Supplementary Information for “Stereoselectivity of model C22-23 aldol coupling for spirangiens A & B”

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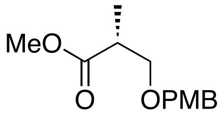
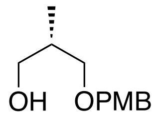
Experimental Procedures



38

(2*R*)-Methyl-3-(4-methoxybenzyl)oxy-2-methyl-propionate (38).[1]

To a stirred solution of (*R*)-3-hydroxy-2-methyl-propionic acid methyl ester **[(*R*)-9]** (0.94 mL; 8.47 mmol) and *para*-methoxybenzyl imidate (3.59 g; 12.7 mmol) in Et_2O (25 mL) was added triflic acid (6 x 5 µL aliquots over 6 h with monitoring by TLC (5% Et_2O/CH_2Cl_2)). The reaction was terminated by addition of 10 mL of Et_2O and the organic mixture was washed with sat. aq. $NaHCO_3$ (30 mL), brine (30 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a white crystalline solid. The solid was triturated with X4 (3 x 15 mL), filtered, and the filtrate was concentrated *in vacuo* to give a yellow oil. Distillation under reduced pressure gave PMB ether **38** (2.02 g; 100%) as a colourless oil. **bp.** 170-172 ^{o}C at 0.2 mmHg; **R*f*** = 0.50 (5% Et_2O/CH_2Cl_2); $[\alpha]^{20}_D$ = -5.1 (c 1.18, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23 (2H, d, J = 8.8 Hz, Ar*H*), 6.87 (2H, d, J = 8.8 Hz, Ar*H*), 4.45 (2H, ABq, J = 12.4 Hz, OCH_2PMP), 3.80 (3H, s, $ArOCH_3$), 3.68 (3H, s, $C(=O)OCH_3$), 3.63 (1H, dd, J = 9.2, 7.2 Hz, CH_AH_BOPMB), 3.45 (1H, dd, J = 9.2, 6.0 Hz, CH_AH_BOPMB), 2.77 (1H, ddq, J = 7.2, 6.0, 6.0 Hz, $CHCH_3$), 1.17 (3H, d, J = 7.2 Hz, $CHCH_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.4, 159.3, 130.4, 129.3, 113.9, 72.9, 71.8, 55.4, 51.8, 40.3, 14.1.

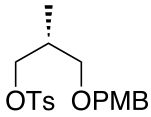


39

(2*S*)-3-(4-methoxybenzyl)oxy-2-methyl-propan-1-ol (39).[1]

A solution of ester **38** (2.04 g; 8.56 mmol) in THF (10 mL) was added *via* cannula to a stirring solution of $LiAlH_4$ (780 mg; 20.6 mmol) in THF (20 mL) at 0 ^{o}C. The resulting mixture was warmed to rt and stirred for 30 min, then recooled to 0 ^{o}C. The reaction was quenched by dropwise addition of H_2O (1.1 mL), NaOH (5 M; 1.1 mL) and H_2O (2.2 mL). The mixture was dried (Na_2SO_4), filtered (Et_2O) and concentrated *in vacuo*. Purification by column chromatography (30% Et_2O/CH_2Cl_2) gave alcohol **39** (1.76 g; 98%) as a colourless oil. **R*f*** = 0.37 (30% Et_2O/CH_2Cl_2); $[\alpha]^{20}_D$ = -16.9 (c

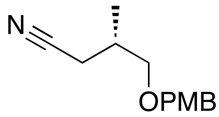
1.13, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 (2H, d, J = 8.4 Hz, Ar*H*), 6.87 (2H, d, J = 8.8 Hz, Ar*H*), 4.43 (2H, s, OCH_2PMP), 3.79 (3H, s, OCH_3), 3.61-3.55 (2H, m, CH_2OH), 3.49 (1H, dd, J = 8.8, 4.4 Hz, CH_AH_BOPMB), 3.39 (1H, dd, J = 9.2, 7.6 Hz, CH_AH_BOPMB), 2.61 (1H, br s, O*H*), 2.09-2.01 (1H, m, C*H*CH_3), 0.87 (3H, d, J = 6.8 Hz, CHCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.4, 130.4, 129.4, 114.0, 75.1, 73.2, 67.8, 55.4, 35.8, 13.7.



40

(2*R*)-3-(4-methoxyphenyl)oxy-2-methyl-1-(toluene-4-sulfonyloxy)-propane (40).[2]

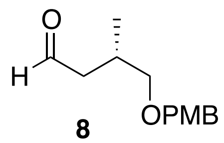
To a mixture of alcohol **39** (1.74 g; 8.28 mmol) in dry pyridine (5.5 mL) at 0 °C was added tosyl chloride (2.21 g; 11.6 mmol) and the resulting mixture stirred at 0 °C for 9 h. Cold water (50 mL) was added to quench the reaction and after 15 min the mixture was extracted with Et_2O (3 x 15 mL). The combined organic extracts were washed successively with 1 M HCl (20 mL), sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (100% CH_2Cl_2) gave tosylate **40** (2.99 g; 99%) as a colourless oil. **R*f*** = 0.47 (100% CH_2Cl_2); **$[\alpha]^{20}_D$** = -3.1 (c 1.31, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 (2H, d, J = 8.4 Hz, Ar*H*), 7.32 (2H, d, J = 8.0 Hz, Ar*H*), 7.16 (2H, d, J = 8.8Hz, Ar*H*), 6.86 (2H, d, J = 8.8 Hz, Ar*H*), 4.33 (2H, s, OCH_2PMP), 4.03 (1H, dd, J = 9.2, 5.6 Hz, CH_AH_BOPMB), 3.97 (1H, dd, J = 9.2, 5.6 Hz, CH_AH_BOPMB), 3.81 (3H, s, OCH_3), 3.32 (1H, dd, J = 9.2, 5.2 Hz, CH_AH_BOTs), 3.28 (1H, dd, J = 9.2, 5.2 Hz, CH_AH_BOTs), 2.43 (3H, s, ArCH_3), 2.09 (1H, m, C*H*CH_3), 0.92 (3H, d, J = 7.2 Hz, CHCH_3); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.3, 144.7, 133.3, 130.5, 129.9, 129.2, 128.0, 113.9, 72.9, 72.4, 71.0, 55.4, 33.8, 21.7, 13.8.



41

(3*S*)-4-(4-methoxyphenyl)oxy-3-methyl-butanenitrile (41).[2]

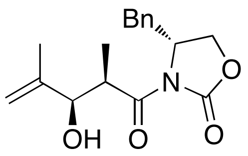
To a solution of tosylate **40** (8.06 g; 22.1 mmol) in anhydrous DMSO (88 mL) was added sodium cyanide (2.28 g; 46.4 mmol). The mixture was stirred at 60 °C for 18 h and then allowed to cool to rt, whereupon it was slowly poured into brine (200 mL). The resulting mixture was extracted with Et_2O (3 x 100 mL), the combined organic extracts dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (100% CH_2Cl_2) gave nitrile **41** (4.81 g; 99%) as a colourless oil. **R*f*** = 0.40 (100% CH_2Cl_2); **$[\alpha]^{20}_D$** = -15.9 (c 1.45, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 (2H, d, J = 9.2 Hz, Ar*H*), 6.88 (2H, d, J = 8.8 Hz, Ar*H*), 4.44 (2H, s, OC*H*$_2$PMP), 3.81 (3H, s, OC*H*$_3$), 3.43 (1H, dd, J = 9.6, 4.8 Hz, C*H*$_A$H$_B$OPMB), 3.27 (1H, dd, J = 9.2, 7.6 Hz, CH$_A$*H*$_B$OPMB), 2.49 (1H, dd, J = 16.4, 5.2 Hz, C*H*$_A$H$_B$CN), 2.37 (1H, dd, J = 16.8, 7.2 Hz, CH$_A$*H*$_B$CN), 2.15-2.09 (1H, m, C*H*CH$_3$), 1.07 (3H, d, J = 6.8 Hz, CHC*H*$_3$); **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.5, 130.2, 129.4, 118.8, 114.0, 73.1, 73.0, 55.4, 31.3, 21.6, 16.4.



8

(3*R*)-4-(4-methoxybenzyl)oxy-3-methyl-propanal (8). [2]

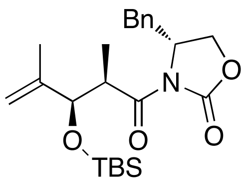
To a stirred solution of nitrile **41** (1.09 mg; 4.97 mmol) in CH_2Cl_2 (50 mL) at -78 °C was added diisobutylaluminium hydride (1 M in toluene; 14.9 mL; 14.9 mmol) dropwise. The reaction mixture was stirred at -78 °C for 2 h, whereupon 1 M HCl (15 mL) was added and the mixture allowed to warm to rt before pouring into 1 M HCl (50 mL). The mixture was extracted with CH_2Cl_2 (3 x 50 mL), the combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by flash chromatography (buffered silica, 5% Et_2O/CH_2Cl_2) gave aldehyde **8** (980 mg; 89%) as a colourless oil. **R*f*** = 0.35 (5% Et_2O/CH_2Cl_2); **$[\alpha]^{20}_D$** = -6.5 (c 1.38, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.75 (1H, apt t, J = 2.0 Hz, C*H*O), 7.23 (2H, d, J = 8.8 Hz, Ar*H*), 6.88 (2H, d, J = 8.8 Hz, Ar*H*), 4.41 (2H, s, OC*H*$_2$PMP), 3.80 (3H, s, OC*H*$_3$), 3.39 (1H, dd, J = 9.2, 5.2 Hz, C*H*$_A$H$_B$OPMB), 3.22 (1H, dd, J = 8.8, 7.6 Hz, CH$_A$*H*$_B$OPMB), 2.53 (1H, ddd, J = 16.0, 6.4, 2.4 Hz, C*H*$_A$H$_B$CHO), 2.46-2.35 (1H, m, C*H*CH$_3$), 2.26 (1H, ddd, J = 16.0, 6.8, 2.0 Hz, CH$_A$*H*$_B$CHO), 0.97 (3H, d, J = 6.8 Hz, CHC*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 202.5, 159.3, 103.5, 129.3, 113.9, 74.8, 72.9, 55.4, 48.7, 29.3, 17.2.



42

[[3-(2*R*,3*R*)-4*R*]-3-(3-hydroxy-2,4-dimethyl-1-oxo-pent-4-enyl)-4-(phenylmethyl)]-2-oxazolidinone (42).

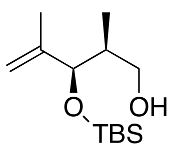
To a stirred solution of oxazolidine **(*R*)-13** (2.05 g; 8.78 mmol) in CH_2Cl_2 (18 mL) at 0 ^oC was added Bu_2BOTf (10.5 mL; 1M in CH_2Cl_2; 10.5 mmol) dropwise giving a red solution. After 30 min Et_3N (1.59 mL; 11.4 mmol) was added and the resulting yellow solution was stirred for a further 30 min before cooling to -78 ^oC. Methacrolein (1.45 mL; 17.6 mmol) in CH_2Cl_2 (5 mL) was added dropwise *via* cannula and the reaction mixture stirred at -78 ^oC for 30 min and then at 0 ^oC for 4 h, at which time the reaction was quenched by addition of pH 7 buffer (8 mL) and MeOH (8 mL). A solution of 2:1 MeOH/H_2O_2 (16 mL) was then added and the mixture stirred at room temperature for 1 h. The volatiles were removed *in vacuo* and the resulting slurry was extracted with CH_2Cl_2 (3 x 20 mL), the combined organic extracts washed with sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 5% Et_2O/CH_2Cl_2) gave aldol adduct **42** (2.61 g; 98%, >98% ds) as a white solid. **R*f*** = 0.31 (5% Et_2O/CH_2Cl_2); $[\alpha]^{20}_D$ = -19.6 (c 1.12, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35-7.31 (2H, m, Ar*H*), 7.29-7.25 (1H, m, Ar*H*) 7.22-7.19 (2H, m, Ar*H*), 5.12 (1H, m, $CH_AH_BC(CH_3)CHOH$), 4.97 (1H, m, $CH_AH_BC(CH_3)CHOH$), 4.71 (1H, m, C*H*CH_2O), 4.42 (1H, s, C*H*OH), 4.23 (1H, dd, J = 9.6, 9.2 Hz, $CHCH_AH_BO$), 4.19 (1H, dd, J = 8.8, 3.2 Hz, $CHCH_AH_BO$), 3.98 (1H, dq, J = 7.2, 3.2 Hz, CH(OH)C*H*(CH_3)C=O), 3.27 (1H, dd, J = 13.6, 3.6 Hz, CH_AH_BPh), 2.94 (1H, br s, O*H*), 2.80 (1H, dd, J = 13.2, 9.2 Hz, CH_AH_BPh), 1.74 (3H, s, $CH_2C(CH_3)CHOH$), 1.19 (3H, d, J = 7.2 Hz, CH(OH)CH(CH_3)C=O); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 177.2, 153.1, 143.9, 135.2, 129.6, 129.1, 127.6, 111.9, 74.1, 66.4, 55.4, 40.3, 37.9, 19.5, 10.2.



43

[[3-(2*R*,3*R*)-4*R*]-3-(3-(*tert*-butyldimethylsilyloxy)-2,4-dimethyl-1-oxo-pent-4-enyl)-4-(phenylmethyl)]-2-oxazolidinone (43).

The previous procedure used for the preparation of TBS ether **11** was followed with alcohol **42** (2.67 g; 8.79 mmol), 2,6-lutidine (2.05 mL; 17.6 mmol), TBSOTf (3.03 mL; 13.2 mmol) and CH_2Cl_2 (88 mL). Purification by column chromatography (buffered silica, 20% X4/CH_2Cl_2) gave TBS ether **43** (3.66 g; 100%) as a while solid. **R*f*** = 0.55 20% X4/CH_2Cl_2); **$[\alpha]^{20}_D$** = -48.1 (c 1.85, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33-7.29 (2H, m, Ar*H*), 7.26-7.22 (1H, m, Ar*H*) 7.21-7.18 (2H, m, Ar*H*), 4.94 (1H, m, $CH_AH_BC(CH_3)CHOH$), 4.83 (1H, m, $CH_AH_BC(CH_3)CHOH$), 4.56 (1H, m, C*H*CH_2O), 4.36 (1H, d, J = 6.4 Hz, C*H*OTBS), 4.15-4.08 (2H, m, J = 9.6, 9.2 Hz, CHC*H*$_2$O), 4.03 (1H, dq, J = 6.8, 6.8 Hz, CH(OTBS)C*H*(CH_3)C=O), 3.25 (1H, dd, J = 13.6, 3.2 Hz, CH_AH_BPh), 2.76 (1H, dd, J = 13.6, 9.6 Hz, CH_AH_BPh), 1.72 (3H, s, $CH_2C(CH_3)CHOTBS$), 1.21 (3H, d, J = 6.8 Hz, CH(OH)CH(C*H*$_3$)C=O), 0.91 (9H, s, OSiC(C*H*$_3$)$_3$), 0.02 (3H, s, OSi(C*H*$_3$)CH_3), -0.01 (3H, s, OSi(CH_3)C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 174.9, 153.2, 145.8, 135.5, 129.6, 129.0, 127.5, 112.7, 77.1, 66.1, 55.8, 42.6, 37.8, 25.9, 18.3, 17.9, 12.5, -4.6, -5.2.

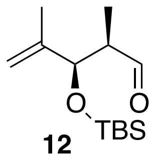


44

(2*S*,3*R*)-3-(tert-butyldimethylsilyloxy)-2,4-dimethyl-pent-4-en-1-ol (44).

To a stirred solution of oxazolidinone **43** (2.71 g; 6.48 mmol) in Et_2O (80 mL) at -10 ^oC was added EtOH (911 μL; 15.6 mmol) and $LiBH_4$ (15.6 mL; 1 M in THF; 15.6 mmol) and the resulting mixture was stirred at -10 ^oC for 4 h. The reaction mixture was warmed to 0 ^oC and quenched by addition of 1 M NaOH (50 mL). The mixture was poured into brine (50 mL) and extracted with Et_2O (4 x 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. Purification by column chromatography (buffered silica, 5% Et_2O/CH_2Cl_2) gave alcohol **44** (1.24 g;

78%) as a colourless oil. **R*f*** = 0.47 (5% Et_2O/CH_2Cl_2); **[α]$^{20}_{D}$** = +17.9 (c 1.45, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 4.93 (1H, m, C*H*$_A$H$_B$C(CH_3)CHOH), 4.87 (1H, m, C*H*$_A$H$_B$C(CH_3)CHOH), 4.05 (1H, d, J = 5.6 Hz, C*H*OTBS), 3.57 (1H, dd, J = 10.4, 6.8 Hz, C*H*$_A$H$_B$OH), 3.47 (1H, dd, J = 10.8, 5.2 Hz, CH$_A$*H*$_B$OH), 2.01 (1H, br s, O*H*), 1.89-1.80 (1H, m, C*H*(CH_3)CH_2OH), 1.70 (3H, s, CH_2C(C*H*$_3$)CHOTBS), 0.90 (9H, s, OSiC(C*H*$_3$)$_3$), 0.86 (3H, d, J = 6.8Hz, CH(C*H*$_3$)CH_2OH), 0.06 (3H, s, OSi(C*H*$_3$)CH_3), 0.00 (3H, s, OSi(CH_3)C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 146.6, 112.1, 78.3, 66.0, 39.7, 26.0, 18.8, 18.3, 12.1, -4.5, -5.1.



12

(2*R*,3*R*)-3-(*tert*-butyldimethylsilyloxy)-2,4-dimethyl-pent-4-enal (12).[3]

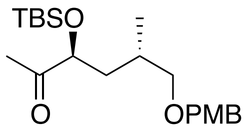
To a stirred solution of DMSO (1.02 mL; 14.3 mmol) in CH_2Cl_2 (48 mL) at -78 °C was added $(COCl)_2$ (3.58 mL; 2 M in CH_2Cl_2; 7.16 mmol) dropwise and the resulting solution was stirred at -78 °C for 30 min. Alcohol **44** (1.17 g; 4.77 mmol) was added dropwise *via* cannula (CH_2Cl_2, 8 mL) and the mixture stirred at -78 °C for 45 min before Et_3N Et_3N (3.99 mL; 28.6 mmol) was added dropwise. The mixture was stirred at -78 °C for a further 30 min before warming to 0 °C for 30 min and the reaction was quenched by addition of sat. aq. NH_4Cl (120 mL). The product was extracted with CH_2Cl_2 (3 x 40 mL), the combined organic extracts dried (Na_2SO_4) and concentratrated *in vacuo*. Purification by column chromatography (buffered silica, 100% CH_2Cl_2) gave aldehyde **12** as a colourless oil. **R*f*** = 0.40 (100% CH_2Cl_2); **[α]$^{20}_{D}$** = +32.9 (c 1.10, CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.69 (1H, d, J = 1.6 Hz, C*H*O), 4.97 (1H, m, C*H*$_A$H$_B$C(CH_3)CHOH), 4.91 (1H, m, C*H*$_A$H$_B$C(CH_3)CHOH), 4.40 (1H, d, J = 4.8 Hz, C*H*OTBS), 2.47 (1H, ddq, J = 6.8, 4.8, 1.6, C*H*(CH_3)CHO), 1.68 (3H, s, CH_2C(C*H*$_3$)CHOTBS), 1.04 (3H, d, J = 6.8 Hz, CH(C*H*$_3$)CHO), 0.87 (9H, s, OSiC(C*H*$_3$)$_3$), 0.03 (3H, s, OSi(C*H*$_3$)CH_3), 0.00 (3H, s, OSi(CH_3)C*H*$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 204.7, 115.0, 113.1, 76.0, 53.6, 50.7, 25.9, 18.6, 8.5, -4.4, -5.1.

References:

[1] Walkup, R. D.; Boatman Jr., P. D.; Kane, R. R.; Cunningham, R. T. *Tetrahedron Lett*. **1991**, 32, 3937–3940

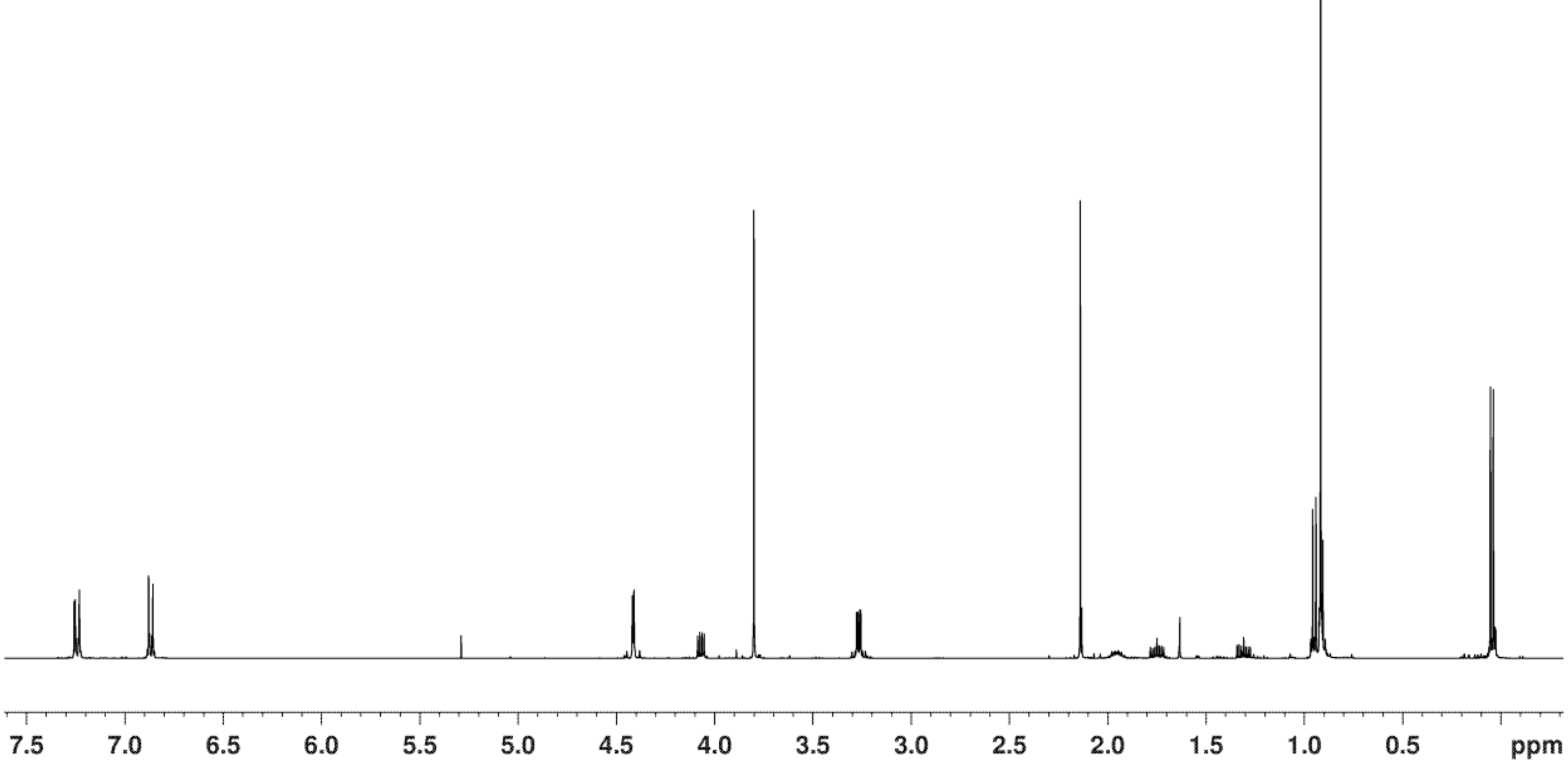
[2] (i) Mulzer, J., Hanbauer, M. *Tetrahedron Lett.* **2000**, *41*, 33-36. (ii) Ahmed, A., Hoegnauer, E. K., Enev, V. S., Hanbauer, M., Kaehlig, H., Ohler, E., Mulzer, J. *J. Org. Chem.* **2003**, *68*, 3026-3042.

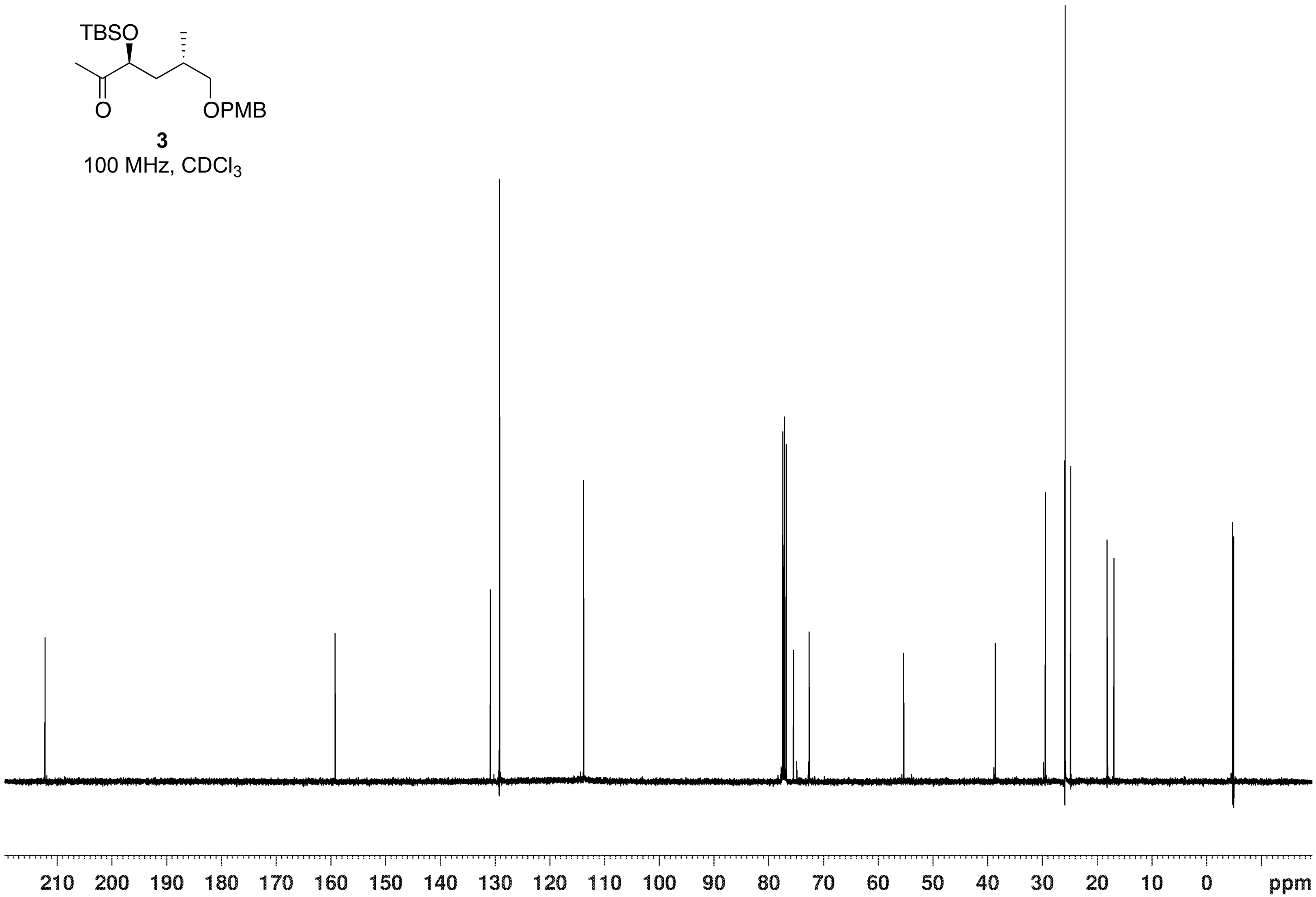
[3] (i) Smith, A. B., Barbosa, J., Wong, W., Wood, J. L. *J. Am. Chem. Soc.* **1995**, *117*, 10777-10778. (ii) Smith, A. B., Barbosa, J., Wong, W., Wood, J. L. *J. Am. Chem. Soc.* **1996**, *118*, 8316-8328.



3

400 MHz, $CDCl_3$

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O
OPMB
3
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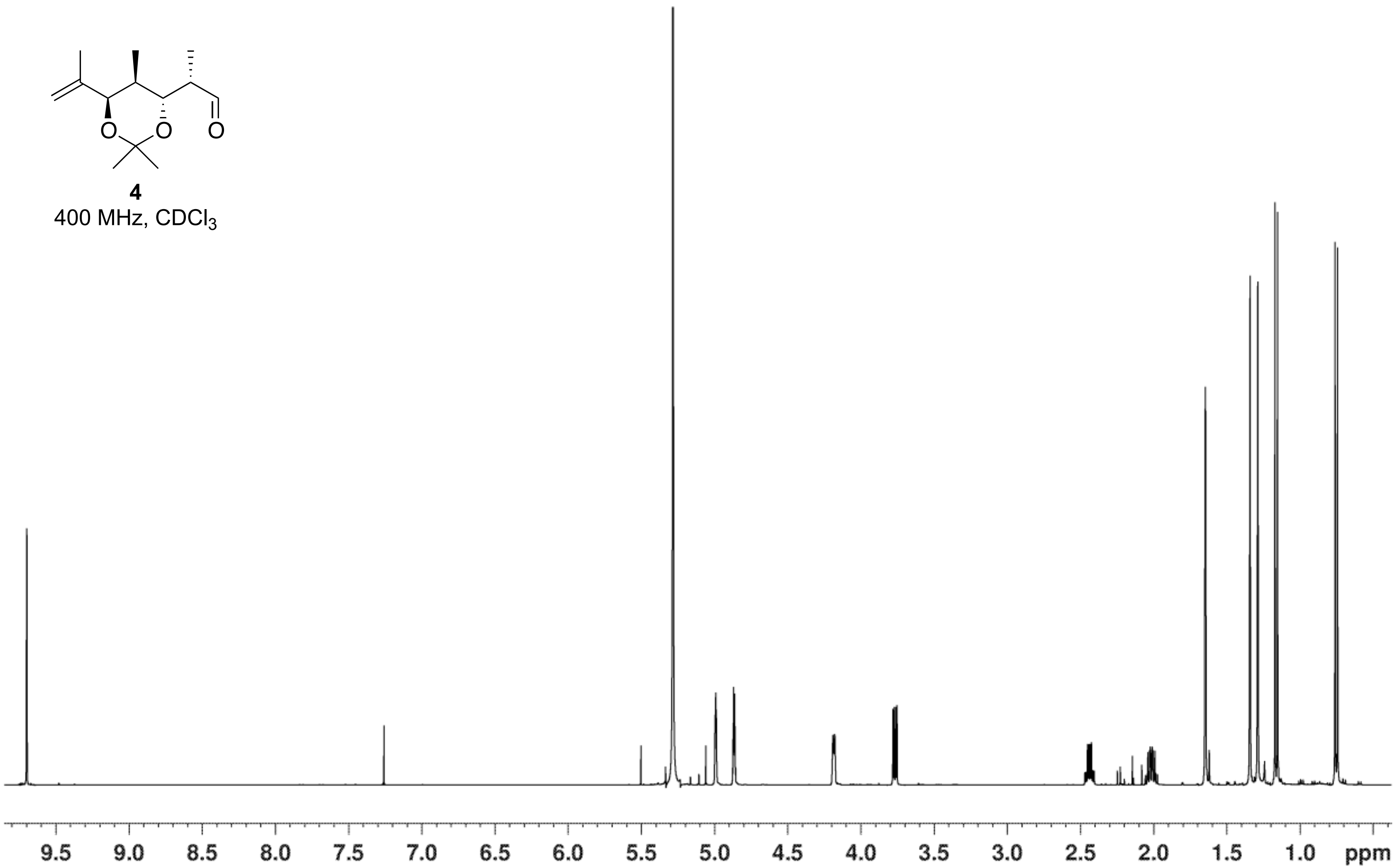
4
400 MHz, $CDCl_3$
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9.0
8.5
8.0
7.5
7.0
6.5
6.0
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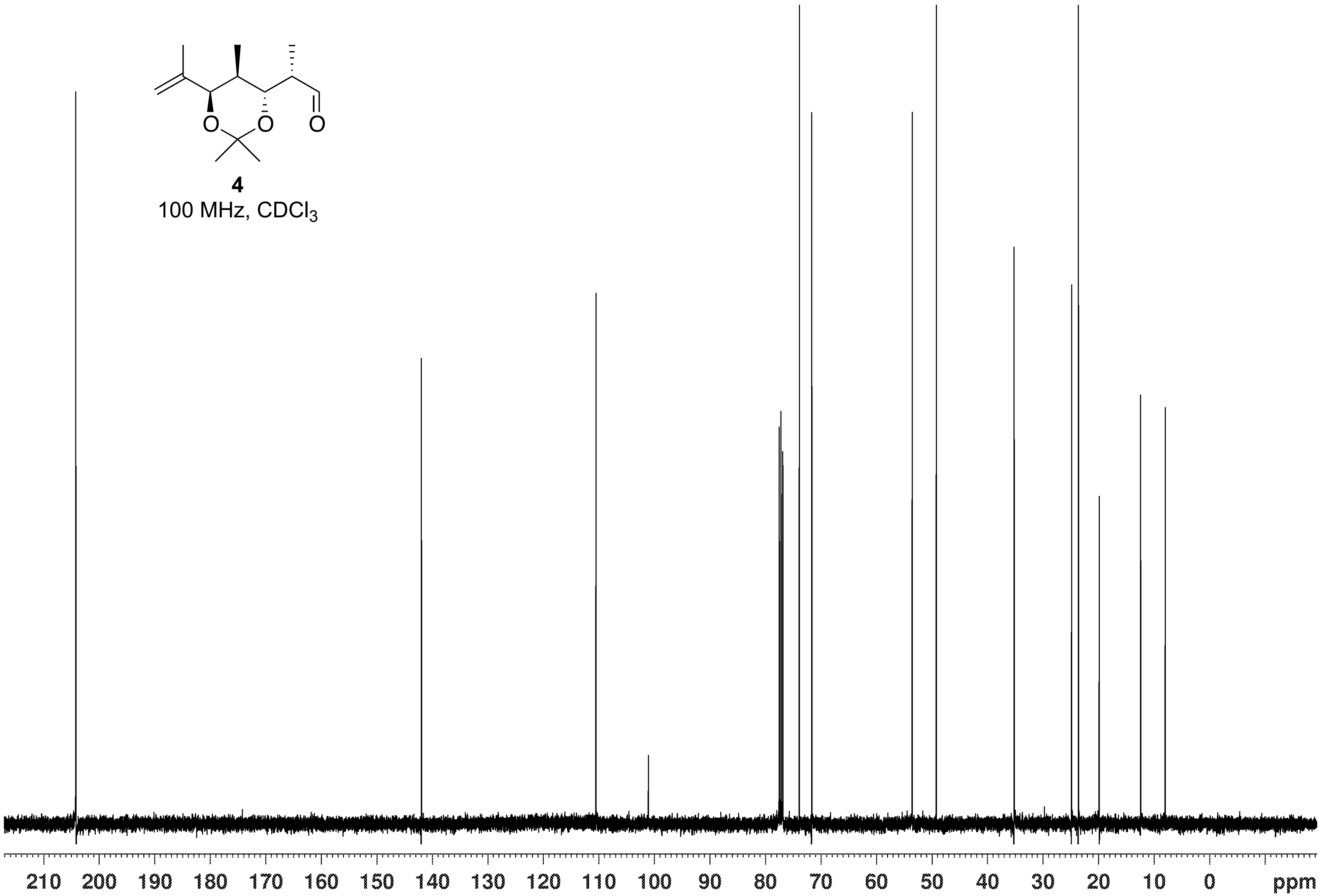
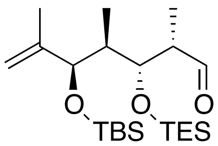
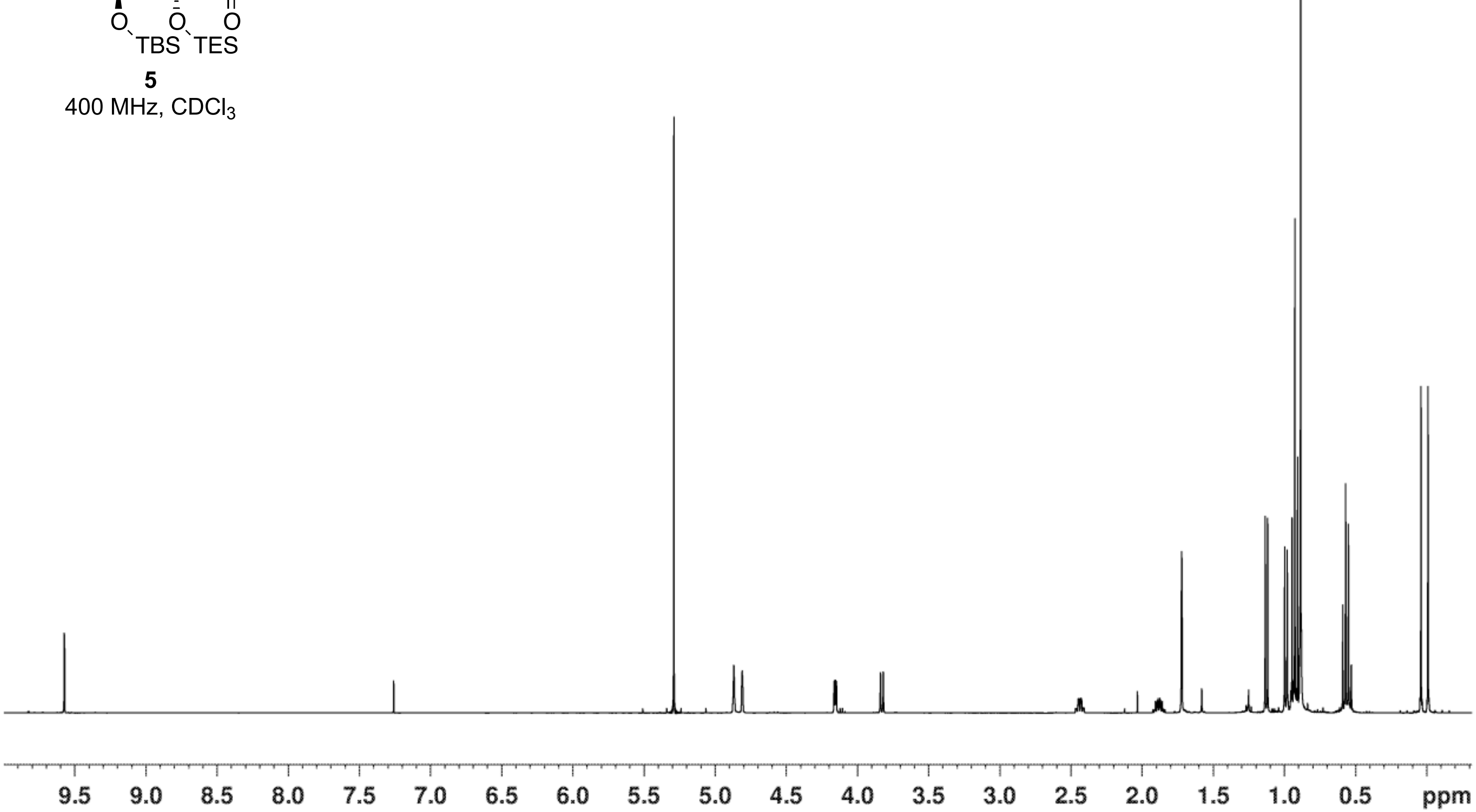
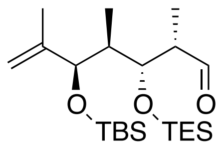
1.5
1.0
ppm


4
100 MHz, $CDCl_3$
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm



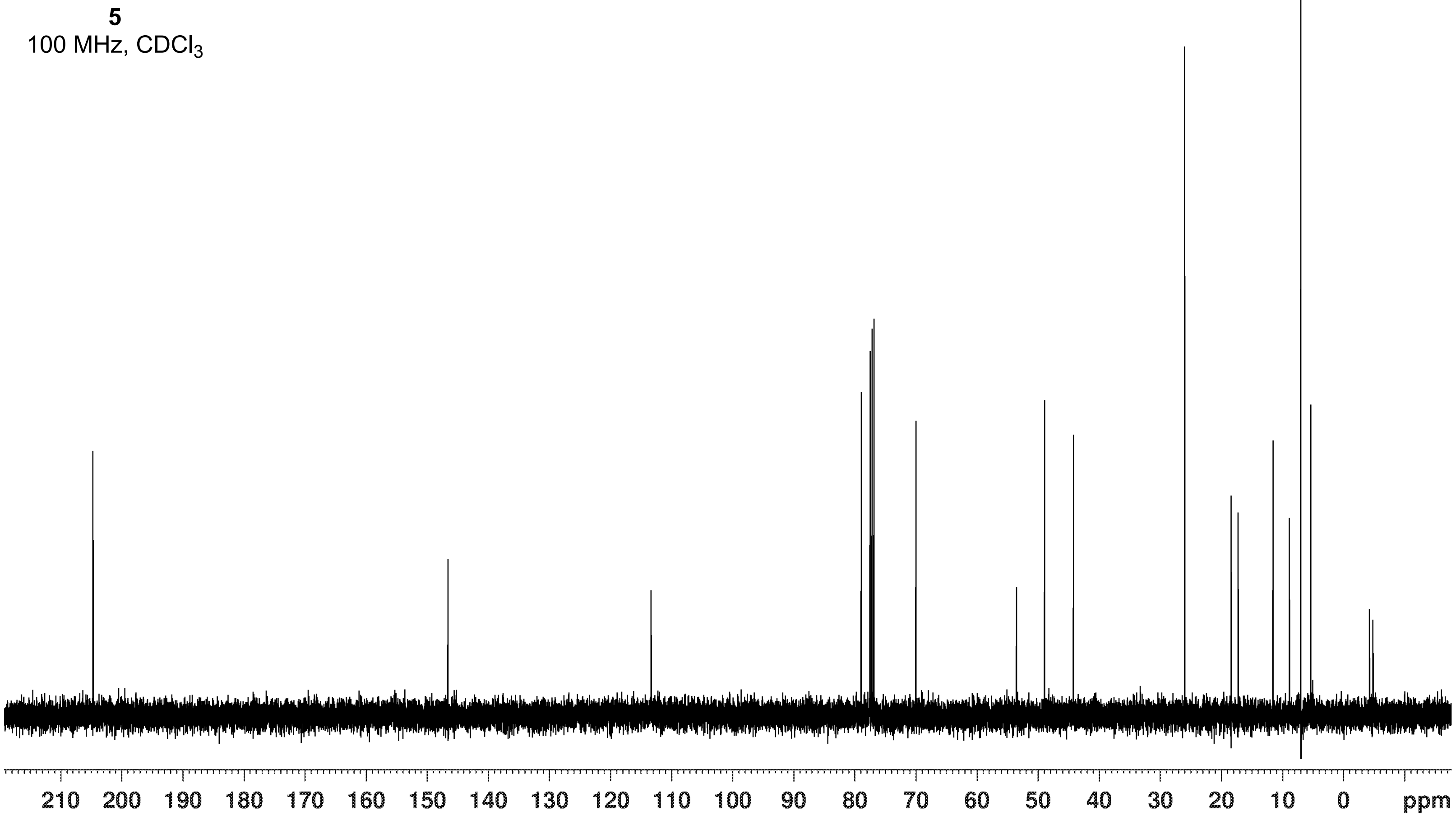
5
400 MHz, $CDCl_3$

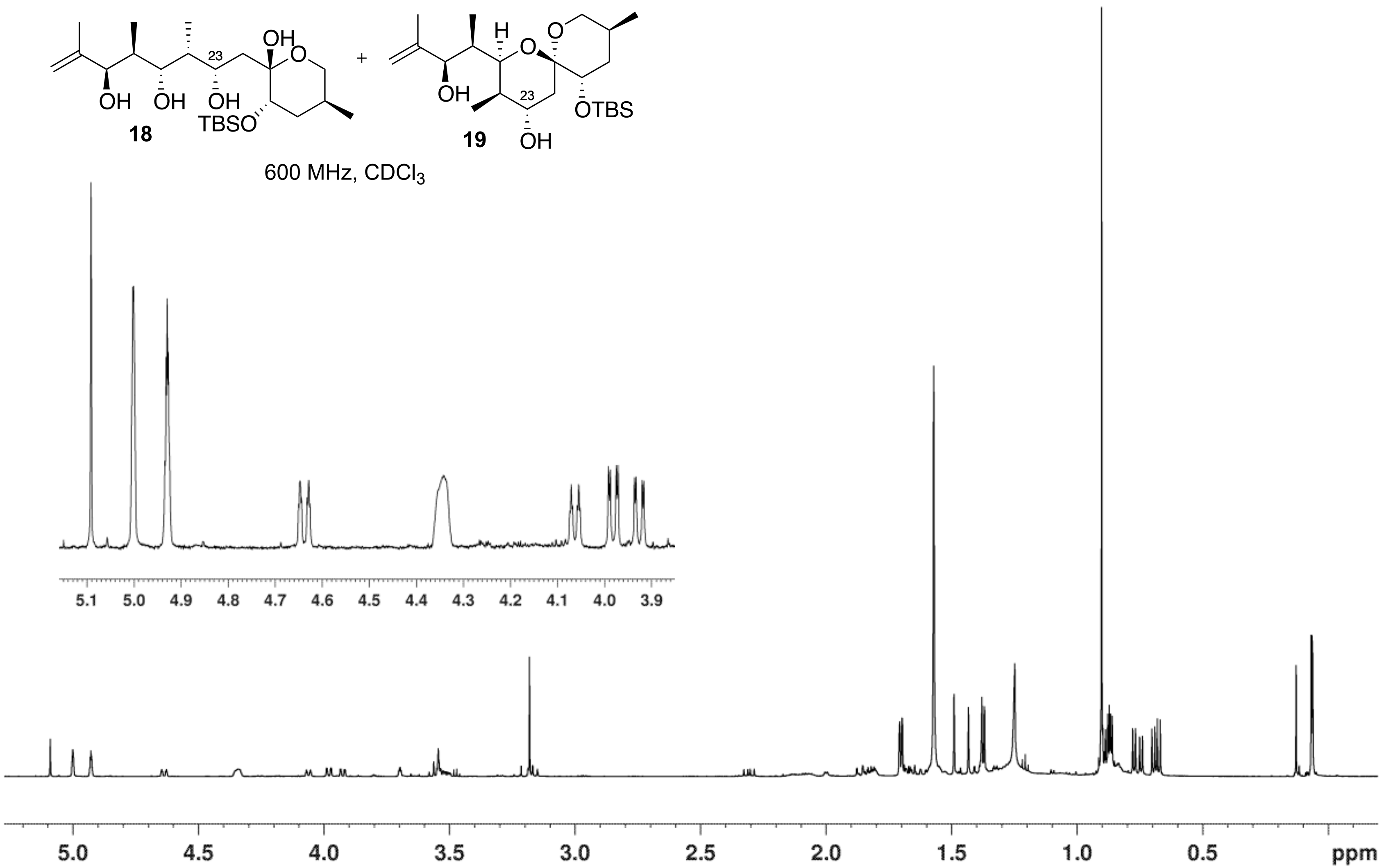




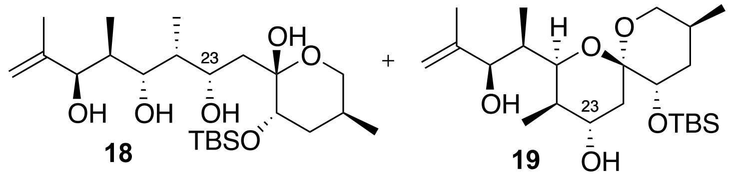
5

100 MHz, $CDCl_3$

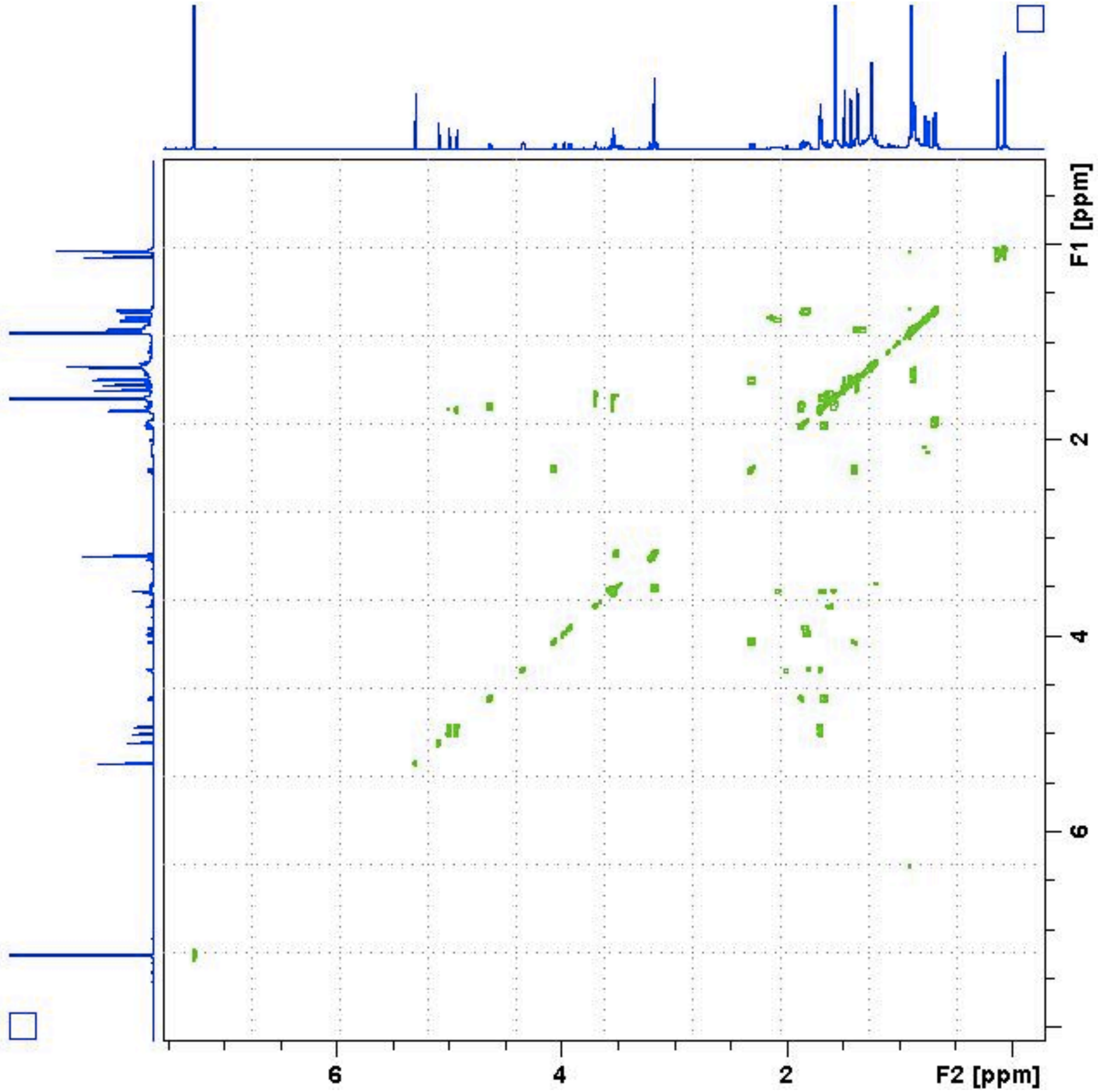


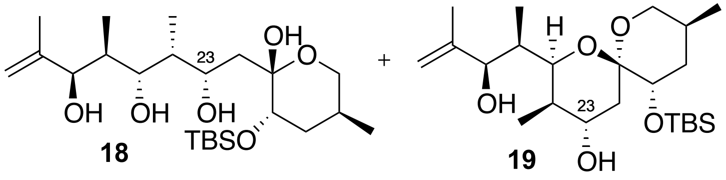


18
+
19
600 MHz, $CDCl_3$
ppm

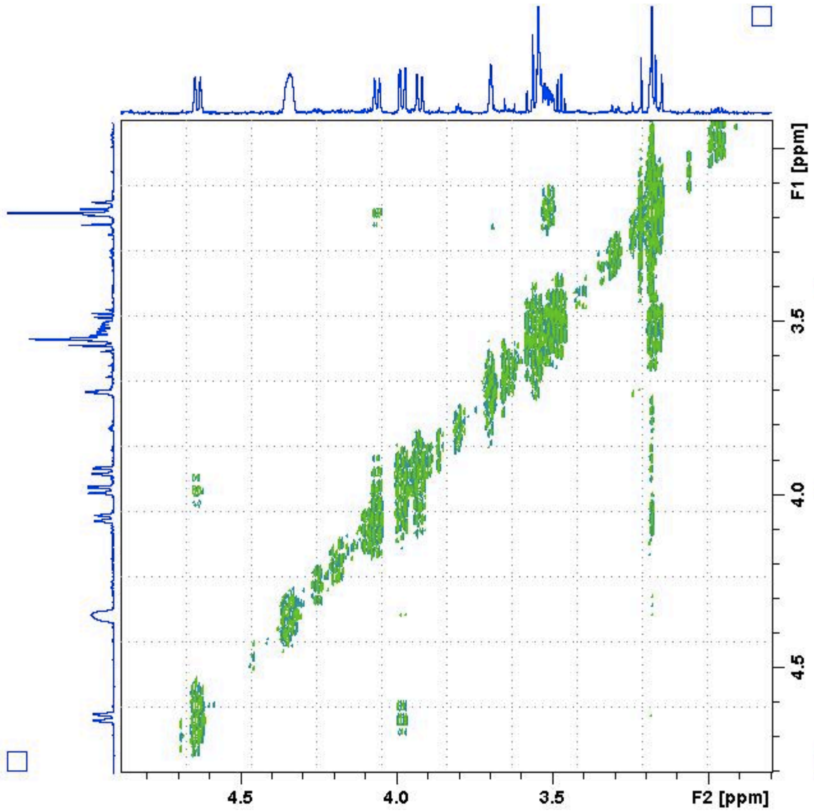


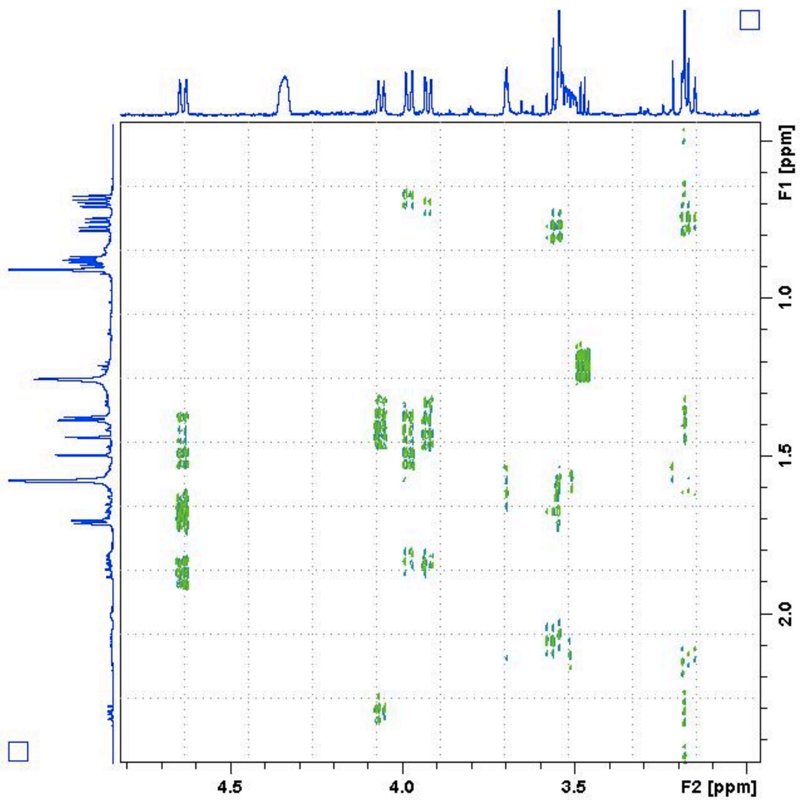
COSY, 600 MHz, $CDCl_3$

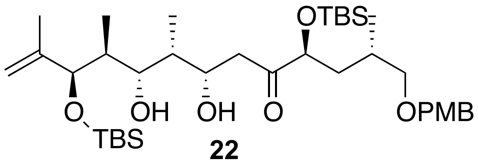




NOESY, 600 MHz, $CDCl_3$

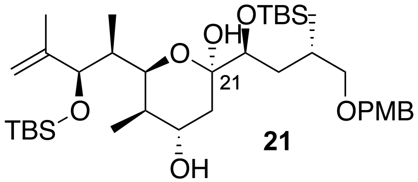






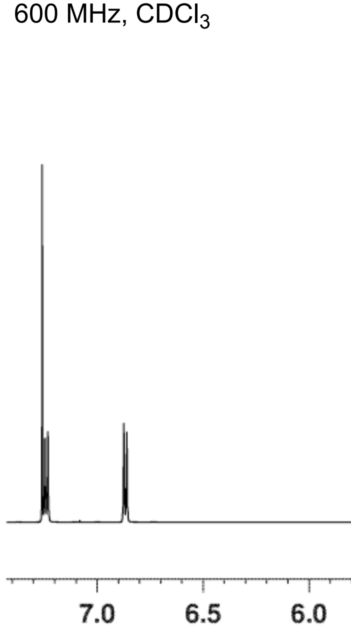
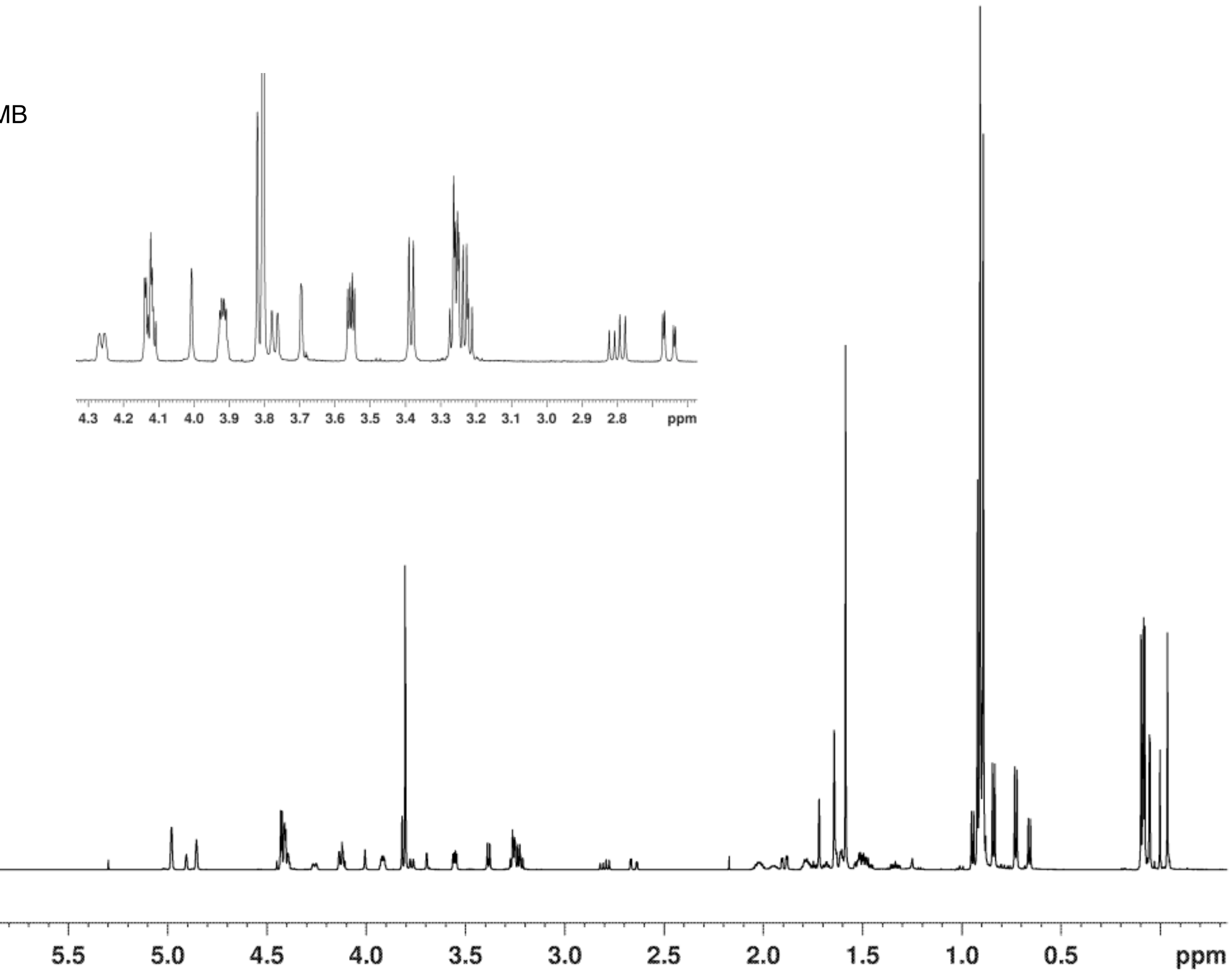
22

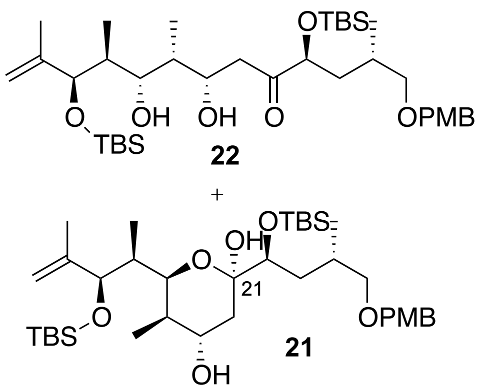
+



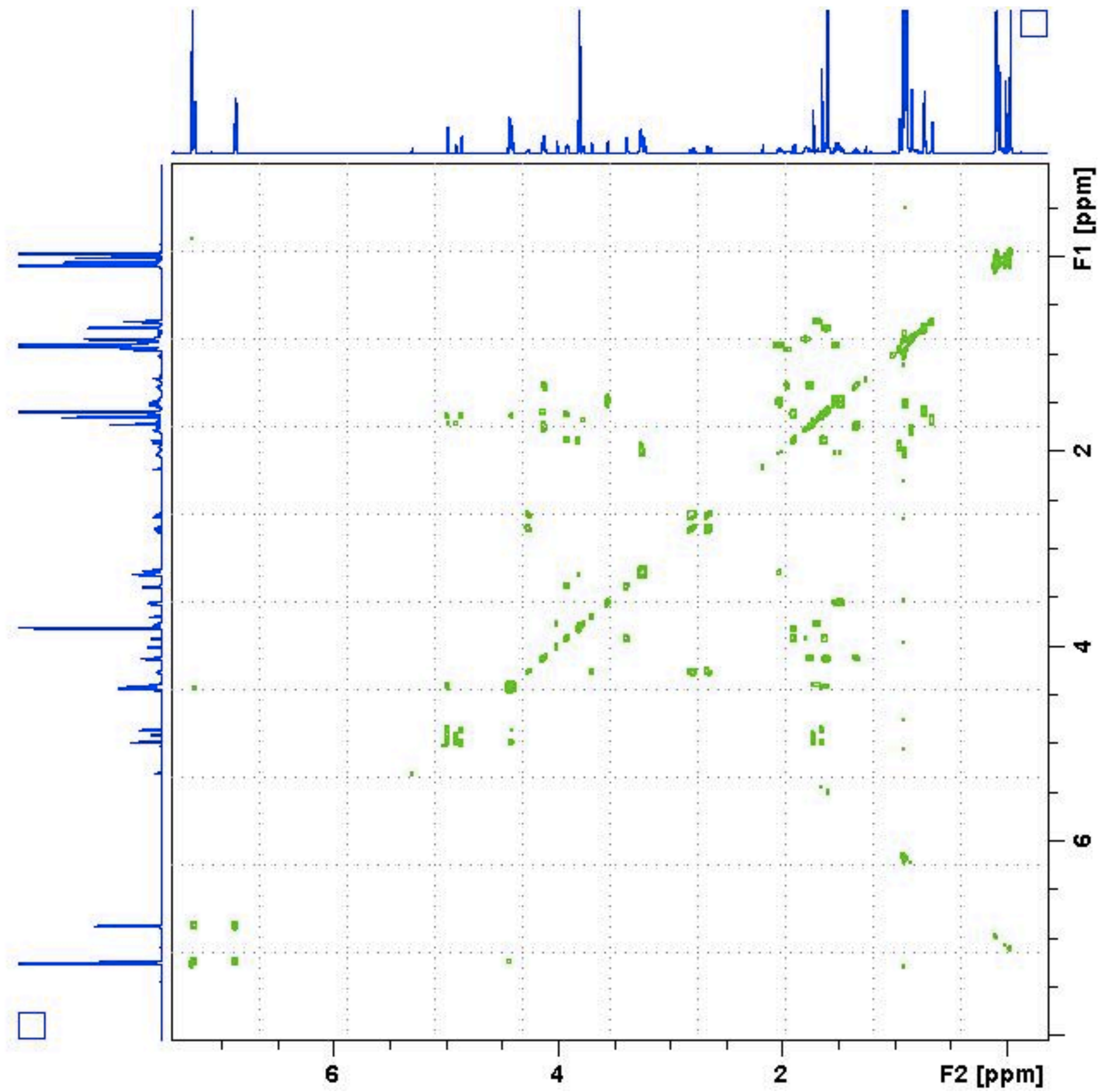
21

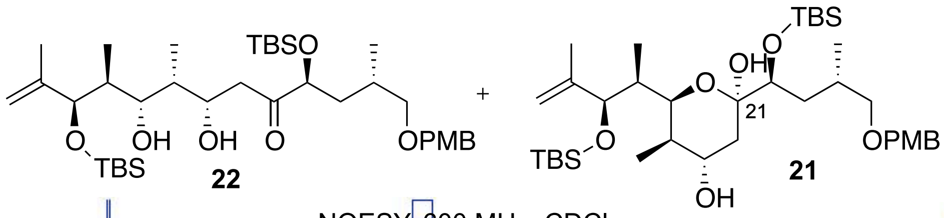
600 MHz, $CDCl_3$

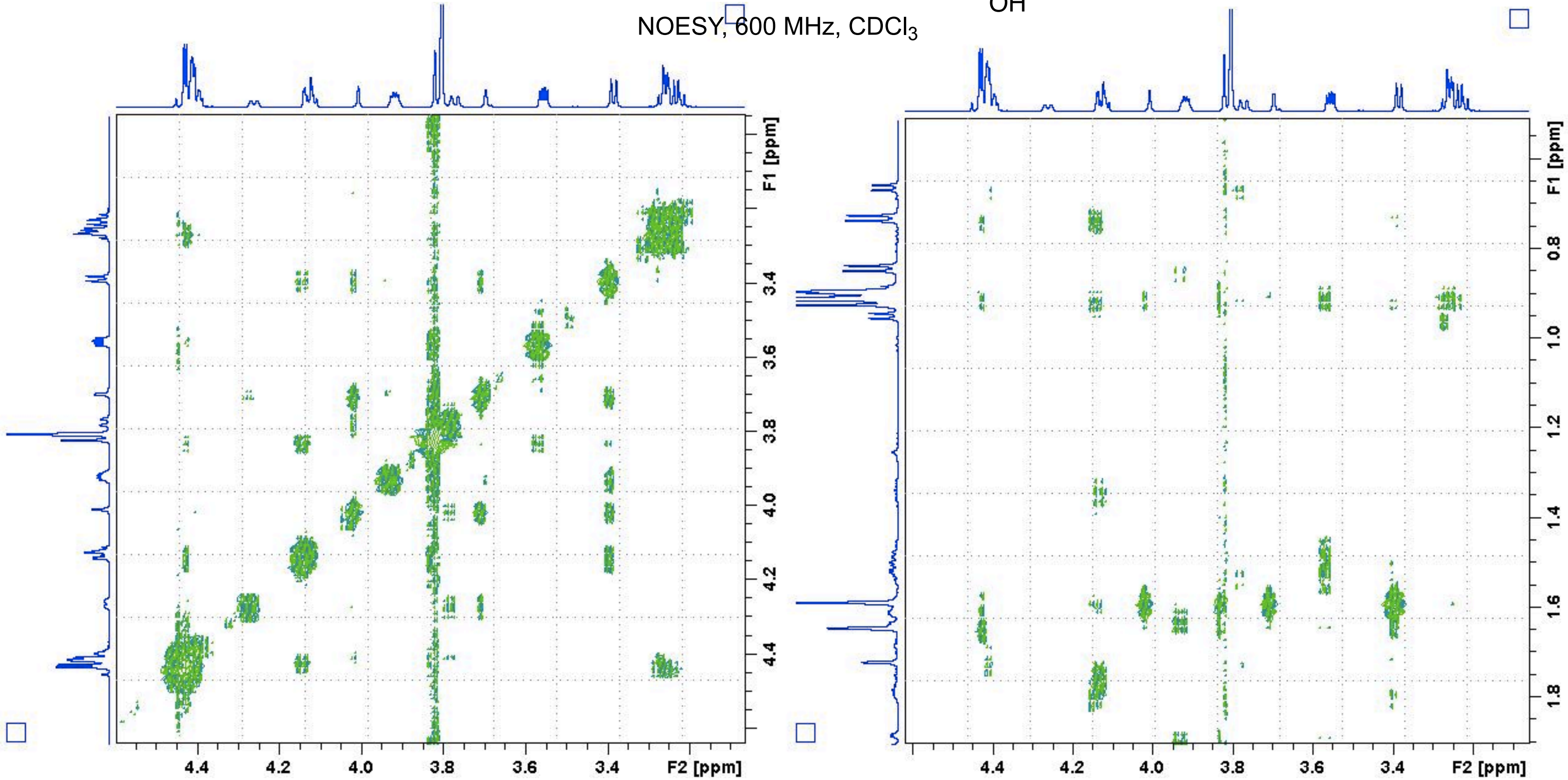


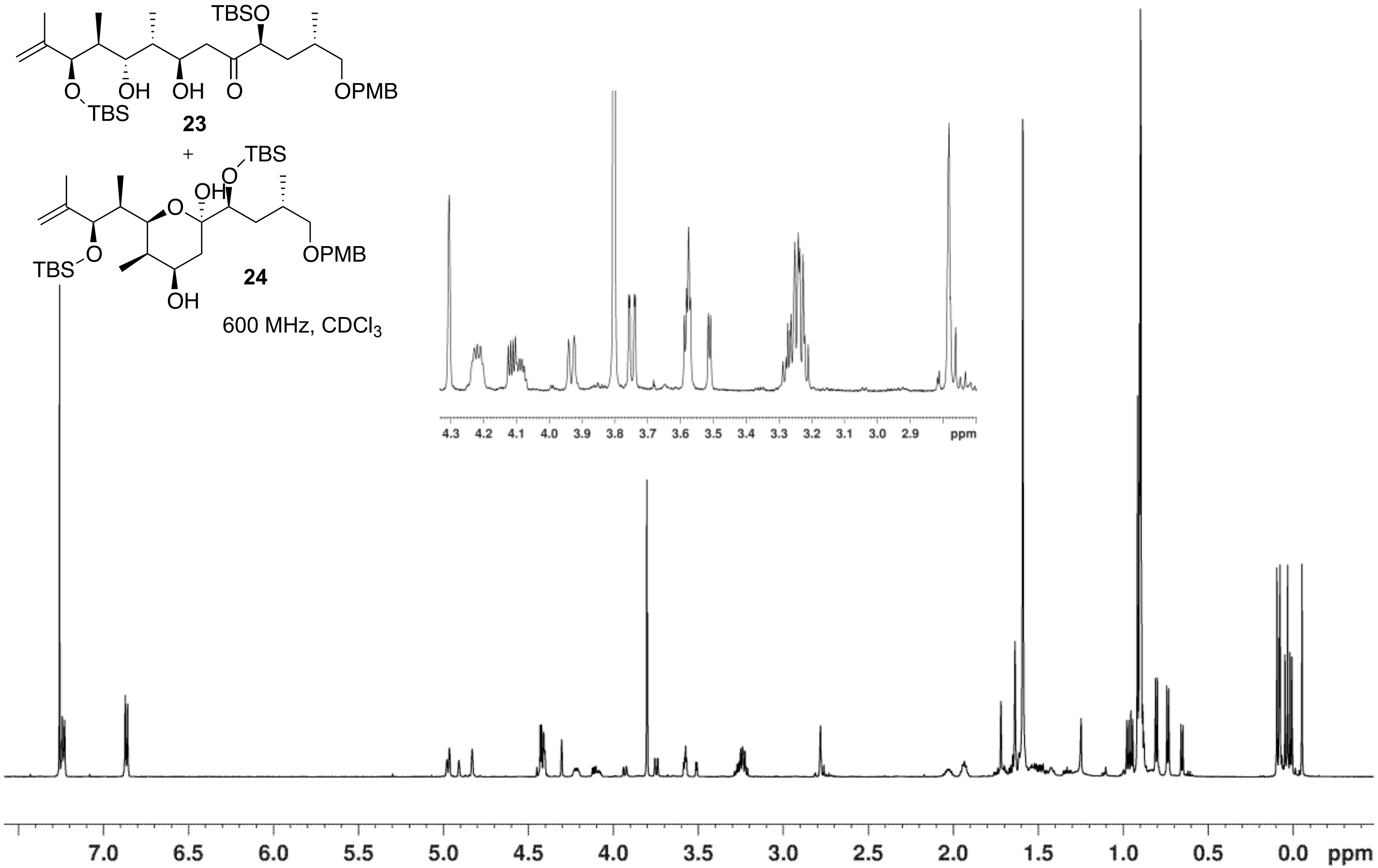
COSY, 600 MHz, $CDCl_3$

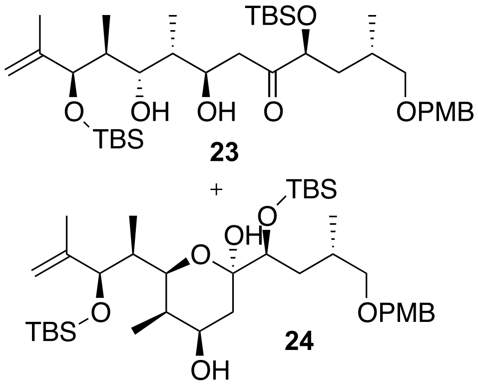




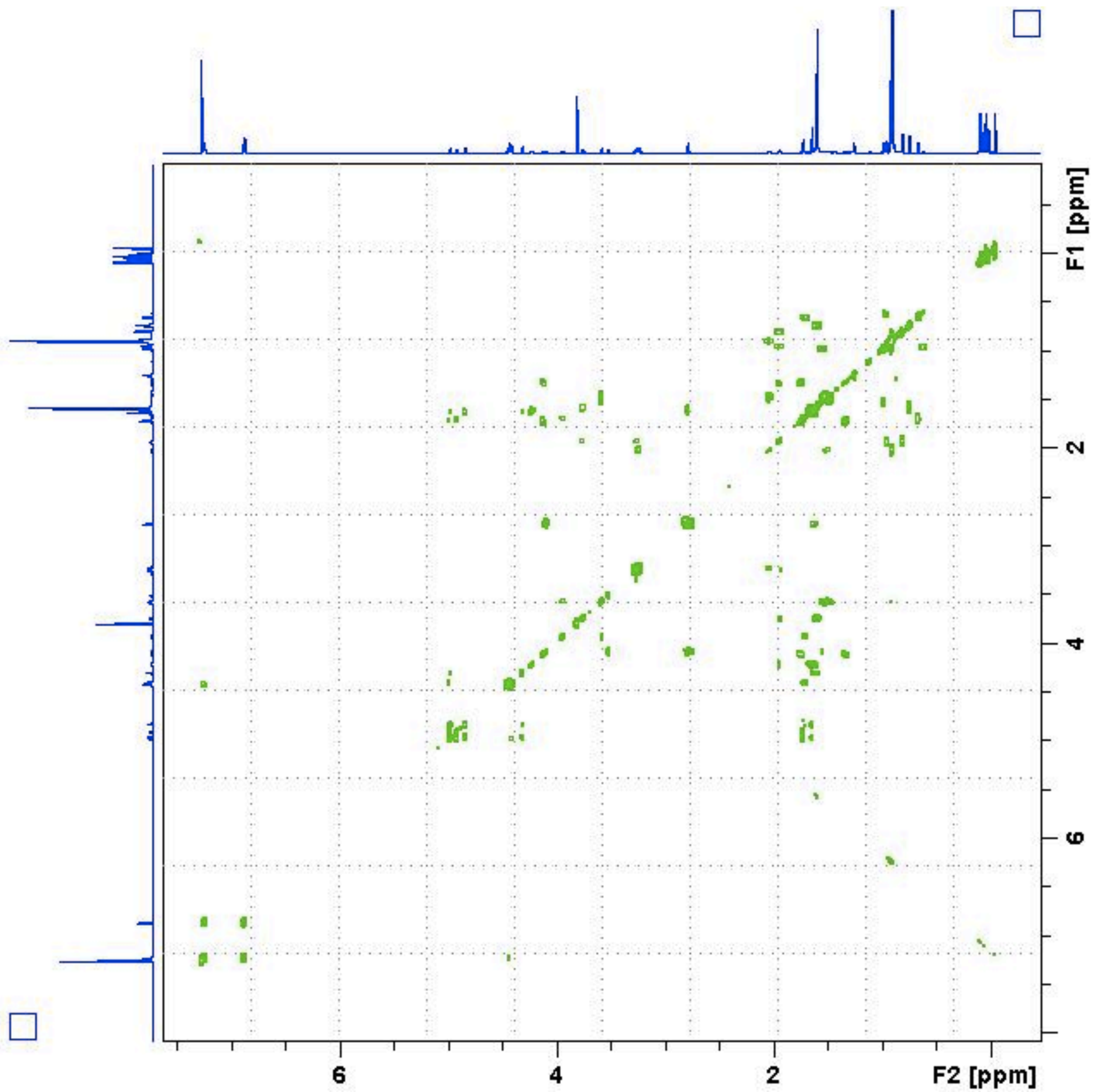
NOESY, 600 MHz, $CDCl_3$

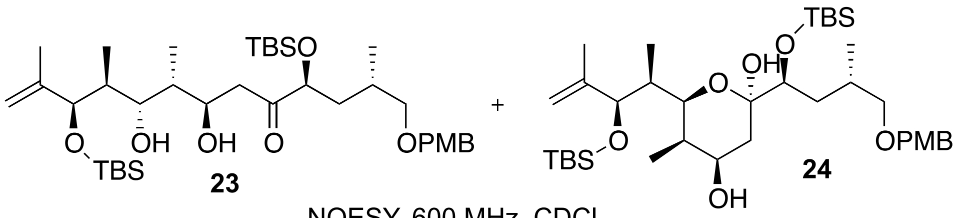



TBSO
OH
OH
O
O
TBS
OPMB
23
+
TBS
O
OH
O
TBS
O
OPMB
OH
24
600 MHz, $CDCl_3$
4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 ppm
7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm



COSY, 600 MHz, $CDCl_3$





NOESY, 600 MHz, $CDCl_3$