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Synthesis of non-steroidal 2-methoxyestradiol mimetics based on the bicyclo[3.3.1]nonane structural motif

Evgeniya V. Nurieva, Nikolay A. Zefirov, Alexandra V. Mamaeva, Yuri K. Grishin, Sergei A. Kuznetsov and Olga N. Zefirova

Computer overlay of the structures was carried out using visualization system USCF Chimera.

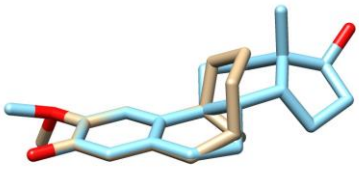


Figure S1 Computer superimposition of 2-methoxyestradiol and structural template **2a** in the *distorted chair – boat* conformation created using visualization system USCF Chimera.

General information

All reaction temperatures correspond to internal temperatures unless otherwise noted. Solvents for the reactions, extraction and chromatography were of technical grade and were distilled from the standard drying agents. Flash and column chromatography was performed on silica gel Acros (40–60 μm). Reaction course was monitored by thin-layer chromatography on "Silufol-UV254" plates. ^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature on spectrometer Bruker Avance 400 and Agilent 400 MR in $CDCl_3$ at 400 and 100 MHz correspondingly. Chemical shifts are referenced to solvent signals (δ 7.26 ppm ^{1}H; δ 77.0 ppm ^{13}C). Elemental analysis was performed on CNH analyser "Vario Micro Cube". Infrared spectra (IR) were registered on Fourier Transform IR spectrometer IR-200 (Thermo Nicolet) in KBr and presented in cm^{-1}. Melting points (uncorrected) were determined in sealed capillary tubes. MALDI-TOF mass spectra were registered using VISION-2000 spectrometer.

1-Benzyloxy-4-bromo-2-methoxybenzene was obtained as described [1, 2].

***rac*-5-Butylcyclohex-2-en-1-one (6)** was synthesized according to the literature [3] from ethyl acetoacetate (1.97 ml, 15 mmol), *(E)*-hept-2-enal (1.68 g, 15 mmol) and potassium *tert*-butoxide (0.008 g, 0.071 mmol). Chromatography of the crude product [1:7, then 1:5, EtOAc/petroleum ether (40–70°C)] gave product **6** (colourless oily liquid; 1.412 g; yield 62%).

^{1}H NMR (δ): 0.90 (3H, t, *J*=6.6 Hz, Me), 1.22–1.45 (6H, m), 1.98–2.19 (3H, m), 2.40–2.58 (2H, m), 6.01 (1H, d, *J*=9.8 Hz, H^2), 6.97 (1H, ddd, *J*=9.8, 5.5, 2.1 Hz, H^3). NMR ^{1}H spectroscopic data are in accordance with literature [4].

^{13}C NMR (δ): 13.95 (Me), 22.64, 28.63, 32.27, 35.14, 35.44, 44.51 (C^6), 129.70 (C^2), 149.91 (C^3), 200.15 (C=O).

IR (cm^{-1}): 1041; 1094; 1156; 1174; 1217; 1238; 1373; 1466; 1616; 1677; 1712; 1731; 2860; 2929; 2956.

***rac*-5-(2-Benzyloxyethyl)cyclohex-2-en-1-one (7)** was synthesized analogously to compound **6** (see above) from ethyl acetoacetate (0.867 g, 6.67 mmol), *(E)*-5-benzyloxypent-2-enal (obtained in several steps as described [5]) (1.27 g, 6.67 mmol) and potassium *tert*-butoxide (0.183 g, 1.63 mmol). Product **7** was isolated as a colourless oily liquid (0.760 g, yield 50%) [6].

^{1}H NMR (δ): 1.27 (1H, m), 1.72 (1H, m), 2.09–2.20 (2H, m), 2.33 (1H, m), 2.47 (1H, dt, *J*=18.3, 4.6 Hz), 2.55 (1H, dd, *J*=15.9, 3.3 Hz), 3.55 (2H, t, *J*=6.3 Hz, CH_2CH_2O), 4.50 (2H, s, CH_2Ph), 6.04 (1H, dd, *J*=10.0, 1.4 Hz, H^2), 6.97 (1H, ddd, *J*=10.0, 5.6, 2.7 Hz, H^3), 7.24–7.45 (5H, m, Ph).

^{13}C NMR (δ): 32.17; 32.37; 35.49; 44.29 (C^6); 67.40 (CH_2CH_2O); 73.09 (CH_2Ph); 127.64; 128.41; 128.76; 129.76 (C^2); 138.27; 149.72 (C^3); 199.65 (C=O).

IR (cm^{-1}): 1028; 1101; 1172; 1205; 1248; 1365; 1389; 1454; 1496; 1675; 1724; 2861; 2925; 3032; 3063.

Found, %: C, 78.30; H, 7.91. Anal Calcd for $C_{15}H_{18}O_2$, %: C, 78.23; H, 7.88.

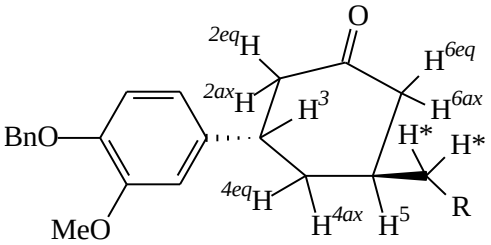


Figure S2 The numeration of atoms in compounds **8a,b**.

***rac-trans*-3-(4-Benzyloxy-3-methoxyphenyl)-5-butylcyclohexanone** (**8a**). A mixture of 1-benzyloxy-4-bromo-2-methoxybenzene (12.76 g, 43.55 mmol) in THF (30 ml) and magnesium turnings (1.04 g, 43.5 mmol) preactivated with iodine (0.05 mg) and 1,2-dibromoethane (2 ml) was refluxed under argon atmosphere until complete dissolving of magnesium. Then a solution of CuBr·Me_2S (0.453 g, 2.2 mmol) and hexamethylphosphoramide (HMPA, 16.33 g, 91.3 mmol) in THF (20 ml) was syringed at room temperature. The mixture was cooled to –78ºC and a solution of *rac*-5-butylcyclohex-2-en-1-one **6** (5.10 g, 33.55 mmol) and Me_3SiCl (6.150 g, 57.0 mmol) in THF (10 ml) was added dropwise (30 min) under argon atmosphere. The mixture was stirred at –78ºC for 3 h and then for 10 h at room temperature, diluted with Et_3N (20 ml) and petroleum ether (200 ml) and washed with water (5×80 ml). The combined organic layers were dried over Na_2SO_4 and evaporated in vacuum. Column chromatography of the residue [1:7, then 1:5 EtOAc/petroleum ether (40–70ºC)] gave product **8a** (yellowish oil; 4.30 g; yield 35%).

^{1}H NMR (δ): 0.88 (3H, t, *J*=6.6 Hz, Me), 1.25–1.34 (6H, m), 1.91 (1H, ddd, *J*=14.2, 6.9, 4.2 Hz, H^{4eq}), 2.03 (1H, ddd, *J*=14.2, 9.4, 3.9 Hz, H^{4ax}), 2.05 (1H, m, H^5), 2.22 (1H, dd, *J*=13.9, 6.1 Hz, H^{6ax}), 2.54 (1H, dd, *J*=13.9, 5.1 Hz, H^{6eq}), 2.58 (2H, d, *J*=7.3 Hz, H^2), 3.27 (1H, m, *J*=9.4, 7.3 Hz, H^3), 3.90 (3H, s, OMe), 5.14 (2H, s, OCH_2Ph), 6.69 (1H, dd, *J*=8.2, 2.1 Hz, $H^{6\text{-}Ar}$), 6.76 (1H, d, *J*=2.1 Hz, $H^{2\text{-}Ar}$), 6.83 (1H, d, *J*=8.2 Hz, $H^{5\text{-}Ar}$), 7.31 (1H, d, *J*=7.1 Hz, Ph), 7.37 (2H, m, Ph), 7.43–7.46 (2H, m, Ph).

NOESY 1D: H^3–2H* (2.4%), H^3–$H^{4ax,4eq}$ (0.4%, 1.1%), H^3–$2H^2$ (2.7%).

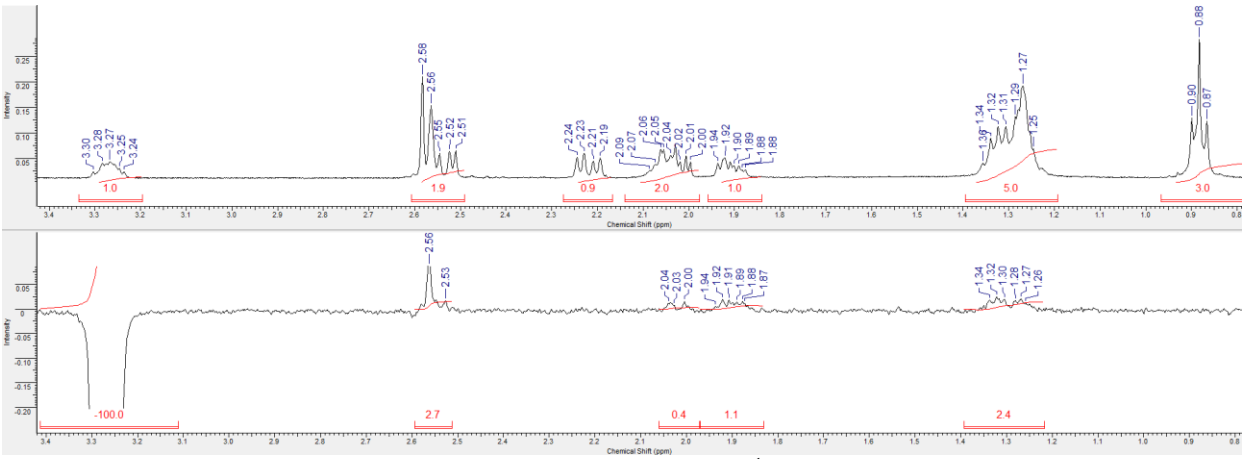


Figure S3 Spectral data for the compound **8a** (at the top – ^{1}H NMR, at the bottom – NOESY 1D, irradiation of H^3 proton resonance).

^{13}C NMR (δ): 14.04 ($CH_2\underline{C}H_3$); 22.69; 29.26; 33.92; 34.36; 37.42; 39.20 (C^3); 46.80 (C^6); 47.80 (C^2); 56.05 (OMe); 71.12 ($\underline{C}H_2Ph$); 110.95 ($C^{2\text{-}Ar}$); 114.06 ($C^{5\text{-}Ar}$); 118.70 ($C^{6\text{-}Ar}$); 127.26; 127.81; 128.54; 134.72; 137.26; 146.77 ($C^{4\text{-}Ar}$); 149.60 ($C^{3\text{-}Ar}$); 211.77 (C=O).

IR (cm^{-1}): 1024; 1078; 1142; 1182; 1226; 1251; 1353; 1380; 1420; 1454; 1464; 1514; 1591; 1605; 1708; 2857; 2871; 2926; 2955; 3033; 3064.

MS m/z: 389 (M^+ + Na), 405 (M^+ + K).

Found, %: C, 78.66; H, 8.27. Anal Calcd for $C_{24}H_{30}O_3$, %: C, 78.65; H, 8.25.

***rac-trans*-5-(2-Benzyloxyethyl)-3-(4-benzyloxy-3-methoxyphenyl)cyclohexanone (8b)**. To a solution of commercially available 4-benzyloxy-3-methoxyphenylboronic acid (0.445 g, 1.72 mmol) in a dioxane – H_2O mixture (6:1, 5 ml) and $NaHCO_3$ (0.005 g) was added $[Rh(COD)Cl]_2$ (0.009 g) and compound **7** (0.255 g, 1.10 mmol) under argon atmosphere. The mixture was stirred at room temperature for 24 h, diluted with water (10 ml), extracted with CH_2Cl_2 (3×15 ml) and washed with brine. The combined organic layers were dried over Na_2SO_4 and evaporated in vacuum. Column chromatography of the residue [1:7, then 1:5 EtOAc/petroleum ether (40–70°C)] gave product **8b** (colourless oily liquid; 0.290 g; yield 59%).

^{1}H NMR (δ): 1.64 (2H, dt, *J*=6.9, 6.3 Hz, $C\underline{H}_2CH_2O$), 1.91 (1H, ddd, *J*=13.8, 6.2, 4.1 Hz, H^{4eq}), 2.03 (1H, ddd, *J*=13.8 Hz, 9.3, 4.0 Hz, H^{4ax}), 2.21 (1H, dd, *J*=13.9, 6.2 Hz, H^{6ax}), 2.30 (1H, m, H^5), 2.52 (1H, dd, *J*=13.9, 5.1 Hz, H^{6eq}), 2.56 (2H, d, *J*=7.3 Hz, H^2), 3.25 (1H, m, H^3), 3.47 (2H, m, $C\underline{H}_2OBn$), 3.84 (3H, s, OMe), 4.44 (2H, s, $C\underline{H}_2Ph$), 5.11 (2H, s, $C\underline{H}_2Ph$), 6.63 (1H, dd, *J*=8.2, 2.0 Hz, $H^{6\text{-}Ar}$), 6.71 (1H, d, *J*= 2.0 Hz, $H^{2\text{-}Ar}$), 6.80 (1H, d, *J*=8.2 Hz, $H^{5\text{-}Ar}$), 7.24–7.30 (6H, m, Ph), 7.33–7.36 (2H, m, Ph), 7.41–7.43 (2H, m, Ph).

NOESY 1D: H^3–2H* (3.0%), H^3–$H^{4ax,4eq}$ (0.4%, 1.5%), H^3–$2H^2$(2.8%).

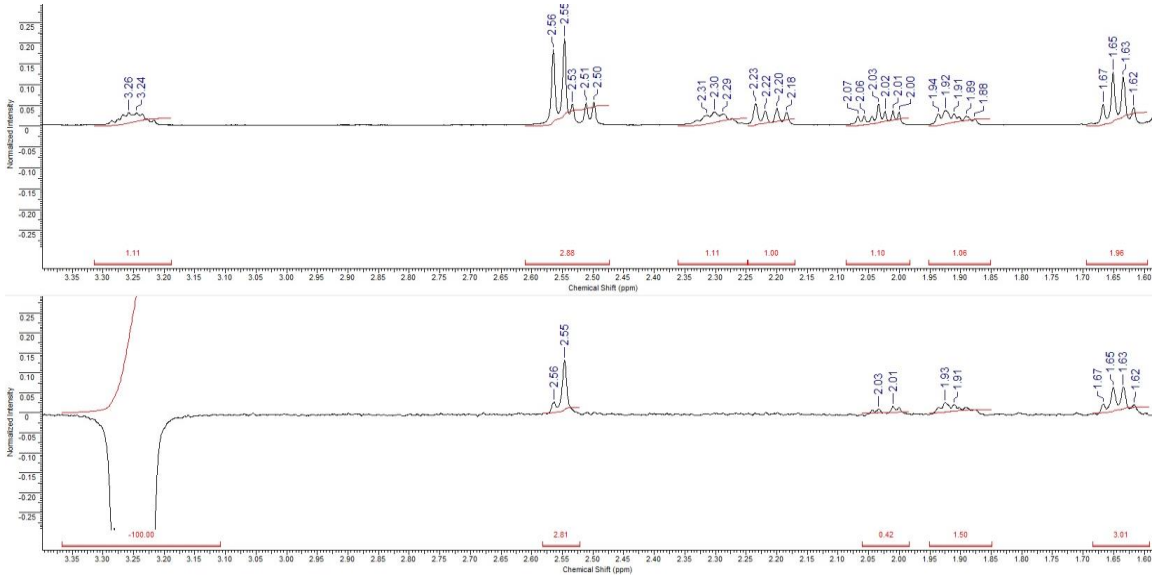


Figure S4 Spectral data for the compound **8b** (at the top – ^{1}H NMR, at the bottom – NOESY 1D, irradiation of H^3 proton resonance).

^{13}C NMR (δ): 31.46 (C^5); 33.92 ($\underline{C}H_2CH_2OBn$); 37.38 (C^4); 39.24 (C^3); 46.49 (C^6); 47.72 (C^2); 55.98 (OMe); 67.78 ($\underline{C}H_2OBn$); 71.04 ($\underline{C}H_2Ph$); 73.01 ($\underline{C}H_2Ph$); 110.84 ($C^{2\text{-}Ar}$); 113.97 ($C^{5\text{-}Ar}$); 118.63 ($C^{6\text{-}Ar}$); 127.20; 127.57; 127.78; 128.36; 128.51; 137.21; 137.37; 138.22; 146.75 ($C^{4\text{-}Ar}$); 149.54 ($C^{3\text{-}Ar}$); 208.86 (C=O).

MS m/z: 467 (M^+ + Na), 483 (M^+ + K).

Found, %: C, 78.30; H, 7.23. Anal Calcd for $C_{29}H_{32}O_4$, %: C, 78.35; H, 7.26.

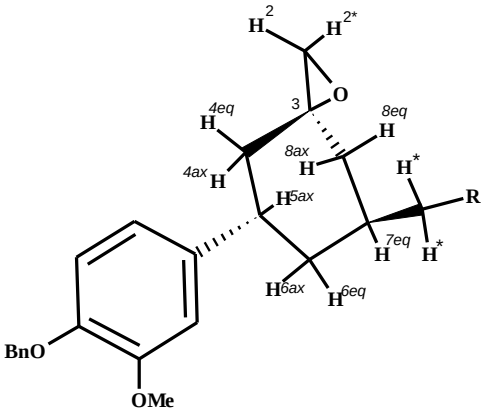


Figure S5 The numeration of atoms in compounds **9a,b**.

(3*RS*,5*RS*,7*RS*)-5-(4-Benzyloxy-3-methoxyphenyl)-7-butyl-1-oxaspiro[2.5]octane (9a). A solution of NaH (60% dispersion in mineral oil, 0.274 g, 9.3 mmol) and $Me_3S^+O\ I^-$ (1.38 g, 6.28 mmol) in DMSO (7 ml) was stirred until the gas evolution terminated (~15 min). After additional stirring in the ultrasound bath (10 min), ketone **8a** (2.09 g, 5.71 mmol) in DMSO (5 ml) was added. The mixture was kept at room temperature for 1 h, at 55°C for 1.5 h, and then poured into ice water (200 ml), extracted with CH_2Cl_2 (3×50 ml) and washed with brine. The combined organic layers were dried over Na_2SO_4 and evaporated in vacuum. Column chromatography of the residue [1:3, EtOAc/petroleum ether (40–70°C)] gave product **9a** (yellowish oil; 1.034 g; yield 48%).

^{1}H NMR (δ): 0.91 (3H, t, *J*=6.8 Hz, Me), 1.25–1.38 (5H, m, H^8 + $4H^{n\text{-}Bu}$), 1.51 (1H, m, *J*=13.7, 2.0, 1.8 Hz, H^{4eq}), 1.61 (2H, q, *J*=7.5 Hz, C^7CH_2*n*-Pr), 1.73 (1H, ddd, *J*=13.4, 11.4, 4.1 Hz, H^{6ax}), 1.87 (1H, m, *J*=13.4 Hz, H^{6eq}), 1.93–2.06 (3H, m, H^{4ax} + H^7 + H^8), 2.51 (1H, d, *J*=4.8 Hz, H^2), 2.56 (1H, d, *J*=4.8 Hz, H^{2*}), 3.09 (1H, tt, *J*=11.4, 3.6 Hz, H^5), 3.90 (3H, m, OMe), 5.14 (2H, s, OCH_2Ph), 6.72 (1H, dd, *J*=8.3, 1.8 Hz, $H^{6\text{-}Ar}$), 6.79 (1H, d, *J*=1.8 Hz, $H^{2\text{-}Ar}$), 6.83 (1H, d, *J*=8.3 Hz, $H^{5\text{-}Ar}$), 7.31 (1H, d, *J*=7.3 Hz), 7.37 (2H, m), 7.45 (2H, d, *J*=7.3 Hz).

NOESY 1D: H^5–$2H^{n\text{-}Bu}$ (3.7%), H^5–H^{4eq} (1.3%), H^5–H^{6eq} (0.5%), $2H^2$–H^{4eq} (2.1%), $2H^2$–H^8 (0.4%).

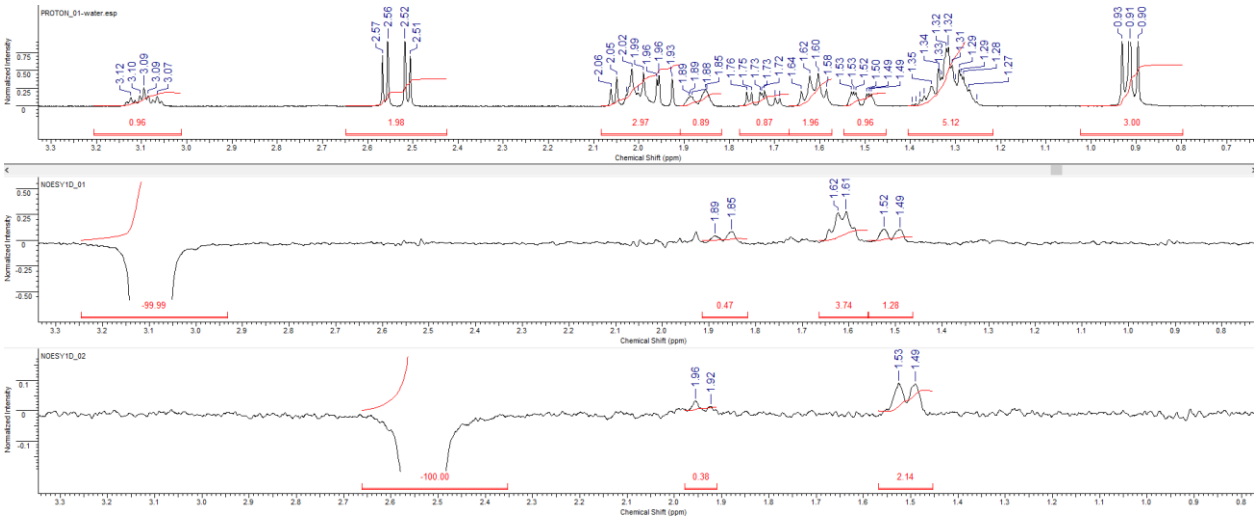


Figure S6 Spectral data for the compound **9a** (at the top – ^{1}H NMR; in the middle – NOESY 1D, irradiation of H^5 proton resonance; at the bottom – NOESY 1D, irradiation of $2H^2$ proton resonances).

^{13}C NMR (δ): 14.16 (Me); 22.81 ($CH_2^{n\text{-}Bu}$); 30.29 ($CH_2^{n\text{-}Bu}$); 32.70 (C^7CH_2-*n*-Pr); 33.78 (C^7); 35.72 (C^5); 36.33 (C^8); 36.41(C^6); 41.33 (C^4); 51.94 (C^2); 56.02 (OMe); 57.33 (C^3); 71.15

(CH$_2$Ph); 111.15 (C$^{2\text{-}Ar}$); 114.10 (C$^{5\text{-}Ar}$); 118.45 (C$^{6\text{-}Ar}$); 127.24; 127.72; 128.48; 137.40; 139.59; 146.49 (C$^{4\text{-}Ar}$); 149.48 (C$^{3\text{-}Ar}$).

MS m/z: 403 (M^+ + Na), 419 (M^+ + K).

Found, %: C, 78.87; H, 8.43. Anal Calcd for $C_{25}H_{32}O_3$, %: C, 78.91; H, 8.48.

(3*RS*,5*RS*,7*SR*)-5-(4-Benzyloxy-3-methoxyphenyl)-7-(2-benzyloxyethyl)-1-oxaspiro-[2.5]octane (9b) was synthesized from ketone **8b** (0.135 g, 0.30 mmol) in DMSO (0.4 ml), NaH (0.009 g, 0.375 mmol) and $Me_3S^+O\ I^-$ (0.074 g, 0.336 mmol) in DMSO (0.5 ml) analogously to compound **9a**. Chromatography of the crude product [1:3, then 1:1, EtOAc/petroleum ether (40–70°C)] gave product **9b** (colourless oily liquid; 0.077 g; yield 55%).

^{1}H NMR (δ): 1.27 (1H, m, *J*=13.4 Hz, H^{8}), 1.51 (1H, m, *J*=13.6, 1.8, 1.6 Hz, H^{4eq}), 1.77 (1H, ddd, *J*=13.4, 11.7, 4.3 Hz, H^{6ax}), 1.88 (1H, m, *J*=13.5 Hz, H^{6eq}), 1.93–2.08 (4H, m, H^{4ax} + H^{8} + C^{7}CH$_2$CH$_2$O), 2.31 (1H, m, H^{7}), 2.50 (1H, d, *J*=4.7 Hz, H^{2}), 2.54 (1H, d, *J*=4.7 Hz, H^{2*}), 3.11 (1H, tt, *J*=11.7, 3.5 Hz, H^{5}), 3.57 (2H, m, C^{7}CH$_2$CH$_2$O), 3.87 (3H, s, OMe), 4.51 (2H, d, *J*=1.9 Hz, CH$_2$Ph), 5.14 (2H, s, CH$_2$Ph), 6.70 (1H, dd, *J*=8.2, 1.9 Hz, H$^{6\text{-}Ar}$), 6.78 (1H, d, *J*=1.9 Hz, H$^{2\text{-}Ar}$), 6.81 (1H, d, *J*=8.2 Hz, H$^{5\text{-}Ar}$), 7.26–7.39 (8H, m, Ph), 7.45–7.46 (2H, m, Ph).

^{13}C NMR (δ): 30.29; 32.57; 35.74; 35.77; 36.43; 41.10 (C^{4}); 51.79 (C^{2}); 55.90 (OMe); 57.16 (C^{3}); 68.57 (CH$_2$OBn); 71.04 (CH$_2$Ph); 72.72 (CH$_2$Ph); 111.02 (C$^{2\text{-}Ar}$); 114.02 (C$^{5\text{-}Ar}$); 118.34 (C$^{6\text{-}Ar}$); 127.15; 127.36; 127.49; 127.65; 128.22; 128.40; 137.31; 138.54; 139.27; 146.43 (C$^{4\text{-}Ar}$), 149.40 (C$^{3\text{-}Ar}$).

MS m/z: 481 (M^+ + Na).

Found, %: C, 78.60; H, 7.44. Anal Calcd for $C_{30}H_{34}O_4$, %: C, 78.57; H, 7.47.

Compounds (**10a**) **and (11a).** A solution of the oxirane **9a** (0.228 g, 0.6 mmol) in benzene (2 ml) and BF_3•Et_2O (0.085 g, 0.6 mmol) was stirred for 15 min, then poured into iced water (15 ml) and extracted with benzene (3×20 ml). The organic layers were combined and dried over Na_2SO_4 and evaporated in vacuum. Chromatography of the residue [1:5, then 1:3, EtOAc/petroleum ether (40–70°C)] gave sequentially products **11a** (colourless oily liquid, 0.054 g; yield 25%) and crude **10a** (yellowish oily liquid; 0.045 g, crude yield 20%).

(1*RS*,3*SR*)-3-(4-Benzyloxy-3-methoxyphenyl)-5-butylcyclohexanecarbaldehyde (**10a**):

^{1}H NMR (δ) (proton resonances are indicated for the 2:1 mixture of two diastereomers: 0.92 (1H, t, *J*=6.8 Hz, Me) 0.95 (2H, t, *J*=6.8 Hz, Me), 1.12–1.48 (7H, m), 1.66–1.76 (1H, m), 1.78–1.95 (1H, m), 1.99–2.10 (1H, m), 2.14–2.27 (2H, m), 2,38–2.50 (1H, m), 2.52–2.78 (1.3H, m), 3.11 (0.7H, m, H^{3}), 3.92 (2H, s, OMe), 3.94 (1H, s, OMe), 5.16 (1.3H, s, OCH$_2$Ph), 5.18 (0.7H, s, OCH$_2$Ph), 6.69–6.98 (3H, m), 7.30–7.48 (5H, m, Ph), 9.68 (0.7H, s, HC=O), 9.81 (0.3H, s, HC=O).

^{13}C NMR (δ), major isomer: 14.11 (Me); 22.90; 29.25 30.55; 31.92 (C^{5}); 31.98; 35.13 (C^{3}); 36.10; 36.30; 45.98 (C^{1}); 56.11 (OMe); 71.13 (CH$_2$Ph); 111.65 (C$^{2\text{-}Ar}$); 113.96 (C$^{5\text{-}Ar}$); 119.13 (C$^{6\text{-}Ar}$); 127.26; 127.77; 128.53; 137.45; 139.55; 146.33 (C$^{4\text{-}Ar}$); 149.97 (C$^{3\text{-}Ar}$); 204.86 (CHO).

***rac-exo*-5-Benzyloxy-11-butyl-4-methoxytricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene (11a):**

^{1}H NMR (δ): 0.87 (3H, t, *J*=6.8 Hz, Me), 1.13–1.34 (9H, m), 1.70–1.84 (4H, m), 2.26 (1H, m, H^{9}), 2.54 (1H, d, *J*=17.4 Hz, H^{8}), 2.93 (1H, m, H^{1}), 3.02 (1H, dd, *J*=17.4, 7.2 Hz, H^{8}), 3.90 (3H, s, OMe), 5.14 (2H, d, *J*=1.5 Hz, CH$_2$Ph), 6.60 (1H, s, H^{6}), 6.67 (1H, s, H^{3}), 7.32–7.42 (3H, m), 7.50 (2H, d, *J*=7.5 Hz).

^{13}C NMR (δ): 14.08 (Me); 23.02; 27.71 (C^{9}); 28.73 (C^{11}); 28.99; 31.78; 34.78 (C^{1}); 34.88 (C^{8}); 37.29; 40.70; 41.07; 56.06 (OMe); 71.17 (CH$_2$Ph); 111.71 (C^{3}); 113.82 (C^{6}); 127.32; 127.59; 128.39; 129.70 (C^{7}); 134.74 (C^{2}); 137.58; 146.26 (C^{5}); 147.40 (C^{4}).

MS m/z: 364 (M^+).

Found, %: C, 82.40; H, 8.82. Anal Calcd for $C_{25}H_{32}O_2$, %: C, 82.37; H, 8.85.

***rac-exo*-5-Benzyloxy-4-methoxy-11-(2-benzyloxyethyl)tricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene (11b).** A solution of the oxirane **9b** (0.168 g, 0.37 mmol) in benzene (2 ml) and

BF_3•Et_2O (0.057 g, 0.4 mmol) was stirred for 2 h at room temperature, then poured into water (10 ml) and extracted with benzene (2×10 ml). The combined organic layers were dried over Na_2SO_4 and evaporated in vacuum. Column chromatography of the residue [1:5 EtOAc/petroleum ether (40–70ºC)] gave sequentially a fraction (yellowish oily liquid; 0.007 g), which contained traces of *rac*-3-(2-benzyloxyethyl)-5-(4-benzyloxy-3-methoxyphenyl)-cyclohexanecarbaldehyde [^{1}H NMR (δ): 9.66 (1H, s, CHO)] and a fraction of the product **11b** (waxy white solid, 0.055 g; yield 33%).

^{1}H NMR (δ): 1.25–1.34 (2H, m), 1.42–1.50 (3H, m), 1.69–1.82 (4H, m), 2.27 (1H, m, H^9), 2.54 (1H, d, *J*=17.4 Hz, H^8), 2.93 (1H, m, H^1), 3.01 (1H, dd, *J*=17.4, 7.0 Hz, H^8), 3.41 (2H, t, *J*=6.5 Hz, CH_2OBn), 3.86 (3H, s, OMe), 4.41 (2H, s, CH_2Ph), 5.10 (2H, s, CH_2Ph), 6.59 (1H, s, H^6), 6.66 (1H, s, H^3), 7.23 (2H, d, *J*=7.0 Hz), 7.26–7.36 (4H, m), 7.38–7.41 (2H, m), 7.49 (2H, d, *J*=7.5 Hz).

^{13}C NMR (δ): 25.95 (C^9); 27.63 (C^{11}); 31.63; 34.64 (C^1); 34.76 (C^8); 37.18; 40.43; 41.05; 56.06 (OMe); 68.16 (CH_2OBn); 71.13 (CH_2Ph); 72.74 (CH_2Ph); 111.70 (C^3); 113.75 (C^6); 127.28; 127.38; 127.44; 127.61; 128.27, 128.41, 129.61 (C^7), 134.38 (C^2), 137.56, 138.59, 146.38 (C^5), 147.41 (C^4).

Found, %: C, 81.43; H, 7.70. Anal Calcd for $C_{30}H_{34}O_3$, %: C, 81.41; H, 7.74.

***rac-exo*-11-Butyl-4-methoxytricyclo[7.3.1.0^{2,7}]trideca-2,4,6-trien-5-ol (3a).** A mixture of compound **11a** (0.054 g, 0.15 mmol) and 5% Pd/C (0.020 g) in methanol (10 ml) was stirred in a hydrogen gas atmosphere (1 bar) for 5 h. The catalyst was filtered off, and the filtrate was evaporated under reduced pressure to give pure product **3a** (white solid; 0.018 g; yield 44%), m.p. 252–257ºC.

^{1}H NMR (δ): 0.83 (3H, t, *J*=6.7 Hz, Me), 1.09–1.28 (9H, m), 1.64–1.82 (4H, m), 2.24 (1H, m, H^9), 2.54 (1H, d, *J*=17.3 Hz, H^8), 2.88 (1H, m, H^1), 3.02 (1H, dd, *J*=17.3, 7.1 Hz, H^8), 3.87 (3H, s, OMe), 5.41 (1H, s, OH), 6.52 (1H, s, H^3), 6.65 (1H, s, H^6).

^{13}C NMR (δ): 14.10 (Me); 23.06; 27.67 (C^9); 28.75 (C^{11}); 29.02; 31.86; 34.77 (C^1); 34.88 (C^8); 37.33; 40.94; 41.06; 55.92 (OMe); 110.20 (C^3); 113.58 (C^6); 130.51 (C^7); 133.52 (C^2); 143.31 (C^5); 144.28 (C^4).

MS m/z: 274 (M^+).

Found, %: C, 78.72; H, 9.51. Anal Calcd for $C_{18}H_{26}O_2$, %: C, 78.79; H, 9.55.

***rac-exo*-11-(2-Hydroxyethyl)-4-methoxytricyclo[7.3.1.0^{2,7}]trideca-2,4,6-trien-5-ol (3b)** was obtained by hydrogenolysis of dibenzyl derivative **11b** (0.047 g, 0.11 mmol) analogously to compound **3a**. Product **3b** was isolated as a white solid (0.024 g; yield 86%), m.p. 274–278ºC.

^{1}H NMR (δ): 1.30–1.42 (5H, m), 1.66 (1H, d, *J*=12 Hz), 1.73–1.83 (3H, m), 2.26 (1H, m, H^9), 2.55 (1H, d, *J*=17.4 Hz, H^8), 2.90 (1H, m, H^1), 3.02 (1H, dd, *J*=17.4, 7.3 Hz, H^8), 3.31–3.49 (2H, br.s., OH), 3.56 (2H, t, *J*=6.5 Hz, CH_2OH), 3.87 (3H, s, OMe), 6.51 (1H, s, H^3), 6.64 (1H, s, H^6).

^{13}C NMR (δ): 25.67 (C^9); 27.52 (C^{11}); 31.65; 34.63 (C^1); 34.67 (C^8); 40.39; 40.76; 40.94; 55.89 (OMe); 60.77 (CH_2OH); 110.22 (C^3); 113.69 (C^6); 130.29 (C^7); 133.06 (C^2); 143.46 (C^5); 144.39 (C^4).

Found, %: C, 73.23; H, 8.42. Anal Calcd for $C_{16}H_{22}O_3$, %: C, 73.25; H, 8.45.

***endo*-7-(*tert*-Butyldimethylsilyloxy)bicyclo[3.3.1]nonane-*exo*-3-carboxylic acid (12)** was obtained as described [7, 8]. A solution of the *endo*-7-hydroxybicyclo[3.3.1]nonane-*exo*-3-carboxylic acid (0.560 g, 3.04 mmol), *tert*-butyldimethylsilyl chloride (TBSCl, 1.0 g, 6.67 mmol) and imidazole (0.460 g, 6.76 mmol) in DMF (2 ml) was stirred at room temperature for 12 h. The mixture was diluted with water (10 ml) and extracted with CH_2Cl_2 (3×10 ml); the solvent was evaporated in vacuum. Chromatography of the residue [1:1 EtOAc/petroleum ether (40–70ºC)] gave product **12** (colourless oily liquid; 0.580 g; yield 65%).

^{1}H NMR (δ): 0.06 (6H, s, $SiMe_2$); 0.90 (9H, s, *t*-Bu); 1.28–1.35 (1H, m); 1.46–1.66 (5H, m); 1.85–1.88 (2H, m); 2.00–2.07 (4H, m); 3.80 (1H, m, H^3); 3.95 (1H, m, H^7).

^{13}C NMR (δ): -4.87 ($SiMe_2$); 17.96 ($SiCMe_3$); 25.79 ($SiCMe_3$); 26.48; 31.32 (C^9); 33.75; 34.18 (C^3); 37.78; 64.37 (C^7); 183.71 (C=O).

Found, %: C, 64.42; H, 10.10. Anal Calcd for $C_{16}H_{30}O_3Si$, %: C, 64.38; H, 10.13.

3-(*tert*-Butyldimethylsilyloxy)-4-methoxybenzyl *endo*-7-*tert*-butyldimethylsilyloxy bicyclo[3.3.1]nonane-*exo*-3-carboxylate (14). To a solution of acid **12** (0.300 g, 1.01 mmol) in CH_2Cl_2 (10 ml) were added [3-(3-*tert*-butyldimethylsilyloxy)-4-methoxyphenyl]methanol **13** (0.292 g, 1.09 mmol) obtained as described [9], N,N'-dicyclohexylcarbodiimide (DCC, 0.250 g, 1.21 mmol) and 4-dimethylaminopyridine (DMAP) (0.01 g). After stirring for 24 h at room temperature, acetic acid (5–10 μl) was added, and after 15 min the solvent was removed in vacuum. The residue was dissolved in ethyl acetate (10 ml) and kept at 4°C for 2–3 h. The solid was filtered off, washed with cold ethyl acetate (2×10 ml), and the filtrate was washed with brine (10 ml), water (10 ml), dried over Na_2SO_4 and evaporated. The product was purified by column chromatography (1:9–1:6, ethyl acetate/petroleum ether) to give product **14** (colourless oily liquid; 0.365 g, yield 66%).

^{1}H NMR (δ): 0.04 (6H, s, $Si(Me)_2$), 0.17 (6H, s, $SiMe_2$), 0.87 (9H, s, *t*-Bu), 1.02 (9H, s, *t*-Bu), 1.32 (1H, m, *J*=12.7, 1.4 Hz), 1.42 (1H, dd, *J*=5.1 Hz), 1.46 (1H, d, *J*=4.0 Hz), 1.51 (1H, m, *J*=12.7, 3.1, 1.8 Hz), 1.61 (2H, td, *J*=12.9, 3.9 Hz), 1.83 (2H, m, *J*=13.6 Hz), 1.98–2.09 (4H, m), 3.73 (1H, m, H^3), 3.81 (3H, s, OMe), 3.93 (1H, m, H^7), 4.99 (2H, s, $ArCH_2O$), 6.82 (1H, d, *J*=8.2 Hz, $H^{5\text{-}Ar}$), 6.86 (1H, d, *J*=2.0 Hz, $H^{2\text{-}Ar}$), 6.90 (1H, dd, *J*=8.2, 2.0 Hz, $H^{6\text{-}Ar}$).

^{13}C NMR (δ): -4.88 ($SiMe_2$); -4.63 ($SiMe_2$); 17.89 ($SiCMe_3$); 18.42 ($SiCMe_3$); 25.71 ($SiCMe_3$); 25.75 ($SiCMe_3$); 26.52; 31.14 (C^9); 34.12; 34.43 (C^3); 37.68; 55.48 (OMe); 64.42 (C^7); 65.45 ($ArCH_2O$); 111.81 ($C^{5\text{-}Ar}$); 121.04 ($C^{2\text{-}Ar}$); 121.70 ($C^{6\text{-}Ar}$); 129.18 ($C^{1\text{-}Ar}$); 144.87 ($C^{3\text{-}Ar}$); 150.75 ($C^{4\text{-}Ar}$); 177.32 (C=O).

IR (cm^{-1}): 1513, 1727, 2929.

Found, %: C, 65.60; H, 9.52. Anal Calcd for $C_{30}H_{52}O_5Si_2$, %: C, 65.64; H, 9.55.

3-Hydroxy-4-methoxybenzyl *endo*-7-hydroxybicyclo[3.3.1]nonane-*exo*-3-carboxylate (4). To a solution of compound **14** (0.365 g, 0.67 mmol) in MeOH (10 ml) was added AcCl (0.015 g, 0.19 mmol). After stirring at room temperature for 2 h, the reaction mixture was diluted with water (20 ml) and extracted with CH_2Cl_2 (3×20 ml). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum. Column chromatography of the residue [1:6–2:1 EtOAc/petroleum ether (40–70°C)] gave product **4** (yellowish oily liquid; 0.070 g; yield 33%).

^{1}H NMR (δ): 1.21 (1H, d, *J*=12.6 Hz), 1.30 (2H, m), 1.53–1.63 (3H, m), 1.75 (1H, br.s., OH), 1.81 (2H, m, *J*=14.3, 2.2, 1.6 Hz), 2.10–2.18 (4H, m), 3.33 (1H, m, H^3), 3.88 (3H, s, OMe), 3.97 (1H, m, H^7), 5.00 (2H, s, $ArCH_2O$), 5.85 (1H, br.s., ArOH), 6.80–6.83 (2H, m, $H^{5\text{-}Ar}$ + $H^{6\text{-}Ar}$), 6.92 (1H, d, *J*=1.5 Hz, $H^{2\text{-}Ar}$).

^{13}C NMR (δ): 26.06; 29.68 (C^9); 34.28 (C^3); 34.59; 36.46; 55.91 (OMe); 64.21 (C^7); 65.71 ($ArCH_2O$); 110.48 ($C^{5\text{-}Ar}$); 114.53 ($C^{2\text{-}Ar}$); 120.02 ($C^{6\text{-}Ar}$); 129.50 ($C^{1\text{-}Ar}$); 145.55 ($C^{3\text{-}Ar}$); 146.45 ($C^{4\text{-}Ar}$); 176.91 (C=O).

IR (cm^{-1}): 1513, 1727, 2917.

MS m/z: 343 (M^+ + Na), 359 (M^+ + K).

Found, %: C, 67.48; H, 7.55. Anal Calcd for $C_{18}H_{24}O_5$, %: C, 67.52; H, 7.57.

Methyl *endo*-7-hydroxybicyclo[3.3.1]nonane-*exo*-3-carboxylate (15) was synthesized from *endo*-7-hydroxybicyclo[3.3.1]nonane-*exo*-3-carboxylic acid as described [10].

Methyl *endo*-7-[3-(*tert*-butyldimethylsilyloxy)-4-methoxybenzoyloxy]bicyclo-[3.3.1]nonane-*exo*-3-carboxylate (17) was synthesized from the 3-(*tert*-butyldimethylsilyloxy)-4-methoxybenzoic acid **16** [11] (0.089 g, 0.32 mmol), alcohol **15** (0.070 g, 0.35 mmol), DCC

(0.080 g, 0.39 mmol) and DMAP analogously to compound **14**. Chromatography of the residue gave product **17** (colourless oily liquid; 0.070 g; yield 49%).

^{1}H NMR (δ): 0.17 (6H, s, $SiMe_2$), 1.01 (9H, s, *t*-Bu), 1.38 (1H, m, *J*=13.1 Hz), 1.60–1.72 (5H, m), 1.85–1.88 (2H, m), 2.17–2.23 (2H, m), 2.25–2.33 (2H, m), 3.39 (1H, m, H^3), 3.68 (3H, s, CO_2Me), 3.87 (3H, s, ArOMe), 5.23 (1H, m, H^7), 6.86 (1H, d, *J*=8.5 Hz, $H^{5\text{-}Ar}$), 7.52 (1H, d, *J*=2.0 Hz, $H^{2\text{-}Ar}$), 7.67 (1H, dd, *J*=8.5, 2.0 Hz, $H^{2\text{-}Ar}$).

^{13}C NMR (δ): -4.61 ($SiMe_2$); 18.47 ($SiCMe_3$); 25.71 ($SiCMe_3$); 25.94; 30.02 (C^9); 31.16, 34.38 (C^3); 34.44; 51.58 (CO_2Me); 55.48 (OMe); 67.61 (C^7); 110.92 ($C^{5\text{-}Ar}$); 121.96 ($C^{2\text{-}Ar}$); 123.36 ($C^{6\text{-}Ar}$); 124.14 ($C^{1\text{-}Ar}$); 144.67 ($C^{3\text{-}Ar}$); 155.05 ($C^{4\text{-}Ar}$); 165.78 ($ArCO_2$); 177.36 (CO_2Me).

IR (cm^{-1}): 1714, 1731, 2917.

MS m/z: 485 (M^+ + Na), 501 (M^+ + K).

Found, %: C, 64.94; H, 8.24. Anal Calcd for $C_{25}H_{38}O_6Si$, %: C, 64.90; H, 8.28.

Methyl *endo*-7-(3-hydroxy-4-methoxybenzoyloxy)bicyclo[3.3.1]nonane-*exo*-3-carboxylate (5). To a solution of compound **17** (0.070 g, 0.15 mmol) in MeCN : H_2O (99:1, 5 ml total volume) was added 1,8-diazabicycloundec-7-ene (DBU, 0.027 g, 0.18 mmol). After stirring at room temperature for 2 h the reaction mixture was diluted with water (20 ml) and extracted with CH_2Cl_2 (3×20 ml). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum. Chromatography of the residue [1:8, then 1:6 EtOAc/petroleum ether (40–70ºC)] gave product **5** (colourless oily liquid; 0.040 g; yield 77%).

^{1}H NMR (δ): 1.42 (1H, m, *J*=13.1 Hz), 1.60–1.72 (5H, m), 1.84–1.88 (2H, m), 2.19 (2H, m), 2.24–2.31 (2H, m), 3.49 (1H, m, H^3), 3.69 (3H, s, CO_2Me), 3.94 (3H, s, ArOMe), 5.25 (1H, m, H^7), 5.44–5.95 (1H, br.s., OH), 6.87 (1H, d, *J*=8.9 Hz, $H^{5\text{-}Ar}$), 7.62–7.65 (2H, m, $H^{2\text{-}Ar}$, $H^{6\text{-}Ar}$).

^{13}C NMR (δ): 25.86; 30.46 (C^9); 33.55; 34.19; 34.37 (C^3); 51.54 (CO_2Me); 55.97 (ArOMe); 67.39 (C^7); 109.79 ($C^{5\text{-}Ar}$); 115.57 ($C^{2\text{-}Ar}$); 122.74 ($C^{6\text{-}Ar}$); 123.79 ($C^{1\text{-}Ar}$); 145.23 ($C^{3\text{-}Ar}$); 150.37 ($C^{4\text{-}Ar}$); 165.62 ($ArCO_2$); 177.49 (CO_2Me).

IR (cm^{-1}): 1708, 1731, 2917.

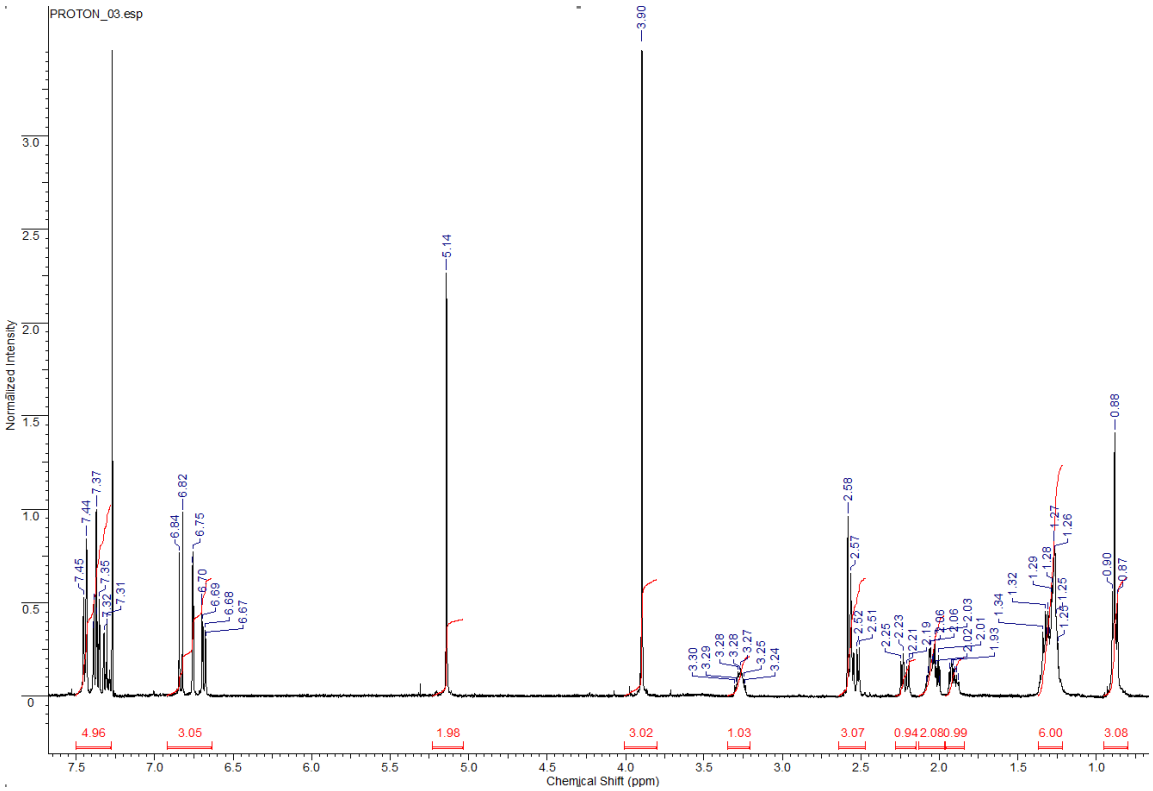
MS m/z: 348 (M^+), 371 (M^+ + Na), 387 (M^+ + K).

Found, %: C, 65.50; H, 6.94. Anal Calcd for $C_{19}H_{24}O_6$, %: C, 65.53; H, 6.95.

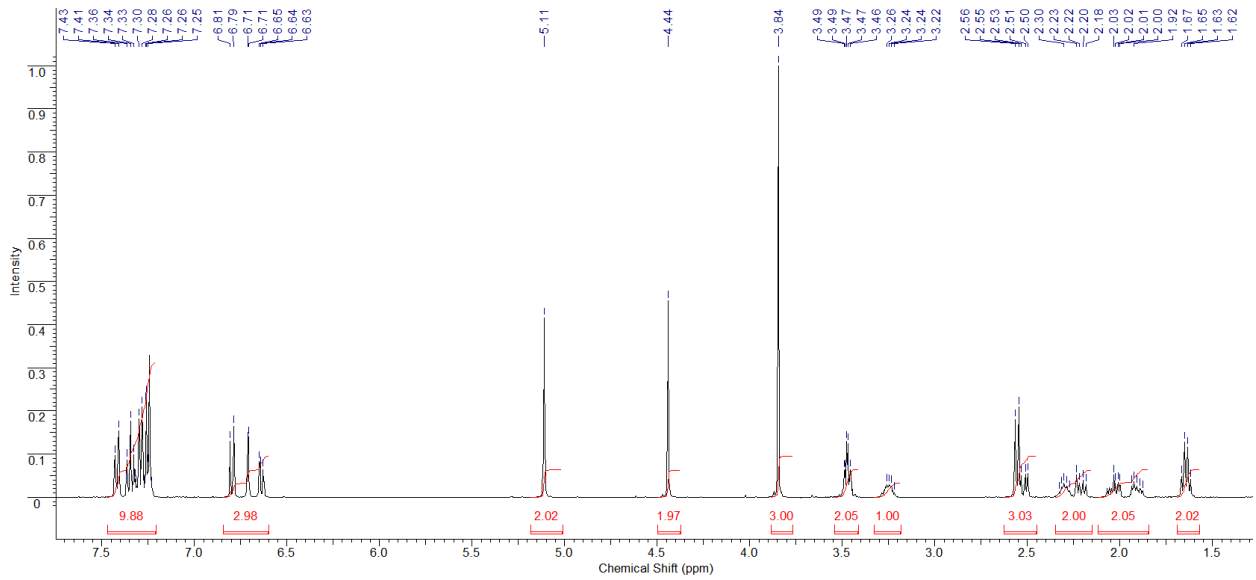
References and notes

1. N. Fujikawa, T. Ohta, T. Yamaguchi, T. Fukuda, F. Ishibashi and M. Iwao, *Tetrahedron*, 2006, **62**, 594.
2. S. Cardinal and N. Voyer, *Tetrahedron Lett*., 2013, **54**, 5178.
3. B.-D. Chong, Y.-I. Ji , S.-S. Oh , J.-D. Yang , W. Baik and S. Koo, *J. Org. Chem*., 1997, **62**, 9323.
4. G. P.-J. Hareau, M. Koiwa, S. Hikichi and F. Sato, *J. Am. Chem. Soc*., 1999, **121**, 3640.
5. S. Lin, L. Deiana, A. Tseggai and A. Córdova, *Eur. J. Org. Chem*., 2012, 398.
6. The synthesis of 6 is mentioned in the literature (see *e.g.* L. A. Brozek, J. D. Sieber and J. P. Morken, *Org. Lett*., 2011, **13**, 995), but no spectral data are available.
7. G. E. Renzoni and W. T. Borden, *J. Org. Chem*., 1983, **48**, 5231.
8. R. Partch, W. Brewser and B. Stokes, *Croat. Chem. Acta*, 1985, **58**, 661.
9. K. Odlo, J. Fournier-Dit-Chabert, S. Ducki, O. A. B. S. M. Gani, I. Sylte and T. V. Hansen, *Bioorg. Med. Chem*., 2010, **18**, 6874.
10. O. N. Zefirova, E. V. Nurieva, V. N. Nuriev, A. A. Ivanov, N. V. Zyk and N. S. Zefirov, *Russ. J. Org. Chem*., 2008, **44**, 1134 (*Zh. Org. Khim*., 2008, **44**, 1149).
11. G. R. Pettit, B. Toki, D. L. Herald, P. Verdier-Pinard, M. R. Boyd, E. Hamel and R. K. Pettit, *J. Med. Chem*., 1998, **41**, 1688.

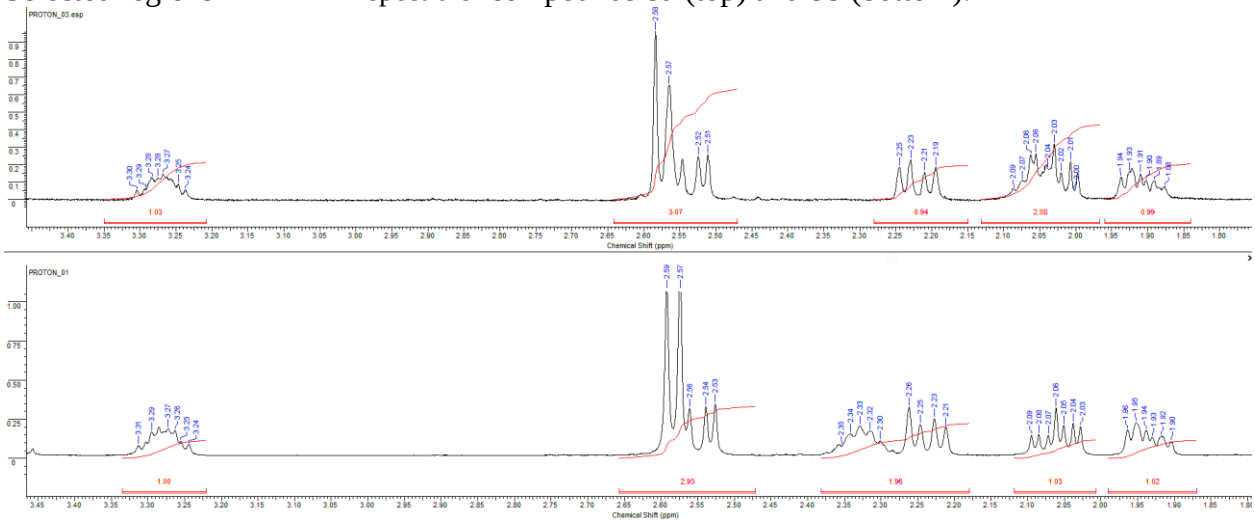
^{1}H NMR spectrum of compound **8a**



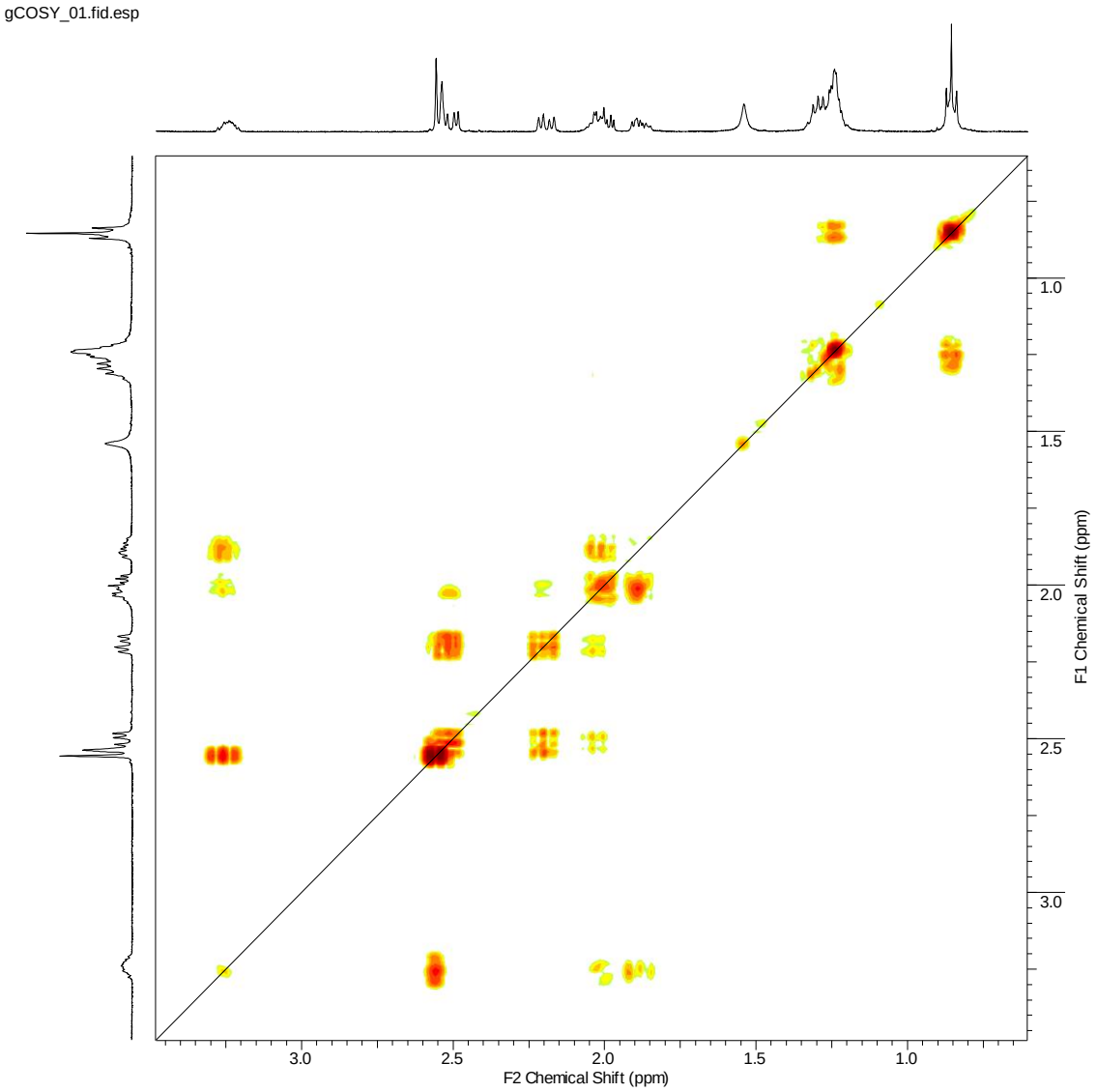
^{1}H NMR spectrum of compound **8b**



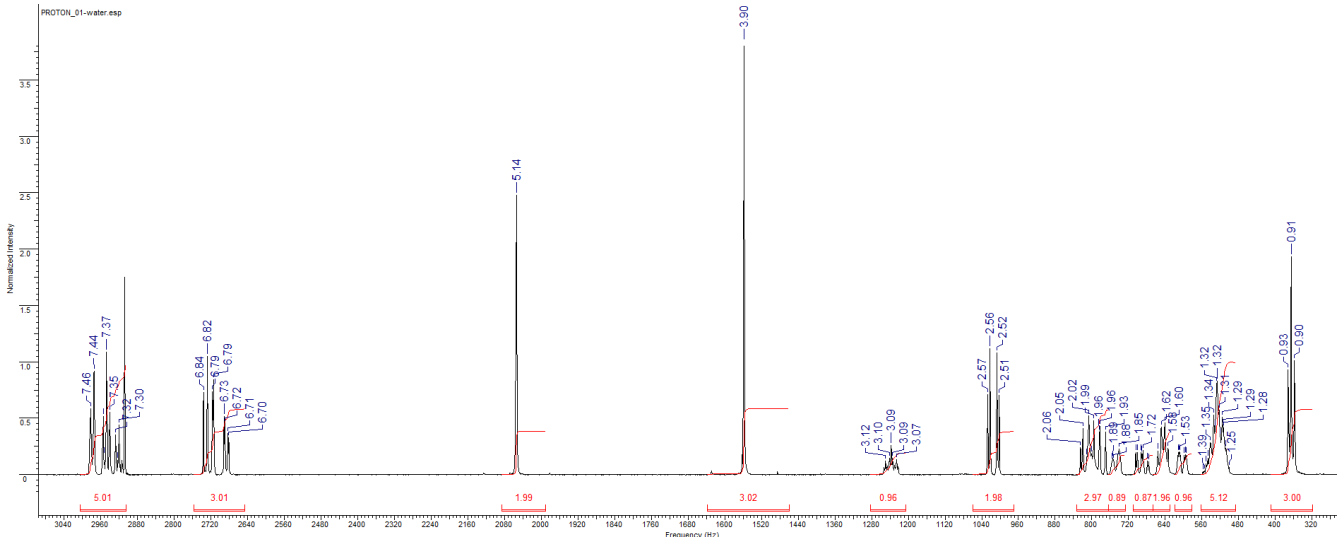
Selected regions in ^{1}H NMR spectra of compounds **8a** (top) and **8b** (bottom).

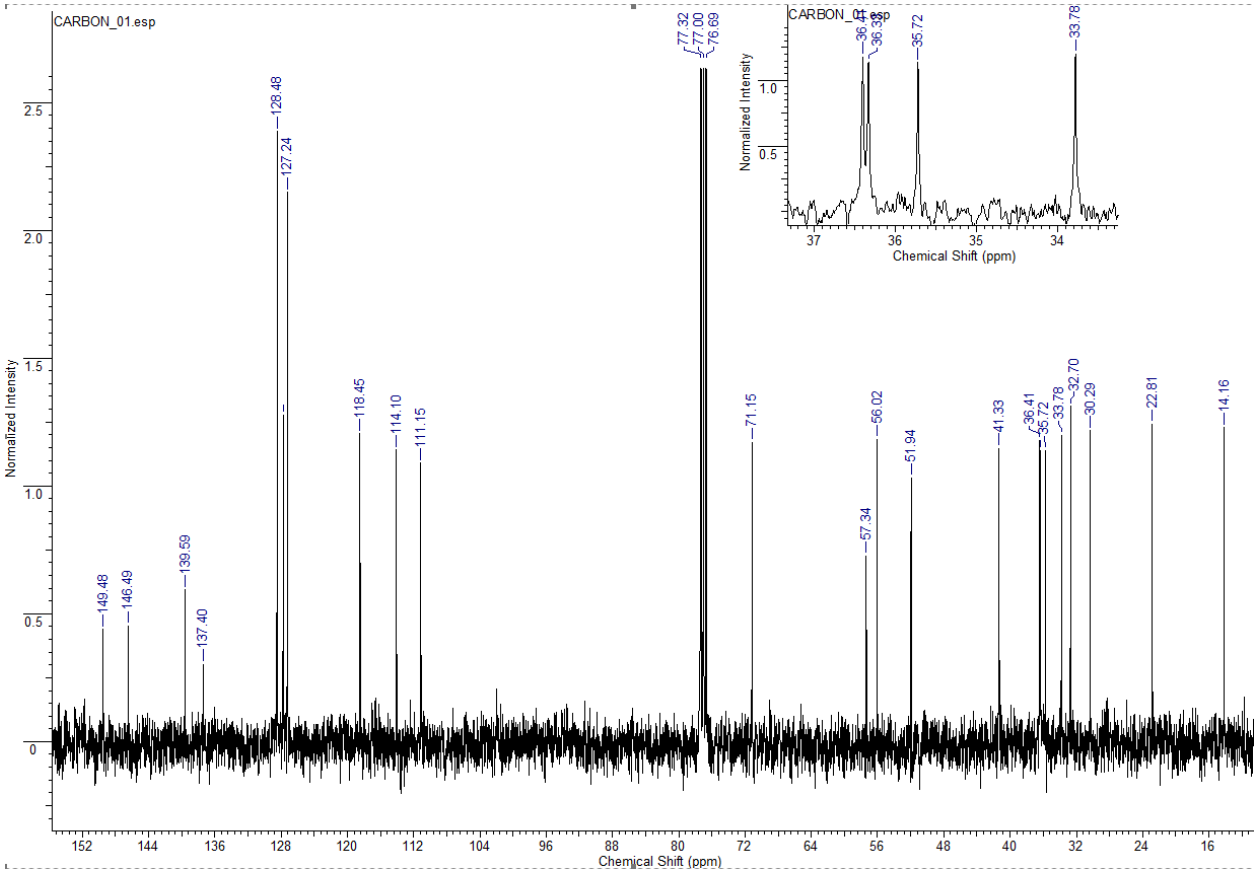


^{1}H – ^{1}H COSY NMR spectrum of compound **8a**

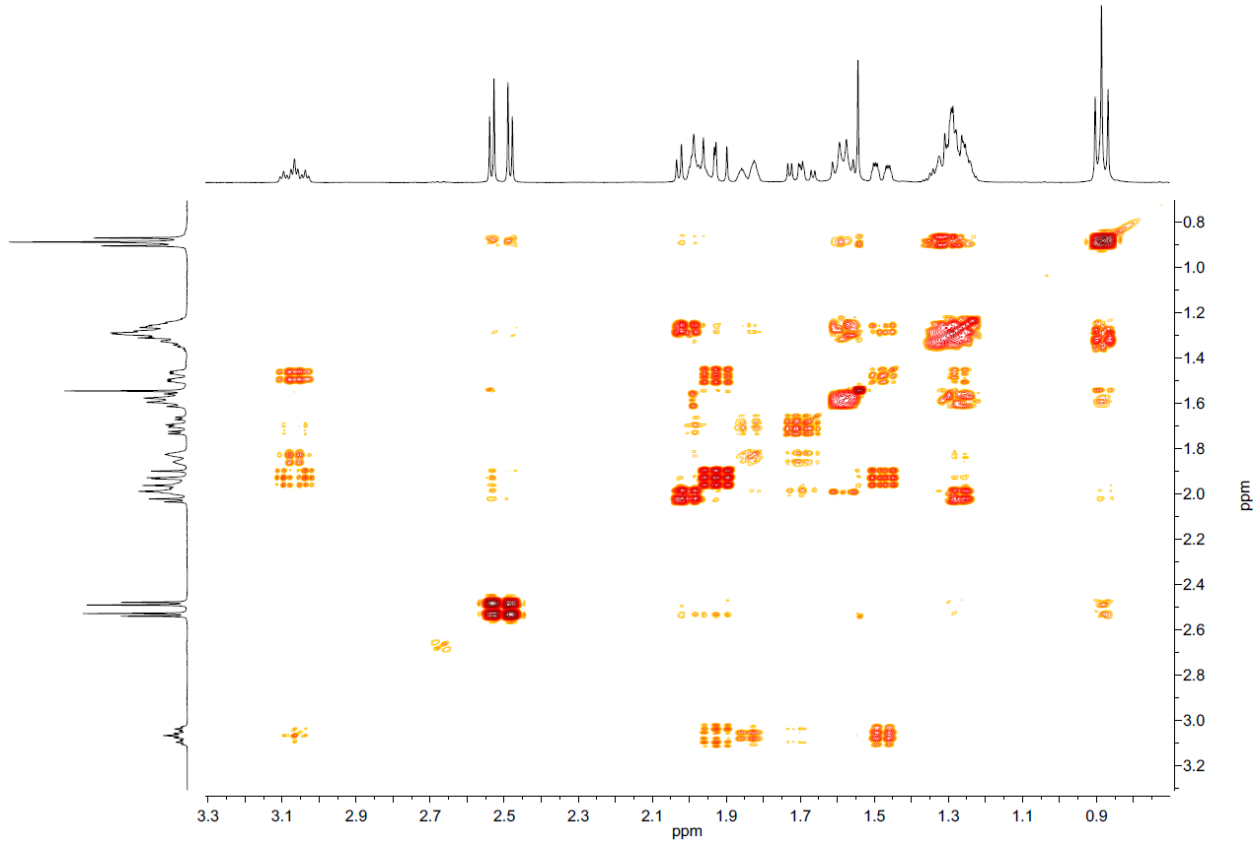


^{1}H and ^{13}C NMR spectra of compound **9a**

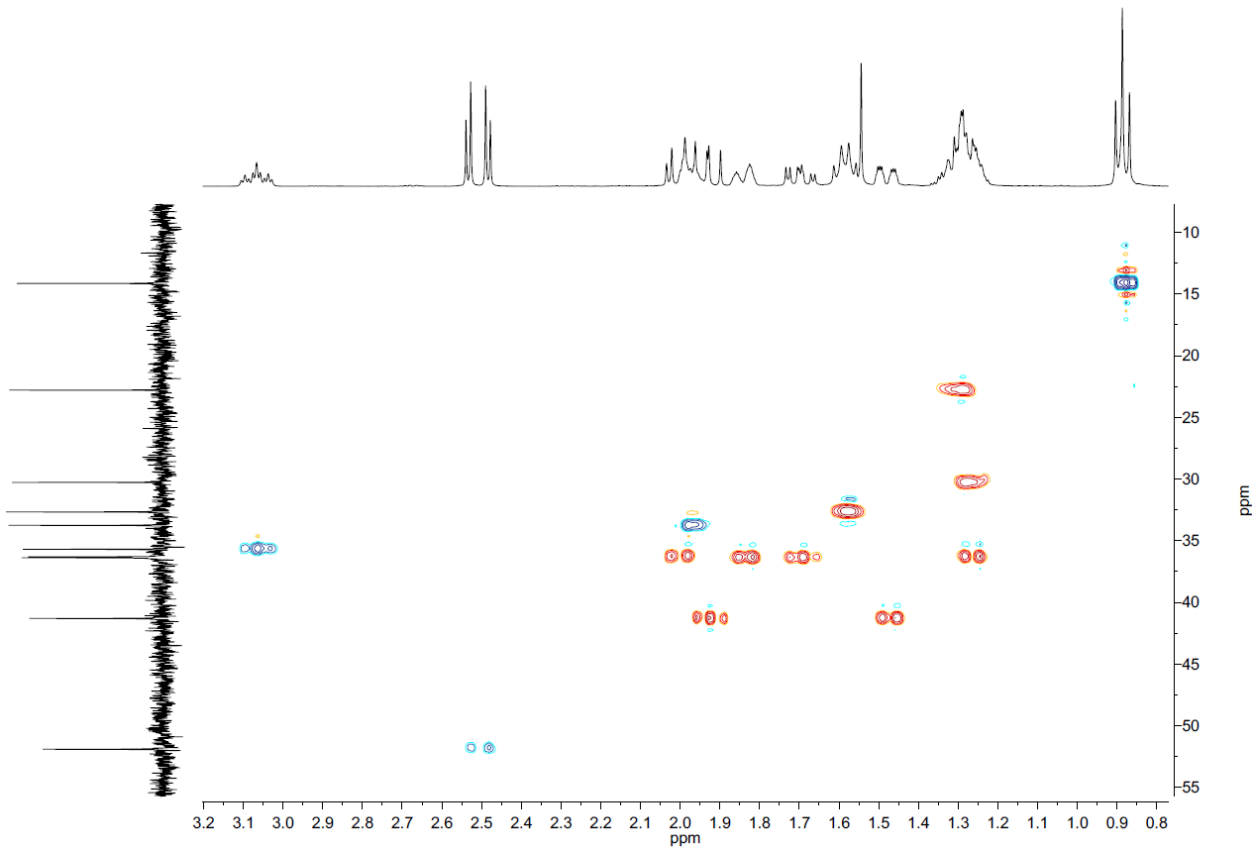




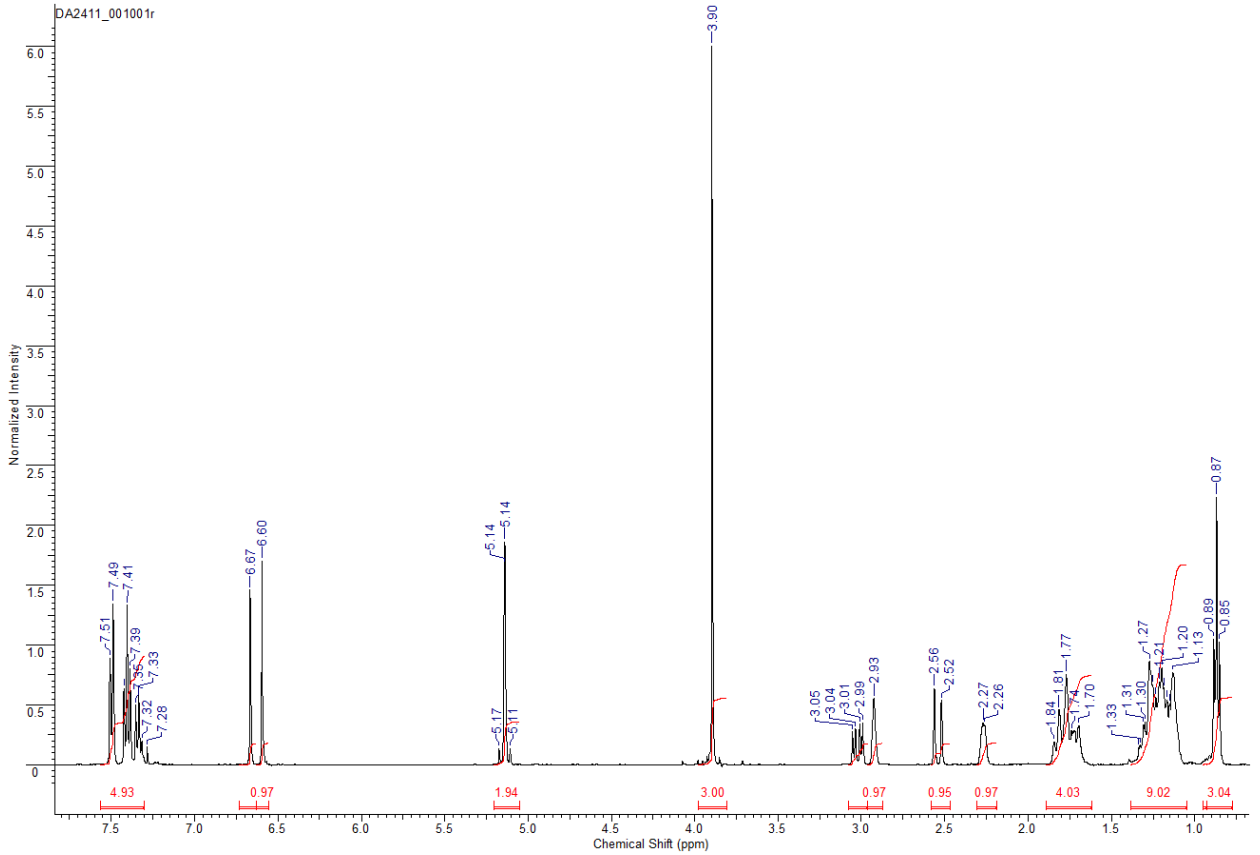
^{1}H – ^{1}H COSY NMR spectrum of compound **9a**

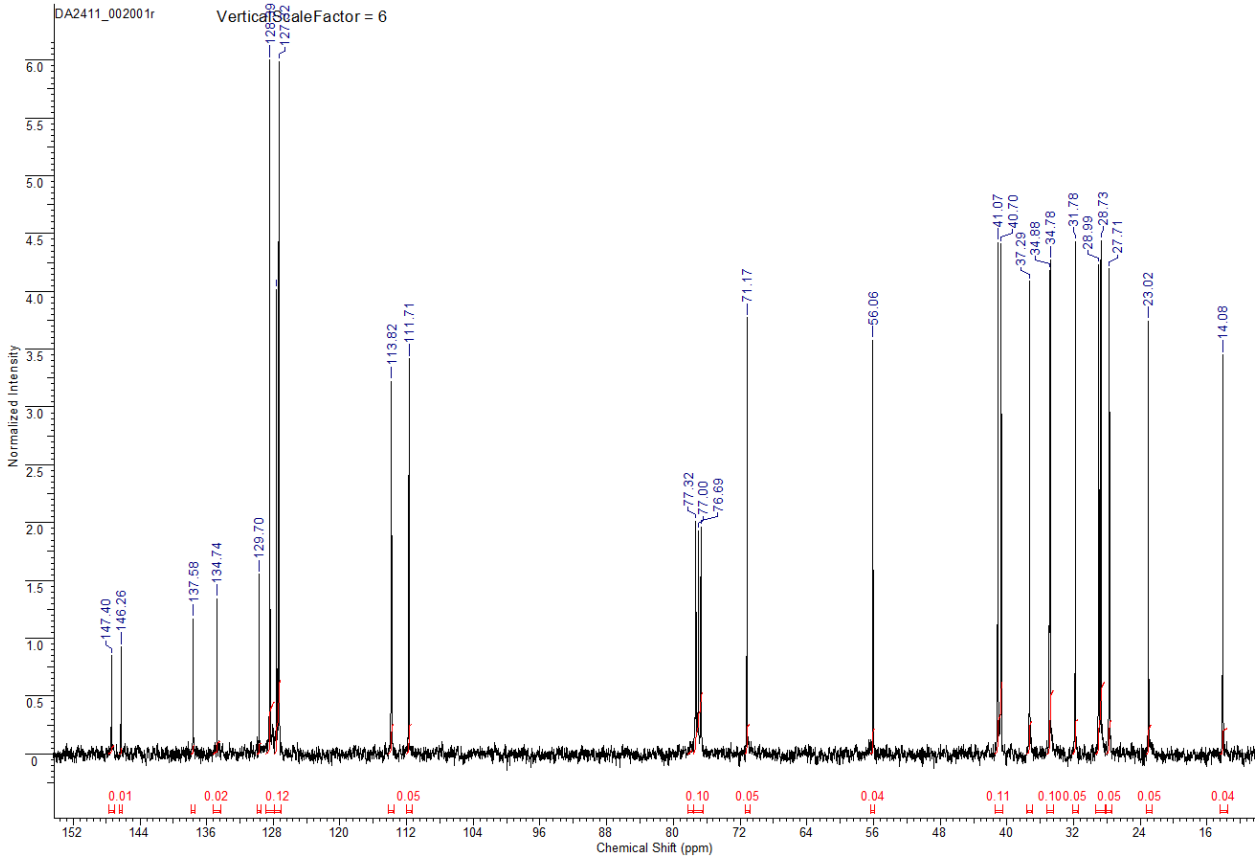


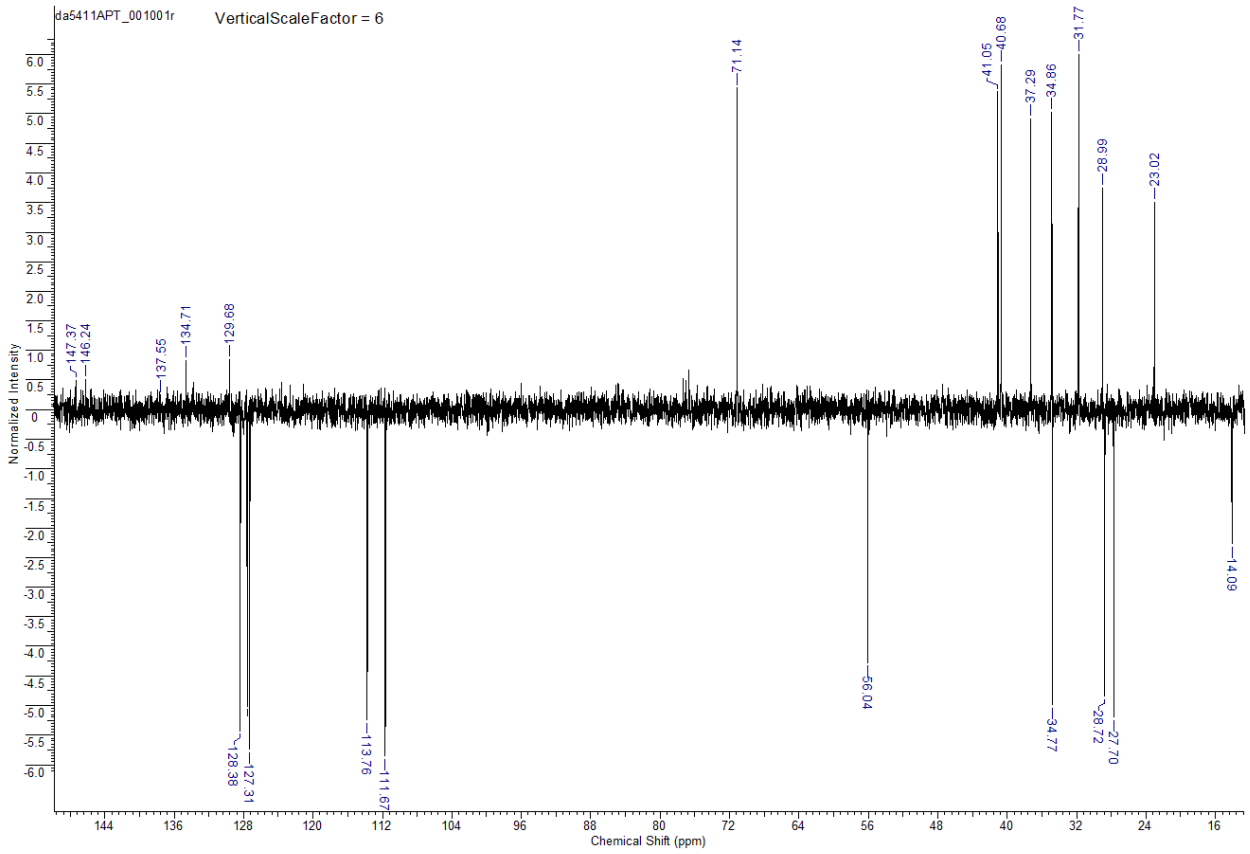
^{1}H – ^{13}C HSQC NMR spectrum of compound **9a**



^{1}H, ^{13}C and ^{13}C-APT NMR spectra of compound **11a**



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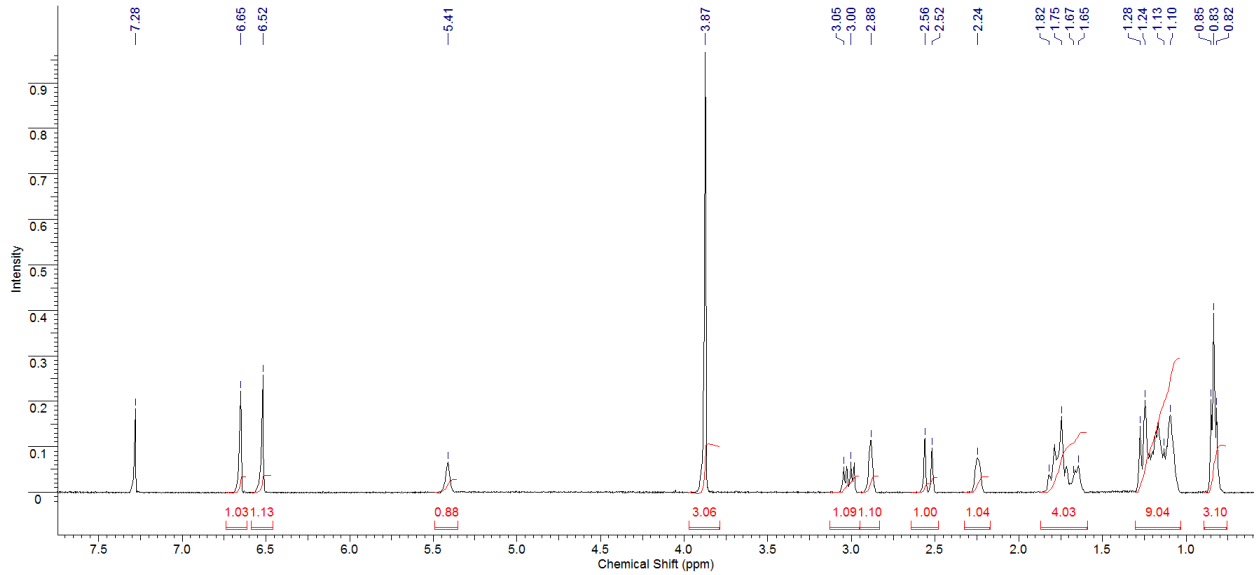
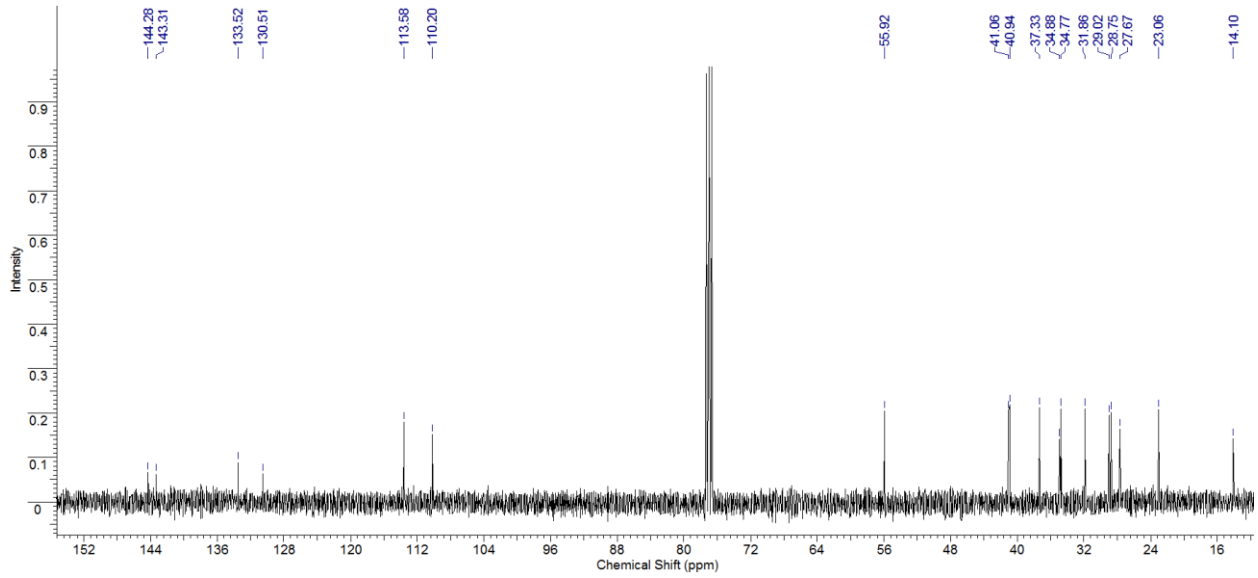
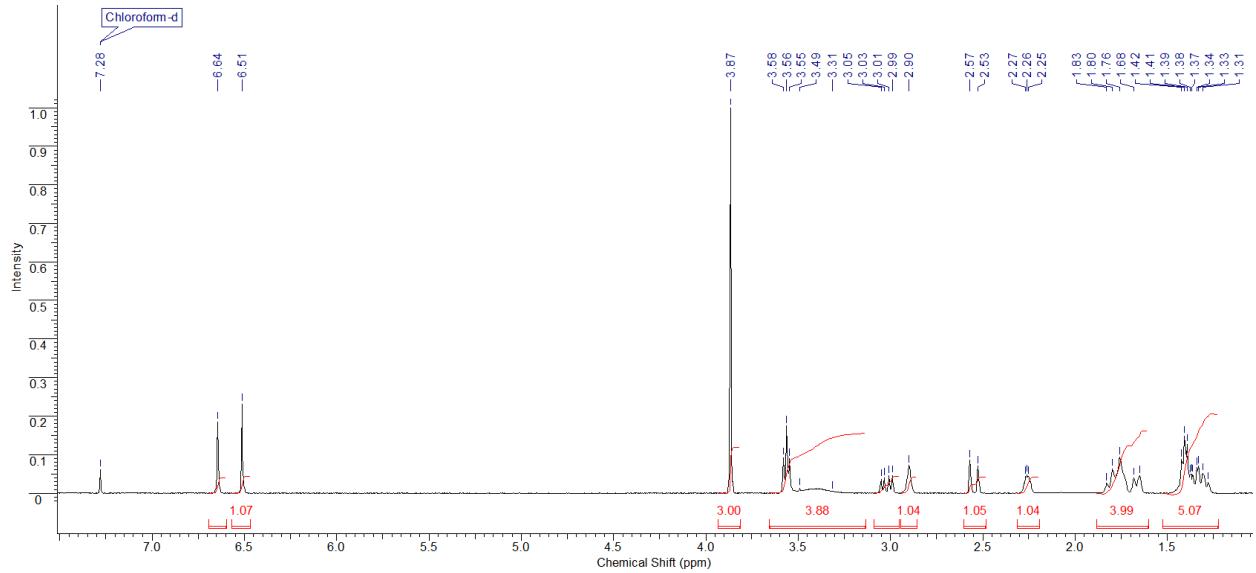
14.09

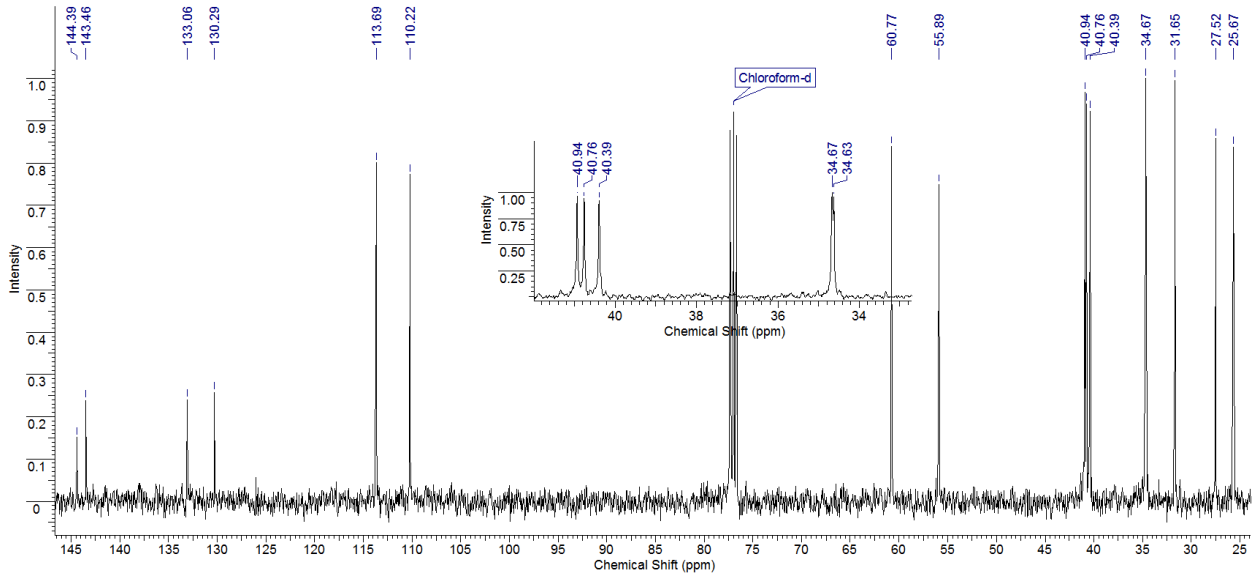
^{1}H and ^{13}C NMR spectra of compound **3a**



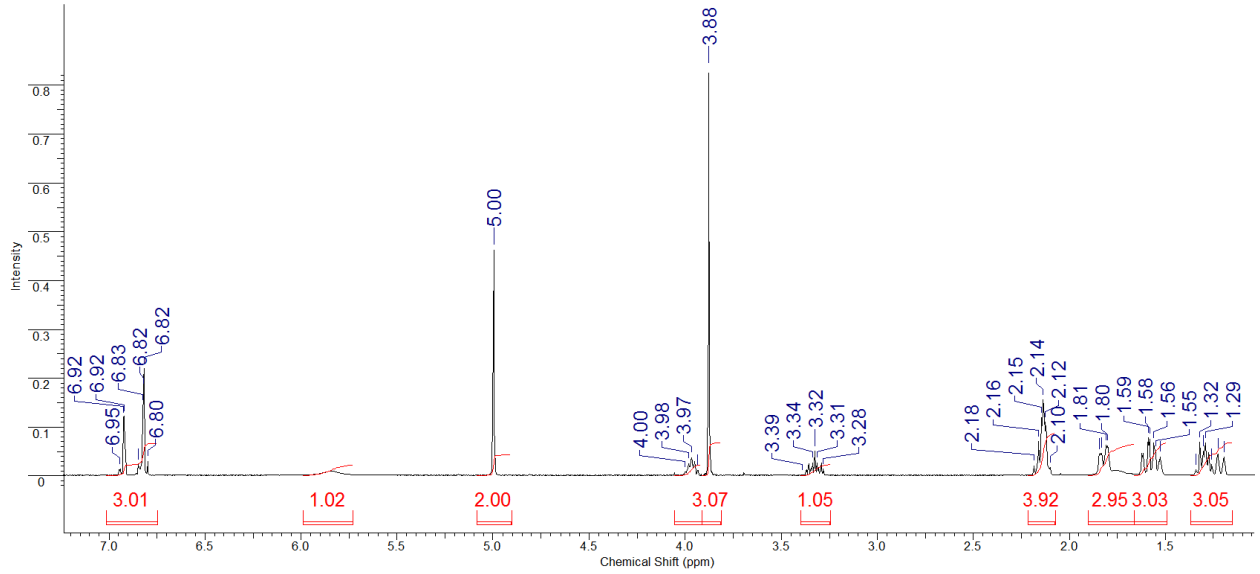


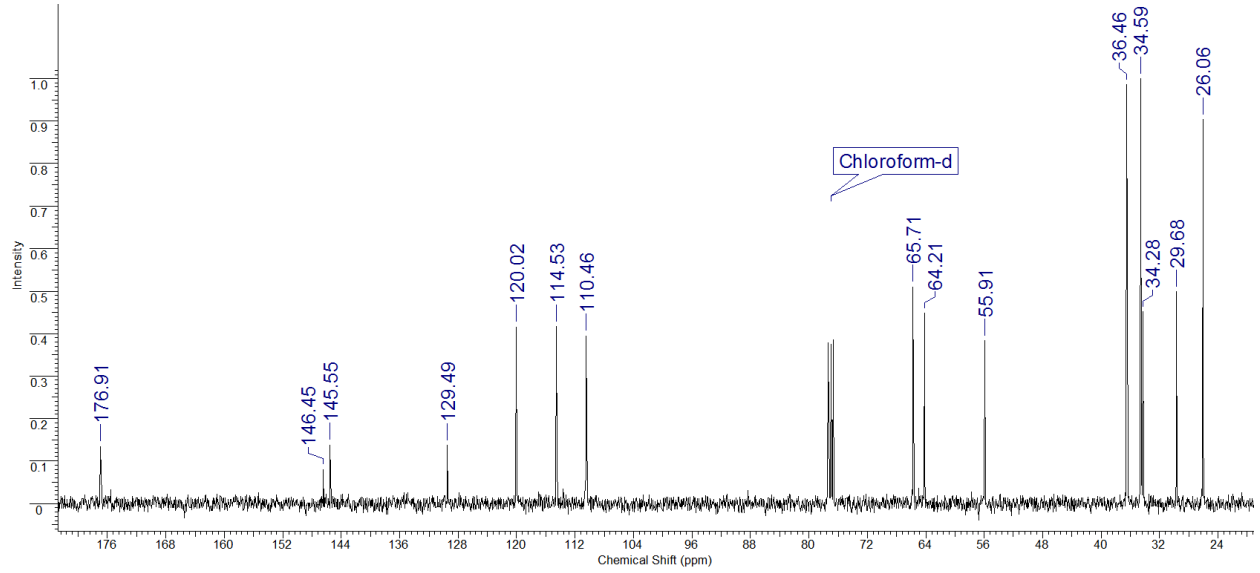
^{1}H and ^{13}C NMR spectra of compound **3b**





^{1}H and ^{13}C NMR spectra of compound **4**





^{1}H and ^{13}C NMR spectra of compound **5**