Electronic Supplementary Information

New rearrangement of isoxazolidines to tetrahydro-1,3-oxazines for the synthesis of chiral pyrrolidines

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General Experimental

Unless otherwise stated, all chemicals were purchased as the highest purity commercially available and were used without further purification. IR spectra were recorded on a BOMEM 100 FT-IR or an AVATAR 370 FT-IR Thermo Nicolet spectrophotometers. ^{1}H and ^{13}C NMR spectra were performed in $CDCl_3$ and referenced to the residual peak of $CHCl_3$ at δ 7.26 ppm and δ 77.0 ppm, for ^{1}H and ^{13}C, respectively, using Varian 200 VX and Bruker DRX 400 instruments. Chemical shifts are reported in δ ppm and coupling constants *(J)* are given in hertz. MS were performed at a VG-TS 250 spectrometer at 70 eV ionising voltage. Mass spectra are presented as *m/z* (% rel int.). HRMS were recorded on a VG Platform (Fisons) spectrometer using chemical ionisation (ammonia as gas) or Fast Atom Bombardment (FAB) technique. For some of the samples, QSTAR XL spectrometer was employed for electrospray ionisation (ESI). Optical rotations were determined on a Perkin-Elmer 241 polarimeter in 1 dm cell. Dichloromethane was distilled from calcium hydride; tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone ketyl under argon atmosphere prior to use. Hexane was distilled prior to use.

N-O cleavage of Isoxazolidines using $Mo(CO)_6$: Standard Procedure.

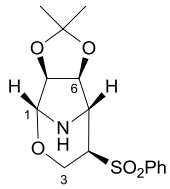
To a stirred solution of isoxazolidine (1 mmol) in 1 mL of H_2O and 15 mL of MeCN was added 0.7 mmol of $Mo(CO)_6$ and heated at reflux. The solution was stirred for 24 h. Then it was concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 1:1) to obtain rearranged compound.

Alkylation of Heterocycles: Standard Procedure.

To a stirred solution of isoxazolidine (1 mmol) in $CHCl_3$ (0.06M) was added dropwise RBr (1 mmol) and heated at 60ºC. The solution was stirred at 60 ºC for 20 h. Then it was quenched with saturated aqueous solution of NH_4Cl and the product was extracted with DCM (3x15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 8:2) to obtain rearranged compound.

Addition of Organometallic Reagents: Standard Procedure.

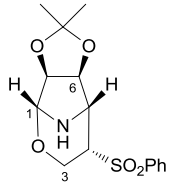
To a stirred solution of Rearranged compound (1 mmol) in Et_2O (0.08M) was added dropwise RMgBr (10 mmol) at -60ºC. The solution was stirred at -60 ºC for 2 h. Then the mixture was allowed to warm slowly to room temperature. It was quenched with saturated aqueous solution of NH_4Cl and the product was extracted with DCM (3x15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 1:1) to obtain pyrrolidines.



10

(1*R*,4*R*,5*R*,6*S*,7*S*)-4-phenylsulfonyl-6,7-isopropilidendioxi-2-oxa-8-azabicyclo[3.2.1]octane 10.

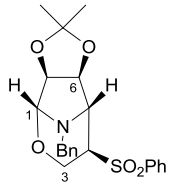
To a stirred solution of isoxazolidine **2c** (460 mg, 1.42 mmol) in 1.50 mL of H_2O and 21 mL of MeCN was added 265 mg (1 mmol) of $Mo(CO)_6$ and heated at 80ºC. The solution was stirred for 24 h. Then it was concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 8:2) to obtain **10** (232 mg, 50%) and **4c** (232 mg, 50%). $[\alpha]_D^{20}$ = -2.7 (c=0.7, $CHCl_3$); IR (film): 2981.95, 2933.73, 2881.65, 1301.41, 1147.65, 732.95 cm^{-1};^{1}H NMR (200 MHz, $CDCl_3$) δ 7.94 (2H, d, *J* = 8.0 Hz, H_{orto}), 7.70-7.56 (3H, m, H_{meta} and H_{para}), 4.86 (1H, s, H-1), 4.75 (1H, dd, *J* = 1.2 and 5.4 Hz, H-6), 4.55 4.48 (2H, m, H-7 and H_B-3), 3.87 (1H, dd, *J* = 5.8 and 14.2 Hz, H_A-3), 3.77 (1H, sa, H-5), 2.73 (1H, dd, *J* = 3.0 and 5.8 Hz, H-4), 1.45 (3H, s, Me-acetonide), 1.31 (3H, s, Me acetonide);^{13}C NMR (50 MHz, $CDCl_3$) δ 137.5, 134.6, 129.8, 128.9, 112.9, 88.8, 81.9, 78.7, 59.1, 57.9, 56.5, 26.1, 24.9; HRMS (EI) calcd for $C_{15}H_{20}NO_5S$ requires $(M+H)^+$ 326.1056; found 326.1068.



11

(1*R*,4*S*,5*R*,6*S*,7*S*)-4-phenylsulfonyl-6,7-isopropilidendioxi-2-oxa-8-azabicyclo[3.2.1]octane 11.

To a stirred solution of isoxazolidine **3c** (530 mg, 1.63 mmol) in 1.70 mL of H_2O and 25 mL of MeCN was added 300 mg (1.14 mmol) of $Mo(CO)_6$ and heated at 80ºC. The solution was stirred for 24 h. Then it was concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 8:2) to obtain **11** (282 mg, 53%) and **5c** (105 mg, 20%). $[\alpha]_D^{20}$ = +20.0 (c=0.9, $CHCl_3$); IR (film): 3412, 3338, 2974, 2929, 1373, 1140, 1033 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (2H, d, *J* = 8.0 Hz, H_{orto}), 7.70 (1H, t, *J* = 7.6 Hz, H_{para}), 7.60 (2H, d, *J* = 7.6 Hz, H_{meta}), 5.32 (1H, d, *J* = 5.4 Hz, H-6), 4.77 (1H, s, H-1), 4.72 (1H, d, *J* = 5.4 Hz, H-7), 4.01 (1H, dd, *J* = 5.8 and 11.8 Hz, H_B-3), 3.87 (1H, t, *J* = 11.8 Hz, H_A-3), 3.77 (1H, sa, H-5), 3.50 (1H, ddd, *J* = 2.6, 5.8 and 8.4 Hz, H-4), 1.45 (3H, s, Me-acetonide), 1.38 (3H, s, Me acetonide);^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 134.4, 129.6, 128.2, 111.7, 88.8, 81.8, 78.7, 61.3, 59.6, 57.9, 25.7, 24.4; HRMS (EI) calcd for $C_{15}H_{20}NO_5S$ requires $(M+H)^+$ 326.1056; found 326.1068.

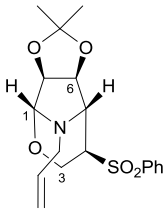


12a

(1*R*,4*R*,5*R*,6*S*,7*S*)-8-benzyl-4-phenylsulfonyl-6,7-isopropilidendioxi-2-oxa-8-azabicyclo[3.2.1]octane 12a.

To a stirred solution of isoxazolidine **2c** (37.40 mg, 0.11 mmol) in $CHCl_3$ (1.50 mL) was added dropwise BnBr (13.6 μL, 0.11 mmol) and heated at 60ºC. The solution was stirred at 60 ºC for 20 h. Then it was quenched with saturated aqueous solution of NH_4Cl and the product was extracted with DCM (3x15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 8:2) to obtain **12a** (21.7 mg, 46%). $[\alpha]_D^{20}$ = -31.7 (c=0.6, $CHCl_3$);IR (film): 3391, 3060, 2970, 2921, 1446, 1385, 1152 cm^{-1};^{1}H NMR (200 MHz, $CDCl_3$) δ 7.85-7.30 (10H, m, H*Ar*), 4. 71 (1H, s, H-1), 4.62 (1H, d, *J* = 5.0 Hz, H-7), 4.52 (1H, d, *J* = 5.0 Hz, H-6), 4.38 (1H, d, *J* = 12.0 Hz, H_A-1'), 4.26-4.23 (1H, m, H_A-3), 4.20 (1H, d, *J* = 12.0 Hz, H_B-1'), 4.13 (1H, s, H-5), 3.85-3.75 (1H, m, H_B-3), 3.10 (1H, t, *J* = 6.2 Hz, H-4), 1.52 (3H, s, Me-acetonide), 1.29 (3H, s, Me-acetonide);^{13}C NMR (50 MHz, $CDCl_3$) δ 138.9, 138.5, 134.4, 129.8, 128.7, 128.4, 127.3,

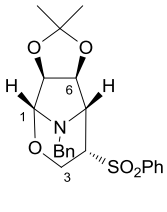
113.3, 90.1, 84.6, 83.1, 61.8, 59.6, 58.4, 52.6, 25.9, 24.8;HRMS (EI) calcd for $C_{22}H_{25}NO_5S$ requires $(M+H)^+$ 416.1526; found 416.1538.



12b

(1*R*,4*R*,5*R*,6*S*,7*S*)-4-phenylsulfonyl-8-propenyl-6,7-isopropilidendioxi-2-oxa-8-azabicyclo[3.2.1]octane 12b.

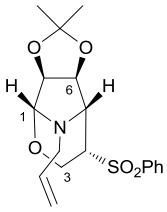
To a stirred solution of isoxazolidine **2c** (49.60 mg, 0.15 mmol) in $CHCl_3$ (2.60 mL) was added dropwise AllylBr (14 μL, 0.15 mmol) and heated at 60ºC. The solution was stirred at 60 ºC for 20 h. Then it was quenched with saturated aqueous solution of NH_4Cl and the product was extracted with DCM (3x15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 8:2) to obtain **12b** (32.9 mg, 60%). $[\alpha]_D^{20}$ = -31.7 (c=0.6, $CHCl_3$);IR (film): 3068.75, 2981.95, 2931.80, 2860.43, 1446.61, 1305.81, 1209.37, 1449.57, 1072.42, 731.02, 605.65 cm^{-1};^{1}H NMR (200 MHz, $CDCl_3$) δ 7.89 (2H, d, *J* = 8.2 Hz, H*orto*), 7.70-7.52 (3H, m, H*para* and H*meta*), 5.75-5.58 (1H, m, H-2'), 5.31 (1H, dd, *J* = 1.8 and 13.6 Hz, H_A-3'), 5.14 (1H, dd, *J* = 1.8 and 13.6 Hz, H_B-3'), 4.70 (1H, s, H-1), 4.62 (1H, d, *J* = 5.4 Hz, H-6), 4.51 (1H, d, *J* = 5.4 Hz, H-7), 4.20-4.09 (2H, m, 2H-3), 4.05 (1H, s, H-5), 3.80-3.55 (2H, m, H-4 and H_A-1'), 3.07-3.01 (1H, m, H_B-1'), 1.48 (3H, s, Me-acetonide), 1.26 (3H, s, Me-acetonide);^{13}C NMR (50 MHz, $CDCl_3$) δ 138.7, 135.3, 134.3, 129.7, 128.8, 117.3, 113.4, 90.3, 84.7, 83.5, 62.3, 59.8, 58.4, 51.9, 26.1, 25.0;HRMS (EI) calcd for $C_{18}H_{24}NO_5S$ requires $(M+H)^+$ 366.1369; found 366.1351.



13a

(1*R*,4*S*,5*R*,6*S*,7*S*)-8-benzyl-4-phenylsulfonyl-6,7-isopropilidendioxi-2-oxa-8-azabicyclo[3.2.1]octane 13a.

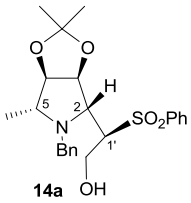
To a stirred solution of isoxazolidine **3c** (28.30 mg, 0.09 mmol) in $CHCl_3$ (1.30 mL) was added dropwise BnBr (10 μL, 0.09 mmol) and heated at 60ºC. The solution was stirred at 60 ºC for 20 h. Then it was quenched with saturated aqueous solution of NH_4Cl and the product was extracted with DCM (3x15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 8:2) to obtain **13a** (24 mg, 67%). $[\alpha]_D^{20}$ = -28.3 (c=0.7, $CHCl_3$); IR (film): 3387, 2978, 2864, 1589, 1397, 1140 cm^{-1};^{1}H NMR (200 MHz, $CDCl_3$) δ 7.84-7.52 (10H, m, H*Ar*), 5.34 (1H, d, *J* = 5.8 Hz, H-6), 4.72 (1H, d, *J* = 5.8 Hz, H-7), 4.50 (1H, s, H-1), 4.14-3.97 (3H, m, CH_2-Bn and 1H-3), 3.84 (1H, t, *J*= 14.8 Hz, H-3), 3.73 (1H, ddd, *J* = 2.6, 6.2 and 8.8 Hz, H-4), 3.56 (1H, s, H-5), 1.52 (3H, s, Me-acetonide), 1.37 (3H, s, Me acetonide);^{13}C NMR (50 MHz, $CDCl_3$) δ 138.1, 137.3, 134.4, 129.8, 128.7, 128.3, 127.5, 112.5, 89.6, 81.4, 77.4, 59.9, 59.8, 54.1, 48.3, 26.4, 25.4; HRMS (EI) calcd for $C_{22}H_{25}NO_5NaS$ requires (M+Na) 438.1345; found 438.1349.



13b

(1*R*,4*S*,5*R*,6*S*,7*S*)-4-phenylsulfonyl-8-propenyl-6,7-isopropilidendioxi-2-oxa-8-azabicyclo[3.2.1]octane 13b.

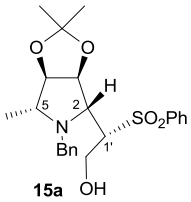
To a stirred solution of isoxazolidine **3c** (74 mg, 0.23 mmol) in $CHCl_3$ (4 mL) was added dropwise AllylBr (20 μL, 0.23 mmol) and heated at 60ºC. The solution was stirred at 60 ºC for 20 h. Then it was quenched with saturated aqueous solution of NH_4Cl and the product was extracted with DCM (3x15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 8:2) to obtain **13b** (113 mg, 74%). $[\alpha]_D^{20}$ = -13.7 (c=0.6, $CHCl_3$); IR (film): 3066.82, 2981.95, 2935.66, 1309.67, 1246.02, 1101.35, 902.69, 866.04, 731.02, 603.72 cm^{-1};^{1}H NMR (200 MHz, $CDCl_3$) δ 7.85 (2H, d, *J*= 8.0 Hz, H*orto*), 7.72-7.52 (3H, m, H*para* and H*meta*), 5.71-5.63 (1H, m, H-2'), 5.33 (1H, d, *J* = 5.4 Hz, H-6), 5.20 (1H, dd, *J* = 1.8 and 7.2 Hz, H_A-3'), 5.02 (1H, dd, *J* = 1.8 and 7.2 Hz, H_B-3'), 4.70 (1H, d, *J* = 5.4 Hz, H-7), 4.51 (1H, s, H-1), 4.02-3.87 (2H, m, 2H-3), 3.60 (1H, s, H-5), 3.59-3.42 (2H, m, H-4 and H_A-1'), 3.29-3.19 (1H, m, H_B-1'), 1.45 (3H, s, Me-acetonide), 1.36 (3H, s, Me-acetonide).);^{13}C NMR (50 MHz, $CDCl_3$) δ 138.1, 134.5, 134.3, 129.9, 128.4, 117.6, 112.6, 89.5, 81.5, 77.9, 59.9, 59.8, 53.9, 46.9, 26.4, 25.5; HRMS (EI) calcd for $C_{18}H_{24}NO_5S$ requires $(M+H)^+$ 366.1369; found 366.1372.



14a

(1'*R*,2*R*,3*S*,4*R*,5*R*)-1-Benzyl-5-methyl-2-(1-phenylsulfonyl-2-hidroxyethyl)-3,4-isopropylidenedioxypyrrolidine 14a.

To a stirred solution of **12a** (10 mg, 0.023 mmol) in Et_2O (1.0 mL) was added dropwise a 3.0 M Et_2O solution of MeMgBr (0.10 mL) at -60ºC. The solution was stirred at -60 ºC for 2 h. Then the mixture was allowed to warm slowly to room temperature. It was quenched with saturated aqueous solution of NH_4Cl and the product was extracted with DCM (3x15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford **14a** (8.50 mg, 85%). $[\alpha]_D^{20}$ = -4.3 (c=0.4, $CHCl_3$); IR (film): 2958.80, 2920.23, 2850.79, 1143.79, 1051.20, 800.46, 584.43 cm^{-1};^{1}H NMR (200 MHz, $CDCl_3$) δ 7.92-7.25 (10H, m, H*Ar*), 5.04 (1H, dd, *J* = 2.6 and 6.0 Hz, H-3), 4.35 (1H, dd, *J* = 3.2 and 6.0 Hz, H-4), 4.01 (1H, dd, *J* = 4.4 and 12.0 Hz, H_A-2'), 3.89 (1H, d, *J* = 13.2 Hz, H_A-CH_2Bn), 3.66-3.56 (2H, m, H-2 and H-21), 3.64 (1H, d, *J* = 13.2 Hz, H_B- CH_2Bn), 3.42-3.36 (1H, m, H-1'), 3.12 (1H, dq, *J* = 3.2 and 7.0 Hz, H-5), 1.45 (3H, s, Me-acetonide), 1.30 (3H, s, Me-acetonide), 1.20 (3H, d, *J* = 7.0 Hz, Me-C-5);^{13}C NMR (50 MHz, $CDCl_3$) δ 138.0, 135.7, 134.2, 129.8, 129.4, 128.8, 128.7, 127.8, 112.5, 86.4, 84.2, 69.0, 66.9, 64.1, 60.0, 59.4, 27.6, 25.3, 19.8;HRMS (EI) calcd for $C_{23}H_{30}NO_5NaS$ requires (M+Na) 454.1658; found 454.1640.

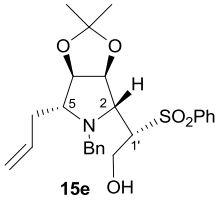


15a

(1'*S*,2*R*,3*S*,4*R*,5*R*)-1-Benzyl-5-methyl-2-(1-phenylsulfonyl-2-hidroxyethyl)-3,4-isopropylidenedioxypyrrolidine 15a.

To a stirred solution of **13a** (50 mg, 0.12 mmol) in Et_2O (1.50 mL) was added dropwise a 3.0 M Et_2O solution of MeMgBr (0.40 mL) at -60ºC. The solution was stirred at -60 ºC for 2 h. Then the mixture was allowed to warm slowly to room temperature. It was quenched with saturated aqueous solution of NH_4Cl and the product was extracted with DCM (3x15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford **15a** (49 mg, 98%). $[\alpha]_D^{20}$ = +5.8 (c=0.7, $CHCl_3$);IR (film): 3473.80, 2985.81, 2964.59, 2933.73, 1448.54, 1381.03, 1307.74, 1043.49, 690.52 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94-7.55 (10H, m, H*Ar*), 4.76 (1H, d, *J*= 6.0 Hz, H-3), 4.09 (1H, t, *J*= 6.5 Hz, H-4), 4.06 (1H, ddd, *J* = 1.0, 4.7 and 11.6 Hz, H_A-2'), 3.96 (1H, dd, *J* = 7.5 and 11.6 Hz, H_B-2'), 3.82 (1H, d, *J* = 13.6 Hz, H_A- CH_2Bn), 3.59 (1H, s, H-2), 3.49 (1H, d, *J* = 13.6 Hz, H_B- CH_2Bn), 3.03-2.99(1H, m, H-1'), 2.70-2.67

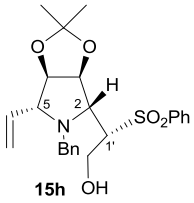
(1H, m, H-5), 1.41 (3H, s, Me-acetonide), 1.29 (3H, s, Me-acetonide), 1.20 (3H, d, *J* = 6.0 Hz, Me-C-5);^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 135.7, 133.9, 129.5, 129.2, 128.8, 128.6, 127.7, 112.5, 84.6, 78.6, 65.7, 63.5, 63.3, 58.4, 56.3, 27.9, 25.8, 17.6;HRMS (EI) calcd for $C_{23}H_{30}NO_5S$ requires $(M+H)^+$ 432.1815; found 432.1824.



15e

(1'*S*,2*R*,3*S*,4*R*,5*R*)-1-Benzyl-2-(1-phenylsulfonyl-2-hidroxyethyl)-5-propenyl-3,4-isopropylidenedioxypyrrolidine 15e.

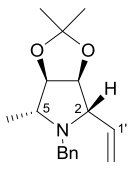
To a stirred solution of **13a** (61.50 mg, 0.15 mmol) in Et_2O (2.20 mL) was added dropwise a 1.0 M Et_2O solution of AllylMgBr (1.50 mL) at -60ºC. The solution was stirred at -60 ºC for 2 h. Then the mixture was allowed to warm slowly to room temperature. It was quenched with saturated aqueous solution of NH_4Cl and the product was extracted with DCM (3x15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford **15e** (58 mg, 85%). $[\alpha]_D^{20}$ = +4.3 (c=0.5, $CHCl_3$);IR (film): 3502.73, 2981.95, 2916.37, 2848.46, 1448.54, 1149.57, 1070.49, 736.81, 590.22 cm^{-1};^{1}H NMR (200 MHz, $CDCl_3$) δ 7.91-7.24 (10H, m, *Ar*), 5.90-5.76 (1H, m, H-2"), 5.20-5.03 (2H, m, H-3"), 4.78 (1H, dd, *J* = 2.0 and 6.2 Hz, H-3), 4.31 (1H, t, *J* = 6.2 Hz, H-4), 4.09-3.98 (2H, m, H-2'), 3.91 (1H, d, *J* = 13.2 Hz, H_A- CH_2Bn), 3.58 (1H, s, H-2), 3.56 (1H, d, *J* = 13.2 Hz, H_B- CH_2Bn), 3.09-2.95 (1H, m, H-1'), 2.48-2.16 (3H, m, H-5, H-1"), 1.42 (3H, s, Me-acetonide), 1.29 (3H, s, Me-acetonide).;^{13}C NMR (50 MHz, $CDCl_3$) δ 138.8, 138.3, 136.2, 135.7, 134.3, 129.7, 129.4, 129.3, 128.5, 127.3, 118.4, 112.7, 82.4, 79.0, 67.6, 65.4, 64.1, 58.4, 57.1, 36.2, 28.1, 26.0;HRMS (EI) calcd for $C_{25}H_{32}NO_5S$ $(M+H)^+$, 458.1995.; found 458.1978.



15h

(1'*S*,2*R*,3*S*,4*R*,5*R*)-1-Benzyl-2-(1-phenylsulfonyl-2-hidroxyethyl)-5-vinyl-3,4-isopropylidenedioxypyrrolidine 15h.

To a stirred solution of **13a** (42 mg, 0.10 mmol) in Et_2O (1.5 mL) was added dropwise a 1.0 M THF solution of VinylMgBr (20 mL) at -60ºC. The solution was stirred at -60 ºC for 2 h. Then the mixture was allowed to warm slowly to room temperature. It was quenched with saturated aqueous solution of NH_4Cl and the product was extracted with DCM (3x15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford **15h** (24 mg, 54%). $[\alpha]_D^{20}$ = +40 (c=0.3, $CHCl_3$);IR (film): 2983.88, 2920.23, 2848.80, 1448.54, 1215.15, 1070.44, 690.52 cm^{-1};^{1}H NMR (200 MHz, $CDCl_3$) δ 7.97-6.95 (10H, m, *Ar*), 5.79-5.61 (1H, m, H-1"), 5.40-5.29 (2H, m, H-2"), 4.79 (1H, dd, *J* = 1.2 and 5.6 Hz, H-3), 4.26 (1H, t, *J* = 7.0 Hz, H-4), 4.07 (1H, dd, *J* = 4.2 and 11.8 Hz, H-2_A'), 3.93 (1H, dd, *J* = 5.8 and 11.8 Hz, H-2_B'), 3.89 (1H, d, *J* = 13.2 Hz, H_A- CH_2Bn), 3.60 (1H, s, H-2), 3.35 (1H, d, *J* = 13.2 Hz, H_B- CH_2Bn), 3.08 (1H, t, *J* = 7.8 Hz, H-1"), 2.93-2.95 (1H, m, H-1'), 1.46 (3H, s, Me-acetonide), 1.30 (3H, s, Me-acetonide).;^{13}C NMR (50 MHz, $CDCl_3$) δ 138.2, 137.3, 135.8, 134.4, 129.9, 129.5, 129.2, 128.8, 128.1, 120.1 112.8, 83.2, 79.3, 72.4 64.9, 63.7, 58.5, 56.1, 28.2, 26.1;HRMS (EI) calcd for $C_{25}H_{32}NO_5NaS$ (M+ Na), 466.1658.; found 466.1660.



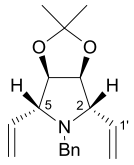
16

(2*S*,3*S*,4*R*,5*R*)-1-Benzyl-3,4-isopropylidenedioxy-5-methyl-2-vinylpyrrolidine 16.

a) To a solution of pyrrolidine **15a** (40 mg, 0.09 mmol) in MeOH (1.5 mL) was added 128 mg (0.28 mmol) of 5% Na (Hg) amalgam at r.t. The mixture was stirred for 2 h at this temperature under an

argon atmosphere. Next, it was filtered to eliminate the Hg residue and diluted with DCM, 30mL. The mixture was washed with brine, dried (Na_2SO_4), filtered, and concentrated. The resulting crude residue was purified by flash chromatography (silica gel, n-hexane/EtOAc 6:4) to obtain **16** (25 mg, 100%). $[\alpha]_D^{20}$ = -5.0 (c=0.5, CH_2Cl_2);IR (film): 2980.02, 2964.59, 2929.87, 1448.54, 1246.02, 1147.65, 1070.49, 866.04 cm^{-1};^{1}H NMR (200 MHz, $CDCl_3$) δ 7.31-7.21 (5H, m, H*Ar*), 5.84-5.66 (1H, m, H-1'), 5.39-5.20 (2H, m, H-2'), 4.29 (1H, dd, *J*= 5.0 and 6.8 Hz, H-3), 4.16 (1H, dd, *J*= 4.8 and 6.8 Hz, H-4), 3.84 (1H, d, *J* = 14.6 Hz, H_A- CH_2Bn), 3.57 (1H, d, *J* = 14.6 Hz, H_B- CH_2Bn), 3.09 (1H, dd, *J*= 5.0 and 8.4 Hz, H-2), 2.70-2.64 (1H, m, H-5), 1.43 (3H, s, Me-acetonide), 1.29 (3H, s, Me-acetonide), 1.22 (3H, d, *J* = 5.6 Hz, Me-C-5);^{13}C NMR (50 MHz, $CDCl_3$) δ 138.8, 137.6, 129.5, 128.2, 127.1, 118.9, 113.5, 85.4, 83.5, 72.9, 63.9, 53.4, 27.5, 25.6, 18.5;HRMS (EI) calcd for $C_{17}H_{24}NO_2$ requires $(M+H)^+$ 274.1801; found 274.1800.

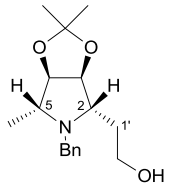
b) To a solution of pyrrolidine **14a** (10 mg, 0.02 mmol) in MeOH (1 mL) was added 48 mg (0.06 mmol) of 5% Na (Hg) amalgam at r.t. The mixture was stirred for 2 h at this temperature under an argon atmosphere. Next, it was filtered to eliminate the Hg residue and diluted with DCM, 30mL. The mixture was washed with brine, dried (Na_2SO_4), filtered, and concentrated. The resulting crude residue was purified by flash chromatography (silica gel, n-hexane/EtOAc 6:4) to obtain **16** (6 mg, 100%).



17

(2*S*,3*S*,4*R*,5*R*)-1-Benzyl-2,5-divinyl-3,4-isopropylidenedioxypyrrolidine 17.

To a solution of pyrrolidine **15h** (24 mg, 0.06 mmol) in MeOH (1 mL) was added 75 mg (0.16 mmol) of 5% Na (Hg) amalgam at r.t. The mixture was stirred for 2 h at this temperature under an argon atmosphere. Next, it was filtered to eliminate the Hg residue and diluted with DCM, 30mL. The mixture was washed with brine, dried (Na_2SO_4), filtered, and concentrated. The resulting crude residue was purified by flash chromatography (silica gel, n-hexane/EtOAc 6:4) to obtain **17** (17 mg, 100%). IR (film): 2981.95, 2924.09, 1375.25, 1267.23, 1072.42, 921.97, 866.04, 704.02 cm^{-1};^{1}H NMR (200 MHz, $CDCl_3$) δ 7.26-7.21 (5H, m, H*Ar*), 5.82-5.84 (2H, m, H-1'), 5.38 (2H, d, *J*= 1.8 Hz, H_A-2'), 5.20 (2H, dd, *J*= 5.0 and 6.8 Hz, H_B-2'), 4.30 (2H, dd, *J*= 1.2 and 3.0 Hz, H-3 and H-4), 3.70 (2H, bs, CH_2Bn), 3.12 (2H, dd, *J*= 1.8 and 7.8 Hz, H-2 and H-5), 1.42 (3H, s, Me-acetonide), 1.27 (3H, s, Me-acetonide);^{13}C NMR (50 MHz, $CDCl_3$) δ 138.5, 136.5, 130.1, 128.1, 127.1, 118.9, 113.7, 83.7, 77.3, 71.7, 52.6, 27.4, 25.6;HRMS (EI) calcd for $C_{18}H_{24}NO_2$ requires $(M+H)^+$ 286.1803; found 286.1801.

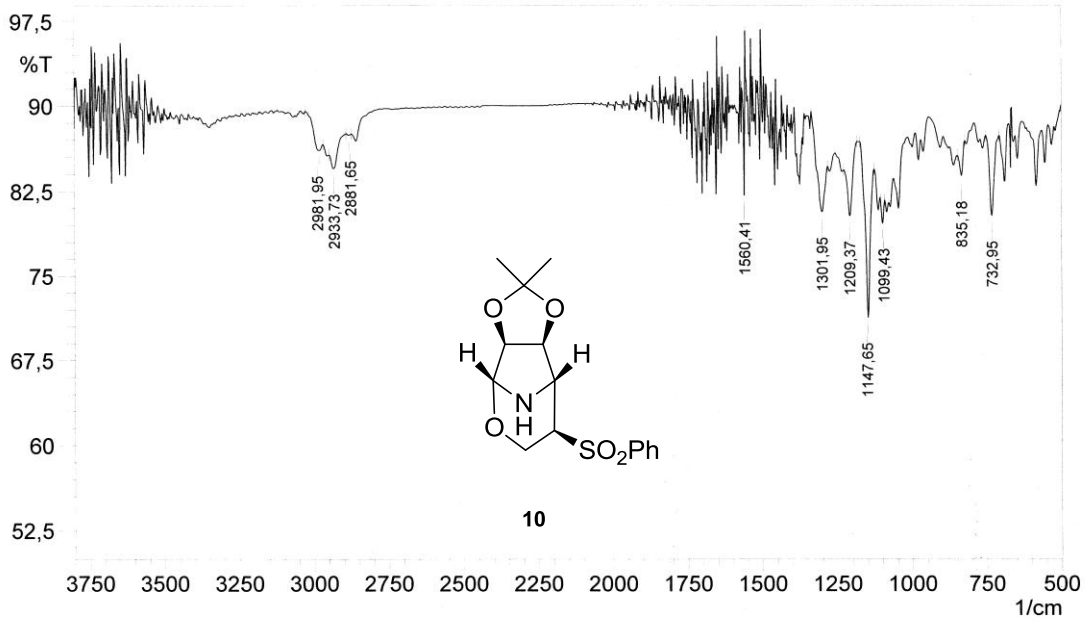


18

(2*S*,3*S*,4*R*,5*R*)-1-Benzyl-3,4-isopropylidenedioxy-5-methylpyrrolidine-2-ethanol 18.

9-BBn (1.8 ml, 0.9 mmol) was added to a solution of vinylpyrrolidine **16** (50 mg, 0.18 mmol) in THF (1.50 mL) at 0ºC. The reaction mixture was stirred at r.t. for 4h. a saturated aqueous solution of $NaBO_3$ was added and the resulting mixture was stirred at r.t. for 18h. The reaction product was then extracted with DCM (3x15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The resulting crude residue was purified by flash chromatography (silica gel, n-hexane/EtOAc 6:4) to obtain **18** (15 mg, 30%). $[\alpha]_D^{20}$ = -12.8 (c=0.8, CH_3Cl); IR (film): 3396.7, 2980.02, 2931.80, 2866.22, 1452.40, 1340.53, 1028.06, 732.95, 702.09 cm^{-1};^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33-7.17 (5H, m, H*Ar*), 4.29 (1H, dd, *J*= 5.0 and 6.8 Hz, H-3), 4.16 (1H, dd, *J*= 4.6 and 6.8 Hz, H-4), 4.05-3.99 (1H, m, H_A-2'), 3.84 (1H, d, *J* = 14.3 Hz, H_A- CH_2Bn), 3.59 (1H, d, *J* = 14.3 Hz, H_B- CH_2Bn), 3.54-3.40 (1H, m, H_B-2'), 3.12-3.05 (1H, m,

H-2), 2.70-2.64 (1H, m, H-5), 1.95-1.85 (1H, m, H_A-1'), 1.83-1.75 (1H, m, H_B-1'), 1.44 (3H, s, Me-acetonide), 1.29 (3H, s, Me-acetonide), 1.17 (3H, d, *J* = 5.6 Hz, Me-C-5);^{13}C NMR (50 MHz, $CDCl_3$) δ 135.2, 132.3, 130.4, 128.6, 113.2, 83.5, 81.2, 72.7, 68.663.5, 54.4, 27.6, 24.3, 17.6;HRMS (EI) calcd for $C_{17}H_{26}NO_3$ requires $(M+H)^+$ 292.1907; found 292.1911.



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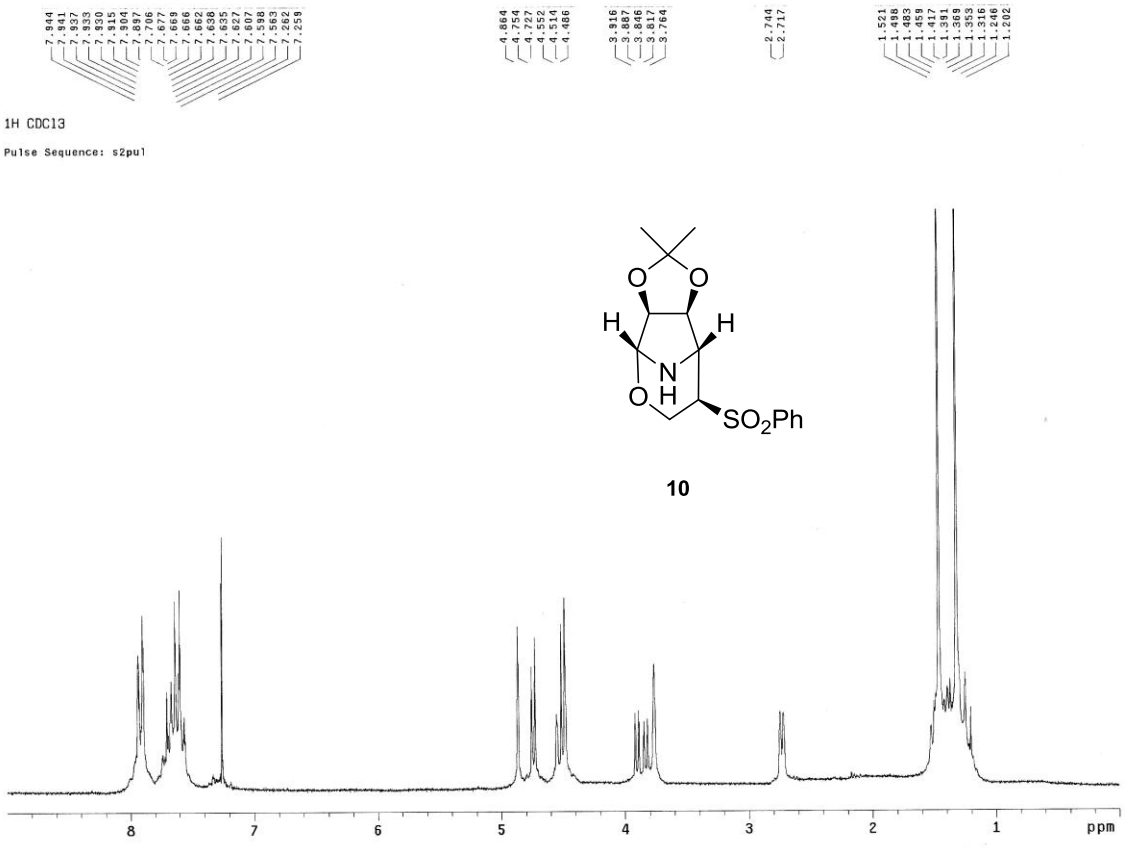

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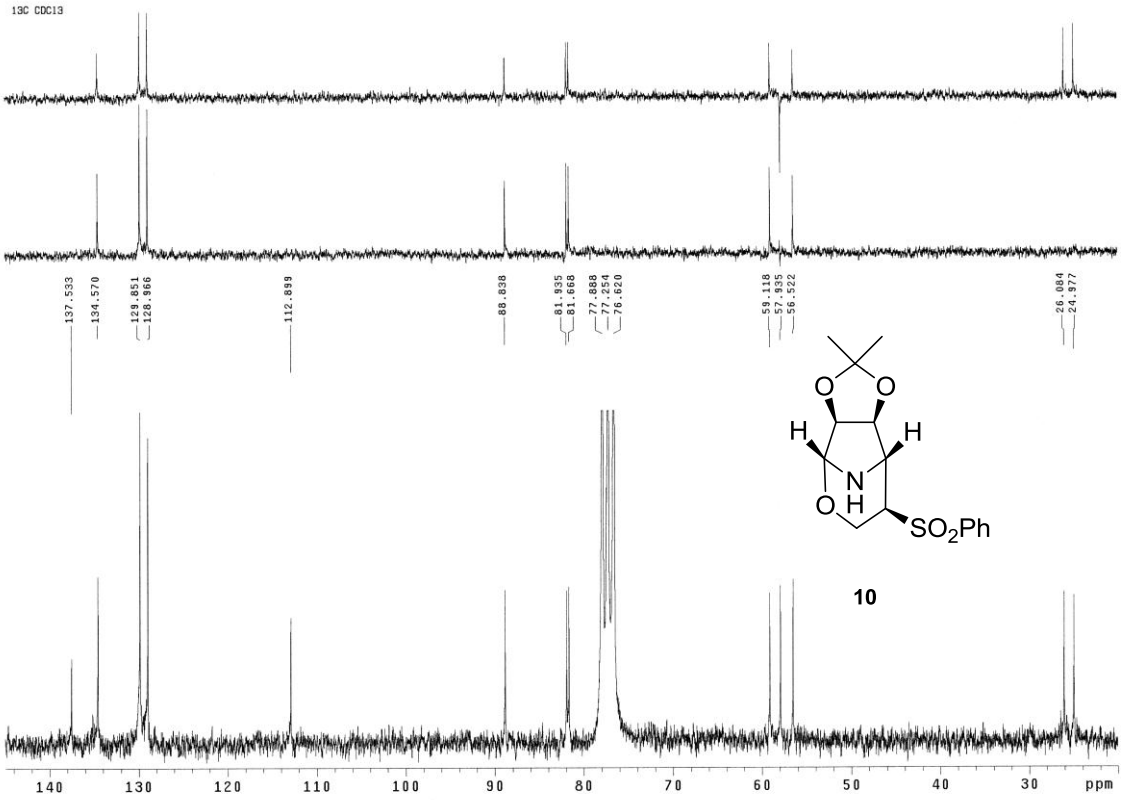

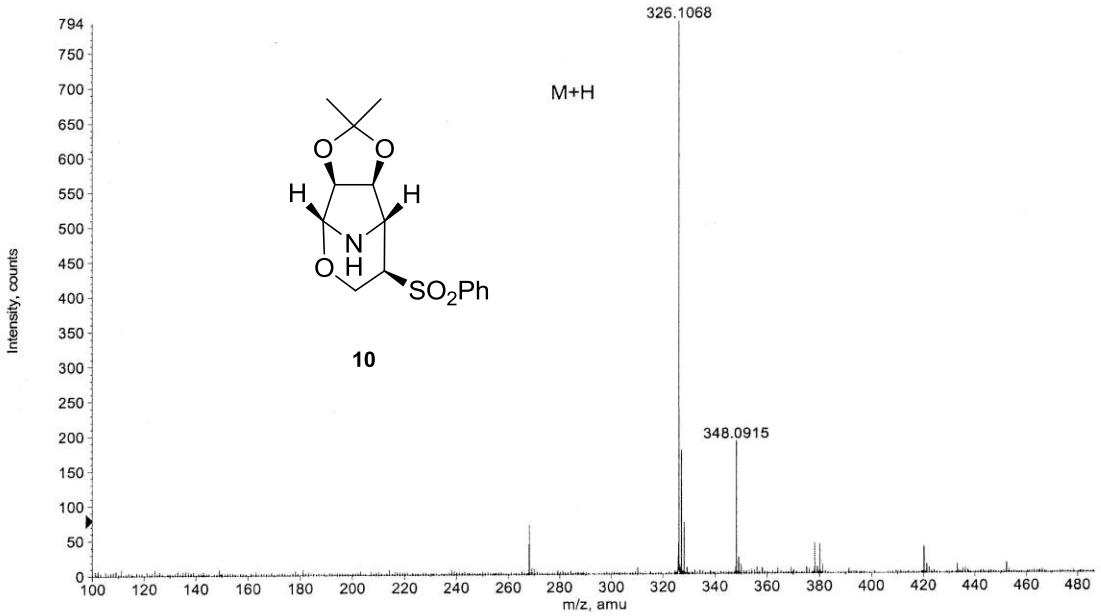

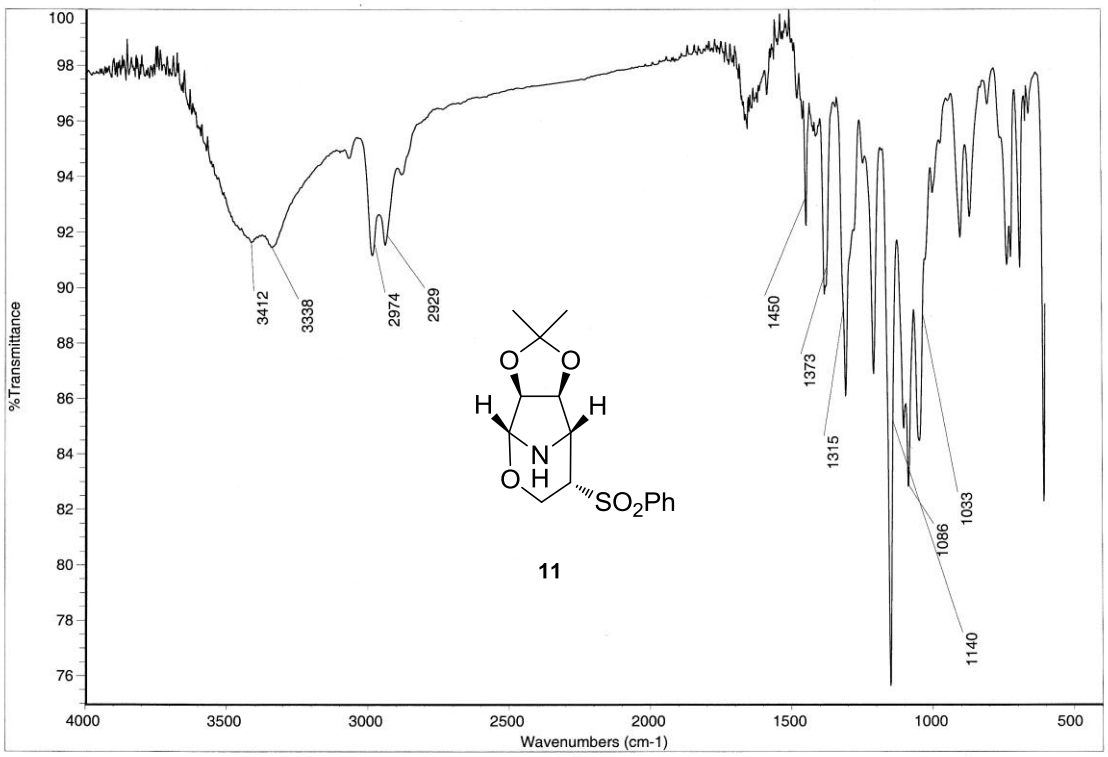

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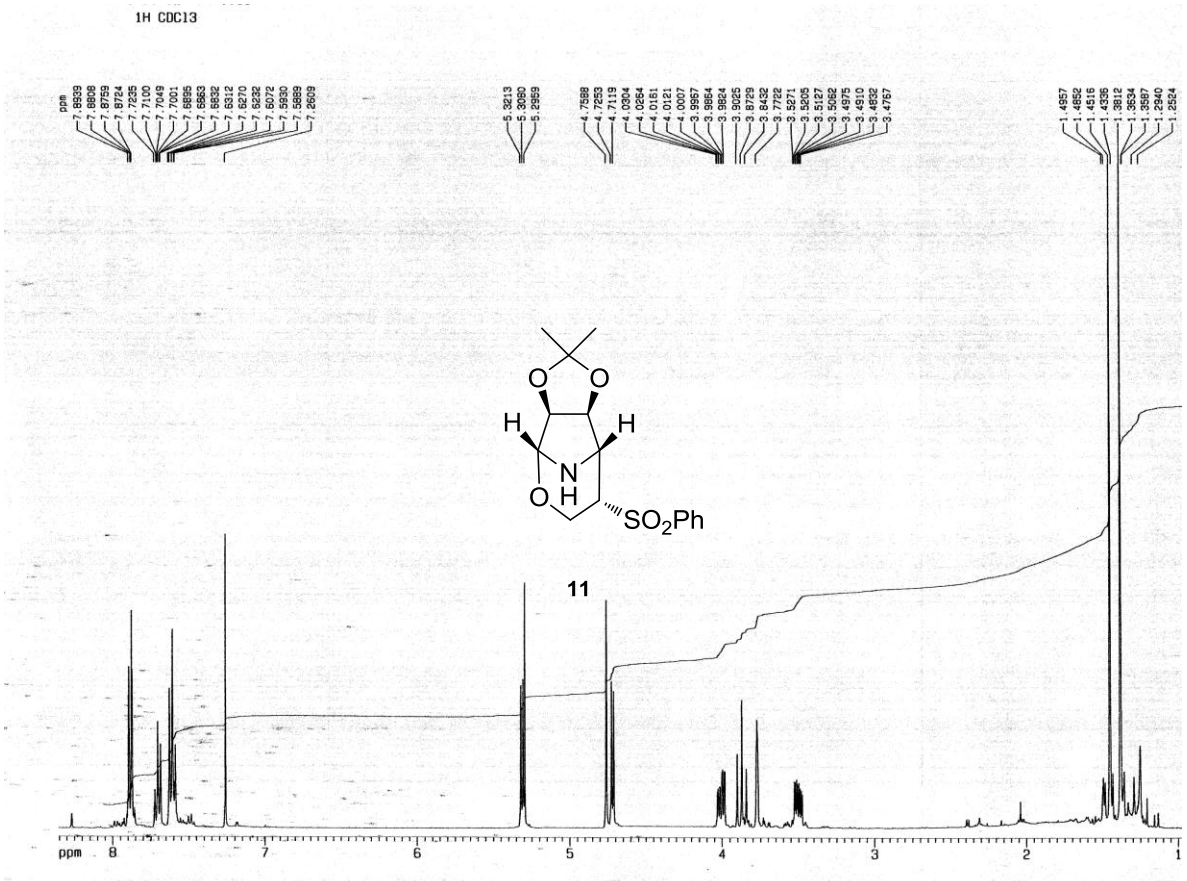

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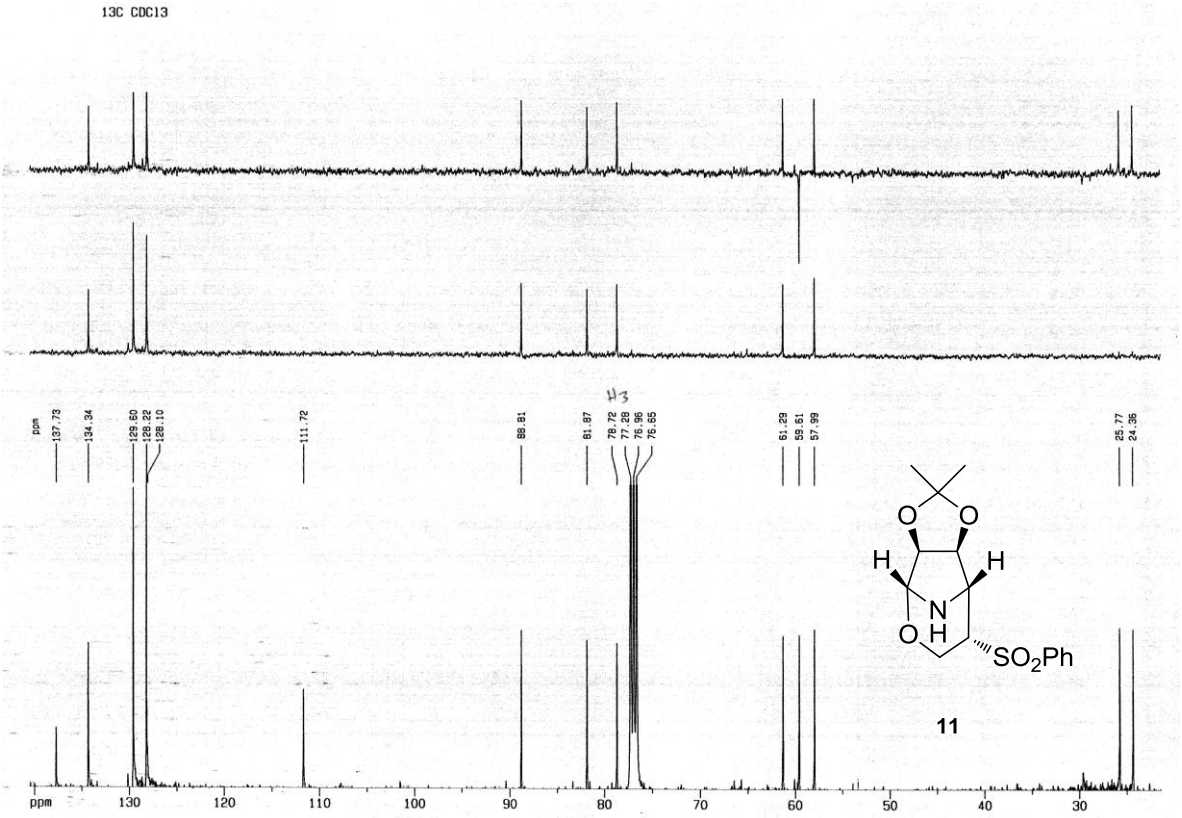
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H
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H
SO2Ph
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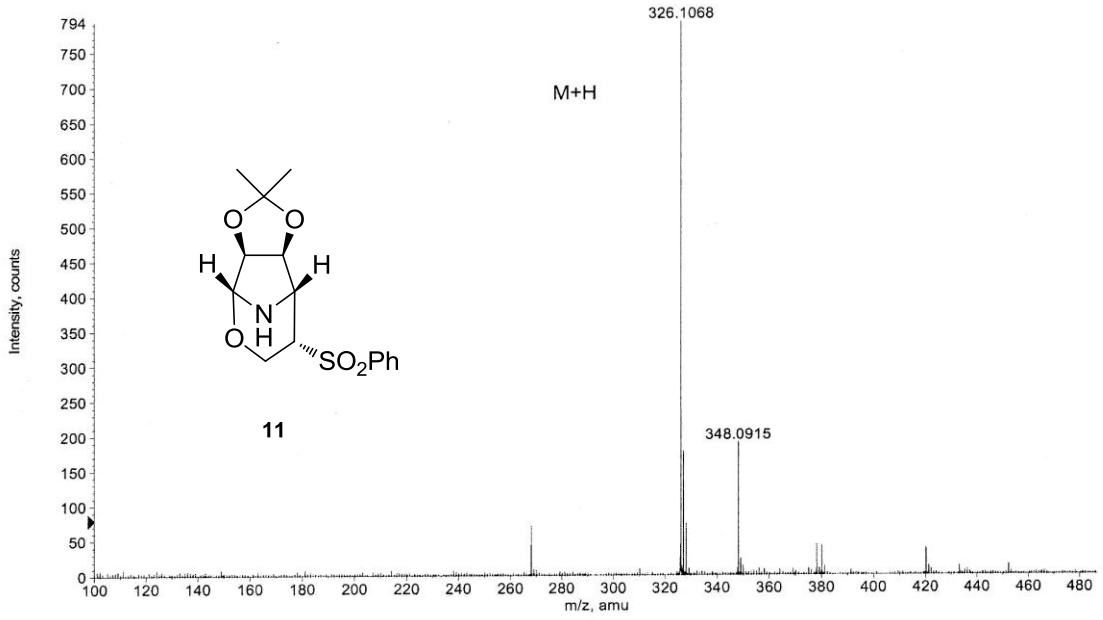
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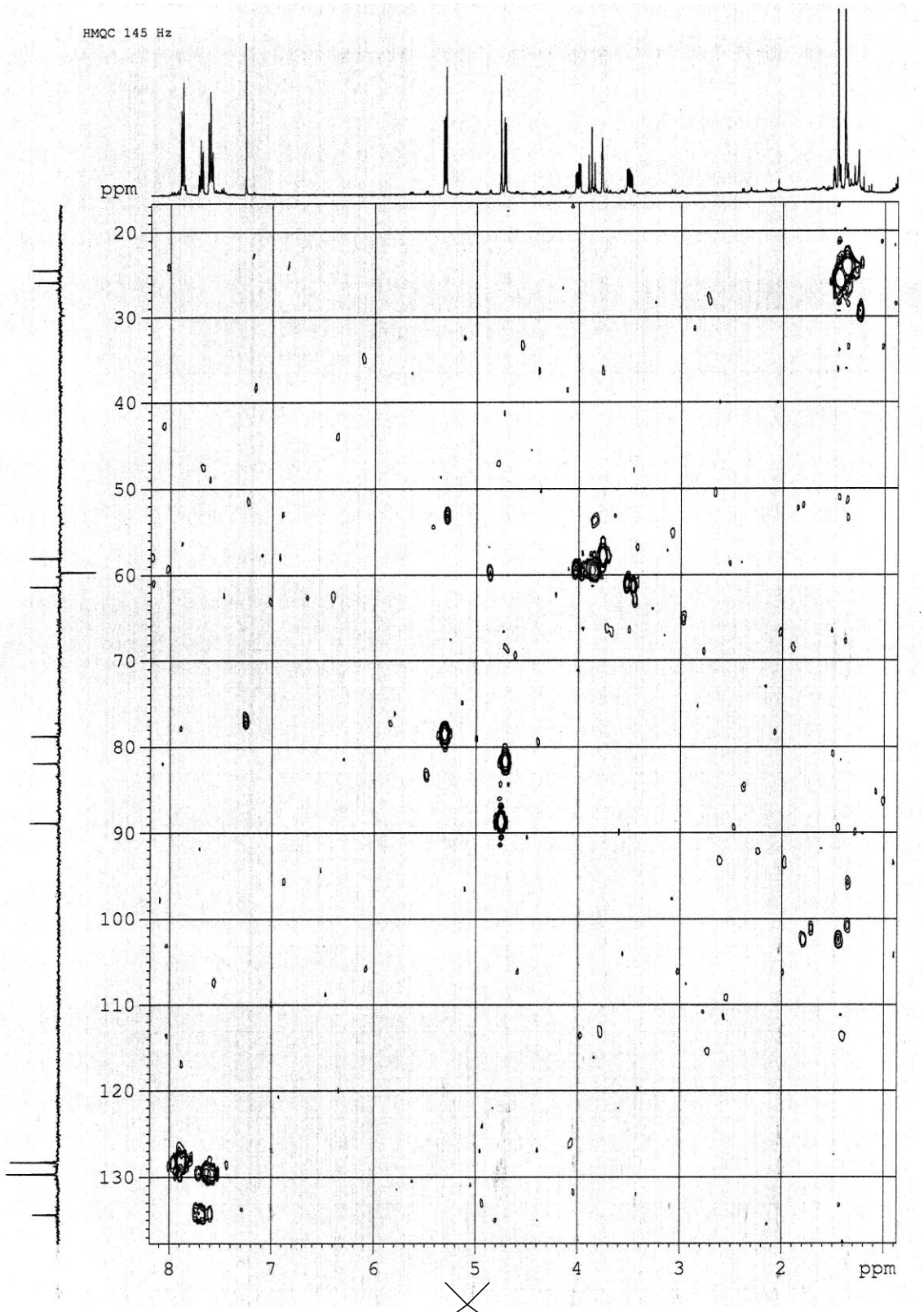

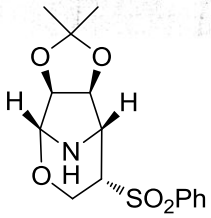

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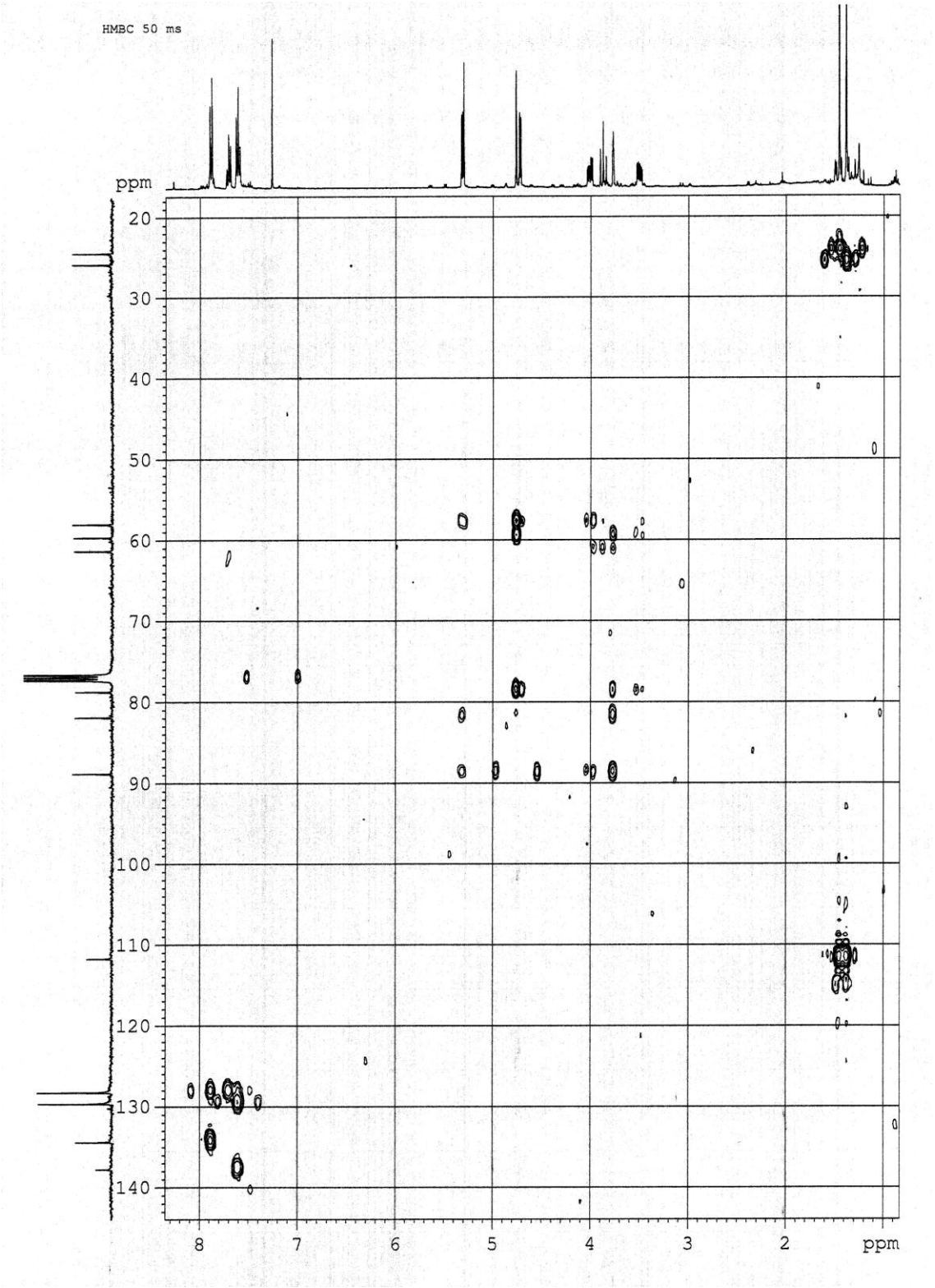

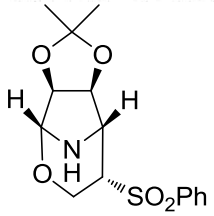

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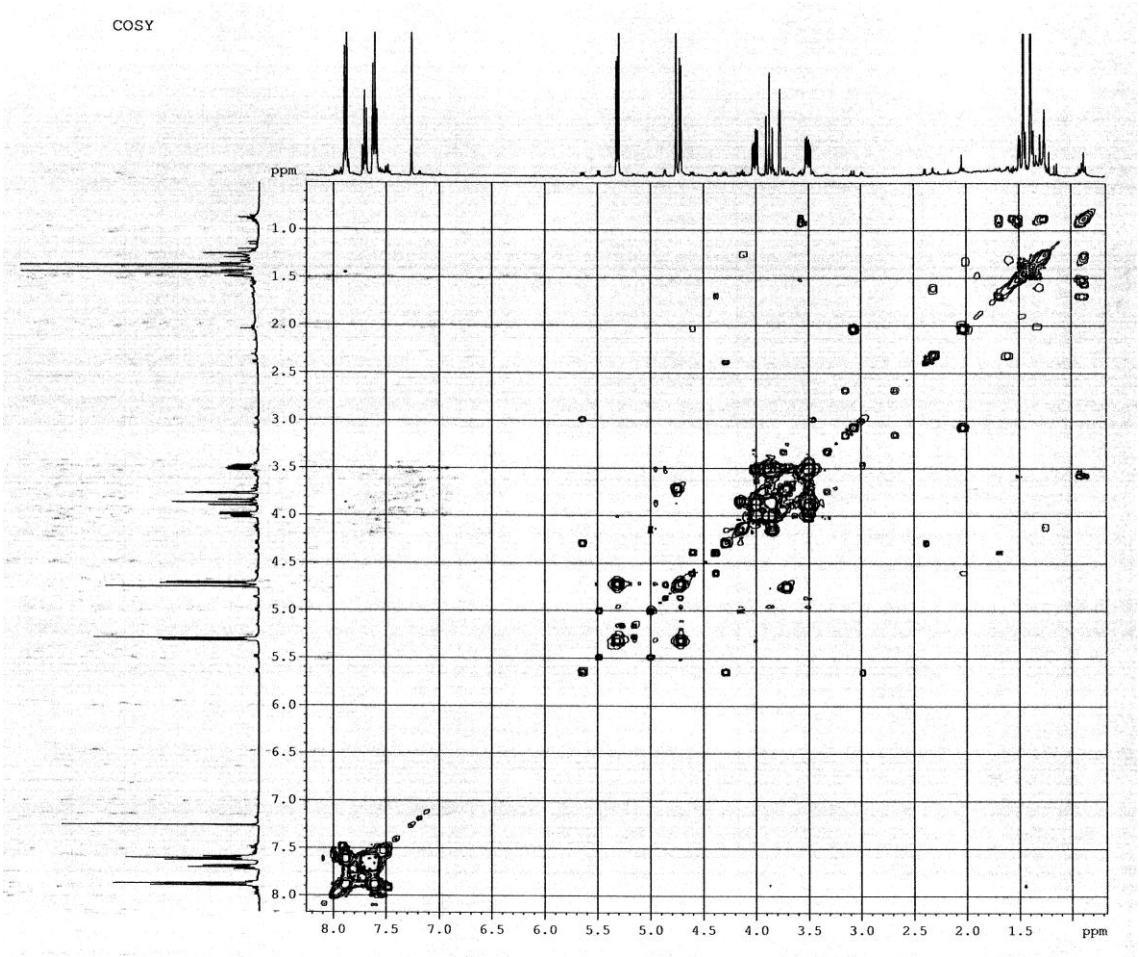

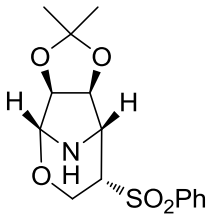

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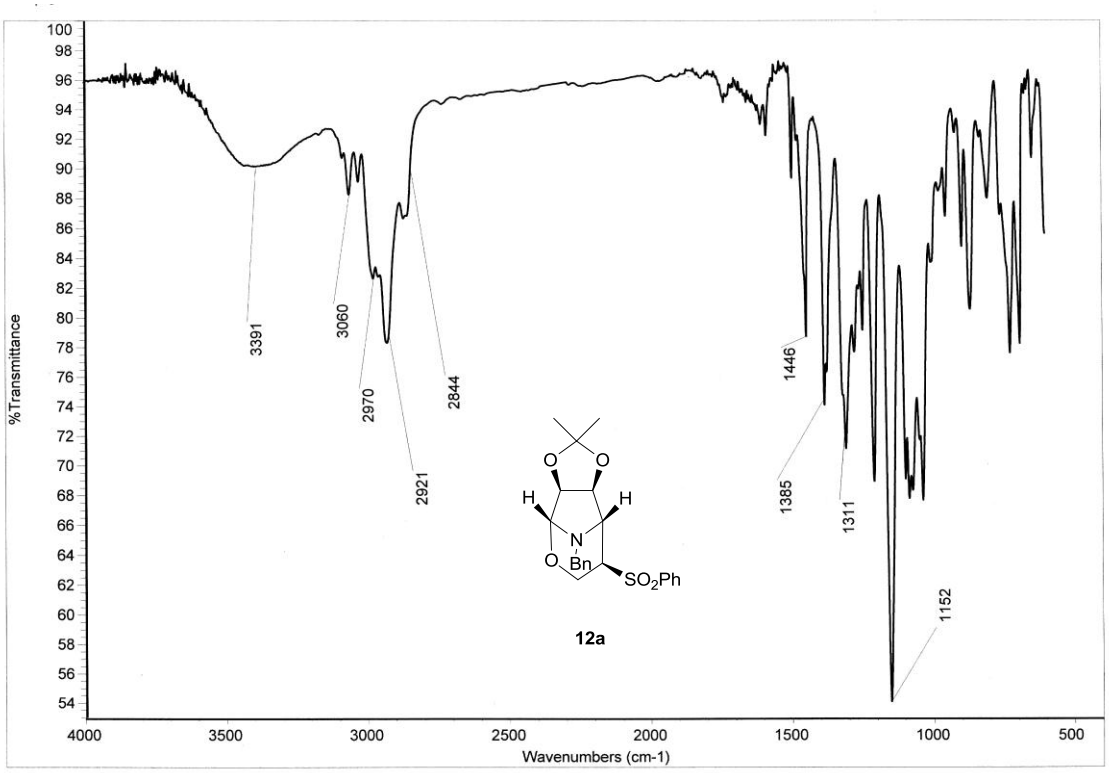

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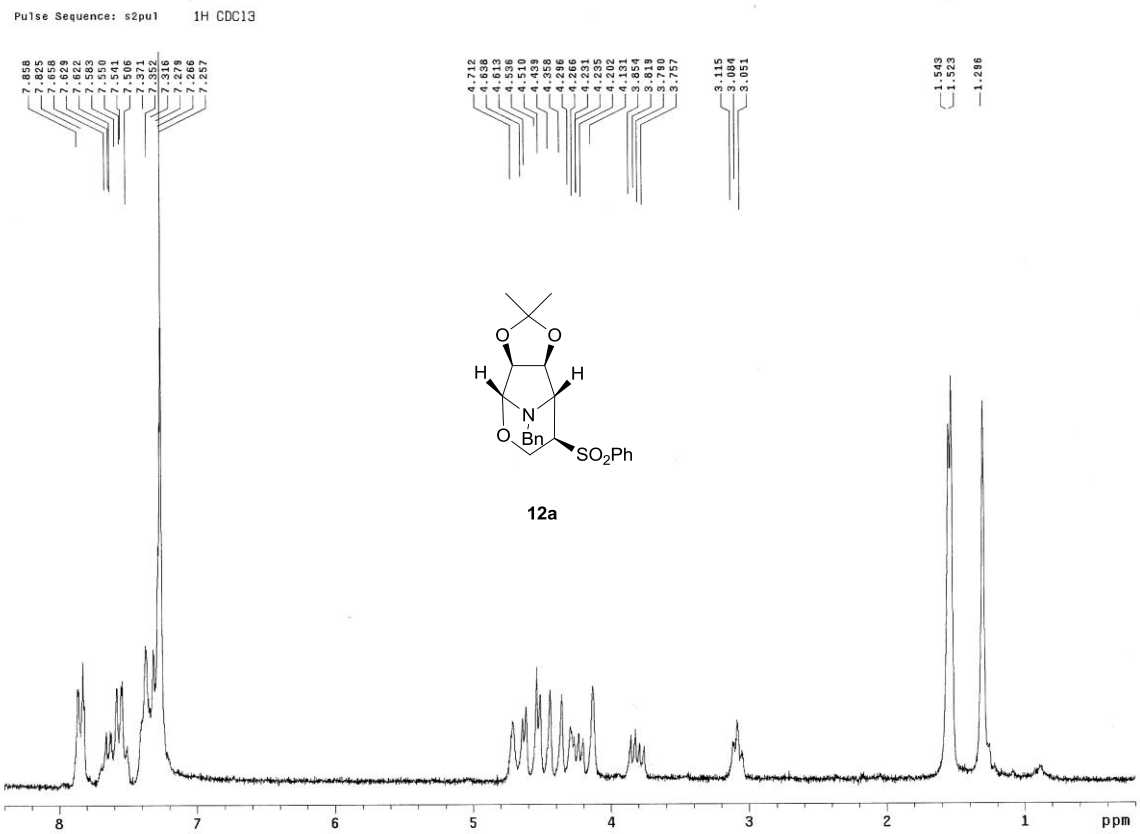

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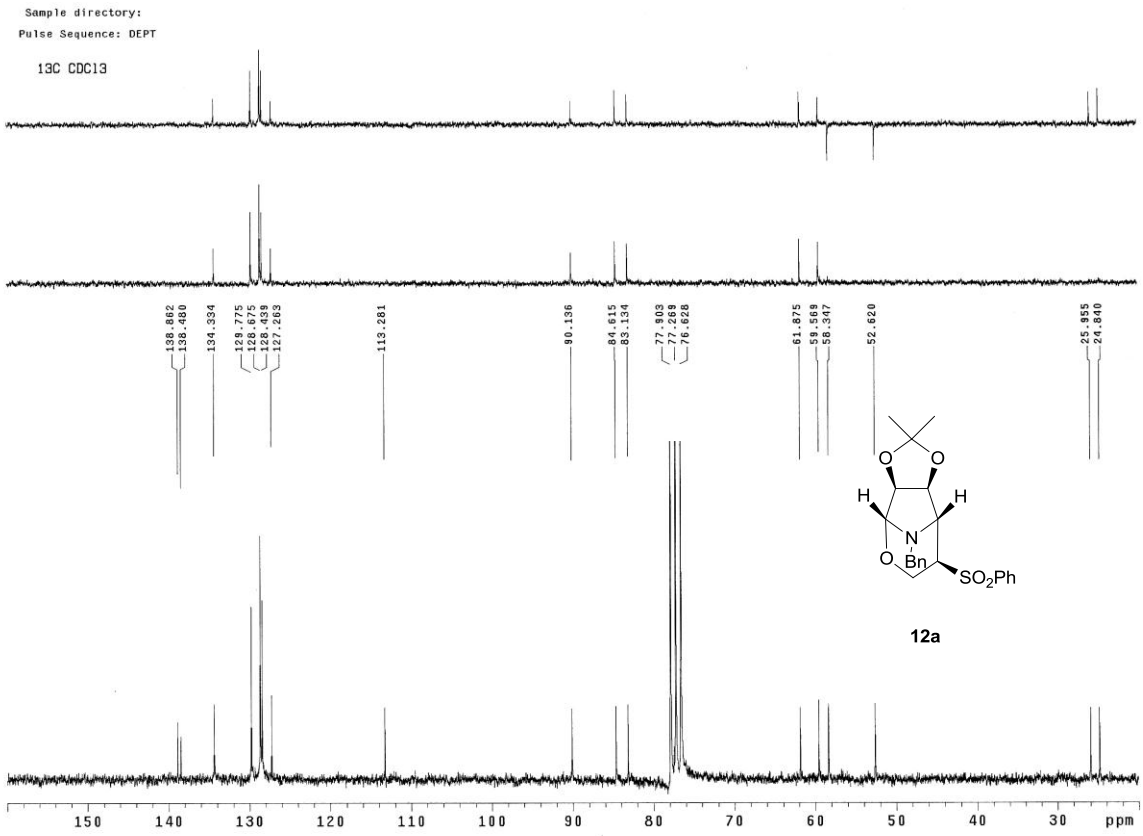

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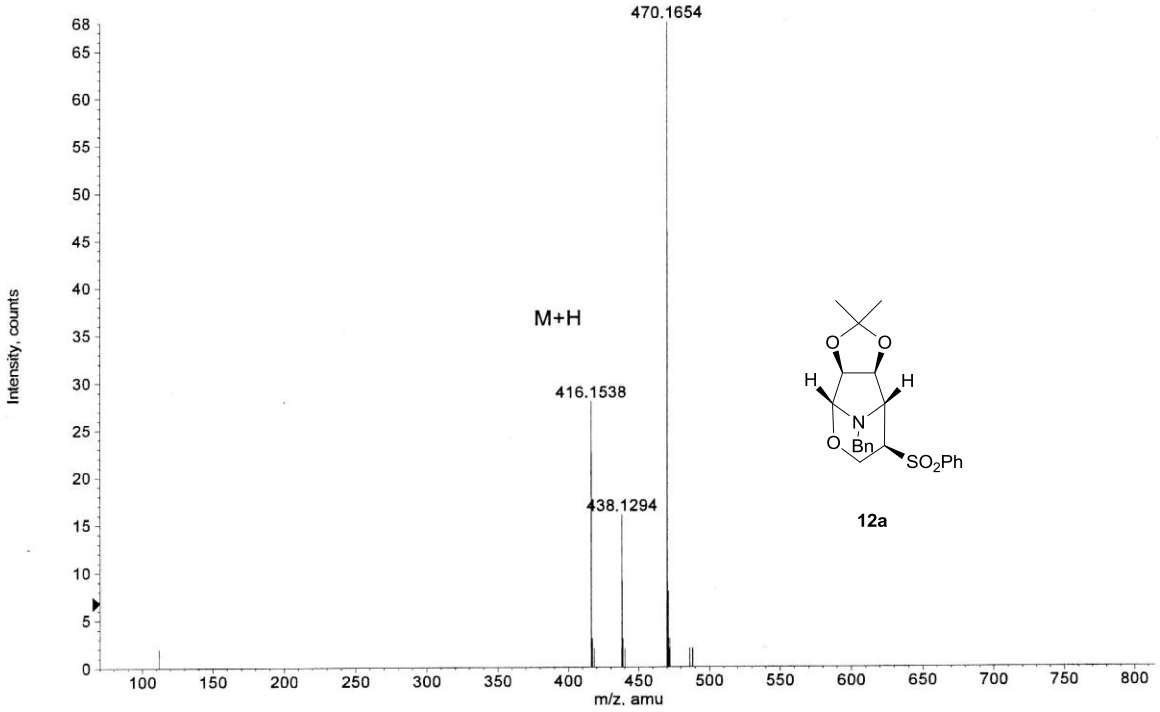

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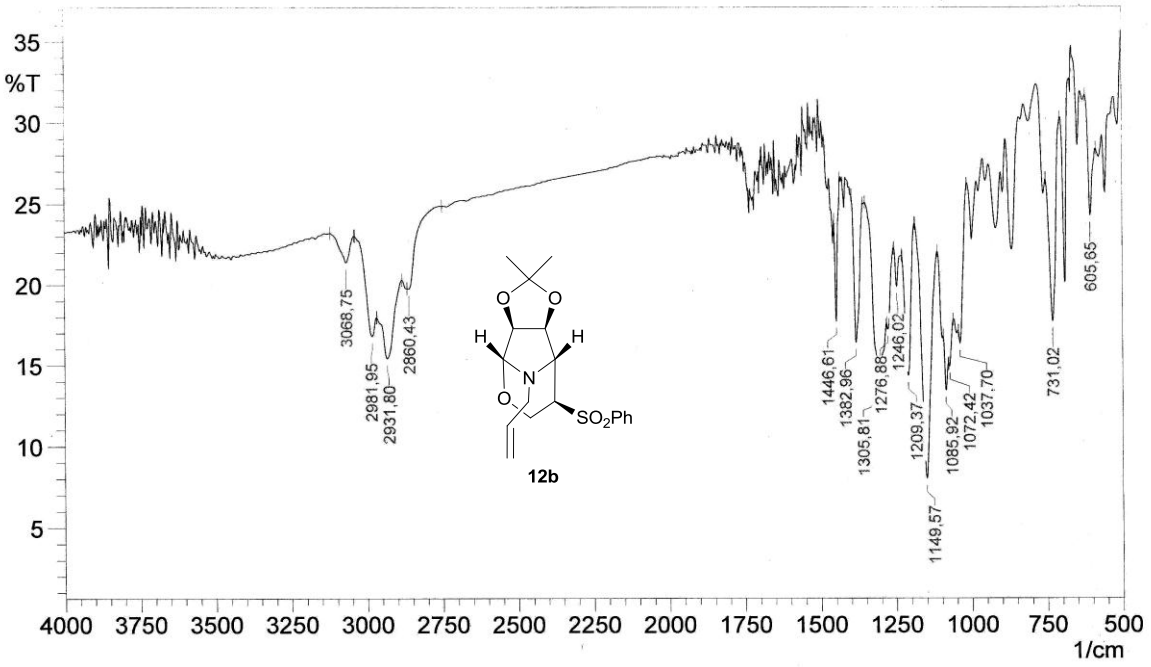

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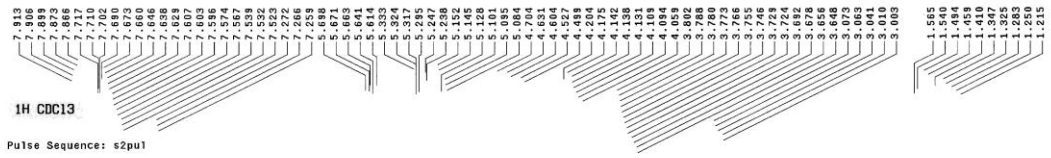

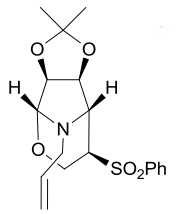

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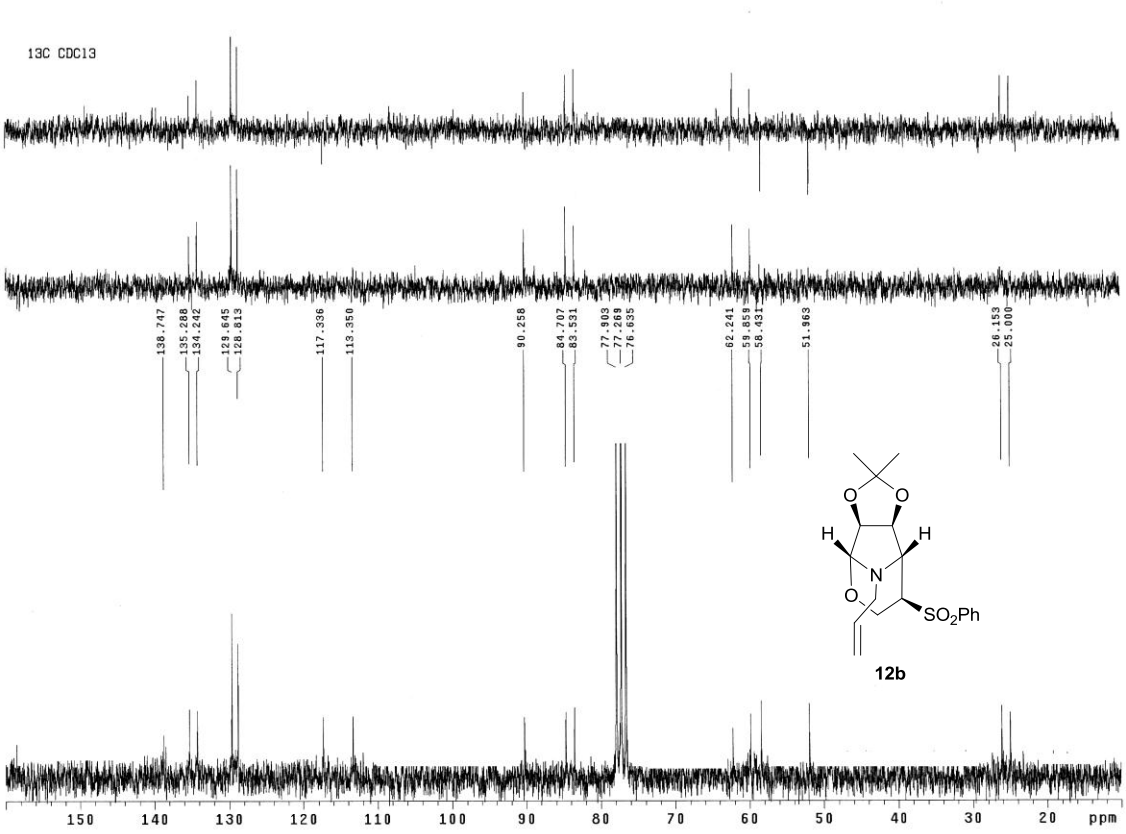

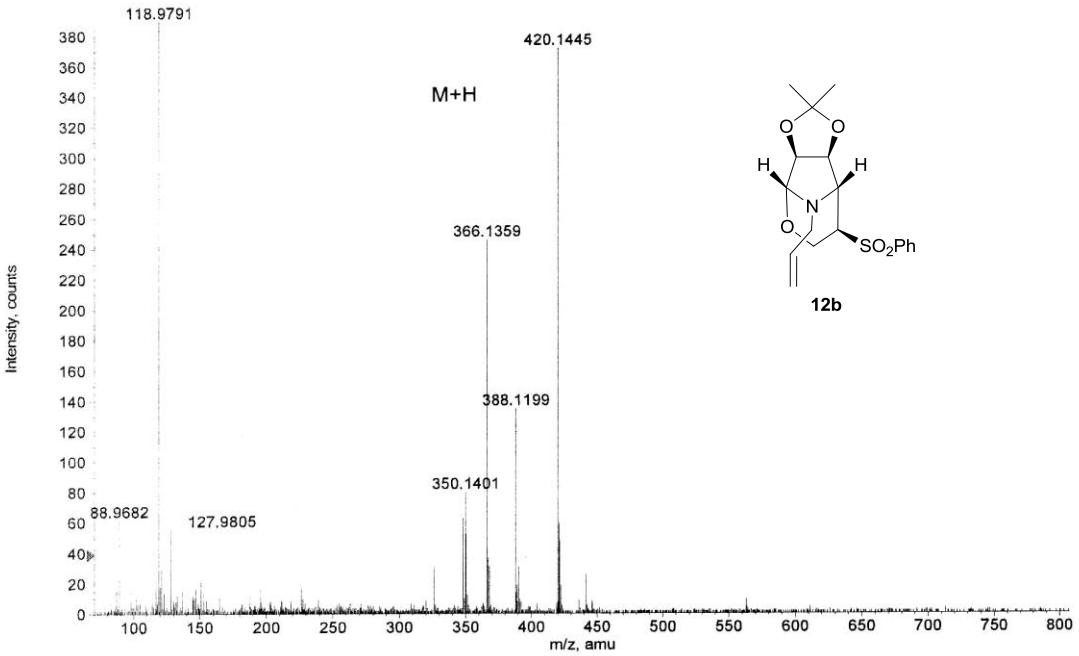

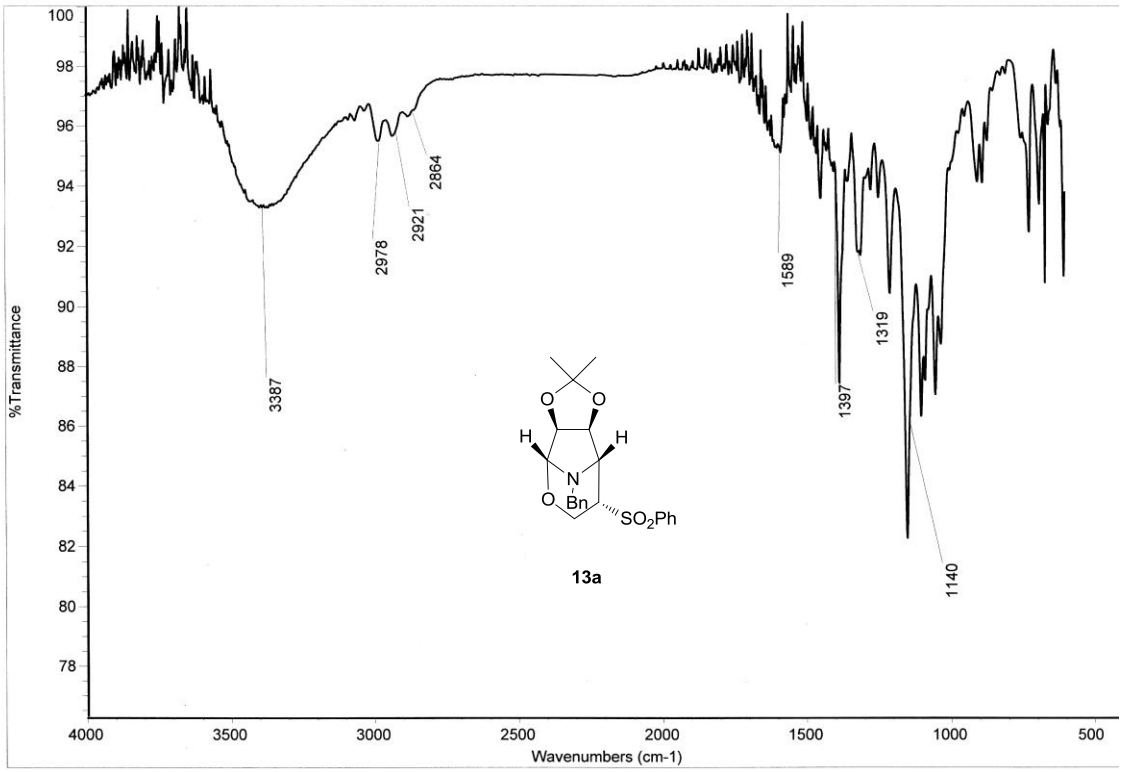

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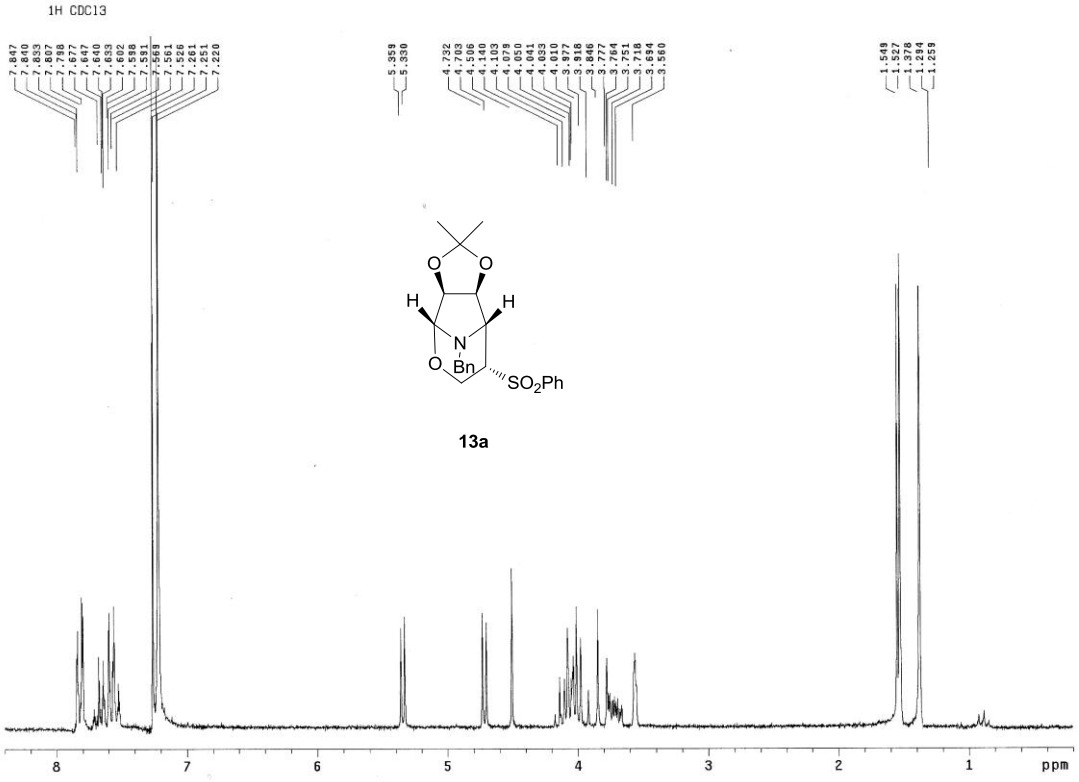

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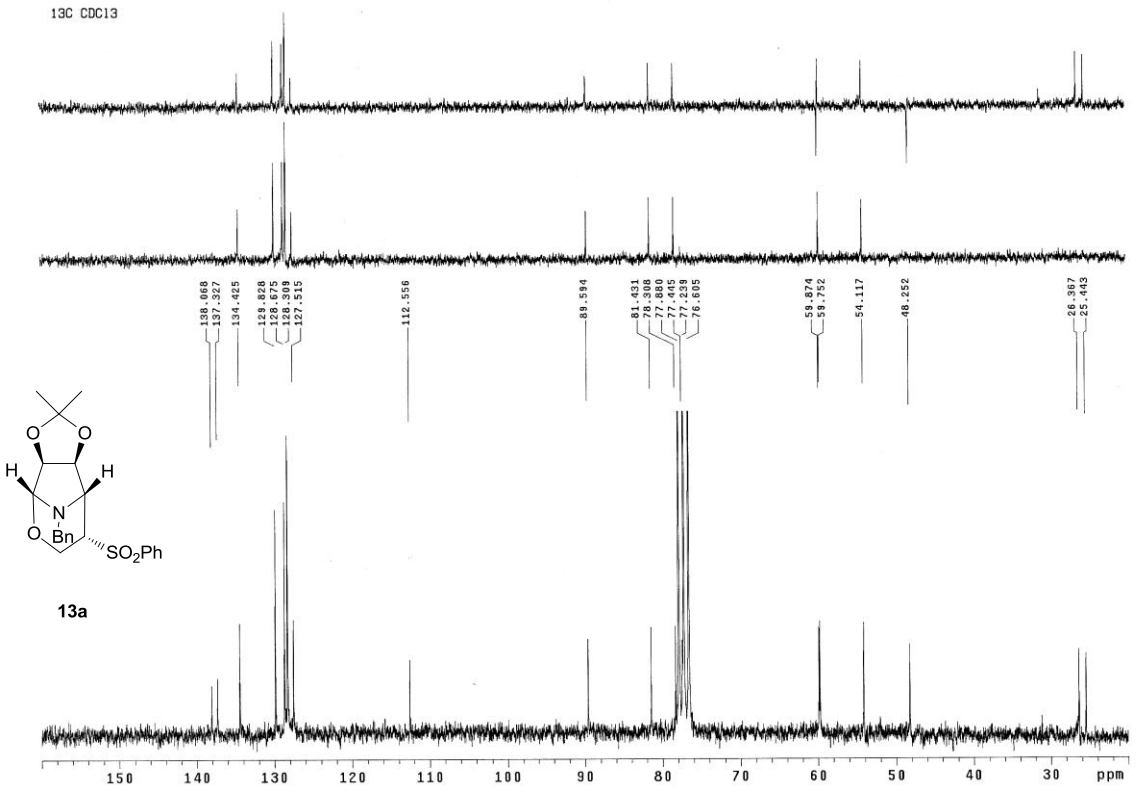

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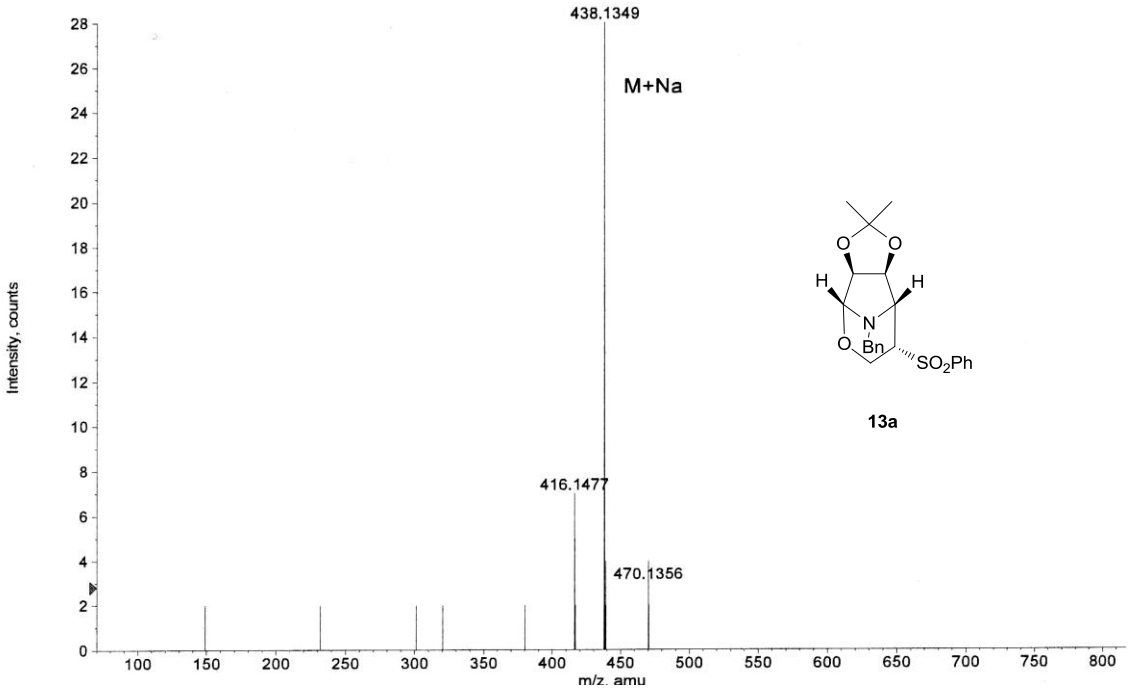

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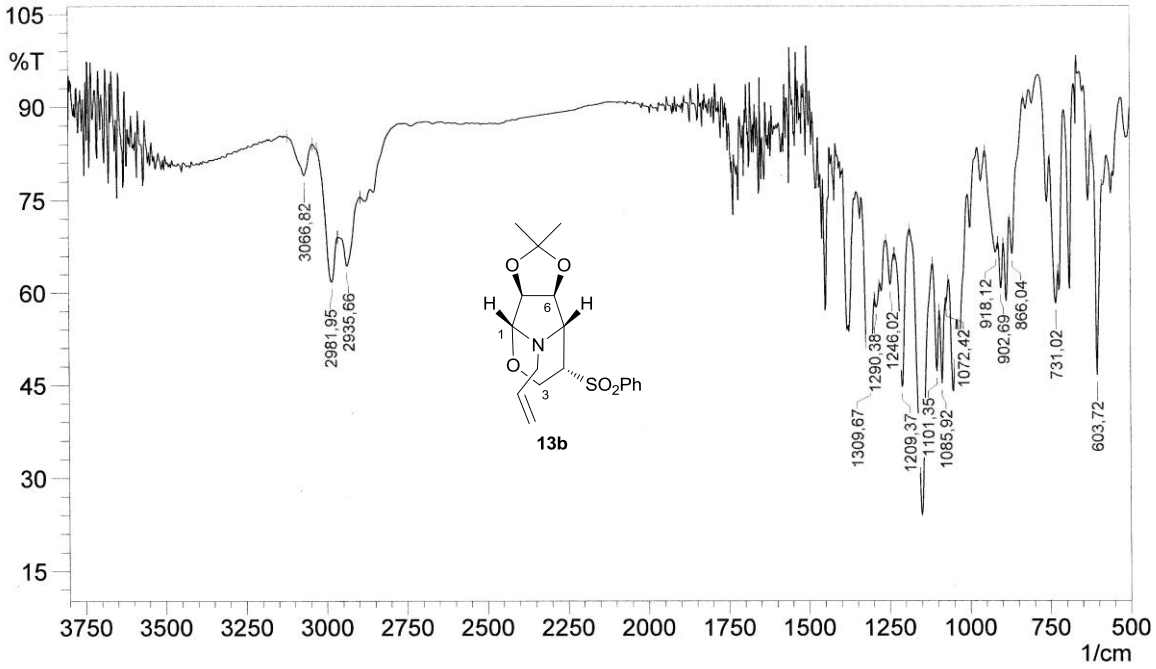
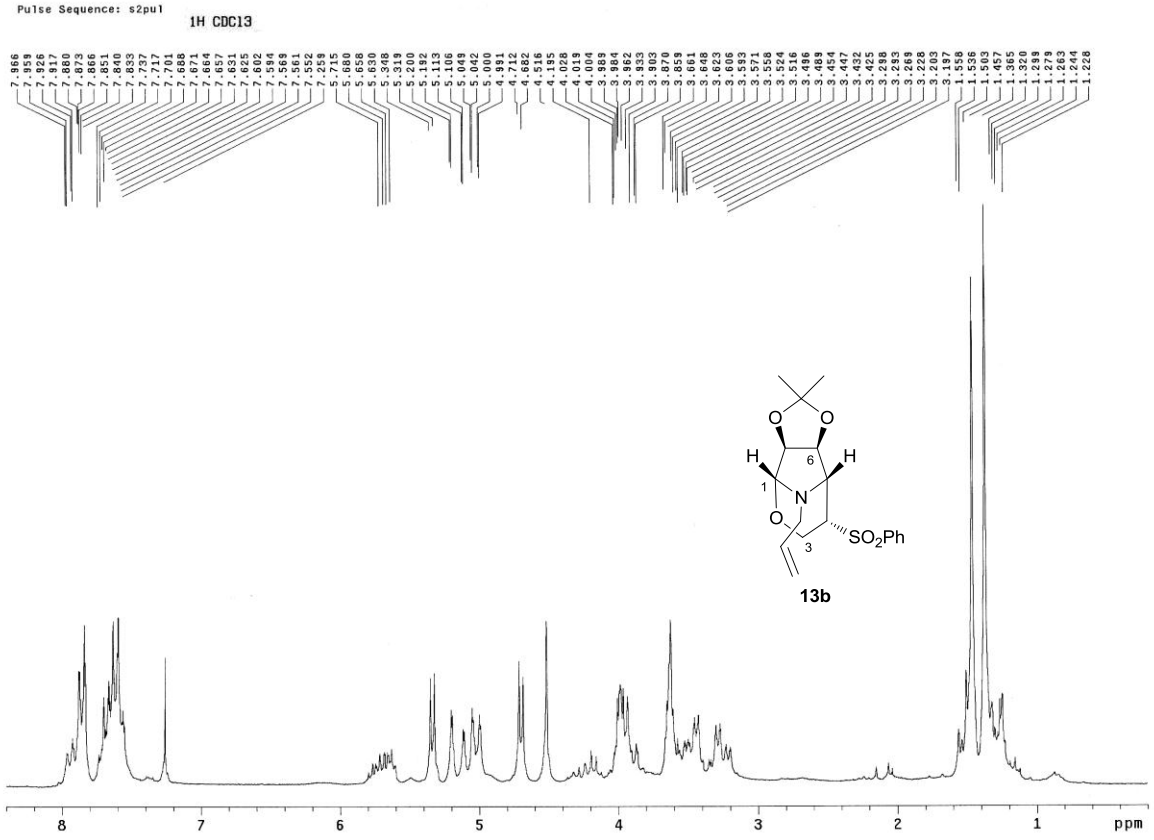
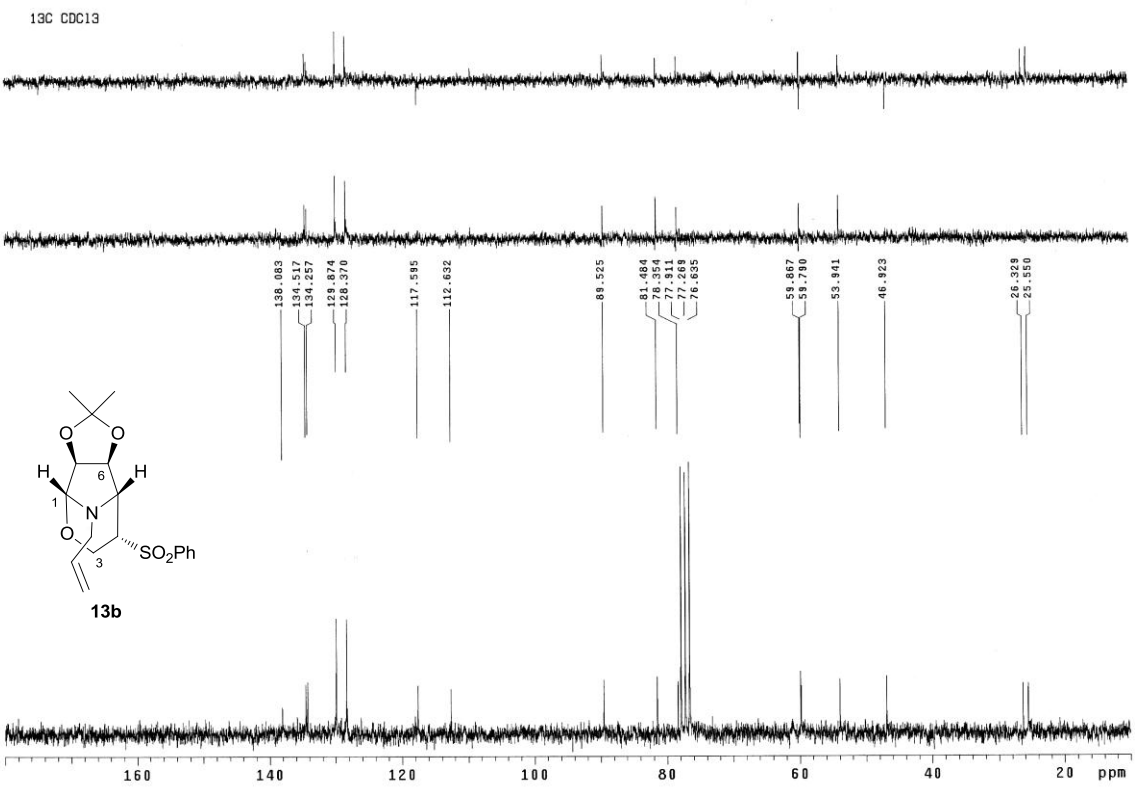
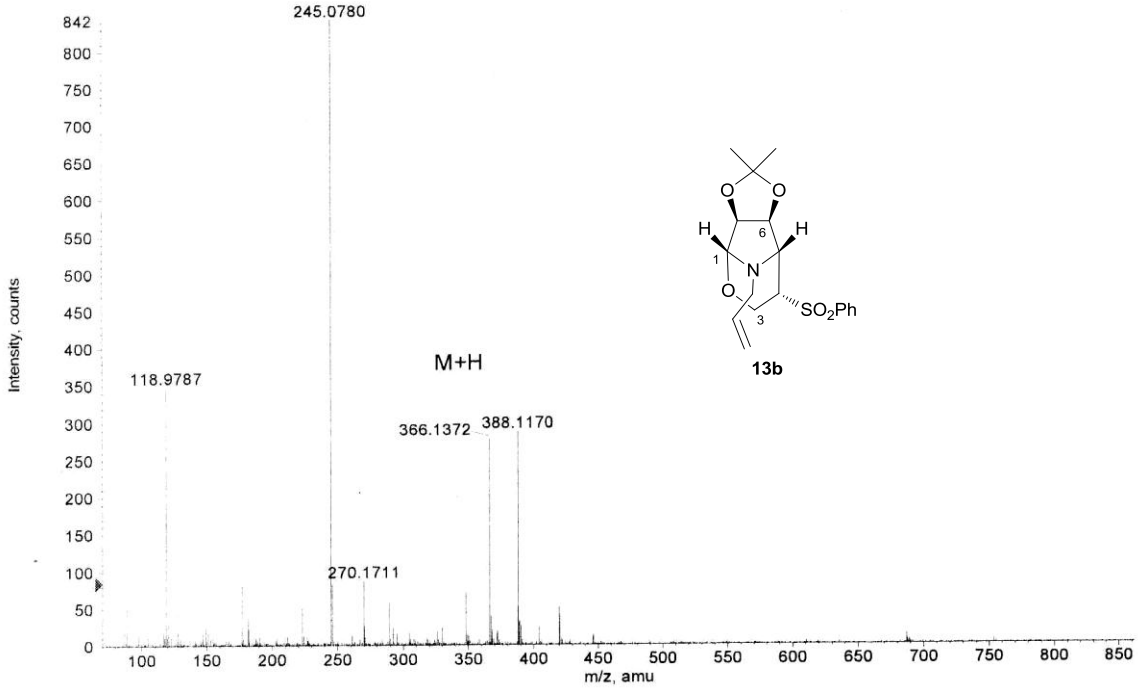


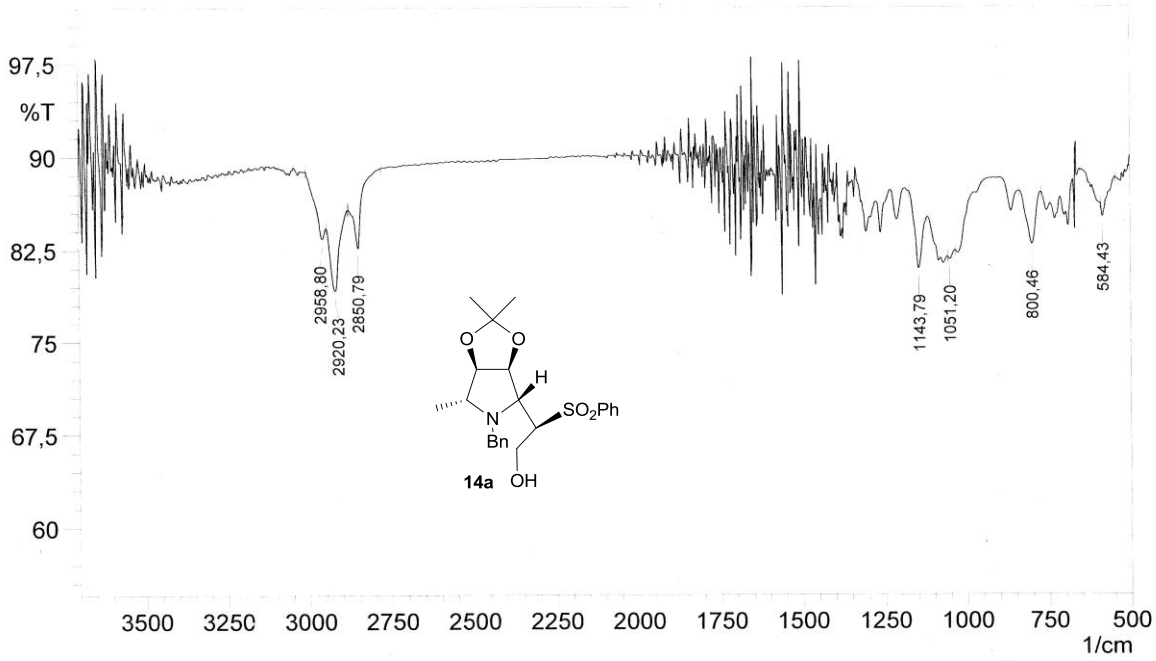


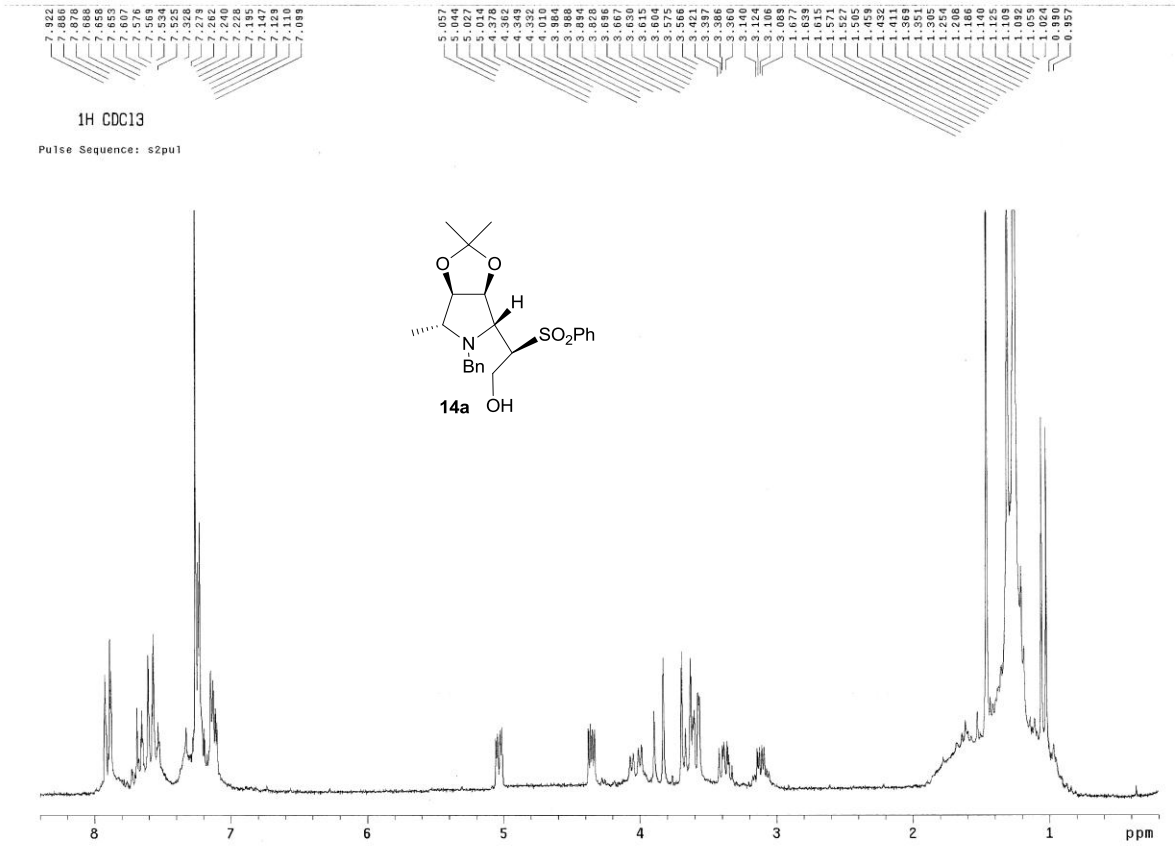


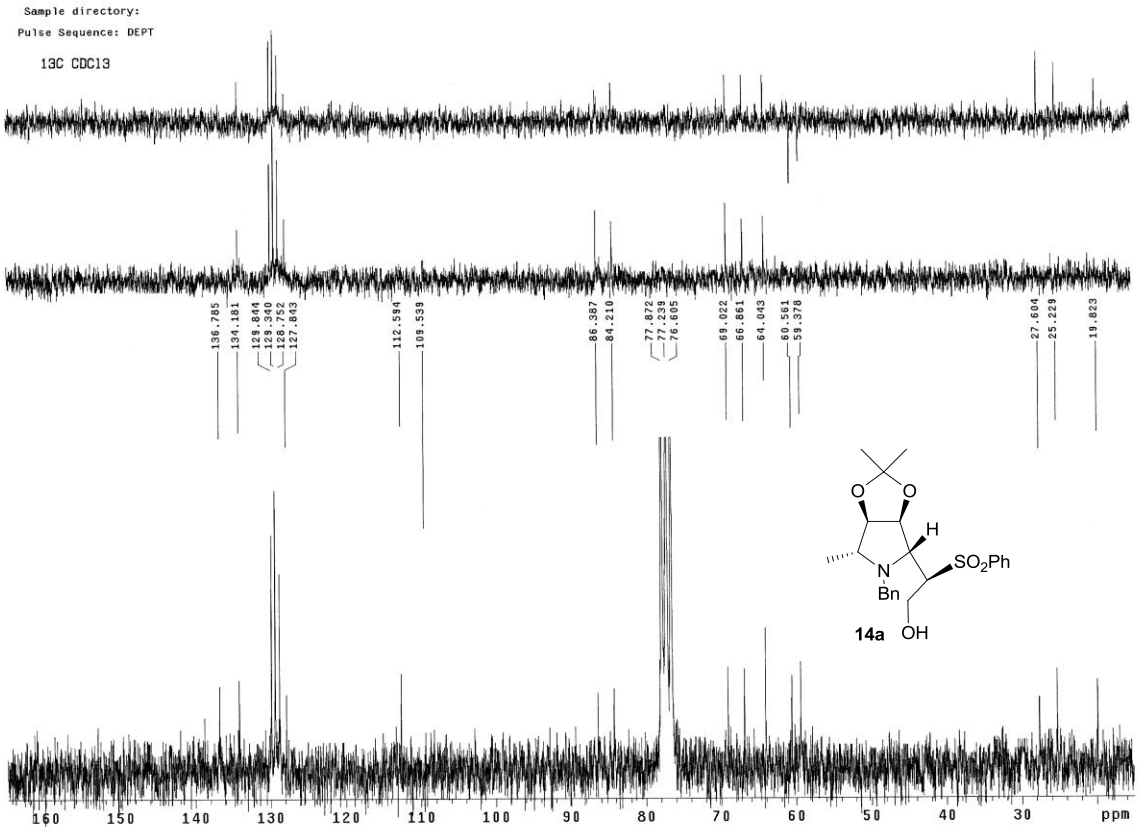
13b

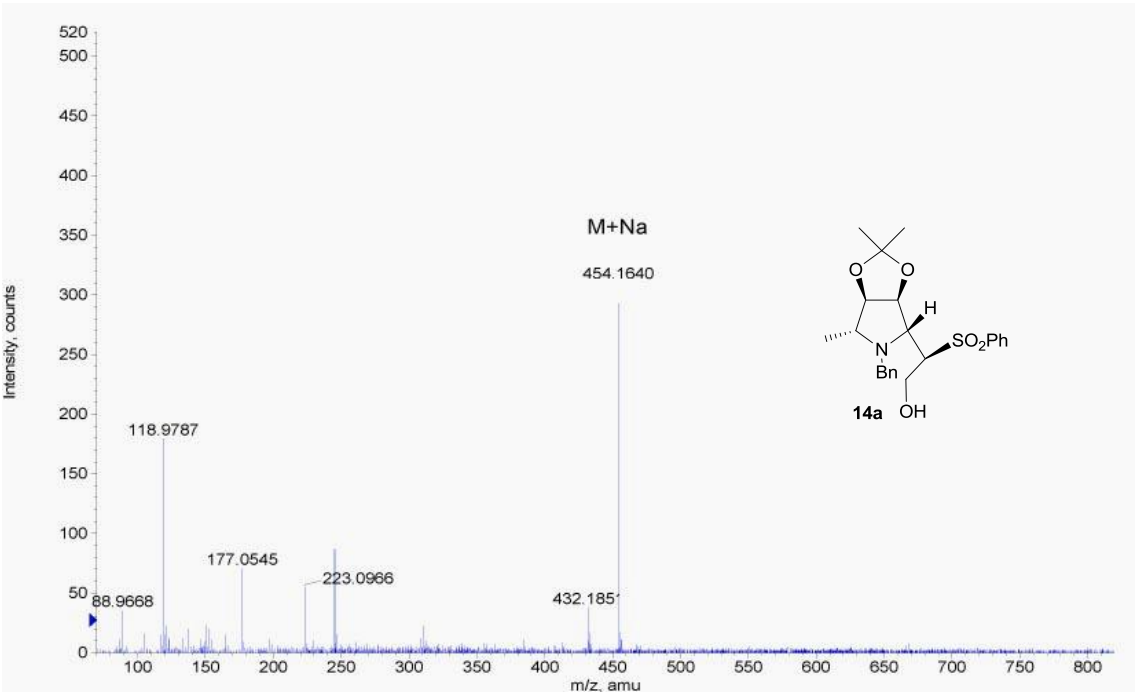


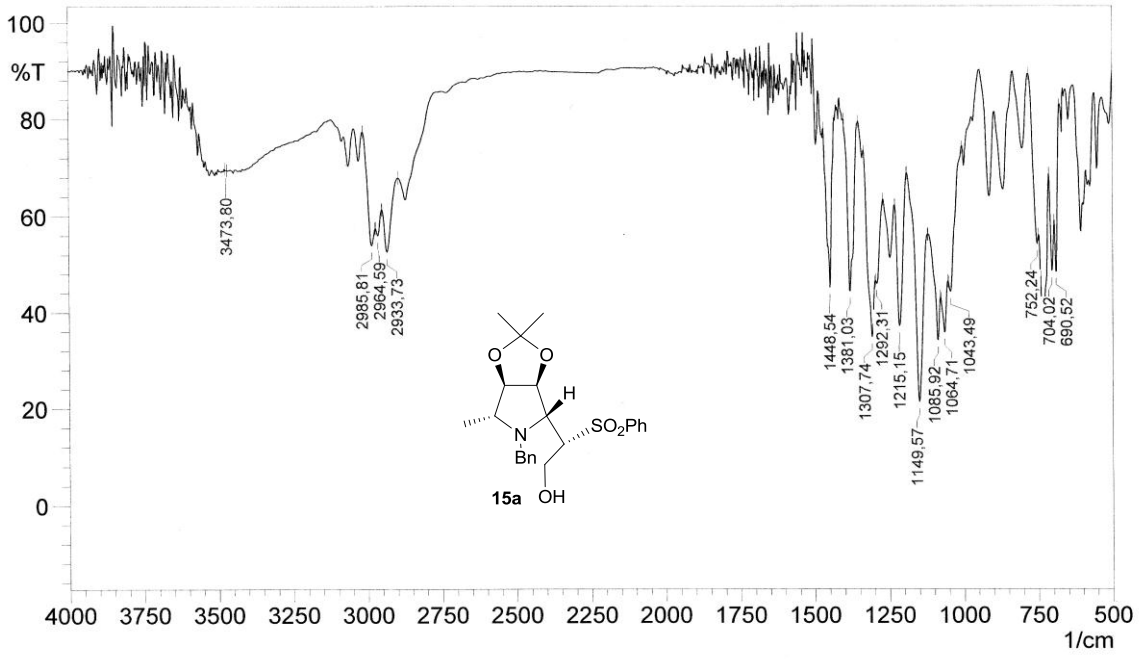
13b

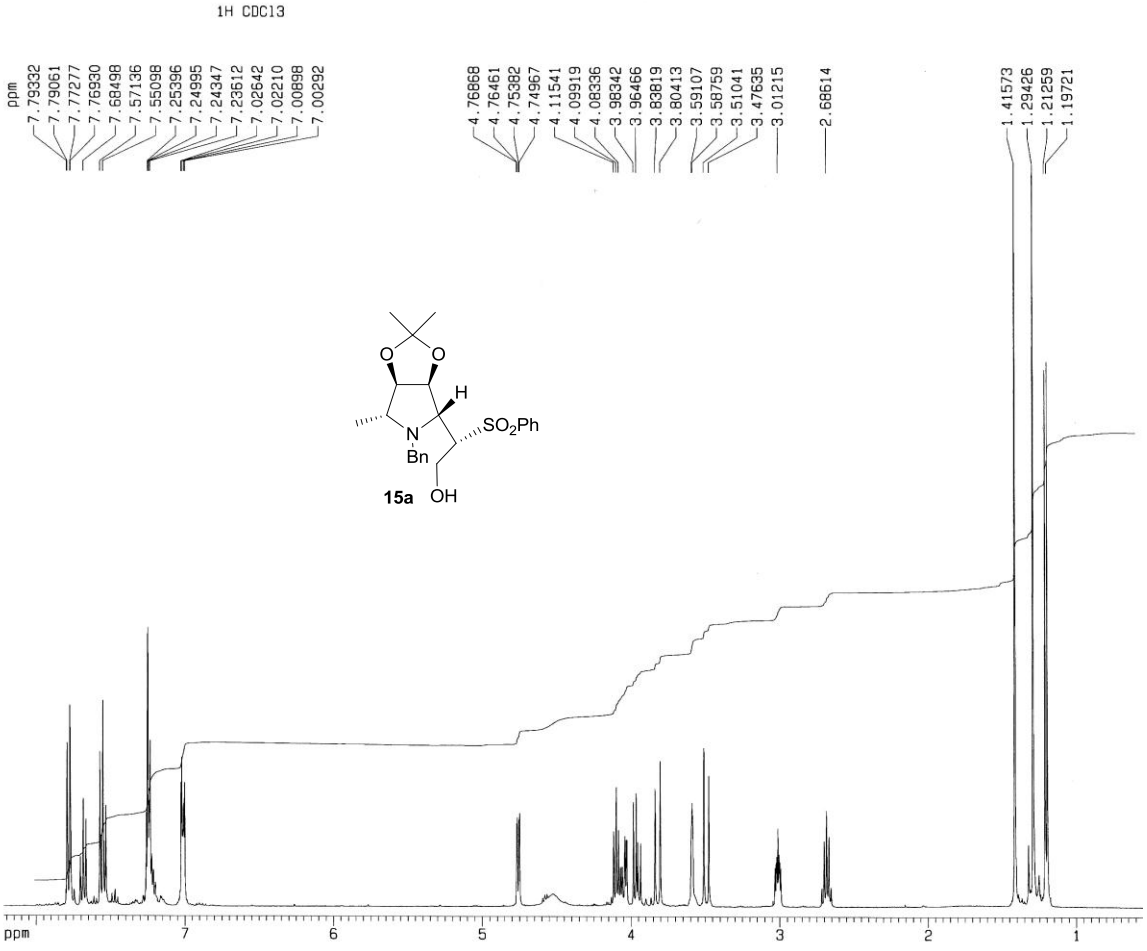


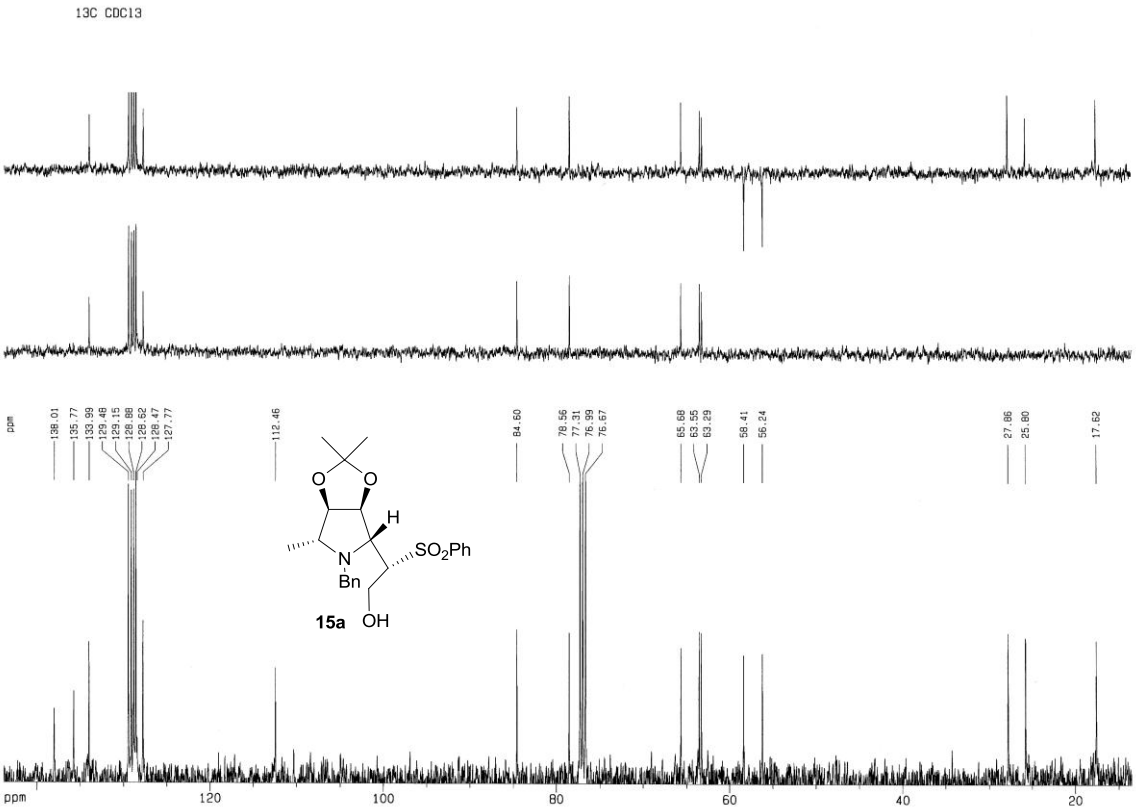


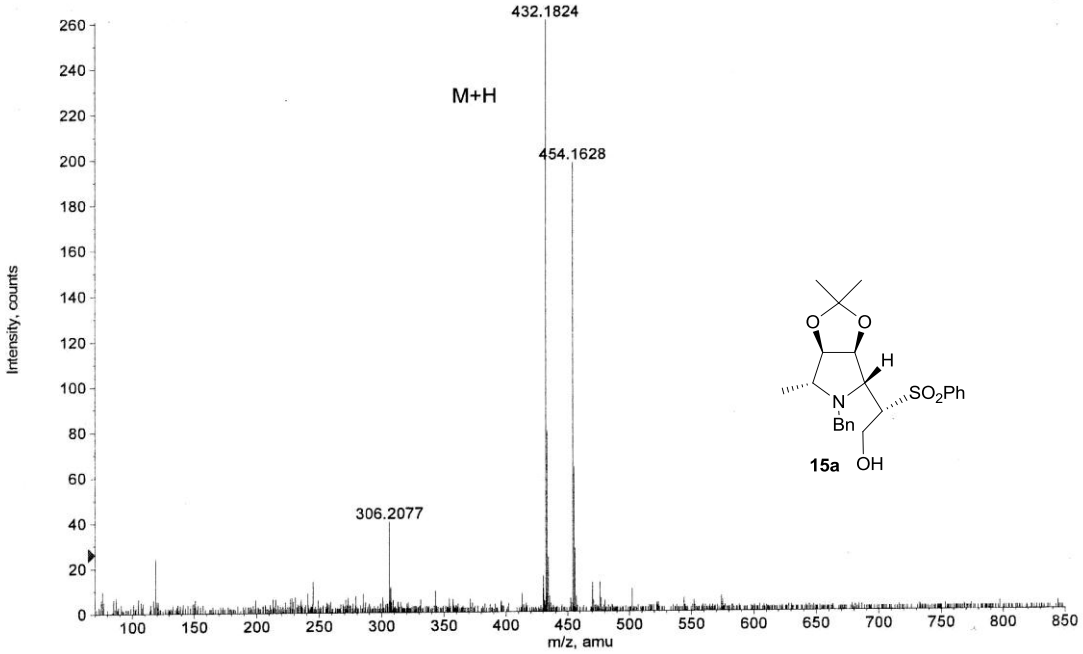


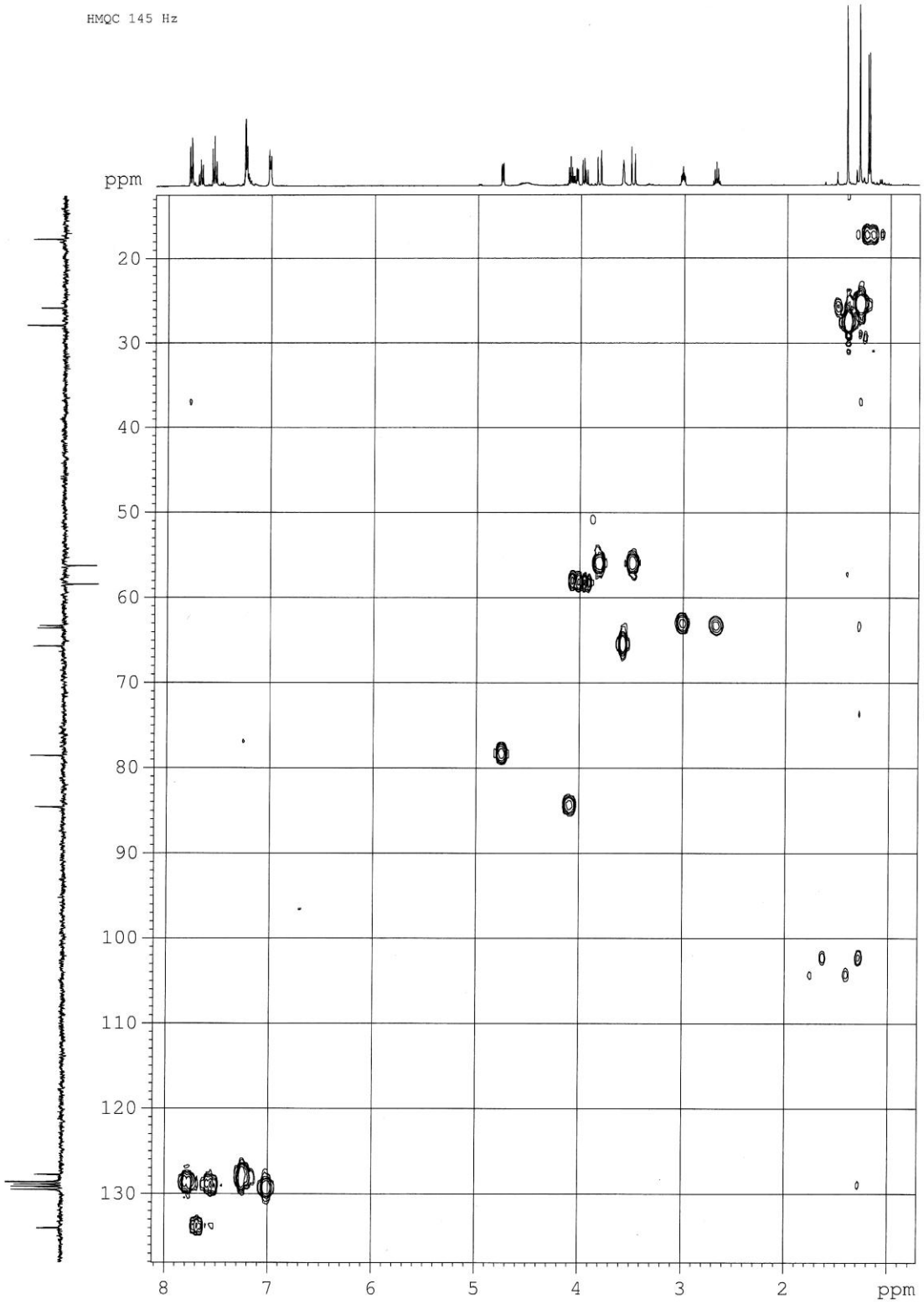


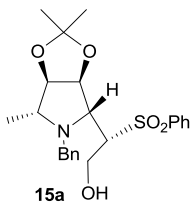




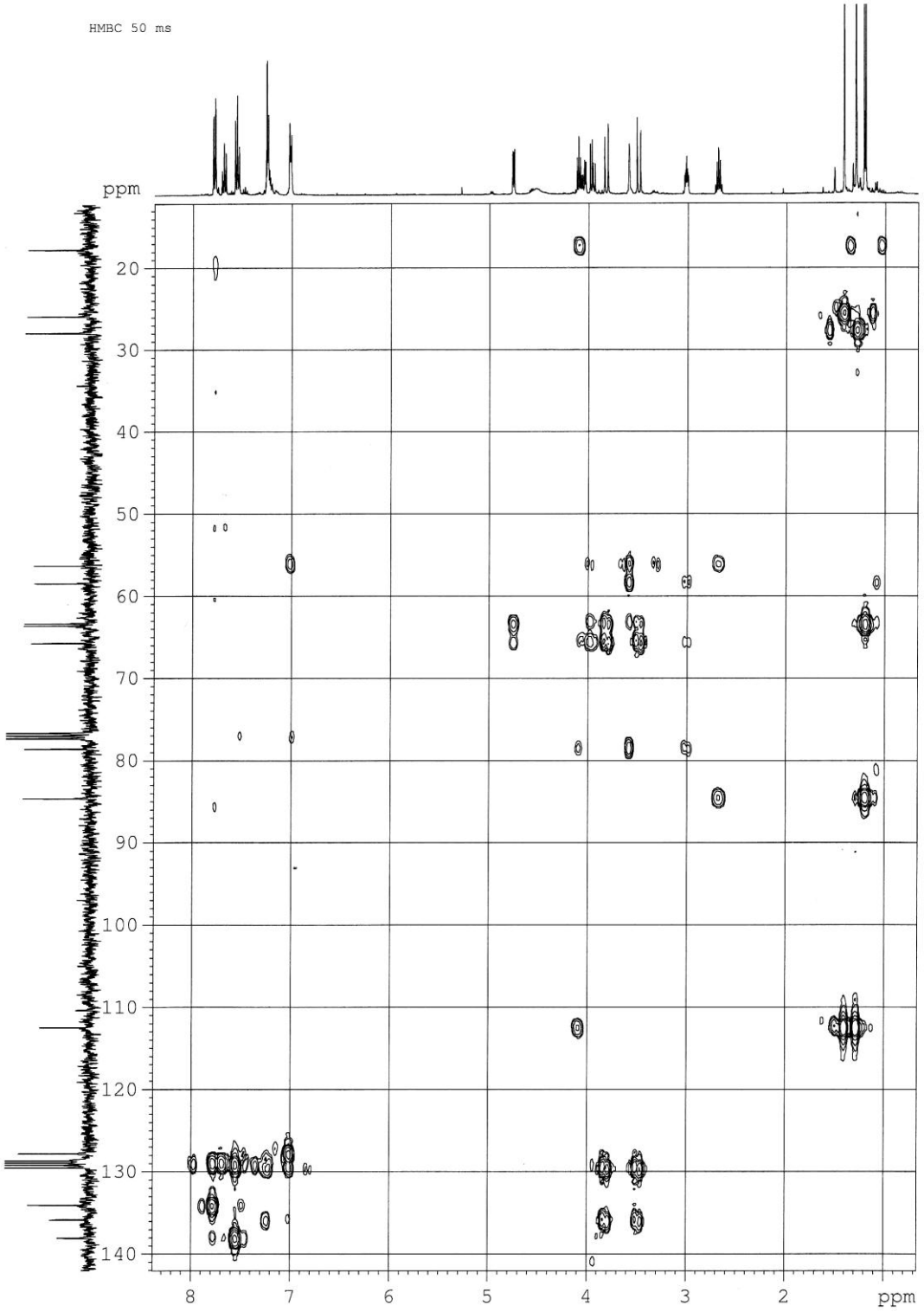


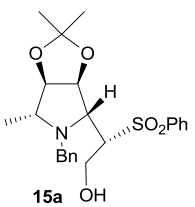




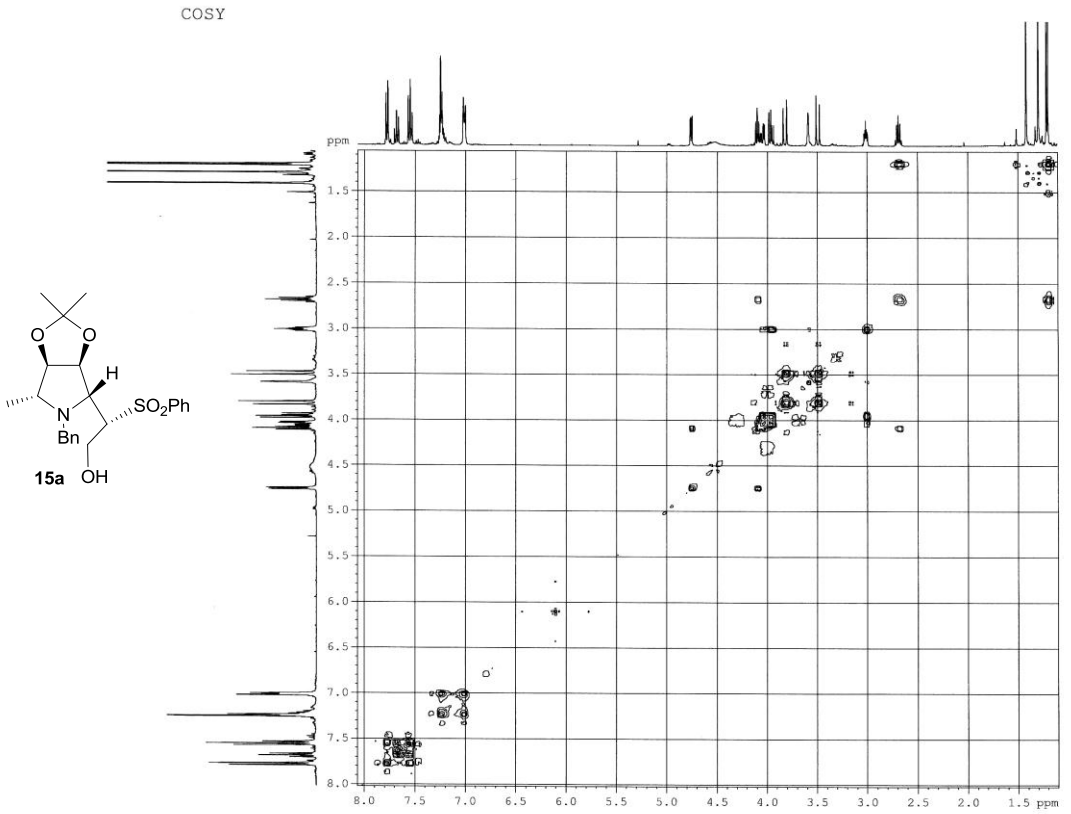


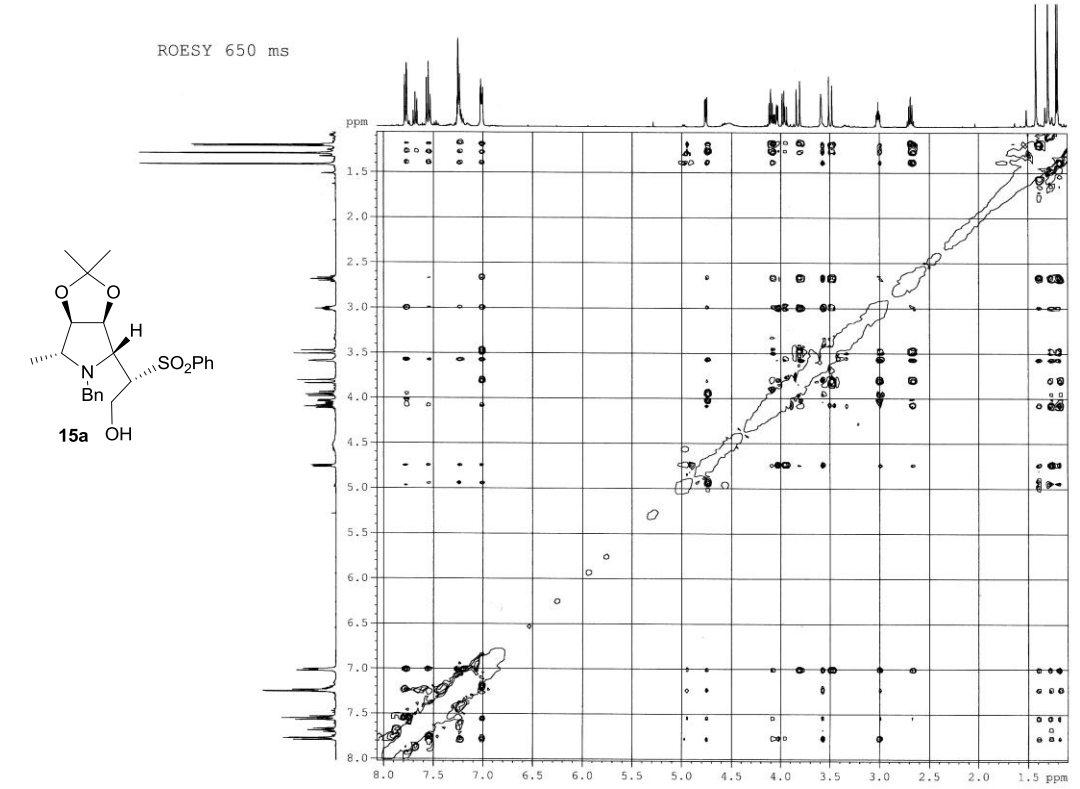
15a

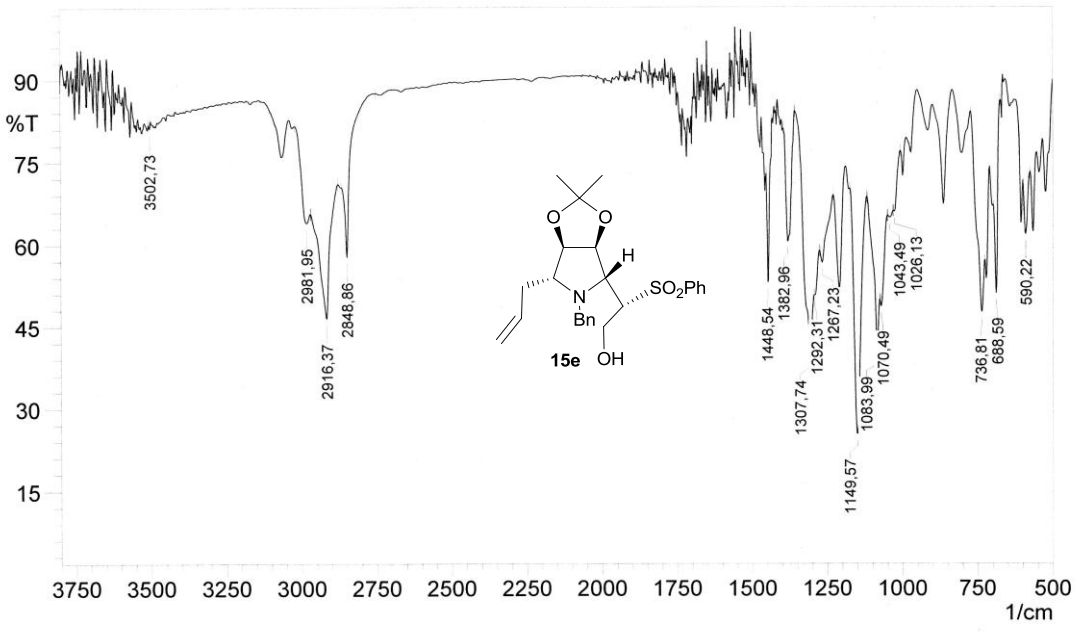


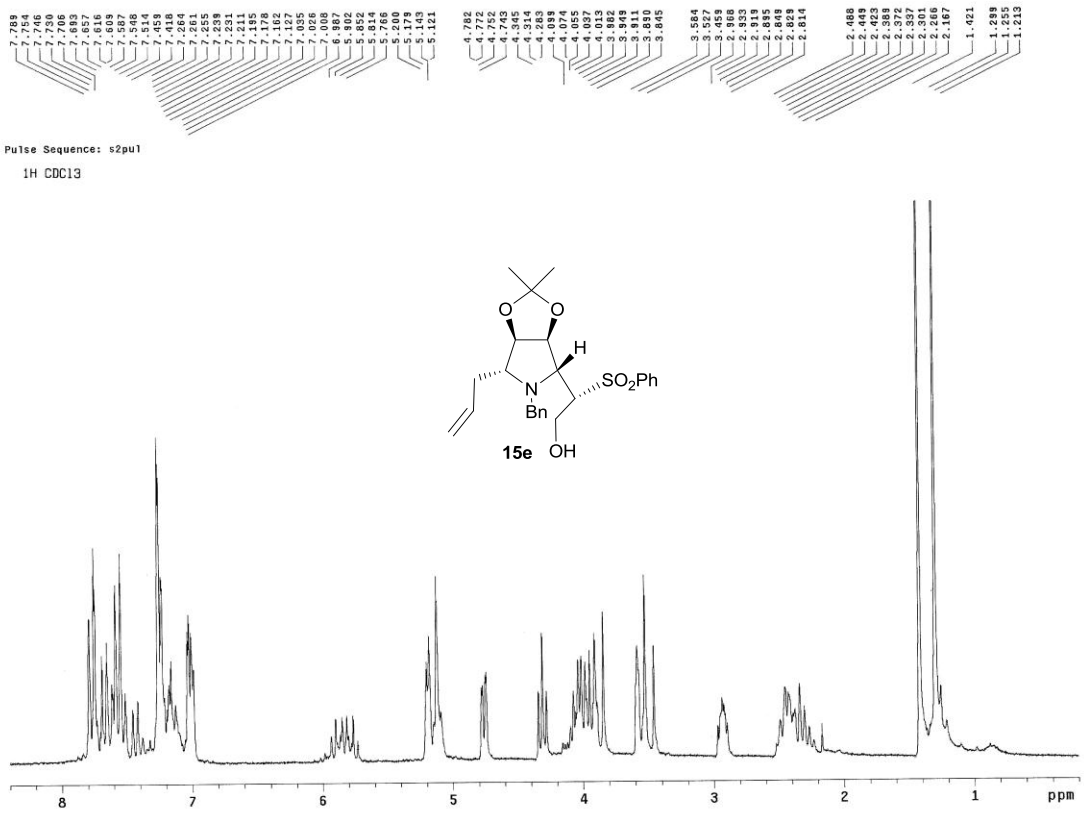


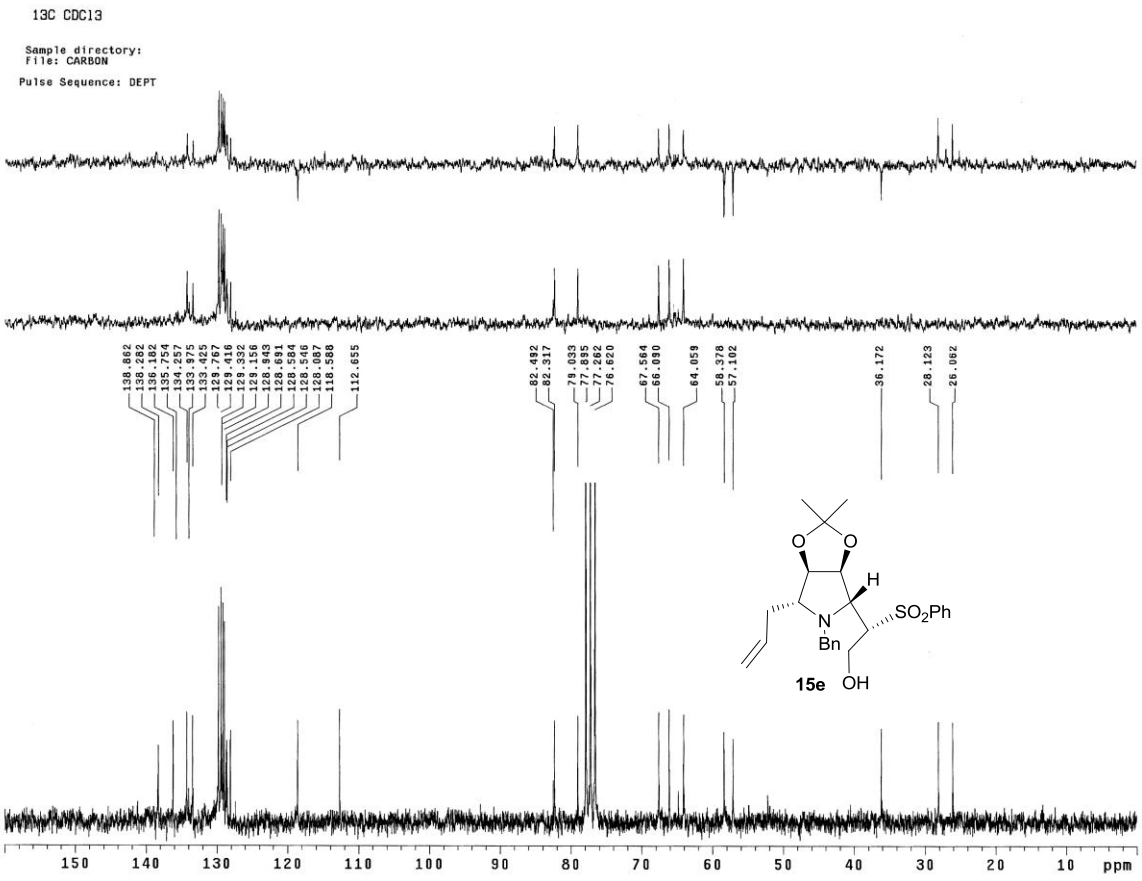
15a

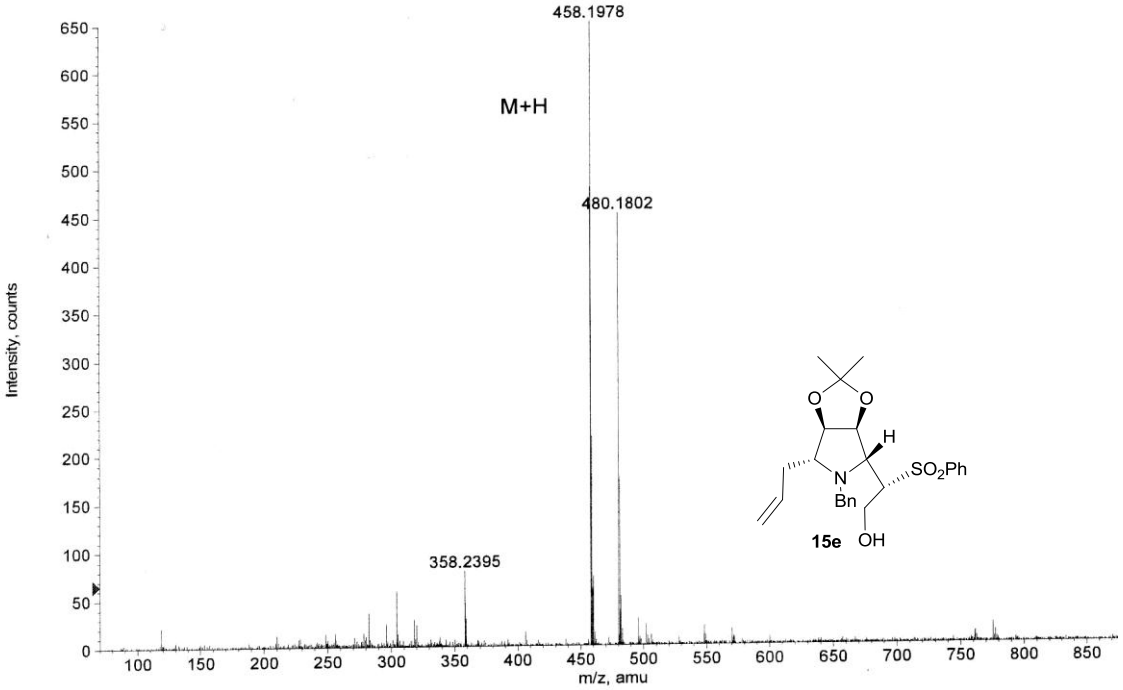


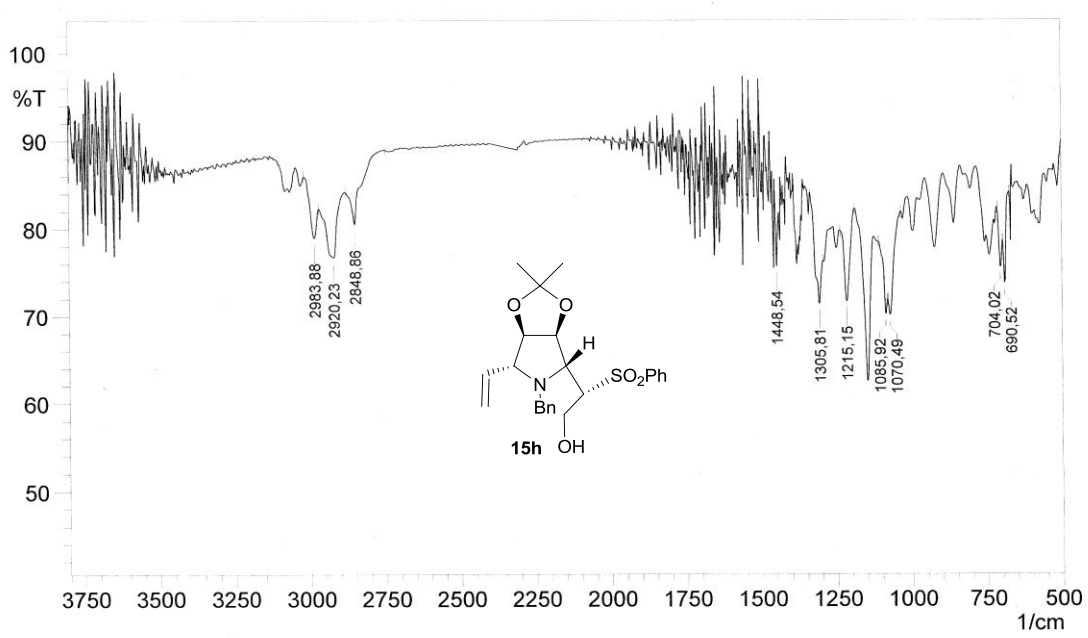


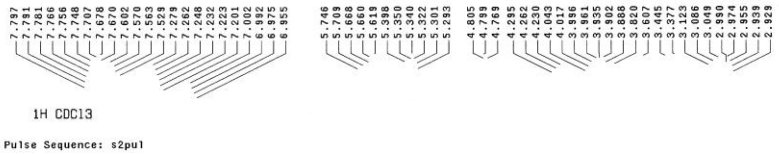

90
%T
75
60
45
30
15
3502,73
2981,95
2916,37
2848,86
1448,54
1382,96
1307,74
1292,31
1267,23
1149,57
1083,99
1070,49
1043,49
1026,13
736,81
688,59
590,22
O
O
H
N
Bn
SO2Ph
OH
15e
3750 3500 3250 3000 2750 2500 2250 2000 1750 1500 1250 1000 750 500
1/cm

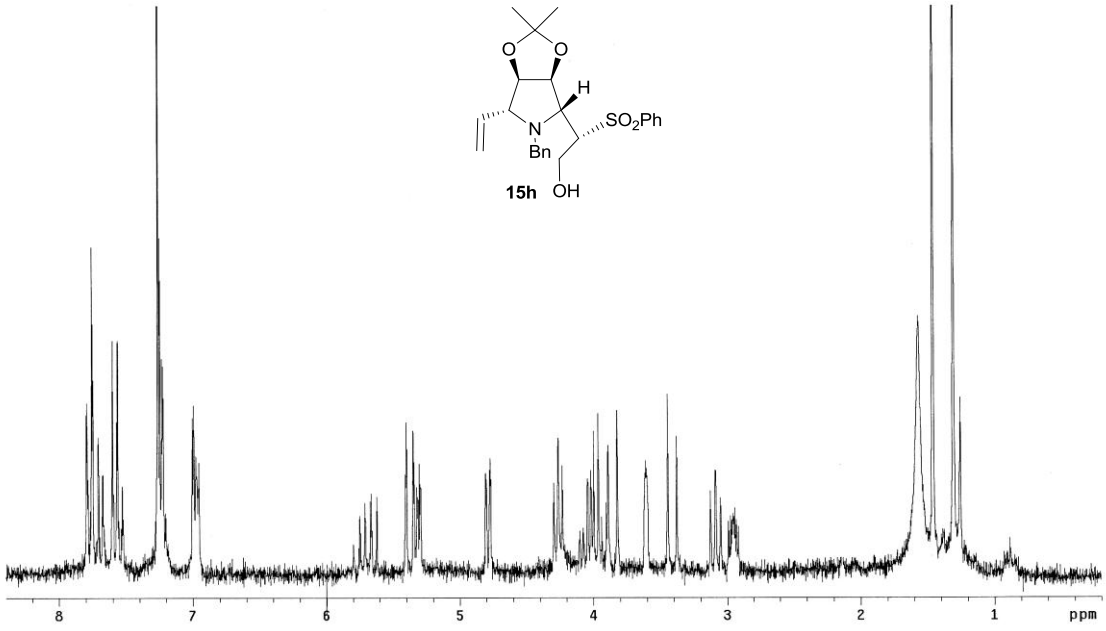

Pulse Sequence: s2pul
1H CDCl3
O
O
H
N
Bn
SO2Ph
OH
15e
8 7 6 5 4 3 2 1 ppm

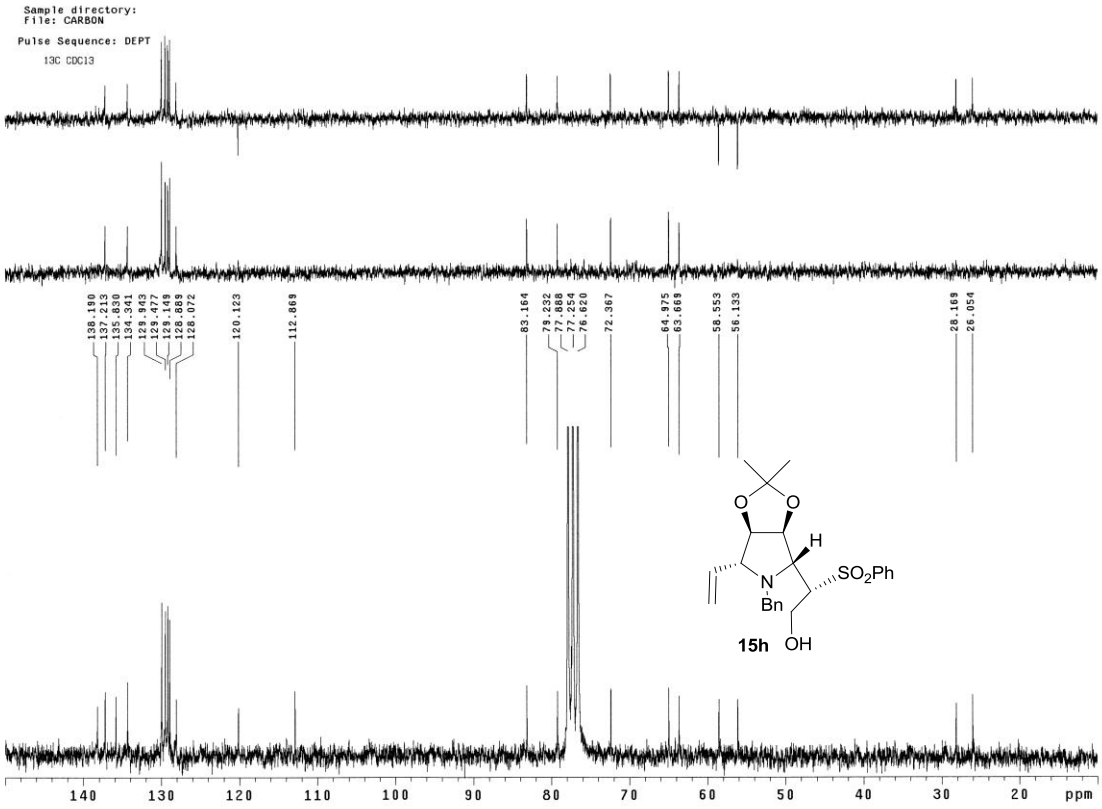

13C CDCl3
Sample directory:
File: CARBON
Pulse Sequence: DEPT
136.862
136.282
136.102
135.754
134.257
133.975
133.425
129.760
129.410
129.332
129.156
128.943
128.691
128.584
128.546
128.087
118.588
112.655
82.492
82.317
79.033
77.895
77.282
76.620
67.564
66.090
64.059
58.378
57.102
36.172
28.123
26.062
O
O
H
N
Bn
SO2Ph
OH
15e
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

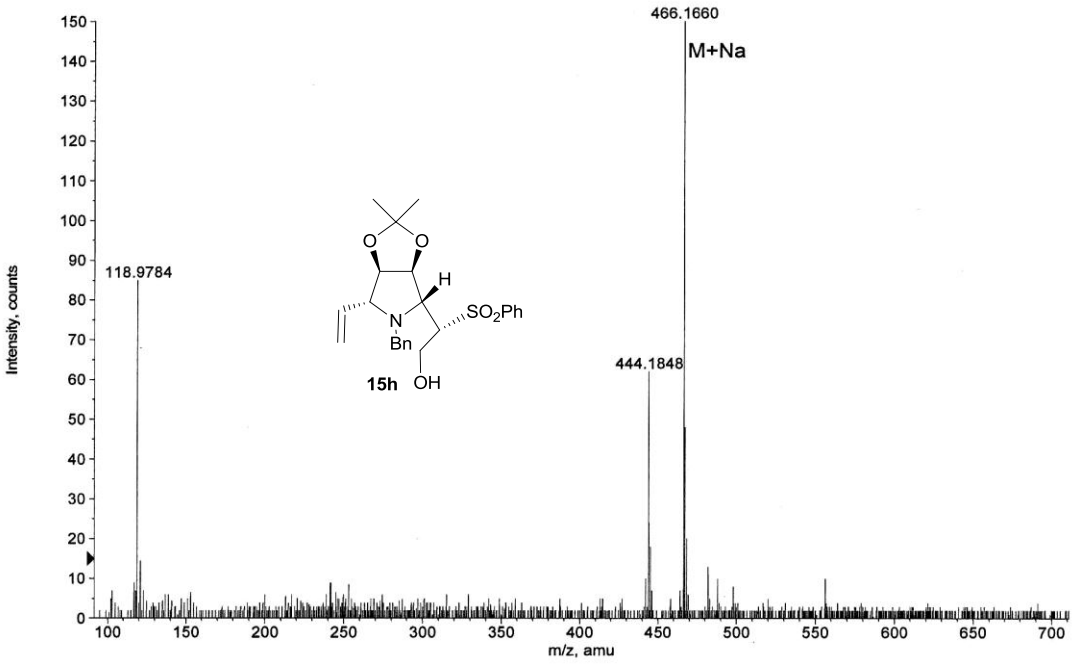

458.1978
M+H
480.1802
358.2395
Intensity, counts
650
600
550
500
450
400
350
300
250
200
150
100
50
0
100
150
200
250
300
350
400
450
500
550
600
650
700
750
800
850
m/z, amu
O
O
H
N
Bn
SO2Ph
OH
15e

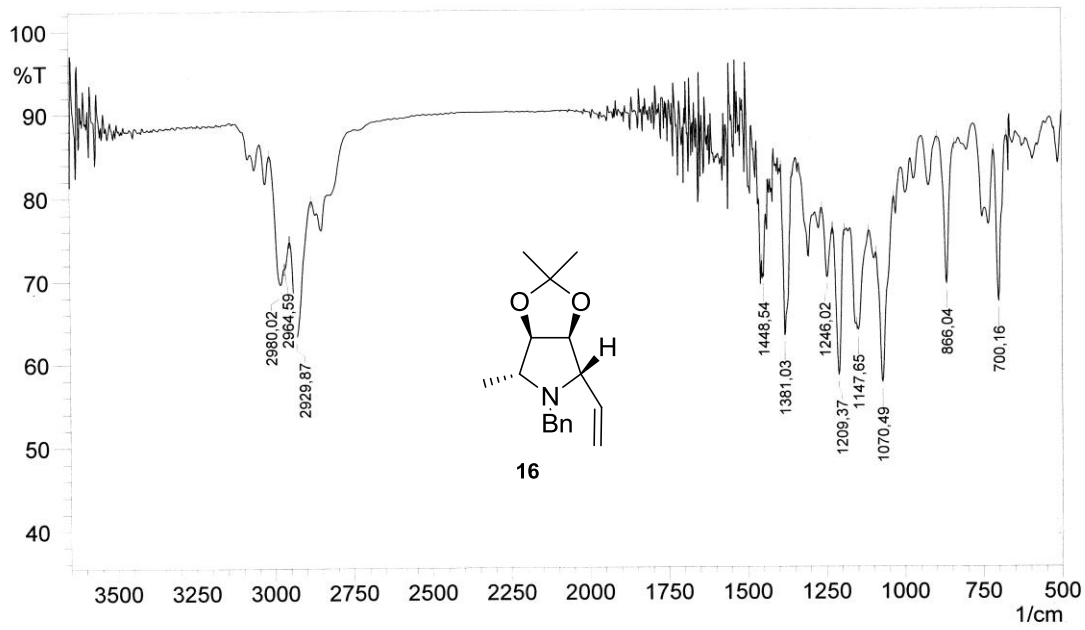




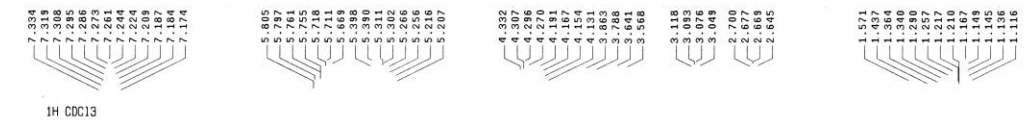



Sample directory:
File: CARBON
Pulse Sequence: DEPT
13C CDCl3
138.190
137.213
135.830
134.341
129.943
129.477
129.148
128.868
128.072
120.123
112.869
83.164
79.232
77.868
77.254
76.620
72.367
64.975
63.669
58.553
56.133
28.169
26.054
O
O
H
N
Bn
SO2Ph
OH
15h
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

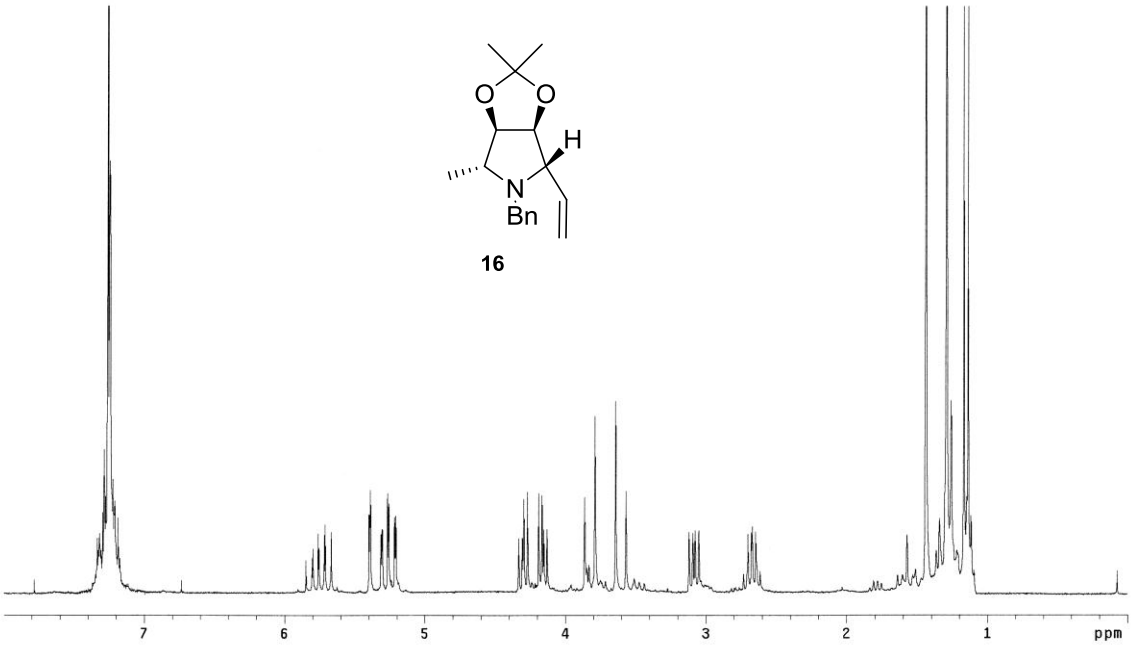

466.1660
M+Na
118.9784
444.1848
Intensity, counts
m/z, amu
O
O
H
N
Bn
SO2Ph
OH
15h



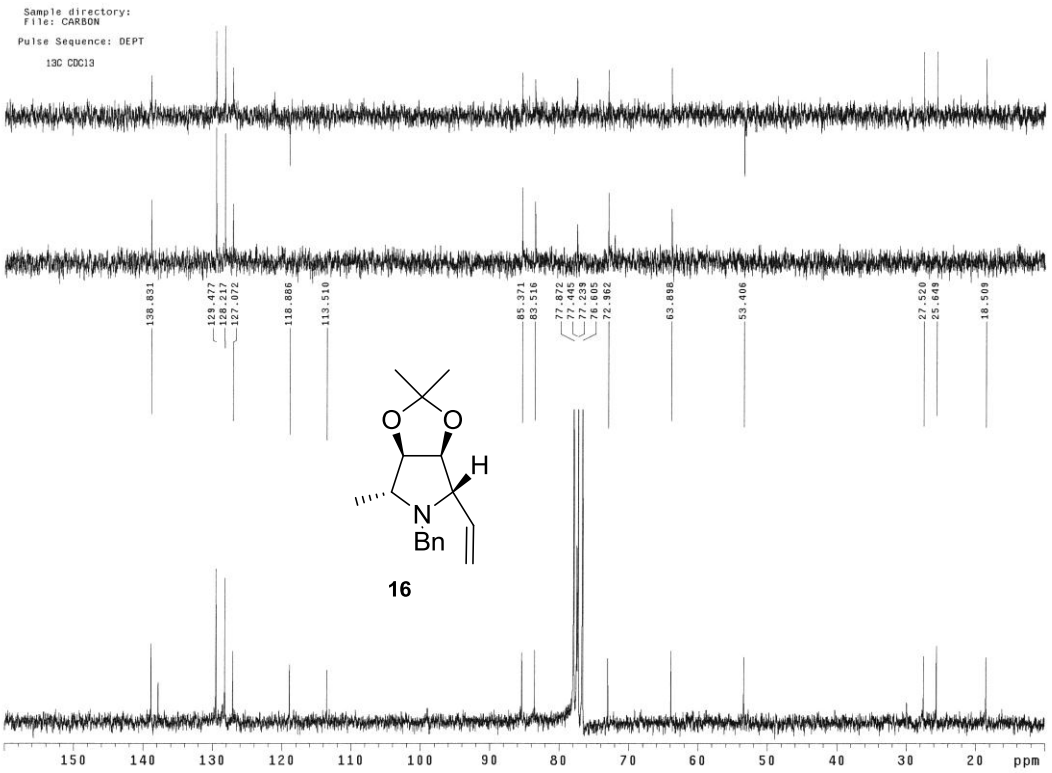
16



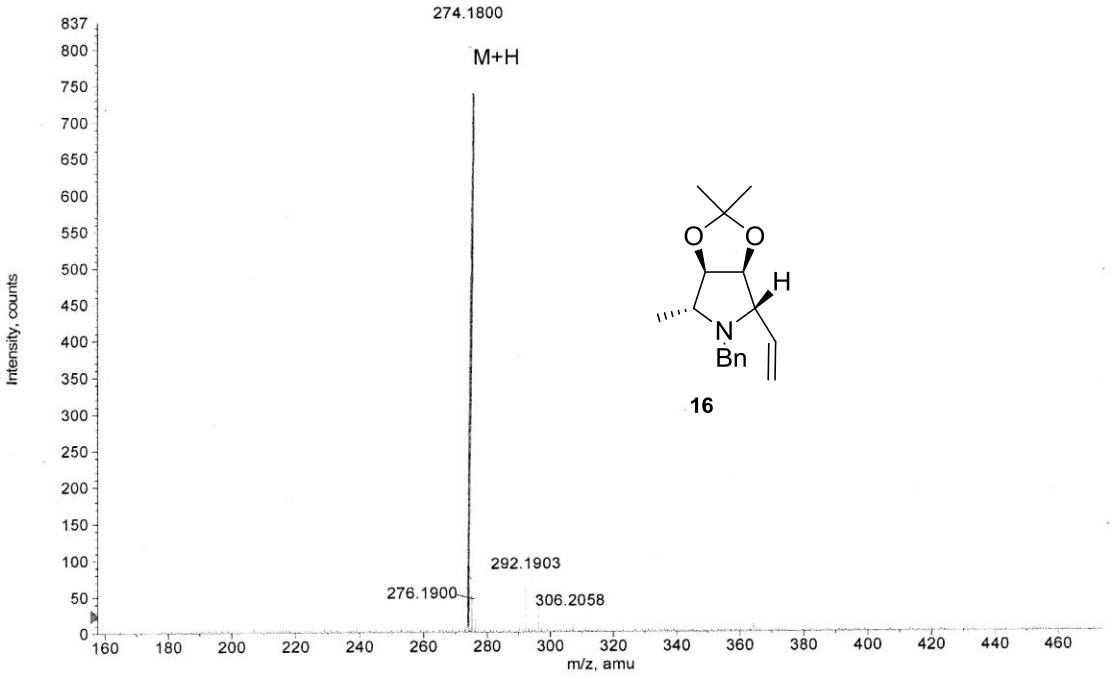
Pulse Sequence: s2pul



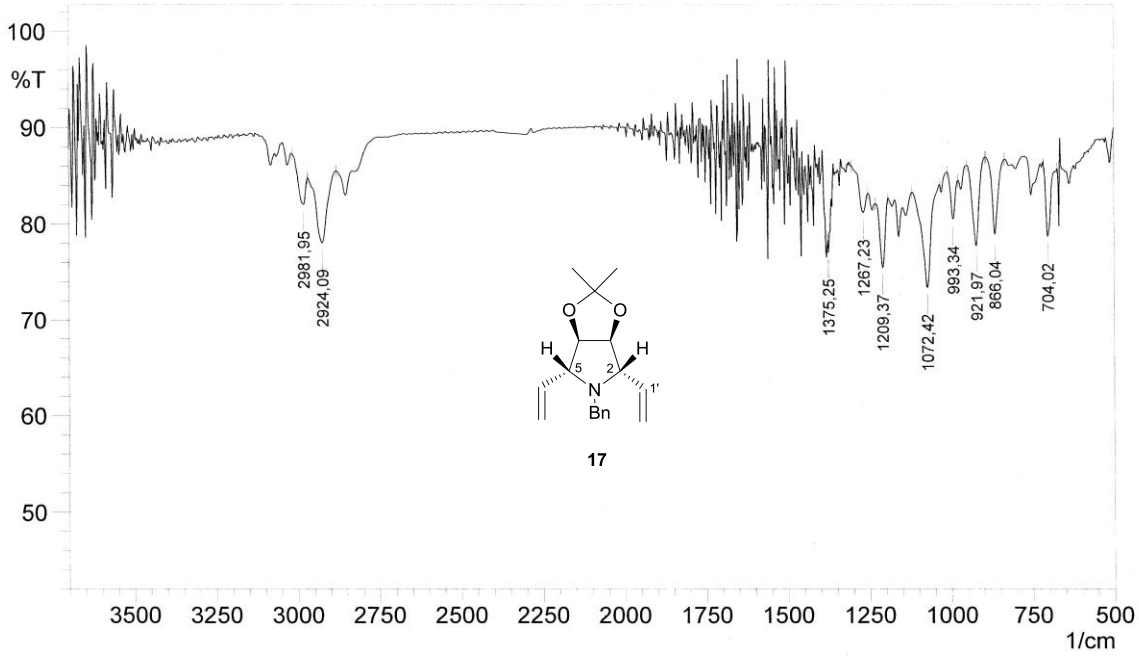
16


Sample directory:
File: CARBON
Pulse Sequence: DEPT
13C CDCl3
138.831
129.477
128.217
127.072
118.886
113.510
85.371
83.516
77.872
77.445
77.238
76.605
72.962
63.898
53.406
27.520
25.649
18.509
O
O
H
N
Bn
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

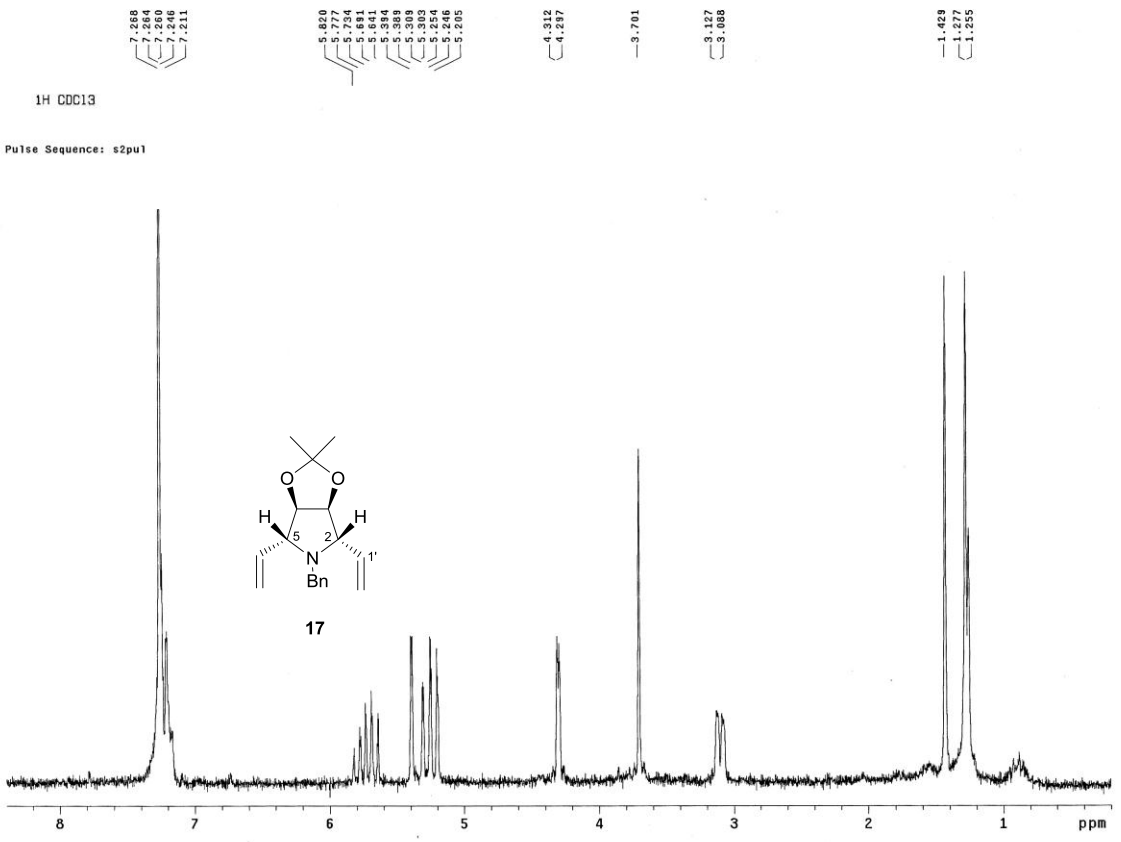
16


274.1800
M+H
837
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
Intensity, counts
292.1903
276.1900
306.2058
160
180
200
220
240
260
280
300
320
340
360
380
400
420
440
460
m/z, amu
O
O
H
N
Bn

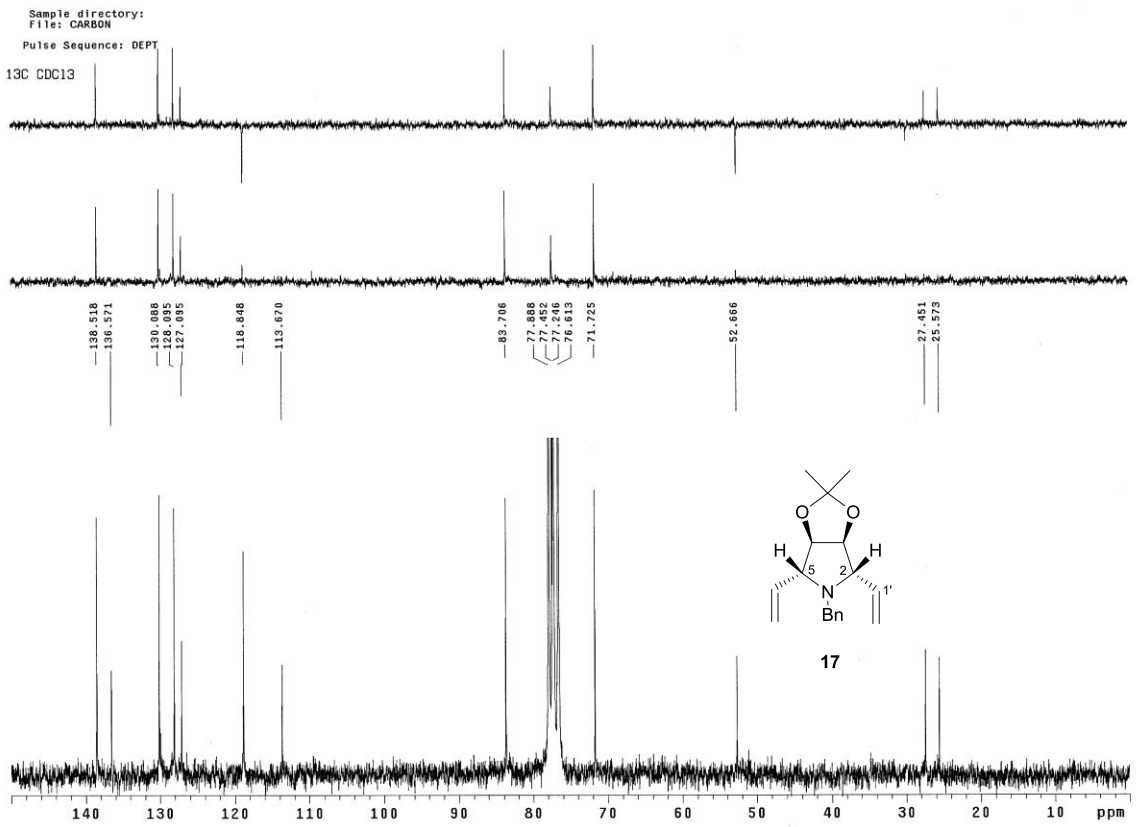
16

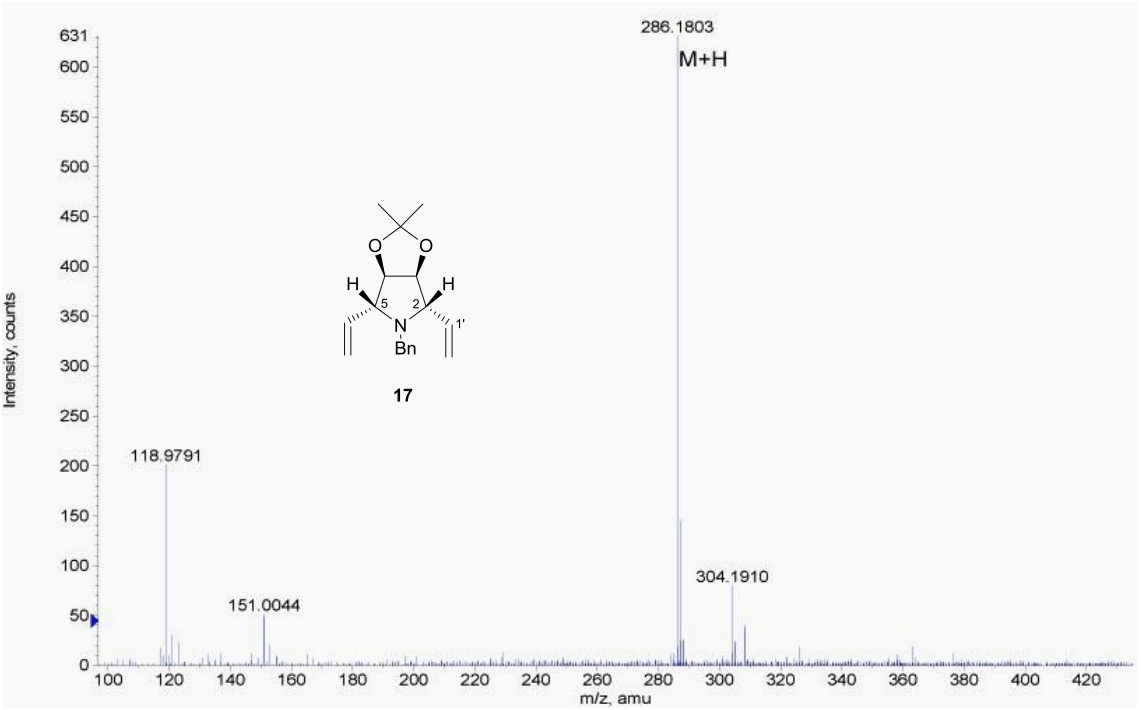


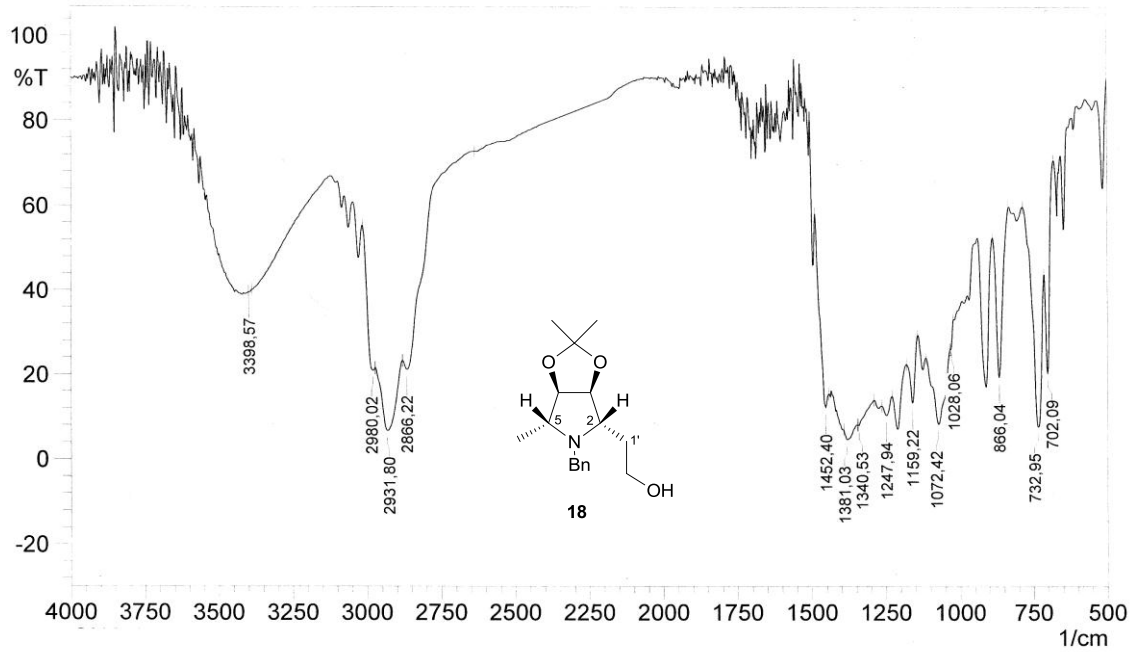
17

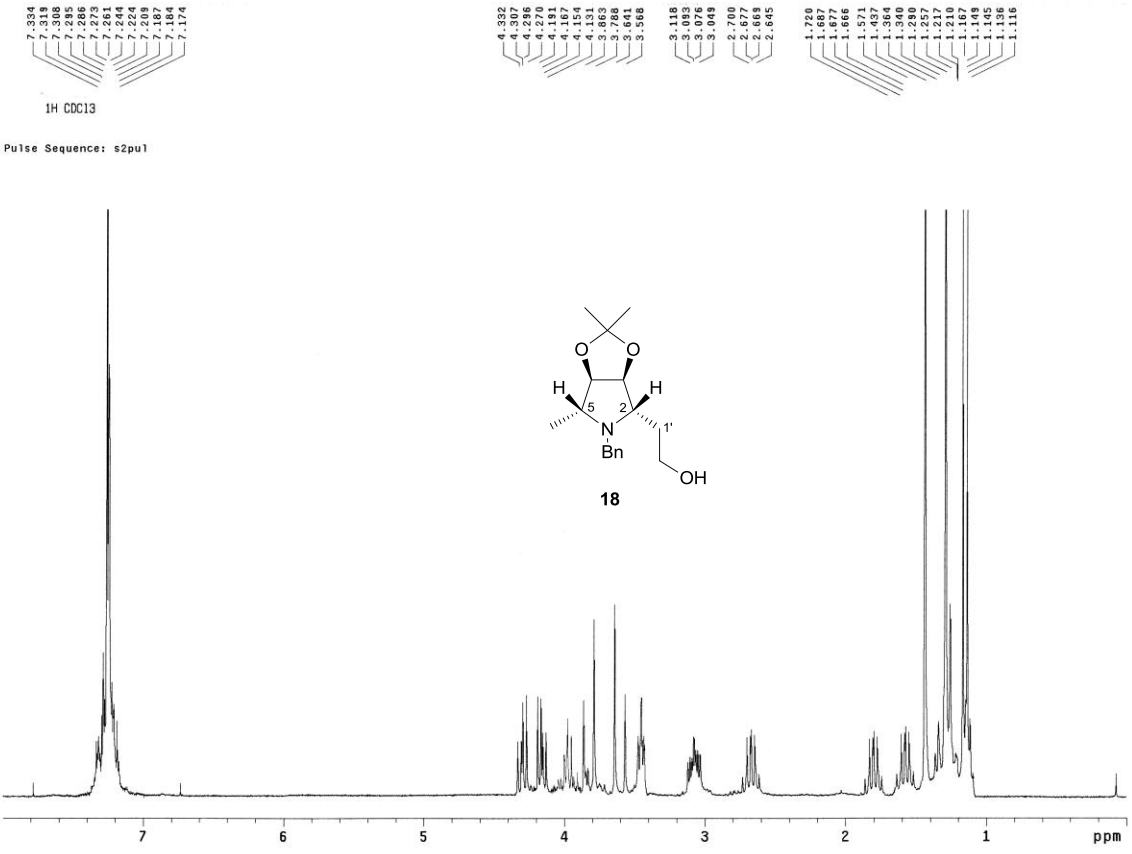


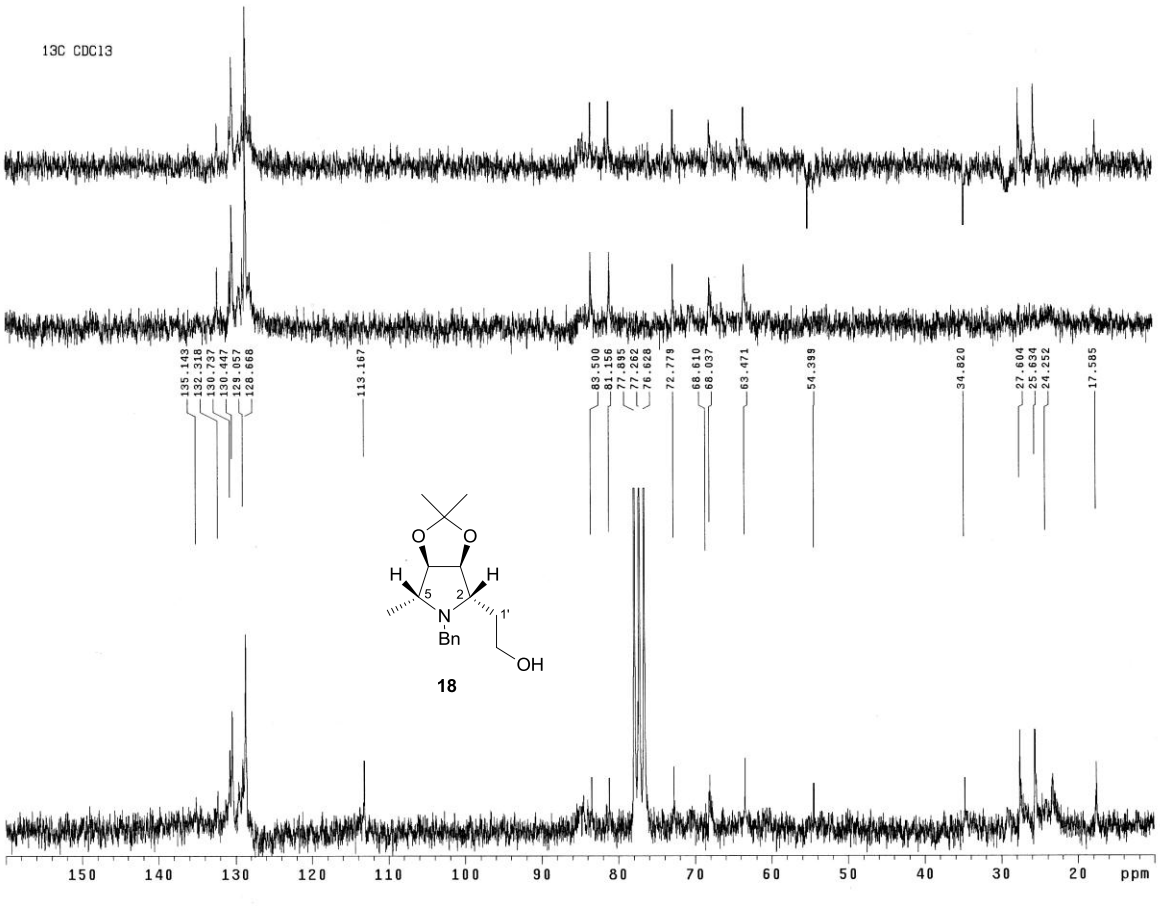
17

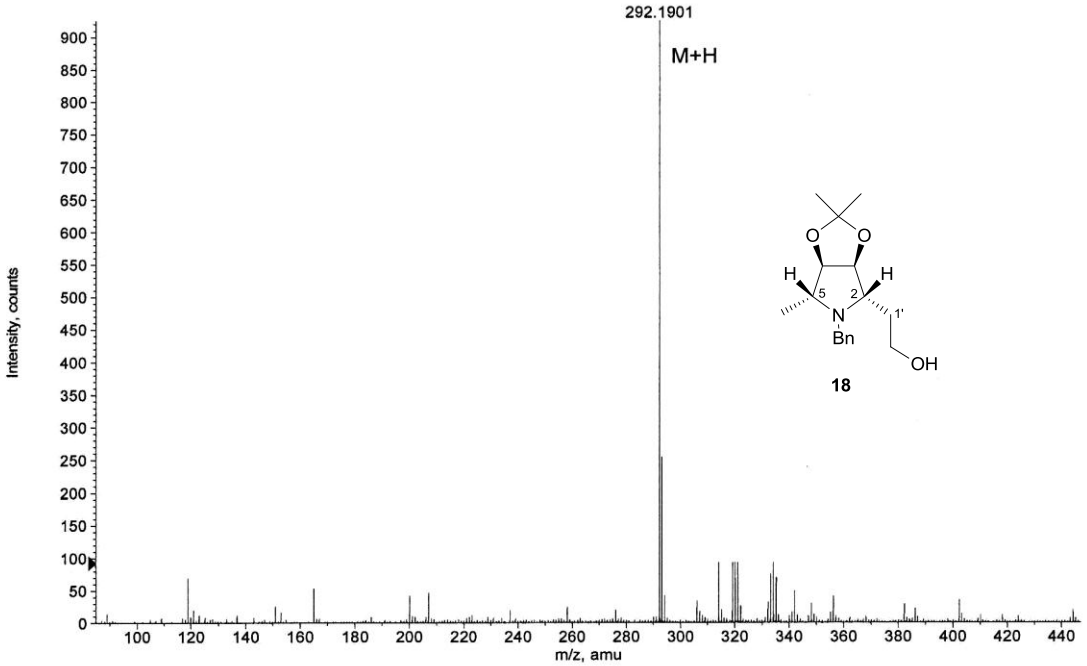









13C CDCl3
135.143
132.318
130.737
130.447
129.057
128.668
113.167
83.500
81.156
77.895
77.262
76.628
72.779
68.610
68.037
63.471
54.399
34.820
27.604
25.634
24.252
17.585
O
O
H
H
5
2
N
Bn
1'
OH
18
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


292.1901
M+H
Intensity, counts
900
850
800
750
700
650
600
550
500
450
400
350
300
250
200
150
100
50
0
100
120
140
160
180
200
220
240
260
280
300
320
340
360
380
400
420
440
m/z, amu
O
O
H
H
5
2
N
Bn
1'
OH
18

Crystal data for 13a: $C_{22}H_{25}NO_5S$, CH_2Cl_2, M = 500.42, monoclinic, space group $P2_1$, a = 6.0659(2) Å, b = 15.5656(6) Å, c = 12.9608(5) Å, $\alpha = \gamma = 90$ °, $\beta = 99.791(3)$ °, V = 1205.93(8) Å^3, Z = 2, D_C = 1.378 Mg/m^3, μ(Cu-K$_\alpha$) = 3.521 mm^{-1}, F(000) = 524. 6938 reflections were collected at 4.48 ≤ 2θ ≤ 67.01 and merged to give 3318 unique reflections (R_{int} = 0.0254), of which 3132 with I > 2 σ (I) were considered to be observed. Final values are R_1 = 0.0379, wR_2 = 0.1017, GOF = 1.039, max/min residual electron density 0.355 and -0.352 e. Å^{-3}. A suitable single crystal of the **13a** compound was mounted on glass fibre for data collection on a Bruker Kappa APEX II CCD (charge coupled device) diffractometer. Data were collected at 298 K using Cu K$_\alpha$ radiation (λ = 1.54178 Å) and ω scan technique, and were corrected for Lorentz and polarization effects. Structure solution, refinement and data output were carried out with the SHELXTL^{TM} program package. The structure was solved by direct methods combined with difference Fourier synthesis and refined by full-matrix least-squares procedures, with anisotropic thermal parameters in the last cycles of refinement for all non-hydrogen atoms. Hydrogen atom positions were calculate by geometrical methods and refined as a riding model. CCDC 888605. See https://www.ccdc.cam.ac.uk/services/structure_deposit/ for crystallographic data in .cif or other electronic format.

ORTEP of 13a.

The crystal contains an unique molecule of **13a** compound and a molecule of solvent in the asymmetric unit. The title compound consists of a pyrrolidine-oxazine bicyclic ring with an isopropylidenedioxy group, a benzyl group and a phenylsulfone group as substituents. All the bond lengths and angles are within the normal ranges. The C-S-C and O-S-O angles are 104.7(1)º and 118.2(2)º, respectively. The large O-S-O angle and its deviation from the optimal 109.5º angle can be explained by the repulsion of the lone pairs of the oxygen placing the oxygen atoms as far away from each other as possible and thus minimizing the C-S-C angle. The molecule is twisted at the C-S bond being the C13-C7-S1-C6 torsion angle of 155.6(2)º.

In the crystal structure, each solvent molecule is involved in two type of intermolecular C-H···O and C-H···Cl interactions with different molecule of **13a** compound, which lead to infinite molecular chains running along [010] directions (Fig. 1). The first one occurs between the carbon atom (C8) of the oxazine group and the chlorine atom (Cl1) with d(C8-H8···Cl1) = 3.590(4) Å and < C8-H8···Cl1> = 134.7(2)º. The other exists between the carbon atom of solvent and the oxygen atom (O5) of the isopropylidenedioxy group with d(C23-H23···O5) = 3.363(6) Å and < C8-H8···Cl1> = 157.1(3)º. A view of intermolecular C-H···O (dotted light blue lines) and C-H···Cl (dotted violet lines) interactions is shown in Fig. 2.

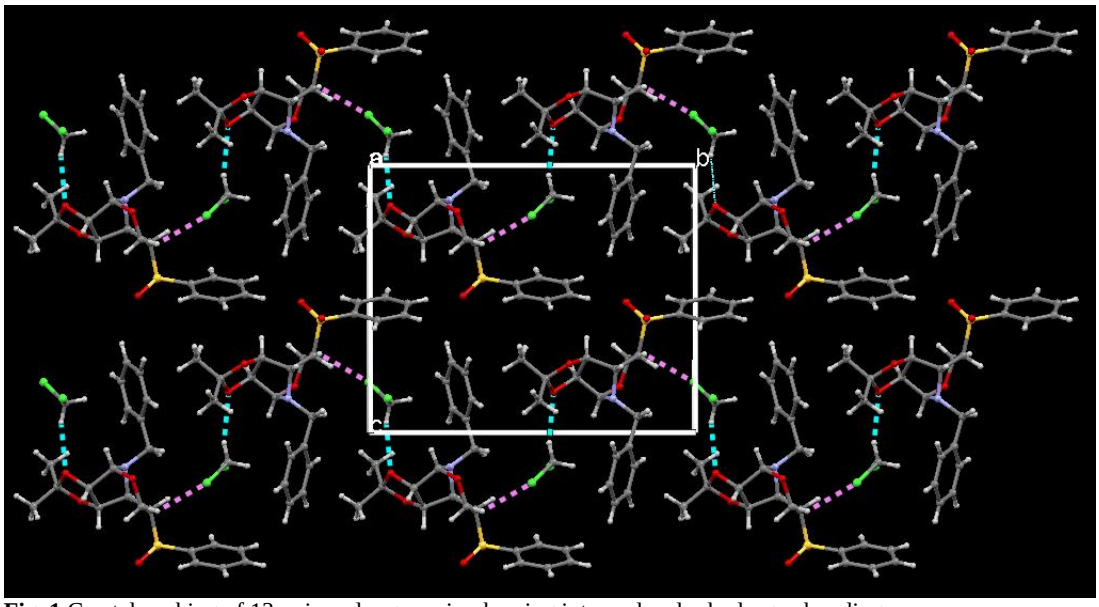


Fig. 1 Crystal packing of 13a·view along a-axis, showing intermolecular hydrogen bonding.

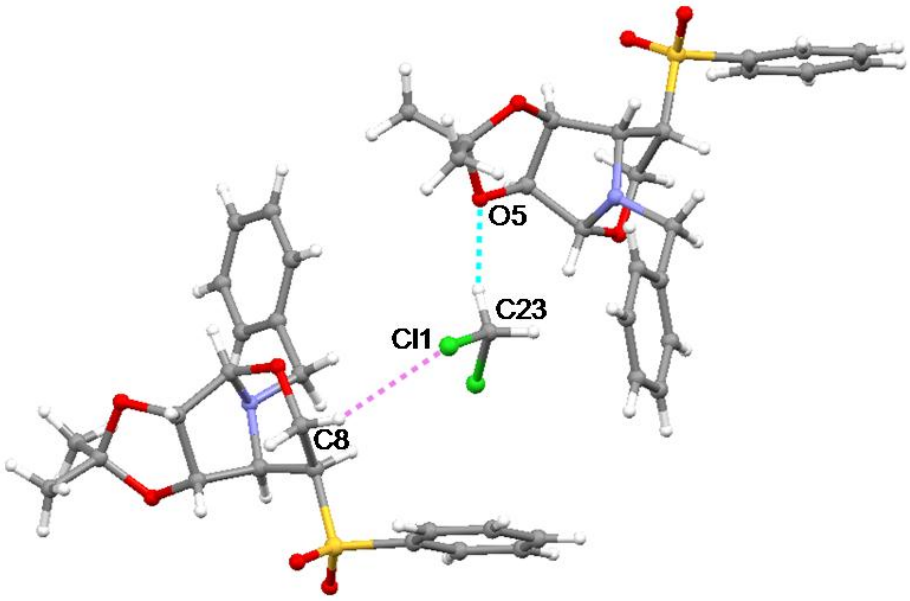


Fig. 2 Perspective view of intermolecular interactions for **13a**

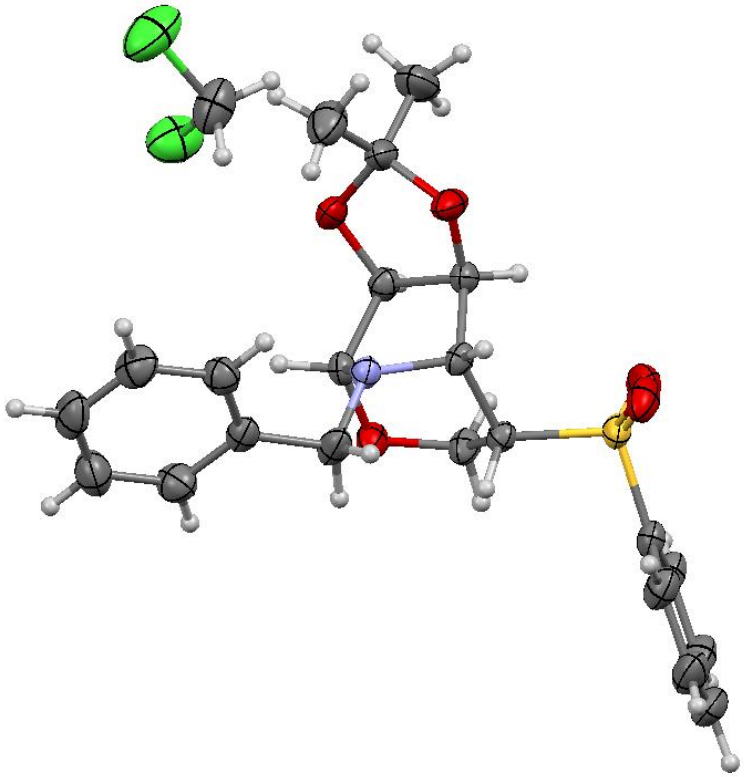


Fig. 3 X-ray crystal structure of **13a** compound. Displacement ellipsoids are drawn at the 30 % probability level. Hydrogen atoms are shown as spheres of arbitrary radius.