Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications

Synthesis and anti-*Helicobacter pylori* activity of analogues of spirolaxine methyl ether

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Supporting information

General information 2

NMR spectra of **9** 3

NMR spectra of **12** 4

NMR spectra of **8** 5

NMR spectra of **11** 6

NMR spectra of **38** 7

NMR spectra of **6** 8

NMR spectra of **7** 9

NMR spectra of **10** 10

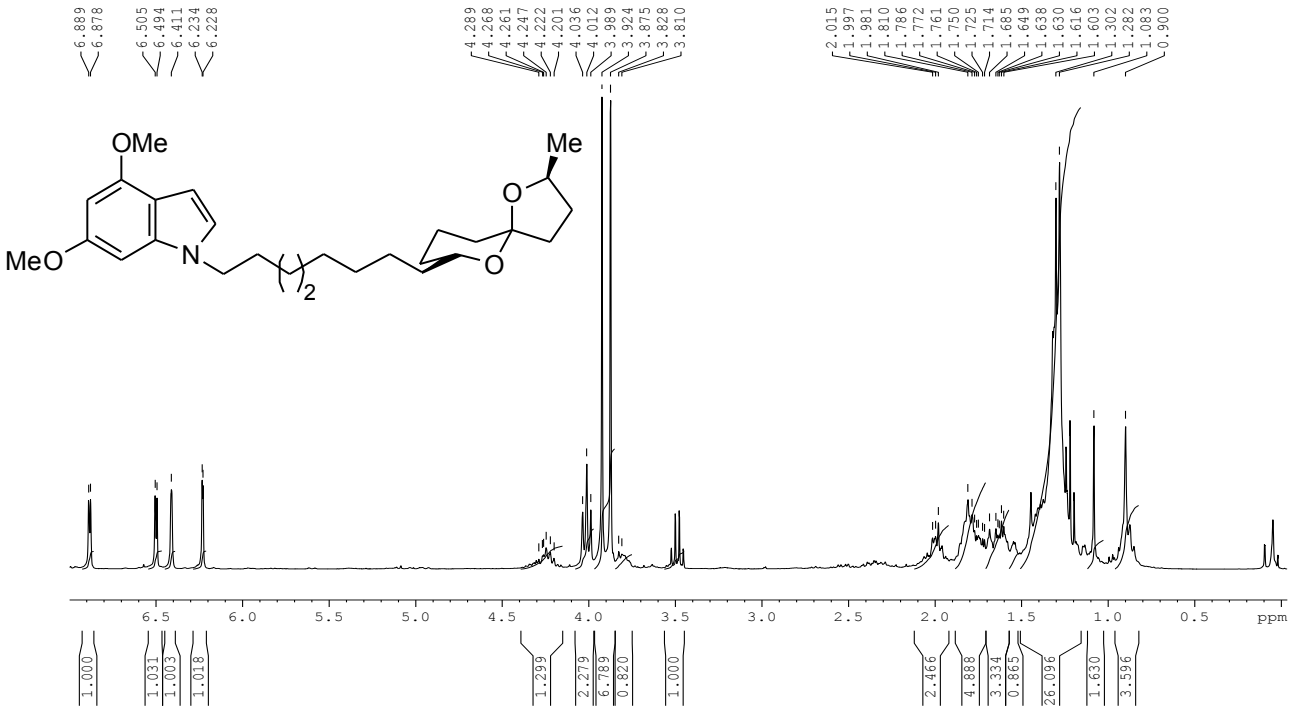
NMR spectra of **5** 12

Experimental Procedures 13

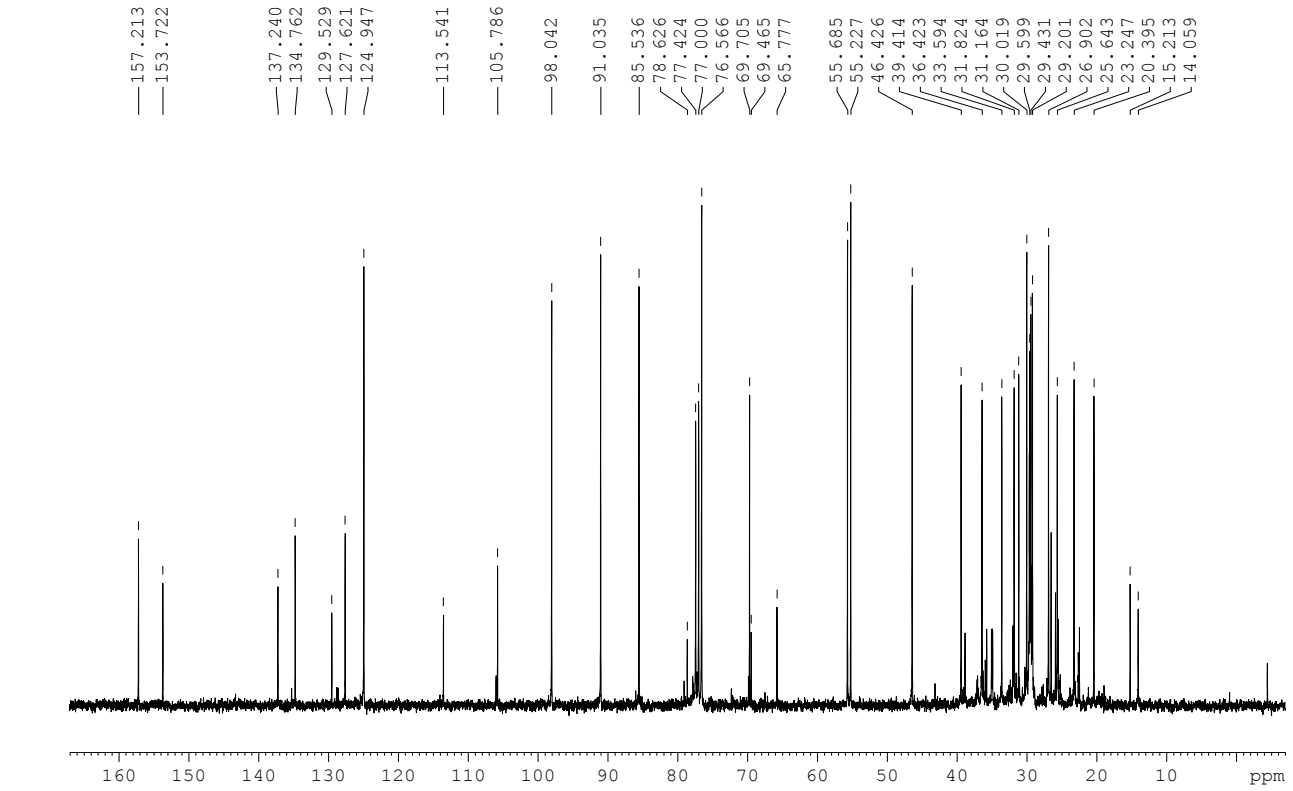
General information

All reagents were purchased as reagent grade and used as supplied. Solvents were used as supplied or dried according to standard methods.[1] RP-HPLC solvents were purchased as HPLC grade and used without further purification. Analytical thin layer chromatography was performed on 0.2 mm aluminium plates of silica gel 60 F_{254} (Merck) and compounds were visualised by ultra-violet fluorescence. Flash
chromatography was performed using Davisil® chromatographic silica (LC60Å 40-63 micron) (Grace GmbH & Co.KG) with indicated solvents. Infrared spectra were obtained using a Perkin Elmer Spectrum One Fourier Transform infrared spectrometer with a universal ATR sampling accessory. Nuclear magnetic resonance (NMR) spectra were recorded as indicated on either a Bruker AVANCE DRX300 spectrometer operating on 300 MHz for ^{1}H nuclei and 75 MHz for ^{13}C nuclei or on a Bruker AVANCE DRX400 spectrometer operating on 400 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei. Chemical shifts are reported in parts per million (ppm) relative to the tetramethylsilane signal at δ_H 0.00 ppm (^{1}H NMR) in $CDCl_3$-$SiMe_4$ solvent or The ^{13}C values were referenced to the residual chloroform signal at δ_C 77.0 ppm in $CDCl_3$-$SiMe_4$ solvent. ^{1}H NMR data is reported as chemical shift, relative integral, multiplicity (s, singlet; d, doublet; dd, doublet of doublets; dq, doublet of quartets; t, triplet; m, multiplet), coupling constant (*J* in Hz) and assignment. ^{13}C values are reported as chemical shift (δ_C), degree of hybridisation and assignment. Optical rotations were determined at 20 °C with a Perkin-Elmer 341 polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}. Melting points were determined on a Electrothermal® melting point apparatus and are uncorrected. Electrospray ionisation mass spectra (ESI-MS) were recorded on a Thermo Finnigan Surveyor MSQ Plus spectrometer or a Bruker micrOTOF-Q II spectrometer. Samples were introduced using direct flow injection at 0.1-0.2 mL/min into an ESI source in positive mode. Major and significant fragments are quoted in the form *x* (mass to charge ratio).

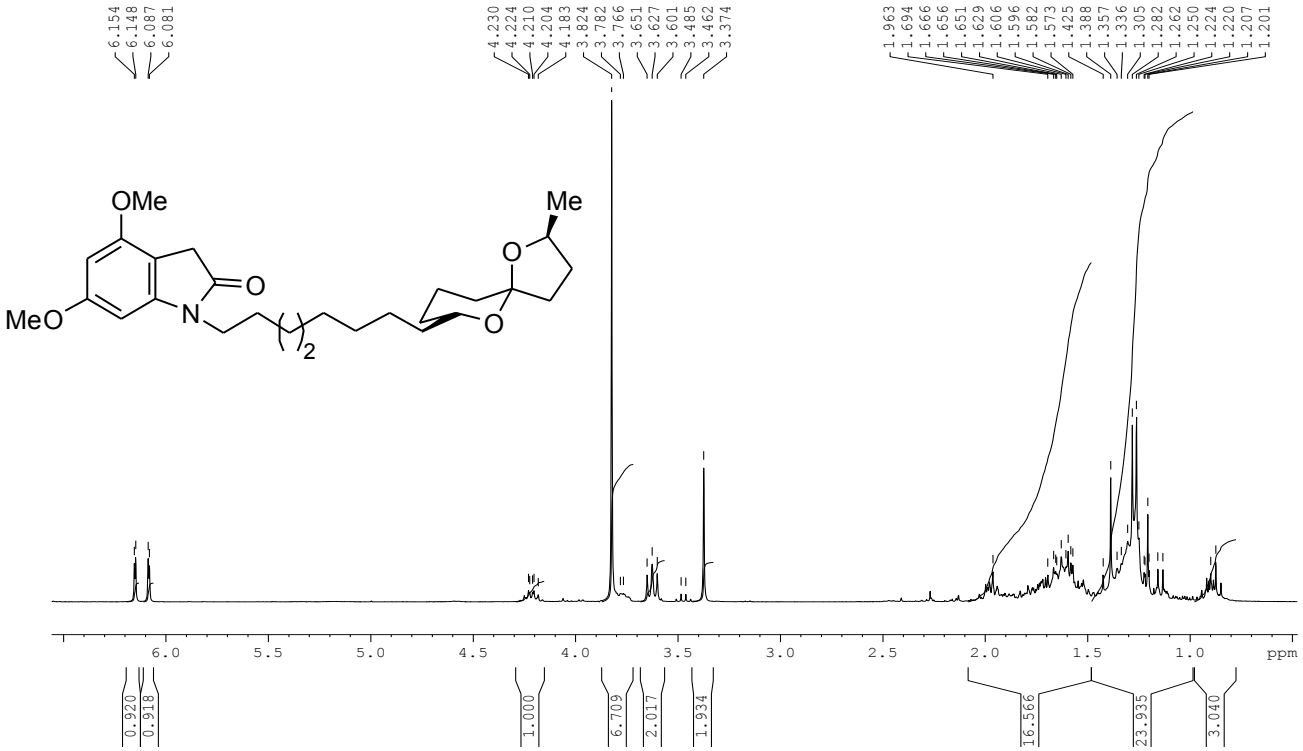
^{1}H NMR spectrum of **9** at 300 MHz, $CDCl_3$



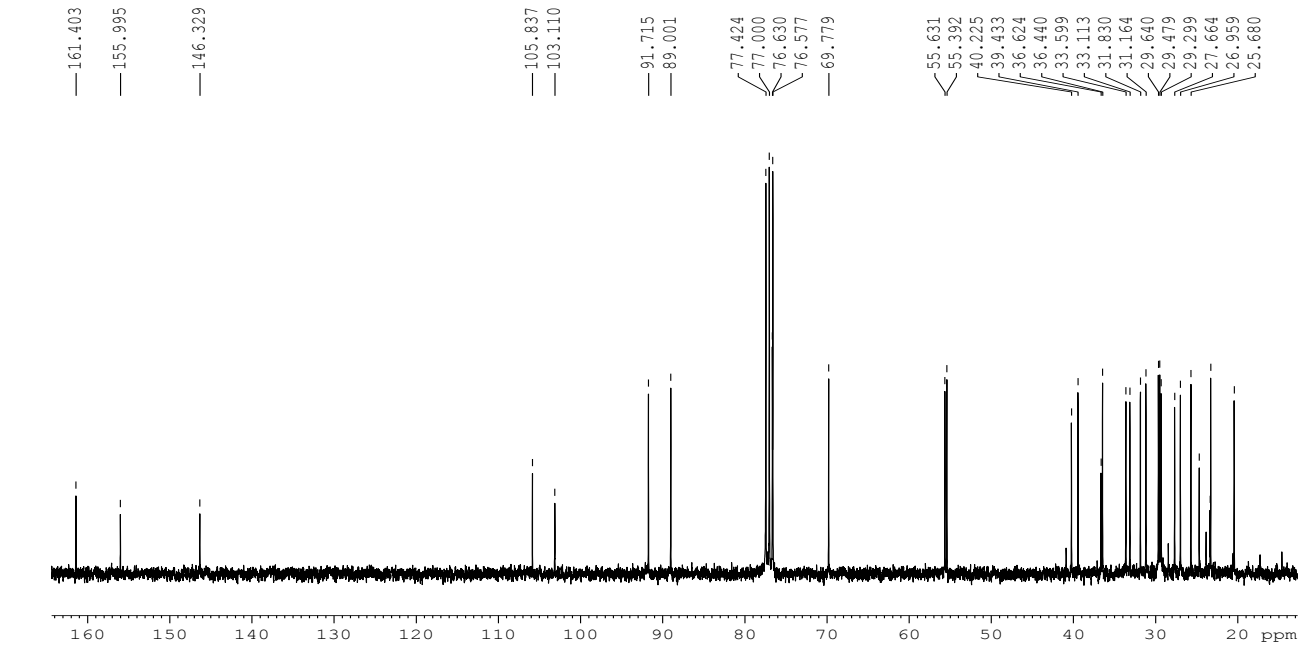
^{13}C NMR spectrum of **9** at 75 MHz, $CDCl_3$



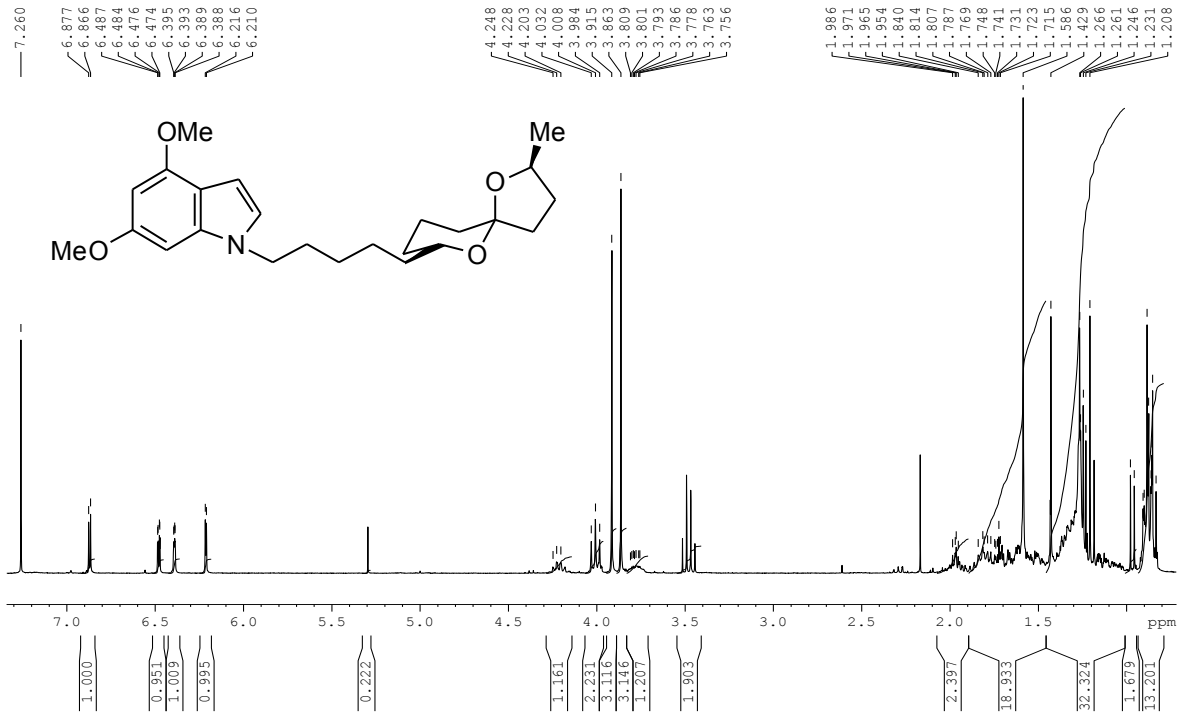
^{1}H NMR spectrum **12** at 300 MHz, $CDCl_3$



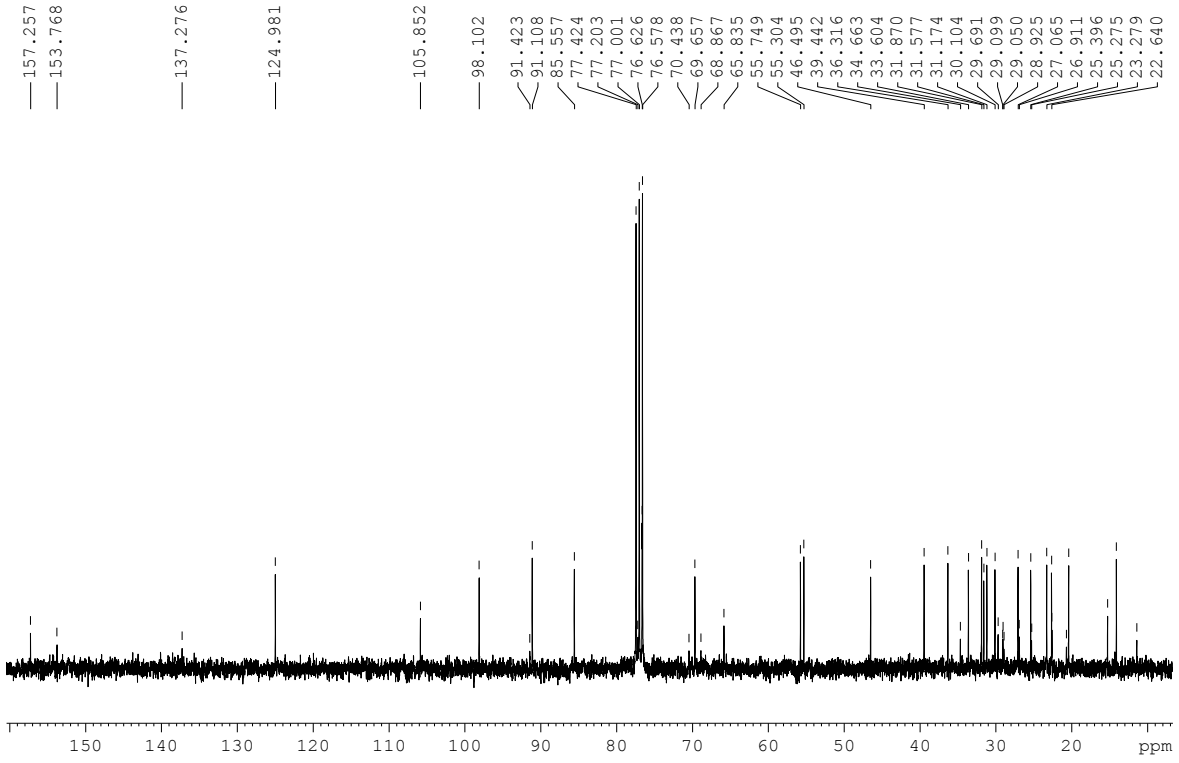
^{13}C NMR spectrum of **12** at 75 MHz, $CDCl_3$



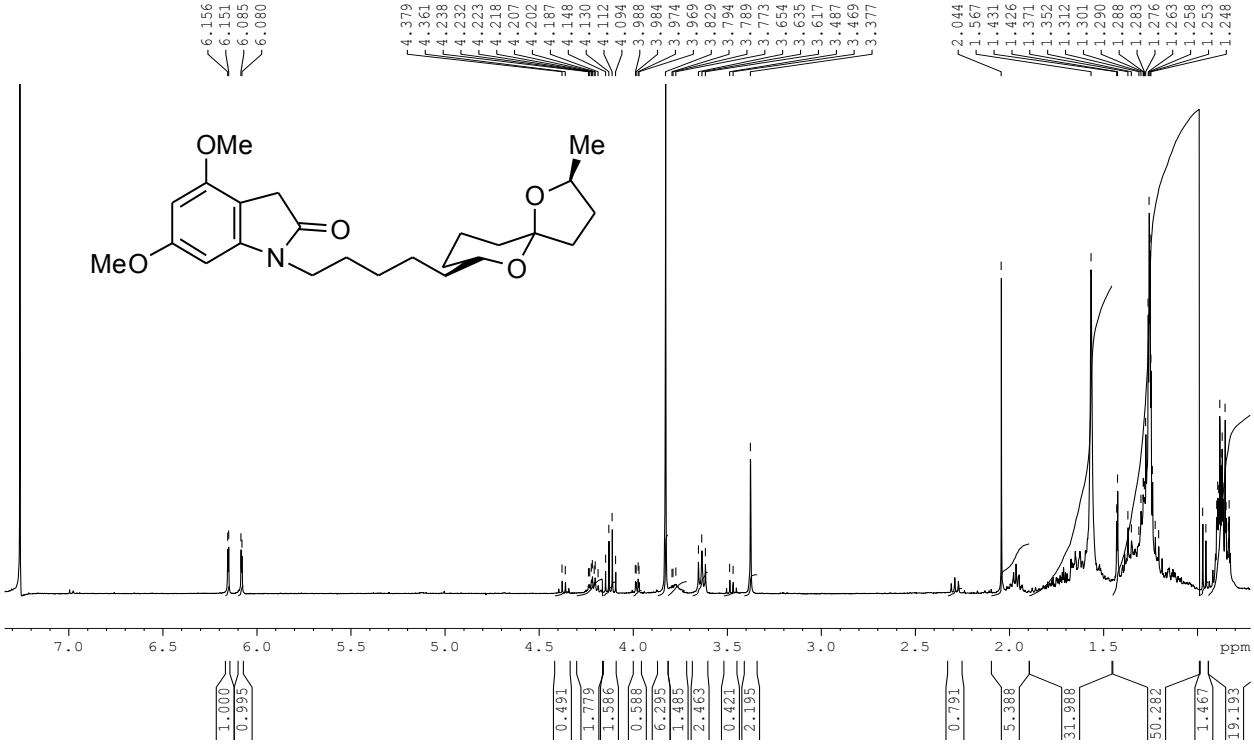
^{1}H NMR spectrum of **8** at 300 MHz, $CDCl_3$



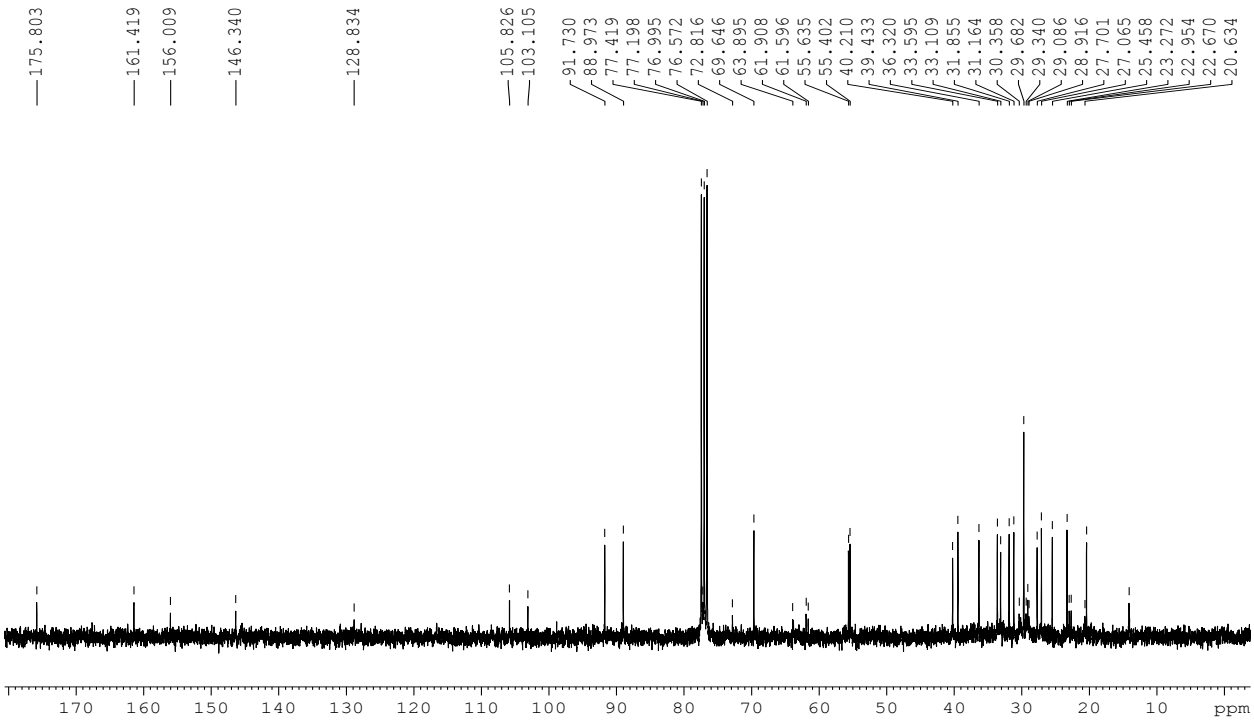
^{13}C NMR spectrum of **8** at 75 MHz, $CDCl_3$



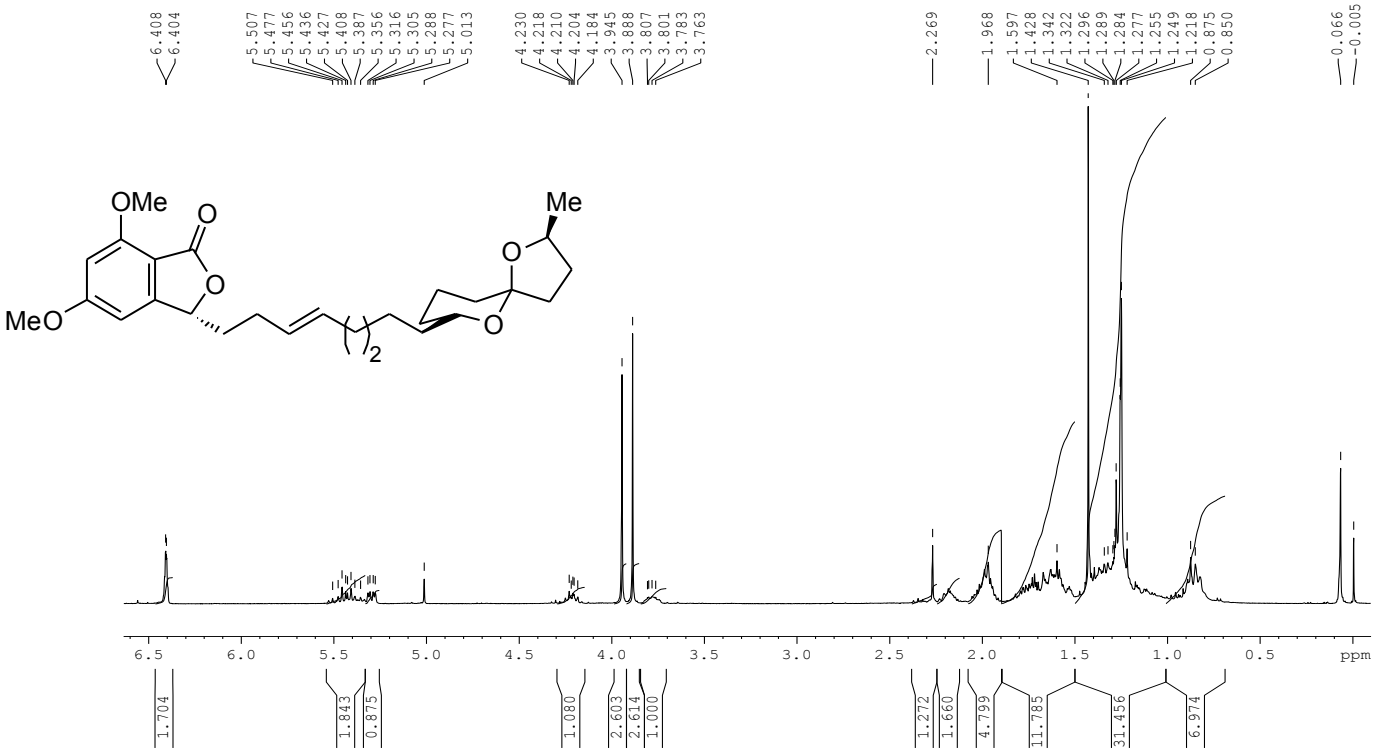
^{1}H NMR spectrum of **11** at 400 MHz, $CDCl_3$



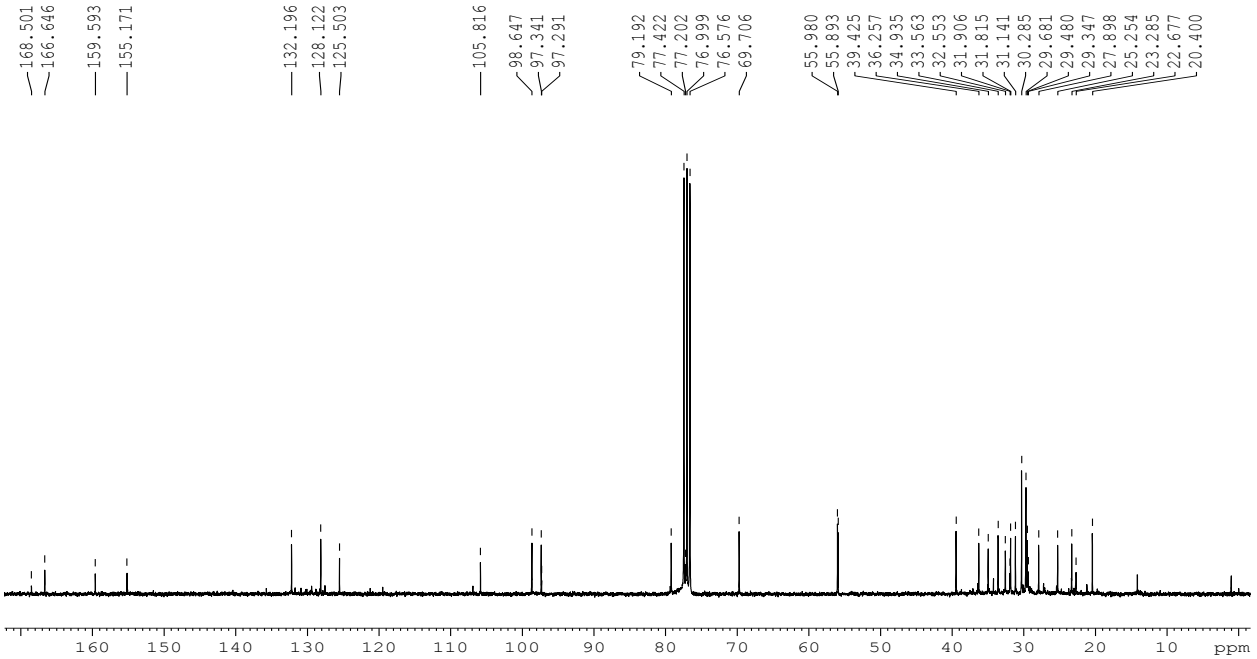
^{13}C NMR spectrum of **11** at 100 MHz, $CDCl_3$



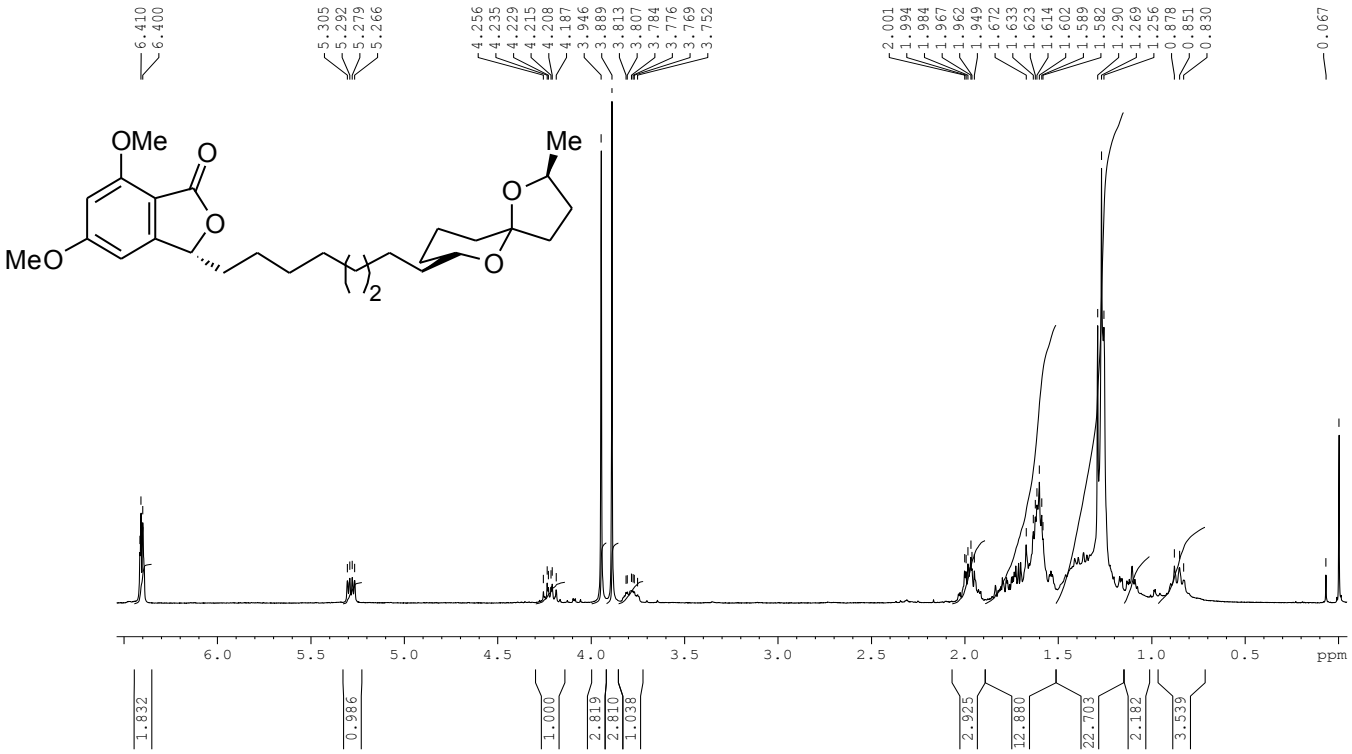
^{1}H NMR spectrum of **38** at 400 MHz, $CDCl_3$



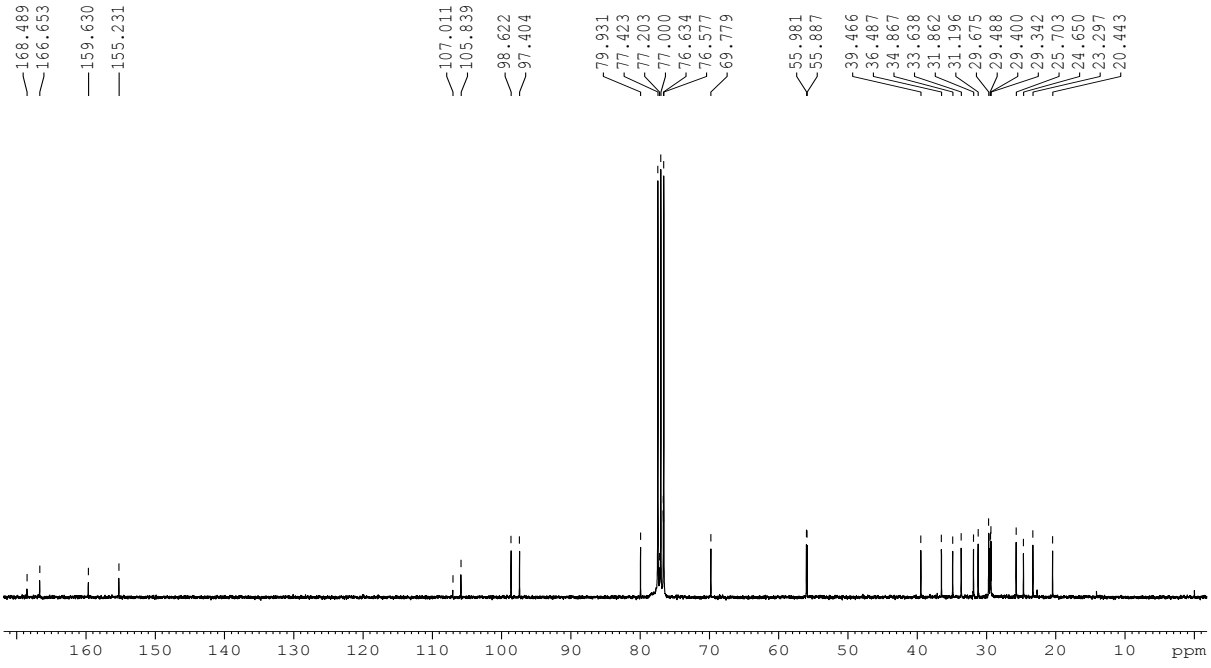
^{13}C NMR spectrum of **38** at 75 MHz, $CDCl_3$



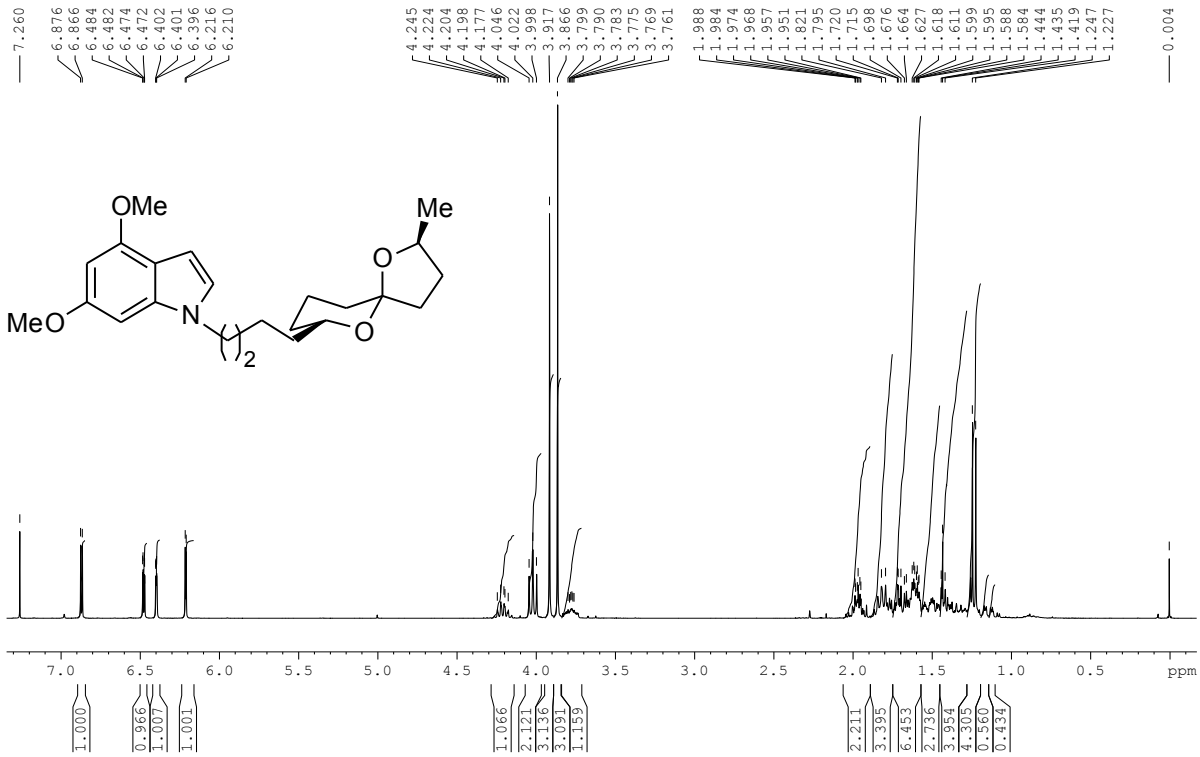
^{1}H NMR spectrum of **6** at 300 MHz, $CDCl_3$



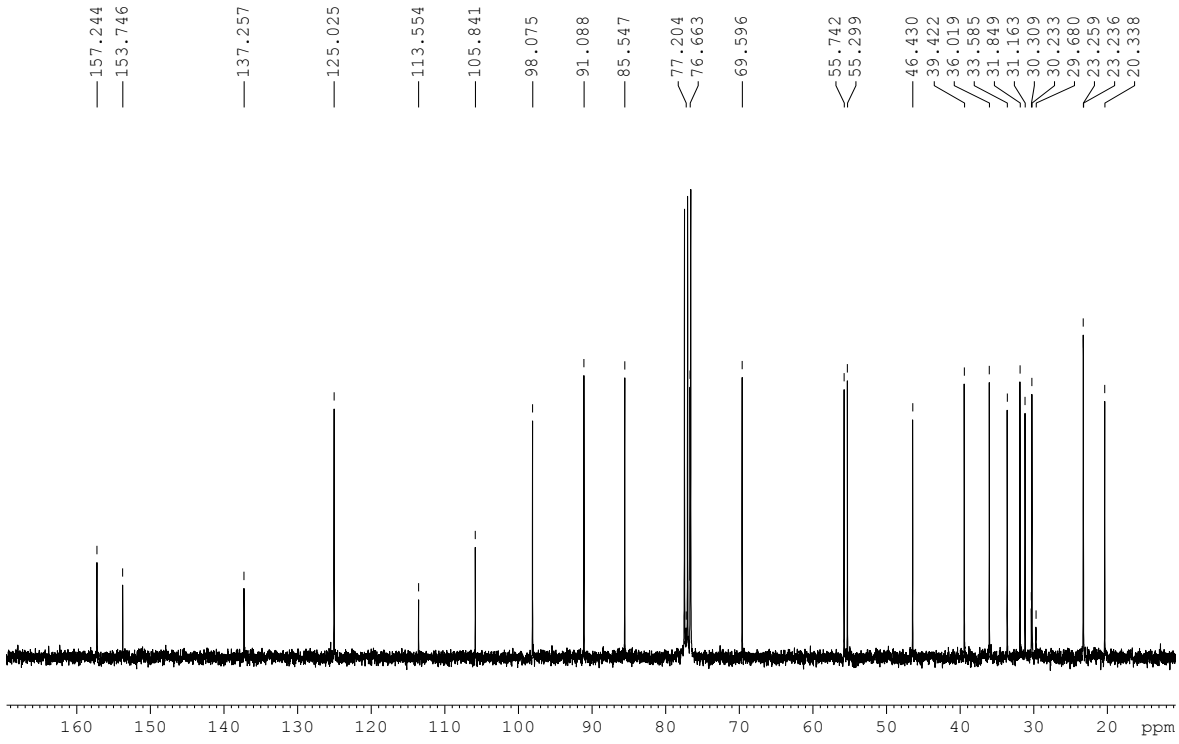
^{13}C NMR spectrum of **6** at 75 MHz, $CDCl_3$



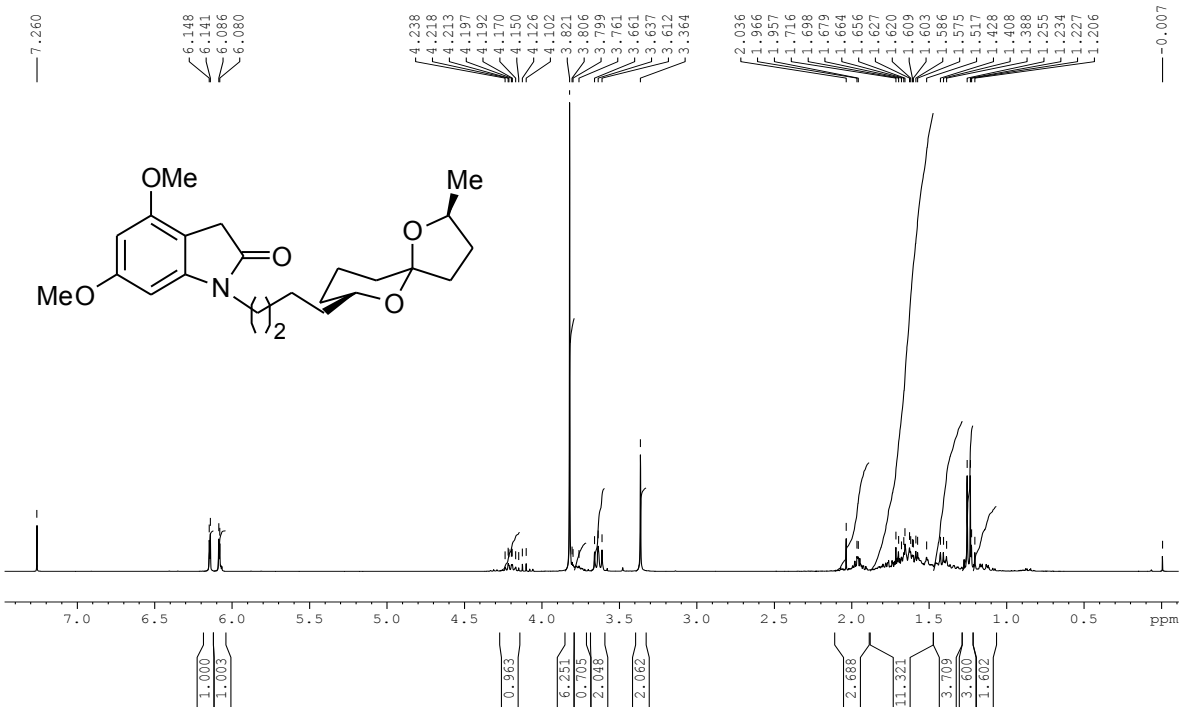
^{1}H NMR spectrum of **7** at 300 MHz, $CDCl_3$



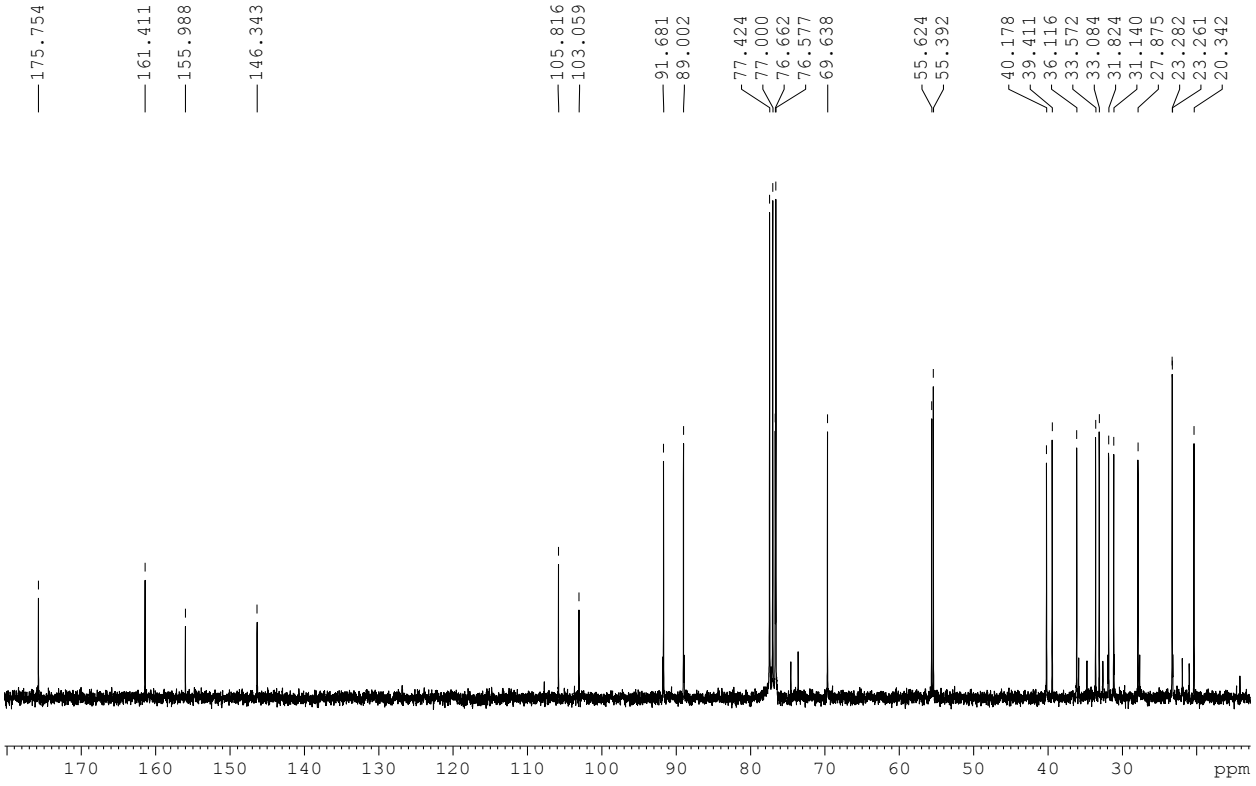
^{13}C NMR spectrum of **7** at 75 MHz, $CDCl_3$



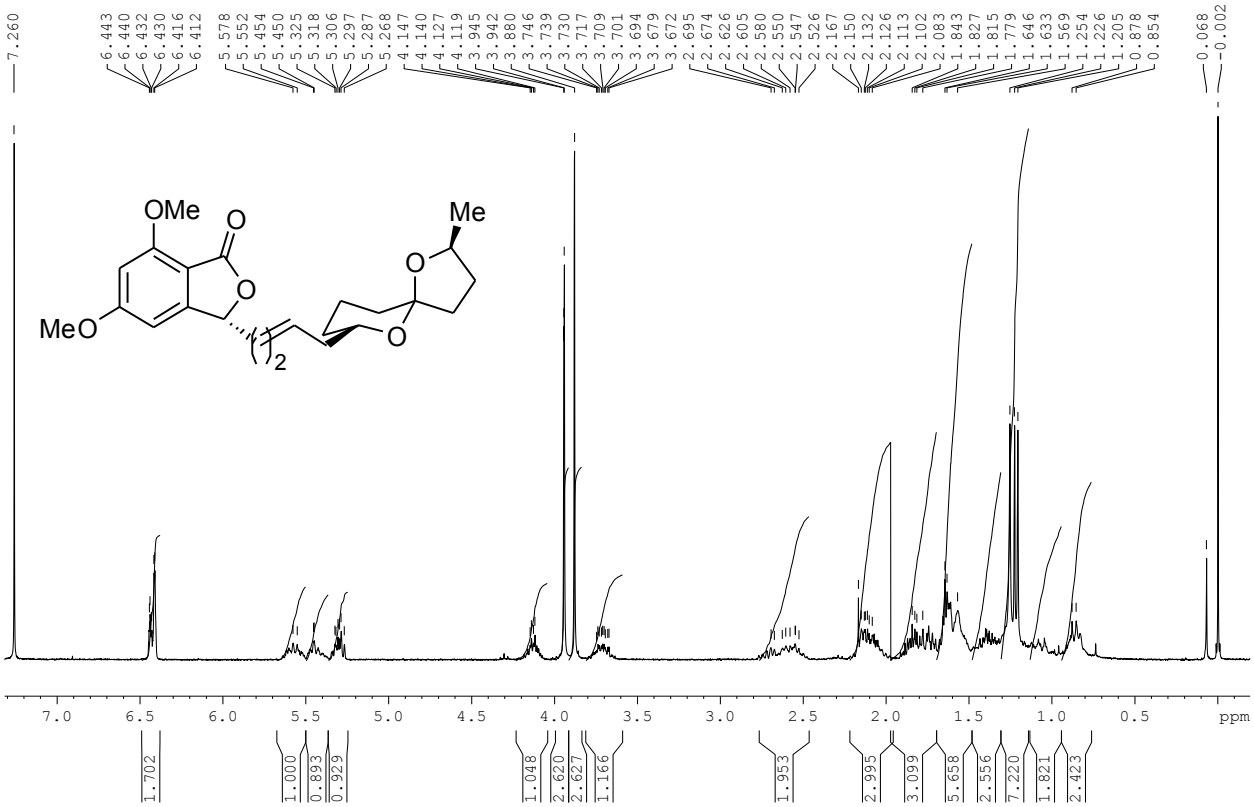
^{1}H NMR spectrum of **10** at 300 MHz, $CDCl_3$



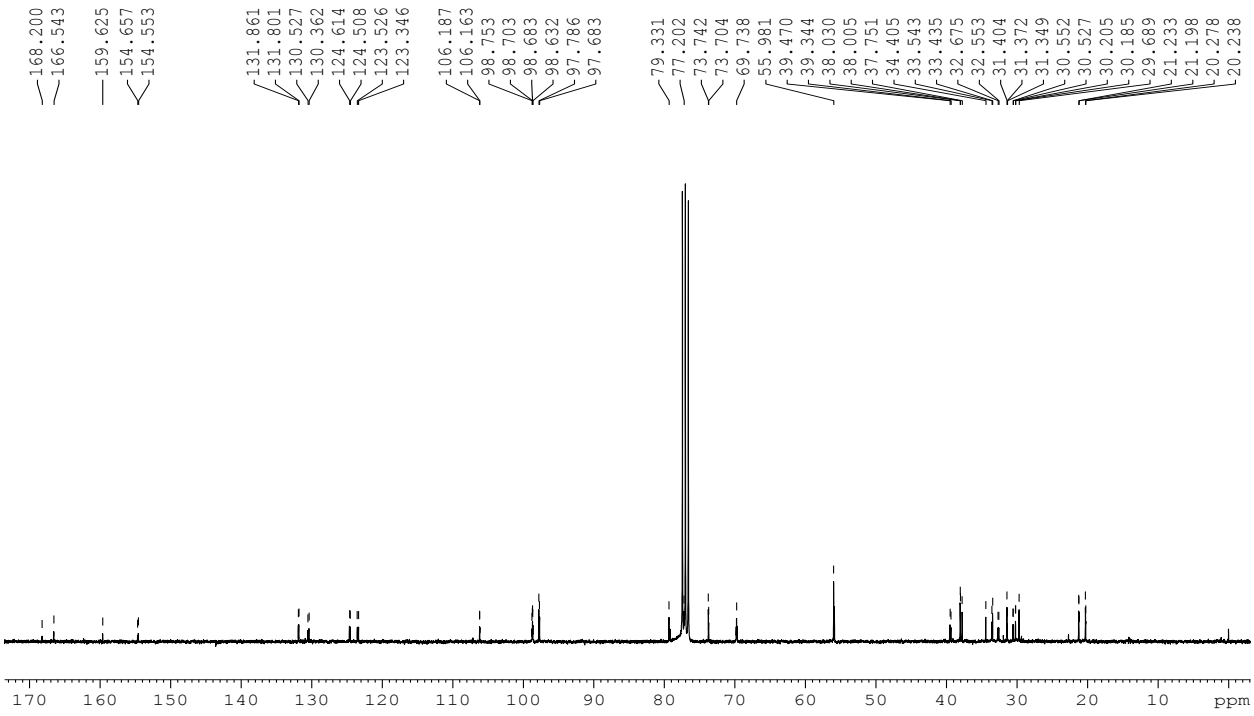
^{13}C NMR spectrum of **10** at 75 MHz, $CDCl_3$



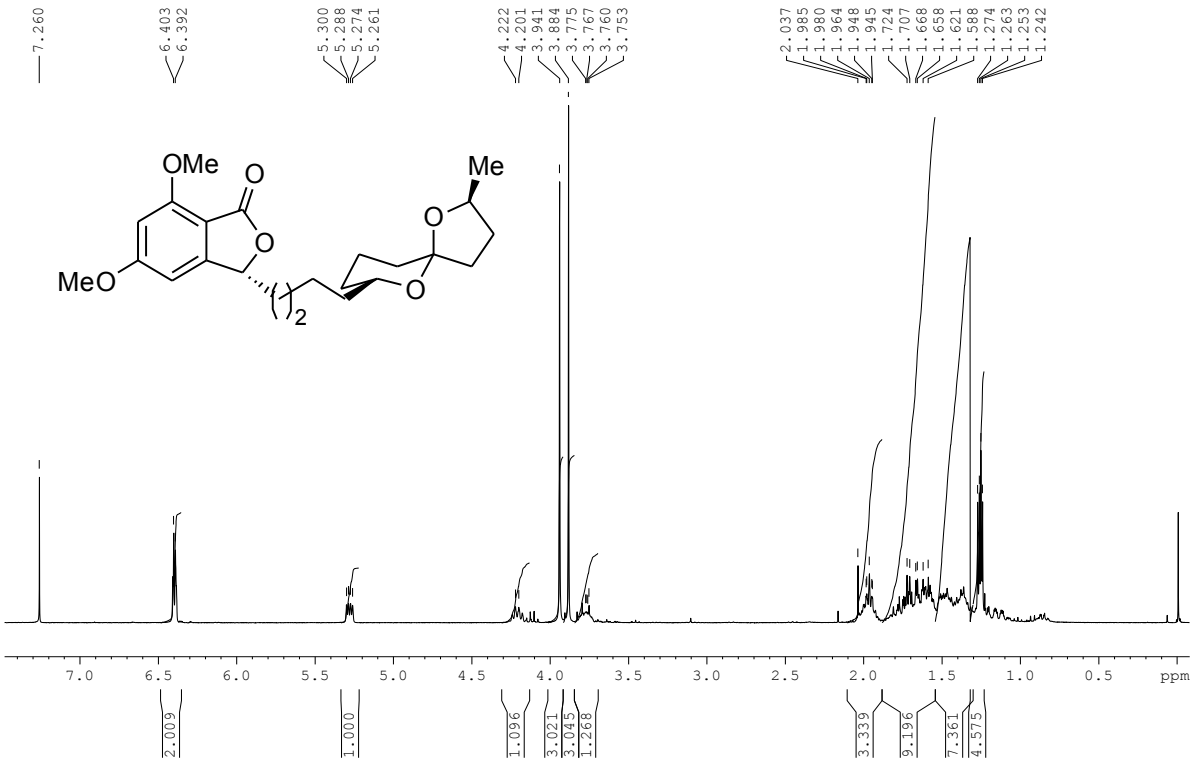
^{1}H NMR spectrum at 300 MHz, $CDCl_3$



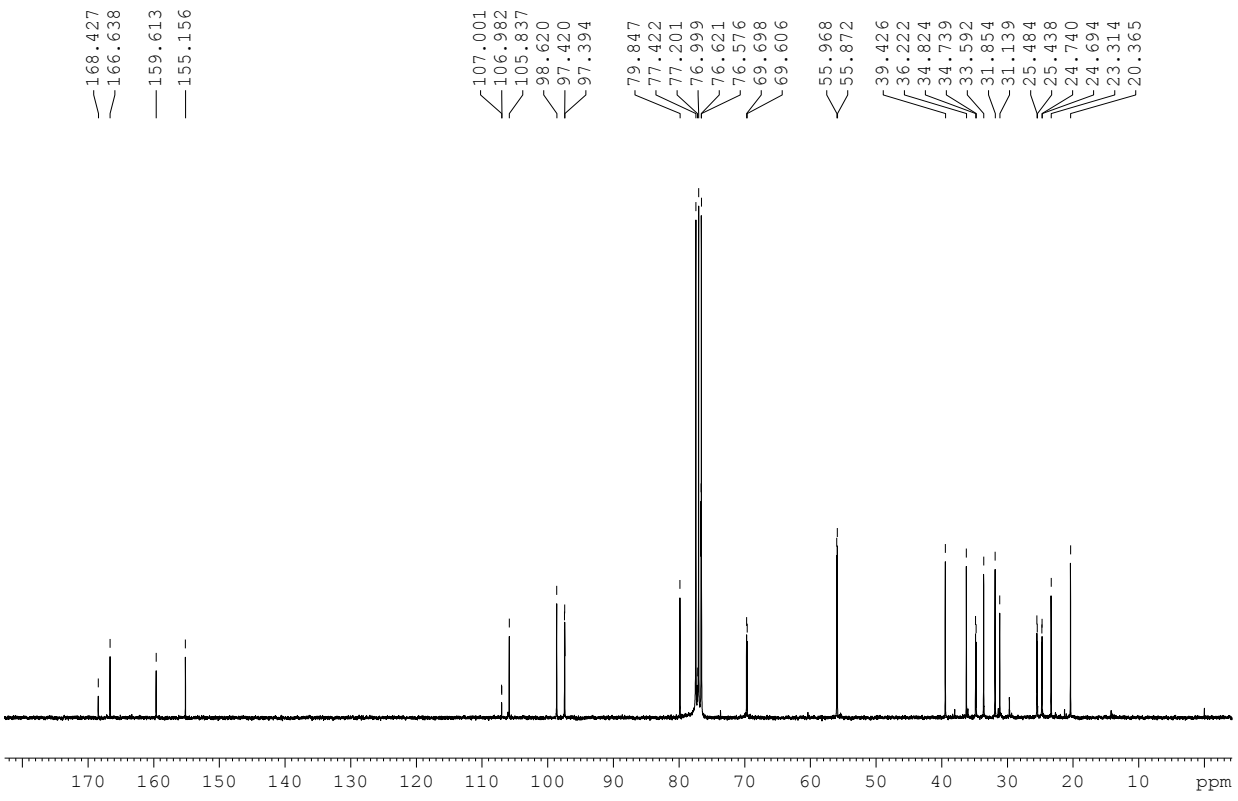
^{13}C NMR spectrum at 75 MHz, $CDCl_3$



^{1}H NMR spectrum of **5** at 300 MHz, $CDCl_3$



^{13}C NMR spectrum of **5** at 75 MHz, $CDCl_3$



Experimental Procedures

4,6-Dimethoxy-1-(7-((2*S*)-2-methyl-1,6-dioxaspiro[4.5]decan-7-yl)heptyl)-1H-indole (9)

A solution of 4,6-dimethoxyindole (**19**) (46.0 mg, 260 µmol) in DMSO (2 mL) was added dropwise to a stirred solution of powdered KOH (33.0 mg, 580 µmol) in DMSO (2 mL) and the mixture was stirred for 45 min at room temperature under an atmosphere of nitrogen. Iodide **22**(86.0 g, 220 µmol) dissolved in DMSO (1 mL) was added to the resultant green solution. After stirring the mixture for 2 h at room temperature, water (4 mL) was added. The solution was extracted with diethyl ether (3 x 5 mL) and ethyl acetate (3 x 5 mL). The combined organic extracts were dried with brine (3 x 3 mL) and magnesium sulfate. The solvents were removed under reduced pressure, flash chromatography (hexanes/diethyl ether 8:1) afforded the *title compound* (52.0 mg, 54%) as a yellow oil; $[\alpha]_D$ +43.4 (c 1.10, $CHCl_3$).

IR γ_{max}(film): 2927, 2854, 1622, 1587, 1499, 1455, 1373, 1249, 1209, 1146, 1068, 1049, 974, 936, 874, 804, 756, 732, 703, 627 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): 6.89 (1H, d, *J* 3.3, H2), 6.51 (1H, d, *J* 3.0, H1), 6.41 (1H, apparent s, H4), 6.23 (1H, d, *J* 1.5, H6), 4.20-4.30 (1H, m, H2"), 4.01 (2H, t, *J* 7.2, H1'), 3.93 (3H, s, OMe), 3.88 (3H, s, OMe), 3.81-3.83 (1H, m, H7"), 2.29-2.39 (2H, m, H3"), 1.91-2.06 (4H, m, H4" and H8'), 1.60-1.86 (6H, m, H10", H9" and H8"), 1.22-1.45 (12H, m, H2'-7'), 1.28 (3H, d, *J* 6.2, Me); **^{13}C NMR** (75 MHz, $CDCl_3$): 155.2 (quat., C5), 153.7 (quat., C7), 137.2 (quat., C4a), 124.9 (CH, C2), 113.4 (quat., C7a), 105.8 (quat., C5"), 98.1 (CH, C1), 91.0 (CH, C6), 85.7 (CH, C4), 76.7 (CH, C2"), 69.7 (CH, C7"), 55.7 (CH_3, OMe), 55.2 (CH_3, OMe), 46.5 (CH_2, C1'), 39.4 (CH_2, C4"), 36.4 (CH_2, C8'), 33.6 (CH_2, C7'), 31.8 (CH_2, C10"), 31.2 (CH_2, C3"), 29.9 (CH_2, C8"), 29.6 (CH_2, C3'), 29.4 (CH_2, C5'), 29.3 (CH_2, C4'), 26.9 (CH_2, C2'), 25.6 (CH_2, C6'), 23.3 (CH_3, Me), 20.4 (CH_2, C9"); ***m/z*** (EI): 443 (100), 429 (10), 399 (8), 343 (17), 315 (9), 289 (7), 232 (4), 190 (11), 155 (6), 98 (16), 55 (14), 41 (22); **HRMS** (EI): Found M^+, 443.30408, $C_{27}H_{41}NO_4$, requires 443.30356.

4,6-Dimethoxy-1-(7-((2*S*)-2-methyl-1,6-dioxaspiro[4.5]decan-7-yl)heptyl)indolin-2-one (12)

NaH (2.60 mg, 0.11 mmol, 60% w/w dispersion in mineral oil) was washed with pentane (3 x 1 mL) under an atmosphere of nitrogen and dried *in vacuo*. DMF (1mL) was added to the solid and the resulting slurry was stirred at room temperature. 4,6-Dimethoxyoxindole (**23**) (39.0 mg, 0.200 mmol) dissolved in DMF (1 mL) was added to the slurry, resulting in a red-brown mixture which was stirred at room temperature for 15 min. Iodide **22** (42.0 mg, 0.11 mmol) was dissolved in DMF (1 mL) and added to the mixture. After stirring for 2.5 h at room temperature, water (3 mL) was added. The solution was extracted with diethyl ether (3 x 5 mL) and ethyl acetate (3 x 5 mL). The combined organic extracts were dried with brine (3 x 3 mL) and magnesium sulfate. The solvents were removed under reduced pressure, flash chromatography (hexanes/EtOAc 5:1) afforded the *title compound* (32.0 mg, 68%) as a yellow oil; $[\alpha]_D$ +60.3 (c 1.10, $CHCl_3$).

IR γ_{max}(film): 2928, 2857, 1712, 1607, 1509, 1454, 1365, 1345, 1290, 1270, 1220, 1202, 1143, 1113, 1067, 974, 935, 871, 810, 787, 687 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): 6.15 (1H, d, *J* 3.1, H4), 6.09 (1H, d, *J* 3.0, H6), 4.20-4.30 (1H, m, H2"), 3.82 (6H, s, OMe), 3.77-3.79 (1H, m, H7"), 3.63 (2H, t, *J* 6.0, H1'), 3.37 (2H, s, H1), 1.82-1.96 (2H, m, H3"), 1.57-1.69 (12H, m, H8', H10", H4", H6', H8" and H2'), 1.13-1.42 (10H, m, H9", H7', H4', H3' and H5'), 1.28 (CH_3, d, *J* 6.0, Me); **^{13}C NMR** (75 MHz, $CDCl_3$): 175.9 (quat., C=O), 164.4 (quat., C7), 156.0 (quat., C5), 146.3 (quat., C4a), 105.8 (quat., C5"), 103.1 (quat., C7a), 97.7 (CH, C4), 89.0 (CH, C6), 76.6 (CH, C2"), 69.8 (CH, C7"), 55.6 (CH_3, OMe), 55.4 (CH_3, OMe), 40.2 (CH_2, 1'), 39.4 (CH_2, C4"), 36.6 (CH_2, C3"), 33.6 (CH_2, C10"), 33.1 (CH_2, C8"), 31.8 (CH_2, C6'), 31.2 (CH_2, C1), 29.6 (CH_2, C2'), 29.5 (CH_2, C8'), 29.3 (CH_2, C4'), 27.7 (CH_2, C7'), 26.9 (CH_2, C5'), 25.7 (CH_2, C3'), 23.3 (CH_3, Me), 20.4 (CH_2, C9"); ***m/z*** (ESI): 460 (100), 428 (5), 381 (8), 341 (4), 258 (6); **HRMS** (ESI): Found $(MH)^+$, 460.3049, $C_{27}H_{42}NO_5$, requires 460.3057.

4,6-Dimethoxy-1-(5-((2*S*)-2-methyl-1,6-dioxaspiro[4.5]decan-7-yl)pentyl)-1H-indole (8)

A solution of 4,6-dimethoxyindole (9.1 mg, 0.051 mmol) in DMSO (1 mL) was added dropwise to a stirred solution of powdered KOH (4.3 mg, 0.077 mmol) in DMSO (1 mL) and the resultant mixture was stirred for 50 min at room temperature under an atmosphere of nitrogen. Iodide **21** (10.0 mg, 0.029 mmol) dissolved in DMSO (1 mL) was added to the resultant green solution giving a brown solution upon addition. After stirring the mixture for 2 h at room temperature, water (4 mL) was added. The solution was extracted with diethyl ether (3 x 5 mL) and ethyl acetate (3 x 5 mL). The combined organic extracts were washed with brine (3 x 3 mL) and dried over magnesium sulfate. The solvent was removed under reduced pressure, flash chromatography (hexanes/diethyl ether 8:1) afforded the *title compound* (6.80 mg, 59%) as a yellow oil; $[\alpha]_D$ +49.5 (c 1.00, $CHCl_3$).

IR γ_{max}(film): 2925, 2855, 1732, 1622, 1588, 1499, 1456, 1433, 1364, 1251, 1208, 1146, 1070, 1050, 976, 937, 878 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): 6.89 (1H, d, *J* 3.0, H2), 6.49 (1H, d, *J* 3.0, H1), 6.39 (1H, apparent s, H4), 6.23 (1H, d, *J* 3.0, H6), 4.20-4.30 (1H, m, H2"), 4.01 (2H, t, *J* 6.0, H1'), 3.90 (3H, s, OMe), 3.89 (3H, s, OMe), 3.80-3.83 (1H, m, H7"), 1.97-2.17 (2H, m, H3"), 1.71-1.81 (4H, m, H4" and H5'), 1.52-1.79 (6H, m, H10", H9" and H8"), 1.22-1.45 (6H, m, H2'-4'), 1.22 (3H, d, *J* 6.1, Me); **^{13}C NMR** (75 MHz, $CDCl_3$): 157.3 (quat., C5), 153.7 (quat., C7), 137.3 (quat., C4a), 124.9 (CH, C2), 113.6 (quat., C7a), 105.9 (quat., C5"), 98.1 (CH, C1), 91.0 (CH, C6), 85.6 (CH, C4), 76.7 (CH, C2"), 69.7 (CH, C7"), 55.8 (CH_3, OMe), 55.3 (CH_3, OMe), 46.5 (CH_2, C1'), 39.4 (CH_2, C4"), 36.3 (CH_2, C5'), 33.6 (CH_2, C4'), 31.9 (CH_2, C10"), 31.2 (CH_2, C3"), 30.3 (CH_2, C8"), 29.7 (CH_2, C3'), 29.4 (CH_2, C4'), 27.1 (CH_2, C2'), 23.3 (CH_3, Me), 20.5 (CH_2, C9"); ***m/z*** (ESI): 424 (100)$(M+Na)^+$, 402 (40), 365 (1), 325 (5), 311 (9), 278 (2); **HRMS** (ESI): Found $(MH)^+$, 402.2649, $C_{24}H_{36}NO_4$, requires 402.2639.

(3*R*)-5,7-Dimethoxy-3-(7-((2*S*)-2-methyl-1,6-dioxaspiro[4.5]decan-7-yl)hept-3-enyl)isobenzofuran-1(3H)-one (38)

To a solution of sulfone **16** (12.0 mg, 0.03 mmol) in THF (1 mL) under an inert atmosphere at -78 ^oC was added potassium hexamethyldisilazide (77.0 µL, 0.5 M in toluene, 0.04 mmol) dropwise. The mixture was stirred for 20 min at -78 ^oC then a solution of aldehyde **14** (13.0 mg, 0.05 mmol) in THF (1 mL) was added. and the mixture was stirred at that temperature for 1.5 h. The mixture was then warmed to room temperature and stirred for an additional hour. Diethyl ether (3 mL) was added followed by saturated aqueous sodium chloride (3 mL). The aqueous layer was extracted with diethyl ether (2 x 3 mL) and the combined organic extracts were dried over magnesium sulfate and the solvent removed under reduced pressure The crude oil was purified by flash chromatography (hexanes/EtOAc 2:1) to afford the *title compound* (8.3 mg, 64%); **$[\alpha]_D$** +48.0 (c 1.60, $CHCl_3$).

IR γ_{max}(film): 2923, 2853, 1733(C=O), 1603, 1461, 1363, 1219, 1158, 1119, 1070, 1026, 974, 937, 809, 757, 689; **^{1}H NMR** (300 MHz, $CDCl_3$): 6.40-6.41 (2H, m, H4 and H6), 5.33-5.53 (2H, m, (*E*)-H3' and (*Z*)-H3', (*E*)-H4' and (*Z*)-H4'), 5.30 (1H, dd, *J* 8.4 and 3.3, H3), 4.18-4.25 (1H, qd, *J* 6.0, 1.5, H2"), 3.94 (3H, s, OMe), 3.89 (3H, s, OMe), 3.76-3.80 (1H, m, H7"), 1.94-2.04 (4H, m, (*E*)-H2' and (*Z*)-H2', (*E*)-H5' and (*Z*)-H5'), 1.58-1.70 (8H, m, H1', H8', H3" and H4"), 1.25-1.43 (10H, m, H6', H7', H8", H9" and H10"), 1.28 (3H, d, *J* 6.0, Me); **^{13}C NMR** (75 MHz, $CDCl_3$): 168.5 (quat., C1), 166.7 (quat., C5), 159.6 (quat., C7), 155.2 (quat., C3a), 132.2 (CH, (*E*)-C4' and (*Z*)-C4'), 128.1 (CH, (*E*)-C3' and (*Z*)-C3'), 107.0 (quat., C7a), 105.8 (quat., C5"), 98.7 (CH, C4), 97.3 (CH, C6), 79.2 (CH, C3), 76.6 (CH, C2"), 69.7 (CH, C7"), 55.9 (CH_3, OMe), 55.8 (CH_3, OMe), 39.4 (CH_2, C5'), 36.3 (CH_2, C2'), 34.9 (CH_2, C1'), 33.6 (CH_2, C8'), 32.6 (CH_2, C3"), 31.9 (CH_2, C8"), 31.8 (CH_2, C10"), 29.7 (CH_2, C4"), 29.4 (CH_2, C6'), 27.9 (CH_2, C7'), 23.3 (CH_3, Me), 20.4 (CH_2, C9"); ***m/z*** (ESI): 481(25)$(M+Na)^+$, 452 (100), 459 (45)(MH^+), 413 (10), 373 (15), 301 (10), 267 (15), 245 (10), 219 (15), 149 (15); **HRMS** (ESI): Found $(MH)^+$, 459.2727 $C_{27}H_{38}O_6$, requires 459.2714.

(3*R*)-5,7-Dimethoxy-3-(7-((2*S*)-2-methyl-1,6-dioxaspiro[4.5]decan-7-yl)heptyl)isobenzofuran-1-(3*H*)-one (6)

Alkene **38** (8.40 mg, 0.02 mmol) was dissolved in methanol/THF (1 mL, 1:1) and hydrogenated under an atmosphere of hydrogen in the presence of PtO_2 (0.63 mg, 0.003 mmol) for 6 h. The catalyst was removed by filtration through a pad of Celite® and the filtrate concentrated *in vacuo*. Flash chromatography (hexanes/diethyl ether 1:3) afforded the *title compound* (5.80 mg, 69%) as a yellow oil; **$[\alpha]_D$** +48.3 (c 1.50, $CHCl_3$).

IR γ_{max}(film): 2926, 2854, 17543(C=O), 1604, 1495, 1461, 1433, 1337, 1219, 1158, 1028, 837; **^{1}H NMR** (300 MHz, $CDCl_3$): 6.40-6.41 (2H, m, H4 and H6), 5.29 (1H, dd, *J* 7.8 and 3.9, H3), 4.19-4.26 (1H, qd, *J* 6.3, 1.8, H2"), 3.95 (3H, s, OMe), 3.89 (3H, s, OMe), 3.78-3.81 (1H, m, H7"), 1.95-2.00 (3H, m, H1'$_b$, H3"$_b$ and H4"$_b$), 1.58-1.67 (12 H, m, H1'$_a$, H3"$_a$, H4"$_a$, H9"$_a$, H8', H10", H8" and H7'), 1.22-1.43 (13H, m, H2', H4', H3', H9"$_b$, H5', H6' and H7'), 1.29 (3H, d, *J* 6.3, Me); **^{13}C NMR** (75 MHz, $CDCl_3$): 168.5 (quat., C1), 166.7 (quat., C5), 159.6 (quat., C7), 155.2 (quat., C3a), 107.0 (quat., C7a), 105.8 (quat., C5"), 98.6 (CH, C4), 97.4 (CH, C6), 79.9 (CH, C3), 76.6 (CH, C2"), 69.8 (CH, C7"), 55.9 (CH_3, OMe), 55.8 (CH_3, OMe), 39.5 (CH_2, C4"), 36.5 (CH_2, C8'), 34.9 (CH_2, C1'), 33.6 (CH_2, C10"), 31.9 (CH_2, C3"), 31.2 (CH_2, C8"), 29.7 (CH_2, C2') 29.5 (CH_2, C3'), 29.4 (CH_2, C7'), 29.3 (CH_2, C6'), 25.7 (CH_2, C5'), 24.6 (CH_2, C4"), 23.3 (CH_3, Me), 20.4 (CH_2, C9"); ***m/z*** (ESI): 483 (100)$(M+Na)^+$, 461 (30)(MH^+), 373 (20), 289 (10), 267 (9), 245 (10), 223 (5); **HRMS** (ESI): Found $(MH)^+$, 461.2887 $C_{27}H_{41}O_6$, requires 461.2898.

4,6-Dimethoxy-1-(4-((2*S*,5*R*,7*R*)-2-methyl-1,6-dioxaspiro[4.5]decan-7-yl)butyl)-1*H*-indole (7)

A solution of 4,6-dimethoxyindole (**19**) (33.0 mg, 0.19 mmol) in DMSO (2 mL) was added dropwise to a stirred solution of powdered KOH (16.0 mg, 0.28 mmol) in DMSO (2 mL) and the resultant mixture was stirred for 45 min at room temperature under an atmosphere of nitrogen. Iodide **20** (35.0 mg, 0.10 mmol) dissolved in DMSO (1 mL) was added to the green solution resulting in a brown solution upon addition. After stirring the mixture for an addtional 2.5 h at room temperature, water (5 mL) was added. The solution was extracted with diethyl ether (3 x 5 mL) and ethyl acetate (3 x 5 mL). The combined extracts were

washed with brine (3 x 3 mL) and dried over magnesium sulfate and concentrated *in* vacuo. Flash chromatography (hexanes/diethyl ether 8:1) afforded the *title compound* (30.0 mg, 75%) as a yellow oil; $[\alpha]_D$ +48.3 (c 1.70, $CHCl_3$).

IR γ_{max}(film): 2933, 2867, 1622, 1586, 1499, 1455, 1438, 1372, 1312, 1248, 1210, 1145, 1068, 1048, 1021, 973, 951, 935, 874, 855, 805, 757, 735, 704, 663; ; **^{1}H NMR** (300 MHz, $CDCl_3$): 6.88 (1H, d, *J* 3.0, H2), 6.48 (1H, d, *J* 3.0, H1), 6.40 (1H, apparent s, H4), 6.23 (1H, d, *J* 3.0, H6), 4.20-4.30 (1H, m, H2"), 4.02 (2H, t, *J* 6.0, H1'), 3.92 (3H, s, OMe), 3.87 (3H, s, OMe), 3.76-3.80 (1H, m, H7"), 1.95-1.99 (2H, m, H4"), 1.60-1.82 (10H, m, H4", H4', H2', H3' and H8"), 1.39-1.44 (4H, m, H9" and H10"), 1.25 (3H, d *J* 6.0, Me); **^{13}C NMR** (75 MHz, $CDCl_3$): 157.2 (quat., C5), 153.8 (quat., C7), 137.3 (quat., C4a), 125.0 (CH, C2), 113.6 (quat., C7a), 105.8 (quat., C5"), 98.1 (CH, C1), 91.1 (CH, C6), 85.6 (CH, C4), 76.7 (CH, C2"), 69.6 (CH, C7"), 55.7 (CH_3, OMe), 55.3 (CH_3, OMe), 46.5 (CH_2, C1'), 39.4 (CH_2, C4"), 36.0 (CH_2, C4'), 33.6 (CH_2, C3'), 31.9 (CH_2, C10"), 30.3 (CH_2, C3"), 29.7 (CH_2, C8), 23.3 (CH_3, Me), 20.3 (CH_2, C9"); ***m/z*** (ESI): 410 (10)$(M+Na)^+$, 388 (100)$(MH)^+$, 370 (10); **HRMS** (ESI): Found $(MH)^+$, 388.2473 $C_{20}H_{34}NO_4$, requires 388.2456.

4,6-Dimethoxy-1-(4-((2*S*)-2-methyl-1,6-dioxaspiro[4.5]decan-7-yl)butyl)indolin-2-one (10)

NaH (2.40 mg, 0.10 mmol, 60% w/w dispersion in mineral oil) was washed with pentane (3 x 1 mL) under an atmosphere of nitrogen and dried *in vacuo*. DMF (1mL) was added to the solid. 4,6-Dimethoxyoxindole (**23**) (36.0 mg, 0.190 mmol) in DMF (1 mL) was added to the slurry. The resulting red-brown mixture was stirred at room temperature for 15 min. Iodide **20** (34.0 mg, 0.100 mmol) was dissolved in DMF (1 mL) and then added to the anion. After stirring the mixture for 2.5 h at room temperature, water (3 mL) was added. The solution was extracted with diethyl ether (3 x 5 mL) and ethyl acetate (3 x 5 mL). The combined extracts were dried over magnesium sulfate. The solvents were removed under reduced pressure, flash chromatography (hexanes/EtOAc 5:1) afforded the *title compound* (28.0 mg, 70%) as a yellow oil; $[\alpha]_D$ +38.4 (c 1.60, $CHCl_3$).

IR γ_{max}(film): 2930, 2865, 1700, 1615, 1511, 1459, 1362, 1349, 1280, 1210, 1198, 1150, 1067, 971, 934, 873, 809, 798 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): 6.15 (1H, d, *J* 3.0, H4), 6.09 (1H, d, *J* 3.0, H6), 4.19-4.24 (1H, m, H2"), 3.82 (6H, s, OMe), 3.77-3.79 (1H, m, H7"), 3.64 (2H, t, *J* 6.0, H1'), 3.36 (2H, s, H1), 1.87-1.96 (2H, m, H3"), 1.57-1.72 (10H, m, H4", H4', H2', H3' and H8"), 1.39-1.43 (4H, m, H9" and H10"), 1.25 (3H, d *J* 6.0, Me); **^{13}C NMR** (75 MHz, $CDCl_3$): 175.8 (quat., C2), 164.4 (quat., C7), 155.9 (quat., C5), 146.3 (quat., C4a), 105.8 (quat., C5"), 103.0 (quat., C7a), 91.7 (quat., C4), 89.0 (quat., C6), 76.6 (CH, C2"), 69.6 (CH, C7"), 55.6 (CH_3, OMe), 55.4 (CH_3, OMe), 40.2 (CH_2, C1'), 39.4 (CH_2, C4"), 36.1 (CH_2, C3"), 33.6 (CH_2, C10"), 33.1 (CH_2, C4'), 31.8 (CH_2, C1), 31.1 (CH_2, C8"), 27.9 (CH_2, C2'), 23.3 (CH_3, Me), 20.3 (CH_2, C9"); ***m/z*** (ESI): 426 (100)$(M+Na)^+$, 404 (85)$(MH)^+$, 386 (10); **HRMS** (ESI): Found $(MH)^+$, 404.2415 $C_{23}H_{34}NO_5$, requires 404.2431.

(3*R*)-5,7-Dimethoxy-3-(4-((2"*S*,7"*R*)-2-methyl-1,6-dioxaspiro[4.5]decan-7-yl)but-2-enyl)isobenzofuran-1-(3H)-one

To a solution of sulfone **44** (0.046 g, 0.12 mmol) in THF (2 mL) under an inert atmosphere at -78 ^oC was added potassium hexamethyldisilazide (0.300 mL, 0.5 M in toluene, 0.151 mmol) dropwise. The reaction was stirred at -78 ^oC for 20 min then aldehyde **45** (0.028 g 0.12 mmol) in THF (2 mL) was added dropwise to the mixture. The reaction was stirred at -78 ^oC for 1.5 h then warmed to room temperature and stirred for an additional hour. Diethyl ether (10 mL) was added followed by brine (8 mL). The aqueous layer was extracted with ethyl acetate and the combined organic fractions dried over magnesium sulfate. Solvent removal under reduced pressure followed by flash chromatography (hexanes/EtOAc 4:1) afforded the *title compound* (30.1 mg, 62%) as a yellow oil; $[\alpha]_D$ +38.2 (c 1.00, $CHCl_3$).

IR γ_{max}(film): 2928, 1751, 1602, 1494, 1457, 1432, 1332, 1212, 1156, 1027, 977, 878, 834, 690 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): 6.41-6.44 (2H, m, H4 and H6), 5.45-5.58 (2H, m, (*E*)-H2' and (*Z*)-H2', (*E*)-H3' and (*Z*)-H3'), 5.26-5.32 (1H, m, H3), 4.12-4.15 (1H, m, H2"), 3.94 (3H, s, OMe), 3.88 (3H, s, OMe), 3.67-3.75 (1H, m, H7"), 2.52-2.69 (2H, m, H1'), 2.08-2.17 (2H, m, H4'), 1.65-1.84 (8H, m, H3", H4", H9" and H10"), 1.56 (2H, m, H8"), 1.25 (3H, d, *J* 6.4 Me); **^{13}C NMR**[1#] (75 MHz, $CDCl_3$): 168.2 (quat., C1), 166.5 (quat., C5), 159.6 (quat., C7), 154.7 (quat., C4a*), 154.6 (quat., C4a), 131.9 (CH, C3'*), 124.6 (CH, C3'), 130.5 (CH, C2'*), 123.4 (CH, C2'), 107.1 (quat., C7a), 106.2 (quat., C5"), 98.8 (CH, C4*), 98.6 (CH, C4), 97.8 (CH, C6*), 97.7 (CH, C6), 79.3 (CH, C3*), 79.2 (CH, C3), 73.7 (CH, C2"), 69.8 (CH, C7"*), 69.7 (CH, C7"), 55.9 (CH_3, OMe), 55.8 (CH_3, OMe), 39.5 (CH_2, C4'*), 39.3 (CH_2, C4'), 38.0 (CH_2, C4"*), 37.8 (CH_2, C4"), 34.4 (CH_2, C1'*), 33.5 (CH_2, C10"*), 33.4 (CH_2, C10"), 31.4 (CH_2, C3"*), 31.3 (CH_2, C3"), 30.6 (CH_2, C3"*), 30.5 (CH_2, C3"), 30.2 (CH_2, C8"*), 30.1 (CH_2, C8*), 29.7 (CH_2,

[1#] This symbol (*) is used to denote mixture of (*E*) and (*Z*) isomers.

C1'), 21.2 (CH_3, Me*), 21.2 (CH_3, Me), 20.3 (CH_2, C9"*), 20.2 (CH_2, C9"*); ***m/z*** (ESI): 425 (100)$(M+Na)^+$, 403 (30), 385 (10); **HRMS** (ESI): Found $(MH)^+$, 403.2090 $C_{23}H_{31}O_6$, requires 403.2115.

(3*R*)-5,7-Dimethoxy-3-(4-((2''*S*,7''*R*)-2-methyl-1,6-dioxaspiro[4.5]decan-7-yl)butyl)isobenzofuran-1-(3H)-one (5)

Alkene (13.0 mg, 0.032 mmol) was dissolved in THF/MeOH (2 mL, 1:1) and hydrogenated under an atmosphere of hydrogen in the presence of PtO_2 (0.63 mg, 0.0026 mmol) for 6 h. The catalyst was removed by filtration through a pad of Celite® and the solvents removed under reduced pressure. Flash chromatography (hexanes/EtOAc 1:1) afforded the *title compound* (10.0 mg, 77%) as a yellow oil; $[\alpha]_D$ +25.3 (c 1.50, $CHCl_3$).

IR γ_{max}(film): 2935, 2865, 1754, 1604, 1494, 1458, 1336, 1219, 1158, 1053, 1026, 974, 875, 837, 690 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$): 6.39-6.40 (2H, m, H3 and H6), 5.26-5.30 (1H, dd, *J* 3.6, 7.8, H3), 4.20-4.22 (1H, m, H2"), 3.94 (3H, s, OMe), 3.88 (3H, s, OMe), 3.75-3.78 (1H, m, H7"), 1.95-2.03 (3 H, m, H1'a, H3"a and H4"a), 1.66-1.72 (9H, H1'b, H3"b and H4"b, H9", H10"and H8"), 1.58-1.62 (6H, m, H2', H3' and H4'), 1.26 (3H, d, *J* 6.4 Me); **^{13}C NMR** (75 MHz, $CDCl_3$): 168.4 (quat., C1), 166.6 (quat., C5), 159.6 (quat., C7), 155.2 (quat., C4a), 107.0 (quat., C7a), 105.8 (quat., C5"), 98.6 (CH, C4), 97.4 (CH, C6), 79.9 (CH, C3), 76.6 (CH, C2"), 69.7 (CH, C7"), 55.9 (CH_3, OMe), 55.8 (CH_3, OMe), 39.4 (CH_2, C4"), 36.2 (CH_2, C4'), 34.8 (CH_2, C1'), 34.7 (CH_2, C1'), 33.6 (CH_2, C10"), 31.9 (CH_2, C3"), 31.1 (CH_2, C8"), 25.5 (CH_2, C3'), 24.7 (CH_2, C2'), 23.3 (CH_3, Me), 20.4 (CH_2, C9"); ***m/z*** (ESI): 427 (100)$(M+Na)^+$, 405 (30)(M^+), 280 (10), 231 (15); **HRMS** (ESI): Found M^+, 405.2254, $C_{23}H_{33}O_6$, requires 405.2272.