Michael Addition Of Ortho-Lithiated Aryloxiranes To α,β-Unsaturated Malonates: Synthesis of Tetrahydroindenofuranones

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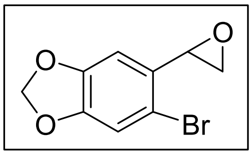
SUPPORTING INFORMATION

Experimental part: table of contents

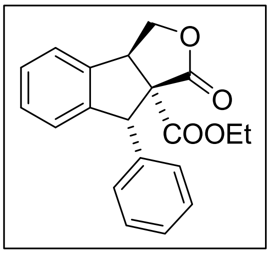
General. Tetrahydrofuran (THF) was freshly distilled under a nitrogen atmosphere over sodium/benzophenone ketyl. Epoxides **1a**,[1] **1b**,[2] **1c**-**d**,[3] and *cis*-**1d**[4] were prepared according to the reported procedures. α,β-Unsaturated malonates **5a–c** were prepared as reported.[5] Petroleum ether refers to the 40-60 °C boiling fraction. For the ^{1}H and ^{13}C NMR spectra (^{1}H NMR 400, 500, 600 MHz; ^{13}C NMR 100, 125, 150 MHz), $CDCl_3$ was used as the solvent if not otherwise specified. MS-ESI analyses were performed on LC/MSD trap system VL. Optical rotation of compounds **2f, 4b, 4f, 6b** was measured with a polarimeter with 1 dm path length cell at 25 °C; the concentration (c) is expressed in g/100 mL. Enantiomeric purity assay for compounds **2f, 4b, 4f, 6b** was ascertained by HPLC employing a Daicel Chiralcel OD-H column (250 x 4.6 mm). Melting points were uncorrected. Analytical thin layer chromatography (TLC) was carried out on precoated 0.25 mm thick plates of Kieselgel 60 F254; visualization was accomplished by UV light (254 nm) or by spraying a solution of 5 % (w/v) ammonium molybdate and 0.2 % (w/v) cerium(III) sulfate in 100 ml 17.6 % (w/v) aq. H_2SO_4 and heating to 200 °C for some time until blue spots appear. All reactions involving air-sensitive reagents were performed under nitrogen in oven-dried glassware using syringe-septum cap technique.

[1] Efange, S. M. N.; Kamath, A. P.; Khare, A. B.; Kung, M.-P.; Mach, R. H.; Parsons, S. M. *N- J. Med. Chem.* **1997,** *40,* 3905-3914.
[2] Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353–1364.
[3] Akguen, E.; Glinski, M. B.; Dhawan, K. L.; Durst, T. *J. Org. Chem.* 1981, 46, 2730–2734.
[4] Capriati, V.; Florio, S.; Luisi, R.; Perna, F. M.; Salomone, A. *J. Org. Chem.* **2006**, *71*, 3984–3987.
[5] Allen, C. F. H.; Spangler, F. W. *Organic Syntheses, Coll. Vol. 3, p.377 (1955).*

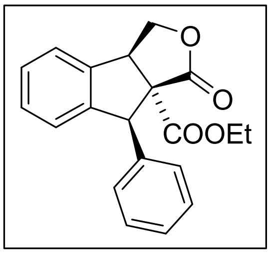


5-Bromo-6-oxiranyl-benzo[1,3]dioxole (1b): white solid, mp 54−55 °C (hexane), 80%; ^{1}H NMR (500 MHz) δ 2.59 (dd, J = 5.6, 2.6 Hz, 1 H), 3.13 (dd, J = 5.6, 4.0 Hz, 1 H), 4.07 (dd, J = 4.0, 2.6 Hz, 1 H), 5.95-5.97 (m, 2 H), 6.69 (s, 1 H), 6.97 (s, 1 H). ^{13}C NMR (125 MHz) δ 50.6, 52.2, 101.7, 105.9, 112.4, 113.0, 130.4, 147.7, 147.9. GC−MS (70eV) *m/z* (%) 244 (M^{+} +2, 44), 242 (M^{+}, 46), 215 (90), 213 (92), 133 (100), 75 (35). FT−IR (KBr, cm^{-1}) 2903, 1502, 1477, 1421, 1263, 1238, 1113, 1039, 932, 863.

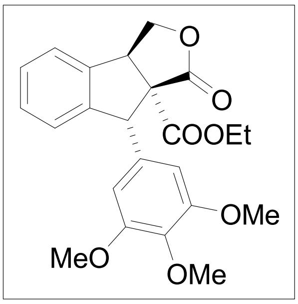
Preparation of Tetrahydroindenofuranones (4a–d). General Procedure. A solution of *n*-BuLi (1.2 mmol, 0.5 mL of a 2.5 M solution in hexanes) was added to a pre-cooled (−78 °C, acetone/dry ice bath) solution of ortho-bromo epoxides **1a-c** (1.0 mmol) in THF (5 mL) under N_2 and stirring. After 15 min at this temperature, a solution of the malonates **5a-c** (1.2 mmol) in THF (2 mL) was added dropwise. The resulting mixture was stirred for 3 hours at −78 °C; after this time, it was allowed to warm to rt, quenched with sat. aq. NH_4Cl and extracted with Et_2O (3 × 15 mL); the combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. The crude was purified by flash column-chromatography (silica gel; petroleum ether/Et_2O 7-3/1-1) to give compounds **4a–d**.



Ethyl (3a*R,8*R**,8a*S**)-1-oxo-8-phenyl-3,3a,8,8a-tetrahydro-1*H*-indeno[1,2-c]furan-8a-carboxylate (4a):** colourless oil, 30%; ^{1}H NMR (500 MHz) δ 0.89 (t, J = 7.0 Hz, 3 H), 3.85 (q, J = 7.0 Hz, 2 H), 4.62 (d, J = 8.6 Hz, 1 H), 4.71–4.77 (m, 2 H), 5.01 (s, 1H), 7.02–7.07 (m, 3 H), 7.18–7.40 (m, 6 H). ^{13}C NMR (125 MHz) δ 13.4, 48.6, 57.9, 62.2, 66.8, 72.0, 123.8, 125.6, 127.4, 128.4, 128.45, 128.5, 129.1, 139.8, 140.1, 144.2, 165.8, 174.4. GC−MS (70eV) *m/z* (%) 322 (M^{+}, 30), 258 (20), 231 (52), 204 (100), 165 (14). FT−IR (film, cm^{-1}) 3031, 2924, 1774, 1737, 1452, 1276, 1172, 1156, 1052, 766, 698.

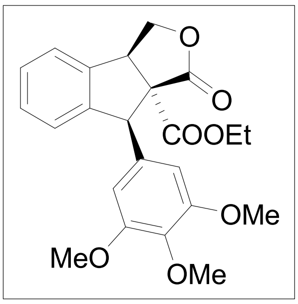


Ethyl (3a*R,8*S**,8a*S**)-1-oxo-8-phenyl-3,3a,8,8a-tetrahydro-1*H*-indeno[1,2-c]furan-8a-carboxylate (4a):** colourless oil, 30%; ^{1}H NMR (500 MHz) δ 1.32 (t, *J* = 7.1 Hz, 3 H), 4.25–4.36 (m, 2 H), 4.39 (dd, *J* = 7.5, 2.3 Hz, 1 H), 4.47 (dd, *J* = 8.7, 2.3 Hz, 1 H), 4.75 (dd, *J* = 8.7, 7.5 Hz, 1 H), 5.53 (s, 1 H), 7.08 (d, *J* = 8.3 Hz, 1 H), 7.21–7.23 (m, 2 H), 7.29–7.38 (m, 6 H); ^{13}C NMR (125 MHz) δ 14.0, 51.8, 56.1, 62.6, 64.9, 71.6, 123.5, 125.7, 127.6, 128.0, 128.3, 128.7, 129.9, 138.0, 140.9, 143.3, 169.3, 171.8; GC−MS (70eV) *m/z* (%) 322 (M^+, 29), 258 (22), 231 (54), 204 (100), 165 (18). FT−IR (film, cm^{-1}) 3032, 2980, 1779, 1739, 1479, 1373, 1238, 1020, 912.



Ethyl (3a*R,8*R**,8a*S**)-8-(3,4,5-trimethoxyphenyl)-1-oxo-3,3a,8,8a-tetrahydro-1*H*-indeno[1,2-c]furan-8a-carboxylate (4b):** white solid, mp 144-146 °C (hexane), 20%; ^{1}H NMR (500 MHz) δ 0.91 (t, *J* = 7.0 Hz, 3 H), 3.74 (s, 6 H), 3.76 (s, 3 H), 3.87–3.98 (m, 2 H), 4.61 (d, *J* = 7.8 Hz, 1 H), 4.71–4.76 (m, 2 H), 4.93 (s, 1 H), 6.24 (s, 2 H), 7.10 (d, *J* = 7.4 Hz, 1 H), 7.25–7.40 (m, 3 H).^{13}C NMR (125 MHz) δ 13.5, 48.6, 56.0, 58.2, 60.7, 62.1, 66.7, 72.0, 105.4, 123.8, 125.5, 128.6, 129.1, 135.8, 137.2, 139.5, 143.8, 153.0, 165.7, 174.4. MS (ESI) *m/z* 435 $[M+Na]^+$. FT−IR (KBr, cm^{-1}) 2967, 2924, 1775, 1731, 1594, 1467, 1239, 1126, 1019, 799, 765. Anal. Calcd for $C_{23}H_{24}O_7$: C 66.98 %; H 5.87 %. Found: C 67.17 %; H 5.88.

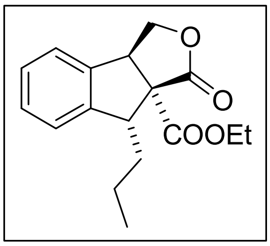
(3a*R*,8*R*,8a*S*)-(−)-4b: 24%, er: 97/3, ($t_{R\ major}$ = 16.1 min, $t_{R\ minor}$ = 18.2 min by HPLC, *n*-hexane/*i*PrOH 8/2, flow 0.7 mL/min, 230 nm), $[\alpha]^{25}_{D}$ = −108 (c 0.9, $CHCl_3$).



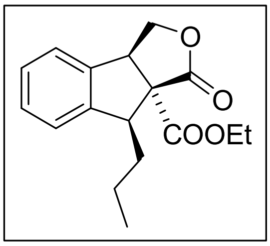
Ethyl (3a*R,8*S**,8a*S**)-8-(3,4,5-trimethoxyphenyl)-1-oxo-3,3a,8,8a-tetrahydro-1*H*-indeno[1,2-c]furan-8a-carboxylate (4b):** white solid, mp 134-136 °C (hexane), 30%; ^{1}H NMR (500 MHz) δ 1.31 (t, *J* = 7.0 Hz, 3 H), 3.76 (s, 6 H), 3.85 (s, 3 H), 4.25–4.37 (m, 3 H), 4.46 (dd, *J* =

8.8, 2.5 Hz, 1 H), 4.74 (dd, J = 8.8, 7.3 Hz, 1 H), 5.43 (s, 1 H), 6.42 (s, 2 H), 7.10 (d, J = 7.4 Hz, 1 H), 7.29–7.37 (m, 3 H). ^{13}C NMR (125 MHz) δ 14.1, 51.9, 56.1, 56.30, 60.9, 62.7, 64.9, 71.6, 107.3, 123.6, 125.8, 128.5, 128.7, 133.4, 137.4, 140.7, 143.2, 152.7, 169.4, 171.8. MS (ESI) *m/z* 435 [M+Na]$^+$. FT–IR (KBr, cm^{-1}) 2936, 1779, 1738, 1592, 1463, 1336, 1239, 1127, 1019, 846, 735. Anal. Calcd for $C_{23}H_{24}O_7$: C 66.98 %; H 5.87 %. Found: C 67.20 %; H 5.91.

(3a*R*,8*S*,8a*S*)-(+)-4b: 36%, er: 97/3, ($t_{R\ minor}$ = 16.0 min, $t_{R\ major}$ = 17.5 min by HPLC, *n*-hexane/*i*PrOH 8/2, flow 0.7 mL/min, 230 nm), $[\alpha]^{25}_{D}$ = +104 (c 1.2, $CHCl_3$).

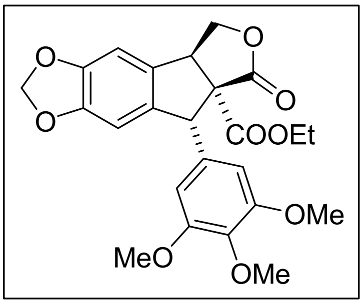


Ethyl (3a*R,8*R**,8a*S**)-1-oxo-8-propyl-3,3a,8,8a-tetrahydro-1*H*-indeno[1,2-*c*]furan-8a-carboxylate (4c):** colourless oil, 34%; ^{1}H NMR (400 MHz) δ 0.86 (t, J = 7.3 Hz, 3 H), 1.12–1.32 (m, 2 H), 1.36 (t, J = 7.1 Hz, 3 H), 1.41–1.51 (m, 1 H), 1.60–1.70 (m, 1 H), 3,84 (dd, J = 9.1, 4.0 Hz, 1 H), 4.25–4.40 (m, 2 H), 4.43 (d, J = 5.5 Hz, 1 H), 4.50 (d, J = 8.8 Hz, 1 H), 4.67 (dd, J = 9.1, 5.5 Hz, 1 H), 7.20 (d, J = 6.6 Hz, 1 H), 7.24–7.30 (m, 3 H). ^{13}C NMR (150 MHz) δ 14.1, 14.1^1, 19.1, 34.8, 48.2, 50.5, 62.4, 65.3, 72.0, 123.8, 125.3, 128.2, 128.2^1, 139.6, 144.1, 166.8, 174.8. GC–MS (70 eV) *m/z* (%) 288 (M$^+$, 49), 270 (16), 230 (30), 186 (100), 155 (70), 129 (94), 115 (40). FT–IR (film, cm^{-1}) 2960, 1780, 1728, 1477, 1369, 1239, 1152, 1055, 960, 762.

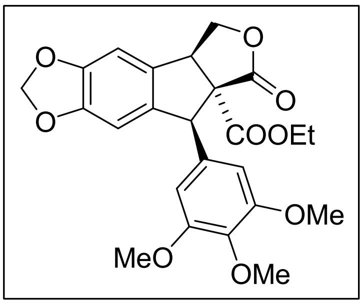


Ethyl (3a*R,8*S**,8a*S**)-1-oxo-8-propyl-3a,8-dihydro-1*H*-indeno[1,2-*c*]furan-8a(3*H*)-carboxylate (4c):** colourless oil, 16%; ^{1}H NMR (400 MHz) δ 1.03 (t, J = 7.3 Hz, 3 H), 1.32 (t, J = 7.3 Hz, 3 H), 1.52–1.76 (2 x m, 2 H), 1.86–1.95 (m, 1 H), 2.01–2.11 (m, 1 H), 4.09 (dd, J = 9.2, 5.5 Hz, 1 H), 4.15 (br d, J = 6.2 Hz, 1 H), 4.26–4.34 (m, 2 H), 4.46 (dd, J = 9.2, 1.8 Hz, 1 H), 4.66 (dd, J = 9.2, 6.2 Hz, 1 H), 7.20–7.21 (m, 1H), 7.24–7.32 (m, 3 H). ^{13}C NMR (150 MHz) δ 14.1, 14.4, 21.8, 31.9, 49.8, 52.3, 62.4, 63.0, 70.9, 123.4, 123.7, 127.9, 128.6, 139.4, 144.9, 169.9, 172.8. GC–MS

(70 eV) *m/z* (%) 288 (M^+, 5), 270 (10), 243 (48), 215 (63), 155 (95), 128 (100), 115 (45). FT−IR (film, cm^{-1}) 2961, 2872, 1777, 1738, 1478, 1372, 1238, 1168, 1061, 958, 743.

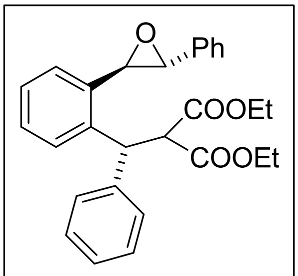


Ethyl (4b*R,7a*S**,8*R**)-8-(3,4,5-trimethoxyphenyl)-7-oxo-4b,5,7a,8-tetrahydro-7*H*-furo[3',4':1,2]-indeno[5,6-d][1,3]dioxol-7a-carboxylate (4d):** white solid, mp 164-165 °C (Et_2O), 30%; ^1H NMR (500 MHz) δ 0.88 (t, J = 7.1 Hz, 3 H), 3.75 and 3.76 (2 x s, 9 H), 3.83−3.97 (m, 2 H), 4.51 (d, J = 9.1 Hz, 1 H), 4.60 (d, J = 5.5 Hz, 1 H), 4.66 (dd, J = 9.1, 5.5 Hz, 1 H), 4.76 (s, 1H), 5.93 and 5.94 (2 x d AB system, J = 1.3 Hz, 2 H), 6.23 (s, 2 H), 6.48 (s, 1 H), 6.77 (s, 1 H). ^{13}C NMR (125 MHz) δ 13.5, 48.3, 56.0, 57.9, 60.7, 62.1, 67.2, 71.8, 101.5, 103.5, 105.2, 132.1, 135.7, 137.0, 137.1, 148.6, 148.8, 153.0, 165.5, 174.4. GC−MS (70 eV) *m/z* (%) 456 (M^+, 100), 366 (18), 338 (30), 308 (10). FT−IR (KBr, cm^{-1}) 2978, 2939, 1777, 1727, 1591, 1476, 1235, 1127, 1038, 1009, 857, 732. Anal. Calcd for $C_{24}H_{24}O_9$: C 63.15 %; H 5.30 %. Found: C 63.34 %; H 5.32.



Ethyl (4b*R,7a*S**,8*S**)-8-(3,4,5-trimethoxyphenyl)-7-oxo-4b,5,7a,8-tetrahydro-7*H*-furo[3',4':1,2]-indeno[5,6-d][1,3]dioxol-7a-carboxylate (4d):** white solid, mp 179-180 °C (Et_2O) 20%; ^1H NMR (400 MHz) δ 1.30 (t, J = 7.1 Hz, 3 H), 3.77 (s, 6 H), 3.83 (s, 3 H), 4.21-4.33 (m, 3 H), 4.37 (dd, J = 8.8, 2.4 Hz, 1 H), 4.67 (dd, J = 8.8, 7.3 Hz, 1 H), 5.28 (s, 1 H), 5.95 (d, J = 2.8 Hz, 1 H), 5.98 (d, J = 2.8 Hz, 1 H), 6.40 (s, 2 H), 6.48 (s, 1 H), 6.68 (s, 1 H). ^{13}C NMR (150 MHz) δ 14.0, 51.5, 55.8, 56.1, 60.8, 62.6, 65.3, 71.4, 101.5, 103.3, 105.7, 107.2, 133.1, 133.3, 136.2, 137.5, 148.4, 148.6, 152.7, 169.2, 171.6. GC−MS (70 eV) *m/z* (%) 456 (M^+, 100), 366 (21), 338 (29), 308 (12). FT−IR (KBr, cm^{-1}) 2939, 1777, 1738, 1591, 1478, 1234, 1126, 1037, 731. Anal. Calcd for $C_{24}H_{24}O_9$: C 63.15 %; H 5.30 %. Found: C 63.28 %; H 5.41.

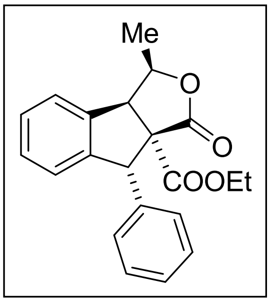
Preparation of β-Epoxyphenylmalonates (2e–g). General Procedure. A solution of PhLi (1.2 mmol, 0.7 mL of a 1.8 M solution in dibuthylether) [or *t*-BuLi (2 mmol, 1.2 mL of a 1.7 M solution in pentane) in the case of oxirane **1c**] was added to a pre-cooled (−78 °C, acetone/dry ice bath) solution of oxirane **1d** (1.0 mmol) in THF (5 mL) under N_2 and stirring. After 45 min at this temperature (10 min in the case of oxirane **1c**), a solution of the malonates **5a,c** (1.2 mmol) in THF (2 mL) was added dropwise. The resulting mixture was stirred for 3 h at −78 °C; then, it was allowed to warm to rt, quenched with sat. aq. NH_4Cl and extracted with Et_2O (3 × 15 ml); the combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. In the case of the reaction of **1d** with malonate **5a** the Michael adduct **2f** was isolated (in order to prove the reaction mechanism) by flash column-chromatography silica gel; petroleum ether/Et_2O 9/1 as the eluent. On the other hand, the crude β-epoxyphenylmalonates **2e,g** were converted in the corresponding tetrahydroindenofuranones **4e,g** without further purification as described below.



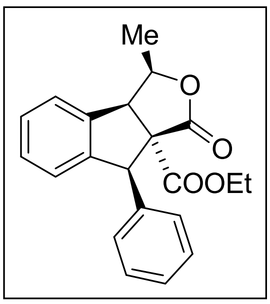
Diethyl ((*R)-phenyl{2-[(2*R**,3*R**)-3-phenyloxiran-2-yl]phenyl} methyl)malonate (2f):** colourless oil, 70%; ^{1}H NMR (500 MHz) δ 0.94 (t, J = 7.1 Hz, 3 H), 1.05 (t, J = 7.1 Hz, 3 H), 3.89–3.93 (m, 3 H), 3.99 (d, J = 2.0 Hz, 1 H) , 4.05 (q, J = 7.1 Hz, 2 H), 4.37 (d, J = 12.0 Hz, 1 H), 5.02 (d, J = 12.0 Hz, 1 H), 7.03−7.05 (m, 2 H), 7.11−7.16 (m, 3 H), 7.25−7.48 (m, 7 H), 7.56−7.57 (m, 2 H). ^{13}C NMR (125 MHz) δ 13.6, 13.7, 46.6, 57.7, 60.9, 61.0, 61.3, 61.4, 125.0, 125.4, 125.7, 126.9, 127.0, 127.8, 128.1, 128.3, 128.4, 128.5, 136.1, 137.2, 139.1, 139.3, 167.3, 167.3. MS (ESI) *m/z* 467 $[M+Na]^+$. FT−IR (film, cm^{-1}) 3032, 2982, 1755, 1732, 1496, 1455, 1369, 1262, 1176, 1033, 758, 699.

(*R*,2*R*,3*R*)-(−)-2f: 72%, er: 98/2, ($t_{R\ minor}$ = 18.7 min, $t_{R\ major}$ = 21.5 min by HPLC, *n*-hexane/*i*PrOH 97/3, flow 1.0 mL/min, 230 nm), $[\alpha]^{25}_D$ = −11 (c 0.9, $CHCl_3$).

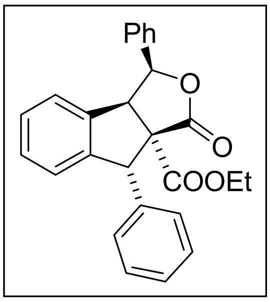
Preparation of Tetrahydroindenofuranones (4e–g). General Procedure. *t*-BuOK (1 mmol) was added to a solution of β-epoxyphenylmalonates **2e-g** (0.5 mmol) in *t*-BuOH (2 mL). The reaction mixture was then stirred at room temperature for 4-6 h until the substrate **2** disappeared (TLC monitoring: petroleum ether/Et_2O 8-9/2-1). Then the resulting reaction mixture was quenched with diluited HCl and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude mixture was dissolved in EtOH (3 mL), treated with catalytic amount of conc. H_2SO_4 and heated at 70 °C for 6-8 h. The resulting reaction mixture was quenched with water and extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with brine (3 × 10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The crude was flash-chromatographed (silica gel; petroleum ether/Et_2O 8-6/2-4) to give compounds **4e–g**.



Ethyl (3*R,3a*R**,8*R**,8a*S**)-3-methyl-1-oxo-8-phenyl-3,3a,8,8a-tetrahydro-1*H*-indeno[1,2-c]furan-8a-carboxylate (4e):** colourless oil, 17%; ^{1}H NMR (600 MHz) δ 0.89 (t, J = 7.1 Hz, 3 H), 1.68 (d, J = 6.6 Hz, 3 H), 3.81–3.87 (m, 2 H), 4.71 (d, J = 5.6 Hz, 1 H), 5.05–5.09 (m, 2 H), 6.99 (d, J = 7.2 Hz, 2 H), 7.09 (d, J = 7.6 Hz, 1 H), 7.17–7.32 (m, 5 H), 7.41 (d, J = 7.7 Hz, 1H). ^{13}C NMR (150 MHz) δ 13.4, 16.8, 52.7, 57.5, 62.1, 69.2, 77.9, 126.2, 126.6, 127.3, 127.6, 128.3, 128.4, 129.0, 136.0, 140.6, 145.4, 166.0,173.9. GC−MS (70 eV) *m/z* (%) 336 (M+, 43), 246 (39), 218 (100), 191 (34), 189 (34), 165 (13). FT−IR (film, cm^{-1}) 2923, 1777, 1728, 1455, 1276, 1239, 1170, 1009, 754, 700

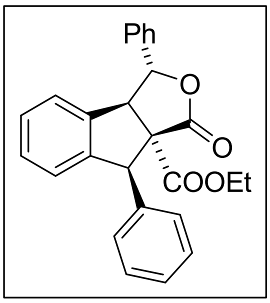


Ethyl (3*R,3a*R**,8*S**,8a*S**)-3-methyl-1-oxo-8-phenyl-3,3a,8,8a-tetrahydro-1*H*-indeno[1,2-c]furan-8a-carboxylate (4e):** colourless oil, 58%; ^{1}H NMR (600 MHz) δ 1.34 (t, J = 7.1 Hz, 3 H), 1.54 (d, J = 6.6 Hz, 3H), 4.28−4.37 (m, 2 H), 4.42 (d, *J* = 7.5 Hz,1 H), 5.07−5.11 (m, 1 H), 5.48 (s, 1 H), 7.09 (d, *J* = 6.7 Hz, 1 H), 7.23−7.35 (m, 8 H). ^{13}C NMR (150 MHz) δ 14.0, 17.5, 55.4, 56.1, 62.6, 66.7, 76.9, 125.9, 126.1, 127.4, 127.5, 128.0, 128.5, 129.9, 136.8, 138.6, 144.6, 169.6, 171.1. GC−MS (70 eV) *m/z* (%) 336 (M+, 48), 246 (43), 218 (100), 191 (81), 189 (46), 165 (20). FT−IR (film, cm^{-1}) 2933, 1776, 1738, 1455, 1354, 1239,1168, 1021, 733, 699

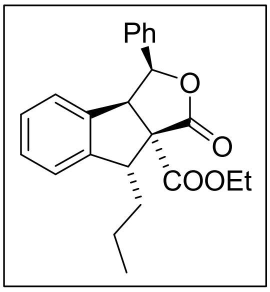


Ethyl (3*R,3a*S**,8*S**,8a*R**)-1-oxo-3,8-diphenyl-3,3a,8,8a-tetrahydro-1*H*-indeno[1,2-*c*]furan-8a-carboxylate (4f):** white solid, mp 157-158 °C (hexane) 50%; ^{1}H NMR (600 MHz) δ 1.29 (t, *J* = 7.2 Hz, 3 H), 4.24−4.35 (m, 2 H), 4.69 (d, *J* = 4.9 Hz, 1 H), 4.80 (s, 1 H), 5.71 (*J* = 4.9 Hz, 1 H), 6.77 (d, *J* = 7.7 Hz, 1 H), 6.92 (m, 2 H), 7.19−7.28 (m, 10 H), 7.40 (d, *J* = 7.4 Hz, 1 H). ^{13}C NMR (150 MHz) δ 13.9, 44.7, 53.5, 60.5, 62.0, 79.5, 127.0, 127.3, 127.4, 127.7, 127.7, 127.7, 128.6, 130.0, 130.7, 132.8, 133.2, 138.2, 140.2, 168.7, 172.0. GC−MS (70 eV) *m/z* (%) 398 (M^+, 5), 354 (49), 307 (100), 281 (53), 263 (68), 231 (39) 203 (57), 202 (54), 195 (59). FT−IR (KBr, cm^{-1}) 3064, 2994, 1783, 1732, 1494, 1453, 1320, 1228, 1109, 1060, 972, 745, 735, 701. Anal. Calcd for $C_{26}H_{22}O_4$: C 78.37 %; H 5.57 %. Found: C 78.24 %; H 5.55.

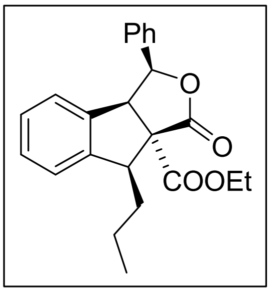
(3*S*,3a*R*,8*R*,8a*S*)-(+)-4f: 55%, er: 98/2, ($t_{R\ minor}$ = 13.0 min, $t_{R\ major}$ = 17.6 min by HPLC, *n*-hexane/*i*PrOH 9/1, flow 0.7 mL/min, 230 nm), $[\alpha]^{25}_{D}$ = +63 (c 1.3, $CHCl_3$).



Ethyl (3*R,3a*R**,8*S**,8a*S**)-1-oxo-3,8-diphenyl-3,3a,8,8a-tetrahydro-1*H*-indeno[1,2-*c*]furan-8a-carboxylate (*diast*-4f):** white solid, 8%; ^{1}H NMR (600 MHz) δ 0.70 (t, *J* = 7.2 Hz, 3 H), 3.70−3.78 (m, 2 H), 3.96 (s, 1 H), 5.41 (s, 1 H), 5.45 (s, 1 H), 7.01 (d, *J* = 8.0 Hz, 1 H), 7.11 (br s, 2 H), 7.25−7.27 (m, 4 H), 7.29−7.37 (m, 7 H). ^{13}C NMR (150 MHz) δ 13.2, 52.2, 57.8, 61.5, 64.0, 80.9, 126.5, 126.9, 127.8, 127.9, 128.1, 128.3, 128.9, 130.1, 130.6, 130.8, 136.8, 136.9, 139.9, 167.2, 170.0. MS (ESI) *m/z* 421 $[M+Na]^+$. FT–IR (KBr, cm^{-1}) 3031, 2985, 1791, 1724, 1456, 1294, 1259, 1021, 947, 743, 701.



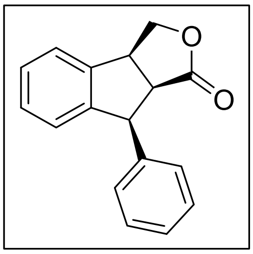
Ethyl (3*R,3a*S**,8*S**,8a*R**)-1-oxo-3-phenyl-8-propyl-3,3a,8,8a-tetrahydro-1*H*-indeno[1,2-*c*]furan-8a-carboxylate (4g):** white solid, mp 89-90 °C (hexane), 10%; ^{1}H NMR (400 MHz) δ 0.81 (t, J = 7.3 Hz, 3 H), 1.00–1.13 (m, 1 H), 1.19–1.31 (m, 1 H), 1.37–1.48 (m, 4 H), 1.56–1.64 (m, 1 H), 3.91 (dd, J = 8.3, 4.1 Hz, 1 H), 4.29–4.45 (m, 2 H), 4.65 (d, J = 5.4 Hz, 1H), 5.62 (d, J = 7.8 Hz, 1 H), 5.99 (d, J = 5.4 Hz, 1 H), 6.77–6.80 (m, 1 H), 7.09–7.15 (m, 2 H), 7.22–7.24 (m, 2 H), 7.36–7.37 (m, 3 H). ^{13}C NMR (150 MHz) δ 14.0, 14.1, 18.8, 35.0, 49.7, 53.7, 62.4, 67.7, 81.9, 124.8, 125.8, 126.6, 126.7, 127.9, 128.3, 128.4, 135.2, 144.8, 166.8, 174.3. GC–MS (70 eV) *m/z* (%) 364 (M^+, 5), 318 (36), 273 (43), 231 (52), 205 (100), 91 (26). FT–IR (KBr, cm^{-1}) 2960, 1788, 1728, 1455, 1244, 1229, 1151, 1025, 760, 716. Anal. Calcd for $C_{23}H_{24}O_4$: C 75.80 %; H 6.64 %. Found: C 75.97 %; H 6.64.



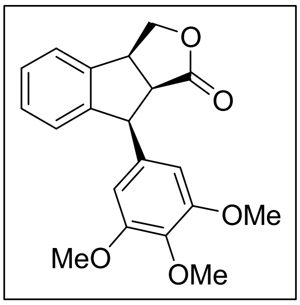
Ethyl (3*R,3a*S**,8*R**,8a*R**)-1-oxo-3-phenyl-8-propyl-3,3a,8,8a-tetrahydro-1*H*-indeno[1,2-*c*]furan-8a-carboxylate (4g):** white solid, mp 128-129 °C (hexane), 40%; ^{1}H NMR (500 MHz) δ 0.94 (t, J = 7.2 Hz, 3 H), 1.35 (t, J = 7.1 Hz, 3 H), 1.51–1.60 (m, 1 H), 1.61–1.71 (m, 2 H), 1.92–1.99 (m, 1H), 3.50 (dd, J = 6.2, 4.1 Hz, 1 H), 4.36–4.40 (m, 2 H), 4.56 (d, J = 5.0 Hz, 1H), 5.59 (d, J = 5.0 Hz, 1H), 6.78–6.80 (m, 2 H), 7.10–7.12 (m, 3 H), 7.18–7.21 (m, 1 H), 7.27–7.30 (m, 3 H). ^{13}C NMR (150 MHz) δ 14.1, 14.5, 23.3, 37.31, 37.6, 52.5, 59.3, 62.1, 80.0, 126.7, 127.4, 127.5, 128.2, 128.4, 130.0, 132.1, 133.1, 139.4, 169.7, 172.7. GC–MS (70 eV) *m/z* (%) 364 (M^+, 7), 318 (32), 273 (47), 231 (52), 205 (100), 91 (23). FT–IR (KBr, cm^{-1}) 2962, 1782, 1738, 1449, 1283, 1223, 1118, 1056, 974, 701. Anal. Calcd for $C_{23}H_{24}O_4$: C 75.80 %; H 6.64 %. Found: C 75.58 %; H 6.72.

Preparation of Tetrahydroindenofuranones (4f–g). One-pot Procedure. A solution of PhLi (1.05 mmol, 0.6 mL of a 1.8 M solution in dibuthylether) was added to a pre-cooled (−78 °C, acetone/dry ice bath) solution of oxirane **1d** (1.0 mmol) in THF (5 mL) under N_2 and stirring. After 45 min at this temperature, a solution of the malonates **5a,c** (1.05 mmol) in THF (2 mL) was added dropwise. The resulting mixture was stirred for 3 h at −78 °C; allowed to warm to rt and then was added EtOH (10 mL). After stirring at rt for one day in the case of malonate **5c** (or 3 days for **5a)** the reaction was quenched with sat. aq. NH_4Cl and extracted with Et_2O (3 × 15 ml); the combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed under reduced pressure. The crude was purified by flash column-chromatography (silica gel; petroleum ether/Et_2O 8-9/2-1) to give compounds **4f–g**.

Preparation of Tetrahydroindenofuranones (6a,b). General Procedure. A solution of **4a,b** (0.2 mmol) in 1,2-dimethoxyethane (2 mL) and LiOH (2M in water, 2mL) was stirred at 50 °C for 5-8 h. The reaction mixture was acidified to pH 3 with 2N HCl (aq) and the acqueous phase extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed in vacuo. The resulting crude was dissolved in toluene (5 mL), treated with catalytic amount of AcOH and refluxed for 12 h. The resulting reaction mixture was poured in water and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude was flash-chromatographed (silica gel; petroleum ether/Et_2O 9-6/1-4) to give compounds **6a,b**.

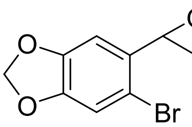


(3a*R,8*R**,8a*R**)-8-phenyl)-3,3a,8,8a-tetrahydro-1*H*-indeno[1,2-c]furan-1-one (6a):** white solid, 55%. ^{1}H NMR (600 MHz) δ 3.69 (t, J = 9.4 Hz, 1 H), 4.20 (td, J = 8.5, 3.6 Hz, 1 H), 4.37 (dd, J = 9.1, 3.6 Hz), 4.63 (t, J = 8.6 Hz, 1 H), 4.91 (d, J = 9.9 Hz, 1 H), 7.05–7.10 (m, 3 H), 7.26-7.32 (m, 6 H). ^{13}C NMR (150 MHz) δ 45.7, 48.5, 53.3, 72.1, 123.9, 125.8, 127.4, 128.1, 128.2, 128.4, 129.4, 139.1, 143.1, 144.3, 175.7**.** GC–MS (70 eV) *m/z* (%) 250 (M^+, 47), 205 (100), 192 (42), 191 (48), 165 (22). FT–IR (film, cm^{-1}) 2922, 1770, 1480, 1372, 1150, 1031, 965, 768, 699.

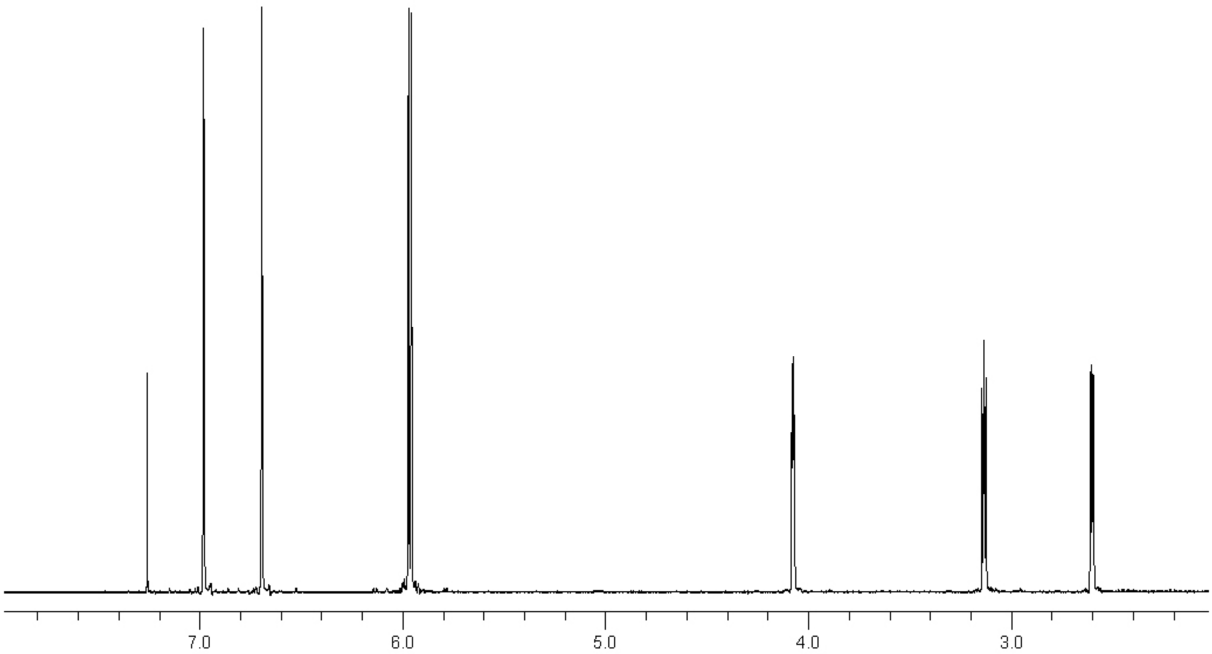


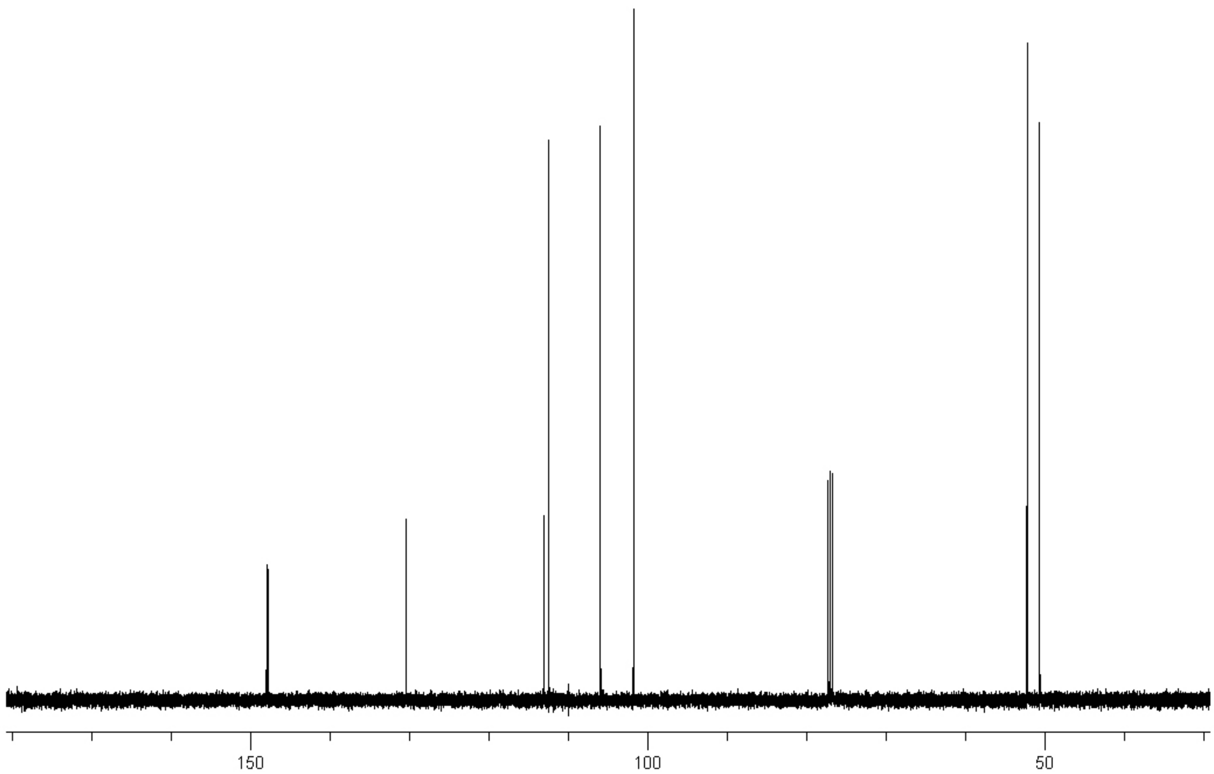
(3a*R,8*R**,8a*R**)-8-(3,4,5-trimethoxyphenyl)-3,3a,8,8a-tetrahydro-1*H*-indeno[1,2-c]furan-1-one (6b):** white solid, mp 152-153 °C (diethyl ether) 70% ^{1}H NMR (500 MHz) δ 3.68 (dd, J = 9.7, 8.8 Hz, 1 H), 3.77 (s, 6 H), 3.85 (s, 3 H), 4.20 (dt, J = 8.3, 3.6 Hz, 1 H), 4.37 (dd, , J = 9.1, 3.6 Hz, 1 H), 4.66 (dd, J = 9.1, 8.3 Hz, 1 H), 4.84 (d, J = 9.7 Hz, 1H), 6.32 (s, 2 H), 7.11 (d, J = 7.5 Hz, 1 H), 7.28–7.35 (m, 3 H). ^{13}C NMR (150 MHz) δ 45.8, 48.6, 53.7, 56.2, 60.9, 72.1, 107.0, 124.0, 126.0, 128.3, 128.4, 134.5, 137.5, 142.9, 144.3, 152.9, 175.5. GC–MS (70 eV) *m/z* (%) 340 (M^+, 100), 281 (13), 263 (9), 178 (8), 152 (11). FT–IR (film, cm^{-1}) 2925, 1770, 1592, 1507, 1461, 1338, 1236, 1125, 1017, 772, 735. Anal. Calcd for $C_{20}H_{20}O_5$: C 70.57 %; H 5.92 %. Found: C 70.74 %; H 5.73.

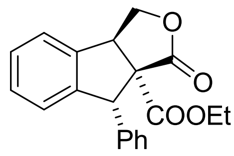
(3a*S*,8*S*,8a*S*)-(+)-6b: 80%, er: 97/3, ($t_{R\ major}$ = 42.0 min, $t_{R\ minor}$ = 51.0 min by HPLC, *n*-hexane/*i*PrOH 8/2, flow 0.7 mL/min, 230 nm), $[\alpha]^{25}_{D}$ = +6 (c 1, $CHCl_3$).



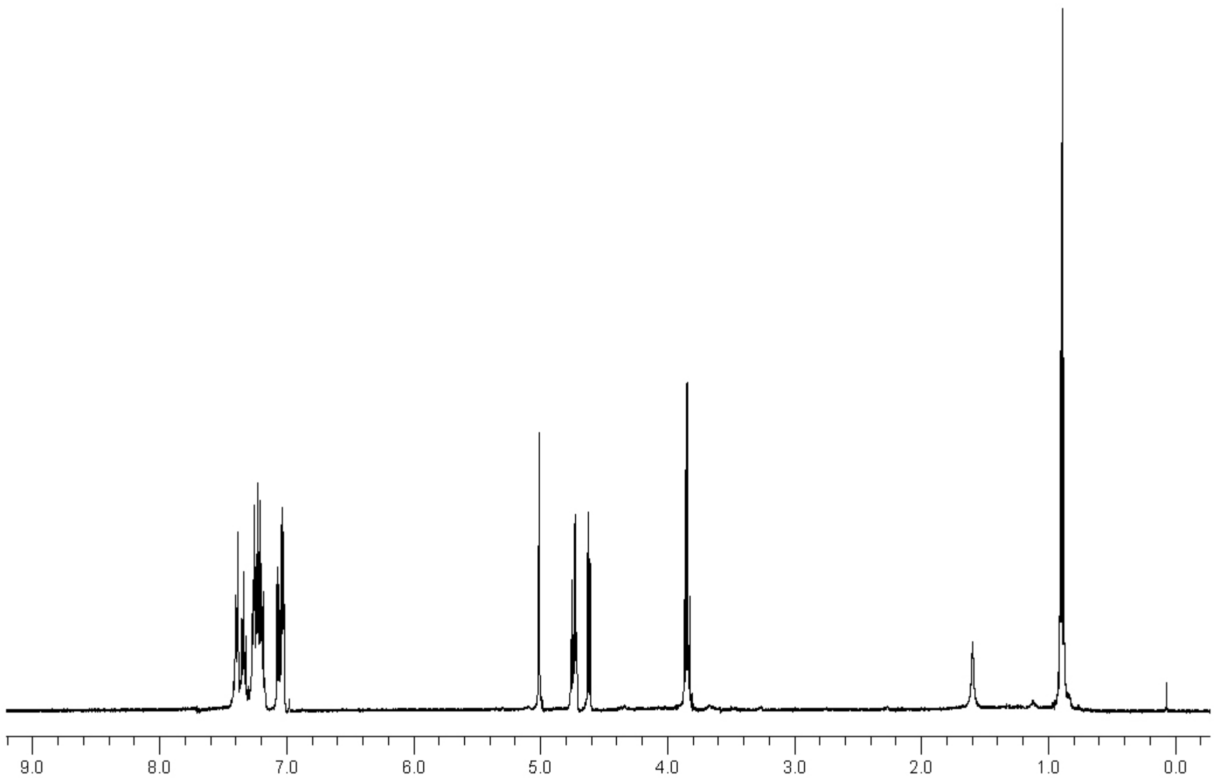
1b

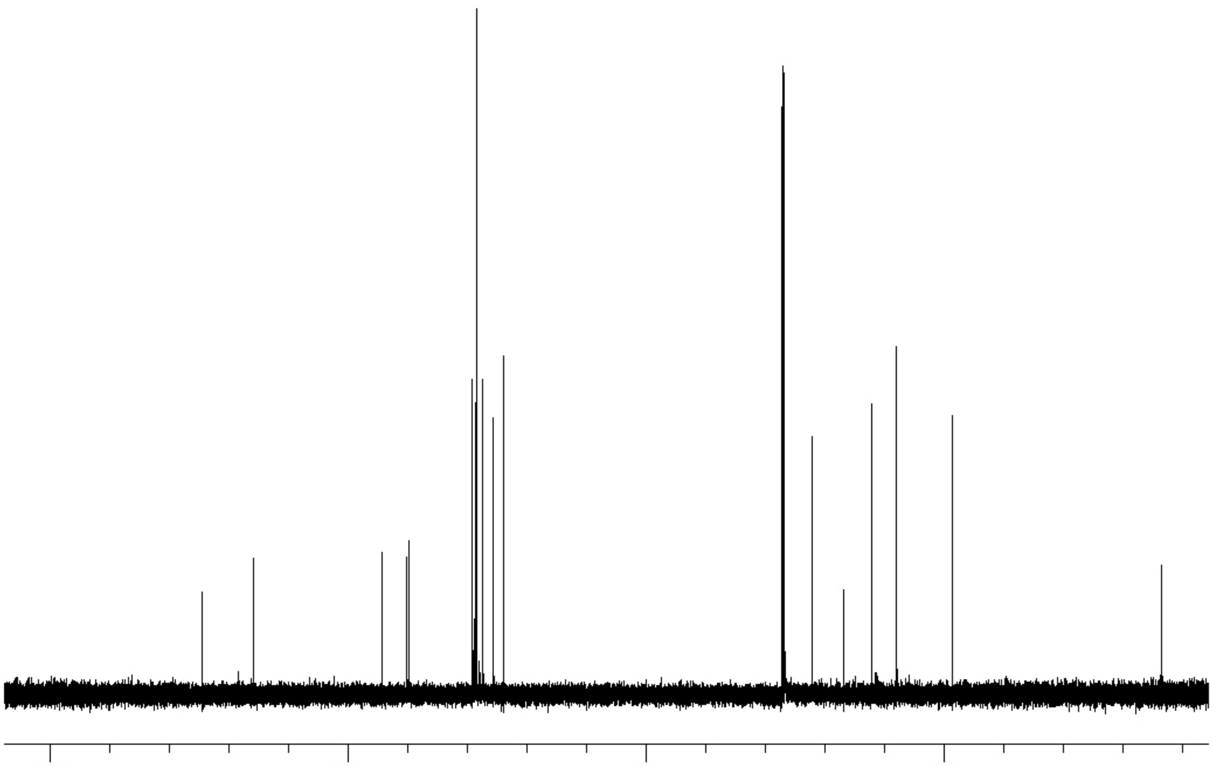


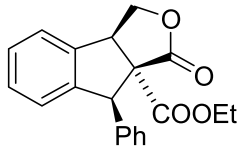




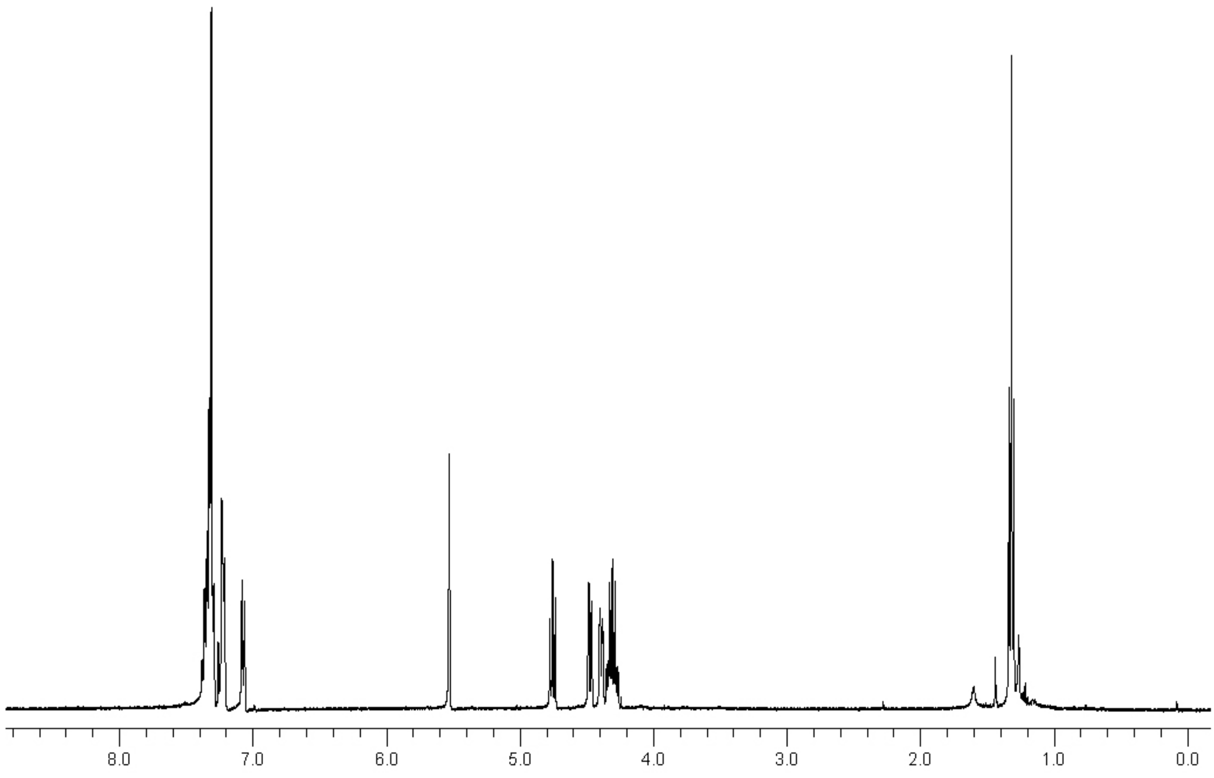
(3a*R**,8*R**,8a*S**)-**4a**

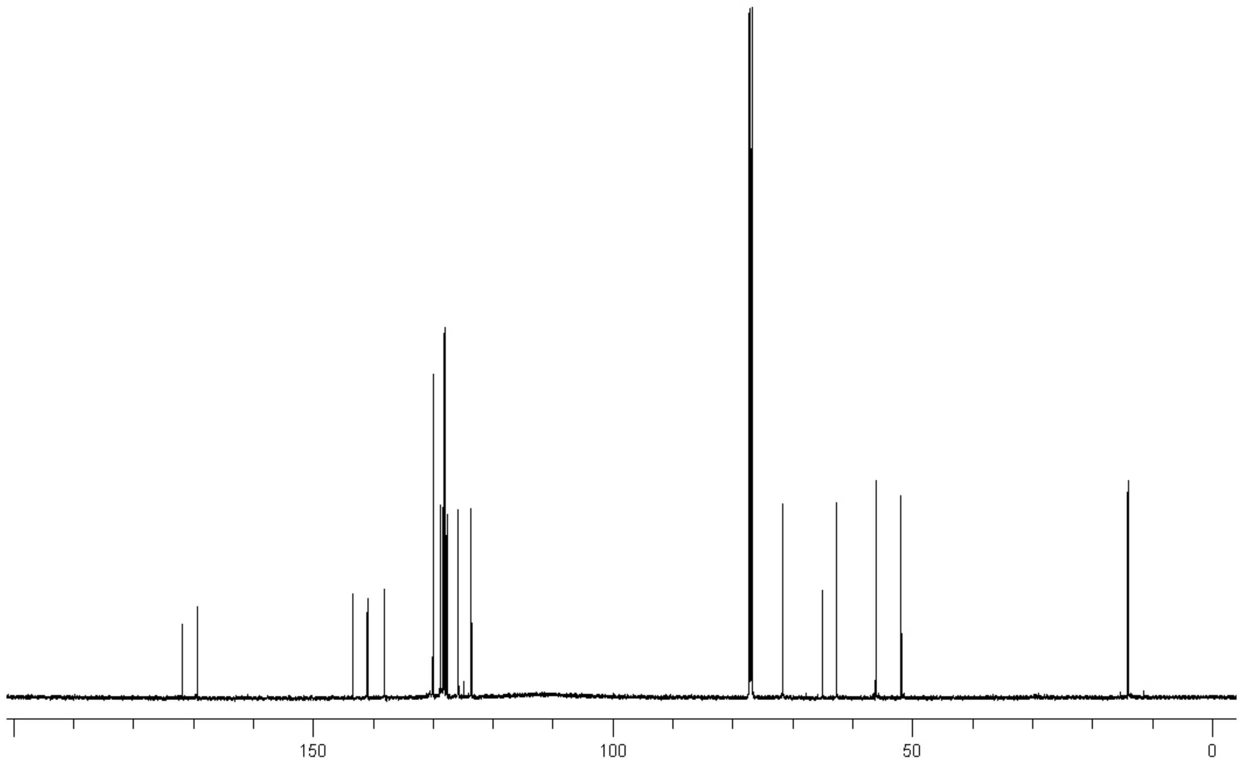


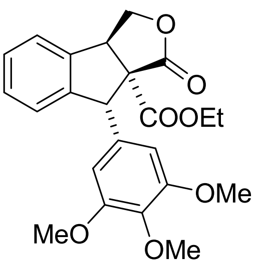




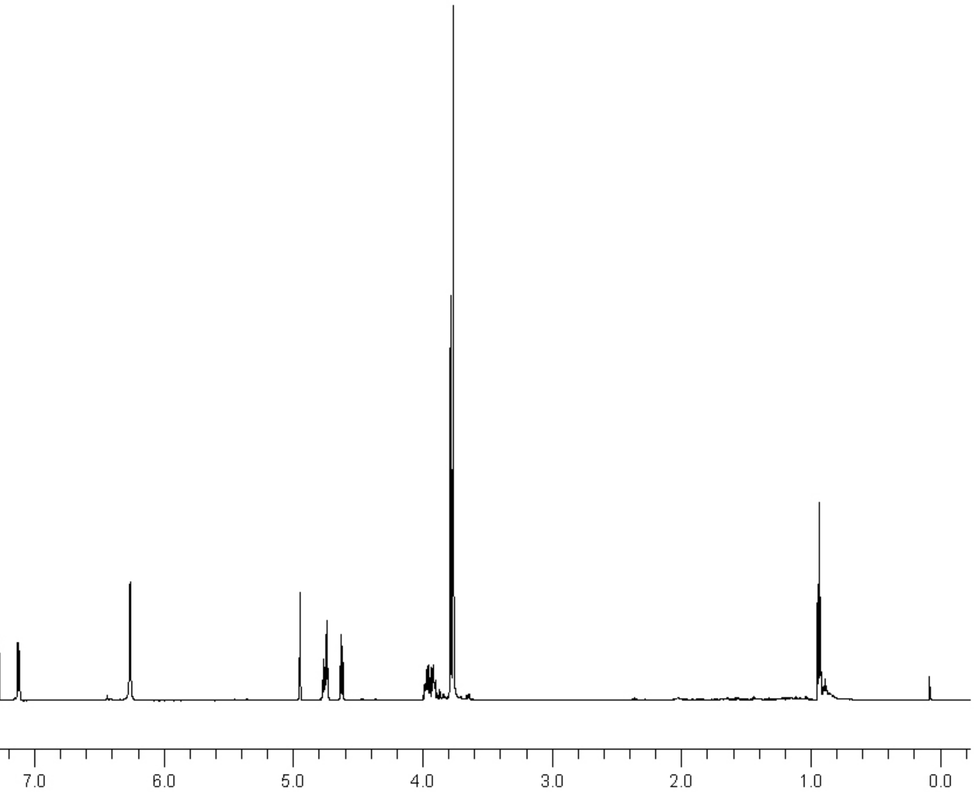
(3a*R**,8*S**,8a*S**)-**4a**

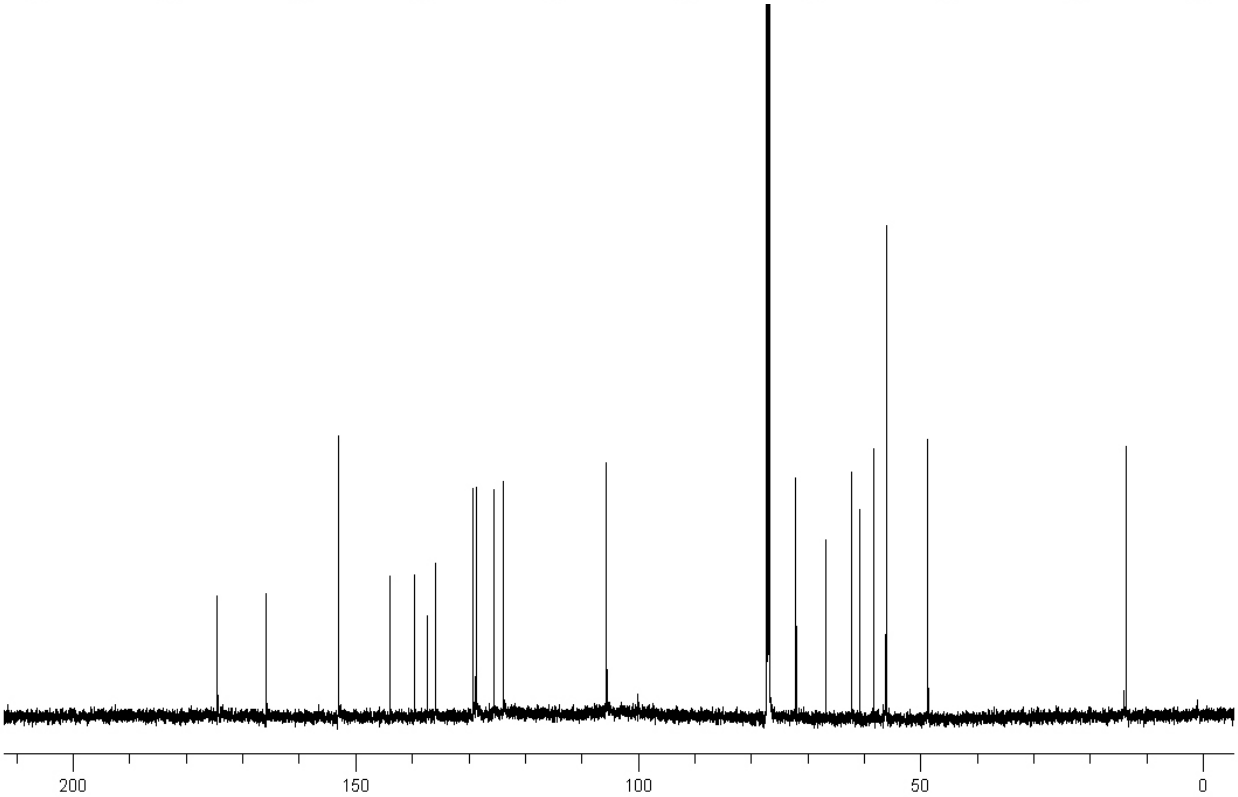


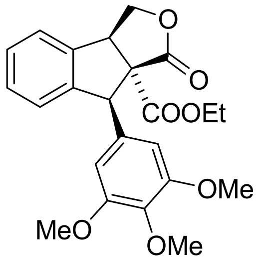




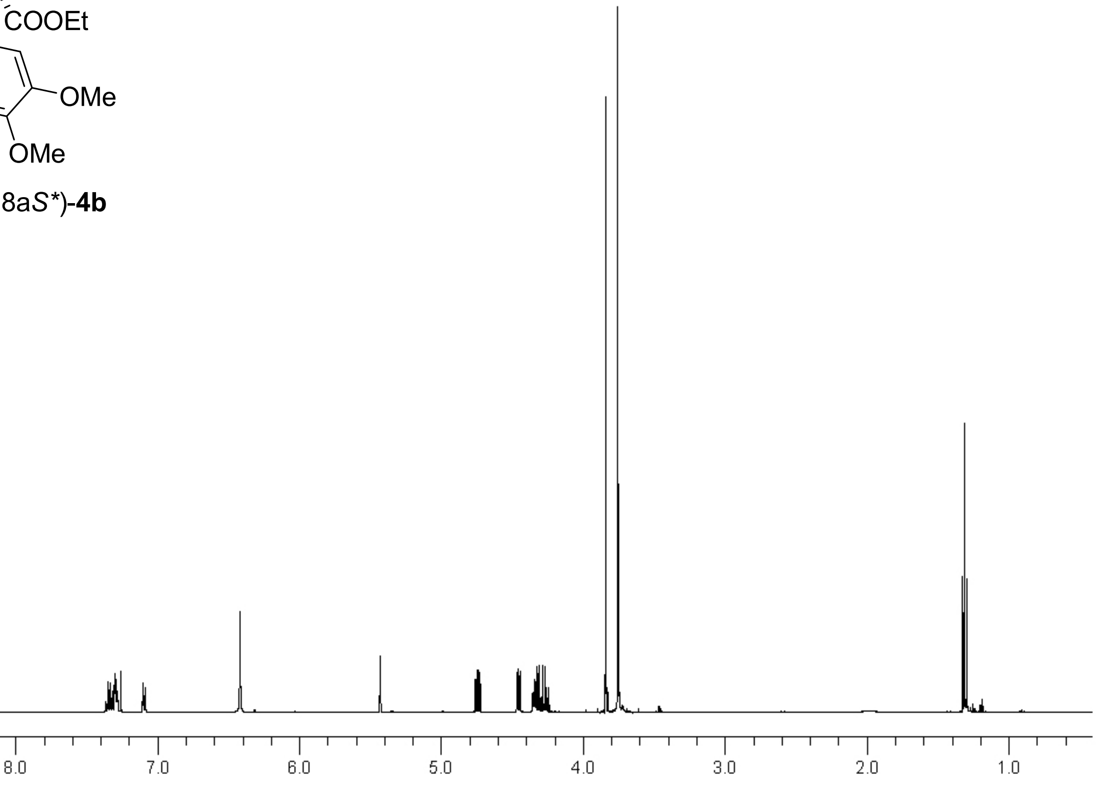
(3a*R**,8*R**,8a*S**)-**4b**

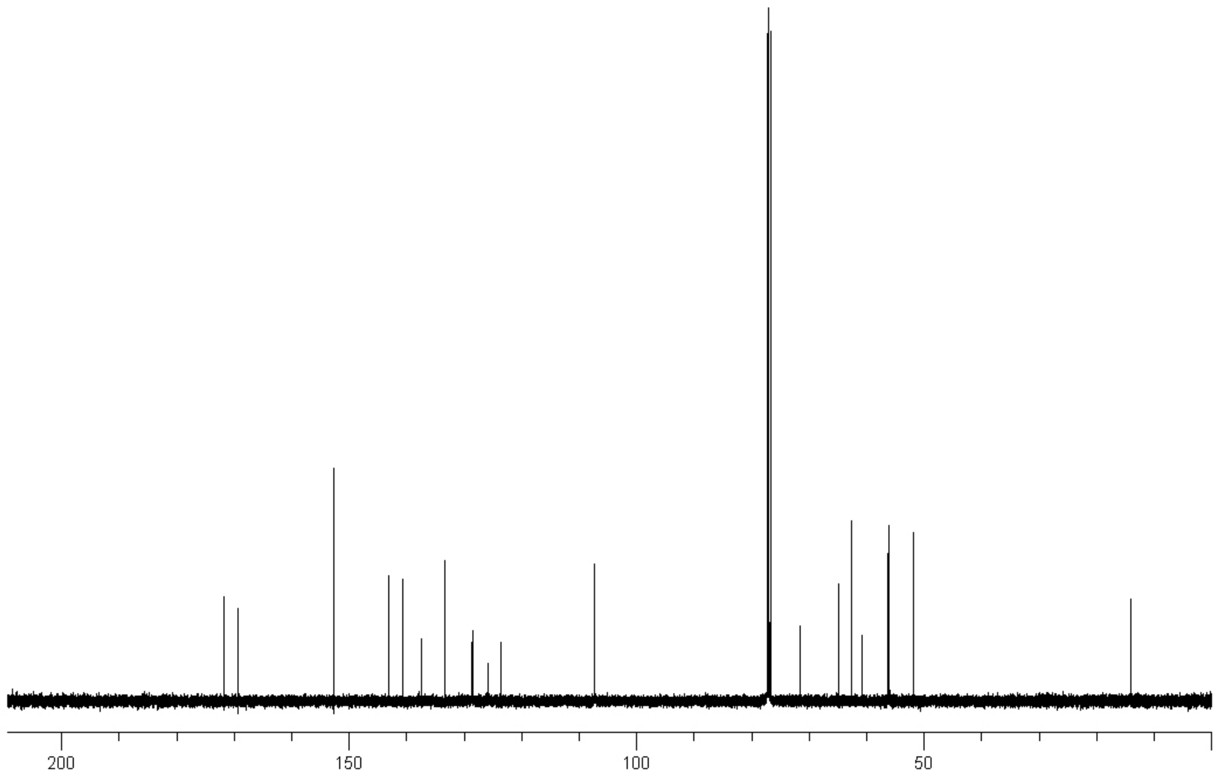


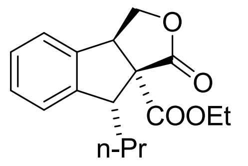




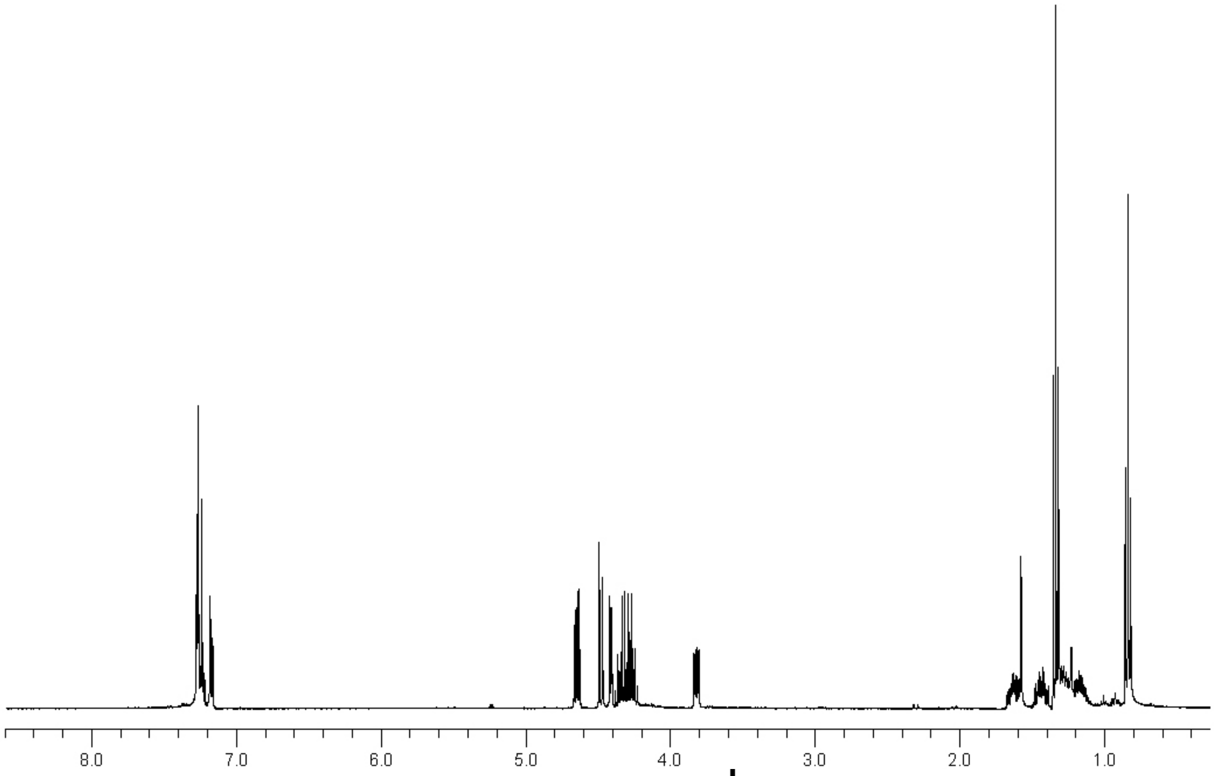
(3a*R**,8*S**,8a*S**)-**4b**

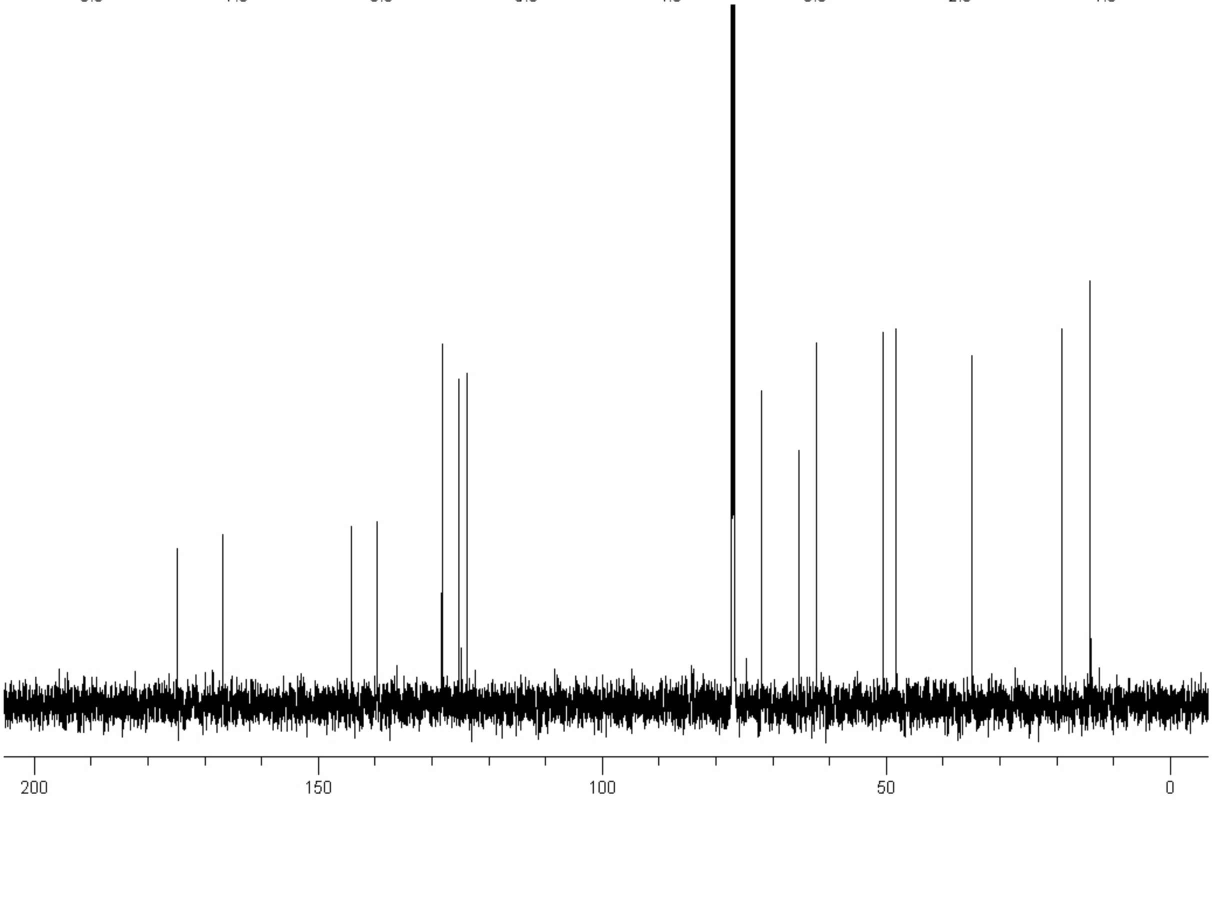


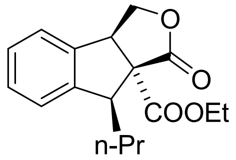




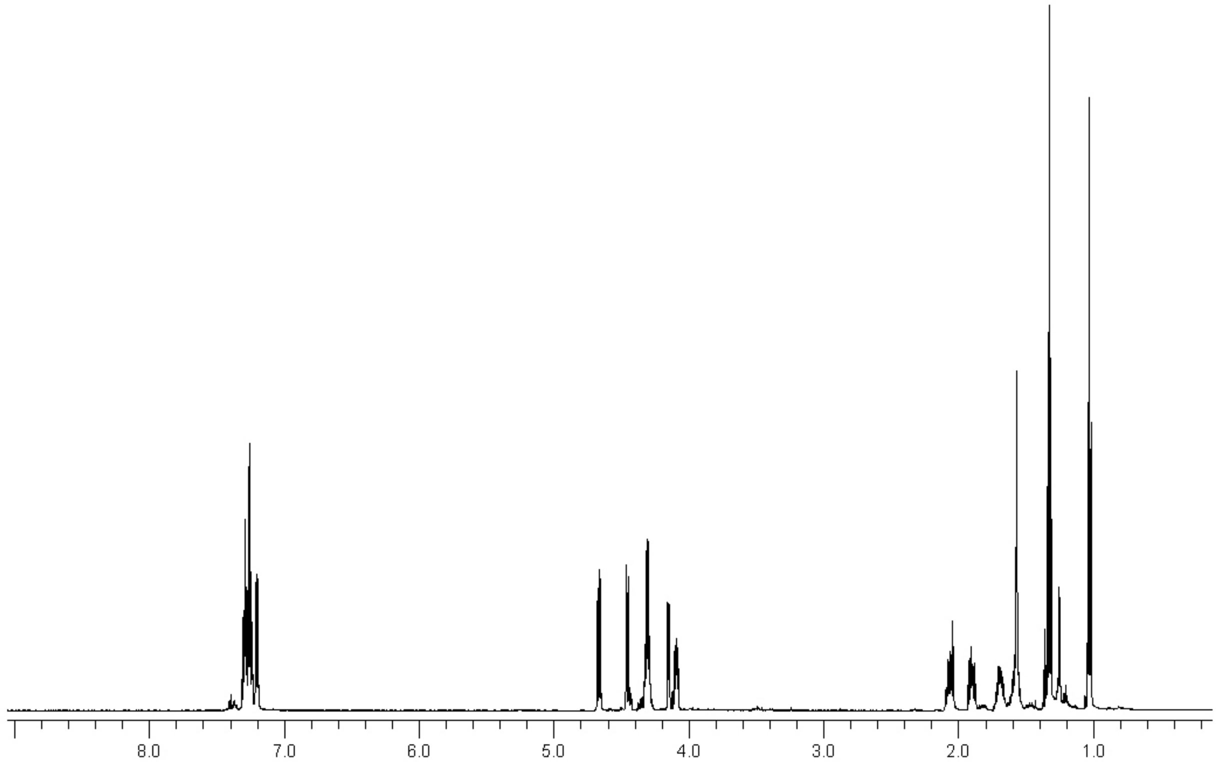
(3aR*,8R*,8aS*)-**4c**

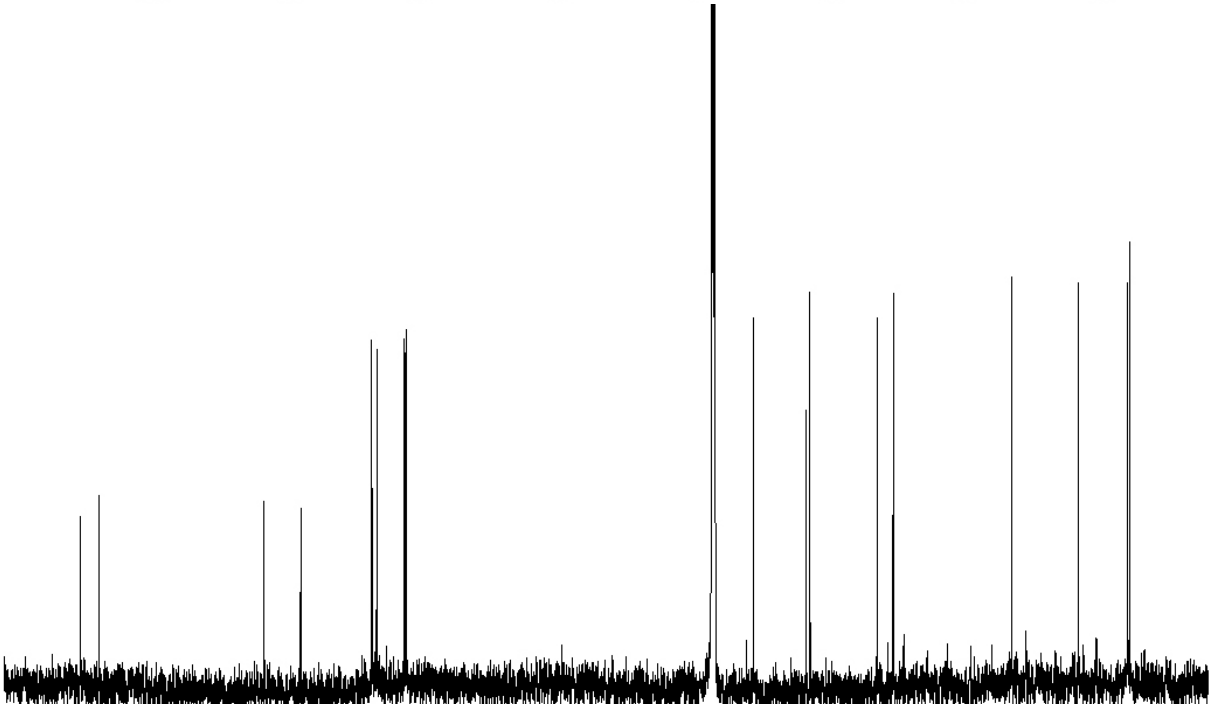


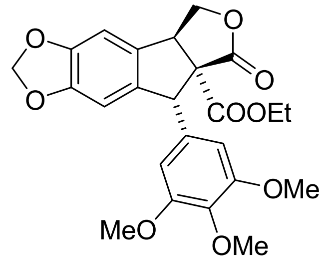




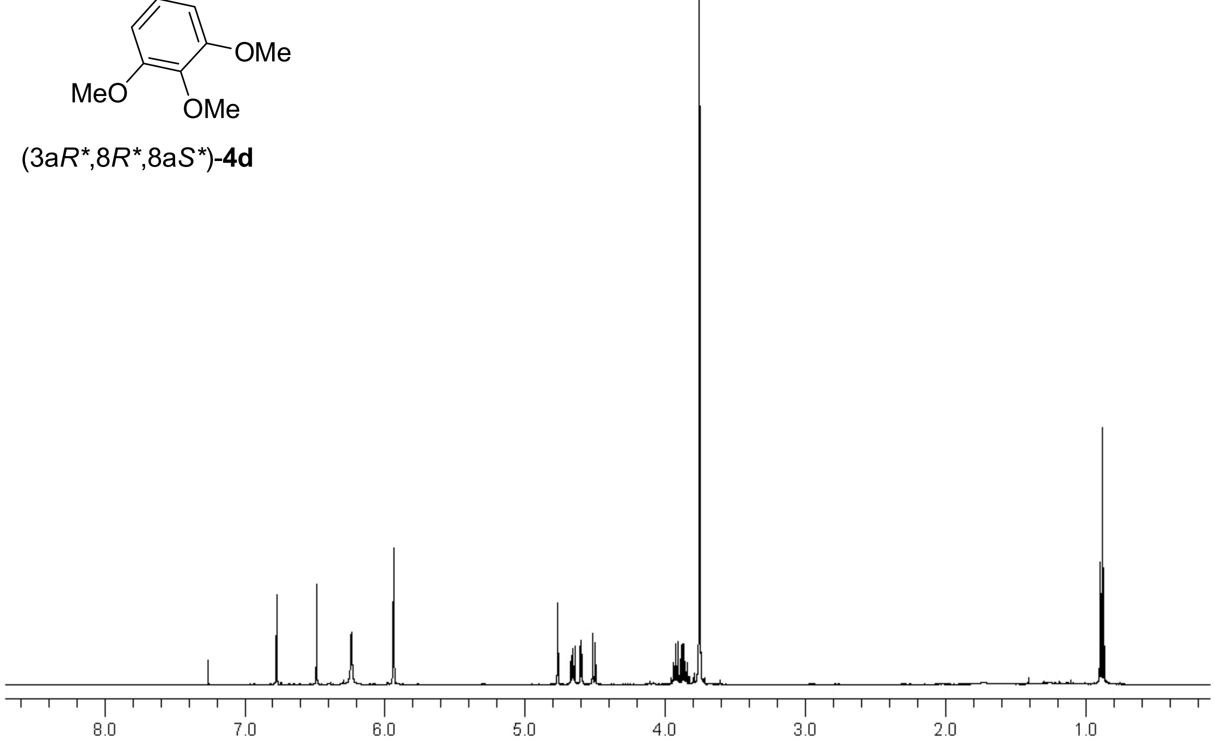
(3a*R**,8*S**,8a*S**)-**4c**

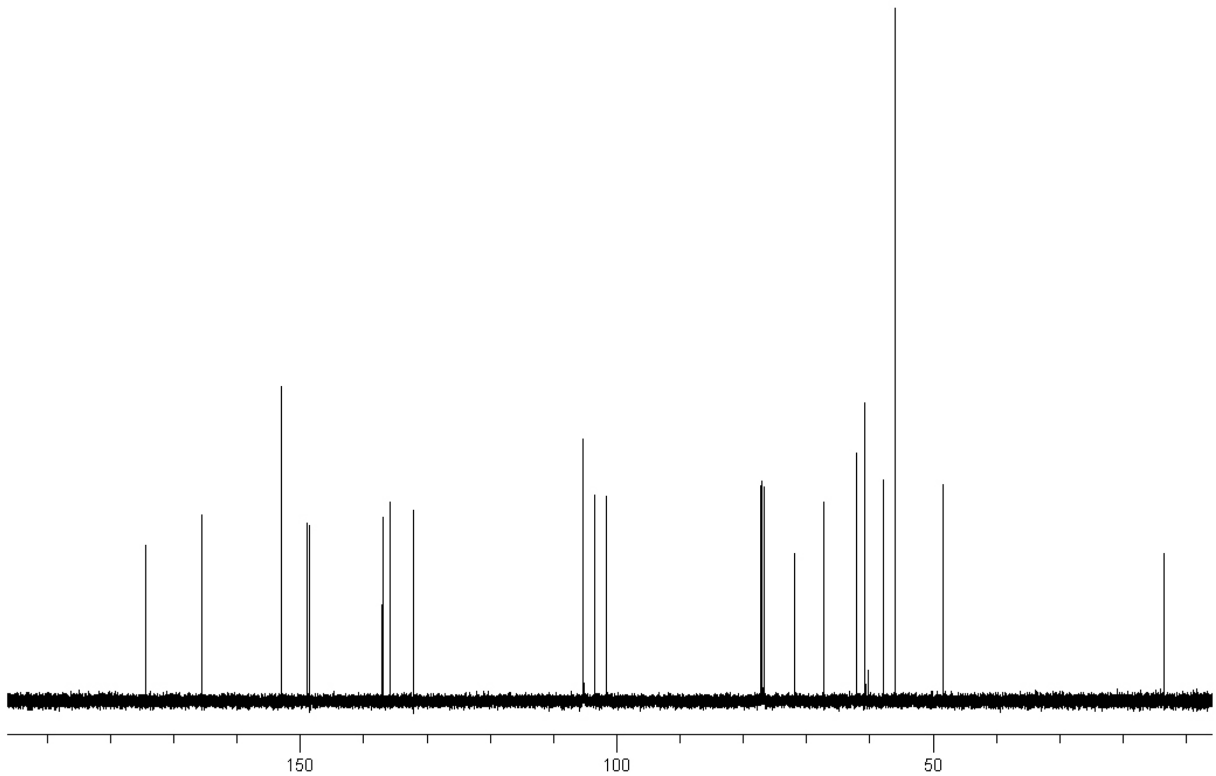


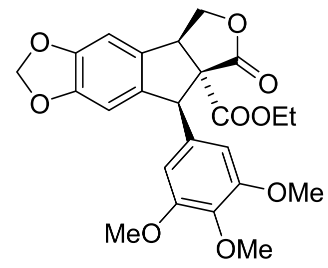




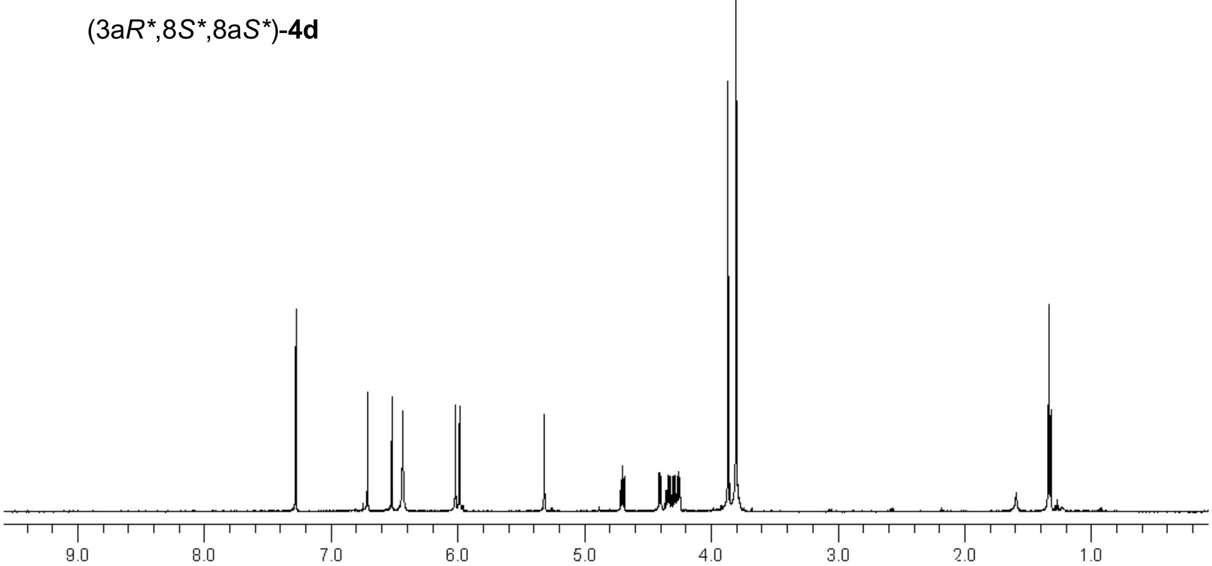
(3a*R**,8*R**,8a*S**)-**4d**

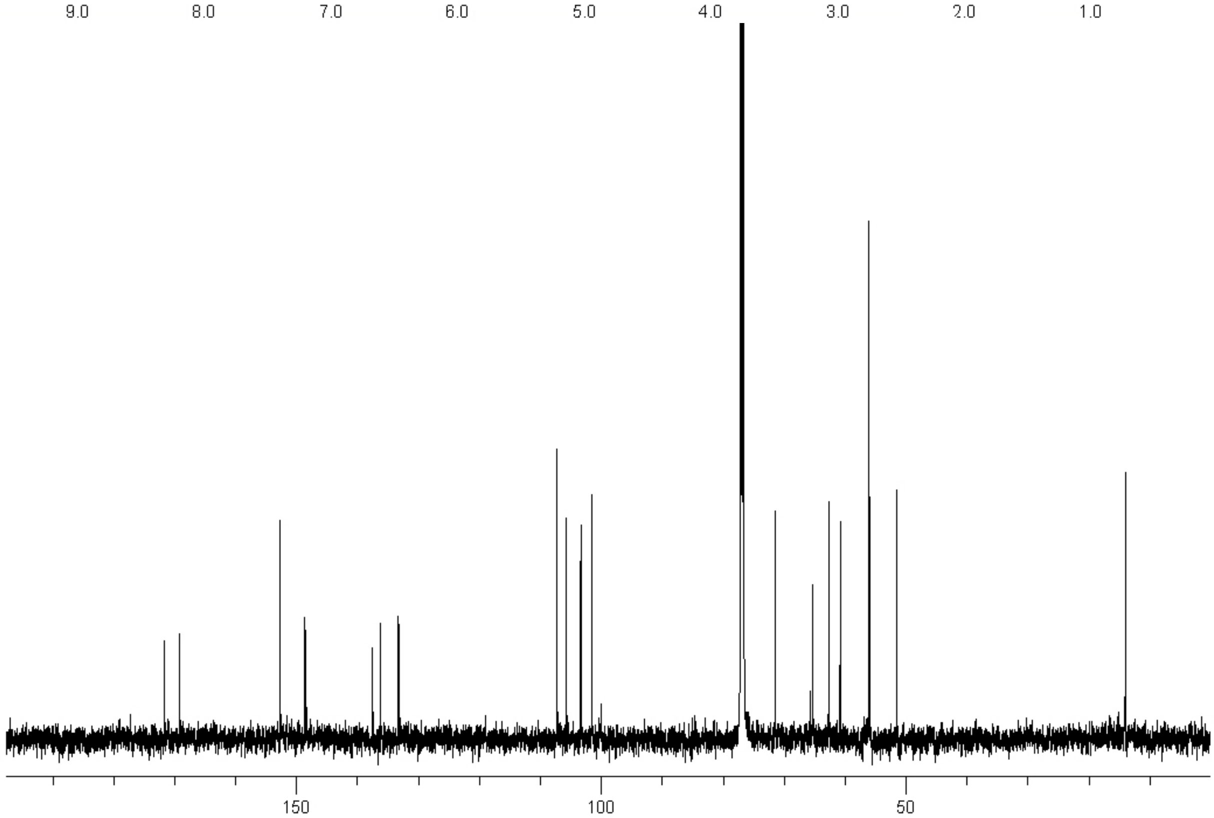


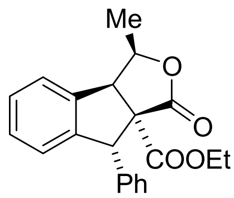




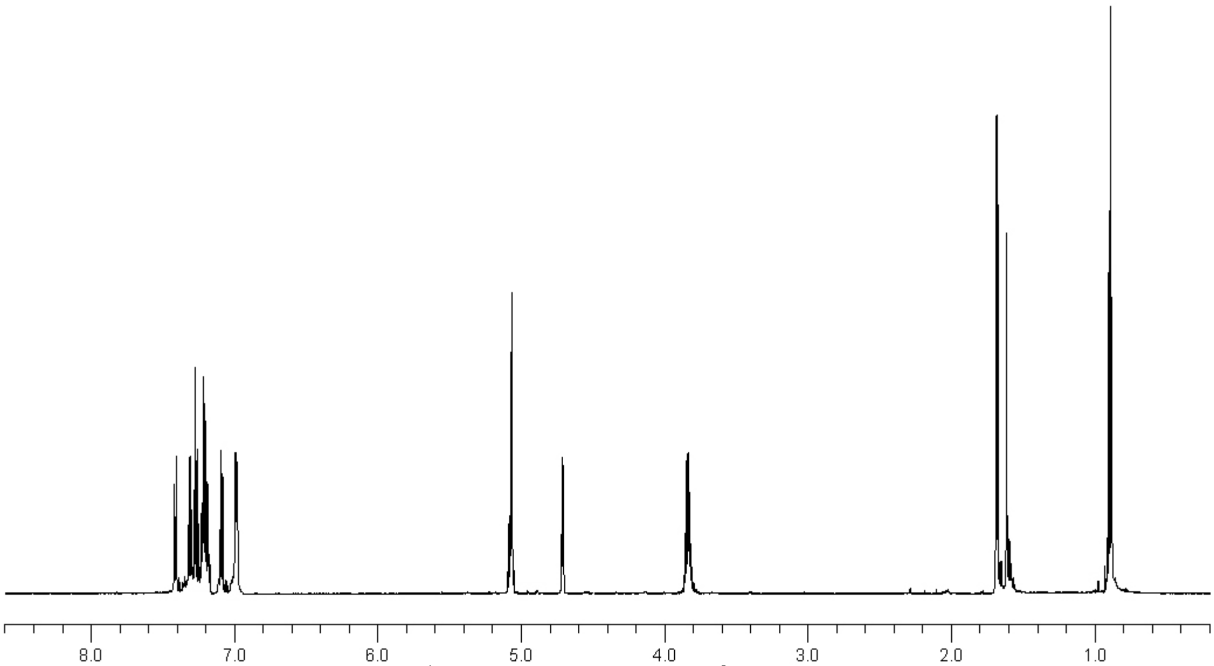
(3a*R**,8*S**,8a*S**)-**4d**

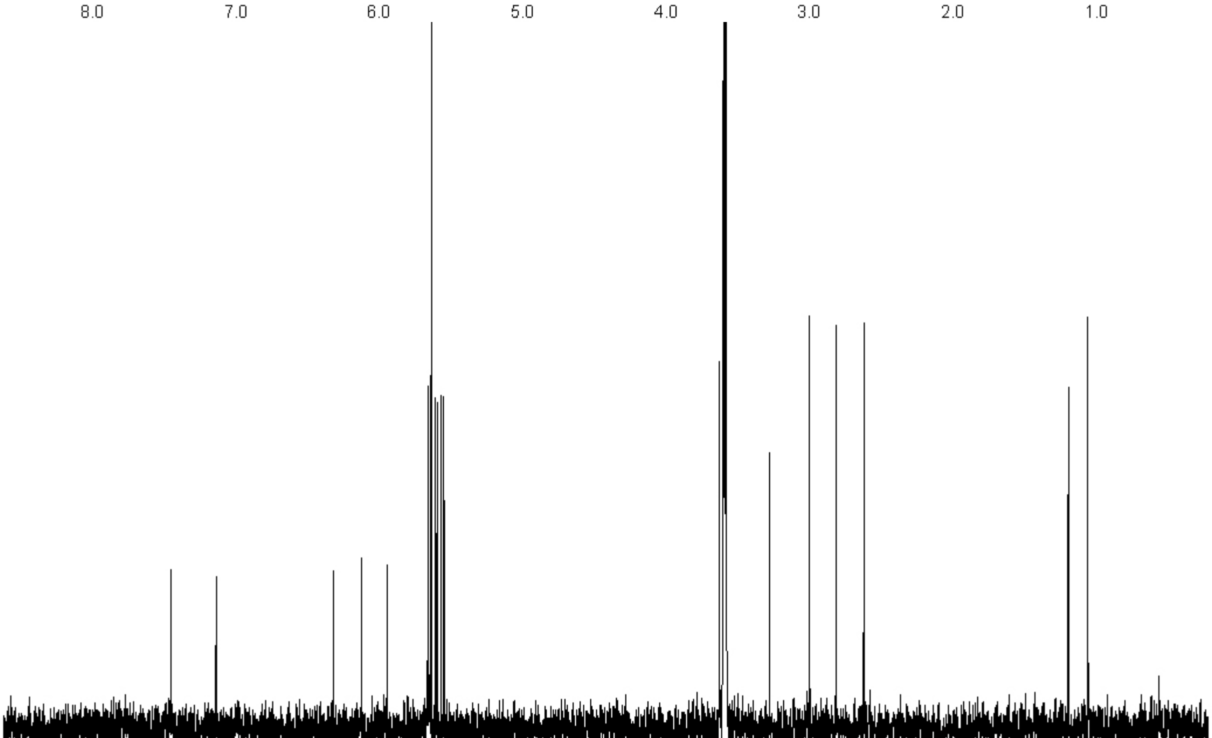


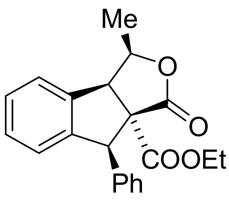




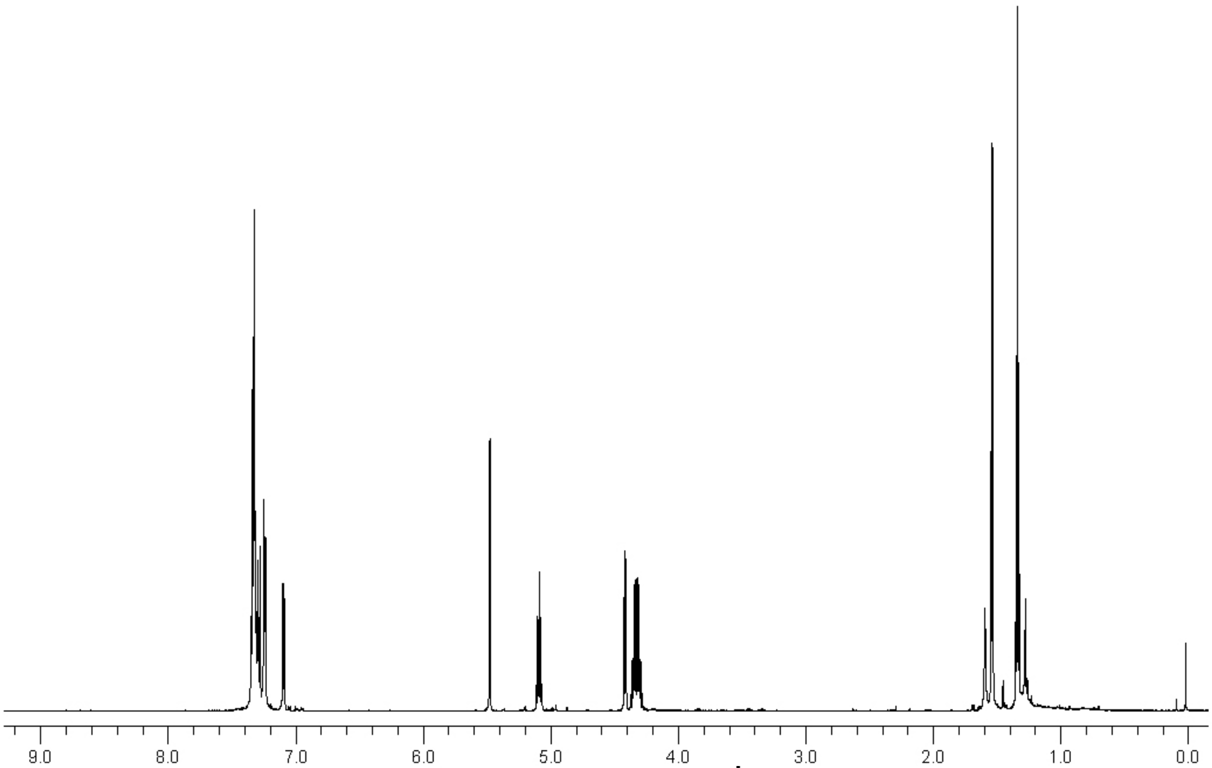
(3*R**,3a*R**,8*R**,8a*S**)-**4e**

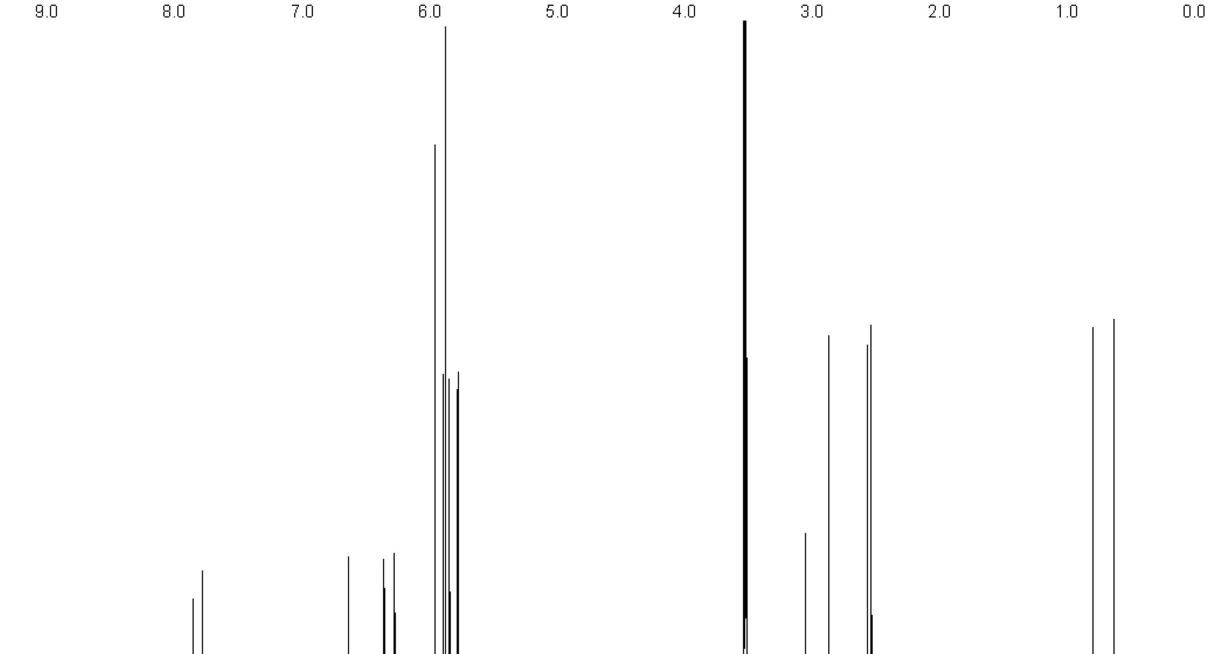


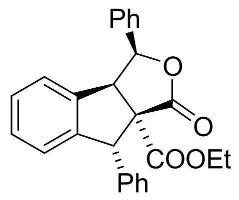




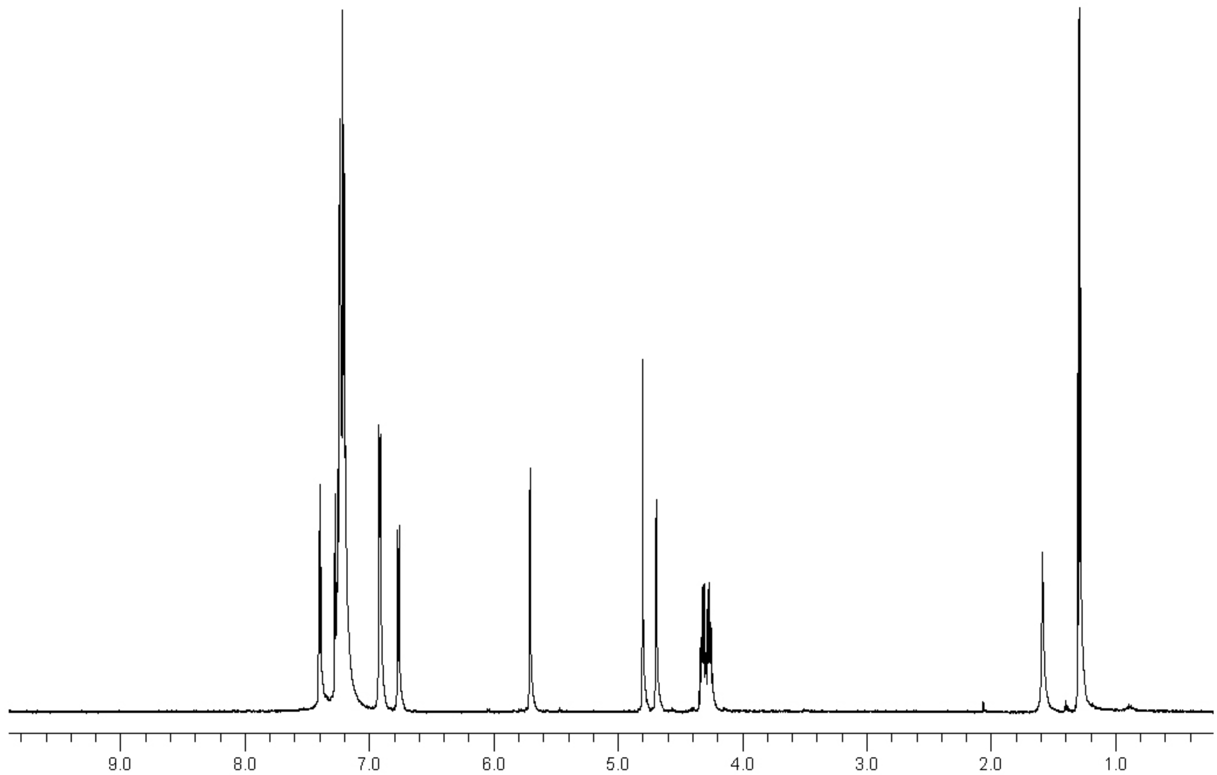
(3*R**,3a*R**,8*S**,8a*S**)-**4e**

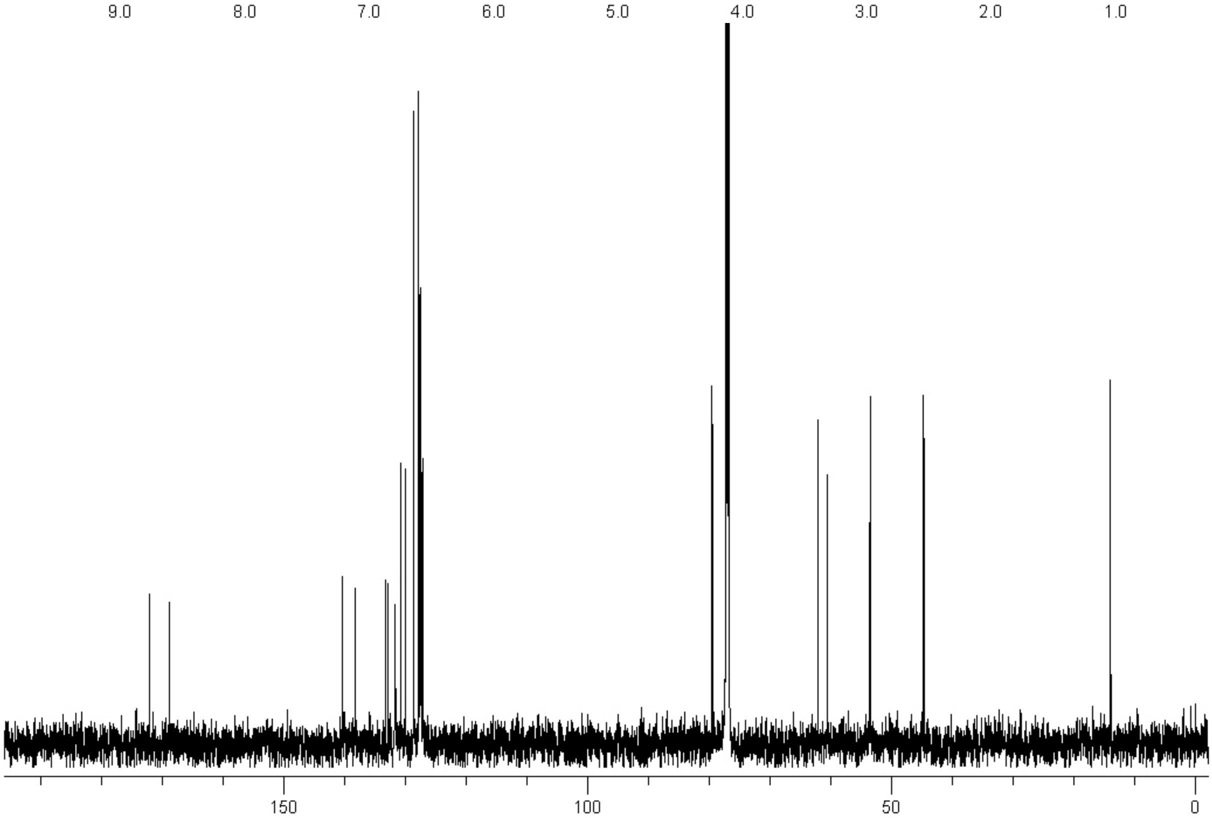


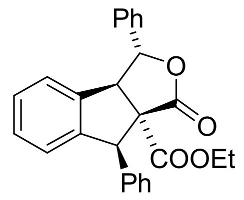




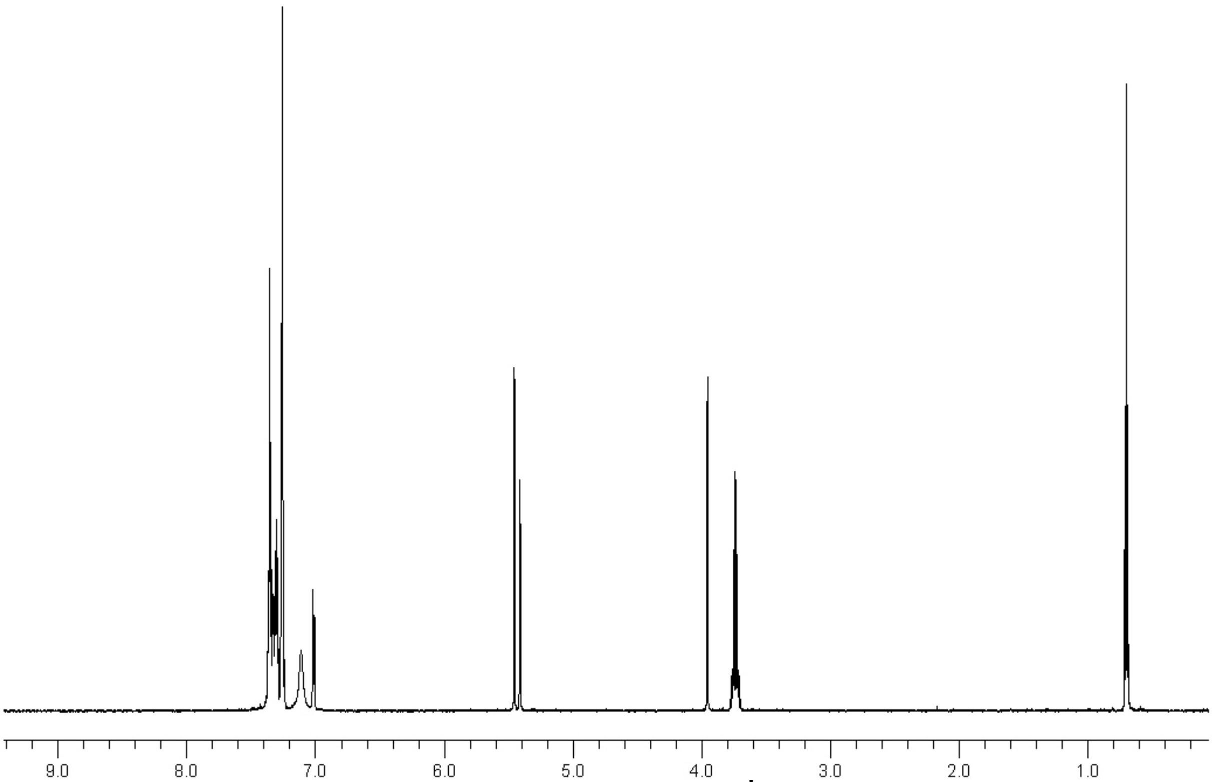
(3*R**,3a*S**,8*S**,8a*R**)-**4f**

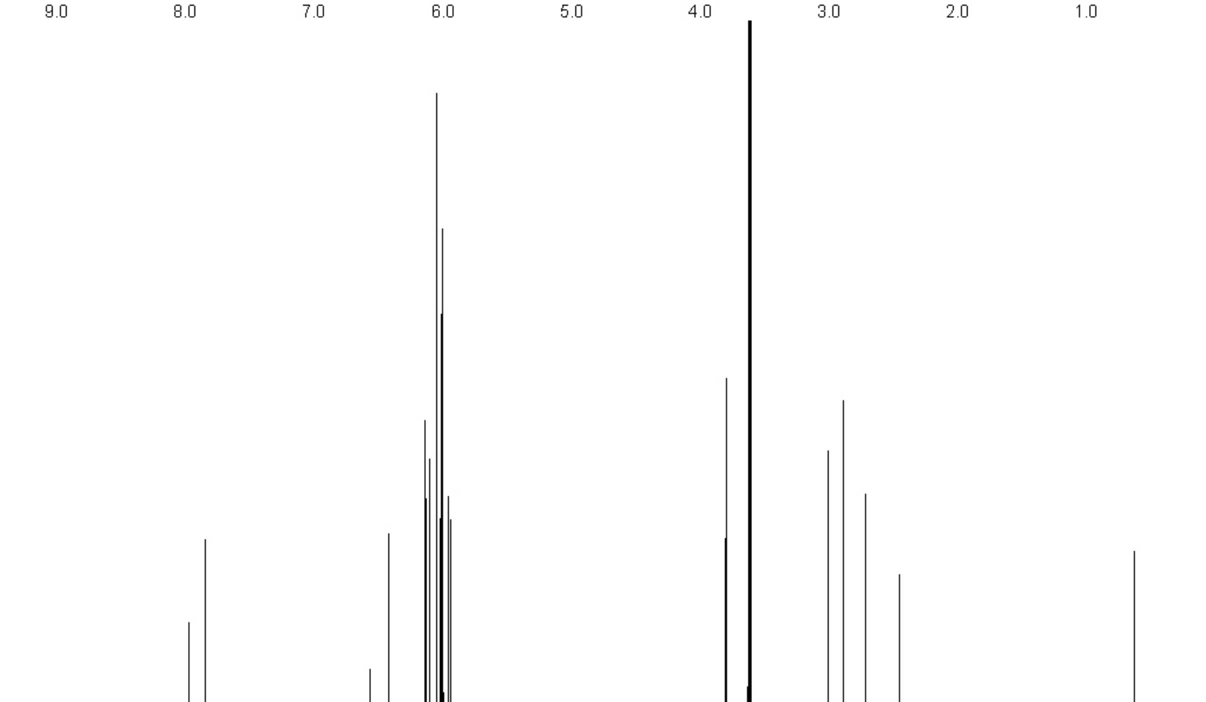


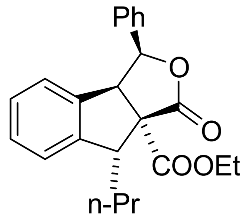




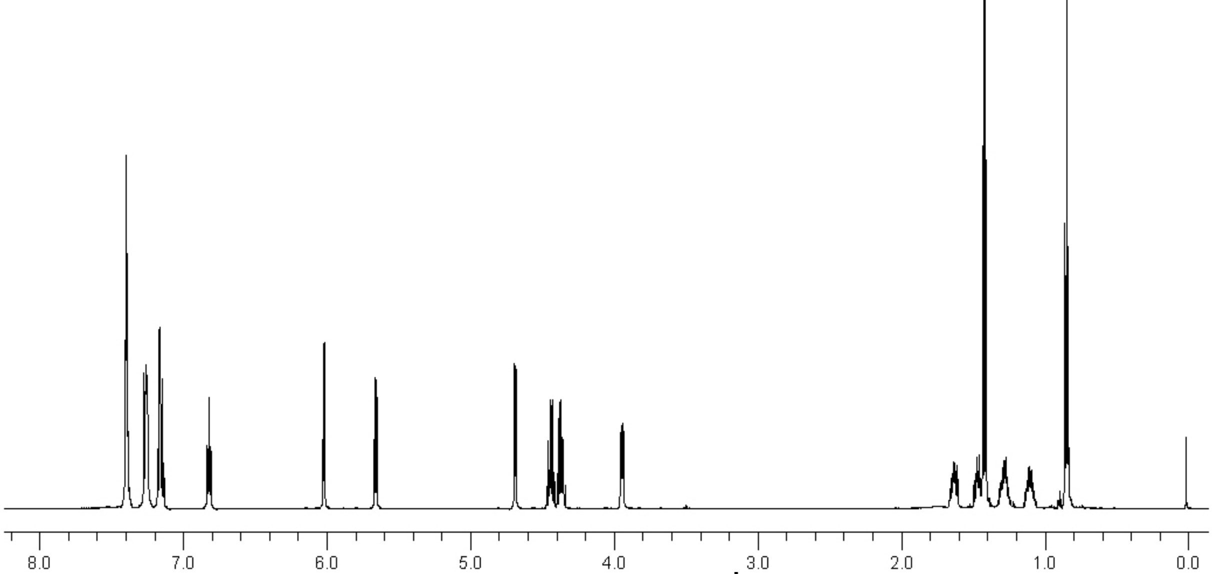
(3R*,3aR*,8S*,8aS*)-***diast*-4f**

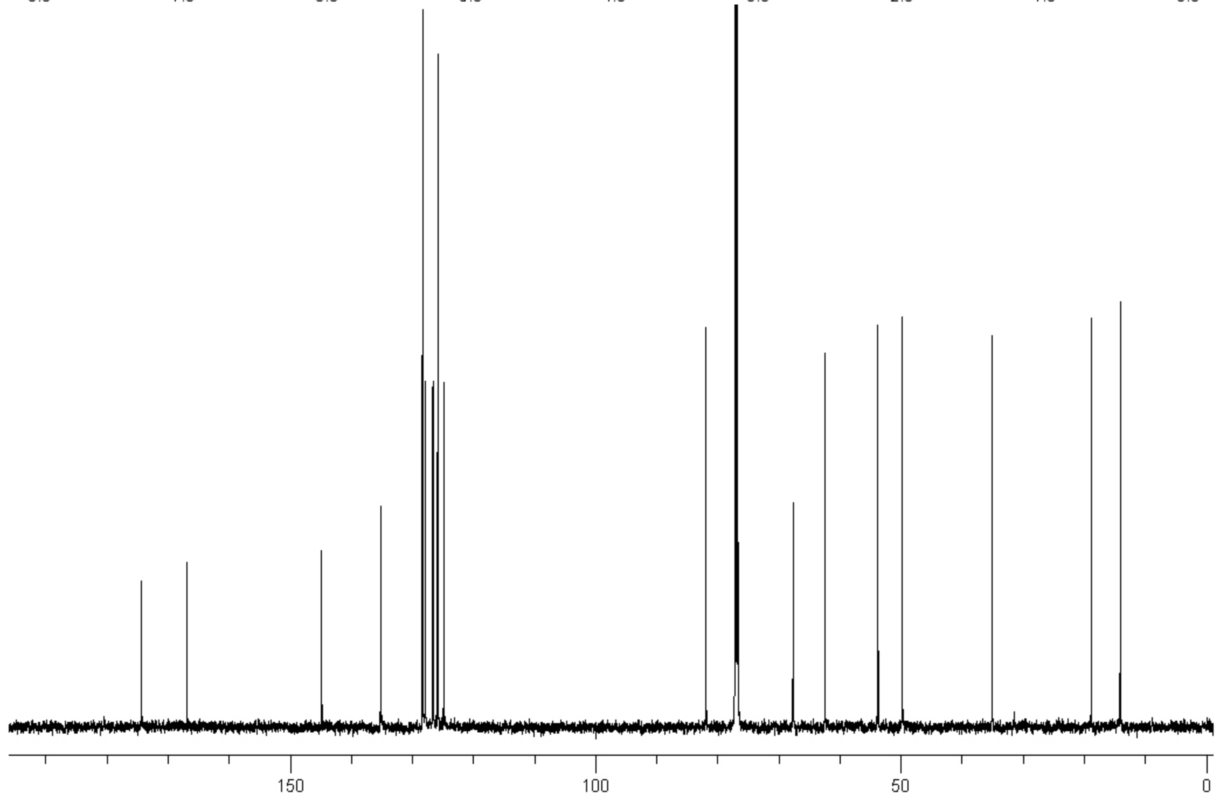


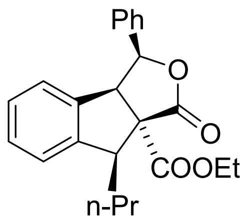




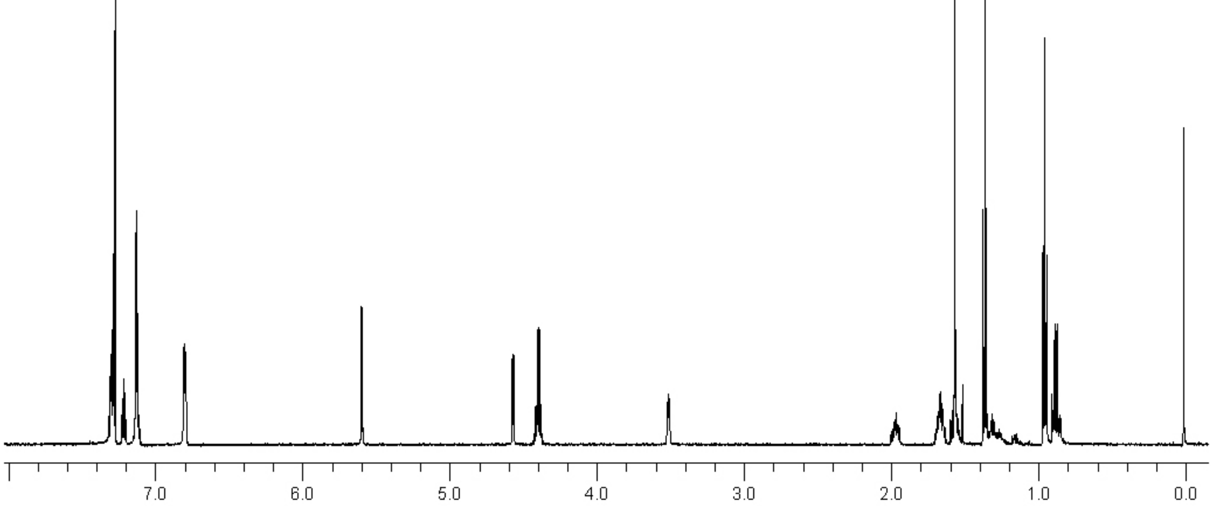
(3R*,3aS*,8S*,8aR*)-**4g**

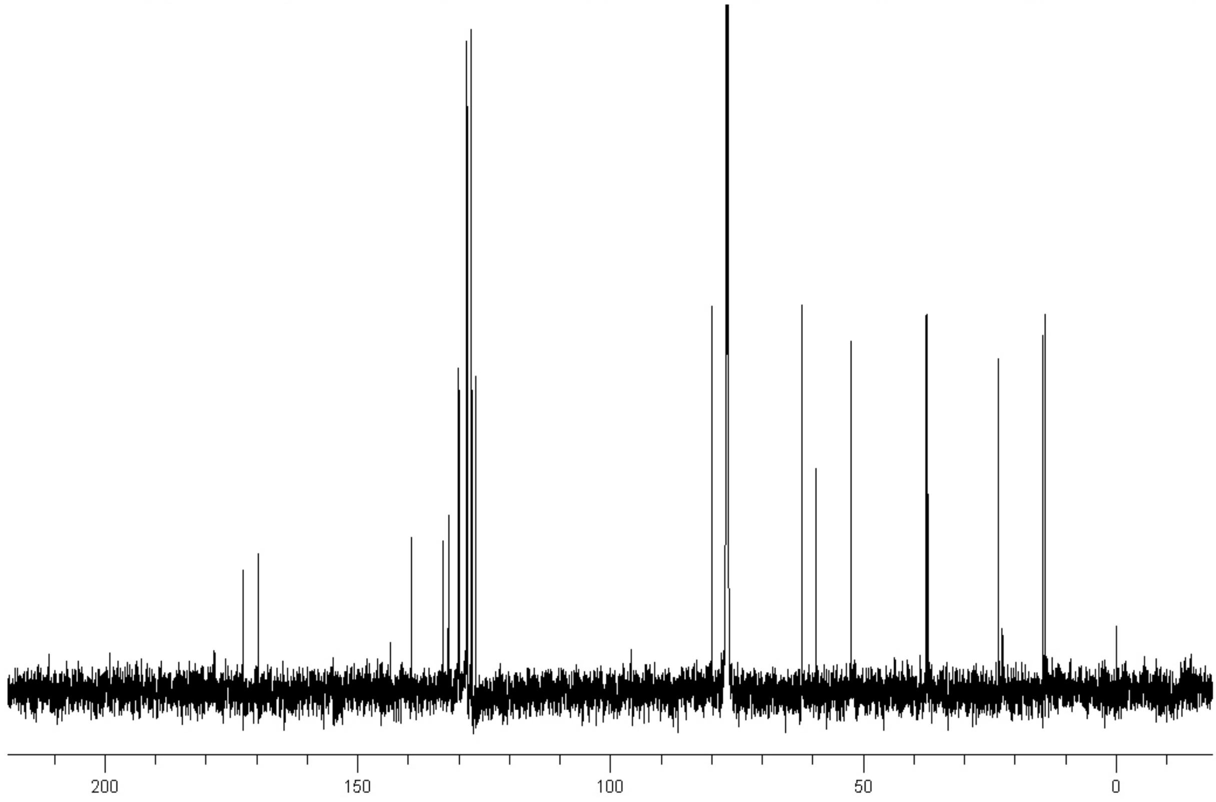


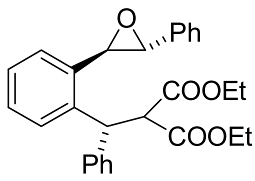




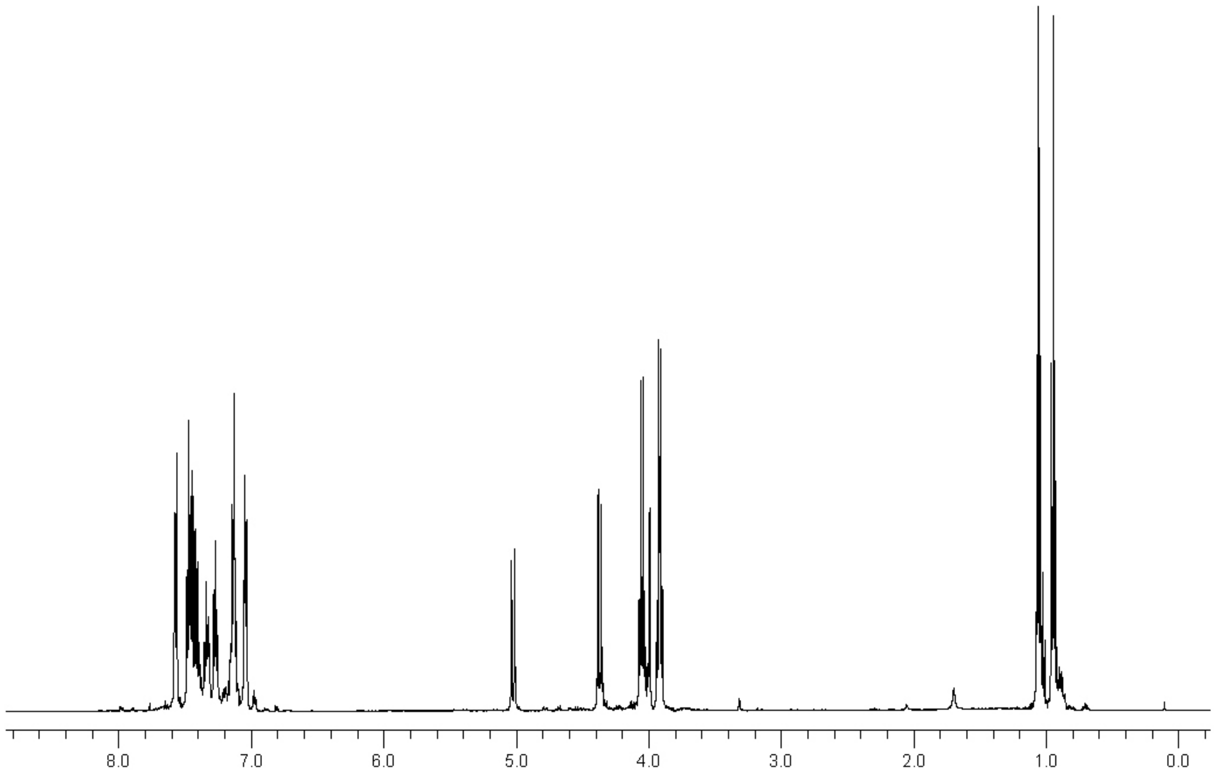
(3R*,3aS*,8R*,8aR*)-**4g**

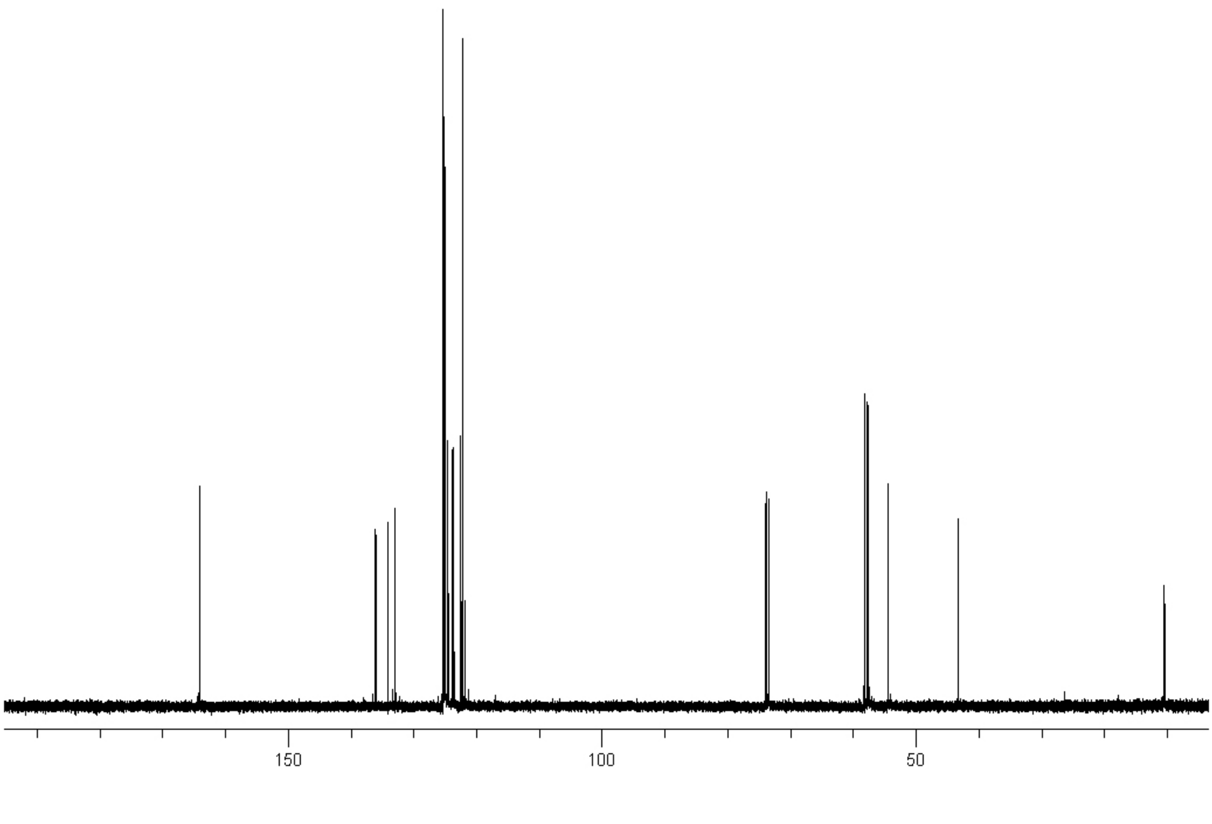


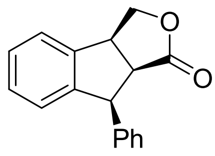




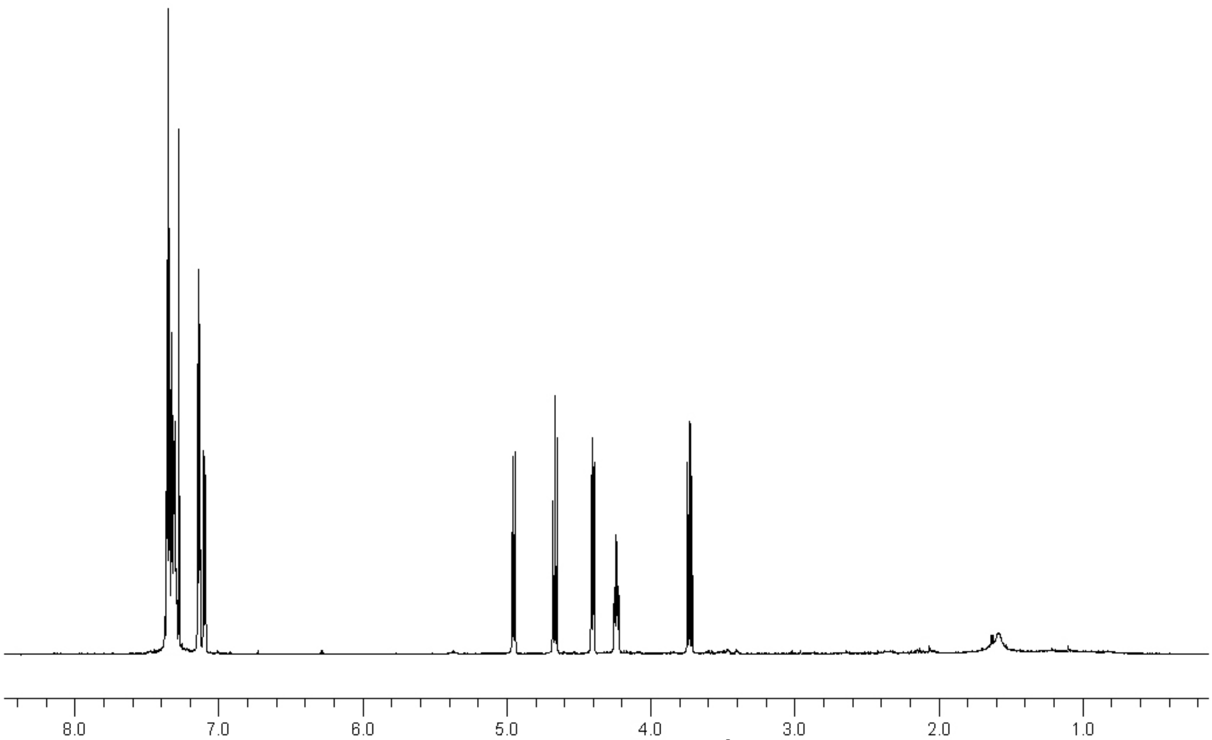
(*R**,*R**,*R**)-**2f**

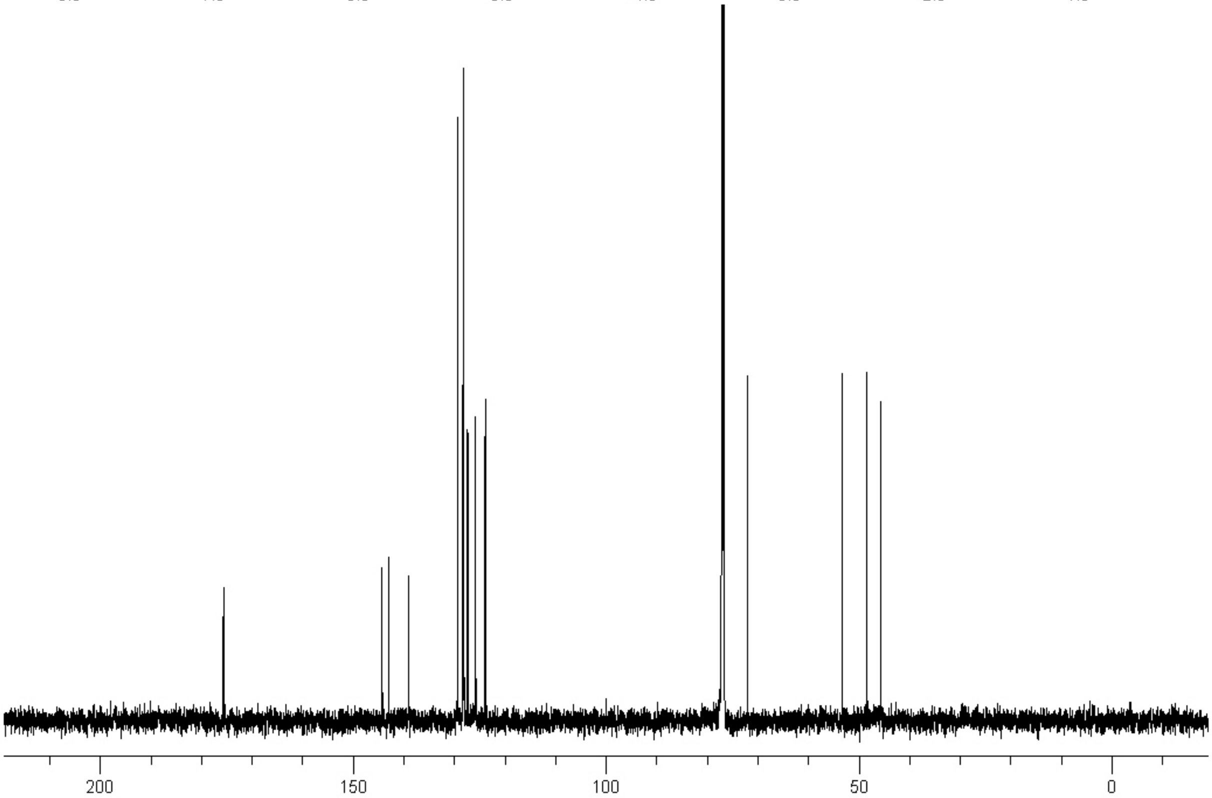


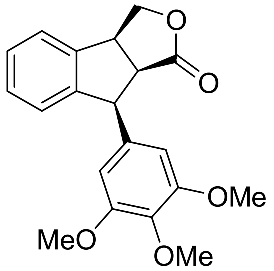




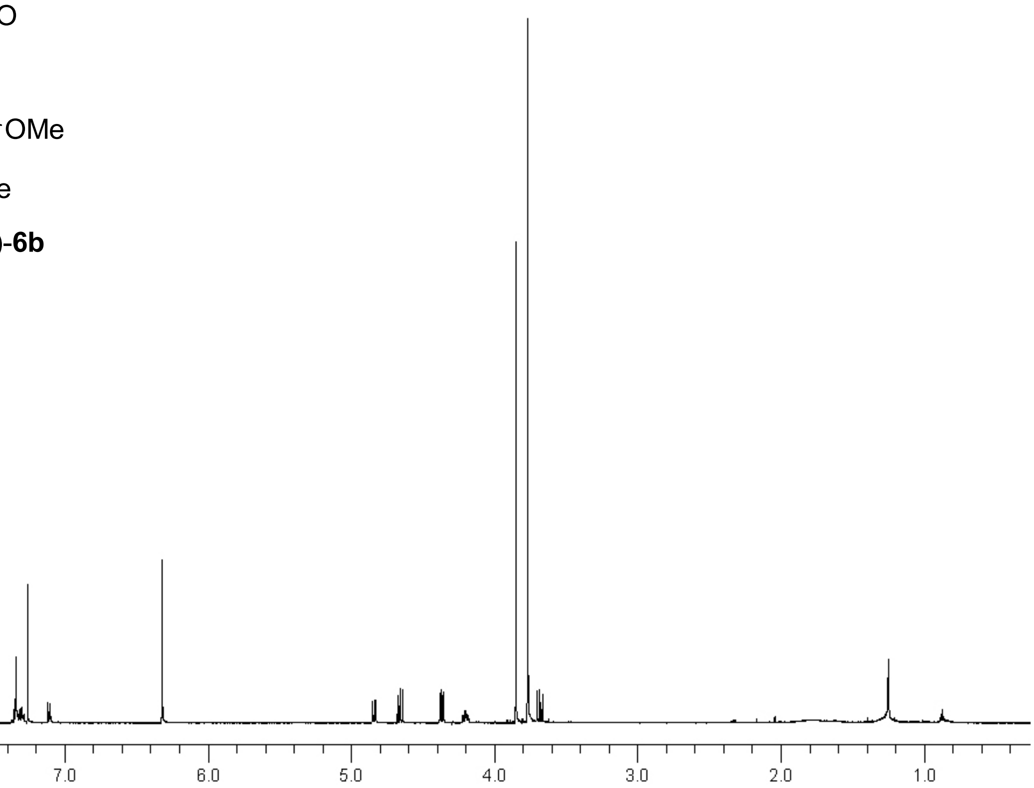
(3aR*,8R*,8aR*)-**6a**

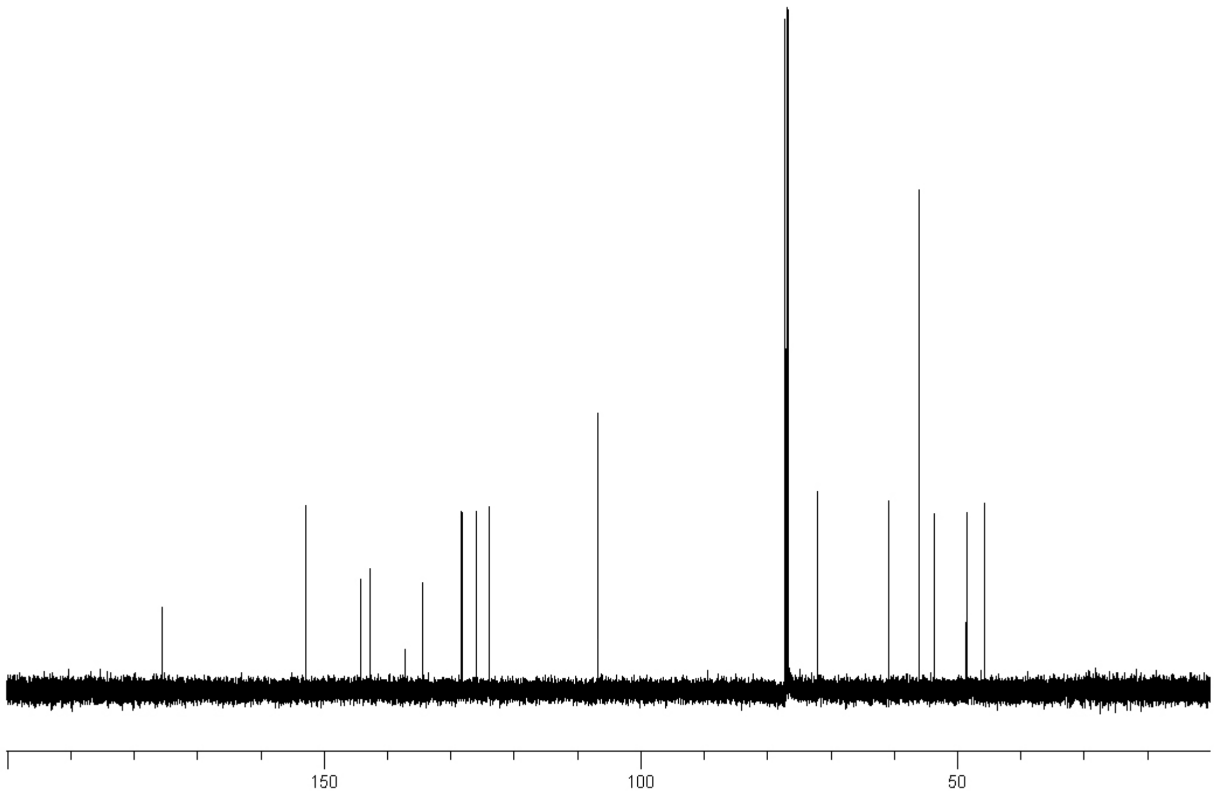


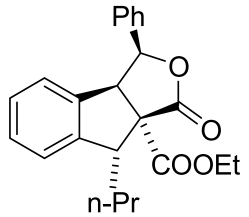




(3a*R**,8*R**,8a*R**)-**6b**







(3R*,3aS*,8S*,8aR*)-**4g**