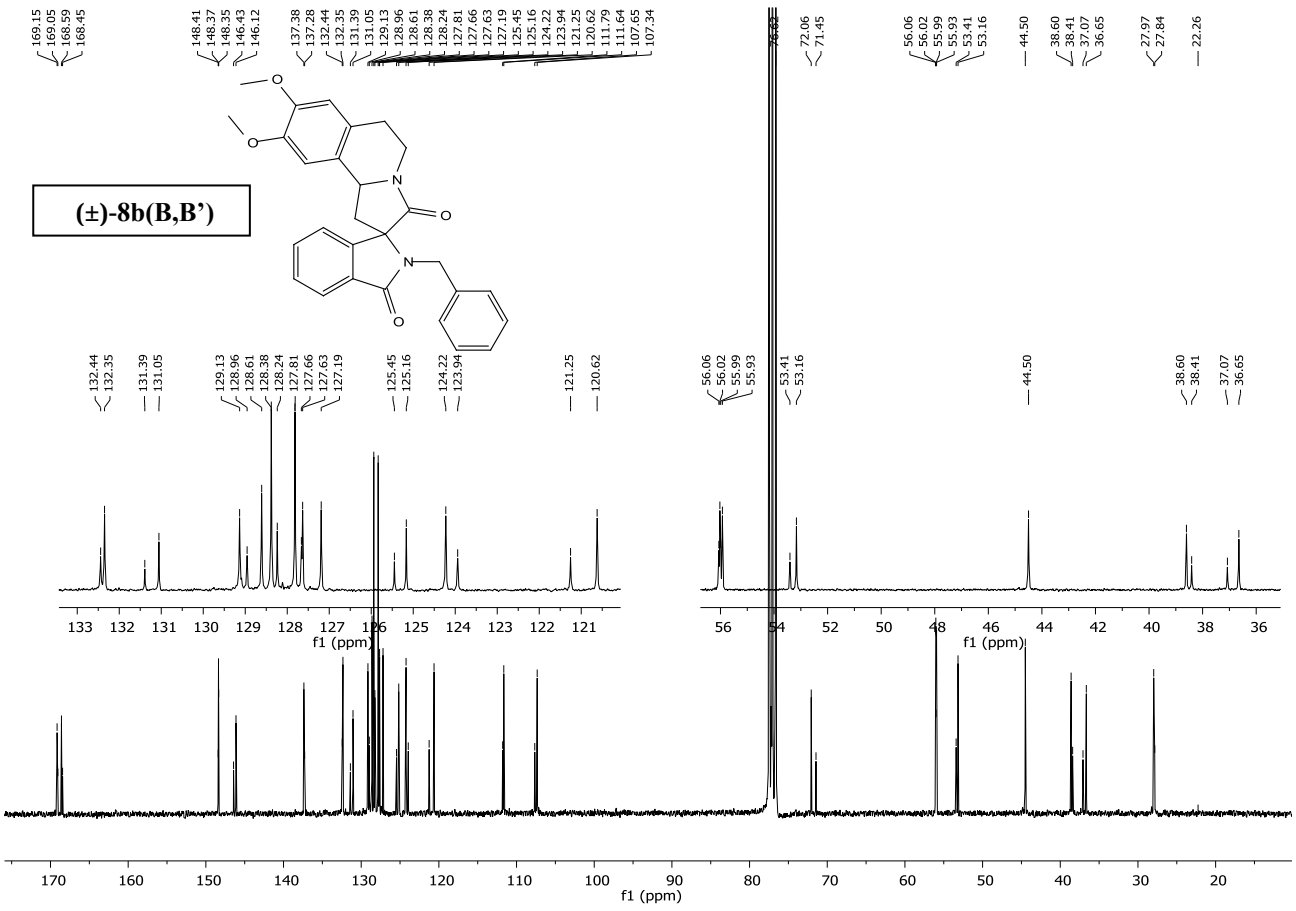

(±)-8aB'
Min
f1 (ppm)


(±)-7b + (±)-8b
80%
20%
f1 (ppm)


Min (±)-7bA
Maj
f1 (ppm)


Min (±)-7bA
Maj
f1 (ppm)
f1 (ppm)
f1 (ppm)


(±)-8b(B,B')
f1 (ppm)


(±)-8b(B,B')
f1 (ppm)


7.85
7.84
7.83
7.82
7.59
7.58
7.56
7.56
7.54
7.53
7.48
7.45
7.43
7.34
7.33
7.31
7.31
7.29
7.28
7.27
7.26
7.24
7.24
7.23
7.22
7.21
7.20
7.18
7.18
7.08
7.07
7.05
7.05
5.41
5.35
4.99
4.94
4.50
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4.19
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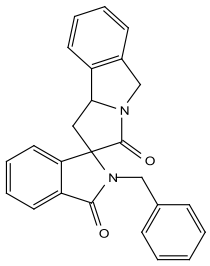
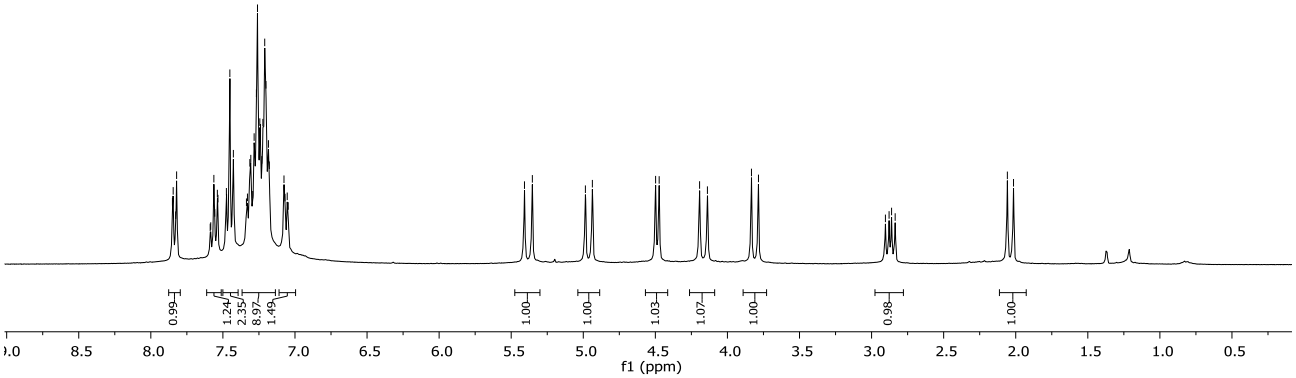
2.90
2.88
2.86
2.84
2.06
2.02

(±)-23




0.99
1.24
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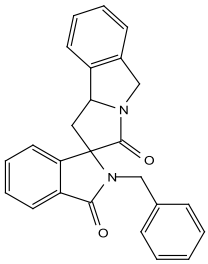
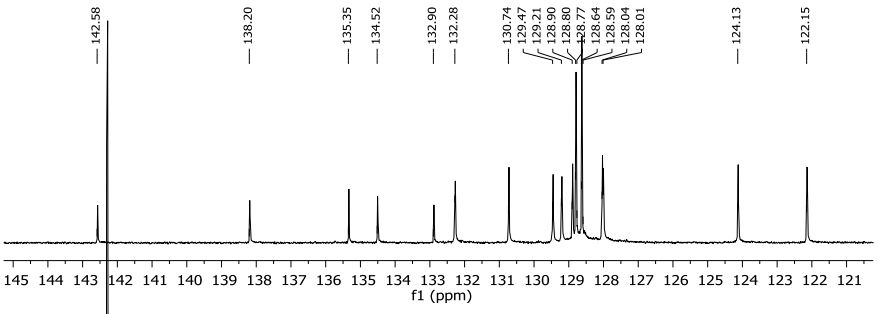
8.97
1.49
1.00
1.00
1.03
1.07
1.00
0.98
1.00
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


169.97
167.34
142.58
138.20
135.35
134.52
132.90
132.28
130.74
129.47
129.21
128.90
128.80
128.77
128.64
128.59
128.04
128.01
124.13
122.15
71.49
60.37
45.63
44.42
41.05

(±)-23




142.58
138.20
135.35
134.52
132.90
132.28
130.74
129.47
129.21
128.90
128.80
128.77
128.64
128.59
128.04
128.01
124.13
122.15
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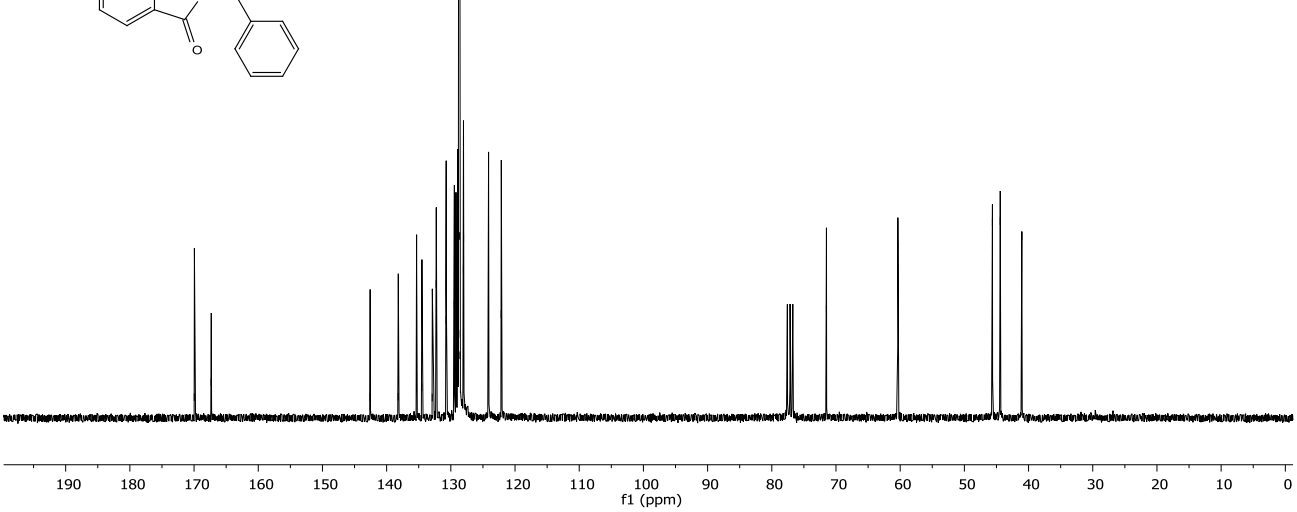
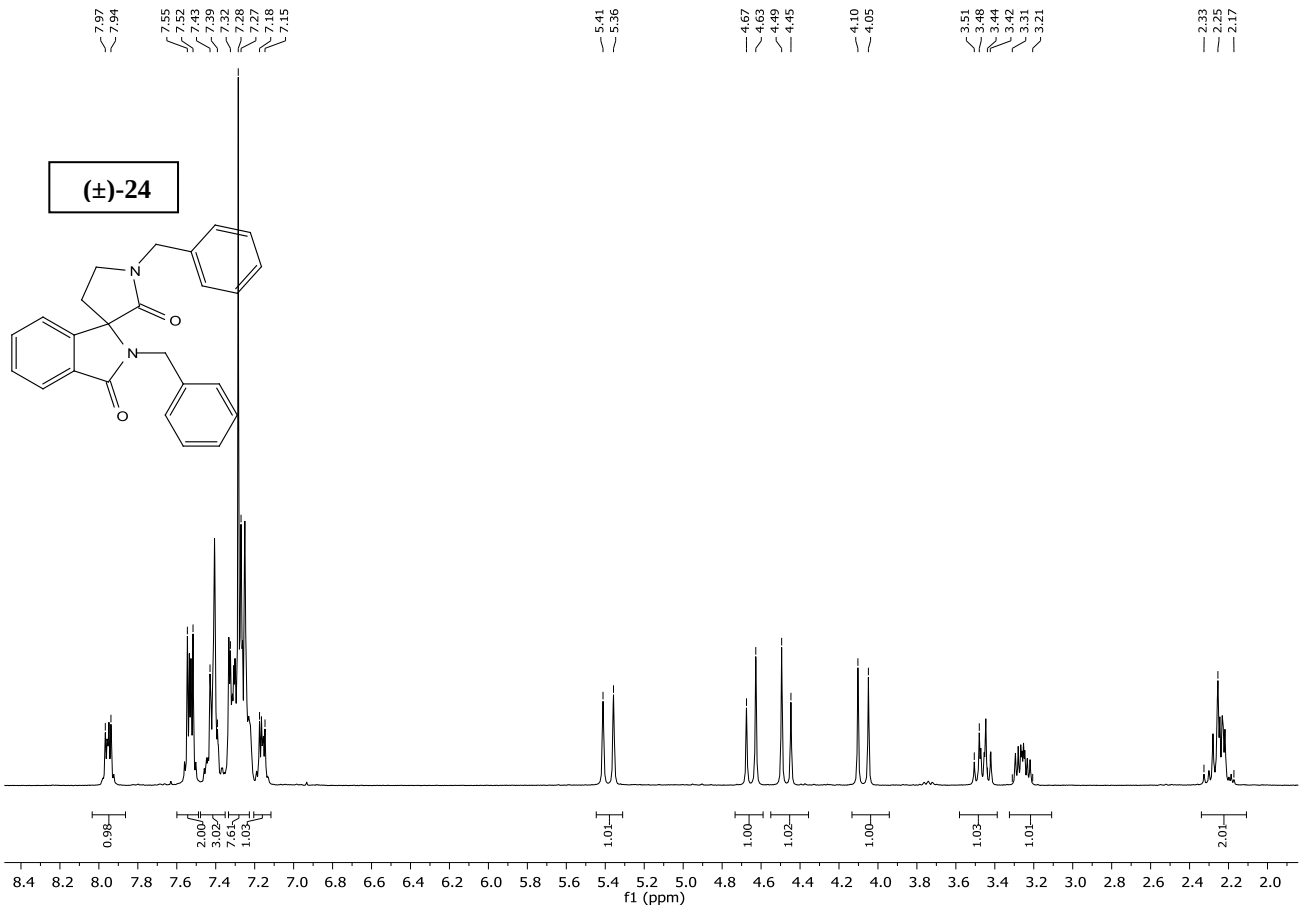
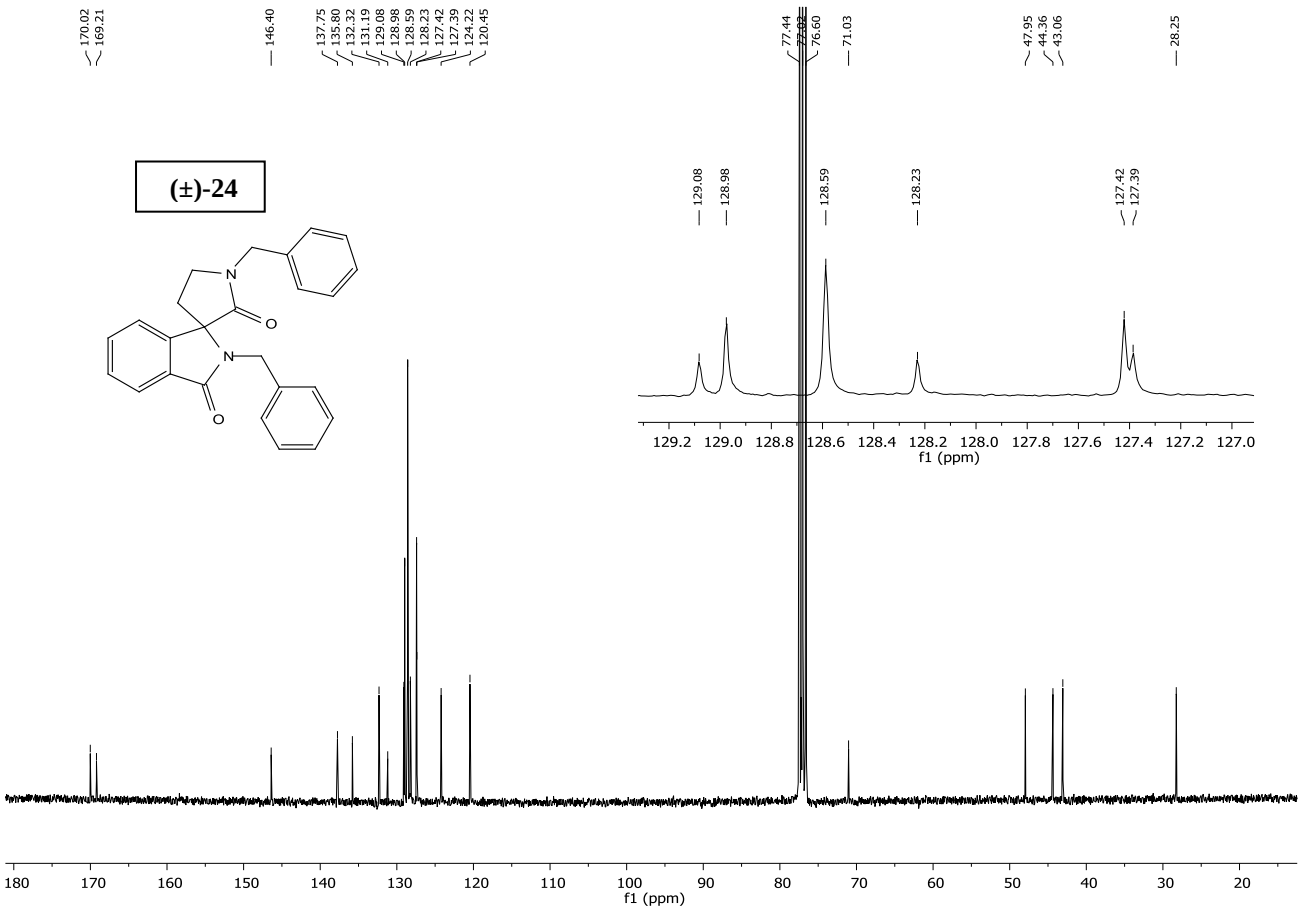
f1 (ppm)


190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


(±)-24
7.97
7.94
7.55
7.52
7.43
7.39
7.32
7.28
7.27
7.18
7.15
5.41
5.36
4.67
4.63
4.49
4.45
4.10
4.05
3.51
3.48
3.44
3.42
3.31
3.21
2.33
2.25
2.17
0.98
2.00
3.02
7.61
1.03
1.01
1.00
1.02
1.00
1.03
1.01
2.01
f1 (ppm)


(±)-24
170.02
169.21
146.40
137.75
135.80
132.32
131.19
129.08
128.98
128.59
128.23
127.42
127.39
124.22
120.45
77.44
77.02
76.60
71.03
47.95
44.36
43.06
28.25
129.08
128.98
128.59
128.23
127.42
127.39
f1 (ppm)

XII. Crystallographic data of compound (±)-7Ba (CCDC n° 1844057)

Table 1. Crystal data and structure refinement for ch060707 (Product **(±)-7bA** in the text).

Identification code	ch060707 (Product **(±)-7bA** in the text)	
Empirical formula	C30 H32 N2 O5	
Formula weight	500.58	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	?	
Space group	?	
Unit cell dimensions	a = 10.4959(12) Å	α= 90°.
	b = 20.229(2) Å	β= 96.215(2)°.
	c = 11.8444(14) Å	γ = 90°.
Volume	2500.0(5) $Å^3$	
Z	4	
Density (calculated)	1.330 Mg/m^3	
Absorption coefficient	0.091 mm^{-1}	
F(000)	1064	
Crystal size	0.40 x 0.30 x 0.10 mm^3	
Theta range for data collection	1.95 to 26.00°.	
Index ranges	-12<=h<=12, -24<=k<=24, -14<=l<=14	
Reflections collected	34813	
Independent reflections	4906 [R(int) = 0.0361]	
Completeness to theta = 26.00°	100.0 %	
Max. and min. transmission	0.9910 and 0.9646	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4906 / 0 / 338	
Goodness-of-fit on F^2	1.067	
Final R indices [I>2sigma(I)]	R1 = 0.0511, wR2 = 0.1246	
R indices (all data)	R1 = 0.0579, wR2 = 0.1291	
Largest diff. peak and hole	0.552 and -0.363 $e.Å^{-3}$	

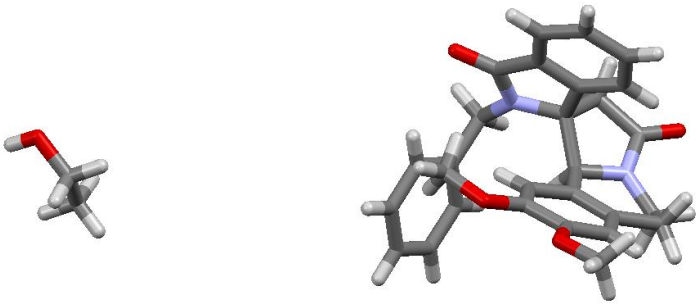


Figure. Stick drawing of spiroindolzine containing the isoindole motif **(±)-7bA** crystallized with one molecule of ethanol.

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for ch060707 (Product **7bA** in the text). U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	9391(2)	9092(1)	78(2)	46(1)
C(2)	7056(2)	11122(1)	-2210(2)	40(1)
C(3)	7751(2)	9904(1)	31(2)	28(1)
C(4)	7434(2)	9748(1)	1090(1)	26(1)
C(5)	6547(2)	10130(1)	1608(1)	23(1)
C(6)	5924(2)	10650(1)	1020(1)	25(1)
C(7)	6234(2)	10796(1)	-72(2)	28(1)
C(8)	7154(2)	10445(1)	-555(1)	27(1)
C(9)	4946(2)	11071(1)	1533(2)	33(1)
C(10)	4433(2)	10737(1)	2536(2)	30(1)
C(11)	6975(2)	10212(1)	4797(1)	25(1)
C(12)	6330(2)	9971(1)	2815(1)	23(1)
C(13)	5796(2)	10600(1)	4375(2)	26(1)
C(14)	7545(2)	10001(1)	3707(1)	22(1)
C(15)	8540(2)	10488(1)	3400(1)	23(1)
C(16)	8430(2)	11156(1)	3161(2)	29(1)
C(17)	9510(2)	11489(1)	2888(2)	33(1)
C(18)	10668(2)	11161(1)	2843(2)	32(1)
C(19)	10777(2)	10494(1)	3083(2)	28(1)
C(20)	9700(2)	10170(1)	3372(1)	24(1)
C(21)	9541(2)	9468(1)	3667(1)	24(1)
C(22)	7778(2)	8746(1)	4141(1)	25(1)
C(23)	7292(2)	8305(1)	3152(2)	25(1)
C(24)	6027(2)	8094(1)	3028(2)	30(1)
C(25)	5576(2)	7693(1)	2123(2)	37(1)
C(26)	6374(2)	7497(1)	1339(2)	40(1)
C(27)	7640(2)	7698(1)	1464(2)	39(1)
C(28)	8097(2)	8096(1)	2364(2)	32(1)
C(29)	7185(3)	2394(2)	5600(3)	72(1)
C(30)	8383(3)	2621(1)	5152(2)	58(1)
N(1)	8282(1)	9383(1)	3806(1)	22(1)
N(2)	5498(1)	10457(1)	3272(1)	26(1)
O(1)	8623(1)	9579(1)	-535(1)	39(1)
O(2)	7565(1)	10565(1)	-1592(1)	35(1)
O(3)	5198(1)	10974(1)	4936(1)	34(1)
O(4)	10365(1)	9035(1)	3772(1)	32(1)
O(5)	9495(2)	2358(1)	5699(2)	81(1)

Table 3. Bond lengths [Å] and angles [°] for ch060707 (Product **(±)-7bA** in the text).

C(1)-O(1)	1.421(2)
C(2)-O(2)	1.416(2)
C(3)-O(1)	1.361(2)
C(3)-C(4)	1.370(2)
C(3)-C(8)	1.407(3)
C(4)-C(5)	1.401(2)
C(5)-C(6)	1.386(2)
C(5)-C(12)	1.506(2)
C(6)-C(7)	1.399(2)
C(6)-C(9)	1.512(2)
C(7)-C(8)	1.372(3)
C(8)-O(2)	1.366(2)
C(9)-C(10)	1.515(3)
C(10)-N(2)	1.456(2)
C(11)-C(13)	1.504(3)
C(11)-C(14)	1.541(2)
C(12)-N(2)	1.458(2)
C(12)-C(14)	1.567(2)
C(13)-O(3)	1.224(2)
C(13)-N(2)	1.342(2)
C(14)-N(1)	1.469(2)
C(14)-C(15)	1.507(2)
C(15)-C(20)	1.381(2)
C(15)-C(16)	1.383(3)
C(16)-C(17)	1.387(3)
C(17)-C(18)	1.390(3)
C(18)-C(19)	1.382(3)
C(19)-C(20)	1.382(2)
C(20)-C(21)	1.475(2)
C(21)-O(4)	1.229(2)
C(21)-N(1)	1.359(2)
C(22)-N(1)	1.464(2)
C(22)-C(23)	1.516(2)
C(23)-C(24)	1.387(3)
C(23)-C(28)	1.390(3)
C(24)-C(25)	1.387(3)
C(25)-C(26)	1.374(3)
C(26)-C(27)	1.383(3)
C(27)-C(28)	1.381(3)
C(29)-C(30)	1.489(4)
C(30)-O(5)	1.379(3)
O(1)-C(3)-C(4)	125.62(16)
O(1)-C(3)-C(8)	114.88(15)
C(4)-C(3)-C(8)	119.50(16)
C(3)-C(4)-C(5)	120.83(16)
C(6)-C(5)-C(4)	119.85(16)
C(6)-C(5)-C(12)	121.83(15)
C(4)-C(5)-C(12)	118.30(15)
C(5)-C(6)-C(7)	118.83(16)
C(5)-C(6)-C(9)	121.95(16)

C(7)-C(6)-C(9)	119.21(16)
C(8)-C(7)-C(6)	121.30(16)
O(2)-C(8)-C(7)	126.01(16)
O(2)-C(8)-C(3)	114.45(15)
C(7)-C(8)-C(3)	119.54(16)
C(6)-C(9)-C(10)	112.26(15)
N(2)-C(10)-C(9)	109.11(15)
C(13)-C(11)-C(14)	104.24(13)
N(2)-C(12)-C(5)	111.53(14)
N(2)-C(12)-C(14)	101.53(13)
C(5)-C(12)-C(14)	115.86(14)
O(3)-C(13)-N(2)	125.65(17)
O(3)-C(13)-C(11)	126.41(16)
N(2)-C(13)-C(11)	107.93(14)
N(1)-C(14)-C(15)	101.71(13)
N(1)-C(14)-C(11)	114.69(13)
C(15)-C(14)-C(11)	111.34(13)
N(1)-C(14)-C(12)	113.82(13)
C(15)-C(14)-C(12)	113.37(13)
C(11)-C(14)-C(12)	102.36(13)
C(20)-C(15)-C(16)	120.32(16)
C(20)-C(15)-C(14)	109.67(15)
C(16)-C(15)-C(14)	130.01(16)
C(15)-C(16)-C(17)	118.03(17)
C(16)-C(17)-C(18)	121.19(18)
C(19)-C(18)-C(17)	120.71(17)
C(20)-C(19)-C(18)	117.62(17)
C(15)-C(20)-C(19)	122.10(17)
C(15)-C(20)-C(21)	108.65(15)
C(19)-C(20)-C(21)	129.23(16)
O(4)-C(21)-N(1)	125.41(16)
O(4)-C(21)-C(20)	127.86(16)
N(1)-C(21)-C(20)	106.72(14)
N(1)-C(22)-C(23)	114.19(14)
C(24)-C(23)-C(28)	118.70(17)
C(24)-C(23)-C(22)	120.01(16)
C(28)-C(23)-C(22)	121.29(16)
C(23)-C(24)-C(25)	120.28(18)
C(26)-C(25)-C(24)	120.61(19)
C(25)-C(26)-C(27)	119.50(18)
C(28)-C(27)-C(26)	120.22(19)
C(27)-C(28)-C(23)	120.68(19)
O(5)-C(30)-C(29)	114.70(2)
C(21)-N(1)-C(22)	121.95(14)
C(21)-N(1)-C(14)	113.09(13)
C(22)-N(1)-C(14)	124.64(13)
C(13)-N(2)-C(10)	125.61(15)
C(13)-N(2)-C(12)	114.89(14)
C(10)-N(2)-C(12)	119.49(14)
C(3)-O(1)-C(1)	117.29(15)
C(8)-O(2)-C(2)	117.87(15)

Table 4. Anisotropic displacement parameters ($Å^2$ x 10^3) for ch060707 (Product **(±)-7bA** in the text). The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	51(1)	51(1)	37(1)	7(1)	14(1)	29(1)
C(2)	53(1)	36(1)	31(1)	8(1)	7(1)	11(1)
C(3)	29(1)	29(1)	25(1)	-5(1)	3(1)	6(1)
C(4)	29(1)	23(1)	25(1)	-2(1)	0(1)	5(1)
C(5)	23(1)	22(1)	24(1)	-4(1)	1(1)	-2(1)
C(6)	24(1)	23(1)	28(1)	-3(1)	0(1)	1(1)
C(7)	30(1)	24(1)	28(1)	1(1)	-1(1)	4(1)
C(8)	30(1)	29(1)	22(1)	-1(1)	1(1)	1(1)
C(9)	32(1)	32(1)	35(1)	0(1)	4(1)	10(1)
C(10)	22(1)	33(1)	35(1)	-4(1)	3(1)	5(1)
C(11)	26(1)	27(1)	23(1)	-3(1)	6(1)	-2(1)
C(12)	21(1)	22(1)	27(1)	-3(1)	3(1)	1(1)
C(13)	25(1)	24(1)	30(1)	-2(1)	8(1)	-5(1)
C(14)	23(1)	21(1)	21(1)	-2(1)	4(1)	0(1)
C(15)	24(1)	26(1)	19(1)	-4(1)	3(1)	-2(1)
C(16)	30(1)	25(1)	33(1)	-2(1)	4(1)	-1(1)
C(17)	40(1)	25(1)	34(1)	1(1)	5(1)	-6(1)
C(18)	31(1)	35(1)	31(1)	-1(1)	8(1)	-12(1)
C(19)	24(1)	35(1)	26(1)	-2(1)	5(1)	-3(1)
C(20)	25(1)	29(1)	18(1)	-4(1)	2(1)	0(1)
C(21)	24(1)	26(1)	21(1)	-3(1)	2(1)	1(1)
C(22)	28(1)	23(1)	25(1)	2(1)	5(1)	-1(1)
C(23)	31(1)	18(1)	28(1)	4(1)	3(1)	2(1)
C(24)	32(1)	25(1)	33(1)	2(1)	4(1)	2(1)
C(25)	37(1)	27(1)	44(1)	0(1)	-3(1)	-4(1)
C(26)	54(1)	25(1)	38(1)	-7(1)	-6(1)	0(1)
C(27)	50(1)	30(1)	38(1)	-7(1)	9(1)	7(1)
C(28)	33(1)	27(1)	37(1)	-3(1)	7(1)	1(1)
C(29)	77(2)	53(2)	84(2)	18(2)	8(2)	-6(2)
C(30)	66(2)	38(1)	69(2)	0(1)	-5(1)	6(1)
N(1)	23(1)	21(1)	23(1)	0(1)	4(1)	1(1)
N(2)	22(1)	27(1)	28(1)	-3(1)	5(1)	3(1)
O(1)	48(1)	45(1)	26(1)	4(1)	11(1)	24(1)
O(2)	42(1)	38(1)	25(1)	5(1)	7(1)	12(1)
O(3)	34(1)	36(1)	36(1)	-10(1)	12(1)	5(1)
O(4)	26(1)	30(1)	39(1)	0(1)	3(1)	5(1)
O(5)	64(1)	46(1)	126(2)	-4(1)	-17(1)	10(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for ch060707 (Product **(±)-7bA** in the text).

	x	y	z	U(eq)
H(1A)	9791	9282	790	69
H(1B)	10058	8941	-380	69
H(1C)	8853	8716	246	69
H(2A)	6136	11058	-2421	59
H(2B)	7488	11174	-2898	59
H(2C)	7193	11519	-1738	59
H(4)	7820	9376	1479	31
H(7)	5798	11146	-488	33
H(9A)	4224	11166	946	39
H(9B)	5344	11497	1783	39
H(10A)	3971	11063	2964	36
H(10B)	3824	10383	2265	36
H(11A)	6749	9821	5237	30
H(11B)	7588	10489	5283	30
H(12)	5930	9524	2840	28
H(16)	7638	11380	3184	35
H(17)	9458	11949	2728	40
H(18)	11392	11399	2644	39
H(19)	11564	10266	3051	34
H(22A)	7068	8828	4609	30
H(22B)	8462	8509	4621	30
H(24)	5467	8226	3566	36
H(25)	4707	7552	2044	44
H(26)	6057	7225	717	47
H(27)	8198	7561	928	47
H(28)	8970	8229	2446	39
H(29A)	7130	1911	5553	108
H(29B)	6442	2590	5148	108
H(29C)	7193	2532	6394	108
H(30A)	8334	2506	4336	70
H(30B)	8429	3109	5212	70
H(5)	9426	1944	5732	121

_____/End.

checkCIF (basic structural check) running

Checking for embedded fcf data in CIF ...
Found embedded fcf data in CIF. Extracting fcf data from uploaded CIF, please wait . .

checkCIF/PLATON (basic structural check)

Structure factors have been supplied for datablock(s) ch060707. (Product **(±)-7bA** in the paper.)

THIS REPORT IS FOR GUIDANCE ONLY. IF USED AS PART OF A REVIEW PROCEDURE FOR PUBLICATION, IT SHOULD NOT REPLACE THE EXPERTISE OF AN EXPERIENCED CRYSTALLOGRAPHIC REFEREE.

No syntax errors found.
Please wait while processing ....

CIF dictionary
Interpreting this report

Structure factor report

Datablock: ch060707

Bond precision: C-C = 0.0025 A Wavelength=0.71073
Cell: a=10.4959(12) b=20.229(2) c=11.8444(14)
alpha=90 beta=96.215(2) gamma=90
Temperature: 173 K

	Calculated	Reported
Volume	2500.0(5)	2500.0(5)
Space group	P 21/c	P 1 21/c 1
Hall group	-P 2ybc	-P 2ybc
Moiety formula	C28 H26 N2 O4, C2 H6 O	C2 H6 O, C28 H26 N2 O4
Sum formula	C30 H32 N2 O5	C30 H32 N2 O5
Mr	500.58	500.57
Dx,g cm-3	1.330	1.330
Z	4	4
Mu (mm-1)	0.091	0.091
F000	1064.0	1064.0
F000'	1064.50	
h,k,lmax	12,24,14	12,24,14
Nref	4908	4907
Tmin,Tmax	0.968,0.991	0.671,0.746
Tmin'	0.964	

Correction method= # Reported T Limits: Tmin=0.671 Tmax=0.746
AbsCorr = MULTI-SCAN
Data completeness= 1.000 Theta(max)= 25.995
R(reflections)= 0.0492(4106) wR2(reflections)= 0.1243(4907)
S = 1.032 Npar= 338

The following ALERTS were generated. Each ALERT has the format
test-name_ALERT_alert-type_alert-level.
Click on the hyperlinks for more details of the test.

Alert level C

DIFMX02_ALERT_1_C The maximum difference density is > 0.1*ZMAX*0.75
The relevant atom site should be identified.
PLAT094_ALERT_2_C Ratio of Maximum / Minimum Residual Density .... 2.13 Report
PLAT097_ALERT_2_C Large Reported Max. (Positive) Residual Density 0.63 eA-3
PLAT244_ALERT_4_C Low 'Solvent' Ueq as Compared to Neighbors of C109 Check
PLAT906_ALERT_3_C Large K Value in the Analysis of Variance ..... 3.676 Check

Alert level G

PLAT007_ALERT_5_G Number of Unrefined Donor-H Atoms ..... 1 Report
PLAT042_ALERT_1_G Calc. and Reported MoietyFormula Strings Differ Please Check
PLAT793_ALERT_4_G Model has Chirality at C12 (Centro SPGR) S Verify
PLAT793_ALERT_4_G Model has Chirality at C14 (Centro SPGR) S Verify
PLAT978_ALERT_2_G Number C-C Bonds with Positive Residual Density. 10 Info

0 ALERT level A = Most likely a serious problem - resolve or explain
0 ALERT level B = A potentially serious problem, consider carefully
5 ALERT level C = Check. Ensure it is not caused by an omission or oversight
5 ALERT level G = General information/check it is not something unexpected

2 ALERT type 1 CIF construction/syntax error, inconsistent or missing data
3 ALERT type 2 Indicator that the structure model may be wrong or deficient
1 ALERT type 3 Indicator that the structure quality may be low
3 ALERT type 4 Improvement, methodology, query or suggestion
1 ALERT type 5 Informative message, check

It is advisable to attempt to resolve as many as possible of the alerts in all categories. Often the minor alerts point to easily fixed oversights, errors and omissions in your CIF or refinement strategy, so attention to these fine details can be worthwhile. In order to resolve some of the more serious problems it may be necessary to carry out additional measurements or structure refinements. However, the purpose of your study may justify the reported deviations and the more serious of these should normally be commented upon in the discussion or experimental section of a paper or in the "special_details" fields of the CIF. checkCIF was carefully designed to identify outliers and unusual parameters, but every test has its limitations and alerts that are not important in a particular case may appear. Conversely, the absence of alerts does not guarantee there are no aspects of the results needing attention. It is up to the individual to critically assess their own results and, if necessary, seek expert advice.

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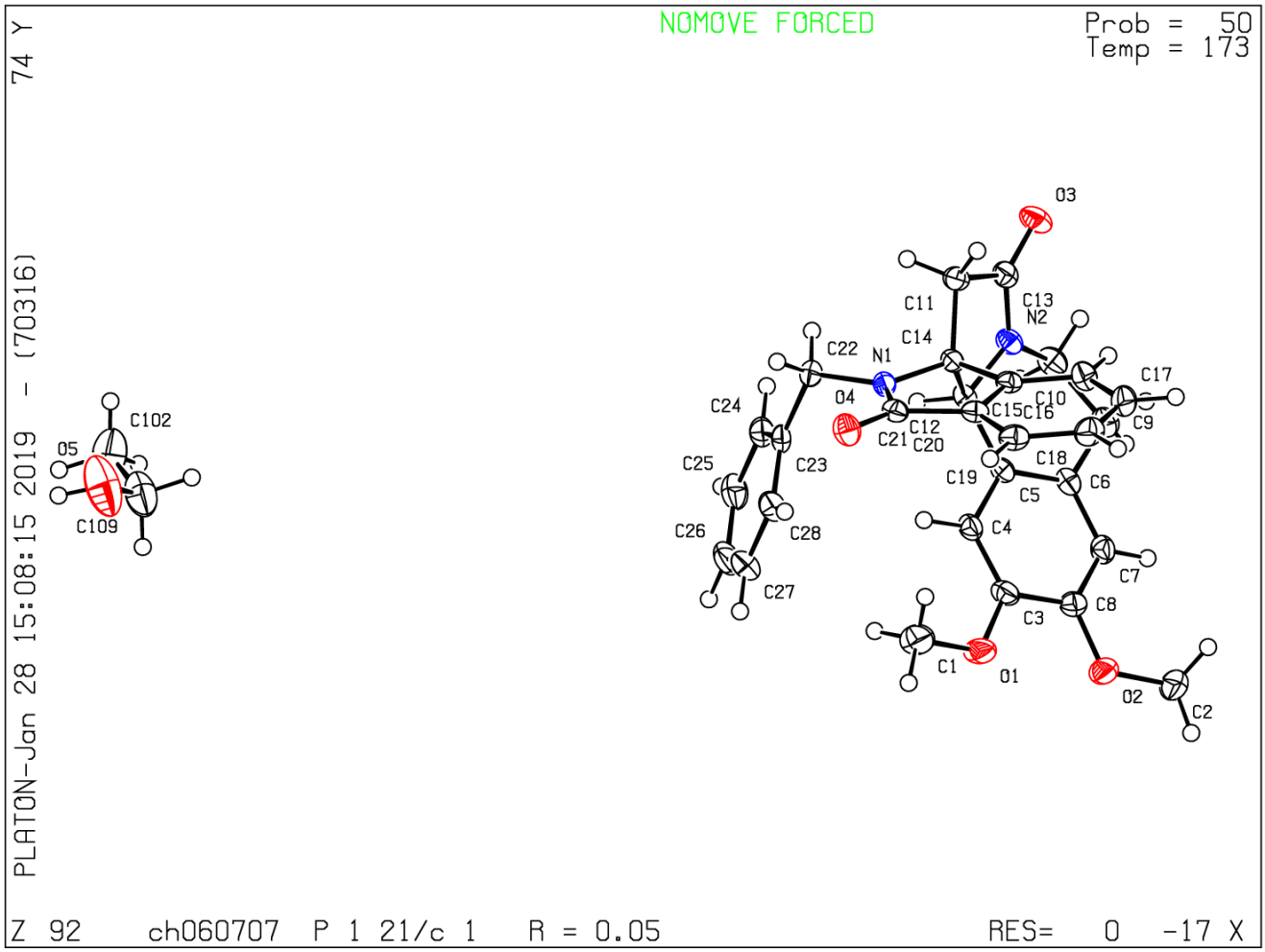
A basic structural check has been run on your CIF. These basic checks will be run on all CIFs submitted for publication in IUCr journals (*Acta Crystallographica*, *Journal of Applied Crystallography*, *Journal of Synchrotron Radiation*); however, if you intend to submit to *Acta Crystallographica Section C* or *E* or *IUCrData*, you should make sure that full publication checks are run on the final version of your CIF prior to submission.

Publication of your CIF in other journals

Please refer to the *Notes for Authors* of the relevant journal for any special instructions relating to CIF submission.

PLATON version of 06/01/2019; check.def file version of 19/12/2018

Datablock ch060707 - ellipsoid plot



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