Rhodium Catalyzed Enantioselective Desymmetrization of *meso*-3,5-Dimethyl Glutaric Anhydrides: A General Strategy to *syn*-Deoxypolypropionate Synthons: Supplementary Material

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General Methods

All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60-F plates. Infrared spectra were obtained on a Nicolet Avatar 320 FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Varian 300 or 400 MHz spectrometers at ambient temperature. Data are reported as follows: chemical shift in parts per million (δ, ppm) from deuterated chloroform ($CDCl_3$) taken as 7.26 ppm, integration, multiplicity (s = singlet, d = doublet, t = triplet, quint = quintet, and m = multiplet), and coupling constant (Hz). ^{13}C NMR spectra were recorded on a Varian 300 or 400 MHz spectrometers at ambient temperature. Chemical shifts are reported in ppm from $CDCl_3$ taken as 77.0 ppm. Mass spectra were obtained on Fisons VG Autospec.

General Procedure A: Enantioselective Desymmetrization of Dimethyl Glutaric Anhydride Using *in situ* Prepared Nucleophiles

To a flame-dried 10 mL round bottom flask was added $[Rh(nbd)Cl]_2$ (4 mg, 0.0088 mmol) and t-Bu-PHOX (6.5 mg, 0.0176 mmol) in a glovebox. The flask was sealed with a septum, removed from the glovebox and purged with argon for 15 minutes. THF (2 mL) was added and a solution of *in situ* prepared nucleophile (0.3 M in THF, 1 mL, 0.3 mmol) was added *via* syringe. The solution was heated to 50 ºC and dimethylglutaric anhydride **1** (25 mg, 0.176 mmol) in THF (1 mL) was added. The reaction was stirred at 50 ºC overnight then subjected to either of 2 workup procedures:

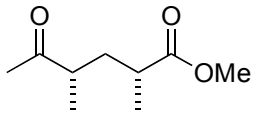
To afford the free acid, the reaction mixture was partitioned between Et_2O (5 mL) and HCl (1 M, 5 mL) and the aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organic washings were extracted with $NaHCO_3$ (saturated, 2 x 5 mL) and the combined aqueous phases were acidified (pH 1) and extracted with Et_2O (3 x 10 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford the pure free acid.

To afford the methyl ester, the reaction mixture was partitioned between Et_2O (5 mL) and HCl (1 M, 5 mL) and the aqueous phase was extracted with Et_2O (3 x 5 mL). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was dissolved in toluene/MeOH (1:1, 5 mL) and $TMSCHN_2$ (2 M in Et_2O, 0.5 mL) was added. Following standing for 10 minutes the solution was concentrated *in vacuo* and chromatographed directly to afford pure methyl ester.

General Procedure B: Formation of Benzyl Esters

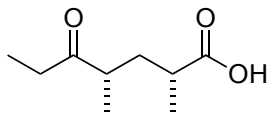
To a solution of free acid (0.1 mmol) in CH_2Cl_2 (2 mL) was added DCC (27.0 mg, 0.13 mmol), DMAP (4.0 mg, 0.03 mmol) and BnOH (14.0 mg, 0.13 mmol) and the reaction stirred for 3 hours. The resulting suspension was applied to the top of a column and chromatographed to afford benzyl ester.

(-)-(2*R*, 4*S*)-2,4-Dimethyl-5-oxo-hexanoic acid methyl ester (2a)



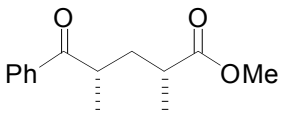
The title compound was prepared according to general procedure A, from 3,5-dimethyl glutaric anhydride **1** (25.0 mg, 0.176 mmol) and a freshly prepared solution of methylzinc bromide (0.3 M in THF, 1 mL, 0.3 mmol) using $[Rh(nbd)Cl]_2$ (4.0 mg, 0.0088 mmol) and *t*-Bu-PHOX (6.5 mg, 0.0176 mmol), which following derivatization to the methyl ester afforded **2a** (25.7 mg, 85%, 95% ee) as a colorless oil. Chiral GC analysis was performed using a Chiraldex BDM-2 column at 110 °C rising to 140 °C (2 °C/min) at 1 mL/min; peaks appear at 13.15 (minor) and 13.33 minutes (major). The absolute stereochemistry deterimined by comparison of optical rotation $[\alpha]_D^{23}$ -11.0 (c = 7.6, CHCl3); (lit. $[\alpha]^{25}_D$ +14.7 (7.6, $CHCl_3$) for (2*S*, 4*R*) enantiomer).[1] All other analytical data was consistent with that reported by Sih and co-workers.

(-)-(2*R*, 4*S*)-2,4-Dimethyl-5-oxo-heptanoic acid (2b)



The title compound was prepared according to general procedure A, from 3,5-dimethyl glutaric anhydride **1** (50.0 mg, 0.352 mmol) and diethyl zinc (86.6 mg, 72.2 μL, 0.704 mmol) using $[Rh(nbd)Cl]_2$ (4.0 mg, 0.0088 mmol) and *t*-Bu-PHOX (6.5 mg, 0.0176 mmol) to afford **2b** (57.5 mg, 95%, 95% ee) as a colorless oil. Chiral HPLC analysis was performed (on the benzyl ester, general procedure B) using a Chiralcel™ OD-H column eluting with 99:1 hexanes-*i*-PrOH at 0.5 mL/min; the peaks eluted at 21.6 (major) and 23.3 (minor) minutes. All spectral data is consistent with previous reports.[2] R_f = 0.15 (1:1 hexane – ethyl acetate); $[\alpha]_D^{23}$ -4.9 (c = 1.1, $CHCl_3$).

(+)-2,4-Dimethyl-5-phenyl-5-oxo-pentanoic acid methyl ester (2c)



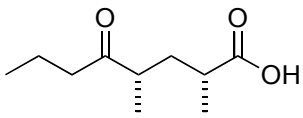
$[Rh(COD)Cl]_2$ (6.3 mg, 0.014 mmol), TADDOL-P-NMe_2 (15.1 mg, 0.028 mmol) and diphenyl zinc (109 mg, 0.50 mmol) were weighed into a flame dried flask in a glovebox. The flask was sealed with a septum and removed from the glove box then diluted with anhydrous DMF (2 mL) and heated to 50 ºC. 3,5-Dimethylglutaric anhydride (50.0

[1] Patel, D. V.; VanMiddlesworth, F.; Donaubauer, J.; Gannett, P.; Sih, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 4603.
[2] Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 247.

mg, 0.352 mmol) in DMF (1 mL) was added and the reaction stirred at 50 ºC overnight. Once cool the reaction was partitioned between Et_2O (x mL) and HCl (x mL, 1M) and the aqueous phase extracted with Et_2O (2 x x mL). The combined organic layers were treated with saturated $NaHCO_3$ (2 x 5 mL) and the combined aqueous phases acidified (pH 1). The acidic solution was extracted with Et_2O (3 x 15 mL) and the combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. The resulting crude acid was esterified using $TMSCHN_2$ and purified *via* column chromatography (9:1 Hexane – EtOAc) to afford the title compound (61.8 mg, 75%, 82% ee) as a colourless oil. Chiral HPLC analysis was performed using using a Chiralcel™ OD-H column eluting with 99:1 hexanes-*i*-PrOH at 0.5 mL/min; the peaks eluted at 15.4 (minor) and 16.8 (major) minutes.

R_f = 0.5 (8:2 hexane – ethyl acetate); $[\alpha]_D^{23}$ +7.2 (*c* = 0.5, $CHCl_3$); IR: ν_{max} (thin film) / cm^{-1} 2973, 1733, 1682, 1596, 1579, 1448, 1377, 1234, 1211, 1173, 1141; ^1H NMR: (300 MHz, $CDCl_3$) δ 8.05-7.99 (2H, m), 7.64-7.57 (1H, m), 7.55-7.47 (2H, m), 3.72 (3H, s), 3.61-3.54 (1H, m), 2.70-2.62 (1H, m), 2.28 (1H, ddd, *J* = 13.9, 9.3, 5.8 Hz), 1.48 (1H, ddd, *J* 13.9, 8.0, 5.4 Hz), 1.25 (3H, d, *J* = 6.8 Hz), 1.21 (3H, *J* = 6.8 Hz); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 203.5, 176.9, 136.2, 133.2, 128.8, 128.5, 51.8, 38.6, 37.4, 37.3, 18.1, 17.2; HRMS (ES-) Calcd. for $C_{14}H_{19}O_3$ $[M+H]^+$, 235.1334. Found 235.1331.

(+)-(2*R*, 4*S*)-2,4-Dimethyl-5-oxo-octanoic acid (2d)

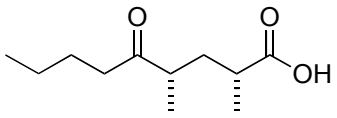


The title compound was prepared according to general procedure A, from 3,5-dimethyl glutaric anhydride **1** (25.0 mg, 0.176 mmol) and a freshly prepared solution of propylzinc bromide (0.3 M in THF, 1 mL, 0.3 mmol) using $[Rh(nbd)Cl]_2$ (4.0 mg, 0.0088 mmol) and *t*-Bu-PHOX (6.5 mg, 0.0176 mmol) to afford **2c** (20.4 mg, 62%, 88% ee) as a colorless oil. Chiral HPLC analysis was performed (on the benzyl ester, general procedure B) using using a Chiralcel™ OD-H column eluting with 99:1 hexanes-*i*-PrOH at 0.5 mL/min; the peaks eluted at 17.6 (major) and 19.1 (minor) minutes.

R_f = 0.2 (1:1 hexane – ethyl acetate); $[\alpha]_D^{23}$ +4.5 (*c* = 0.4, $CHCl_3$); IR: ν_{max} (thin film) / cm^{-1} 3276, 2968, 2936, 1737, 1708, 1463, 1379, 1244, 1123; ^1H NMR: (300 MHz,

$CDCl_3$) δ 2.60 (1H, ddd, *J* = 6.6, 6.6, 6.6 Hz), 2.54-2.49 (1H, m), 2.46 (1H, q, *J* = 7.3 Hz), 2.40 (1H, q, *J* = 7.3 Hz), 2.09 (1H, ddd, *J* = 14.9, 8.8, 6.2 Hz), 1.56 (2H, ddd, *J* = 7.3, 7.3, 7.3 Hz), 1.36 (1H, ddd, *J* = 14.9, 7.6, 6.2 Hz), 1.20 (3H, d, *J* = 7.3 Hz), 1.09 (3H, d, *J* = 7.0Hz), 0.92 (3H, t, *J* = 7.3 Hz); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 214.3, 182.8, 44.2, 43.4, 37.4, 36.2, 17.8, 17.3, 16.6, 14.0; HRMS (ES-) Calcd. for $C_{10}H_{17}O_3$ $[M-H]^+$, 185.1183. Found 185.1182.

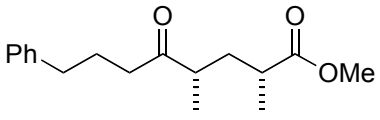
(-)-(2*R*, 4*S*)-2,4-Dimethyl-5-oxo-nonanoic acid (2e)



The title compound was prepared according to general procedure A, from 3,5-dimethyl glutaric anhydride **1** (25.0 mg, 0.176 mmol) and a freshly prepared solution of butylzinc bromide (0.3 M in THF, 1 mL, 0.3 mmol) using $[Rh(nbd)Cl]_2$ (4.0 mg, 0.0088 mmol) and *t*-Bu-PHOX (6.5 mg, 0.0176 mmol) to afford **2d** (24.7 mg, 70%, 90% ee) as a colorless oil. Chiral HPLC analysis was performed (on the benzyl ester, general procedure B) using a Chiralcel™ OD-H column eluting with 99:1 hexanes-*i*-PrOH at 0.5 mL/min; the peaks eluted at 15.7 (major) and 16.9 (minor) minutes.

R_f = 0.2 (1:1 hexane – ethyl acetate); $[\alpha]_D^{23}$ -1.5 (*c* = 1.1, $CHCl_3$); IR: ν_{max} (thin film) / cm^{-1} 3278, 2961, 2933, 1737, 1708, 1463, 1414, 1379, 1242, 1126; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 9.60 (1H, br s), 2.61 (1H, ddd, *J* = 6.9, 6.9, 6.9 Hz), 2.57-2.42 (3H, m), 2.08 (1H, ddd, *J* = 15.4, 8.8, 6.6 Hz), 1.53 (2H, ddd, *J* = 7.0, 7.0, 7.0 Hz), 1.41-1.20 (4H, m), 1.20 (3H, d, *J* = 7.3 Hz), 1.09 (3H, d, *J* = 7.0 Hz), 0.89 (3H, t, *J* = 7.3 Hz); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 214.4, 182.7, 44.2, 40.9, 37.4, 36.2, 26.0, 22.6, 17.8, 16.6, 14.1; HRMS (FAB+) Calcd. for $C_{11}H_{21}O_3$ $[M+H]^+$, 201.1491. Found 201.1489.

(+)-(2*R*, 4*S*)-2,4-Dimethyl-5-oxo-8-phenyloctanoic acid methyl ester (2f)

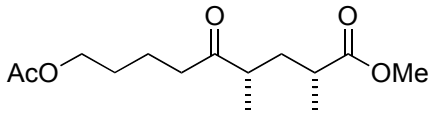


The title compound was prepared according to general procedure A, from 3,5-dimethyl glutaric anhydride **1** (25.0 mg, 0.176 mmol) and a freshly prepared solution of 3-phenylpropylzinc bromide (0.3 M in THF, 1 mL, 0.3 mmol) using $[Rh(nbd)Cl]_2$ (4.0 mg, 0.0088 mmol) and *t*-Bu-PHOX (6.5 mg, 0.0176 mmol), which following conversion to the methyl ester ($TMSCHN_2$) and column chromatography

(9:1 hexane – ethyl acetate) afforded **2e** (30.1 mg, 62%, 92% ee) as a colorless oil. Chiral HPLC analysis was performed using a Chiralcel™ OD-H column eluting with 99:1 hexanes-*i*-PrOH at 0.5 mL/min; the peaks eluted at 26.2 (major) and 27.5 (minor) minutes.

R_f = 0.3 (8:2 hexane – ethyl acetate); $[\alpha]_D^{23}$ +2.5 (c = 0.2, $CHCl_3$); IR: ν_{max} (thin film) / cm^{-1} 2971, 2930, 1735, 1711, 1454, 1435, 1377, 1196, 1173; ^1H NMR: (300 MHz, $CDCl_3$) δ 7.32-7.25 (2H, m), 7.22-7.15 (3H, m), 3.66 (3H, s), 2.62 (2H, t, *J* = 7.3 Hz), 2.56-2.43 (4H, m), 2.05 (1H, ddd, *J* = 13.5, 8.8, 6.3 Hz), 1.89 (1H, dddd, *J* = 11.0, 11.0, 7.3, 7.3 Hz), 1.31 (1H, ddd, *J* = 13.5, 7.6, 5.4 Hz), 1.16 (3H, d, *J* = 7.3 Hz), 1.06 (3H, d, *J* = 7.0 Hz); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 213.8, 176.9, 128.7, 128.6, 126.1, 51.9, 44.3, 40.4, 37.5, 36.6, 35.3, 25.3, 18.0, 16.7; HRMS (FAB+) Calcd. for $C_{17}H_{25}O_3$ $[M+H]^+$, 277.1804. Found 277.1798.

(-)-(2*R*, 4*S*)-9-Acetoxy-2,4-dimethyl-5-oxononanoic acid methyl ester (2g)

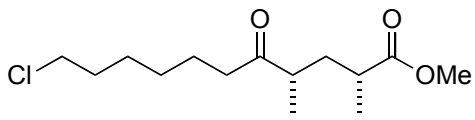


The title compound was prepared according to general procedure A, from 3,5-dimethyl glutaric anhydride **1** (25.0 mg, 0.176 mmol) and a freshly prepared solution of bis(4-acetoxybutyl) zinc[3] (0.3 M in THF, 1 mL, 0.3 mmol) using $[Rh(nbd)Cl]_2$ (4.0 mg, 0.0088 mmol) and *t*-Bu-PHOX (6.5 mg, 0.0176 mmol), which following conversion to the methyl ester ($TMSCHN_2$) afforded **2f** (31.4 mg, 72%) as a colorless oil. HPLC analysis was performed using a Chiralcel™ OD-H column eluting with 99:1 hexanes-*i*-PrOH at 0.5 mL/min; the peaks eluted at 21.6 (major) and 23.3 (minor) minutes.

Rf = 0.2 (8:2 hexane – ethyl acetate); $[\alpha]_D^{23}$ –2.1 (c = 0.6, $CHCl_3$); IR: ν_{max} (thin film) / cm^{-1} 2956, 1730, 1713, 1456, 1394, 1230; ^1H NMR: (300 MHz, $CDCl_3$) δ 4.19 (2H, t, *J* = 7.0 Hz), 3.67 (3H, s), 2.59-2.44 (4H, m), 2.05 (1H, ddd, *J* = 13.5, 9.2, 6.2 Hz), 2.04 (3H, s), 1.65-1.58 (4H, m), 1.34 (1H, ddd, *J* = 13.5, 7.7, 5.5 Hz), 1.15 (3H, d, *J* = 6.9 Hz), 1.07 (3H, d, *J* = 7.0 Hz); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 213.5, 197.9, 171.4, 64.4, 51.9, 44.3, 40.5, 37.5, 36.6, 28.3, 21.2, 20.2, 18.0, 16.6; HRMS (ES+) Calc. for $C_{14}H_{25}O_5$ $[M+1]^+$, 273.1700. Found 273.1695.

[3] Rozema, M. J.; AchyutaRao, S.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 1956-1958.

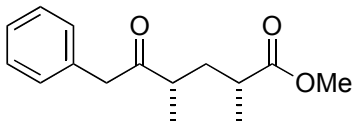
(-)-(2*R*, 4*S*)-11-Chloro-2,4-dimethyl-5-oxoundecanoic acid methyl ester (2h)



The title compound was prepared according to general procedure A, from 3,5-dimethyl glutaric anhydride **1** (25.0 mg, 0.176 mmol) and a freshly prepared solution of bis(6-chlorohexyl) zinc[3] (0.3 M in THF, 1 mL, 0.3 mmol) using $[Rh(nbd)Cl]_2$ (4.0 mg, 0.0088 mmol) and *t*-Bu-PHOX (6.5 mg, 0.0176 mmol), which following conversion to the methyl ester ($TMSCHN_2$) afforded **2g** (36.9 mg, 72%) as a colorless oil. HPLC analysis was performed using a Chiralcel™ OD-H column eluting with 99:1 hexanes-*i*-PrOH at 0.5 mL/min; the peaks eluted at 21.6 (major) and 23.3 (minor) minutes.

R_f = 0.35 (8:2 hexane – ethyl acetate); $[\alpha]_D^{23}$ -2.6 (c = 0.9, $CHCl_3$); IR: ν_{max} (thin film) / cm^{-1} 2941, 1712, 1462, 1369, 1260; ^1H NMR: (300 MHz, $CDCl_3$) δ 3.66 (3H, s), 3.52 (2H, t, *J* = 6.6 Hz), 2.59-2.41 (4H, m), 2.05 (1H, ddd, *J* = 13.9, 9.1, 6.2 Hz), 1.76 (2H, ddq, *J* = 6.6, 6.6, 6.6 Hz), 1.62-1.23 (7H, m), 1.13 (3H, d, *J* = 6.9 Hz), 1.07 (3H, d, *J* = 7.0 Hz); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 214.0, 176.9, 51.9, 45.3, 44.3, 40.9, 37.5, 36.6, 32.6, 28.7, 26.9, 23.6, 18.0, 16.6; HRMS (FAB+) Calcd. for $C_{14}H_{26}{}^{35}ClO_3$ $[M+H]^+$ 277.1570. Found 277.1564.

(-)-(2*R*, 4*S*)-2,4-Dimethyl-5-oxo-6-phenylhexanoic acid methyl ester (2i)

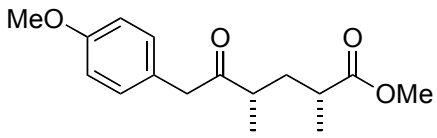


The title compound was prepared according to general procedure A, from 3,5-dimethyl glutaric anhydride **1** (25.0 mg, 0.176 mmol) and a freshly prepared solution of benzylzinc bromide (0.3 M in THF, 1 mL, 0.3 mmol) using $[Rh(nbd)Cl]_2$ (4.0 mg, 0.0088 mmol) and *t*-Bu-PHOX (6.5 mg, 0.0176 mmol), which following conversion to the methyl ester ($TMSCHN_2$) afforded **2h** (31.4 mg, 72%) as a colorless oil. Chiral HPLC analysis was performed using a Chiralcel™ OD-H column eluting with 98:2 hexanes-*i*-PrOH at 0.5 mL/min; the peaks eluted at 18.3 (major) and 19.5 (minor) minutes.

R_f = 0.3 (8:2 hexane – ethyl acetate); $[\alpha]_D^{23}$ -11.2 (c = 2.8, $CHCl_3$); IR: ν_{max} (thin film) / cm^{-1} 2971, 2937, 1733, 1713, 1454, 1435, 1378, 1196, 1173; ^1H NMR: (300 MHz, $CDCl_3$) δ 7.35-7.18 (5H, m), 3.75 (2H, s), 3.65 (3H, s), 2.67 (1H, ddq, *J* = 7.3,

7.3, 7.3 Hz), 2.43-2.35 (1H, m), 2.09 (1H, ddd, *J* = 13.9, 8.5, 6.6 Hz), 1.34 (1H, ddd, *J* = 13.9, 7.3, 6.6 Hz), 1.07 (3H, d, *J* = 7.3 Hz), 1.05 (3H, d, *J* = 7.1 Hz); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 211.1, 176.9, 134.3, 129.7, 128.9, 127.2, 51.9, 48.5, 43.3, 37.5, 36.6, 17.7, 16.8; HRMS (FAB+) Calcd. for $C_{15}H_{21}O_3$ $[M+1]^+$, 249.1491. Found 249.1490.

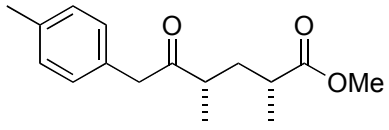
(-)-(2*R*, 4*S*)-2,4-Dimethyl-5-oxo-6-(4-methoxyphenyl) hexanoic acid methyl ester (2j)



The title compound was prepared according to general procedure A, from 3,5-dimethyl glutaric anhydride **1** (25.0 mg, 0.176 mmol) and a freshly prepared solution of (4-methoxybenzyl)zinc bromide (0.3 M in THF, 1 mL, 0.3 mmol) using $[Rh(nbd)Cl]_2$ (4.0 mg, 0.0088 mmol) and *t*-Bu-PHOX (6.5 mg, 0.0176 mmol), which following conversion to the methyl ester ($TMSCHN_2$) afforded **2i** (36.6 mg, 75%, 85% ee) as a colorless oil. HPLC analysis was performed using a Chiralcel™ OD-H column eluting with 98:2 hexanes-*i*-PrOH at 0.5 mL/min; the peaks eluted at 26.9 (major) and 28.7 (minor) minutes.

R_f = 0.2 (8:2 hexane – ethyl acetate); $[\alpha]_D^{23}$ -6.7 (c = 1.7, $CHCl_3$); IR: ν_{max} (thin film) / cm^{-1} 2971, 2957, 1732, 1712, 1512, 1462, 1274, 1249, 1197, 1176; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.11 (2H, d, *J* = 9.0 Hz), 6.85 (2H, d, *J* = 9.0 Hz), 3.79 (3H, s), 3.68 (2H, s), 3.64 (3H, s), 2.66 (1H, ddq, *J* = 6.9, 6.9, 6.9 Hz), 2.48-2.36 (1H, m), 2.09 (1H, ddd, *J* = 13.9, 8.4, 6.9 Hz), 1.32 (1H, ddd, *J* = 13.9, 6.9, 6.2 Hz), 1.07 (3H, d, *J* = 6.9 Hz), 1.06 (3H, d, *J* = 6.9 Hz); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 211.5, 176.9, 158.8, 130.7, 126.3, 114.3, 55.5, 51.9, 47.6, 43.1, 37.5, 36.6, 17.7, 16.8; HRMS (FAB+) Calcd. for $C_{15}H_{19}O_3$ $[M-OMe]^+$, 247.1320. Found 247.1208.

(-)-(2*R*, 4*S*)-2,4-Dimethyl-5-oxo-6-(4-methylphenyl) hexanoic acid methyl ester (2k)

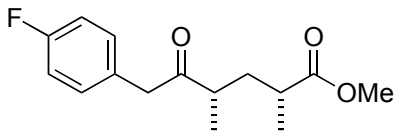


The title compound was prepared according to general procedure A, from 3,5-dimethyl glutaric anhydride **1** (25.0 mg, 0.176 mmol) and a freshly prepared solution of (4-methylbenzyl)zinc bromide (0.3 M in THF, 1 mL, 0.3 mmol) using $[Rh(nbd)Cl]_2$ (4.0 mg, 0.0088 mmol) and *t*-Bu-PHOX (6.5 mg, 0.0176 mmol),

which following conversion to the methyl ester ($TMSCHN_2$) afforded **2j** (31.4 mg, 72%) as a colorless oil. HPLC analysis was performed using a Chiralcel™ OD-H column eluting with 99:1 hexanes-*i*-PrOH at 0.5 mL/min; the peaks eluted at 21.6 (major) and 23.3 (minor) minutes.

R_f = 0.35 (8:2 hexane – ethyl acetate); $[\alpha]_D^{23}$ -8.4 (c = 1.0, $CHCl_3$); IR: ν_{max} (thin film) / cm^{-1} 2972, 2939, 1734, 1712, 1461, 1196, 1172 ; ^1H NMR: (300 MHz, $CDCl_3$) δ 7.15-7.06 (4H, m), 3.70 (2H, s), 3.64 (3H, s), 2.66 (1H, ddq, *J* = 6.9, 6.9, 6.9 Hz), 2.47-2.35 (1H, m), 2.32 (3H, s), 2.09 (1H, ddd *J* = 13.9, 8.6, 6.9 Hz), 1.35 (1H, ddd, *J* = 13.9, 6.9, 6.2 Hz), 1.07 (3H, d, *J* = 6.9 Hz), 1.05 (3H, d, *J* = 6.9 Hz); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 211.4, 176.9, 136.8, 131.1, 129.6, 129.6, 51.9, 48.1, 43.2, 37.5, 36.6, 21.3, 17.7, 16.8; HRMS (FAB+) Calcd. for $C_{16}H_{23}O_3$ $[M+H]^+$, 263.1647. Found 263.1647.

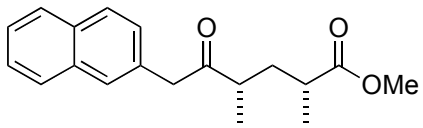
(-)-(2*R*, 4*S*)-2,4-Dimethyl-5-oxo-6-(4-fluorophenyl) hexanoic acid methyl ester (2l)



The title compound was prepared according to general procedure A, from 3,5-dimethyl glutaric anhydride **1** (25.0 mg, 0.176 mmol) and a freshly prepared solution of (4-fluorobenzyl)zinc bromide (0.3 M in THF, 1 mL, 0.3 mmol) using $[Rh(nbd)Cl]_2$ (4.0 mg, 0.0088 mmol) and *t*-Bu-PHOX (6.5 mg, 0.0176 mmol), which following conversion to the methyl ester ($TMSCHN_2$) afforded **2k** (36.5 mg, 78%, 92% ee) as a colorless oil. HPLC analysis was performed using a Chiralcel™ OJ-H column eluting with 95:5 hexanes-*i*-PrOH at 0.5 mL/min; the peaks eluted at 30.9 (minor) and 39.8 (major) minutes.

R_f = 0.15 (8:2 hexane – ethyl acetate); $[\alpha]_D^{23}$ -2.8 (c = 1.6, $CHCl_3$); IR: ν_{max} (thin film) / cm^{-1} 2973, 1732, 1510, 1461, 1436, 1378, 1222, 1197, 1158; ^1H NMR: (300 MHz, $CDCl_3$) δ 7.18-7.11 (2H, m), 7.04-6.98 (2H, m), 3.72 (2H, s), 3.64 (3H, s), 2.65 (1H, ddq, *J* = 6.9, 6.9, 6.9 Hz), 2.50-2.37 (1H, m), 2.09 (1H, ddd, *J* = 13.9, 8.9, 6.9 Hz), 1.33 (1H, ddd, *J* = 13.9, 6.9, 5.8 Hz), 1.08 (6H, d, *J* = 6.9 Hz); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 210.9, 176.8, 162.1 (d, J_{CF} = 243.4 Hz), 131.2 (d, J_{CF} = 9.6 Hz), 131.0 (d, J_{CF} = 2.0 Hz), 115.7 (d, J_{CF} = 20.8 Hz), 51.9, 47.3, 43.6, 37.5, 36.6, 17.9, 16.7; HRMS (FAB+) Calcd. for $C_{15}H_{20}FO_3$ $[M+1]^+$, 267.1391. Found 267.1392.

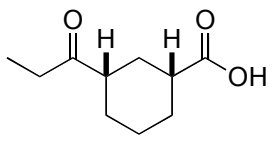
(-)-(2*R*, 4*S*)-2,4-Dimethyl-5-oxo-6-(2-naphthyl)hexanoic acid methyl ester (2m)



The title compound was prepared according to general procedure A, from 3,5-dimethyl glutaric anhydride **1** (25.0 mg, 0.176 mmol) and a freshly prepared solution of (2-naphthylmethyl)zinc bromide (0.3 M, 1 mL, 0.3 mmol) using $[Rh(nbd)Cl]_2$ (4.0 mg, 0.0088 mmol) and *t*-Bu-PHOX (6.5 mg, 0.0176 mmol), which following conversion to the methyl ester ($TMSCHN_2$) afforded **2l** (35.6 mg, 68%, 91% ee) as a colorless oil. HPLC analysis was performed using a Chiralcel™ AS-H column eluting with 97:3 hexanes-*i*-PrOH at 0.5 mL/min; the peaks eluted at 15.7 (major) and 18.4 (minor) minutes.

R_f = 0.3 (8:2 hexane – ethyl acetate); $[\alpha]_D^{23}$ -3.2 (c = 1.0, $CHCl_3$); IR: ν_{max} (thin film) / cm^{-1} 2971, 2934, 1720, 1460, 1434, 1368, 1196, 1173; ^1H NMR: (300 MHz, $CDCl_3$) δ 7.84-7.77 (2H, m), 7.67 (1H, br s), 7.50-7.42 (2H, m), 7.33 (1H, d, *J* = 1.8 Hz), 7.31 (1H, d, *J* = 1.8 Hz), 3.92 (2H, s), 3.60 (3H, s), 2.72 (1H, ddq, *J* = 6.9, 6.9, 6.9 Hz), 2.51-2.39 (1H, m), 2.15 (1H, ddd *J* = 14.0, 9.0, 6.9 Hz), 1.35 (1H, ddd, *J* = 14.0, 7.8, 6.9 Hz), 1.10 (3H, d, *J* = 6.9 Hz), 1.06 (3H, d, *J* = 6.9 Hz); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 211.1, 176.8, 132.6, 131.8, 129.5, 128.5, 128.4, 127.9, 127.8, 126.4, 126.0, 125.7, 51.8, 48.6, 43.4, 37.5, 36.6, 17.7, 16.8; HRMS (FAB+) Calcd. for $C_{19}H_{23}O_3$ $[M+1]^+$, 299.1647. Found 299.1643.

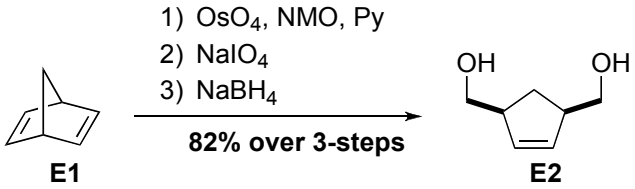
(+)-(1*R*, 3*S*) 3-Propionyl-cyclohexane-1-carboxylic acid (5)



The title compound was prepared according to general procedure A, from 1,3-cyclohexyldicarboxylic anhydride **4** (54.0 mg, 0.352 mmol) and diethyl zinc (86.6 mg, 72.2 μL, 0.704 mmol) using $[Rh(nbd)Cl]_2$ (4.0 mg, 0.0088 mmol) and *t*-Bu-PHOX (6.5 mg, 0.0176 mmol) to afford **5** (56.3 mg, 87%, 85% ee) as a colorless oil. All spectral data is consistent with previous reports.[4] Chiral HPLC analysis was performed (on the benzyl ester, general procedure B) using a Chiralcel™ OD-H column eluting with 97:3 hexanes-*i*-PrOH 0.5 mL/min; the peaks eluted at 21.2 (major) and 22.5 (minor). $[\alpha]_D^{23}$ +2.5 (c = 0.5, CHCl3).

[4] Bercot, E. A.; Rovis, T. *J. Am. Chem. Soc.* **2005**, *127*, 247.

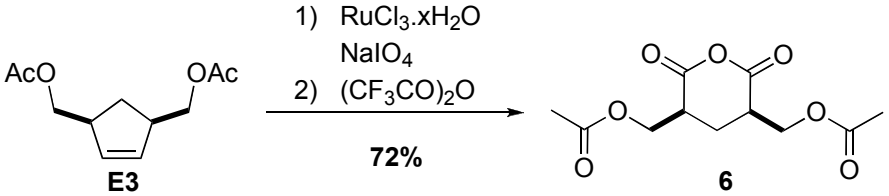
***cis*-3,5-Bis(hydroxymethylene)cyclopent-4-ene (E2)**



Norbornadiene **E1** (10 g, 108 mmol), pyridine (10 mL), *N*-methyl-morpholine-*N*-oxide (8.78 g, 75 mmol) and osmium tetroxide (4% wt. in H_2O, 1.6 mL, 0.27 mmol) were added to a biphasic mixture of *tert*-butanol (100 mL) and H_2O (35 mL) and heated at reflux for 16 hours. The mixture was cooled to room temperature and saturated $Na_2S_2O_3$ solution (50 mL) were added and stirred for 30 minutes. The *tert*-butanol was removed *in vacuo* and the aqueous phase extracted with EtOAc (5 x 100 mL), dried over Na_2SO_4 and concentrated to afford the crude diol (8.93 g, 94% based on NMO) as a 9:1 mixture of diastereomers.

The crude diol (4 g, 31.7 mmol) was dissolved in THF/H_2O (5:1, 150 mL) and cooled to 0 °C were $NaIO_4$ (9.41 g, 44.4 mmol) was added. The mixture was stirred for 15 minutes then partioned between EtOAc (200 mL) and H_2O (50 mL) and the aqueous phase was extracted with EtOAc (4 x 50 mL). The organic phases were combined, dried over Na_2SO_4 and concentrated. The residue was dissolved in EtOH (150 mL) and cooled to –20 °C. $NaBH_4$ (3.38g, 88.8 mmol) was added and the resulting suspension was stirred at –20 °C for 1 hour then carefully quenched with saturated NH_4Cl. The mixture was extracted with EtOAc (5 x 100 mL) and the organic phases dried over Na_2SO_4 and concentrated *in vacuo*. The crude diol was purified *via* column chromatography (EtOAc) to afford the title compound **E2** (3.52 g, 87%) as a colorless solid.[5]

***cis*-3-5-Bis(acetoxymethylene)glutaric anhydride (6)**

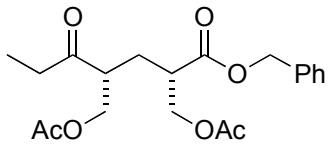


[5] Bridges, A. J.; Raman, P. S.; Ng, G. S. Y.; Jones, J. B. *J. Am. Chem. Soc.***1984**, *106*, 1461.

Diacetate[6] **E3** (1 g, 4.7 mmol) was dissolved in MeCN/H_2O/CCl_4 (2:3:2, 20 mL) and cooled to 0 °C. $NaIO_4$ (8 g, 37.7 mmol) and $RuCl_3.xH_2O$ (50 mg, 0.23 mmol) were added and the mixture stirred overnight. The reaction was then partitioned between EtOAc (50 mL) and H_2O (20 mL) and the aqueous layer extracted with EtOAc (4 x 25 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting diacid was suspended in CH_2Cl_2 (25 mL), cooled to 0 °C and trifluoroacetic anhydride (2.1 mL, 3.15 g, 15 mmol) was added and the reaction stirred for 90 minutes. The solvent was removed *in vacuo* and the residue was taken up in $CHCl_3$ (50 mL) and washed with saturated $NaHCO_3$ solution (10 mL), dried over Na_2SO_4 and concentrated to afford the title compound as a low melting solid (873 mg, 72%) which was used immediately.

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36 (dd, 2H, *J* 11.2, 4.2), 4.30 (dd, 2H, *J* 11.2, 5.1), 3.11-3.02 (m, 2H), 2.14-2.04 ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 166.7, 62.6, 41.0, 23.5, 20.8.

(-)-(2S,4R)-2-(benzyloxycarbonyl)-4-propionylpentane-1,5-diyl diacetate (7)



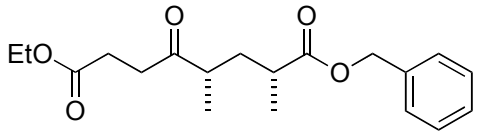
The title compound was prepared according to general procedure A, from 3,5-(acetoxymethyl) glutaric anhydride **6** (91.1 mg, 0.352 mmol) and diethyl zinc (86.6 mg, 72.2 μL, 0.704 mmol) using $[Rh(nbd)Cl]_2$ (4.0 mg, 0.0088 mmol) and *t*-Bu-PHOX (6.5 mg, 0.0176 mmol). The crude acid was derivatized as benzyl ester (general procedure B) before purification to afford **7** (57.5 mg, 95%, 84% ee) as a colorless oil. Chiral HPLC analysis was performed using a Chiralcel™ OD-H column eluting with 97:3 hexanes-*i*-PrOH 1 mL/min; the peaks eluted at 10.9 (major) and 13.6 (minor) minutes. This compound cannot be stored for extended periods of time due decomposition *via* the loss of AcOH.

R_f = 0.5 (1:1hexane – ethyl acetate); $[\alpha]_D^{23}$ -5.7 (c = 1.9, $CHCl_3$); IR: ν_{max} (thin film) / cm^{-1} 2925, 1734, 1717, 1651, 1558, 1456, 1232; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.39-7.31 (5H, m), 5.17 (1H, d, *J* 12.1), 5.11 (1H, d, *J* 12.1), 4.24-4.11 (4H, m), 2.81 (1H, dd, *J* = 6.6, 6.6 Hz), 2.76 (1H, dd, *J* = 6.6, 6.6 Hz), 2.47 (1H, q, *J* = 7.0 Hz), 2.41 (1H, q, *J* = 7.0 Hz), 2.05 (1H, ddd, *J* = 14.2, 9.5, 6.2 Hz), 2.00 (3H, s), 1.95 (3H, s), 1.58

[6] Mekrami, M.; Sicsic, S. *Tetrahedron: Asymm.* **1992**, *3*, 431.

(1H, ddd, J = 14.2, 7.7, 5.1 Hz), 1.01 (3H, t, J = 7.0 Hz); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 210.9, 172.7, 170.8, 170.8, 135.7, 128.8, 128.6, 128.6, 67.0, 64.6, 64.2, 48.2, 42.9, 35.9, 27.2, 21.0, 20.9, 7.7; HRMS (APCI+) Calcd. for $C_{20}H_{25}O_6$ $[M\text{-}OH]^+$, 361.1645. Found 361.1639.

(+)-(2*R*, 4*S*)-2,4-Dimethyl-5-oxo-octandioic acid 8-ethyl ester 1-benzyl ester (2n)



The title compound was prepared according to general procedure A, from 3,5-dimethyl glutaric anhydride **1** (25.0 mg, 0.176 mmol) and a freshly prepared solution of bis(ethyl (0.3 M in THF, 1 mL, 0.3 mmol) using $[Rh(nbd)Cl]_2$ (4.0 mg, 0.0088 mmol) and *t*-Bu-PHOX (6.5 mg, 0.0176 mmol), which following conversion to the methyl ester ($TMSCHN_2$) afforded **2m** (36.7 mg, 81%, 95% ee) as a colorless oil.

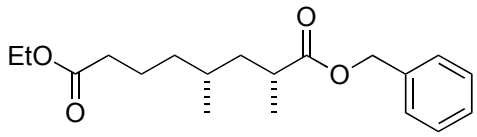
R_f = 0.25 (8:2 hexane – ethyl acetate); $[\alpha]_D^{23}$ +7.0 (*c* = 1.2, $CHCl_3$); IR: ν_{max} (thin film) / cm^{-1} 2975, 1733, 1456, 1374, 1349, 1172, 1081; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 7.39-7.30 (5H, m), 5.10 (2H, s), 4.11 (2H, q, J = 7.0 Hz), 2.77-2.46 (6H, m), 2.09 (1H, ddd, J = 14.0, 11.2, 6.3 Hz), 1.36 (1H, ddd, J, = 14.0, 7.1, 5.5 Hz), 1.23 (3H, t, J = 7.0 Hz), 1.17 (3H, d, J = 7.0 Hz), 1.08 (3H, d, J = 7.0 Hz); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 212.0, 176.2, 172.9, 136.2, 128.8, 128.4, 128.4, 66.4, 60.8, 44.1, 37.6, 36.6, 35.6, 28.1, 17.9, 16.5, 14.4; HRMS (ES+) Calcd. for $C_{19}H_{27}O_5$ $[M+H]^+$, 335.1853. Found 335.1828.

A small amount of free acid was derivatized as the methyl ester ($TMSCHN_2$) to determine the enantiomeric excess. HPLC analysis was performed using a Chiralcel™ OD-H column eluting with 95:5 hexanes-*i*-PrOH at 0.5 mL/min the peaks eluted at 14.4 (major) and 15.3 (minor) minutes.

Data for **2m** 1-Me ester: R_f = 0.15 (8:2 hexane – ethyl acetate); $[\alpha]_D^{23}$ -1.8 (c = 2.0, $CHCl_3$); IR: ν_{max} (thin film) / cm^{-1} 2976, 2938, 1735, 1716, 1462, 1436, 1411, 1375, 1349, 1258, 1197, 1174; ^{1}H NMR: (300 MHz, $CDCl_3$) δ 4.12 (2H, q, J = 7.3 Hz), 3.66 (3H, s), 2.77 (1H, dd, J = 13.5, 7.0 Hz), 2.70-2.42 (5H, m), 2.09 (1H, ddd, J = 13.9, 8.8, 6.6 Hz), 1.36 (1H, ddd, J = 13.9, 7.7, 5.9 Hz), 1.24 (3H, t, J = 7.3 Hz), 1.15 (3H, d, J = 7.0 Hz), 1.11 (3H, d, J = 7.0 Hz); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 212.0, 176.9,

173.0, 60.8, 51.9, 44.2, 37.5, 36.6, 35.6, 28.1, 17.9, 16.7, 14.4; HRMS (ES+) Calcd. for $C_{13}H_{23}O_5$ $[M+H]^+$, 259.1540. Found 259.1532.

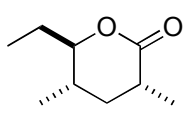
(-)-(2*R*, 4*S*)-2,4-Dimethyloctandioic acid 8-methyl ester 1**-benzyl ester (8)**



(-)-(2*R*, 4*S*)-2,4-Dimethyl-5-oxo-octandioic acid 8-ethyl ester 1-benzyl ester **2m** (50.0 mg, 0.150 mmol) was dissolved in MeOH (0.5 mL) and p-toluenesulfonyl hydrizide (55.0 mg, 0.194 mmol) was added and heated to 40 ºC for 12 hours. The reaction was cooled to room temperature, concentrated *in vacuo* and chromatographed (7:3 hexanes – EtOAc) to afford the tosyl hydrazone (62.0 mg, 0.123 mmol) as a colourless oil. The resulting oil was dissolved in DMF/Sulfolane (1:1) and $NaBH_3CN$ (39.0 mg, 0.615 mmol) and TsOH (23.0 mg, 0.123 mmol) were added and the mixture heated to 120 ºC for 12 hours. The reaction was cooled and partitioned between Et_2O (3 mL) and water (2 mL), the aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organic phases washed with water (3 x 5 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was then subjected to column chromatography (9:1 hexanes – EtOAc) to afford the title compound (29.0 mg, 64 % over 2-steps) as a colourless oil.

R_f = 0.5 (8:2 hexane – ethyl acetate); $[\alpha]_D^{23}$ -4.2 (*c* = 0.5, $CHCl_3$); IR: ν_{max} (thin film) / cm^{-1} 2857, 1734, 1456, 1377, 1252, 1168; ^1H NMR: (300 MHz, $CDCl_3$) δ 7.38-7.28 (5H, m), 5.11 (2H, s), 4.11 (2H, q, *J* = 7.0 Hz), 2.64-2.55 (1H, m), 2.23 (2H, t, *J* = 7.3 Hz), 1.72 (1H, ddd, *J* = 13.9, 9.5, 7.1 Hz), 1.65-1.52 (1H, m), 1.41-1.05 (6H, m), 1.25 (3H, t, *J* = 7.0 Hz), 1.15 (3H, d, *J* = 6.9 Hz), 0.87 (3H, d, *J* = 6.6 Hz); ^{13}C NMR: (75 MHz, $CDCl_3$) δ 177.0, 173.9, 136.4, 128.7, 128.3, 128.3, 66.2, 60.4, 41.5, 37.6, 36.6, 34.7, 30.7, 22.5, 19.5, 18.2, 14.5; HRMS (ES+) Calcd. for $C_{19}H_{29}O_4$ $[M+H]^+$, 321.2060. Found 321.2038.

(3*R*,5*S*,6*R*)-6-Ethyl-3,5-dimethyltetrahydro-2*H*-pyran-2-one (10)



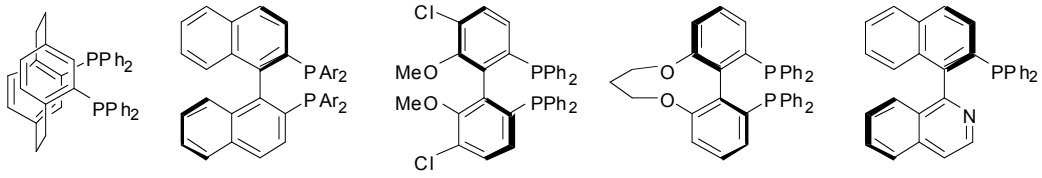
To a solution of (-)-(2*R*, 4*S*)-2,4-Dimethyl-5-oxo-heptanoic acid **3b** (50.0 mg, 0.291 mmol) in THF (2 mL) at -78 ºC was added $LiBHEt_3$ (0.64 mL, 1M in THF, 0.64 mol) and allowed to warm to room temperature overnight. Diethyl ether (3 mL) and HCl (1 mL, 1M) was added

dropwise and the reaction stirred at room temperature for 30 minutes. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 5 mL) and the organic layers combined, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was then purified *via* column chromatography (9:1 hexane – ethyl acetate) to afford the title compound (44.5 mg, 98%, 87:13 mixture of *anti:syn* diastereomers) as a colourless oil. All spectroscopic data was identical to that described by Mori *et al.*[7]

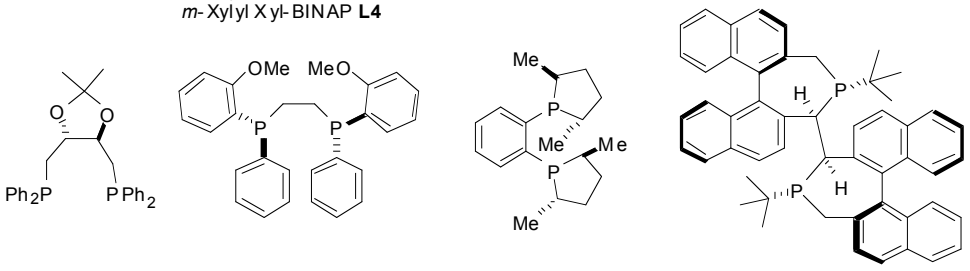
[7] Masuda, Y.; Fujita, K.; Mori, K. *Biosci. Biotechnol. Biochem.* **2003***, 67*, 1744-1752.

Detailed Rh Ligand Screen

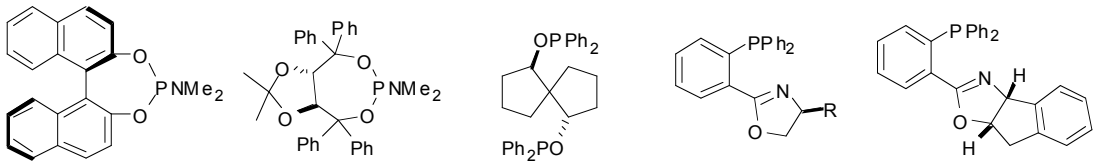
Entry	Ligand	Yield (%)	ee (%)
1	PHANEPHOS **L1**	47	3
2	BINAP **L2**	27	66
3	Tol-BINAP **L3**	15	61
4	Xyl-BINAP **L4**	4	63
5	Cl-MeO-BIPHEP **L5**	15	60
6	TUNEPHOS **L6**	12	22
7	QUINAP **L7**	21	7
8	DIOP **L8**	21	14
9	DIPAMP **L9**	3	25
10	Me-DUPHOS **L10**	7	60
11	BINAPHANE **L11**	trace	-
12	MONOPHOS **L12**	4	15
13	TADDOL-P-NMe$_2$ **L13**	n.r.	-
14	CTH-SPIROP **L14**	17	17
15	*i*-Pr-PHOX **L15**	68	72
16	***t*-Bu-PHOX L16**	**64**	**79**
17	Indane-PHOX **L17**	54	50



PHANEPHOS **L1** Ar = Ph BINAP **L2** Cl-MeO-BIPHEP **L5** TUNEPHOS **L6** QUINAP **L7**
p-Tolyl Tol-BINAP **L3**
m-Xylyl Xyl-BINAP **L4**

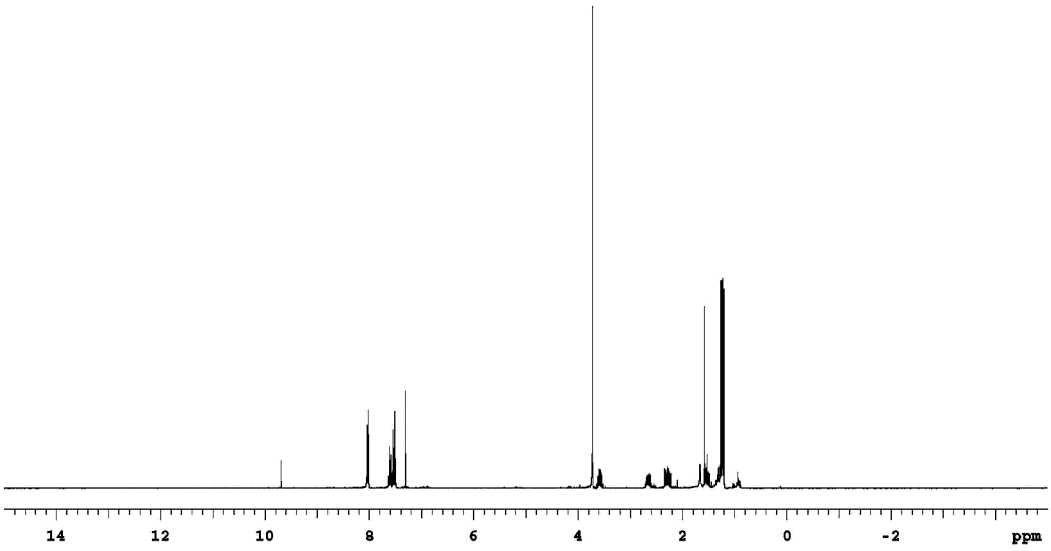


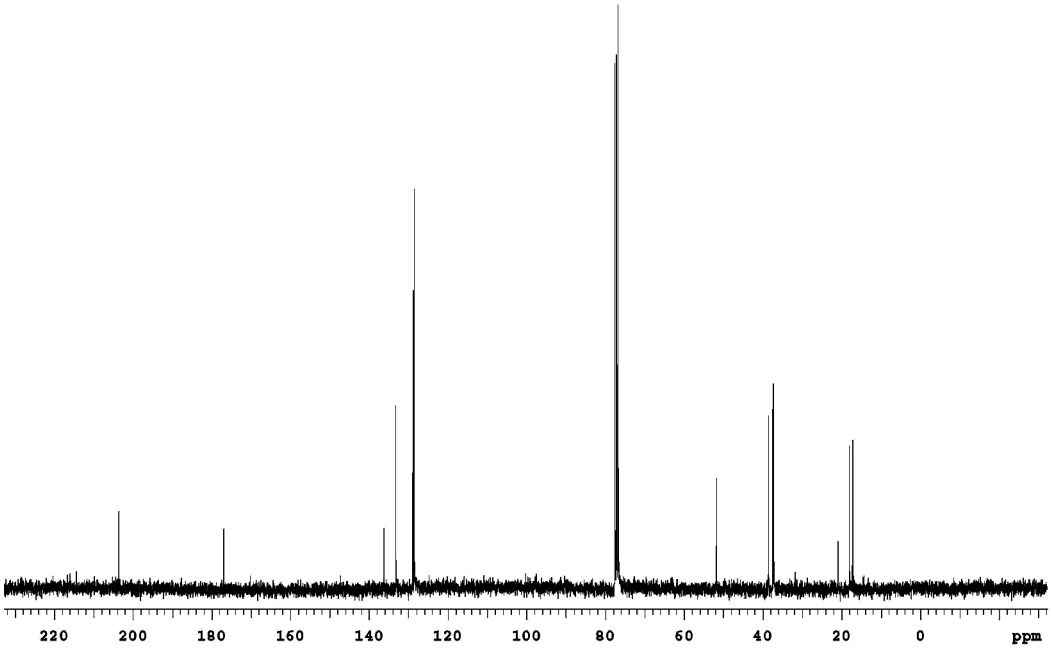
DIOP **L8** DIPAMP **L9** Me-DUPHOS **L10** BINAPHANE **L11**



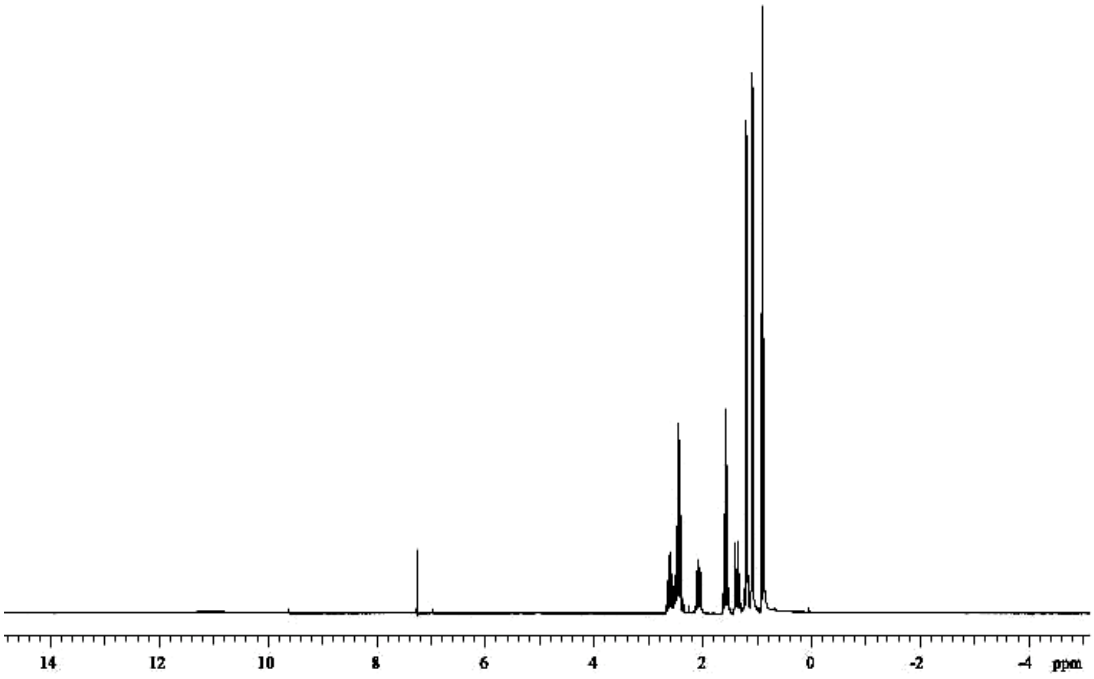
MONOPHOS **L12** TADDOL-P-NMe$_2$ **L13** CTH-SPIROP **L14** R = *i*-Pr *i*-Pr-PHOX **L15** Indane-PHOX **L17**
t-Bu *t*-Bu-PHOX **L16**

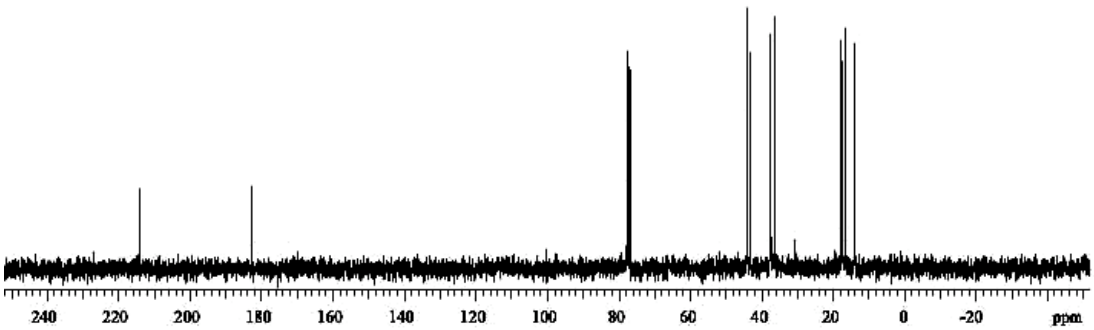
Spectra for **2c**



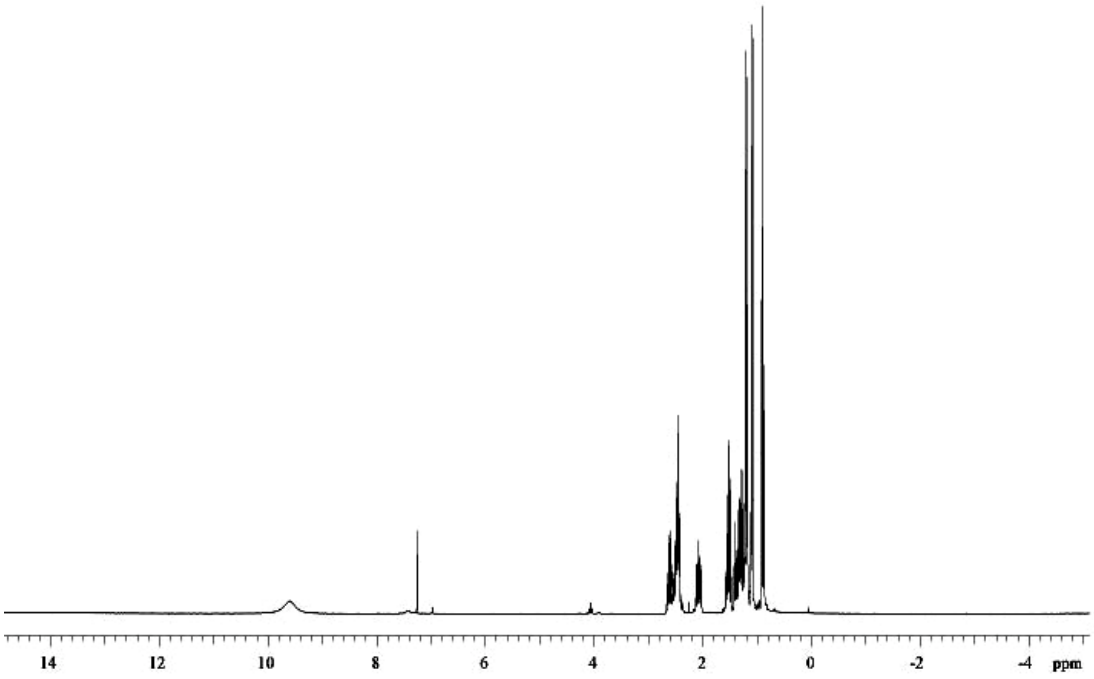


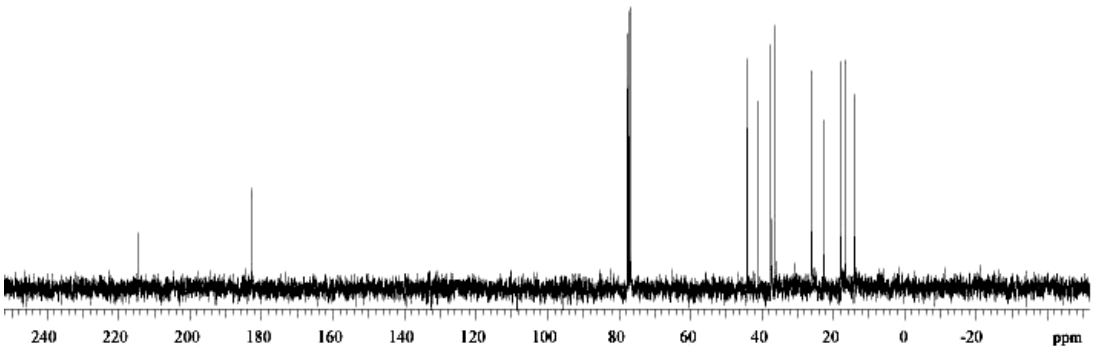
Spectra for **2d**



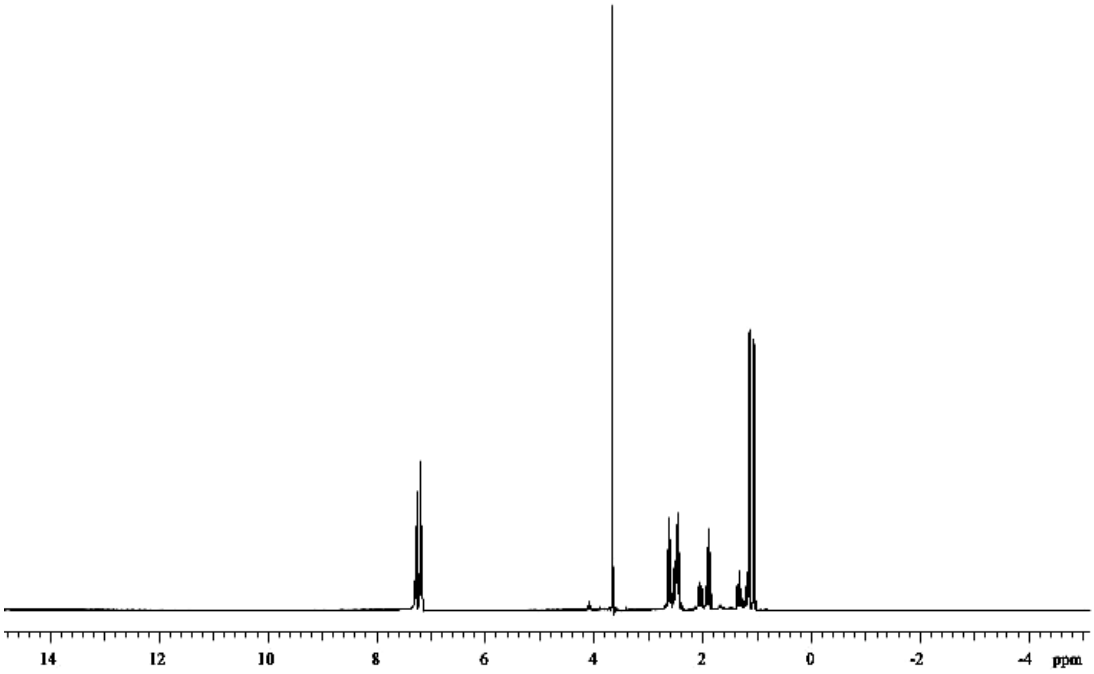


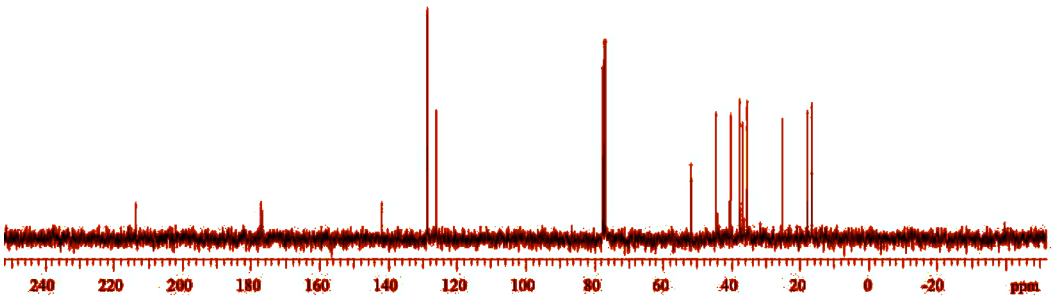
Spectra for compound **2e**



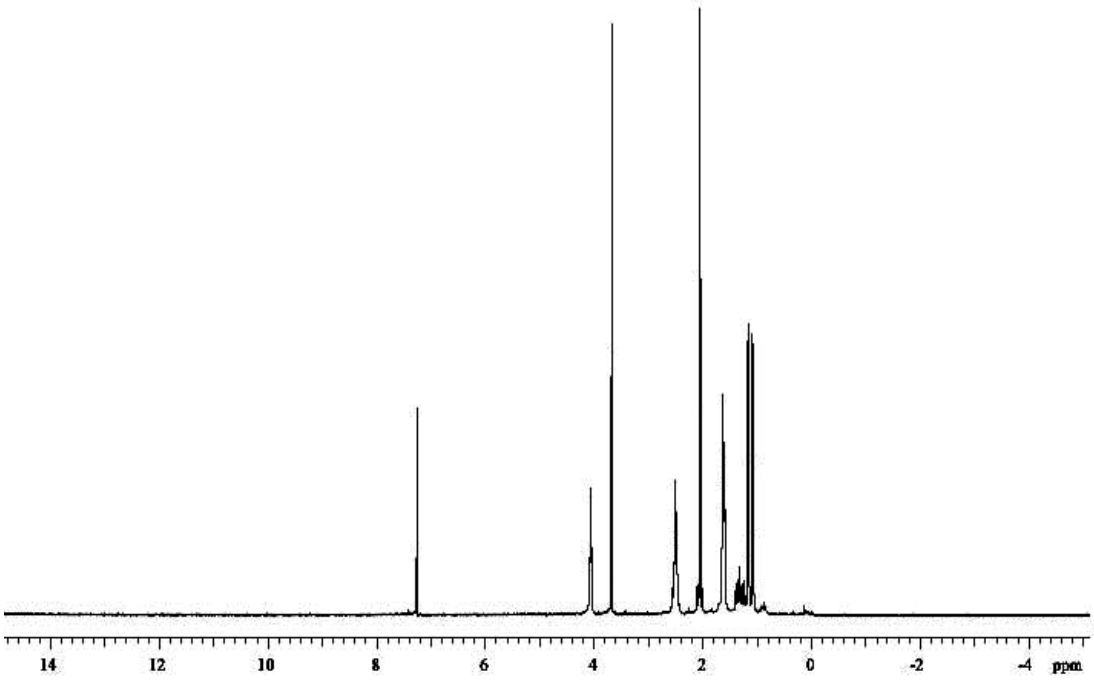


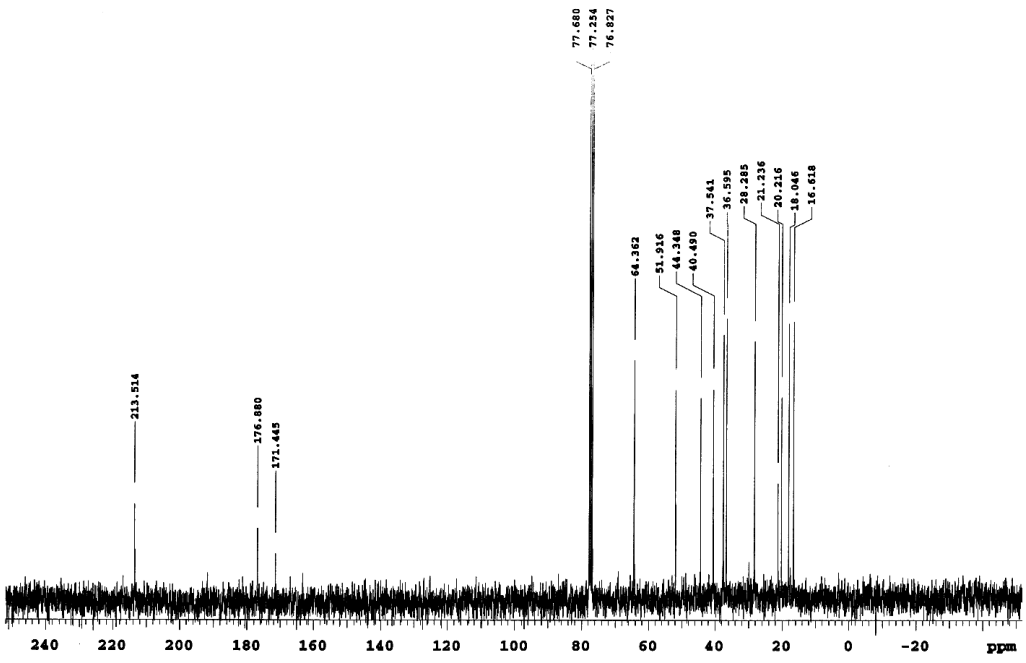
Spectra for compound **2f**



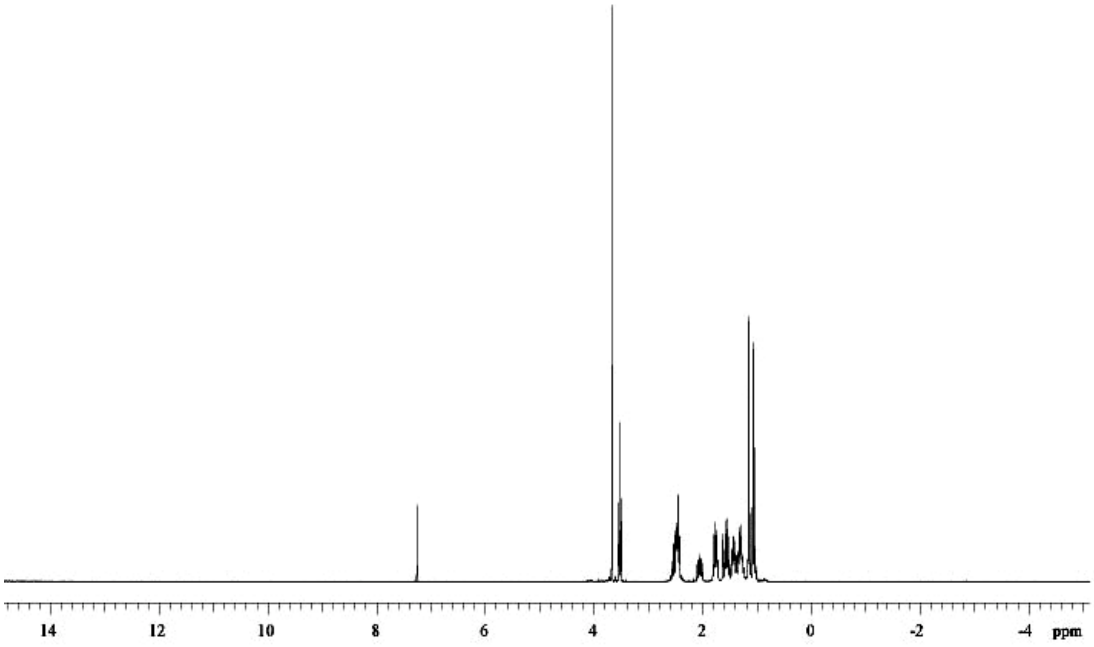


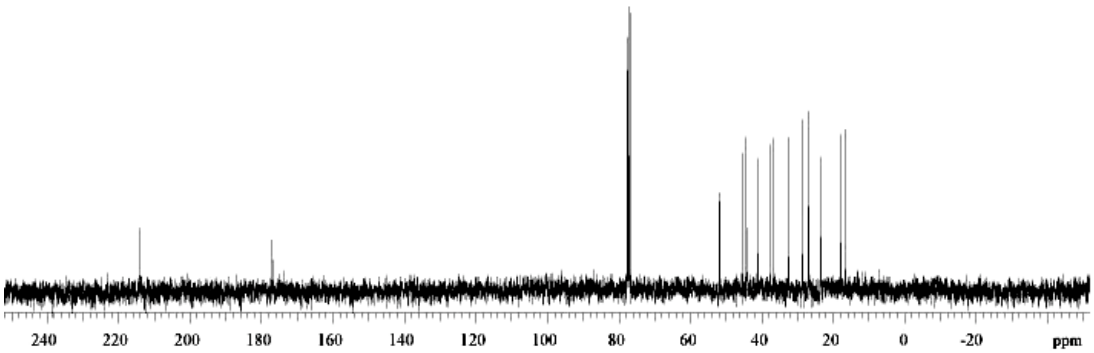
Spectra for **2g**



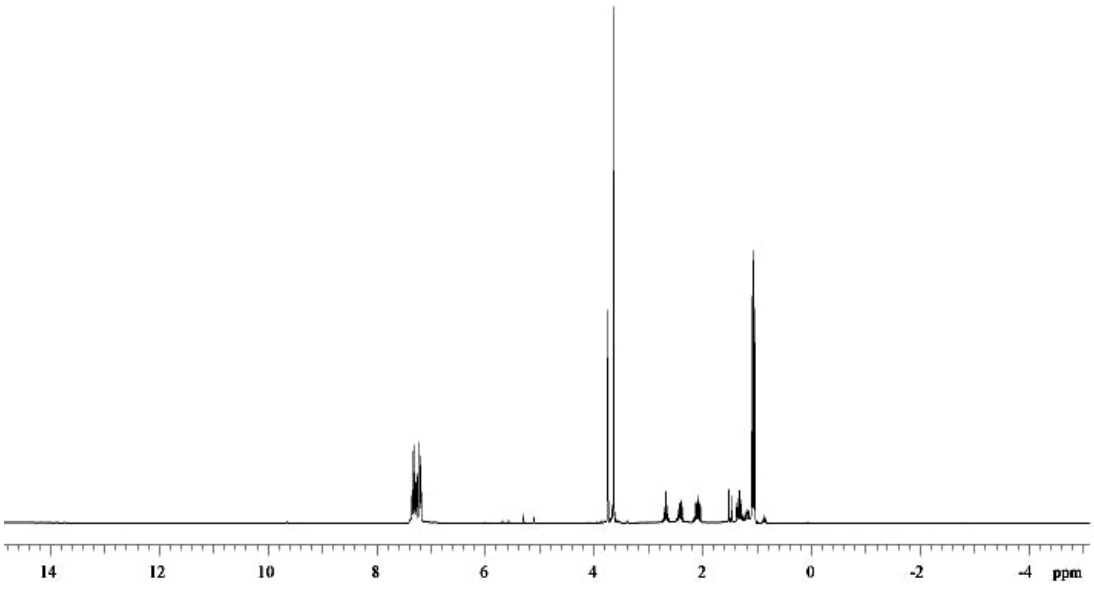


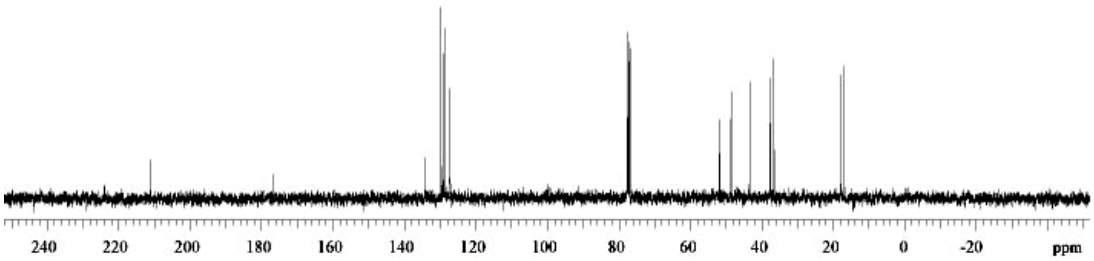
Spectra for **2h**



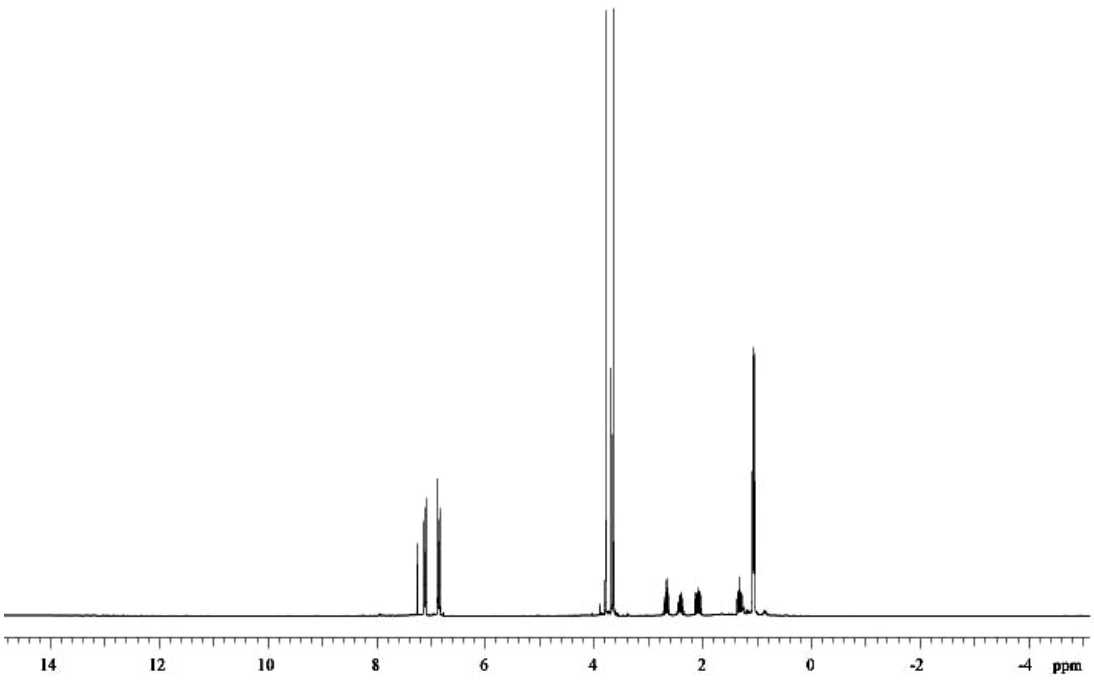


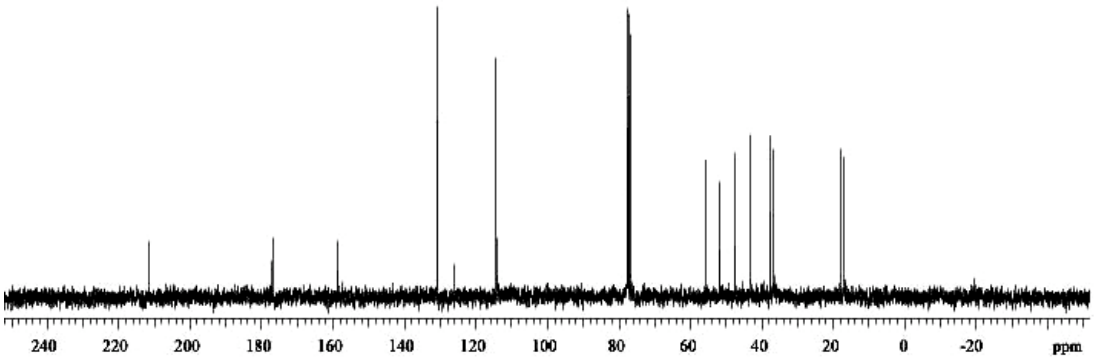
Spectra for **2i**



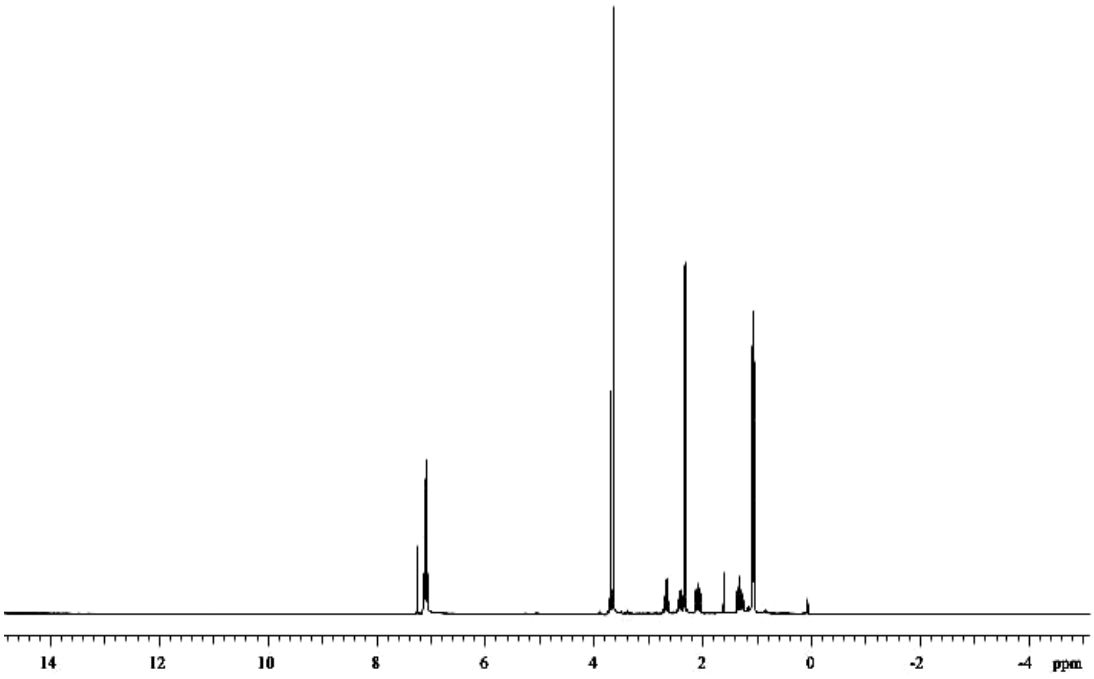


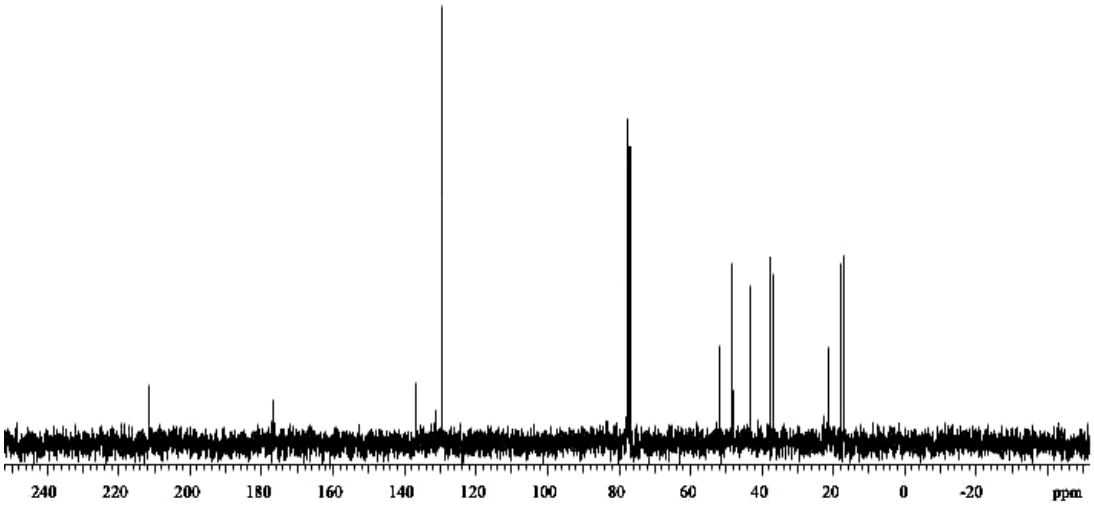
Spectra for **2j**



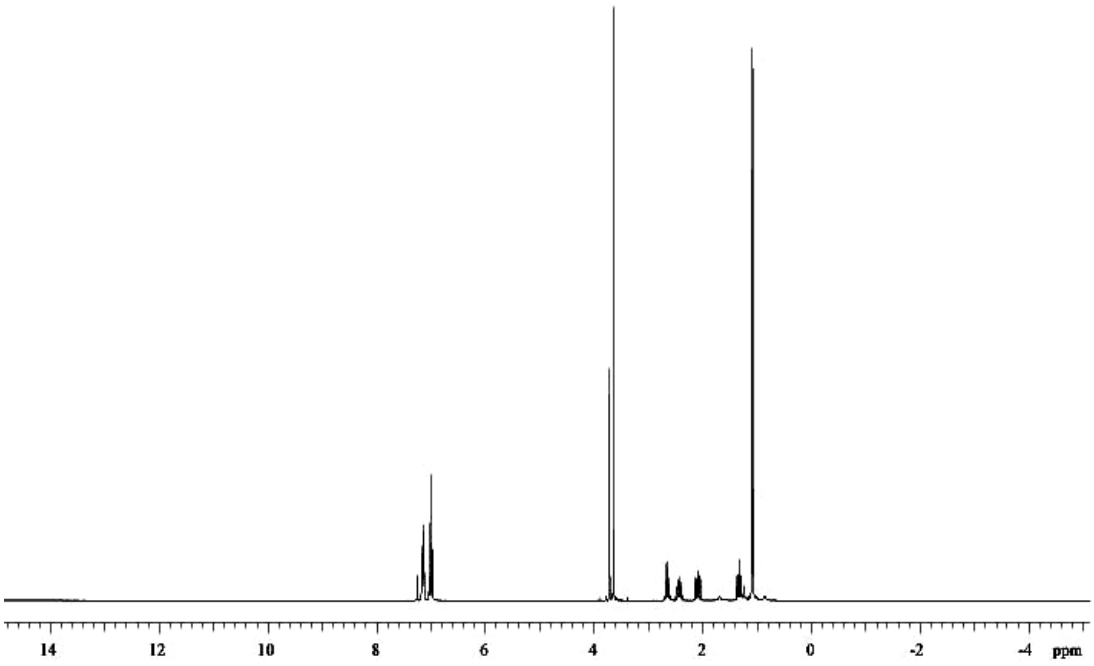


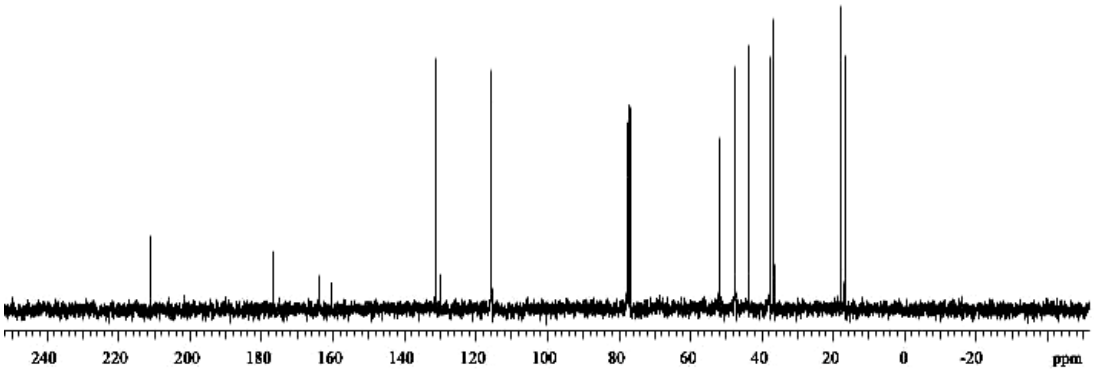
Spectra for **2k**



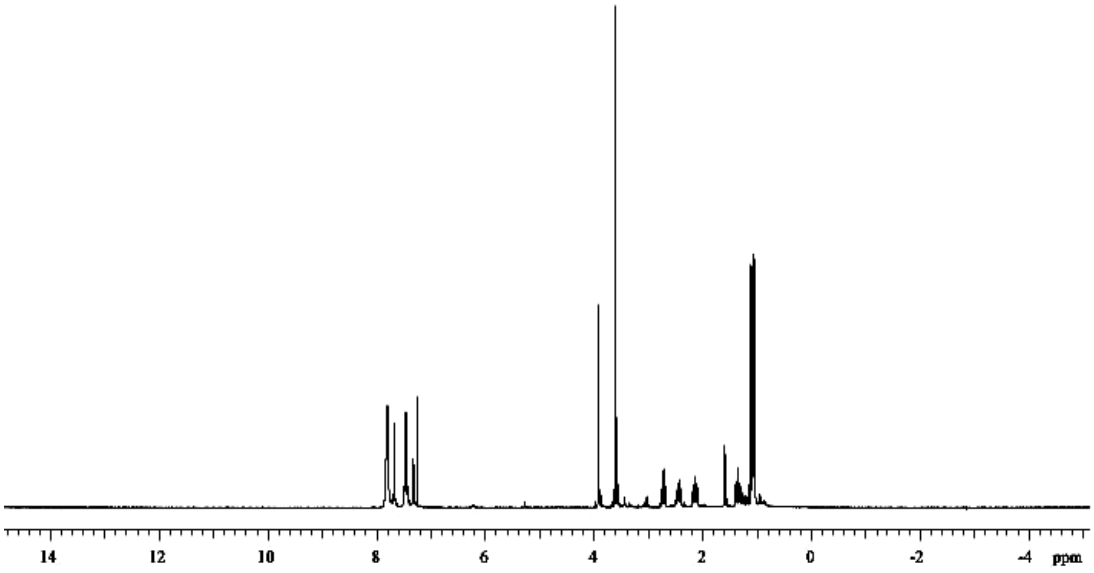


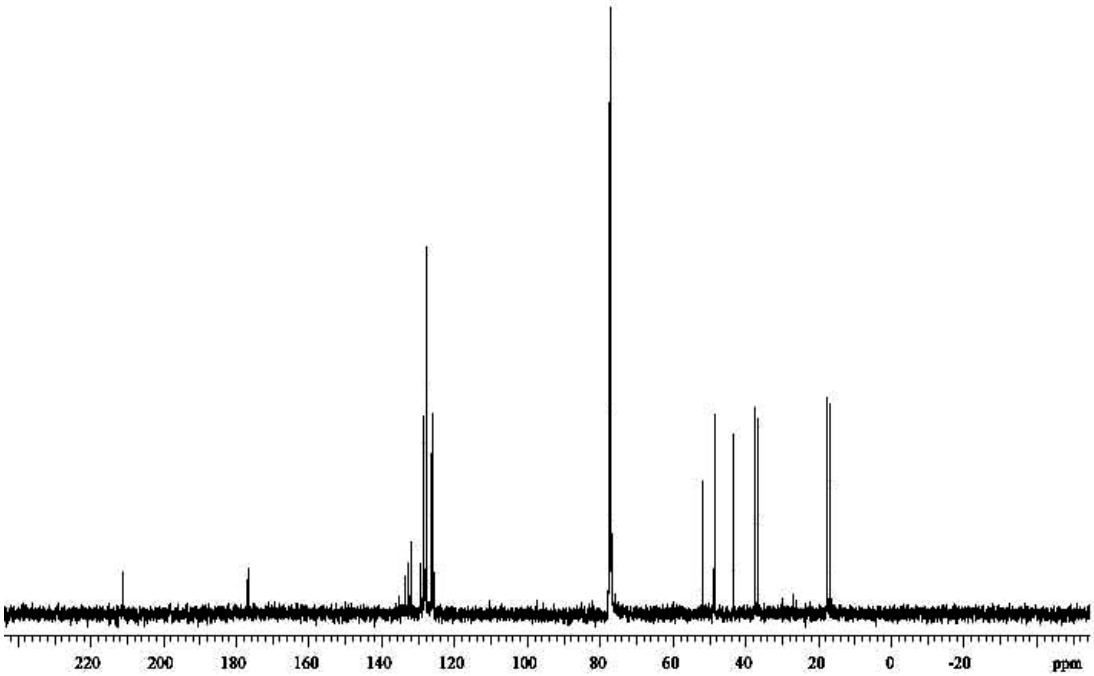
Spectra for **2l**



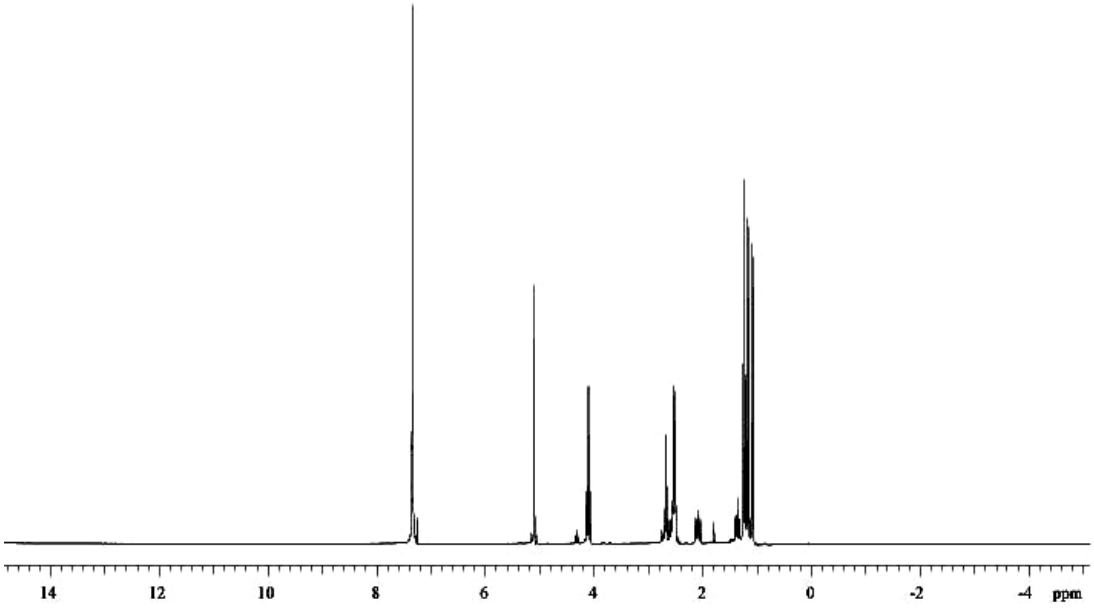


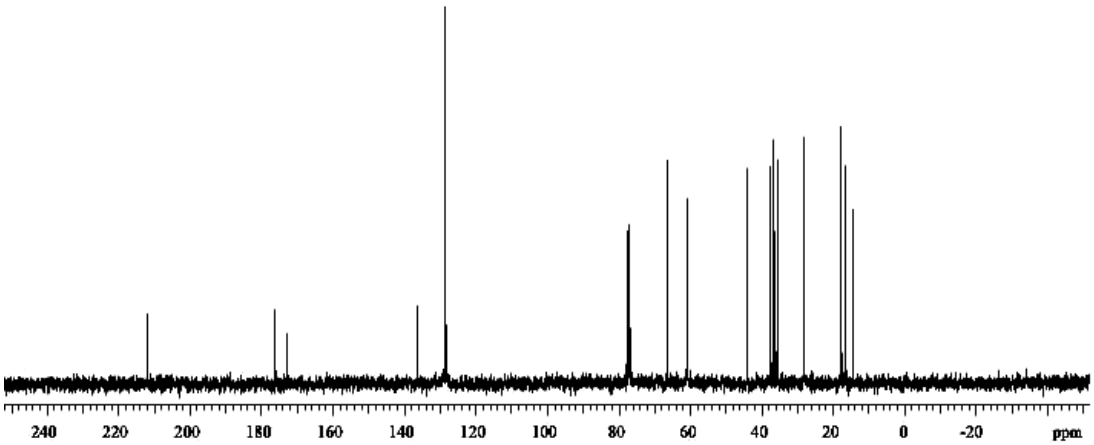
Spectra for **2m**



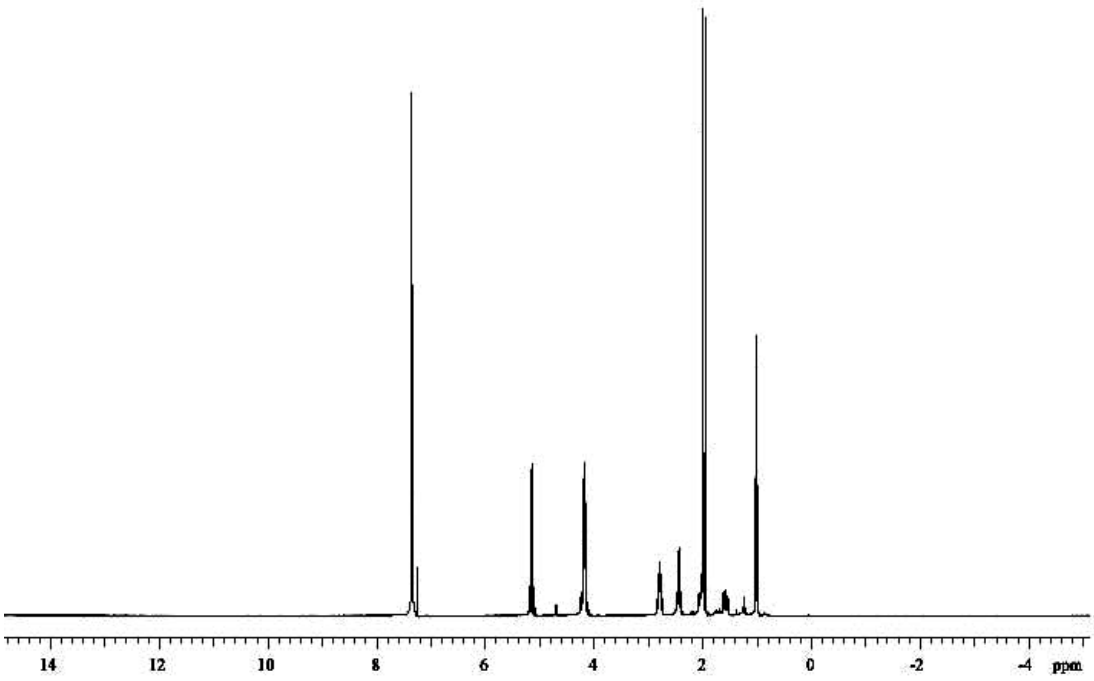


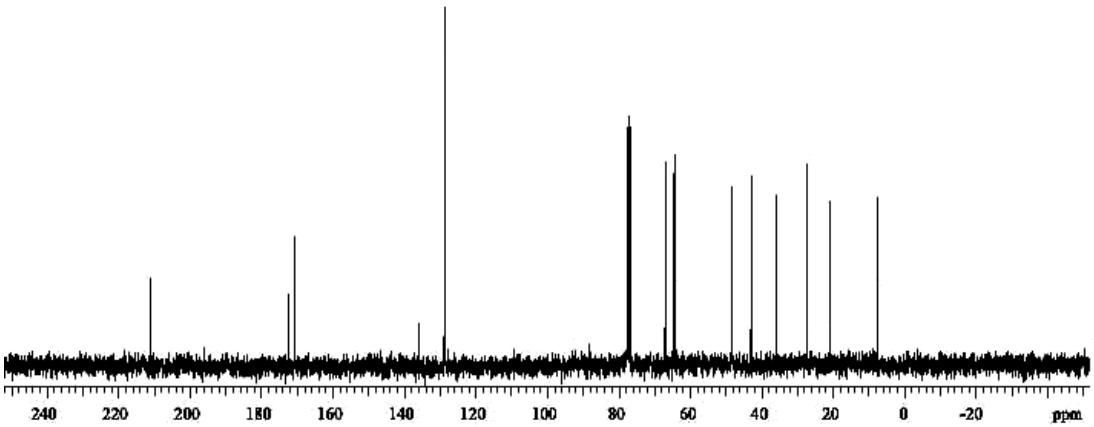
Spectra for **2n**





Spectra for **7**





Spectra for **8**