Supporting Information

Site Isolated Base and Acid Catalyzed Azaspirocyclization Cascades

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Contents

1. General Experimental

Amberlyst® 15, K10 montmorillonite, KSF montmorillonite, Si-TsOH and polymer supported BEMP were used as sold. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was carried out using Merck Kieselgel 60 silica gel (230-400 mesh) or using a medium pressure liquid chromatography. Thin-layer chromatography was carried out using Merck Kieselgel 60 F_{254} (230-400 mesh) fluorescent treated silica which were visualized under UV light (250 nm) or by staining with aqueous potassium permanganate solutions.

^{1}H and ^{13}C spectra were recorded on a Bruker 500 MHz or 400 MHz spectrometer and are using ppm for measurement against a TMS internal standard. Data for ^{1}H are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration and coupling constants (Hz). Data for ^{13}C are reported in terms of chemical shift. IR spectra were recorded on an ATI Mattison: Genesis Series FTIR spectrometer from a thin film deposited on a sodium chloride plate and only diagnostic absorbances (λ_{max}) are reported. Low resolution mass spectra were recorded on a Fissions VG Trio 2000 quadrupole mass spectrometer. High resolution mass spectra were recorded on a Thermo Finnigan Mat 95XP mass spectrometer.

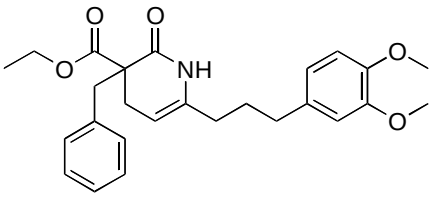
Preparation of starting materials: Michael donors represented by **1** were synthesised by alkylation of commercially available malonamates and cyanoacetamides following the relevant procedure in Ref 1. Michael acceptors represented by **2** were synthesised from the corresponding commercially available carboxylic acids *via* transformation to the Weinreb amide (Ref 2) and subsequent addition of vinyl magnesium bromide (Ref 3). **22** was synthesised from ethyl malonamate and ethyl chloroformate following the relevant procedure in Ref 4 and **23** was synthesised in three steps from 2-ethyl furan (Ref 5).

2. Proof Of Principle Reactions

Michael donor **5** (1 equivalent), acid catalyst (see table) and polymer supported BEMP (0.1 equivalents) were stirred in dichloromethane (2 ml) and Michael acceptor **6** (1.1 equivalents) was added dropwise. The mixtures were stirred for 24 hours at room temperature, filtered through cotton wool and concentrated *in vacuo*. The residues were purified by flash chromatography eluting with ethyl acetate / petroleum ether 4:6.

Acid	Reaction Scale	Loading	Product (Yield)
Amberlyst® 15	0.20 mmol	4.3 mg, 10 mol%	**7** (74%)
MP-TsOH II	0.20 mmol	5.0 mg, 10 mol%	**7** (71%)
K10 montmorillonite	0.20 mmol	52 mg, 100 mass%	**7** (6%), **8** (61%)
KSF montmorillonite	0.20 mmol	52 mg, 100 mass%	**7** (9%), **8** (70%)
Si-TsOH	0.45 mmol	50 mg, 10 mol%	**8** (85%)

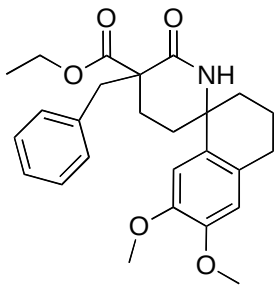
Ethyl 1,2,3,4-tetrahydro-6-(3-(3,4-dimethoxyphenyl)propyl)-2-benzyl-2-oxopyridine-3-carboxylate (7)



The title compound was isolated as a colorless oil.

IR (film): 1672, 1694, 1730 (C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.12 (t, 3H, $OCH_2C\underline{H}_3$, J = 7.5 Hz), 1.67 (quintet, 2H, J = 7.5 Hz), 1.97 (t, 2H, J = 6.7 Hz), 2.15 (m, 1H), 2.47 (m, 2H), 2.58 (dd, 1H, J = 5.7 Hz, J = 16.7 Hz), 3.14 (d, 1H, $PhCH_2^a$, J = 13.6 Hz), 3.23 (d, 1H, $PhCH_2^b$, J = 13.6 Hz), 3.77 (s, 3H, OMe), 3.78 (s, 3H, OMe), 4.07 (q, 2H, $OC\underline{H}_2CH_3$, J = 7.1 Hz), 4.74 (m, 1H, C=C$\underline{H}$), 6.61 (d, 1H, Ar-H, J = 8.4 Hz), 6.70 (d, 1H, Ar-H, J = 7.9 Hz), 7.14-7.19 (m, 6H), 7.28 (br s, 1H, NH); δ_C ($CDCl_3$, 100 MHz): 14.1, 28.3, 28.6, 31.9, 34.4, 38.7, 54.3, 55.8, 55.9, 61.6, 100.1, 111.2, 111.7, 120.2, 126.8, 128.1, 130.6, 134.1, 136.1, 136.3, 147.2, 148.8, 169.9, 171.5**;** MS (ES+) 438 ($[M+H]^+$, 100%), 460 ($[M+Na]^+$, 75%); HRMS (ES+) exact mass calculated for $C_{26}H_{32}NO_5$ $[M+H]^+$ requires *m/z* 438.2275, found *m/z* 438.2278.

3-Benzyl-3-carboxyethylspiro[5.5]-1-azaundecan[{6,7-*d*}(1',2'-dimethoxyphenyl)]-2-one (8)



The title compound was isolated as a colorless oil (3:2 mixture of inseparable diastereomers).

IR (film): 1659, 1729 (C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.22-1.29 (ddd, 1H, *J* = 4.0 Hz, *J* = 11.3 Hz, *J* = 14.9 Hz), 1.38 (t, 6H, $OCH_2C\underline{H}_3$, $OCH_2C\underline{H}_3$', *J* = 7.1 Hz), 1.40-1.42 (m, 1H), 1.49-1.56 (ddd, 1H, *J* = 3.8 Hz, *J* = 9.4 Hz, *J* = 13.6 Hz), 1.57-1.64 (m, 2H), 1.72-1.86 (ddd, 1H, *J* = 3.8 Hz, *J* = 8.3 Hz, *J* = 12.5 Hz), 1.82-2.14 (m, 9H), 2.24-2.30 (ddd, 1H, *J* = 3.9 Hz, *J* = 9.3 Hz, *J* = 13.6Hz), 2.57-2.80 (m, 4H), 3.08 (d, 1H, $C\underline{H}_2^a$Ph, *J* = 13.4 Hz), 3.14 (d, 1H, $C\underline{H}_2^a$Ph', *J* = 13.3 Hz), 3.49 (s, 3H, OMe'), 3.76-3.82 (m, 2H, $C\underline{H}_2^b$Ph, $C\underline{H}_2^b$Ph'), 3.82 (s, 3H, OMe'), 3.86 (s, 3H, OMe), 3.91 (s, 3H, OMe), 4.26-4.39 (m, 4H, $OC\underline{H}_2CH_3$, $OC\underline{H}_2CH_3$'), 5.81 (s, 2H, NH, NH'), 6.16 (s, 1H, Ar-H'), 6.50 (s, 1H, Ar-H), 6.51 (s, 1H, Ar-H'), 7.08 (s, 1H, Ar-H), 7.25-7.43 (m, 10H, $CH_2\underline{Ph}$, $CH_2\underline{Ph}$'); δ_C ($CDCl_3$, 100 MHz): 14.1, 14.2, 19.2, 19.8, 25.6, 26.3, 28.5, 28.9, 32.2, 33.4, 35.6, 38.1, 39.9, 41.0, 54.5, 54.6, 55.7, 56.0, 56.2, 56.9, 57.5, 61.7, 61.8, 77.2, 108.9, 110.0, 110.8, 111.3, 126.7, 126.8, 128.1, 128.3, 129.1, 130.8, 130.9, 132.6, 132.9, 136.5, 136.7, 147.1, 147.7, 148.2, 148.3, 169.6, 170.0, 172.9, 173.0**,** MS (ES+) 438 ($[M+H]^+$, 30%), 460 ($[M+Na]^+$, 75%); HRMS (ES+)

exact mass calculated for $C_{26}H_{32}NO_5$ $[M+H]^+$ requires *m/z* 438.2275, found *m/z* 438.2279.

3. Spirocyclisation Reactions

3.1 General Procedures

General Procedure A

Michael donor (0.45 mmol), Si-TsOH (50 mg, 0.045 mmol) and polymer supported BEMP (20.5 mg, 0.045 mmol) were stirred in dichloromethane (2 ml) and Michael acceptor (0.50 mmol) was added dropwise. The mixture was stirred for 24 hours at room temperature, filtered through cotton wool and concentrated *in vacuo*. The residue was purified by medium pressure liquid chromatography eluting with a gradient of ethyl acetate/iso-hexane 10-50 %.

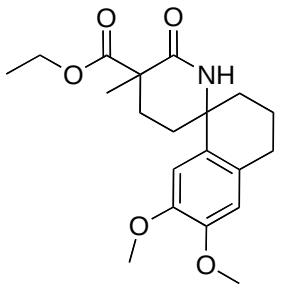
General Procedure B

Michael donor (0.45 mmol) and polymer supported BEMP (20.5 mg, 0.045 mmol) were stirred in dichloromethane (2 ml) and Michael acceptor (0.50 mmol) was added dropwise. The mixture was stirred for 24 hours at room temperature, then Si-TsOH (50 mg, 0.045 mmol) was added in one portion. After a further 24 hours, the reaction was filtered through cotton wool and concentrated *in vacuo*. The residue was purified by medium pressure liquid chromatography eluting with a gradient of ethyl acetate/iso-hexane 10-50 %.

General Procedure C

Michael donor (0.45 mmol), Si-TsOH (50 mg, 0.045 mmol) and polymer supported BEMP (20.5 mg, 0.045 mmol) were stirred in chloroform (2 ml) and Michael acceptor (0.50 mmol) was added dropwise. The mixture was heated to reflux and stirred at this temperature for 24 hours. The reaction was cooled, filtered through cotton wool and concentrated *in vacuo*. The residue was purified by medium pressure liquid chromatography eluting with a gradient of ethyl acetate/iso-hexane 10-50 %.

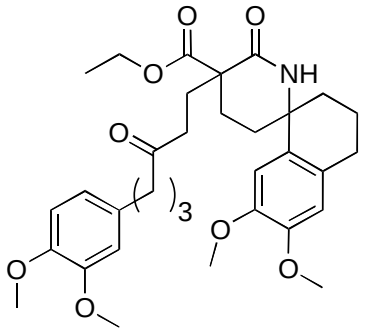
3-Carboxyethyl-3-methylspiro[5.5]-1-azaundecan[{6,7-*d*}(1',2'-dimethoxyphenyl)]-2-one (9)



The title compound was isolated according to general procedure A as a colorless oil (3:2 mixture of inseparable diastereomers, 124 mg, 76 %).

IR (film): 1659, 1728 (C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.26 (t, 6H, $OCH_2C\underline{H}_3$, $OCH_2C\underline{H}_3$', J = 7.1 Hz), 1.52 (s, 3H, $CC\underline{H}_3$), 1.61 (s, 3H, $CC\underline{H}_3$'), 1.72-1.90 (m, 8H), 1.96-1.99 (m, 4H), 2.08-2.12 (m, 1H), 2.16-2.22 (m, 2H), 2.31-2.37 (m, 1H), 2.68-2.76 (m, 4H), 3.82 (s, 3H, OMe'), 3.83 (s, 6H, OMe, OMe'), 3.87 (s, 3H, OMe), 4.16-4.28 (m, 4H, $OC\underline{H}_2CH_3$, $OC\underline{H}_2CH_3$'), 5.73 (s, 1H, NH), 5.74 (s, 1H, NH'), 6.50 (s, 1H, Ar-H), 6.54 (s, 1H, Ar-H'), 6.75 (s, 1H, Ar-H'), 7.15 (s, 1H, Ar-H); δ_C ($CDCl_3$, 100 MHz): 14.0, 14.1, 19.5, 20.0, 22.3, 22.3, 28.6, 28.7, 29.4, 30.1, 32.2, 32.5, 36.8, 37.3, 49.7, 49.9, 55.7, 55.8, 56.0, 56.0, 57.6, 57.9, 61.5, 61.5, 109.2, 110.3, 110.8, 111.4, 128.7, 128.8, 132.7, 133.1, 147.4, 147.6, 148.2, 148.4, 171.3, 171.9, 173.2, 173.4; MS (ES+) 385 ($[M+Na]^+$, 100%), 362 ($[M+H]^+$, 70%); HRMS (ES+) exact mass calculated for $C_{20}H_{28}NO_5$ $[M+H]^+$ requires *m/z* 362.1962, found *m/z* 362.1958.

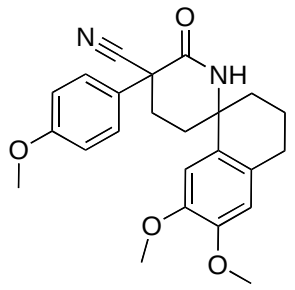
3-Carboxyethyl-3-(6-(1',2'-dimethoxyphenyl)-3-oxohexyl)spiro[5.5]-1-azaundecan[{6,7-*d*}(1',2'-dimethoxyphenyl)]-2-one (10)



The title compound was isolated in a modification to general procedure A (1.00 mmol of Michael acceptor was used) as a colorless oil (1:1 mixture of inseparable diastereomers, 190 mg, 73 %).

IR (film): 1661, 1730 (C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.22-1.33 (m, 6H, $OCH_2C\underline{H}_3$, $OCH_2C\underline{H}_3$'), 1.48-2.81 (m, 40H), 3.81-3.87 (m, 24H, 4 x OMe, 4 x OMe'), 4.16-4.26 (m, 4H, $C\underline{H}_2CH_3$, $C\underline{H}_2CH_3$'), 5.67 (s, 1H, NH), 6.50 (s, 1H, NH'), 6.64-6.71 (m, 6H, 6 x Ar-H), 6.76-6.79 (m, 3H, 3 x Ar-H'), 7.09 (s, 1H, Ar-H); δ_C ($CDCl_3$, 100 MHz): 14.0, 14.2, 20.0, 24.4, 25.4, 26.7, 27.3, 27.8, 28.6, 28.8, 29.2, 31.8, 32.4, 34.7, 34.8, 35.6, 35.8, 36.7, 38.7, 39.8, 41.9, 43.9, 51.0, 53.0, 55.7, 55.8, 55.8, 56.0, 56.0, 57.8, 61.3, 61.4, 61.6, 70.5, 71.8, 72.9, 107.8, 110.2, 110.8, 111.1, 111.2, 111.3, 111.5, 111.6, 111.6, 120.0, 120.1, 120.2, 128.8, 133.1, 133.5, 134.2, 134.6, 134.8, 147.1, 147.4, 147.7, 147.7, 148.3, 148.7, 169.5, 169.5, 170.2, 171.5, 172.6, 210.0; MS (ES+) 582 ($[M+H]^+$, 10%), 604 ($[M+Na]^+$, 100%); HRMS (ES+) exact mass calculated for $C_{33}H_{44}NO_8$ $[M+H]^+$ requires *m/z* 582.3061, found *m/z* 582.3066.

3-(4'-Methoxyphenyl)-3-nitrilospiro[5.5]-1-azaundecan[{6,7-*d*}(1',2'-dimethoxyphenyl)]-2-one (11)

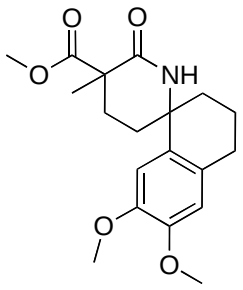


The title compound was isolated according to general procedure A as a colorless oil (4:1 mixture of separable diastereomers, 178 mg, 97 %).

Major isomer: IR (film): 1665 (C=O), 2360 (C≡N) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.85-1.94 (m, 3H), 2.13-2.19 (m, 2H), 2.37-2.43 (m, 3H), 2.72-2.78 (m, 2H), 3.81 (s, 3H, OMe), 3.85 (s, 3H, OMe), 3.91 (s, 3H, OMe), 6.21 (s, 1H, NH), 6.55 (s, 1H, Ar-H), 6.93 (d, 2H, Ar-H', J = 8.0 Hz), 6.99 (s, 1H, Ar-H), 7.38 (d, 2H, J = 8.7 Hz); δ_C ($CDCl_3$, 100 MHz): 19.9, 28.6, 32.6, 33.2, 37.2, 49.4, 55.3, 55.8, 56.0, 58.5, 109.2, 111.1, 114.3, 119.8, 127.9, 128.3, 128.7, 131.8, 147.8, 148.5, 159.5, 166.0; MS (ES+) 429 ($[M+Na]^+$, 100%), 407 ($[M+H]^+$, 10%); HRMS (ES+) exact mass calculated for $C_{24}H_{27}N_2O_4$ $[M+H]^+$ requires *m/z* 407.1965, found *m/z* 407.1965.

Minor isomer : δ_H ($CDCl_3$, 300 MHz): 0.82-0.91 (m, 1H), 1.71-2.79 (m, 8H), 3.67 (s, 3H, OMe), 3.81 (s, 6H, 2 x OMe), 3.83-3.85 (m, 1H), 5.99 (br s, 1H, NH), 6.49 (s, 1H, Ar-H), 6.54 (s, 1H, Ar-H), 6.94 (d, 2H, Ar-H, J = 8.7 Hz), 7.53 (d, 2H, Ar-H, J = 8.7 Hz); δ_C ($CDCl_3$, 75 MHz): 20.0, 28.8, 29.7, 30.8, 31.4, 37.3, 55.5, 55.8, 55.9, 58.7, 109.2, 111.3, 114.7, 120.2, 127.7, 128.3, 129.3, 131.5, 147.7, 148.6, 159.9, 165.7.

3-Carboxymethyl-3-methylspiro[5.5]-1-azaundecan[{6,7-*d*}(1',2'-dimethoxyphenyl)]-2-one (12)

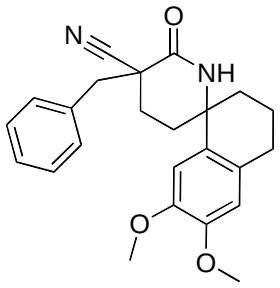


The title compound was isolated according to general procedure A as a colorless oil (3:2 mixture of inseparable diastereomers, 124 mg, 80 %).

IR (film): 1659, 1731 (C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.53 (s, 3H, CC<u>H</u>$_3$), 1.63 (s, 3H, CC<u>H</u>$_3$'), 1.73-1.90 (m, 8H), 1.96-1.99 (m, 4H), 2.08-2.18 (m, 1H), 2.17-2.25 (m, 2H), 2.33-2.39 (m, 1H), 2.69-2.76 (m, 4H), 3.77 (s, 3H, OMe'), 3.78 (s, 3H, OMe), 3.84 (s, 9H, OMe, 2 x OMe'), 3.88 (s, 3H, OMe), 5.73 (s, 2H, NH, NH'), 6.51 (s, 1H, Ar-H), 6.54 (s, 1H, Ar-H'), 6.76 (s, 1H, Ar-H'), 7.12 (s, 1H, Ar-H); δ_C ($CDCl_3$, 100 MHz): 19.6, 19.9, 22.4, 22.4, 28.6, 28.7, 29.4, 30.2, 32.2, 32.6, 37.0, 37.2, 49.8, 50.0, 52.7, 55.8, 55.8, 55.9, 56.0, 57.7, 58.0, 109.2, 110.1, 110.9, 111.4, 128.7, 128.9, 132.6, 133.0, 147.5, 147.6, 148.2, 148.4, 171.2, 171.9, 173.8, 174.0; MS (ES+) 370 ($[M+Na]^+$, 100%), 348 ($[M+H]^+$, 60%); HRMS (ES+) exact mass calculated for $C_{19}H_{26}NO_5$ $[M+H]^+$ requires *m/z* 348.1805, found *m/z* 348.1805.

3-Benzyl-3-nitrilospiro[5.5]-1-azaundecan[{6,7-*d*}(1',2'-dimethoxyphenyl)]-2-one

(13)

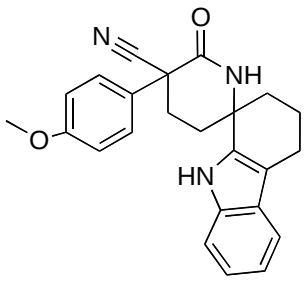


The title compound was isolated according to general procedure A as a colorless oil (3:1 mixture of inseparable diastereomers, 137 mg, 78 %).

IR (film): 1667 (C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.61-2.13 (m, 15H), 2.04-2.26 (m, 1H), 2.65-2.76 (m, 4H), 3.22 (d, 1H, C$\underline{H_2}^a$Ph, *J* = 13.7 Hz), 3.45 (s, 2H, C$\underline{H_2}$Ph'), 3.51 (d, 1H, C$\underline{H_2}^b$Ph, *J* = 13.7 Hz), 3.64 (s, 3H, OMe'), 3.83 (s, 3H, OMe), 3.86 (s, 3H, OMe'), 3.88 (s, 3H, OMe), 5.84 (s, 1H, NH'), 5.89 (s, 1H, NH), 6.44 (s, 1H, Ar-H'), 6.49 (s, 1H, Ar-H), 6.55 (s, 1H, Ar-H'), 6.94 (s, 1H, Ar-H), 7.30-7.37 (m, 10H, $CH_2\underline{Ph}$, $CH_2\underline{Ph}$'); δ_C ($CDCl_3$, 100 MHz): 19.1, 20.0, 26.1, 27.1, 28.2, 28.8, 32.4, 32.5, 36.4, 38.5, 40.9, 41.5, 44.3, 44.3, 55.8, 56.0, 56.2, 57.8, 58.2, 108.9, 109.3, 110.9, 111.8, 120.1, 120.3, 127.6, 127.9, 128.6, 128.7, 128.9, 130.4, 130.6, 131.8, 134.0, 134.4, 147.3, 148.0, 148.5, 148.7, 165.8, 166.4; MS (ES+) 413 ($[M+Na]^+$, 100%), 391 ($[M+H]^+$, 5%); HRMS (ES+) exact mass calculated for $C_{24}H_{27}N_2O_3$ $[M+H]^+$ requires *m/z* 391.2016, found *m/z* 391.2025.

3-(4'-Methoxyphenyl)-3-nitrilospiro[5.5]-1-azaundecan[{7,6-*b*}(indolyl)]-2-one

(14)



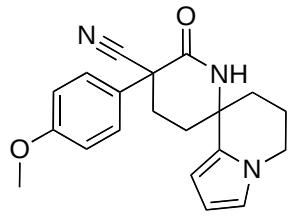
The title compound was isolated according to general procedure B as a white powder (2:1 mixture of separable diastereomers, 133 mg, 77 %).

Major isomer: m.p. dec ~240^{o}C; IR (film): 1658 (C=O), 2365 (C≡N) cm^{-1}; δ_H (DMSO, 400 MHz): 1.65 (t, 1H, *J* = 11.3 Hz), 1.77-1.84 (m, 2H), 1.92-1.97 (m, 1H), 2.04 (t, 1H, *J* = 13.0 Hz), 2.13-2.18 (m, 1H), 2.40-2.45 (m, 1H), 2.58-2.65 (m, 2H), 2.72-2.78 (m, 1H), 3.79 (s, 3H, OMe), 6.97 (t, 1H, Ar-H, *J* = 7.5 Hz), 7.04-7.10 (m, 3H, 3 x Ar-H), 7.35-7.40 (m, 4H, 4 x Ar-H), 8.74 (s, 1H, CONH), 11.25 (s, 1H, Ar-NH); δ_C (DMSO, 100 MHz): 19.6, 20.5, 30.4, 31.5, 40.5, 48.8, 54.2, 55.3, 109.0, 111.2, 114.4, 118.1, 118.4, 121.0, 121.3, 126.5, 128.1, 129.1, 136.1, 137.1, 159.0, 164.5; MS (ES-) 384 ([M-H]$^-$, 100%); HRMS (ES+) exact mass calculated for $C_{24}H_{23}N_3O_2Na$ [M+Na]$^+$ requires *m/z* 408.1672, found *m/z* 408.1671.

Minor isomer: δ_H (DMSO, 300 MHz): 1.82-2.19 (m, 7H), 2.62-2.66 (m, 3H), 3.82 (s, 3H, OMe), 6.97 (t, 1H, *J* = 7.5 Hz), 7.04-7.10 (m, 3H), 7.39 (t, 2H, *J* = 6.9 Hz), 7.60 (d, 2H, *J* = 8.7 Hz), 8.77 (br s, 1H, Amide-NH), 10.63 (br s, 1H, Indole-NH); δ_C (DMSO, 75 MHz): 19.7, 20.4, 28.7, 31.4, 37.4, 48.3, 54.6, 55.3, 110.2, 111.5, 114.2, 118.1, 118.5, 121.2, 121.4, 126.6, 128.7, 129.1, 136.3, 136.4, 159.0, 164.7.

3-(p-Methoxyphenyl)-3-nitrilospiro[5.5]-1-azaundecan[{7,6-*a*}(pyrrolo)]-2-one

(15)



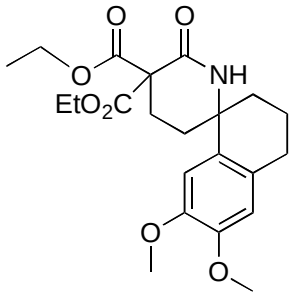
The title compound was isolated using a slight modification to general procedure B (using a 0.36 mmol scale) as a white powder (2:1 mixture of separable diastereomers, 86 mg, 72 %).

Major isomer: m.p. 207-209^{o}C; IR (film): 1662 (C=O), 2397 (C≡N) cm^{-1}; δ_H (DMSO, 400 MHz): 1.65 (ddd, 1H, *J* = 2.6 Hz, *J* = 10.2 Hz, *J* = 14.1 Hz), 1.82-86 (m, 1H), 1.92-2.05 (m, 5H), 2.32-2.38 (m, 1H), 3.72-3.75 (m, 1H), 3.77 (s, 3H, OMe), 3.90-3.95 (m, 1H), 5.95 (dd, 1H, Pyrrole-H, *J* = 1.8 Hz, *J* = 3.5 Hz), 6.05 (dd, 1H, Pyrrole-H, *J* = 2.8 Hz, *J* = 3.5 Hz), 6.65 (dd, 1H, Pyrrole-H, *J* = 1.8 Hz, *J* = 2.4 Hz), 7.01 (d, 2H, Ar-H, *J* = 4.8 Hz), 7.33 (d, 2H, Ar-H, *J* = 4.8 Hz), 8.70 (s, 1H, NH); δ_C (DMSO, 100 MHz): 19.2, 30.8, 31.6, 35.5, 44.3, 48.7, 54.2, 55.3, 104.6, 107.6, 114.3, 119.9, 121.0, 128.1, 128.9, 133.3, 159.0, 164.2; MS (ES-) 334 ([M-H]$^-$, 100%), 362 ([M+H]$^+$, 70%); HRMS (ES+) exact mass calculated for $C_{20}H_{22}N_3O_2$ [M+H]$^+$ requires *m/z* 336.1707, found *m/z* 336.1705.

Minor isomer: δ_H ($CDCl_3$, 300 MHz): 1.79-1.83 (m, 1H), 1.96-2.06 (m, 4H), 2.16-2.34 (m, 1H), 2.59-2.68 (m, 1H), 3.12 (br s, 1H), 3.78 (s, 3H, OMe), 3.87-3.92 (m, 2H), 6.14 (dd, 1H, Pyrrole-H, *J* = 2.7 Hz, *J* = 3.6 Hz), 6.18 (dd, 1H, Pyrrole-H, *J* = 1.5 Hz, *J* = 3.6 Hz), 6.55 (dd, 1H, Pyrrole-H, *J* = 1.8 Hz, *J* = 2.4 Hz), 6.89 (d, 2H,

Ar-H, *J* = 8.7 Hz), 6.91 (br s, 1H, NH), 7.33 (d, 2H, Ar-H, *J* = 8.7 Hz); δ_C ($CDCl_3$, 100 MHz): 20.1, 31.4, 33.0, 36.9, 44.9, 49.4, 55.3, 55.6, 106.2, 108.6, 114.7, 120.7, 128.2, 128.4, 128.8, 132.7, 159.8, 165.6.

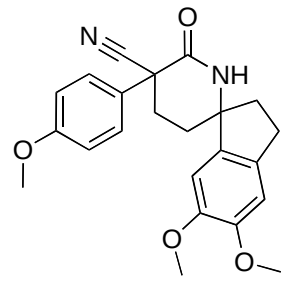
3-Di(carboxyethyl)spiro[5.5]-1-azaundecan[{6,7-*d*}(1'-2'-dimethoxyphenyl)]-2-one (16)



The title compound was isolated according to general procedure A as a colorless oil (153 mg, 81 %).

IR (film): 1666, 1730, 1743 (C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.32 (t, 6H, 2 x $OCH_2C\underline{H}_3$, J = 5.2 Hz), 1.68-1.93 (m, 4H), 2.02-2.06 (m, 1H), 2.17-2.20 (m, 1H), 2.45-2.49 (m, 1H), 2.52-2.58 (m, 1H), 2.68-2.75 (m, 2H), 3.84 (s, 3H, OMe), 3.87 (s, 3H, OMe), 4.29-4.36 (m, 4H, 2 x $OC\underline{H}_2CH_3$), 5.71 (s, 1H, NH), 6.52 (s, 1H, Ar-H), 6.99 (s, 1H, Ar-H); δ_C ($CDCl_3$, 100 MHz): 14.0, 14.1, 20.0, 25.8, 28.6, 32.3, 37.0, 55.8, 56.0, 58.2, 62.4, 62.4, 63.3, 109.9, 110.9, 128.7, 132.7, 147.7, 148.4, 165.5, 167.7, 168.3; MS (ES+) 442 ($[M+Na]^+$, 100%), 420 ($[M+H]^+$, 70%); HRMS (ES+) exact mass calculated for $C_{22}H_{30}NO_7$ $[M+H]^+$ requires *m/z* 420.2017, found *m/z* 420.2010.

3-(4'-Methoxyphenyl)-3-nitrilospiro[5.4]-1-azadecan[{6,7-*d*}(1',2'-dimethoxyphenyl)]-2-one (17)



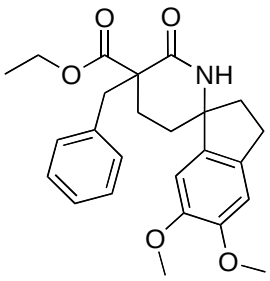
The title compound was isolated according to general procedure C as a white powder (2:1 mixture of separable diastereomers, 172 mg, 98 %).

Major isomer: m.p. 218-214°C; IR (film): 1670 (C=O), 2251 (C≡N) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.75 (dt, 1H, *J* = 2.3 Hz, *J* = 14.4 Hz), 1.82 (m, 1H), 2.20 (m, 1H), 2.49 (m, 2H), 2.65 (dt, 1H, *J* = 2.7 Hz, *J* = 14.2 Hz), 2.82 (quintet, 1H, *J* = 8.2 Hz), 2.94 (ddd, 1H, *J* = 1.7 Hz, *J* = 8.6 Hz, *J* = 15.8 Hz), 3.82 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.85 (s, 3H, OMe), 6.36 (br s, 1H, NH), 6.60 (s, 1H, Ar-H), 6.71 (s, 1H, Ar-H), 6.96 (d, 2H, 2 x Ar-H, *J* = 8.8 Hz), 7.48 (d, 2H, 2 x Ar-H, *J* = 8.8 Hz); δ_C ($CDCl_3$, 100 MHz): 28.8, 30.0, 33.2, 41.5, 48.8, 55.5, 56.1, 67.7, 77.3, 105.3, 107.9, 114.5, 120.3, 127.9, 128.3, 133.8, 136.8, 148.8, 150.1, 159.8, 165.6; MS (ES+) 415 ($[M+Na]^+$, 100%), 393 ($[M+H]^+$, 10%); HRMS (ES+) exact mass calculated for $C_{23}H_{24}N_2O_4Na$ $[M+Na]^+$ requires *m/z* 415.1628, found *m/z* 415.1624.

Minor isomer: δ_H ($CDCl_3$, 300 MHz): 1.96-2.02 (m, 1H), 2.17-2.30 (m, 2H), 2.37-2.59 (m, 3H), 2.80-2.99 (m, 2H), 3.83 (s, 3H, OMe), 3.89 (s, 3H, OMe), 3.93 (s, 3H, OMe), 6.35 (br s, 1H, NH), 6.77 (s, 1H, Ar-H), 6.87 (s, 1H, Ar-H), 6.95 (d, 2H, Ar-H, *J* = 8.7 Hz), 7.40 (d, 2H, Ar-H, *J* = 8.7 Hz); δ_C ($CDCl_3$, 75 MHz): 28.8, 31.1,

34.5, 41.4, 49.4, 55.4, 56.1, 56.3, 67.8, 105.5, 107.9, 114.5, 119.9, 127.9, 128.8, 133.4, 136.9, 149.2, 150.2, 159.6, 165.9.

3-Benzyl-3-carboxyethylspiro[5.4]-1-azadecan[{6,7-*d*}(1',2'-dimethoxyphenyl)]-2-one (18)

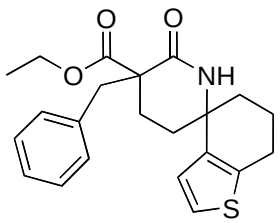


The title compound was isolated according to general procedure C as a colorless oil (3:2 mixture of inseparable diastereomers, 175 mg, 92 %).

IR (film): 1660, 1729 (C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.13-1.20 (1H, m), 1.25-1.31 (2 x t, 6H, $OCH_2C\underline{H}_3$, $OCH_2C\underline{H}_3$', J = 7.1 Hz), 1.36-1.42 (dt, 1H, J = 8.6 Hz, J = 13.1 Hz), 1.50-1.55 (m, 2H), 1.68-1.71 (m, 1H), 1.90-2.00 (m, 4H), 2.07 (dt, 1H, J = 8.6 Hz, J = 12.9 Hz), 2.16-2.25 (m, 2H), 2.53 (quintet, 1H, J = 8.0 Hz), 2.60 (ddd, 1H, J = 2.7 Hz, J = 8.9 Hz, J = 15.6 Hz), 2.66 (quintet, 1H, J = 7.9 Hz), 2.76 (ddd, 1H, J = 2.9 Hz, J = 8.7 Hz, J = 15.7 Hz), 3.00 (d, 1H, $PhCH_2^a$, J = 13.4 Hz), 3.01 (d, 1H, $PhCH_2^{a'}$, J = 13.5 Hz), 3.54 (s, 3H, OMe'), 3.65 (d, 1H, $PhCH_2^b$, J = 13.5 Hz), 3.71 (d, 1H, $PhCH_2^b$, J = 13.4 Hz), 3.74 (s, 3H, OMe'), 3.77 (s, 3H, OMe), 3.79 (s, 3H, OMe), 4.13-4.31 (m, 4H, $OC\underline{H}_2CH_3$', $OC\underline{H}_2CH_3$), 5.79 (s, 1H, NH'), 5.80 (s, 1H, NH), 5.86 (s, 1H, Ar-H'), 6.58 (s, 1H, Ar-H'), 6.59 (s, 1H, Ar-H), 6.72 (s, 1H, Ar-H), 7.15-7.26 (m, 8H), 7.30 (d, 2H, 2 x Ar-H', J = 7.6 Hz) ; δ_C ($CDCl_3$, 100 MHz): 14.2, 14.3, 25.6, 26.7, 27.3, 28.7, 29.7, 30.7, 31.1, 40.0, 40.3, 41.2, 41.9, 54.5, 54.5, 56.0, 56.1, 56.3, 61.8, 66.8, 67.1, 77.3, 105.4, 105.5, 107.5, 107.6, 126.9, 126.9, 128.2, 128.4, 130.9, 130.9, 133.3, 133.6, 136.5, 137.1, 137.6, 137.8, 148.4, 148.8, 149.6, 149.8, 169.9, 173.0, 173.1**;** MS (ES+) 424 ($[M+H]^+$, 100%), 446 ($[M+Na]^+$,

30%); HRMS (ES+) exact mass calculated for $C_{25}H_{30}NO_5$ $[M+H]^+$ requires *m/z* 424.2118, found *m/z* 424.2122.

3-Benzyl-3-carboxyethylspiro[5.5]-1-azaundecan[{7,6-*b*}(thieno)]-2-one (19)



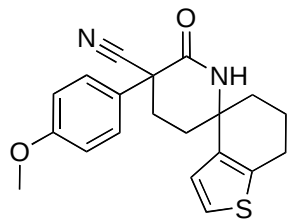
The title compound was isolated in a slight modification to general procedure C (using a 0.20 mmol scale) as a colorless oil (1:1 mixture of separable diastereomers, 77 mg, 100 %).

Least polar isomer (R_f 0.3, EtOAc:petroleum ether 1:1): IR (film): 1664, 1729 (C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.26 (t, 3H, $OCH_2C\underline{H}_3$, *J* = 7.2 Hz), 1.50 (ddd, 1H, *J* = 3.9 Hz, *J* = 8.4 Hz, *J* = 13.7 Hz), 1.62 (ddd, 1H, *J* = 3.9 Hz, *J* = 9.3 Hz, *J* = 13.7 Hz), 1.75-1.89 (m, 4H), 1.98 (ddd, 1H, *J* = 3.8 Hz, *J* = 9.3 Hz, *J* = 14.7 Hz), 2.09 (ddd, 1H, *J* = 3.8 Hz, *J* = 8.4 Hz, *J* = 14.4 Hz), 2.62-2.66 (m, 2H), 3.00 (d, 1H, $PhCH_2^a$, *J* = 13.3 Hz), 3.70 (d, 1H, $PhCH_2^b$, *J* = 13.3 Hz), 4.13-4.19 (m, 1H, $OC\underline{H}_2^aCH_3$), 4.22-4.28 (m, 1H, $OC\underline{H}_2^bCH_3$), 5.56 (d, 1H, Thiophene-H, *J* = 5.3 Hz), 5.74 (br s, 1H, NH), 6.67 (d, 1H, Thiophene-H, *J* = 5.3 Hz), 7.24-7.28 (m, 5H, Ar-H); δ_C ($CDCl_3$, 100 MHz): 14.2, 20.2, 24.6, 26.2, 32.3, 38.3, 40.9, 54.6, 56.0, 61.8, 122.2, 125.6, 127.0, 128.5, 131.1, 136.8, 137.3, 139.4, 169.5, 173.1**;** MS (ES+) 384 ($[M+H]^+$, 100%), 406 ($[M+Na]^+$, 30%); HRMS (ES+) exact mass calculated for $C_{22}H_{26}NO_3S$ $[M+H]^+$ requires *m/z* 384.1628, found *m/z* 384.1634.

Most polar isomer (R_f 0.26, EtOAc:petroleum ether 1:1): 1.11-1.19 (m, 1H), 1.27-1.33 (m, 1H), 1.40 (t, 3H, $OCH_2C\underline{H}_3$, *J* = 7.2 Hz), 1.62-1.76 (m, 3H), 1.94-2.08 (m, 2H), 2.15-2.26 (m, 1H), 2.68-2.75 (m, 2H), 3.06 (d, 1H, $PhC\underline{H}_2^a$, *J* = 13.5 Hz), 3.75 (d, 1H, $PhC\underline{H}_2^b$, *J* = 13.5 Hz), 4.35 (m, 2H, $OC\underline{H}_2CH_3$), 5.99 (br s, 1H, NH), 7.02

(d, 1H, Thiophene-H, *J* = 5.4 Hz), 7.08 (d, 1H, Thiophene-H, *J* = 5.4 Hz), 7.28-7.30 (m, 5H, Ar-H); δ_C ($CDCl_3$, 75 MHz): 14.5, 20.7, 24.9, 25.8, 31.4, 35.8, 40.4, 56.1, 62.2, 77.5, 123.2, 125.8, 127.1, 128.5, 131.2, 136.7, 138.5, 139.7, 169.9, 173.2.

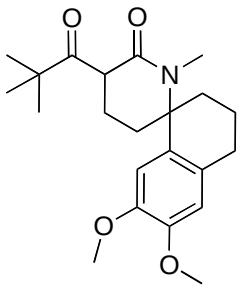
3-(p-Methoxyphenyl)-3-nitrilospiro[5.5]-1-azaundecan[{7,6-*b*}(thieno)]-2-one (20)



The title compound was isolated according to general procedure C as white crystals (3:2 mixture of inseparable diastereomers, 158 mg, 100 %).

m.p. 84-88°C; IR (film): 1670 (C=O), 2246 (C≡N) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.51-1.54 (m, 1H), 1.82-2.05 (m, 10H), 2.33-2.45 (m, 4H), 2.60 (dt, 1H, *J* = 3.5 Hz, *J* = 11.3 Hz), 2.69-2.79 (m, 4H), 3.75 (s, 3H, OMe), 3.77 (s, 3H, OMe'), 6.05 (br s, 2H, NH, NH'), 6.67 (d, 1H, Ar-H', *J* = 5.3 Hz), 6.87 (d, 2H, Ar-H, *J* = 8.7 Hz), 6.91 (d, 2H, Ar-H', *J* = 8.7 Hz), 7.00 (d, 1H, Ar-H', *J* = 5.3 Hz), 7.03 (d, 1H, Ar-H, *J* = 5.3 Hz), 7.09 (d, 1H, Ar-H, *J* = 5.3 Hz), 7.32 (d, 2H, Ar-H, *J* = 8.7 Hz), (d, 2H, Ar-H', *J* = 8.5 Hz); δ_C ($CDCl_3$, 100 MHz): 20.5, 20.6, 24.6, 24.7, 29.9, 31.7, 32.2, 33.3, 37.3, 37.4, 48.7, 49.4, 55.4, 55.4, 56.6, 56.8, 114.5, 114.6, 119.8, 120.2, 123.5, 123.6, 124.9, 125.4, 128.0, 128.0, 128.2, 128.5, 138.3, 138.4, 138.8, 138.8, 159.6, 159.8, 165.2, 165.5**;** MS (ES+) 353 ($[M+H]^+$, 10%), 375 ($[M+Na]^+$, 100%); HRMS (ES+) exact mass calculated for $C_{20}H_{24}N_3O_2S$ $[M+NH_4]^+$ requires *m/z* 370.1584, found *m/z* 370.1583.

3-(tert-Butyl carbonyl)spiro[5.5]-1-azaundecan[{6,7-*d*}(1',2'-dimethoxyphenyl)]-2-one (21)

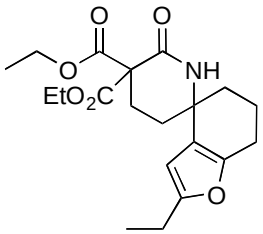


The title compound was isolated as a white powder (4:3 mixture of inseparable diastereomers, 154 mg, 92 %) in a modification to the general procedure A (1,2-dichloroethane was used as solvent and after 24 hours at room temperature the mixture was heated in a microwave to 80^{o}C for 45 mins).

m.p. 125-127^{o}C; IR (film): 1631, 1710 (C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.22 (s, 18H, ^{t}Bu, ^{t}Bu'), 2.17-2.29 (m, 15H), 2.54 (s, 3H, NMe), 2.56 (s, 3H, NMe'), 2.61-2.79 (m, 5H), 3.79 (s, 3H, OMe), 3.82 (s, 6H, OMe, OMe'), 3.93 (s, 3H, OMe'), 4.05-4.14 (m, 2H), 6.49 (s, 1H, Ar-H), 6.51 (s, 2H, Ar-H'), 7.20 (s, 1H, Ar-H); δ_C ($CDCl_3$, 100 MHz): 20.4, 20.5, 21.3, 23.0, 25.8, 25.9, 26.2, 28.9, 29.1, 30.9, 31.2, 31.4, 32.6, 33.0, 35.5, 45.3, 48.1, 49.0, 55.7, 55.7, 56.1, 56.2, 62.9, 63.1, 109.3, 110.2, 110.7, 111.2, 129.0, 129.9, 131.7, 131.7, 147.9, 147.9, 147.9, 148.1, 168.7, 169.6, 213.2, 214.1; MS (ES+) 396 ($[M+Na]^+$, 100%), 374 ($[M+H]^+$, 70%); HRMS (ES+) exact mass calculated for $C_{22}H_{31}NO_4Na$ $[M+Na]^+$ requires *m/z* 396.2145, found *m/z* 396.2141.

Formal Total Synthesis of (+/-) Perhydrohistrionicotoxin

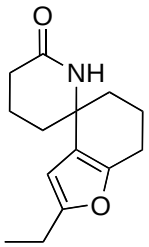
3-Di(carboxyethyl)spiro[5.5]-1-azaundecan[{7,6-*b*}(2-ethylfuryl)]-2-one (24)



The title compound was isolated according to general procedure B on a 0.208 mmol scale as a colorless oil (48 mg, 69 % [76 % based on returned starting material]).

IR (film): 1673, 1731 (C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.19 (t, 3H, $ArCH_2C\underline{H}_3$, J = 7.5 Hz), 1.31 (t, 3H, $OCH_2C\underline{H}_3$, J = 7.1 Hz), 1.35 (t, 3H, $OCH_2C\underline{H}_3$, J = 7.1 Hz), 1.73-1.96 (m, 6H), 2.51-2.59 (m, 6H), 4.25-4.39 (m, 4H, 2 x $OC\underline{H}_2CH_3$), 5.72 (s, 1H, NH), 5.91 (s, 1H, Ar-H); δ_C ($CDCl_3$, 100 MHz): 12.2, 13.9, 14.0, 14.1, 19.6, 21.4, 22.6, 26.1, 31.2, 27.9, 54.9, 62.4, 63.0, 102.2, 122.6, 149.2, 156.7, 165.1, 167.8, 168.0; MS (ES+) 400 ($[M+Na]^+$, 100%), 378 ($[M+H]^+$, 20%); HRMS (ES+) exact mass calculated for $C_{20}H_{28}NO_6$ $[M+H]^+$ requires *m/z* 378.1911, found *m/z* 378.1922.

Spiro[5.5]-1-azaundecan[{7,6-*b*}(2-ethyl furyl)]-2-one[6] (25)



Diester **24** (23.6 mg, 0.063 mmol) was stirred in tetrahydrofuran:water (3:1, 4 ml) and lithium hydroxide monohydrate (26.4 mg, 0.63 mmol) was added in one portion. The reaction was stirred at room temperature for 2.5 hours when all the starting material had been consumed as indicated by tlc (1:1 petroleum ether:ethyl acetate, starting material R_f 0.50 intermediate R_f 0.00). The mixture was acidified to pH~1 by the addition of 1.0 M aqueous hydrochloric acid and extracted 3 times with chloroform:isopropanol 3:1. The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The residue was dissolved in toluene (10 ml) and *p*-toluene sulfonic acid (1 mg, cat) was added before the mixture was heated to reflux. After16h, tlc indicated the formation of a new spot (R_f 0.10) and consumption of intermediate and the solvent was removed *in vacuo*. The residue was purified by medium pressure liquid chromatography eluting with neat ethyl acetate to give the title compound as an amorphous white film (11.4 mg, 78 %).

IR (film): 1673, 1731 (C=O) cm^{-1}; δ_H ($CDCl_3$, 400 MHz): 1.21 (t, 3H, $ArCH_2C\underline{H}_3$, J = 7.5 Hz), 1.76-1.95 (m, 8H), 2.40-2.43 (m, 2H), 2.51-2.61 (m, 4H), 5.65 (s, 1H, NH), 5.91 (s, 1H, Ar-H); δ_C ($CDCl_3$, 100 MHz): 12.2, 17.6, 19.6, 21.4, 22.7, 31.1, 34.3, 37.7, 54.2, 102.2, 123.0, 149.3, 156.6, 171.7; MS (ES+) 256

([M+Na]$^+$, 100%), 234 ([M+H]$^+$, 25%); HRMS (ES+) exact mass calculated for $C_{14}H_{20}NO_2$ [M+H]$^+$ requires *m/z* 234.1489, found *m/z* 234.1485.

5. References

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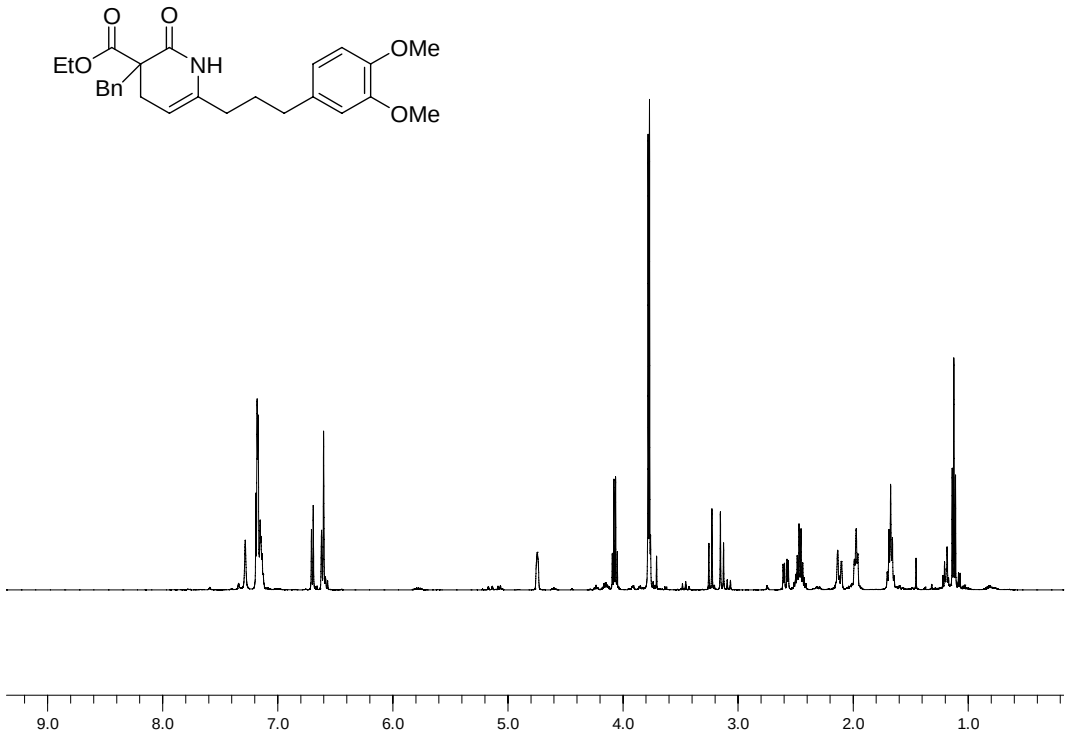
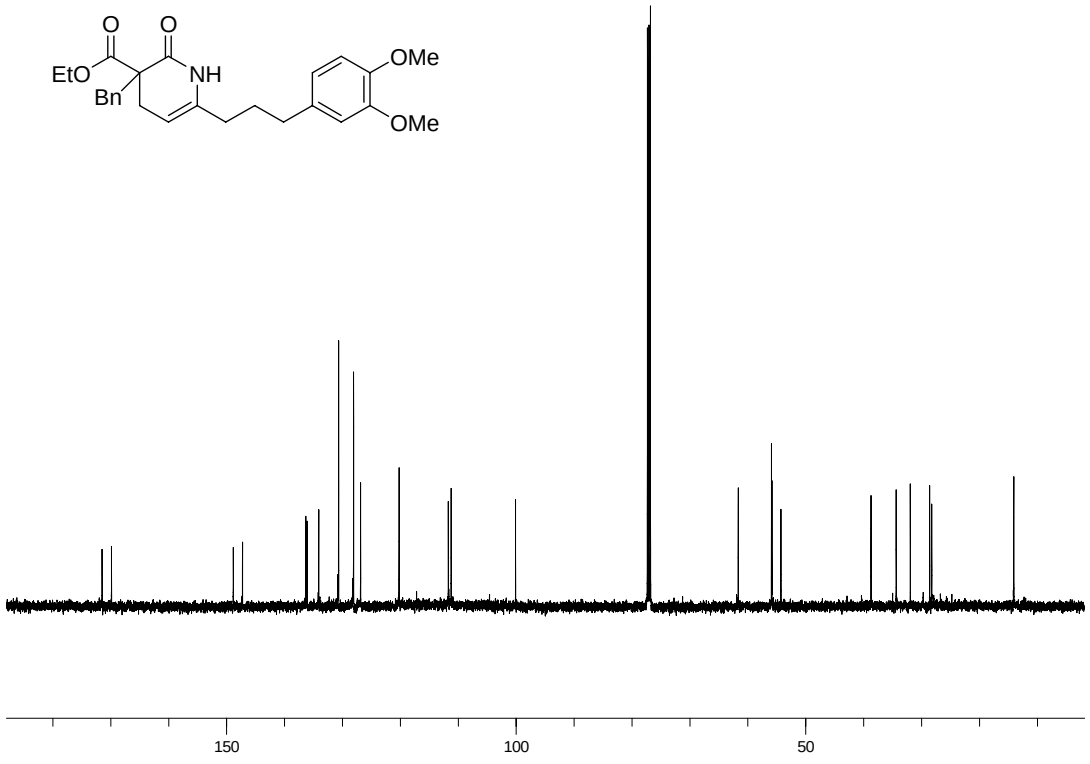
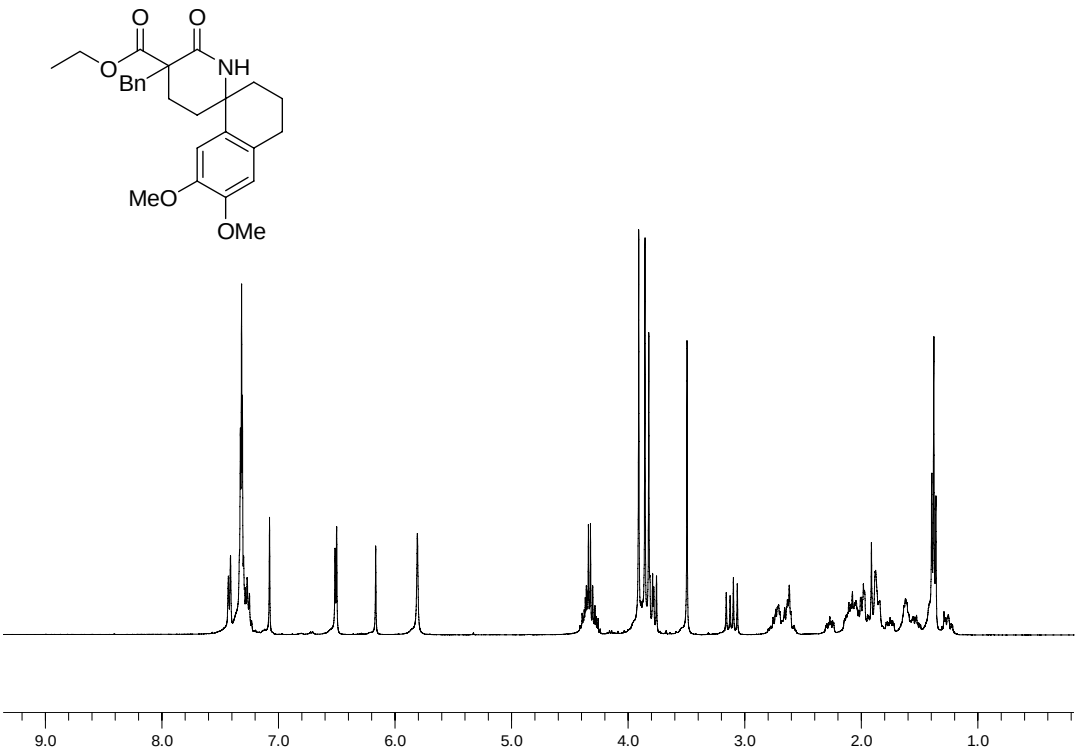

O
O
EtO
NH
Bn
OMe
OMe
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0


O
O
EtO
NH
Bn
OMe
OMe
150
100
50


O
O
O
NH
Bn
MeO
OMe
9.0
8.0
7.0
6.0
5.0
4.0
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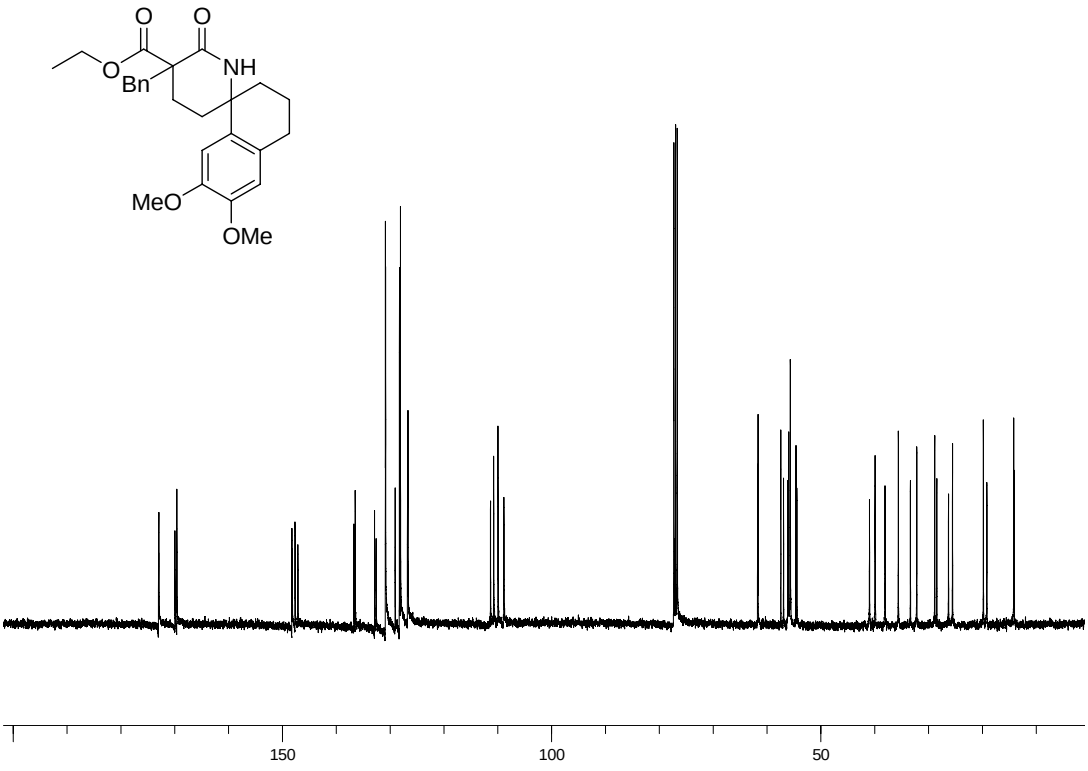
2.0
1.0


O
O
O
NH
Bn
MeO
OMe
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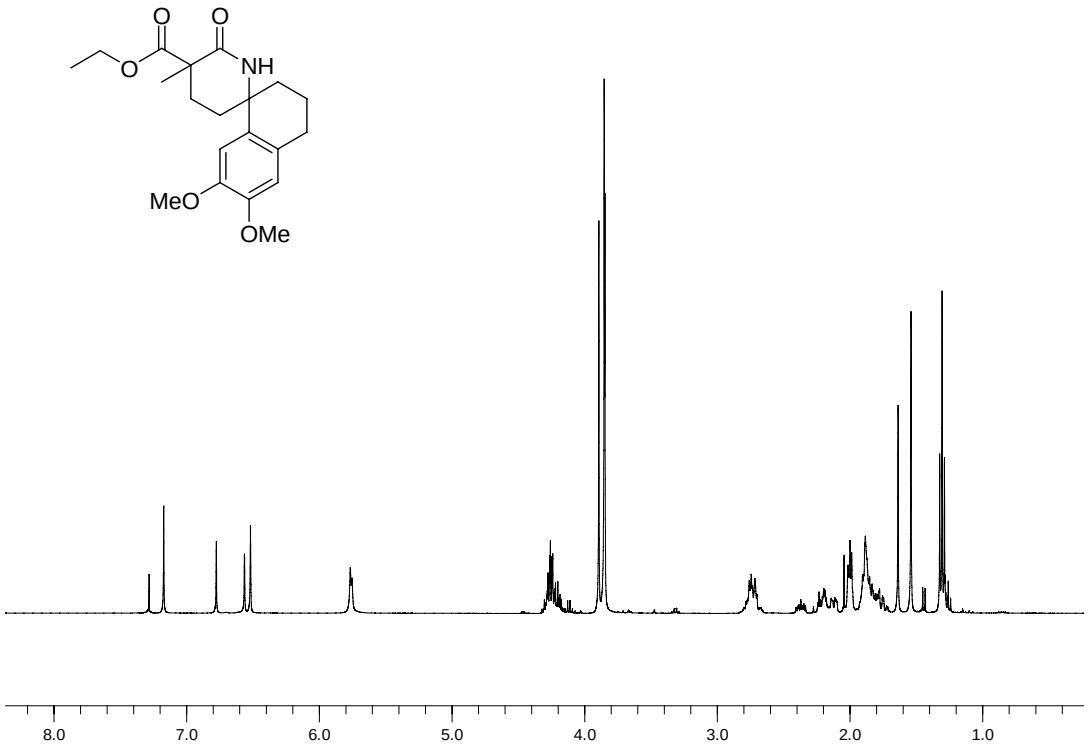
100
50


O
O
NH
O
MeO
OMe
8.0
7.0
6.0
5.0
4.0
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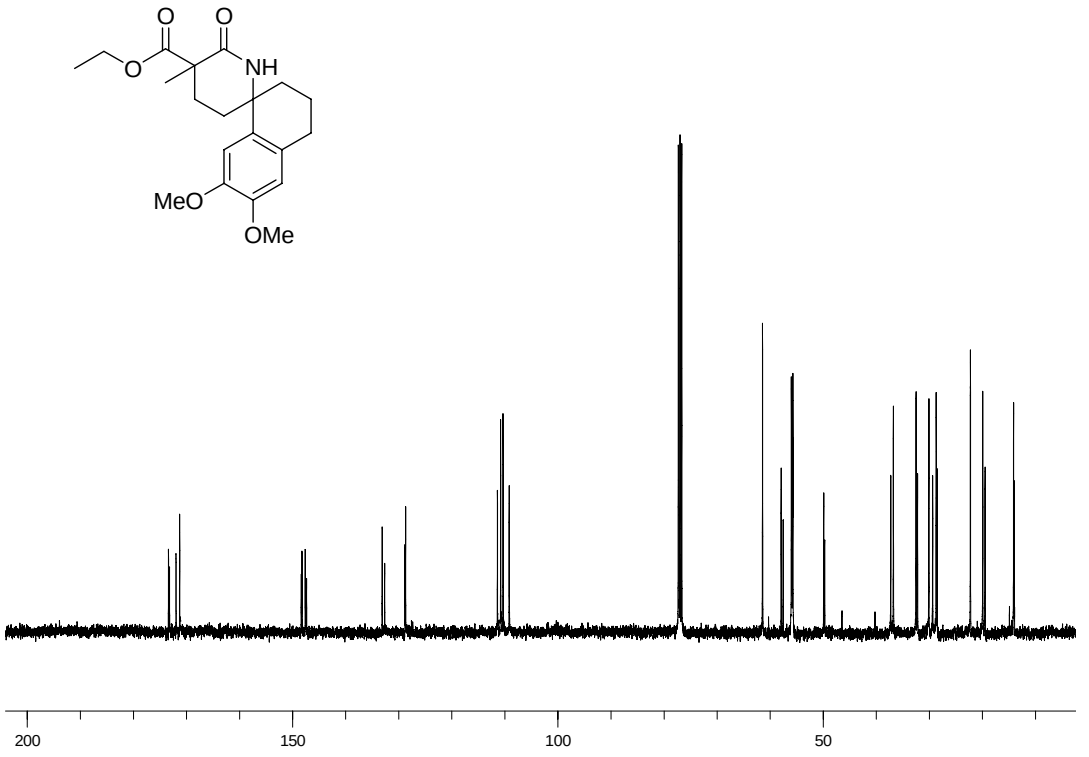
2.0
1.0


O
O
NH
O
MeO
OMe
200
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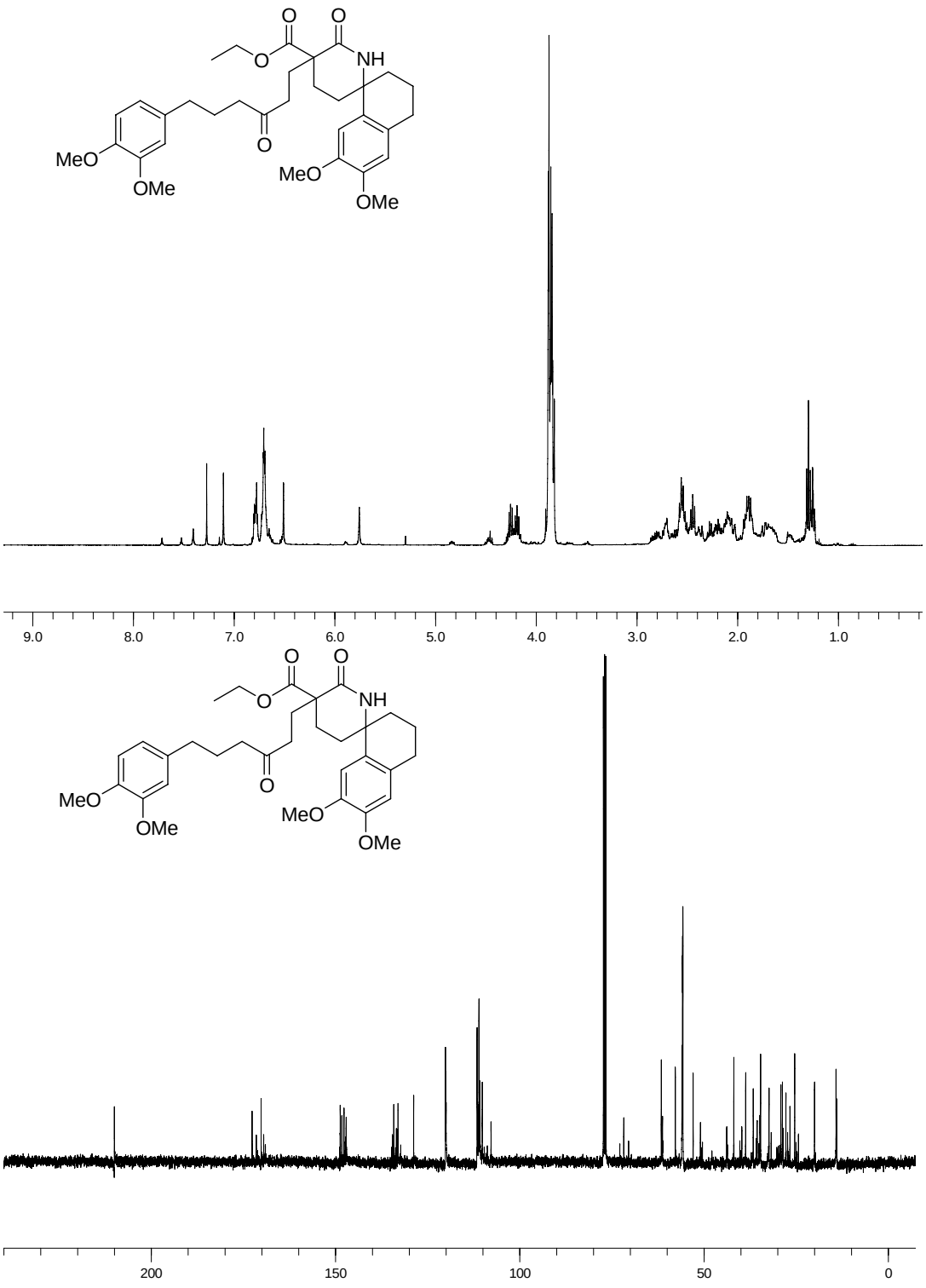
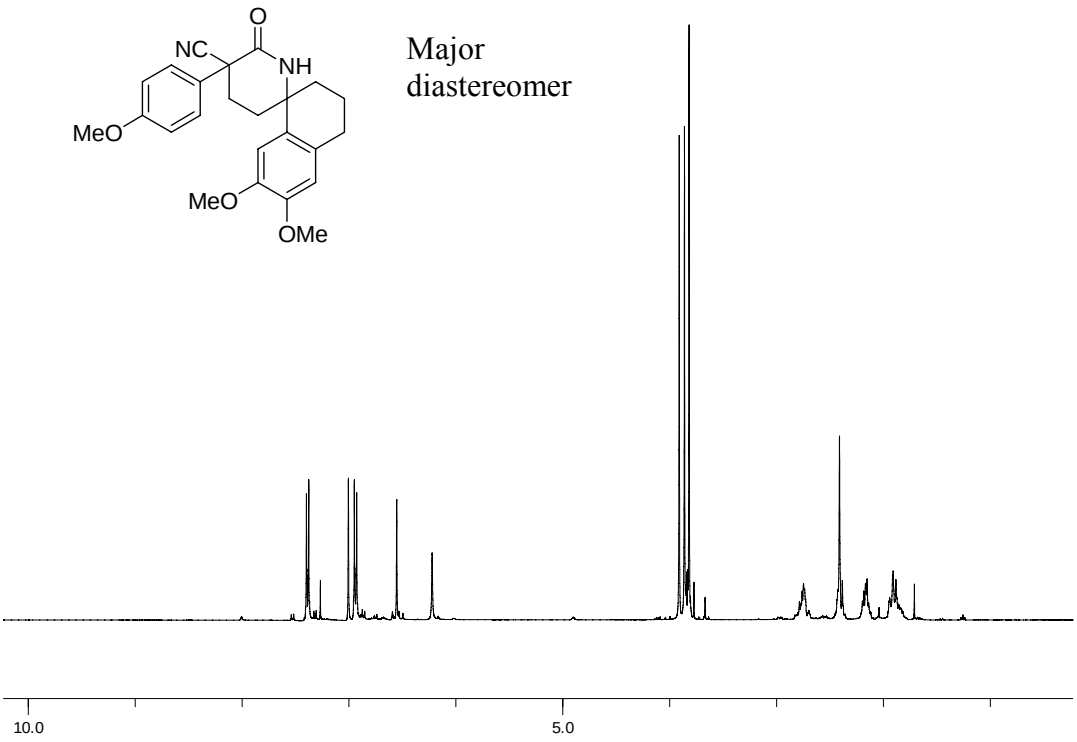
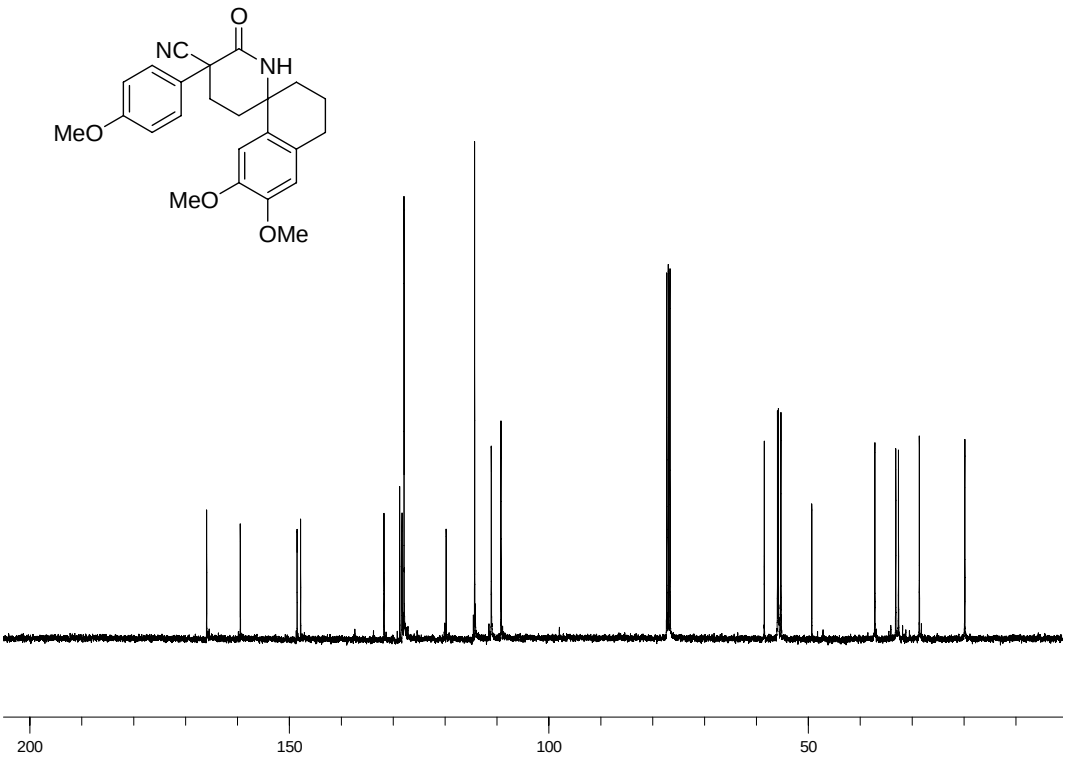
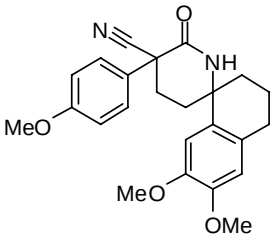
100
50

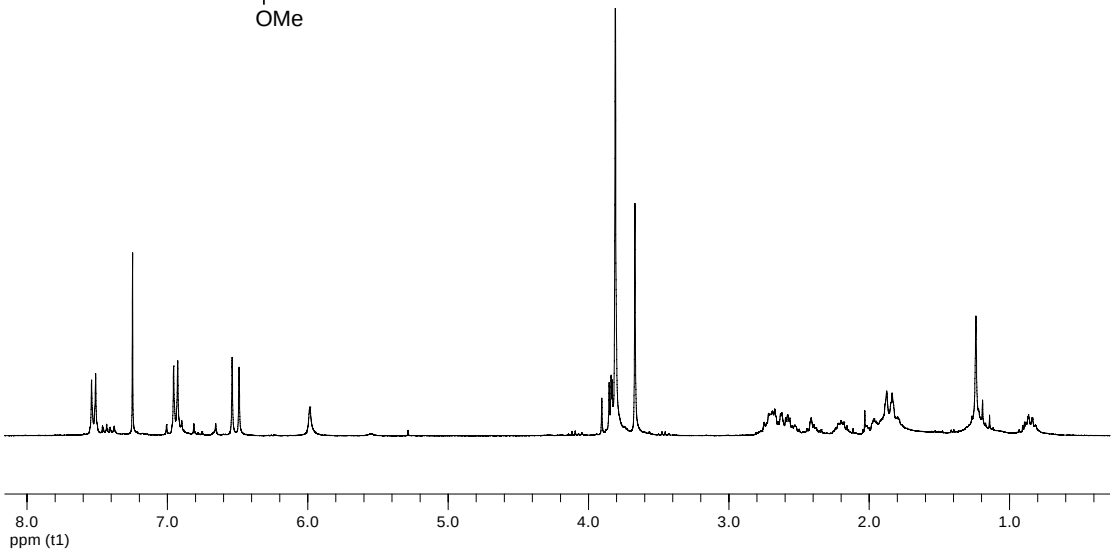

O
O
O
NH
O
MeO
OMe
MeO
OMe
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
200
150
100
50
0

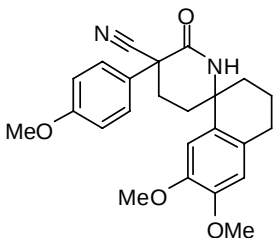

O
NC
NH
MeO
MeO
OMe
Major
diastereomer
10.0
5.0

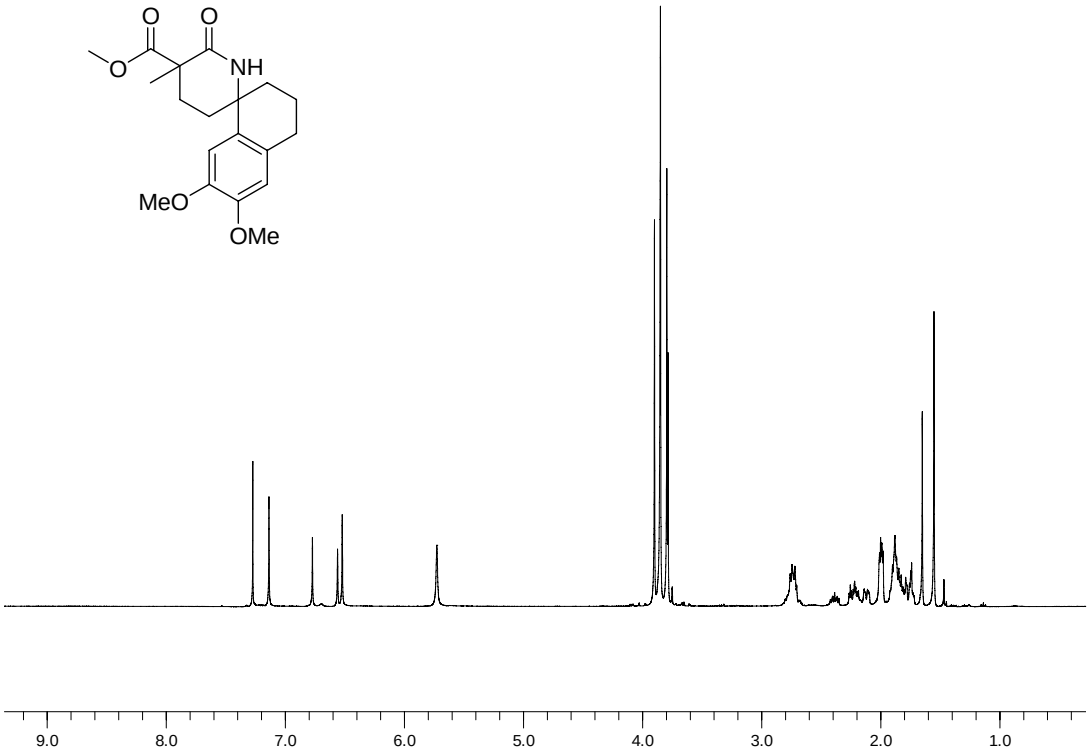

O
NC
NH
MeO
MeO
OMe
200
150
100
50

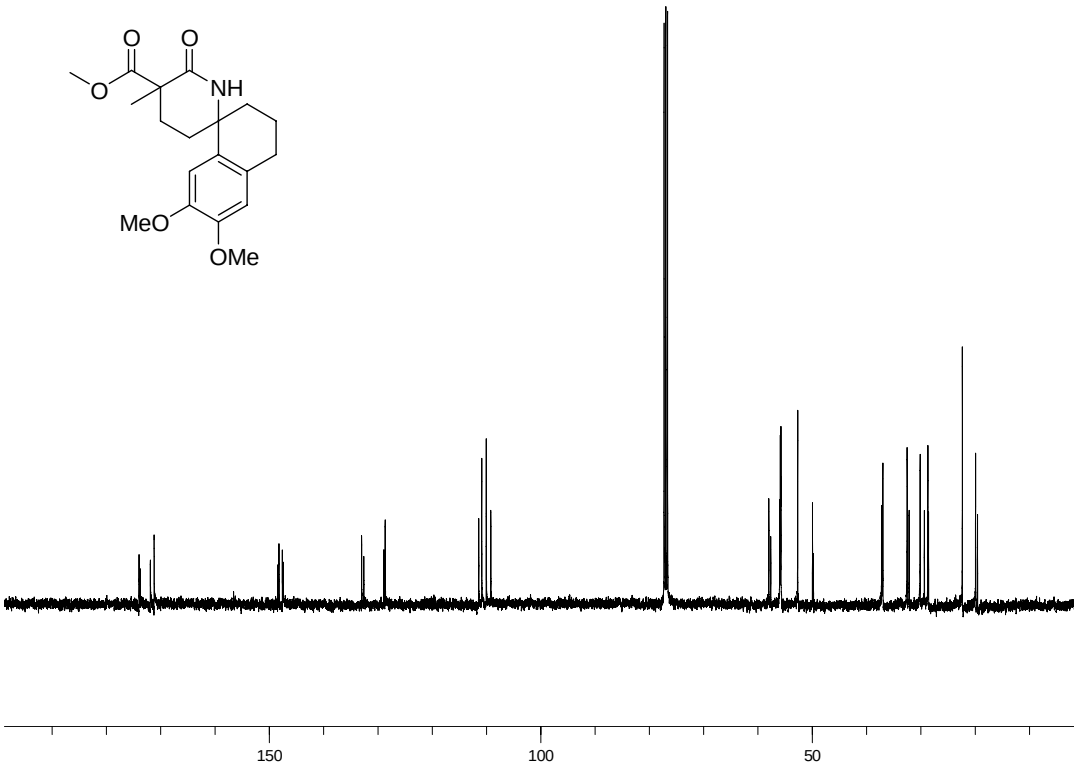


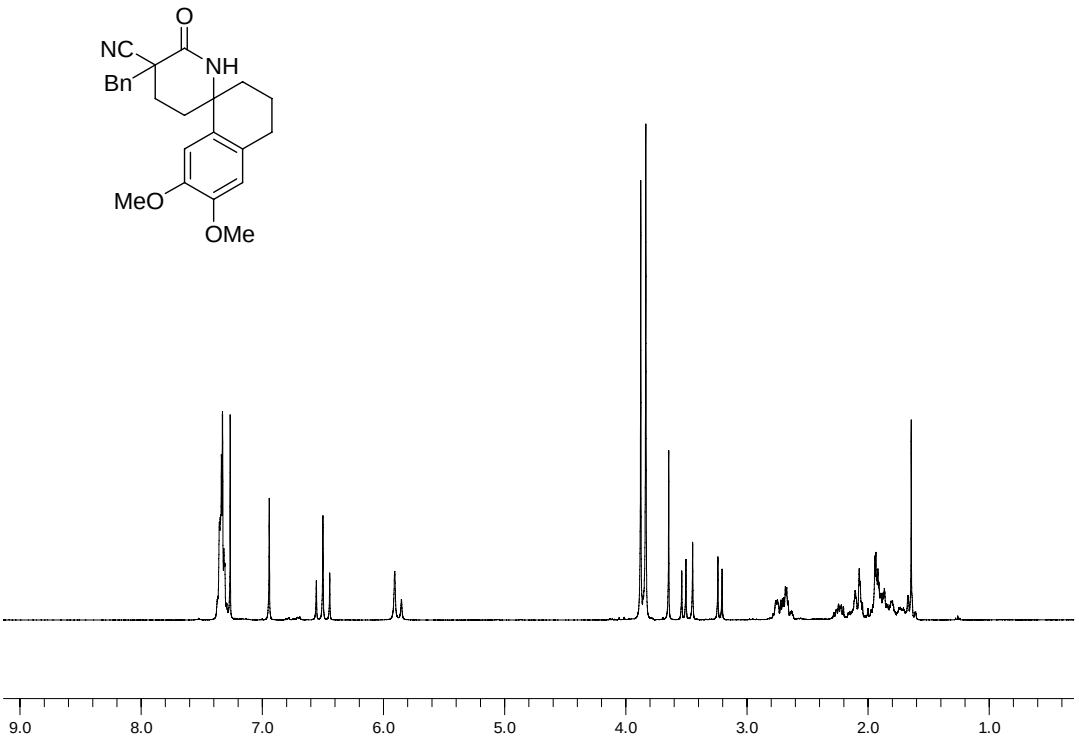
Minor
diastereomer

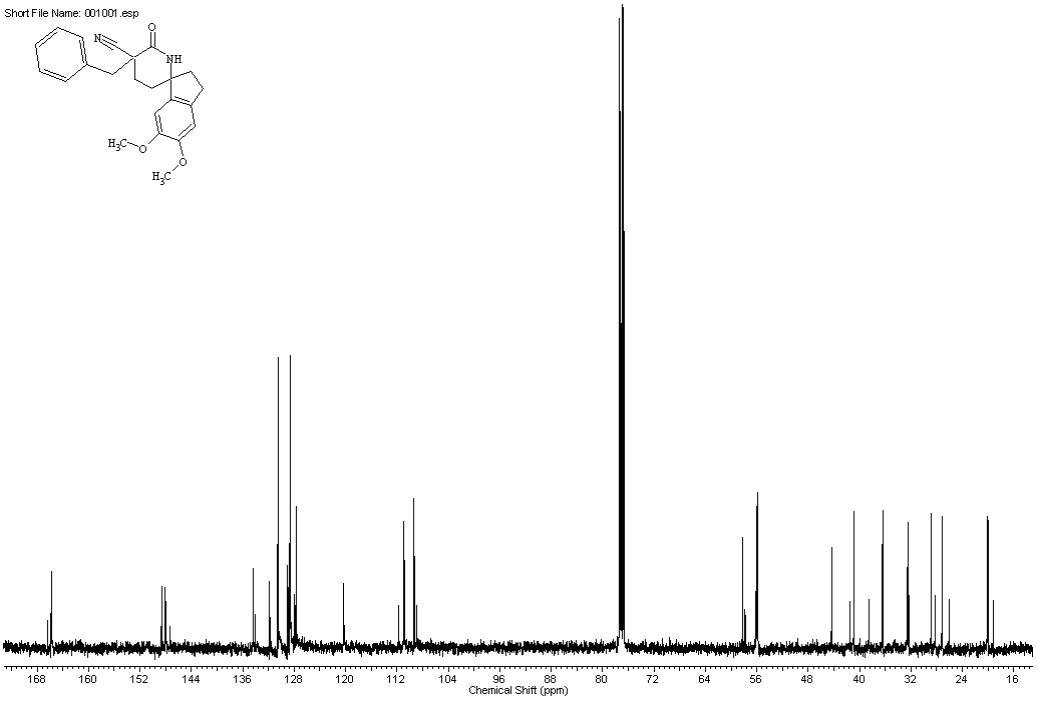


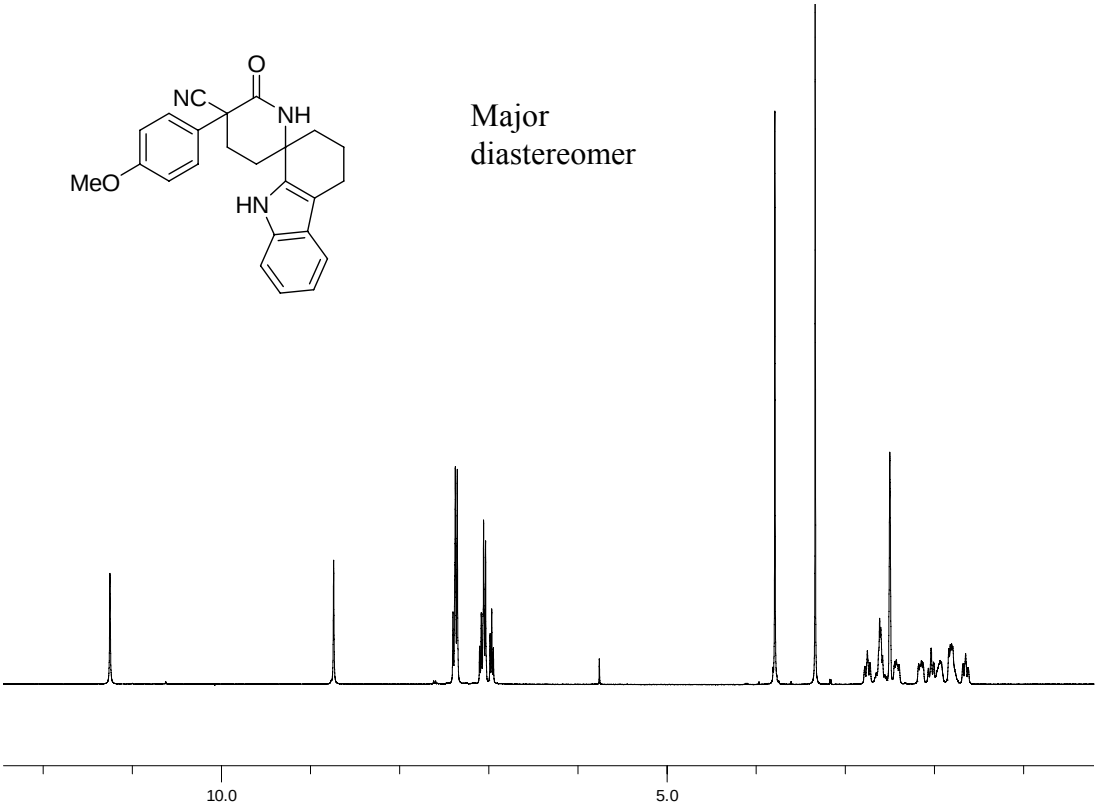


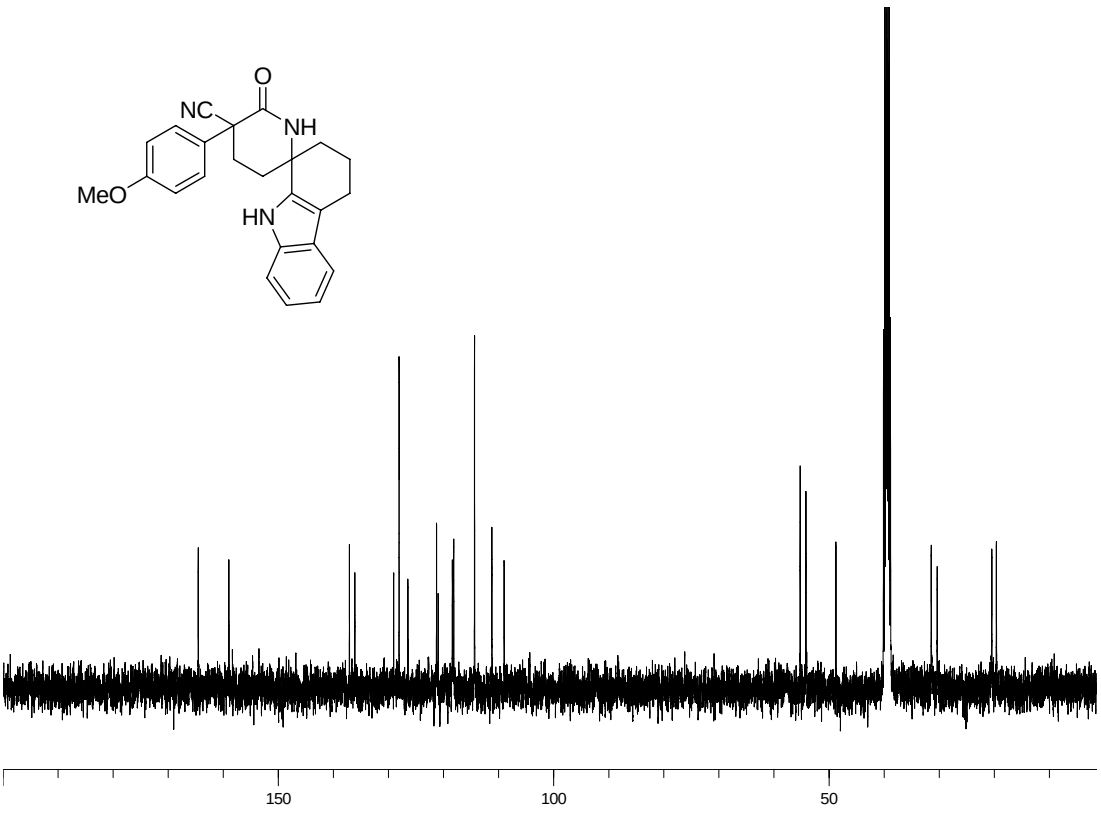

O
O
O
NH
MeO
OMe
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0

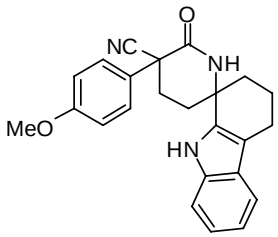

O
O
O
NH
MeO
OMe
150
100
50


O
NC
NH
Bn
MeO
OMe
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0

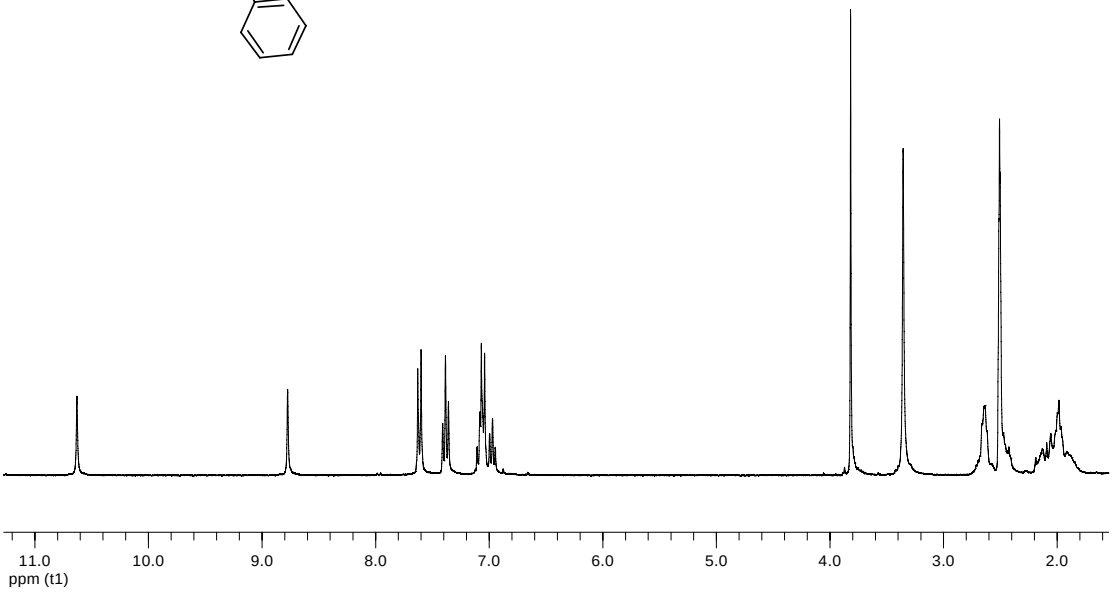

Short File Name: 001001.esp
N
O
NH
H3C
O
O
H3C
168
160
152
144
136
128
120
112
104
96
88
80
72
64
56
48
40
32
24
16
Chemical Shift (ppm)

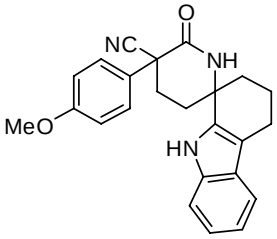

O
NC
NH
MeO
HN
Major
diastereomer
10.0
5.0

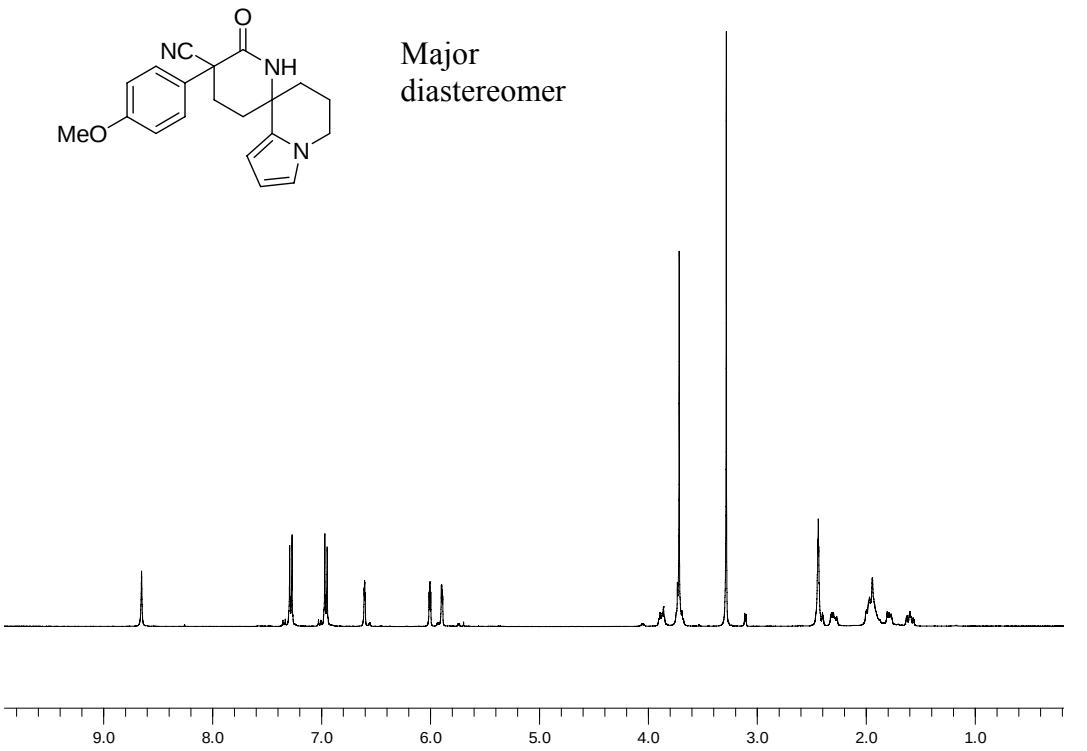

O
NC
NH
MeO
HN
150
100
50

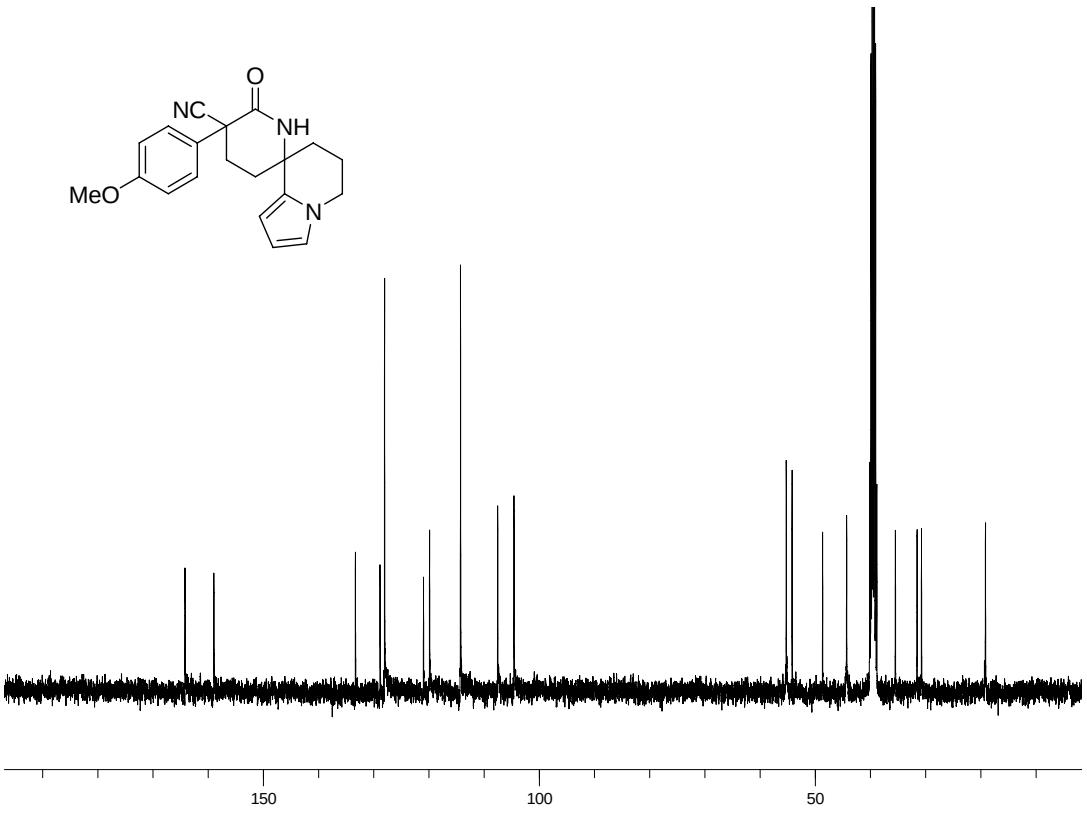


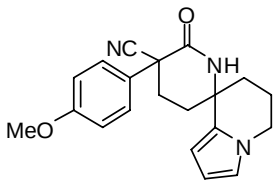
Minor
diastereomer



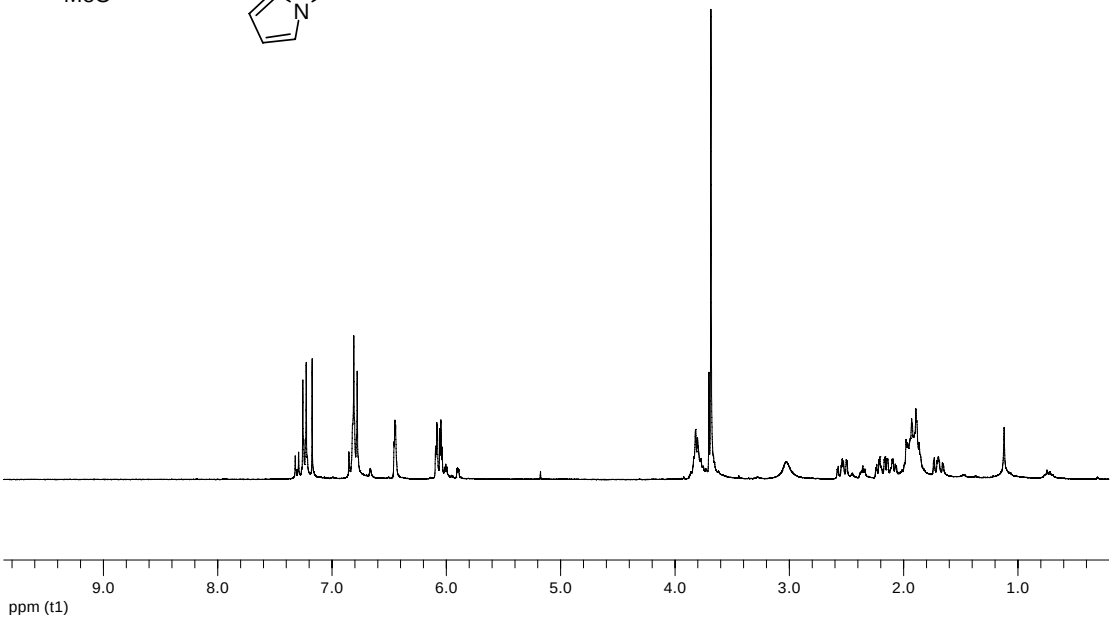


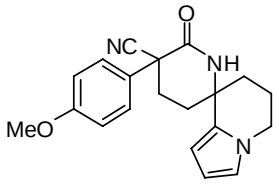

O
NC
NH
MeO
N
Major
diastereomer
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0

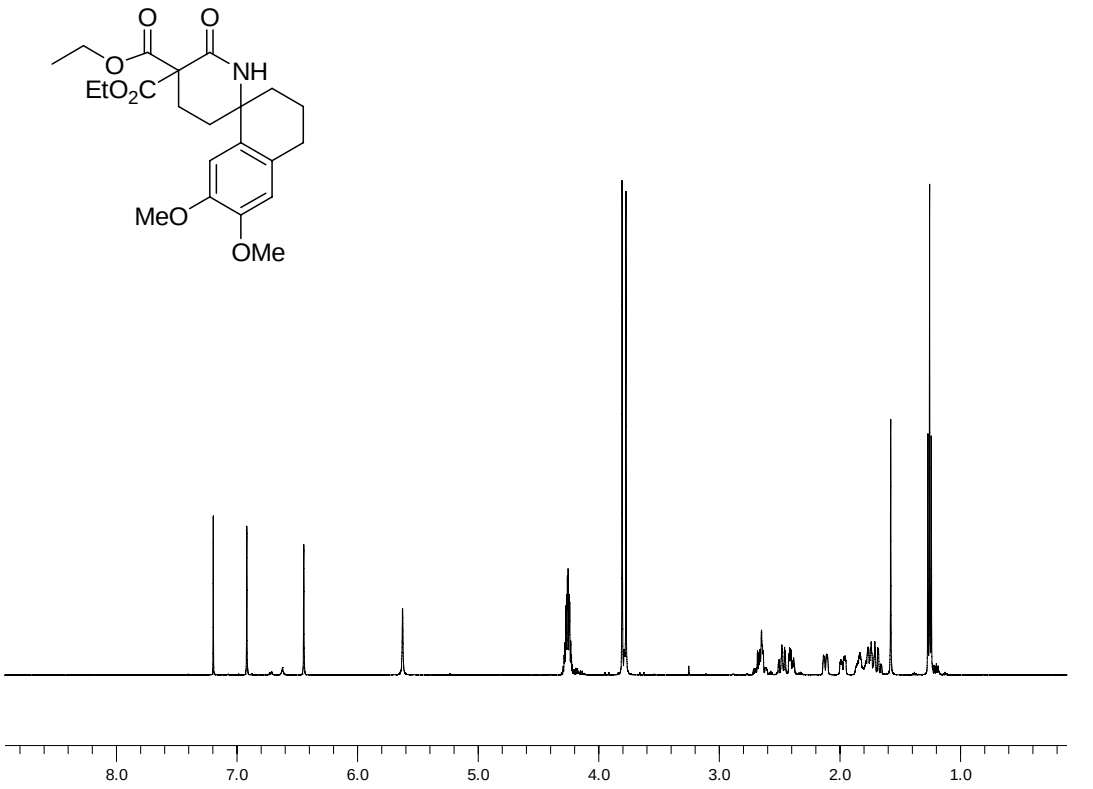

O
NC
NH
MeO
N
150
100
50

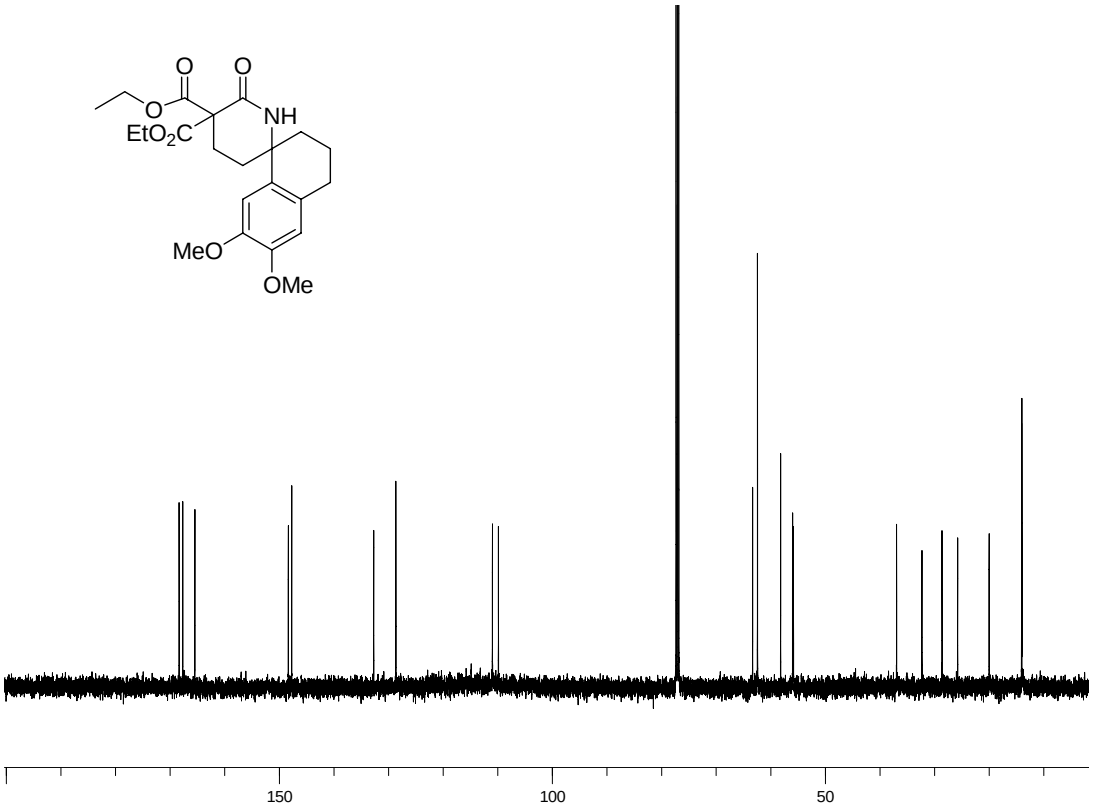


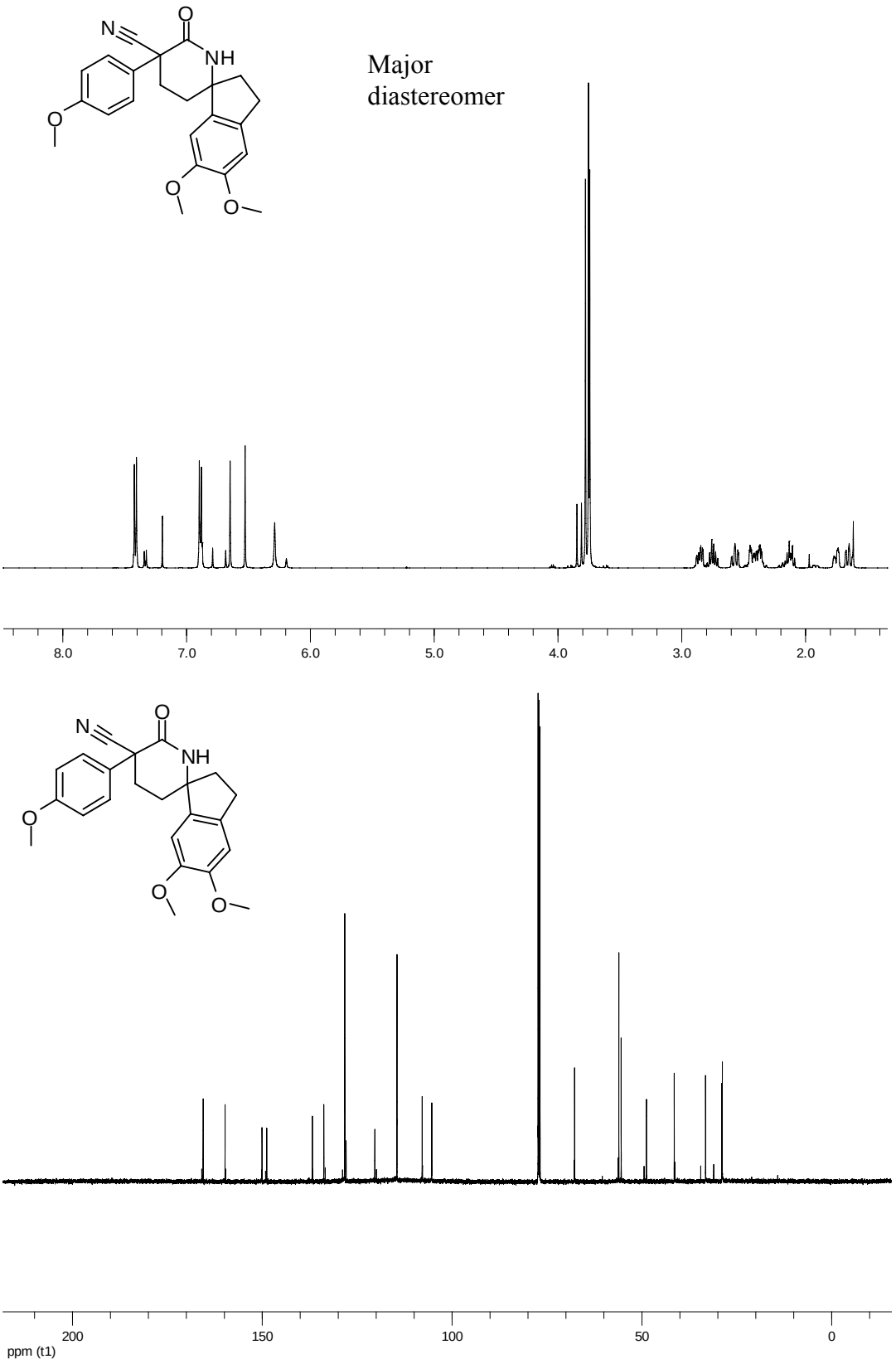
Minor
diastereomer

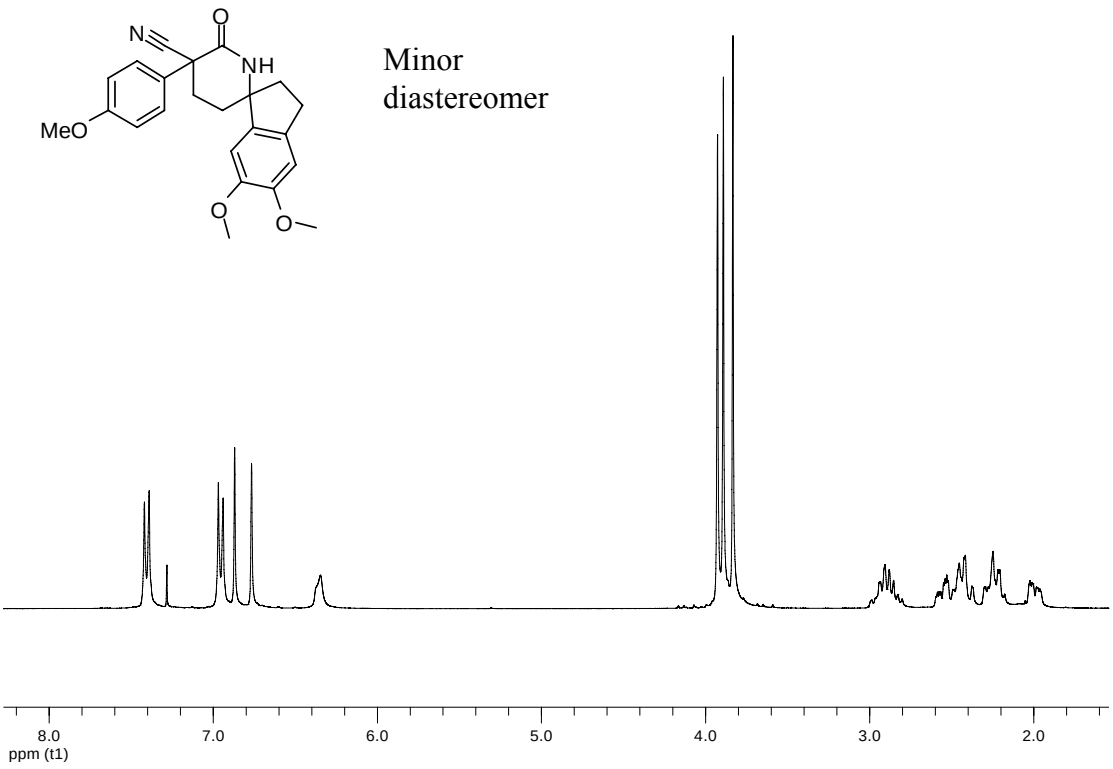


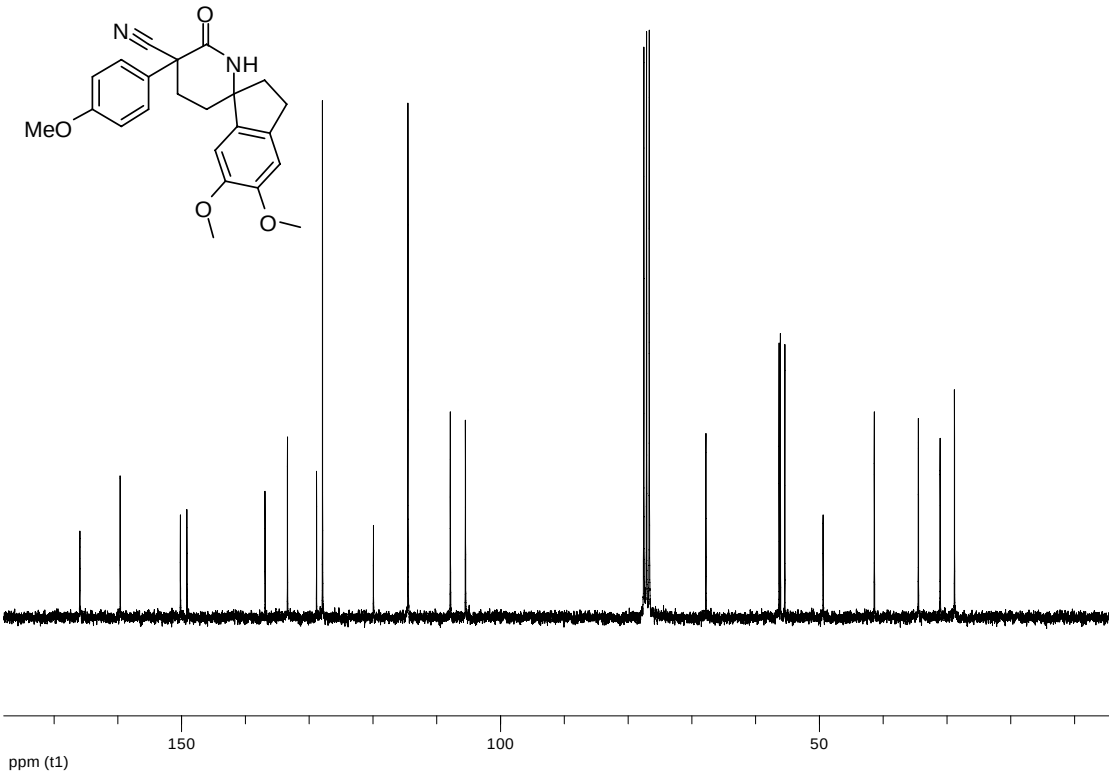


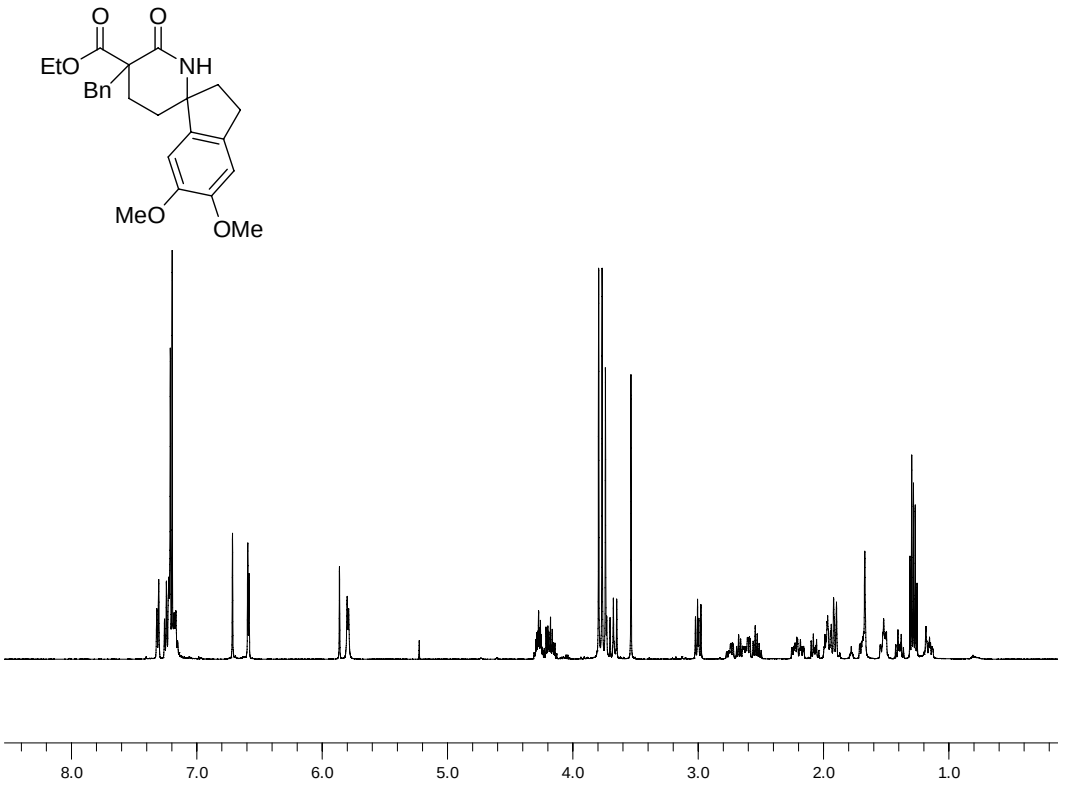

O
O
O
NH
EtO2C
MeO
OMe
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0

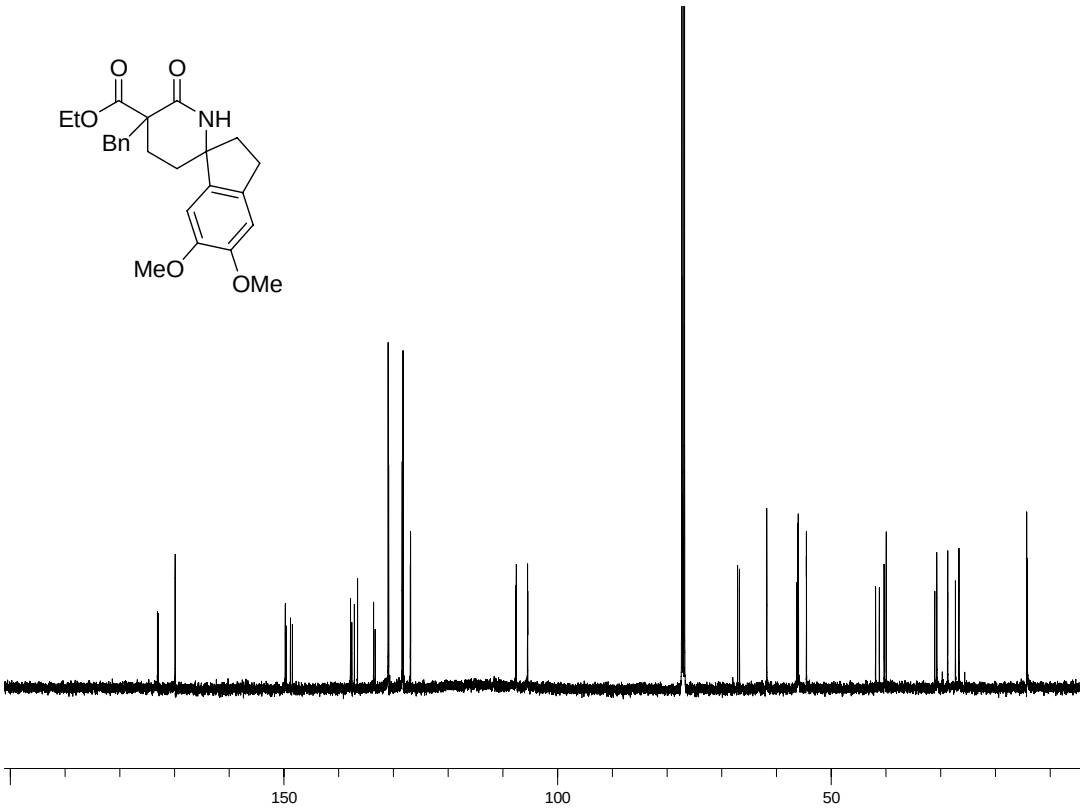

O
O
O
NH
EtO2C
MeO
OMe
150
100
50

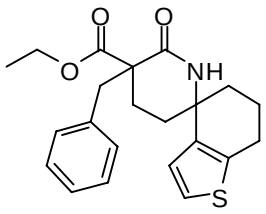

Major
diastereomer
8.0
7.0
6.0
5.0
4.0
3.0
2.0
200
150
100
50
0
ppm (t1)


N
O
NH
MeO
O
O
Minor
diastereomer
8.0
7.0
6.0
5.0
4.0
3.0
2.0
ppm (t1)

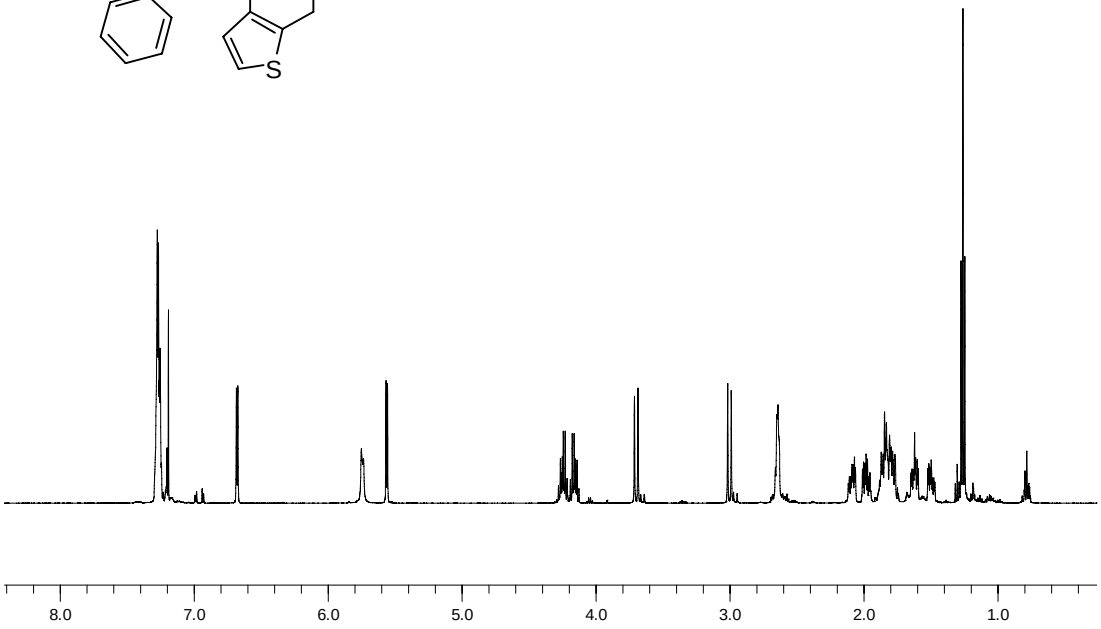

N
O
NH
MeO
O
O
150
100
50
ppm (t1)

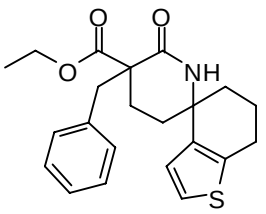

O
O
EtO
NH
Bn
MeO
OMe
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0

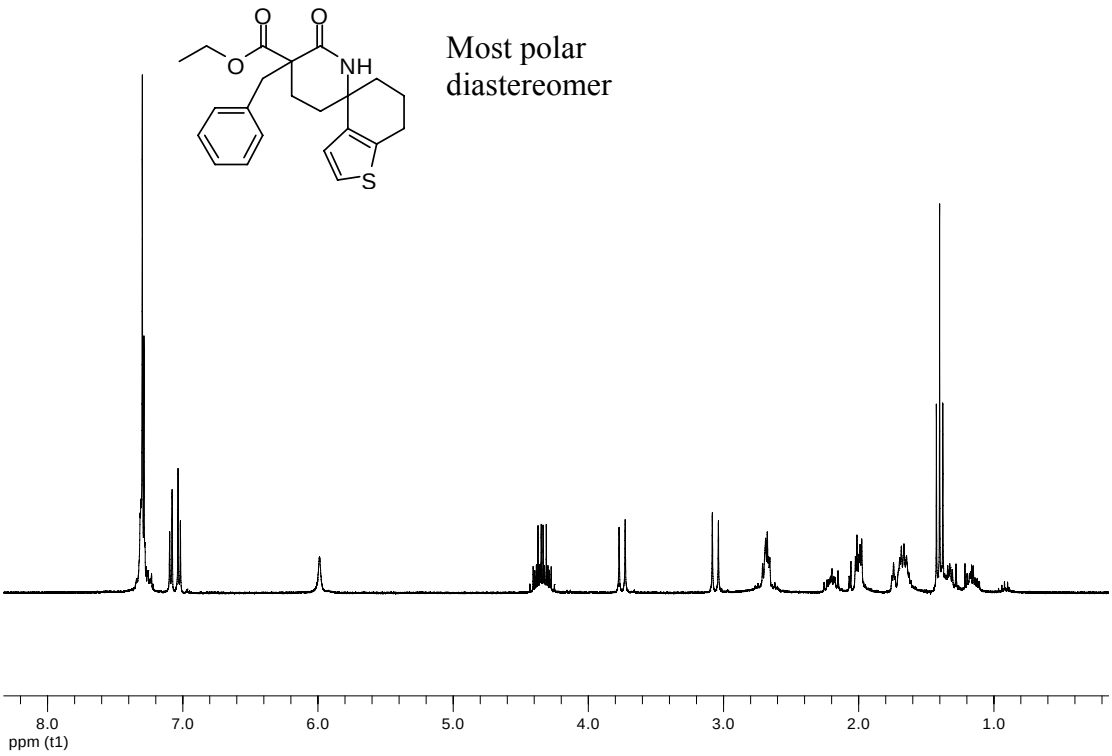

O
O
EtO
NH
Bn
MeO
OMe
150
100
50

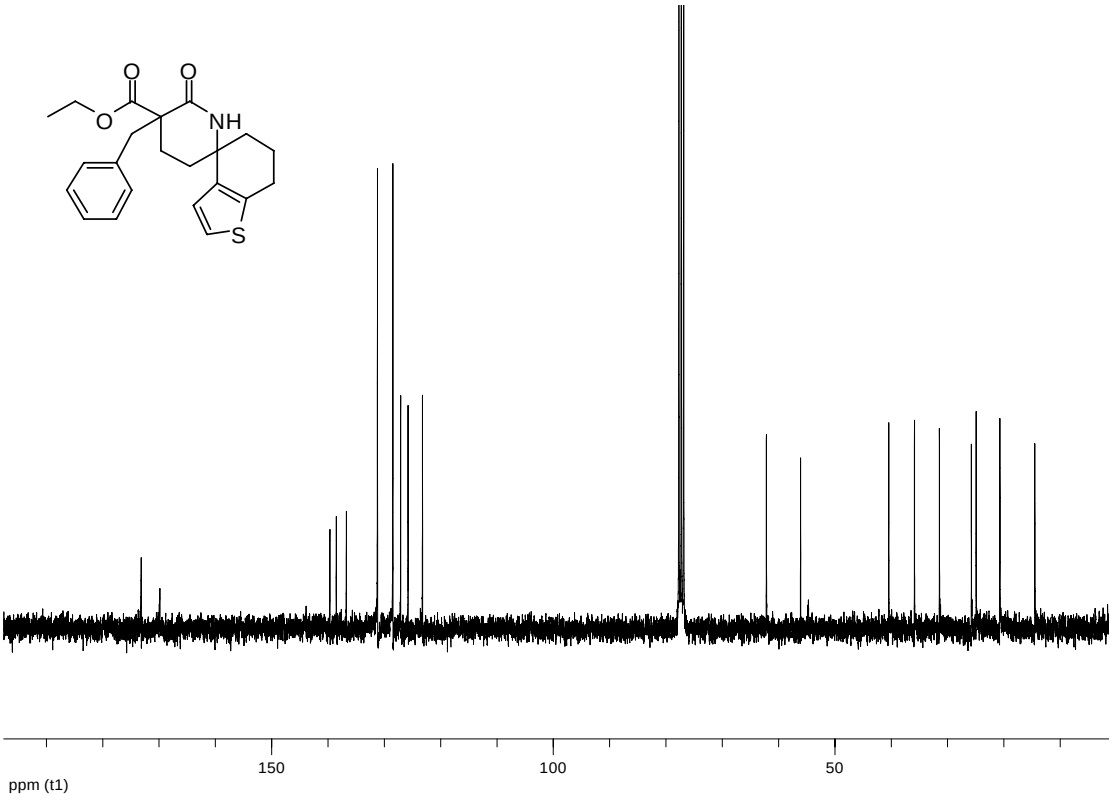


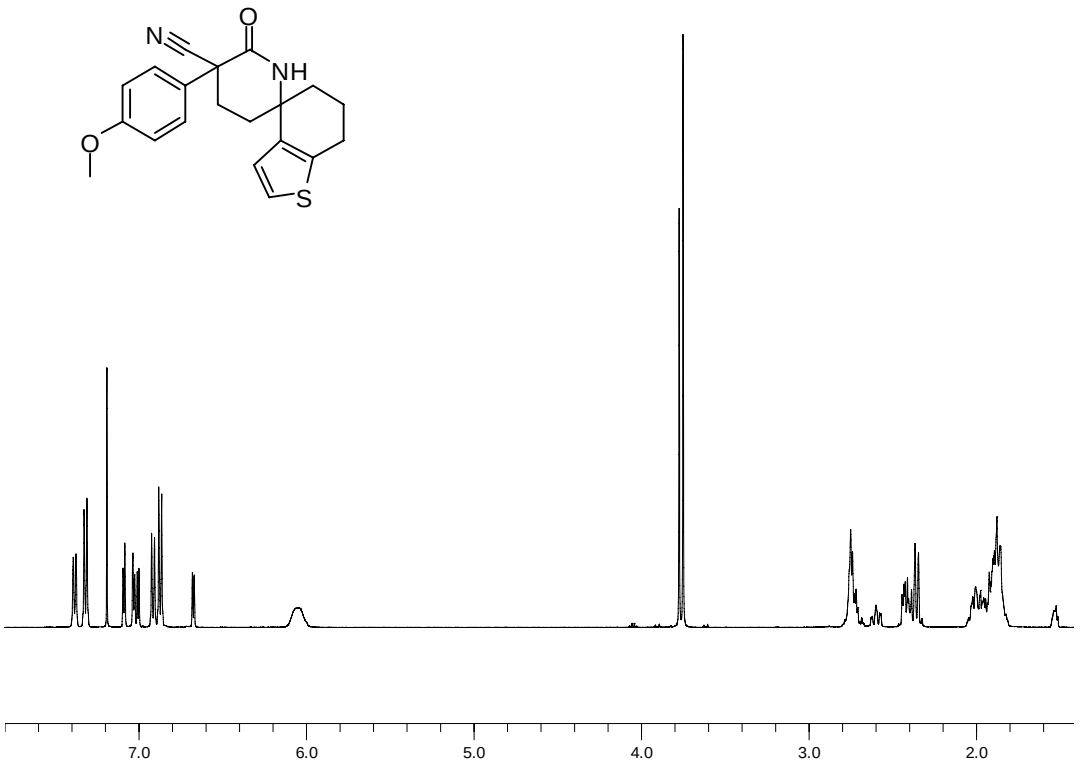
Least polar
diastereomer

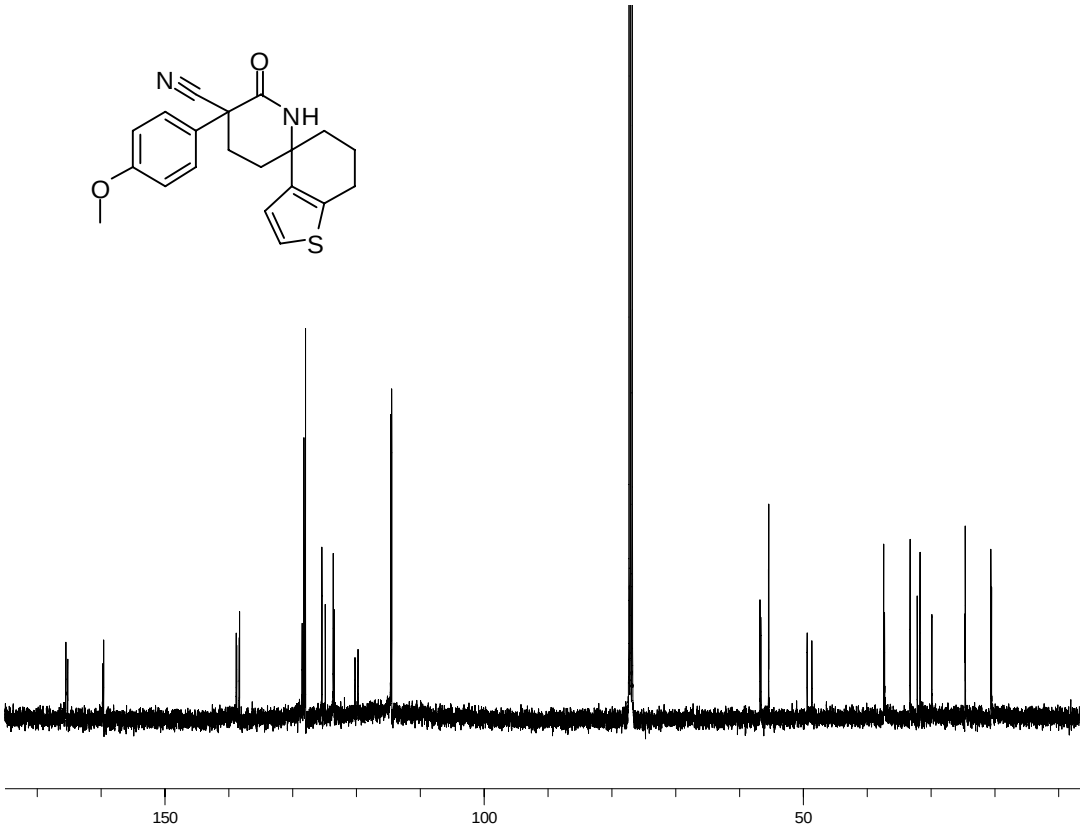


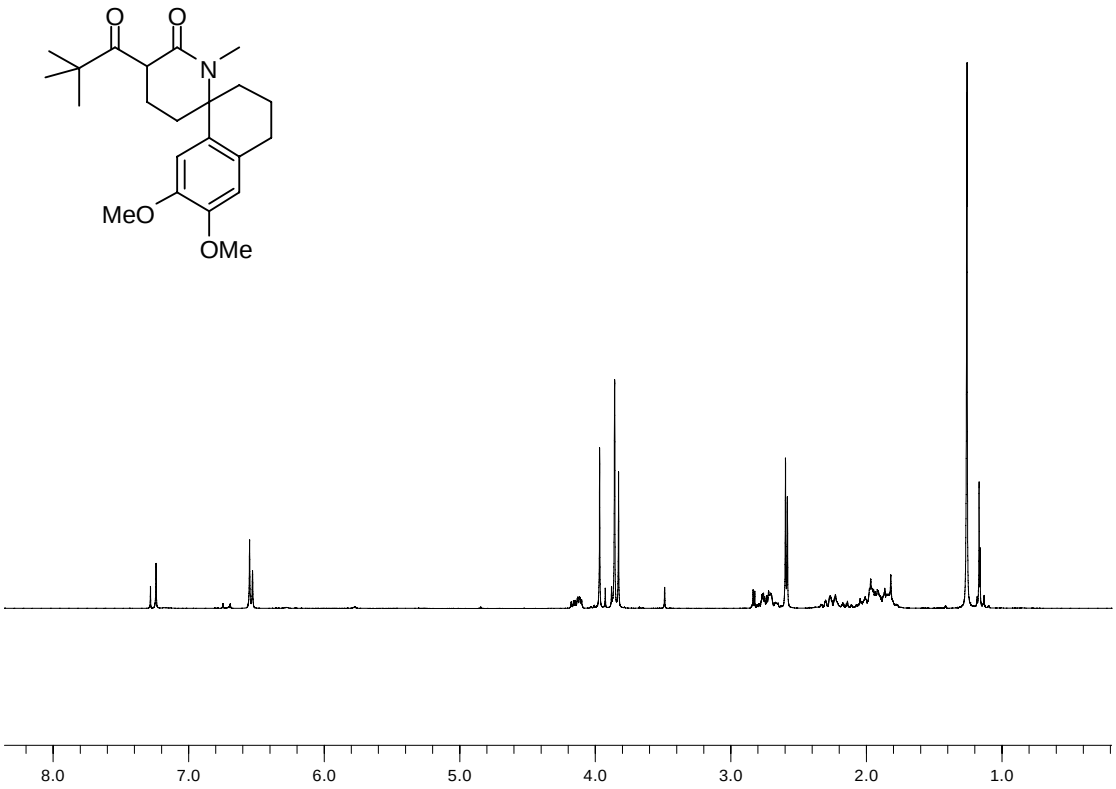


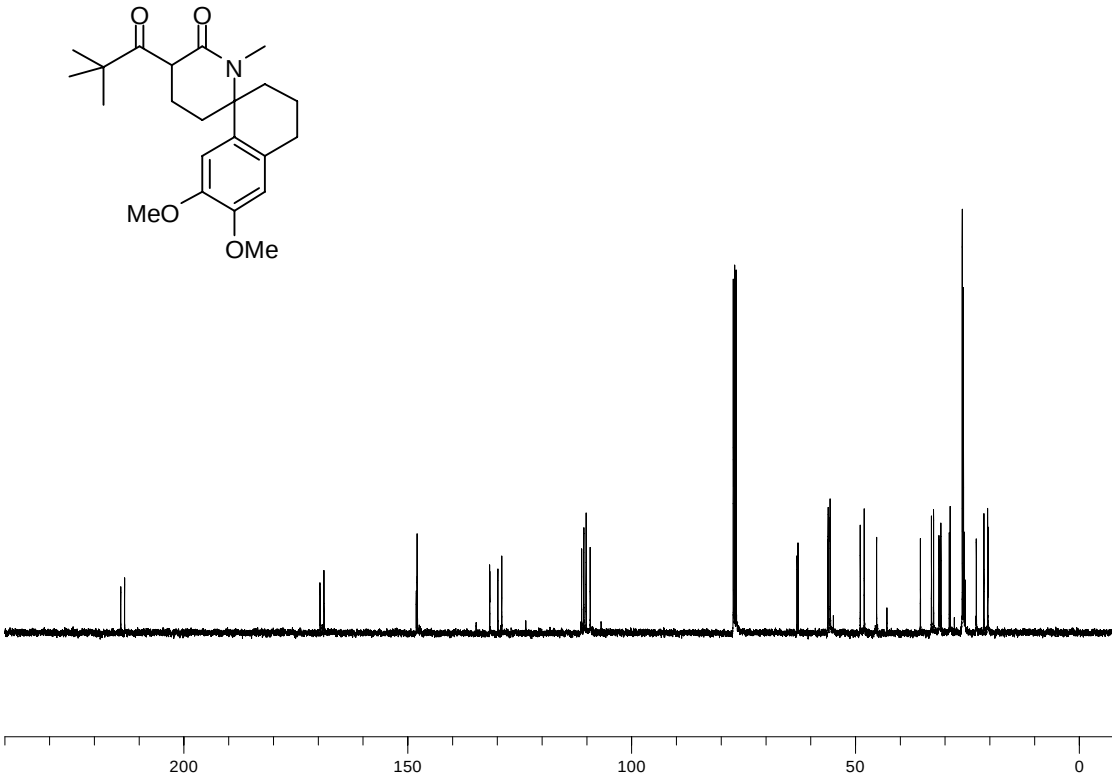

O
O
O
NH
S
Most polar
diastereomer
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

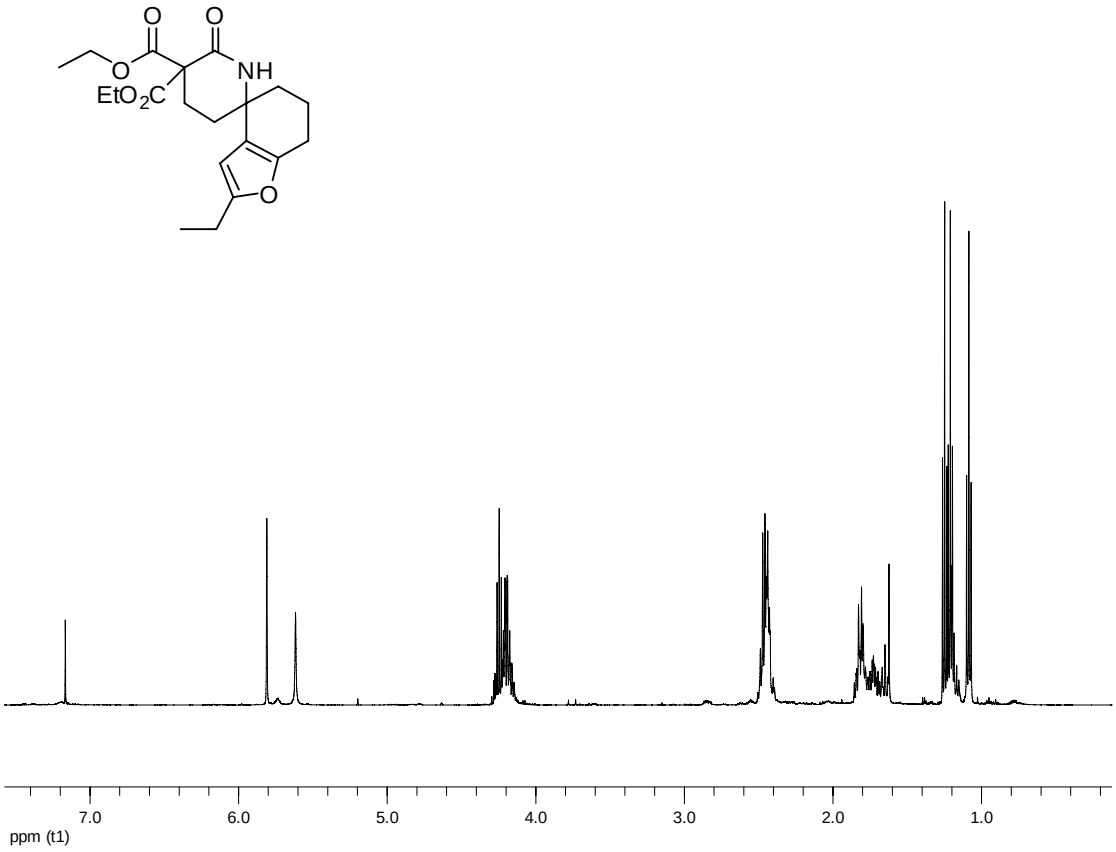

O
O
O
NH
S
150
100
50
ppm (t1)

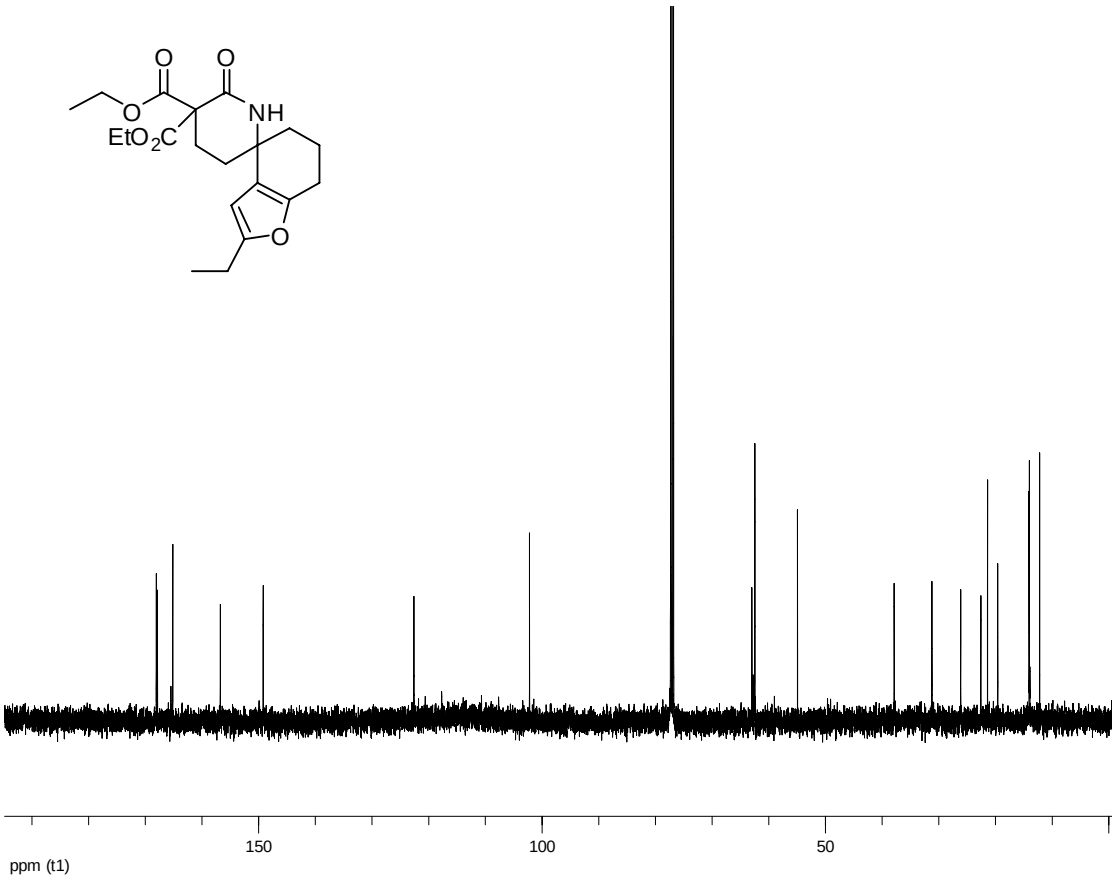

N
O
NH
O
S
7.0
6.0
5.0
4.0
3.0
2.0

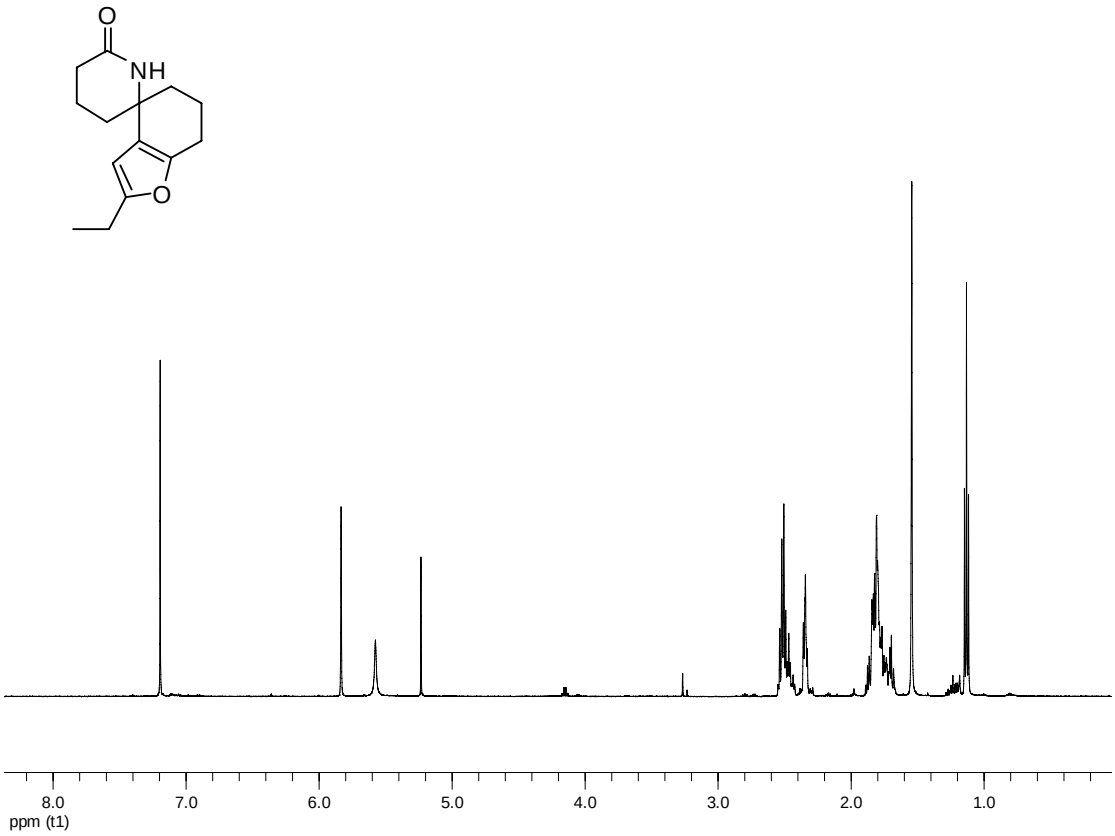

N
O
NH
O
S
150
100
50

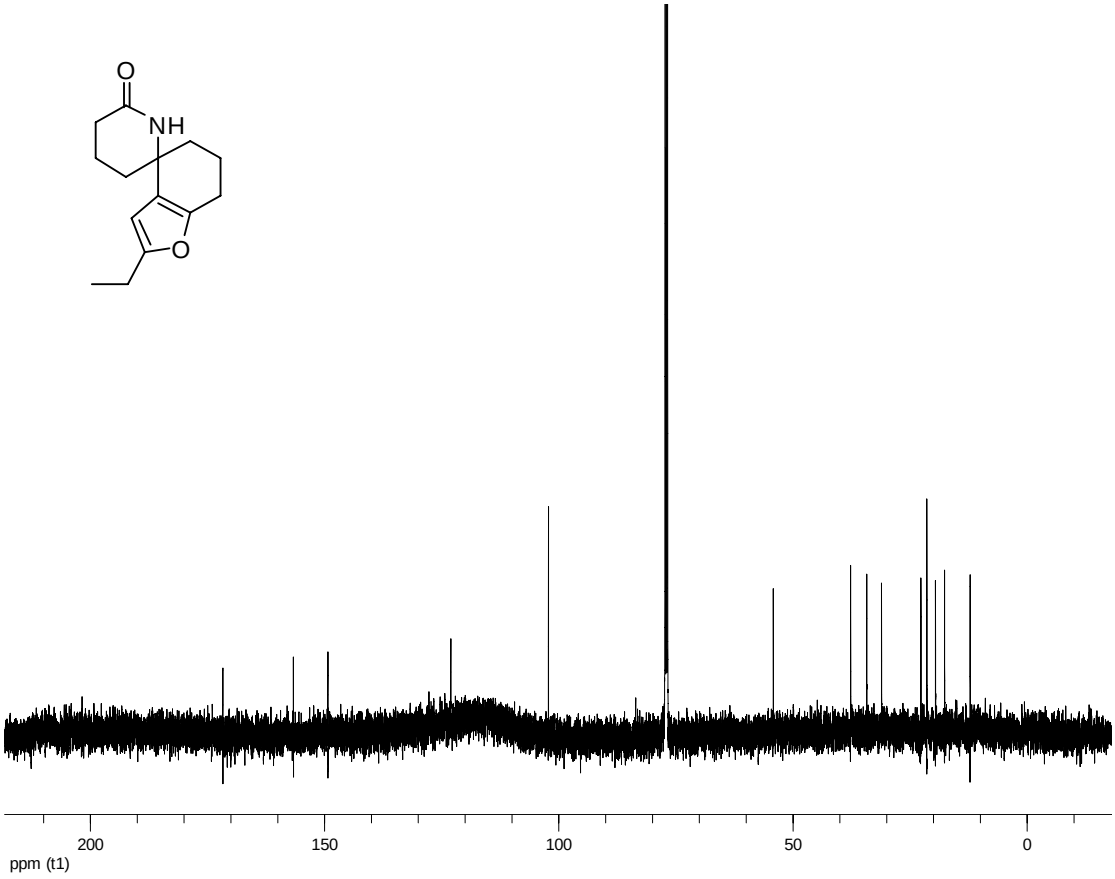

O
O
N
MeO
OMe
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0


O
O
N
MeO
OMe
200
150
100
50
0


O
O
NH
EtO2C
O
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)


O
O
NH
EtO2C
O
150
100
50
ppm (t1)


O
NH
O
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)


O
NH
O
200
150
100
50
0
ppm (t1)