A [3 + 3] Annelation Approach to (+)-Rhopaloic acid B

Julien C.R. Brioche[a], Katharine M. Goodenough[a], David J. Whatrup[b] and Joseph P.A. Harrity*[a]

[a]*Department of Chemistry, University of Sheffield, Brook Hill, Sheffield, S3 7HF*

[b]*Synthetic Chemistry, GlaxoSmithKline,Tonbridge, Kent, TN11 9AN, U.K.*

Supporting Information

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Epoxides **6**[i], **9**[ii], **12**[iii] were prepared according to known procedures.

Preparation of the Grignard reagent

To BuLi (15 mL, 10 M, 2.1 eq.) at 0°C were added anhydrous ether (114 mL) and TMEDA (22.6 mL, 2.1 eq). After cooling the solution at -78°C, methallyl alcohol **5** was added dropwise (6.40 mL, 1 eq.) and the reaction was stirred at -78°C for 1h. The bath was then removed and the resulting mixture was vigorously stirred for 24h. After this time, stirring was stopped for 30 min and the solvent was removed via cannula filtration. Anhydrous ether (100 mL) was then added to the remaining orange solid and the suspension was cooled to 0°C. At this point a solution of freshly prepared $MgBr_2$ [prepared from magnesium (2.1 eq, 3.9 g), dibromoethane (2.1 eq, 13.8 mL) in ether (58 mL)] was transferred quickly via cannula to the suspension. After addition the bath was removed and the suspension was vigorously stirred for 30-45 min. At this stage, the stirring was stopped and the Grignard solution was then separated from colourless solid via cannula. The Grignard solution was titrated and stored in a refrigerator under argon.

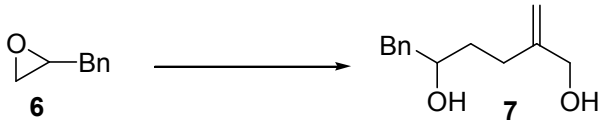
Titration of the Grignard reagent[iv]

To menthol (31 mg, 0.2 mmol) in dry THF (1.5 mL) was added 1,10-phenanthroline (4 mg). The Grignard reagent to be assayed was added dropwise by syringe until a distinct violet or burgundy colour persisted for longer than one minute.

Concentration = (mol. menthol x 1000)/vol. Grignard added (usually 0.8 - 0.15 M)

Grignard addition to epoxides

Preparation of 2-methylene-6-phenylhexane-1,5-diol (7).

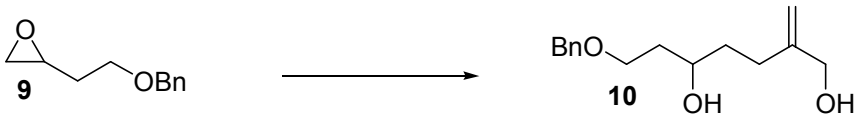


6 **7**

To a solution of Grignard (19 mL, 0.10 M, 1.9 mmol) was added via cannula at RT a solution of epoxide **6** (170 mg, 1.26 mmol) in THF (12.5 mL) and the

reaction stirred for 2h. The remaining organometallic reagent was quenched by the slow addition at 0°C of saturated aqueous NH_4Cl solution. The product was extracted with ethyl acetate. The organic layer was washed with 1N HCl, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (60:40 petroleum ether/ethyl acetate), to give the desired product **7** as an oil (199 mg, 76%); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.37-7.15 (m, 5H, Ar-*H*), 5.02 (br, 1H, alkene-*H*), 4.90 (br, 1H, alkene-*H*), 4.07 (s, 2H, alkene-C*H*$_2$OH), 3.89-3.77 (m, 1H, BnC*H*), 2.82 (dd, *J* = 13.5 Hz, *J* = 4.5 Hz, 1H, C*H*$_2$Ph), 2.67 (dd, *J* = 13.5 Hz, *J* = 8.0 Hz, 1H, C*H*$_2$Ph), 2.37-2.05 (m, 2H, alkene-CH_2C*H*$_2$), 2.01-1.81 (br, 2H, O*H*), 1.78-1.57 (m, 2H, alkene-C*H*$_2$$CH_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 148.7, 138.5, 129.5, 128.7, 126.6, 110.1, 72.4, 66.1, 42.2, 34.8, 29.1; FTIR (CH_2Cl_2): 3436 (br), 2924 (s), 1652 (m), 1603 (m), 1495 (m), 1454 (s), 1082 (s), 1023 (s), 899 (m), 745 (m), 701 (s), 6047 (w), 529 (w) cm^{-1}; HRMS (ES): m/z $[M+Na]^+$ calcd for $C_{13}H_{18}O_2Na$: 229.1204, found: 229.1196.

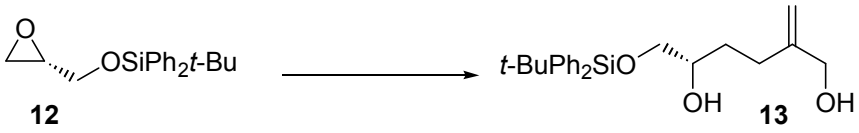
Preparation of 7-(benzyloxy)-2-methyleneheptane-1,5-diol (10).



To a solution of Grignard (14.3 mL, 0.10 M, 1.43 mmol) was added via cannula at RT a solution of epoxide **9** (170 mg, 0.95 mmol) in THF (9.5 mL) and the reaction stirred for 2h. The remaining organometallic reagent was quenched by the slow addition at 0°C of saturated aqueous NH_4Cl solution. The product was extracted with ethyl acetate. The organic layer was washed with 1N HCl, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (60:40 petroleum ether/ethyl acetate), to give the desired product **10** as an oil (174 g, 74%):^{1}H NMR (250 MHz, $CDCl_3$): δ 7.47-7.22 (m, 5H, Ar-*H*), 5.01 (br, 1H, alkene-C*H*$_2$), 4.87 (br, 1H, alkene-C*H*$_2$), 4.51 (s, 2H, OC*H*$_2$Ph), 4.06 (br, 2H, alkene-C*H*$_2$OH), 3.95-3.77 (m, 1H, CH_2C*H*OH), 3.77-3.58 (m, 2H, C*H*$_2$OBn), 3.22 (br, 1H, O*H*), 2.51-1.97 (m, 3H, C*H*$_2$, O*H*), 1.88-1.50 (m, 4H, C*H*$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 149.0, 138.0, 128.6, 127.9, 127.8, 109.8, 73.4, 71.1, 69.3, 66.1, 36.5, 35.6, 29.0; FTIR (CH_2Cl_2):

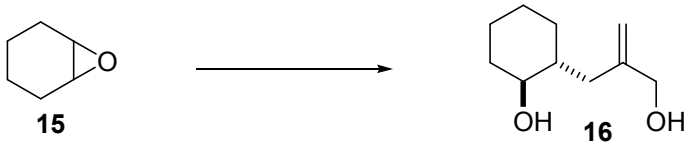
3374 (br), 3088 (m), 3031 (m), 2920 (s), 2854 (s), 1652 (m), 1605 (w), 1586 (w), 1496 (m), 1454 (m), 1366 (m), 1316 (m), 1207 (m), 1174 (m), 1090 (m), 899 (m), 846 (w), 800 (w), 739 (m), 699 (m), 615 (w); HRMS (ES): m/z $[M+Na]^+$ calcd for $C_{15}H_{22}O_3Na$: 273.1467, found: 273.1467.

Preparation of (*S*)-6-(tert-butyldiphenylsilyloxy)-2-methylenehexane-1,5-diol (13).



To a solution of Grignard (17.6 mL, 0.085M, 1.5 mmol) was added via cannula at RT a solution of epoxide **12** (98% ee, 312 mg, 1.0 mmol) in THF (5 mL) and the reaction stirred for 2h. The remaining organometallic reagent was quenched by the slow addition at 0°C of saturated aqueous NH_4Cl solution. The product was extracted with ethyl acetate. The organic layer was washed with 1N HCl, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (60:40 petroleum ether/ethyl acetate), to give the desired product **13** as an oil (313 g, 82%):; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.78-7.54 (m, 4H, Ar-C*H*), 7.50-7.28 (m, 6H, Ar-*H*), 5.01 (br, 1H, alkene-CH_2), 4.40 (br, 1H, alkene-CH_2), 4.04 (d, *J* = 5.0 Hz, 2H, alkene-CH_2OH), 3.81-3.66 (m, 1H, C*H*OH), 3.66 (dd, *J* = 10.0 Hz, *J* = 3.5 Hz, 1H, CH_2OSi), 3.51 (dd, *J* = 10.0 Hz, *J* = 3.5 Hz, 1H, CH_2OSi), 2.68 (d, *J* = 3.5 Hz, 1H, O*H*), 2.32-1.90 (m, 3H, CH_2, O*H*), 1.70-1.49 (m, 2H, CH_2), 1.07 (s, 9H, $OSiPh_2C(CH_3)_3$) ; ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 148.7, 135.6, 133.2, 130.0, 127.9, 109.9, 71.7, 68.0, 66.0, 30.9, 28.9, 27.0, 19.4; FTIR (CH_2Cl_2): 3356 (br), 3071 (m), 3050 (m), 2929 (s), 2857 (s), 1655 (w), 1472 (m), 1428 (m), 1391 (w), 1362 (w), 1308 (w), 1264 (w), 1189 (w), 1113 (s), 1075 (s), 940 (w), 900 (m), 824 (m), 740 (m), 702 (s), 614 (m), 505 (s); HRMS (ES): m/z $[M+Na]^+$ calcd for $C_{23}H_{32}O_3NaSi$: 407.2018, found: 407.2024; $[\alpha]_D^{23}$ = - 0.9 (c = 1.17 in $CHCl_3$).

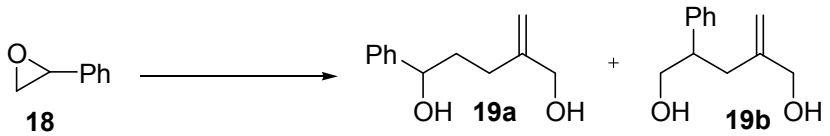
Preparation of 2-(2-(hydroxymethyl)allyl)cyclohexanol (16)



15 **16**

To a solution of Grignard (30 mL, 0.08 M, 2.4 mmol) was added via cannula at RT a solution of epoxide **15** (162 µl, 1.6 mmol) in THF (4 mL) and the reaction stirred for 2h. The remaining organometallic reagent was quenched by the slow addition at 0°C of saturated aqueous NH_4Cl solution. The product was extracted with ethyl acetate. The organic layer was washed with 1N HCl, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (60:40 petroleum ether/ethyl acetate), to give the desired product **16** as a white solid (136 mg, 50%); ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.03 (br, 1H, alkene-C*H*$_2$), 4.87 (br, 1H, alkene-C*H*$_2$), 4.09 (d, *J* = 5.0 Hz, 2H, alkene-C*H*$_2$OH), 3.31-3.16 (m 1H, cyclohexane-C*H*OH), 2.58-2.51 (m, 3H, cyclohexane-C*H*, and C*H*$_2$), 2.00-1.56 (m, 5H, C*H*$_2$, O*H*), 1.50-0.78 (m, 5H, C*H*$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 148.1, 111.8, 75.5, 66.0, 43.7, 37.2, 35.8, 31.1, 25.6, 25.2; FTIR (CH_2Cl_2): 3329 (br), 2927 (s), 2855 (s),1654 (w), 1448 (m), 1355 (w), 1310 (w), 1236 (w), 1133 (w), 1104 (w), 1060 (m), 1034 (s), 928 (w), 897 (m), 852 (w), 827 (w), 668 (w), 563 (w); HRMS (EI): m/z $[M]^+$ calcd for $C_{10}H_{18}O_2$: 170.1307, found: 170.1306; Mp: 73-74°C.

Preparation of 4-methylene-1-phenylpentane-1,5-diol (19a) and 2-methylene-4-phenylpentane-1,5-diol (19b).



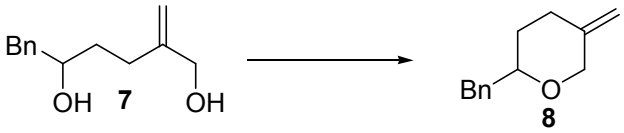
18 **19a** **19b**

To a solution of Grignard (21.2 mL, 0.10 M, 2.12 mmol) was added via cannula at RT a solution of epoxide **18** (170 mg, 1.41 mmol) in THF (14 mL) and the reaction stirred for 2h. The remaining organometallic reagent was quenched by the slow addition at 0°C of saturated aqueous NH_4Cl solution. The product was extracted with ethyl acetate. The organic layer was washed with 1N HCl, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (60:40 petroleum ether/ethyl acetate), to give the

desired products as yellow oils: **19b** (165 mg, 61%) and **19a** (55 mg, 20%); **19b**; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.31-7.05 (m, 5H, Ar-*H*), 4.87 (br, 1H, alkene-*H*), 4.69 (br, 1H, alkene-*H*), 3.85 (br, 2H, alkene-C*H*$_2$OH), 3.6 (d, *J* = 6.5 Hz, 2H, CH(Ph)C*H*$_2$OH), 2.61 (m, 3H, C*H*Ph, and O*H*), 2.49 (dd, 1H, *J* = 14.0 Hz, *J* = 6.0 C*H*$_2$), 2.24 (dd, 1H, *J* = 14.0 Hz, *J* = 6.5 Hz, C*H*$_2$) ; ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 146.7, 142.3,128.9, 128.3, 127.1, 112.5, 67.4, 66.2, 47.0, 35.8; FTIR (CH_2Cl_2): 3335 (br), 3085 (m), 3029 (m), 2926 (s), 2874 (s),1651 (m), 1602 (m), 1583 (w), 1494 (m), 1453 (s), 1337 (m), 1312 (m), 1211 (m), 1062 (s), 1026 (s), 901 (s), 840 (w), 759 (s), 701 (s), 572 (m), 538 (m); HRMS (EI): m/z $[M-H_2O]^+$ calcd for $C_{12}H_{14}O$: 174.1044, found: 174.1049, and **19a**, ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.42-7.20 (m, 5H, Ar-*H*), 5.06 (br, 1H, alkene-*H*), 4.91 (br, 1H, alkene-*H*), 4.68 (dd, *J* = 7.5 Hz, *J* = 5.5 Hz, 1H, PhC*H*), 4.05 (s, 2H, alkene-C*H*$_2$OH), 2.41-1.77 (m, 6H, C*H*$_2$, O*H*) ; ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 148.5, 144.7, 128.6, 127.6, 126.0, 110.0, 74.1, 66.0, 37.1, 29.1; FTIR (CH_2Cl_2): 3336 (br), 2923 (s),1653 (m), 1494 (m), 1453 (s), 1311 (m), 1267 (m), 1204 (m), 1062 (s), 1026 (s), 901 (m), 764 (m), 701 (m), 630 (w), 544 (w); HRMS (EI): m/z $[M]^+$ calcd for $C_{12}H_{16}O_2$: 192.1150, found: 192.1153.

Palladium catalyzed cyclisation

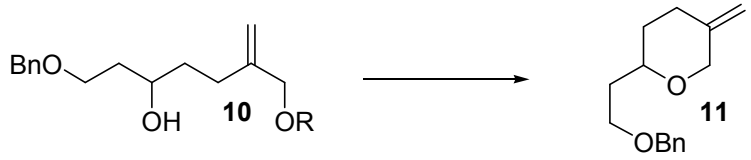
Preparation 2-benzyl-5-methylenetetrahydro-2H-pyran (8).



A round bottom flask with molecular sieves 4Å (500 mg) was flame dried under vacuo and placed under a nitrogen atmosphere. To this was added palladium acetate (34 mg, 0.15 mmol), triphenylphosphine (159 mg, 0.12 mmol) and anhydrous toluene (7 mL). The suspension was stirred for 10 min, and a solution of allylic alcohol **7** (625 mg, 3.03 mmol) in anhydrous toluene (23 mL) was transferred *via* cannula to the reaction mixture. Titanium ispropoxide (224 µL, 0.76 mmol) was added and the reaction mixture was heated at reflux for 1.5 h. After cooling to RT, direct purification by chromatography on silica gel (gradient starting with petroleum ether and ending with 98:2 petroleum ether/EtOAc) provided the pyran **8** as an oil (420 mg, 82%); ^{1}H NMR (250 MHz,

$CDCl_3$): δ 7.41-7.12 (m, 5H, Ar-*H*), 4.83-4.73 (m, 2H, alkene-C*H*$_2$), 4.18 (d, *J* = 12.0 Hz, 1H, pyran-OC*H*$_2$), 3.94 (d, *J* = 12.0 Hz, 1H, pyran-OC*H*$_2$), 3.70-3.55 (m, 1H, pyran-OC*H*), 2.91 (dd, *J* = 14.0 Hz, *J* = 7.0 Hz, C*H*$_2$Ph), 2.66 (dd, *J* = 14.0 Hz, *J* = 6.0 Hz, C*H*$_2$Ph), 2.47-2.33 (m, 1H, C*H*$_2$), 2.29-2.12 (m, 1H, C*H*$_2$), 1.82-1.70 (m, 1H, C*H*$_2$), 1.53-1.33 (m, 1H, C*H*$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 143.9, 138.8, 129.5, 128.4, 126.3, 109.3, 78.4, 72.6, 42.7, 33.0, 31.6; FTIR (CH_2Cl_2): 3066 (m), 3028 (m), 2940 (s), 2834 (s), 1654 (w), 1605 (w), 1496 (m), 1454 (m), 1437 (m), 1371 (m), 1339 (m), 1287 (w), 1250 (w), 1210 (w), 1080 (s), 1029 (m), 899 (s) cm^{-1}; HRMS (EI): m/z [M]$^+$ calcd for $C_{13}H_{16}O$: 188.1201, found: 188.1208.

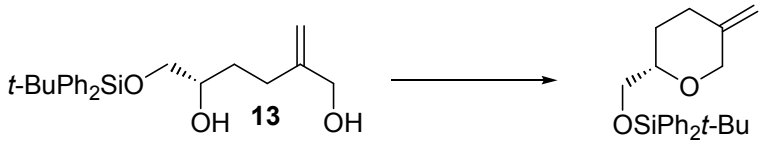
Preparation of 2-(2-(benzyloxy)ethyl)-5-methylenetetrahydro-2H-pyran (11)



Following the representative procedure above, a solution of allylic alcohol **10** (150 mg, 0.60 mmol) in anhydrous toluene (7 mL) was transferred *via* cannula to the suspension (molecular sieves 4Å (150 mg), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol), PPh_3 (31.5 mg, 0.12 mmol) and anhydrous toluene (2 mL)). Titanium ispropoxide (43.0 μL, 0.15 mmol) was added and the reaction mixture was heated at reflux for 1.5 h. After cooling to RT, direct purification by chromatography on silica gel (gradient starting with petroleum ether and ending with 98:2 petroleum ether/EtOAc) provided the desired product **11** as an oil (80 mg, 85%); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.39-7.23 (m, 5H, Ar-*H*), 4.81-4.73 (m, 2H, alkene-C*H*$_2$), 4.51 (s, 2H, OC*H*$_2$Bn), 4.16 (dd, *J* = 12.5 Hz, *J* = 1.5 Hz, 1H, pyran-OC*H*$_2$), 3.95 (d, *J* = 12.5 Hz, 1H, pyran-OC*H*$_2$), 3.67-3.51 (m, 3H, pyran-*OCH*, and C*H*$_2$OBn), 2.46-2.35 (m, 1H, C*H*$_2$), 2.34-2.18 (m, 1H, C*H*$_2$), 1.84-1.70 (m, 3H, C*H*$_2$), 1.50-1.32 (m, 1H, C*H*$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 144.1, 138.7, 128.5, 127.7, 127.6, 109.2, 74.4, 73.1, 72.5, 67.0, 36.3, 33.6, 31.7; FTIR (CH_2Cl_2): 3069 (m), 3030 (m), 2941 (s), 2853 (s), 1656 (m), 1496 (m), 1453 (m), 1441 (m), 1364 (m), 1339 (m), 1206 (m), 1083 (s), 1053 (s), 1028 (m), 900

(m), 884 (m), 736 (m), 698 (m), 670 (w), 612 (w) cm^{-1}; HRMS (EI): m/z $[M]^+$ calcd for $C_{15}H_{20}O_2$: 232.1463, found: 232.1472.

Preparation of (S)-tert-butyl((5-methylenetetrahydro-2H-pyran-2-yl)methoxy)diphenylsilane (14)



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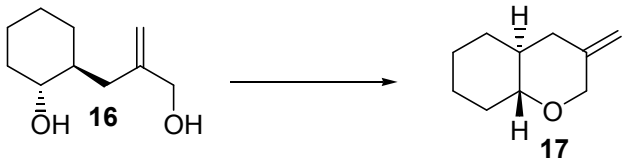
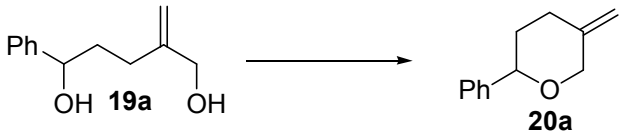
Following the representative procedure above, a solution of allylic alcohol **13** (1.04 g, 2.70 mmol) in toluene (25 mL) was transferred *via* cannula to the suspension (molecular sieves 4Å (450 mg), $Pd(OAc)_2$ (30.4 mg, 0.13 mmol), PPh_3 (142 mg, 0.54 mmol) in anhydrous toluene (10 mL)). Titanium ispropoxide (200 µL, 0.68 mmol) was added and the reaction mixture was heated at reflux for 1.5 h. After cooling to RT, direct purification by chromatography on silica gel (gradient starting with petroleum ether and ending with 98:2 petroleum ether/EtOAc) provided the desired product **14** as an oil (820 mg, 83%, 98% ee) The enantiomeric purity of pyran **14** was determined by chiral HPLC analysis (Chiral Technologies Chiralpak AD, RT, 99.5:0.5 hexane/isopropanol, 1.0 mL/min, t_R (minor) = 5.38 min, t_R (major) = 4.52 min); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.72-7.63 (m, 4H, Ar-*H*), 7.47-7.32 (m, 6H, Ar-*H*), 4.81-4.75 (m, 2H, alkene-CH_2), 4.18 (dd, *J* = 12.5 Hz, *J* = 1.5 Hz, 1H, pyran-OCH_2), 3.96 (d, *J* = 12.5 Hz, 1H, pyran-OCH_2), 3.82-3.70 (m, 1H, pyran-OC*H*), 3.62-3.48 (m, 2H, CH_2OSi), 2.50-2.38 (m, 1H, CH_2), 2.35-2.18 (m, 1H, CH_2), 1.96-1.84 (m, 1H, CH_2), 1.49-1.29 (m, 1H, CH_2), 1.06 (s, 9H, $OSiPh_2C(CH_3)_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 144.2, 135.8, 133.8, 129.7, 127.8, 109.3, 77.8, 72.3, 67.1, 31.3, 30.2, 27.0, 19.4; FTIR (CH_2Cl_2): 3072 (s), 3050 (s), 2999 (s), 2932 (s), 2854 (s), 1657 (m), 1590 (m), 1472 (m), 1428 (m), 1390 (m),1362 (m), 1338 (w), 1325 (w), 1287 (w), 1263 (w), 1240 (w), 1204 (w), 1187 (m), 1135 (m), 1113 (m), 1083 (m), 1047 (m), 1008 (m), 969 (w), 938 (w), 901 (m), 824 (m), 807 (m), 740 (m), 702 (m), 614 (m),cm^{-1}.; HRMS (ES): m/z $[M+Na]^+$ calcd for $C_{23}H_{30}O_2NaSi$: 389.1913, found: 389.1928; $[\alpha]_D^{22}$ = -4.8 (c = 1.16 in $CHCl_3$)

Preparation 3-methyleneoctahydro-2H-chromene (17)



Following the representative procedure above, a solution of allylic alcohol **16** (100 mg, 0.59 mmol) in anhydrous toluene (4 mL) was transferred *via* cannula to the suspension (molecular sieves 4Å (80 mg), $Pd(OAc)_2$ (6.6 mg, 0.029 mmol), PPh_3 (30.9 mg, 0.12 mmol) and anhydrous toluene (1.5 mL)). Titanium ispropoxide (44 µL, 0.68 mmol) was added and the reaction mixture was heated at reflux for 1.5 h. After cooling to RT, direct purification by chromatography on silica gel (gradient starting with petroleum ether and ending with 98:2 petroleum ether/EtOAc) provided the desired product **17** as an oil (60 mg, 67%). The compound showed satisfactory spectra data[v] ; ^{1}H NMR (250 MHz, $CDCl_3$): δ 4.88-4.63 (m, 2H, alkene-C*H*$_2$), 4.21 (dd, *J* = 12.0 Hz, *J* = 2.0 Hz, 1H, pyran-OC*H*$_2$), 3.97 (d, *J* = 12.0 Hz, 1H, pyran-OC*H*$_2$), 3.10-2.90 (m, 1H, pyran-OC*H*), 2.32 (ddd, *J* = 13.5 Hz, *J* = 4.0 Hz, *J* = 1.5 Hz, 1H, alkene-(CH_2)CH), 1.96-1.74 (m, 3H, alkene-(C*H*$_2$)CH, and C*H*$_2$), 1.70-1.63 (m, 2H, C*H*$_2$), 1.43-1.13 (m, 4H, C*H*$_2$), 1.11-0.96 (m, 1H, alkene-C*H*$_2$C*H*); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 144.5, 109.1, 81.5, 72.6, 43.9, 39.1, 32.4, 32.1, 25.6, 25.1; HRMS (EI): m/z $[M]^+$ calcd for $C_{10}H_{16}O$: 152.1201, found: 152.1201.

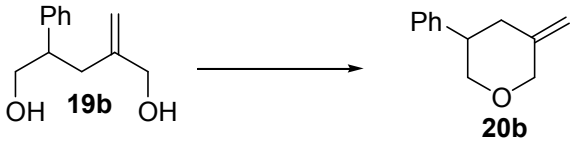
Preparation 5-methylene-2-phenyltetrahydro-2H-pyran (20a).



Following the representative procedure above, a solution of diol **19a** (195 mg, 1.01 mmol) in toluene (8.5 mL) was transferred *via* cannula to the suspension (molecular sieves 4Å (150 mg), $Pd(OAc)_2$ (11.3 mg, 0.05 mmol), PPh_3 (53 mg, 0.20 mmol) and anhydrous toluene 1.5 mL)). Titanium ispropoxide (75 µL, 0.25 mmol) was added and the reaction mixture was heated at toluene reflux for 1.5 h. After cooling to RT, direct purification by chromatography on silica gel (gradient starting with petroleum ether and ending with 98:2 petroleum

ether/EtOAc) provided the desired product **20a** as an oil (116 mg, 66%): ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.40-7.22 (m, 5H, Ar-*H*), 4.90-4.80 (m, 2H, alkene-C*H*$_2$), 4.47 (dd, *J* = 11.0 Hz, *J* = 2.0 Hz, 1H, pyran-OC*H*), 4.36 (dd, *J* = 12.5 Hz, *J* = 1.5 Hz, 1H, pyran-OC*H*$_2$), 4.16 (d, *J* = 12.5 Hz, 1H, pyran-OC*H*$_2$), 2.60-2.37 (m, 2H, alkene-C*H*$_2$), 2.05-1.93 (m, 1H, C*H*$_2$CHPh), 1.84-1.65 (m, 1H, alkene-CH_2C*H*$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 143.5, 142.5, 128.4, 127.6, 126.0, 109.7, 79.7, 72.9, 35.5, 32.2; FTIR (CH_2Cl_2): 3069 (w), 3030 (w), 2942 (s), 2831 (s), 1495 (w), 1452 (m), 1439 (w), 1357 (w), 1337 (w), 1285 (w), 1244 (w), 1089 (s), 1070 (s), 1028 (s), 902 (s), 754 (m), 699 (s) cm^{-1}; HRMS (EI): m/z [M]$^{+}$ calcd for $C_{12}H_{14}O$: 174.1045, found: 174.1051.

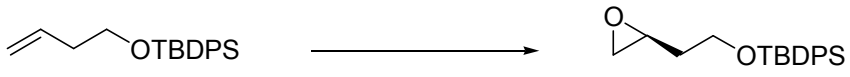
Preparation 3-methylene-5-phenyltetrahydro-2H-pyran (20b)



Following the representative procedure above, a solution of allylic alcohol **19b** (75 mg, 0.39 mmol) in toluene (3.5 mL) was transferred *via* cannula to the suspension (molecular sieves 4Å (60 mg), $Pd(OAc)_2$ (4.4 mg, 0.019 mmol), PPh_3 (20.4 mg, 0.078 mmol) and anhydrous toluene 1.0 mL)). Titanium ispropoxide (75 μL, 0.25 mmol) was added and the reaction mixture was heated at toluene reflux for 1.5 h. After cooling to RT, direct purification by chromatography on silica gel (gradient starting with petroleum ether and ending with 98:2 petroleum ether/EtOAc) provided the desired product **20b** as an oil (54 mg, 79%): ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.40-7.18 (m, 5H, Ar-*H*), 4.95-4.78 (m, 2H, alkene-*H*), 4.87 (d, *J* = 12.0 Hz, 1H, alkene-C*H*$_2$), 4.23 (d, *J* = 12.0 Hz, 1H, pyran-OC*H*), 4.08-3.95 (m, 2H, pyran-OC*H*$_2$), 3.52 (t, *J* = 10.5 Hz, 1H, pyran-OC*H*$_2$), 3.07-2.90 (m, 1H, C*H*Ph), 2.72-2.60 (m, 1H, C*H*$_2$CHPh), 2.57-2.42 (m, 1H, alkene-(CH_2)C*H*Ph; ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 143.1, 141.7, 128.7, 127.4, 126.9, 110.3, 73.2, 72.3, 44.6, 38.7; FTIR (CH_2Cl_2): 3072 (m), 3029 (m), 2957 (s), 2901 (s), 2835 (s),1656 (m), 1603 (m), 1494 (s), 1453 (s), 1436 (m), 1337 (w), 1281 (w), 1252 (w), 1199 (w), 1174 (m), 1085 (s), 1030 (w), 984 (m), 932 (m), 905 (s), 871 (m), 756 (s), 700 (s), 654 (m), 524 (m) cm^{-1}; HRMS (EI): m/z [M]$^{+}$ calcd for $C_{12}H_{14}O$: 174.1045, found: 174.1048.

(+)-Rhopaloic Acid B

Preparation of (*S*)-(2-(oxiran-2-yl)ethoxy)(tert-butyl)diphenylsilane (21)



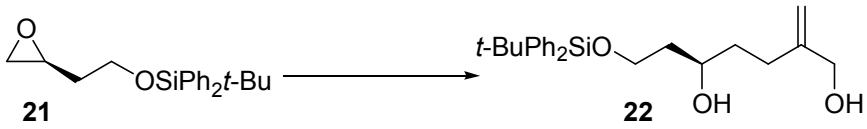
21

To a solution of tert-butyl(but-3-enyloxy)diphenylsilane [vi] (8.76 g, 28.20 mmol) in DCM (65 mL) at 0°C was added portionwise m-CPBA (12.6g, 56.40 mol). The resulting suspension was warmed gradually to temperature, and stirred for 20 h. The reaction mixture was filtered to remove the white precipitate, concentrated *in vacuo*, and re-dissolved in petroleum ether. The suspension was filtered, the filtrate concentrated *in vacuo* and purified by flash chromatography (90:10 petroleum ether/ethyl acetate), to give the racemic epoxide (8.80 g, 95 %) as pale yellow oil.

The kinetic resolution of epoxide **21** was conducted following the procedure of Jacobsen.[vii] The catalyst (*S*, *S*) –salen-Co (145 mg, 0.24 mmol) was dissolved in DCM (3.1 ml) and treated with acetic acid (136 µL, 2.40 mmol). The solution was allowed to stir at RT open to air for 30 min over which time the colour changed from orange-red to dark brown. The solution was concentrated *in vacuo* to leave a crude brown solid. The resulting catalyst residue was dissolved in THF (1.6 mL), and then racemic epoxide **21** (7.8 g, 23.90 mmol) was added to the solution. The reaction was cooled at 0°C and H_2O (236 µL, 13.14 mmol) was added dropwise over a 5 min period. The reaction was allowed to warm to RT and stirred for 40h. Direct purification by flash chromatography on silica gel (90:10 petroleum ether/ethyl acetate) provided the enantioenriched epoxide **21** (3.45 g, 44%, >99% ee). The enantiomeric purity of epoxide **21** was determined by chiral HPLC analysis (Chiral Technologies Chiralpak OD, RT, 98:2 hexane/isopropanol, 1.0 mL/min, t_R (minor) = 5.34 min, t_R (major) = 6.09 min). $[\alpha]_D^{23}$ = - 4.7 (c = 1.06, $CHCl_3$); lit.[viii] $[\alpha]_D^{18}$ = - 6.0 (c = 8.49, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.73-7.60 (m, 4H, Ar-*H*), 7.44-7.33 (m, 6H, Ar-*H*), 3.90-3.74 (m, 2H, C*H*$_2$OSi), 3.14-3.06 (m, 1H, epoxide-C*H*O), 2.78 (dd, *J* = 5.0 Hz, *J* = 4.0 Hz 1H, epoxide-C*H*$_2$O), 2.51 (dd, *J* = 5.0 Hz, *J* = 2.5 Hz 1H, epoxide-C*H*$_2$O), 1.82-1.72 (m, 2H, C*H*$_2$CH$_2$OSi), 1.05 (s, 9H, C*H*$_3$);

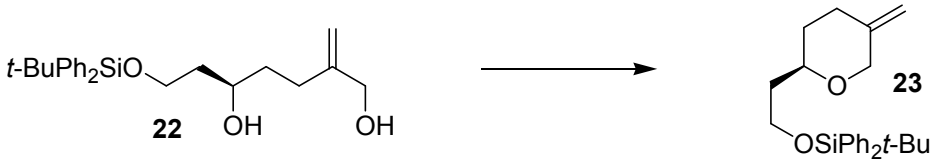
^{13}C NMR (62.9 MHz, $CDCl_3$): δ 135.6, 133.8, 139.8, 127.8, 61.0, 50.2, 47.3, 35.8, 26.9, 19.3.

Preparation of (R)-7-(tert-butyldiphenylsilyloxy)-2-methyleneheptane-1,5-diol (22).



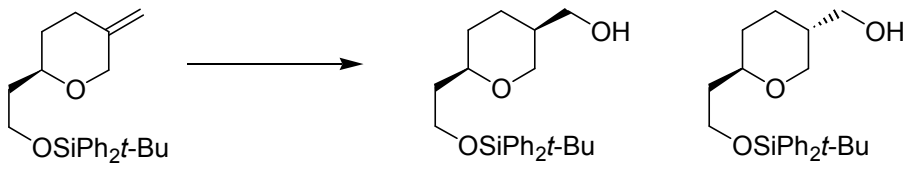
To a solution of Grignard (10 mL, 0.14M, 1.4 mmol) was added via cannula at RT a solution of epoxide **21** (304 mg, 0.93 mmol) in THF (9.5 mL) and the reaction stirred for 2h. The remaining organometallic reagent was quenched by the slow addition at 0°C of saturated aqueous NH_4Cl solution. The product was extracted with ethyl acetate. The organic layer was washed with 1N HCl, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (60:40 petroleum ether/ethyl acetate), to give the desired product **22** as an oil (293 mg, 79%); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.70-7.63 (m, 4H, Ar-*H*), 7.48-7.33 (m, 6H, Ar-*H*), 5.06-5.01 (m, 1H, alkene-*H*), 4.92-4.88 (m, 1H, alkene-*H*), 4.09 (br, 2H, alkene-CH_2OH), 3.99-3.78 (m, 3H, C*H*OH and CH_2OSi), 3.50 (br, 1H, O*H*), 2.33-1.94 (m, 3H, alkene-CH_2CH$_2$ and O*H*), 1.84-1.54 (m, 4H, CH_2CH(OH)CH_2), 1.04 (s, 9H, OSiPh$_2$C(CH_3)$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 149.0, 135.7, 133.1, 133.0, 130.0, 127.9, 109.7, 71.5, 66.1, 63.6, 38.5, 35.7, 29.0, 26.9, 19.1; IR (film, cm^{-1}): 3354 (br), 3071 (w), 3050 (w), 2932 (s), 2858 (s), 1652 (w), 1472 (m), 1428 (s), 1390 (m), 1361 (m), 1112 (s), 1085 (s), 1029 (m), 900 (m), 823 (m), 737 (m), 702 (s), 688 (m), 614 (m), 504 (s); HRMS (ES): m/z [M+H]$^+$ calcd for $C_{24}H_{35}O_3Si$: 399.2355, found: 399.2371; $[\alpha]_D^{23}$ = + 14.4 (c = 1.04 in $CHCl_3$).

Preparation of (2-((R)-tetrahydro-5-methylene-2H-pyran-2-yl)ethoxy)(tert-butyl)diphenylsilane (23)



Following the representative procedure above, a solution of **22** (1.12 g, 2.81 mmol) in toluene (42 mL) was transferred *via* cannula to the suspension (molecular sieves 4Å (750 mg), $Pd(OAc)_2$ (32 mg, 0.14 mmol), PPh_3 (147 mg, 0.56 mmol) and anhydrous toluene 15 mL)). Titanium ispropoxide (208 µL, 0.70 mmol) was added and the reaction mixture was heated at toluene reflux for 1.5 h. After cooling to RT, direct purification by chromatography on silica gel (gradient starting with petroleum ether and ending with 98:2 petroleum ether/EtOAc) provided the desired product as an oil (920 mg, 86%, >99% ee). The enantiomeric purity of pyran **23** was determined by chiral HPLC analysis (Chiral Technologies Chiralpak AD, RT, 99.5:0.5 hexane/isopropanol, 1.0 mL/min, t_R (minor) = 3.86 min, t_R (major) = 4.22 min); ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.72-7.62 (m, 4H, Ar-*H*), 7.46-7.32 (m, 6H, Ar-*H*), 4.79-4.73 (m, 2H, alkene-CH_2), 4.13 (dd, *J* = 12.5 Hz, *J* = 2.0 Hz, 1H, pyran-OCH_2), 3.92 (d, *J* = 12.5 Hz, 1H, pyran-OCH_2), 3.89-3.70 (m, 2H, CH_2OSi), 3.69-3.56 (m, 1H, pyran-OC*H*), 2.46-2.34 (m, 1H, CH_2), 2.33-2.16 (m,1H, CH_2), 1.83-1.67 (m, 3H, CH_2), 1.48-1.28 (m, 1H, CH_2), 1.05 (s, 9H, $OSiPh_2(CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.2, 135.7, 134.2, 134.1, 129.7, 127.7, 109.2, 74.1, 72.4, 60.5, 39.0, 33.6, 31.8, 27.0, 19.4; IR (film, cm^{-1}): 3049 (w), 2932 (s), 2857 (s), 1472 (m), 1428 (m), 1389 (w), 1361 (w), 1263 (w), 1112 (s), 1086 (s), 944 (w), 900 (m), 823 (m), 737 (m), 702 (s), 614 (w), 505 (m) ; HRMS (ES): m/z $[M+Na]^+$ calcd for $C_{24}H_{32}O_2NaSi$: 403.2069, found: 403.2064, $[\alpha]_D^{22}$ = - 5.5 (c = 1.27, $CHCl_3$).

Preparation of *cis*-, *trans*-(6-(2-(tert-butyldiphenylsilyloxy)ethyl)tetrahydro-2H-pyran-3-yl)methanol (24)

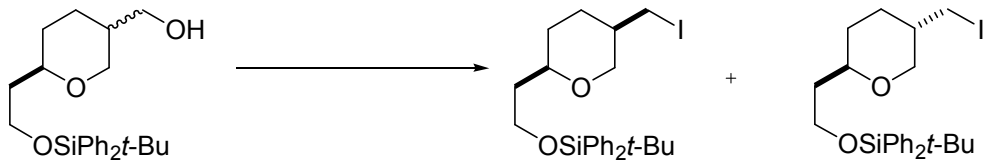


23 *cis*-**24** *trans*-**24**

To a solution of **23** (958 mg, 2.52 mmol) in anhydrous THF (25 mL) and $RhCl(PPh_3)_3$ (117 mg, 0.126 mmol) at -20°C, was added dropwise catecholborane[ix](940 µL, 8.82 mmol). The reaction was stirred for 20h at -20°C

and then quenched with NaOH (1M, 10.1 mL, 10.08 mmol), H_2O_2 (1.16 mL, 10.08 mmol), and stirred for 3h at RT. After this time, saturated aqueous NH_4Cl solution was added to the reaction and the product extracted with EtOAc. The combined organic extracts were washed with saturated aqueous K_2CO_3 solution, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (60:40 petroleum ether/ethyl acetate), to give a mixture of the desired products **24** as yellow oil (876 mg, 88%, 1:3 *trans*/*cis* ratio); δ 7.80-7.57 (m, 4H, Ar-*H,* (***trans*** + ***cis***)), 7.52-7.28 (m, 6H, Ar-*H*, (***trans*** + ***cis***)), 4.06 (ddd, *J* = 11.0 Hz, *J* = 4.0 Hz, *J* = 2.5 Hz, 0.25 H (***trans***), pyran-OC*H*), 3.95 (d, *J* = 12.0 Hz, 0.75 H (***cis***), pyran-OCH_2), 3.89-3.33 (m, 5.75 H, CH_2OSi, pyran-*OCH*$_2$, pyran-OC*H*, CH_2OH (***trans*** + ***cis***)), 3.13 (t, *J* = 11.0 Hz, 0.25 (***trans***), pyran-OCH_2) 2.43-1.15 (m, 8H, CH_2, C*H*, O*H* (***trans*** + ***cis***)), 1.06 (s, 9H, -OSiPh$_2$C(CH_3)$_3$) ; ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 135.7, 134.2, 134.1, 129.6, 127.7, 74.8, 74.7 (***trans***), 71.0 (***trans***), 68.5, 65.1 (***trans***), 63.4, 60.5, 60.3 (***trans***), 39.2 (***trans***), 39.1, 36.0, 31.5 (***trans***), 27.9 , 27.0, 24.6, 19.4; IR (film, cm^{-1}): 3382 (br), 3071 (w), 3050 (w), 2931 (s), 2857 (s), 1472 (m), 1428 (m), 1112 (s), 1091 (s), 823 (m), 737 (m), 702 (s), 614 (m), 505 (m) HRMS (ES): m/z [M+Na]$^+$ calcd for $C_{24}H_{34}O_2NaSi$: 421.2175, found: 421.2177.

Preparation of *cis*-, *trans*-tert-butyl(2-(5-(iodomethyl)tetrahydro-2H-pyran-2-yl)ethoxy)diphenylsilane (25)

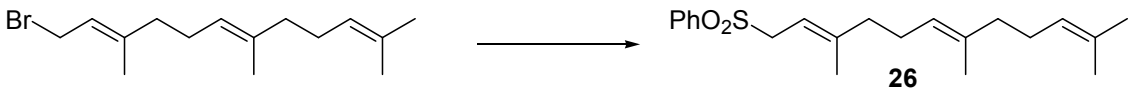


24 *cis*-**25** *Trans*-**25**

A cis/*trans* mixture (3:1) of **24** from (876 mg, 2.19 mmol) was dissolved in anhydrous THF (44 mL). Imidazole (300 mg, 4.40 mmol), triphenylphosphine (866 mg, 3.29 mmol), iodine (837 mg, 3.29 mmol) were added to the solution at RT. The reaction was stirred for 3h at RT, and then quenched with H_2O and EtOAc. The aqueous layer was extracted with EtOAc, and the combined

organic extracts were washed with saturated aqueous $NaHSO_3$ solution, aqueous 1N HCl solution, saturated aqueous $NaHCO_3$ solution, brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (99:1; petroleum ether/EtOAc), to give the desired products as yellow oil; ***cis*-25** (765 mg, 68%) and of ***trans*-25** (258 mg, 23%): (***trans*-25**) ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.72-7.63 (m, 4H, Ar-*H*), 7.48-7.33 (m, 6H, Ar-*H*), 4.09 (ddd, *J* = 11.0 Hz, *J* = 4.0 Hz, *J* = 2.5 Hz, 1H, C*H*$_2$-O), 3.89-3.68 (m, 2H, C*H*$_2$OSi), 3.50-3.38 (m, 1H, C*H*-O), 3.09-2.91 (m, 3H, C*H*$_2$O, C*H*$_2$I) 2.06-1.95 (m, 1H, C*H*CH$_2$I), 1.84-1.62 (m, 4H, C*H*$_2$), 1.42-1.10 (m, 2H, C*H*$_2$), 1.06 (s, 9H, C*H*$_3$) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.9, 134.3, 134.2, 129.9, 127.9, 74.8, 73.4, 60.6, 39.1, 38.3, 31.7, 31.4, 27.2, 19.6, 8.4; IR (film, cm^{-1}): 3070 (w), 3048 (w), 2931 (s), 2856 (s), 1472 (m), 1461 (w), 1428 (m), 1389 (w), 1360 (w), 1297 (w), 1261 (w), 1233 (w), 1188 (m), 1184 (m), 1146 (w), 1112 (s), 1090 (s), 1015 (w), 941 (w), 907 (w), 823 (m), 737 (m), 702 (s), 688 (m), 614 (m), 504 (s), 488 (m); HRMS (ES): m/z [M+Na]$^+$ calcd for $C_{24}H_{33}O_2INaSi$: 531.1192, found: 531.1183, $[\alpha]_D^{22}$ = + 3.4° (c = 1.19 in $CHCl_3$); (***cis*-25**) ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.71-7.63 (m, 4H, Ar-*H*), 7.48-7.33 (m, 6H, Ar-*H*), 3.93 (dt, *J* = 12.0 Hz, *J* = 2.0 Hz, 1H, C*H*$_2$-O), 3.88-3.67 (m, 2H, C*H*$_2$-O and C*H*-O), 3.64-3.42 (m, 3H, C*H*$_2$OSi and C*H*$_2$I), 3.31 (dd, 1H, *J* = 9.5 Hz, *J* = 7.0 Hz, 1H, C*H*$_2$I), 2.00-1.57 (m, 5H, C*H*$_2$), 1.48-1.25 (m, 2H, C*H*$_2$ and C*H*CH$_2$I), 1.06 (s, 9H, C*H*$_3$) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.7, 134.1, 134.0, 129.7, 127.7, 74.6, 70.4, 60.5, 39.0, 37.4, 28.2, 27.2, 27.1, 19.6, 9.9; IR (film, cm^{-1}): 3070 (w), 3048 (w), 2931 (s), 2856 (s), 1472 (m), 1446 (w), 1428 (m), 1389 (w), 1360 (w), 1295 (w), 1271 (w), 1207 (w), 1177 (w), 1112 (s), 1090 (s), 1024 (m), 1007 (w), 969 (w), 940 (w), 906 (w), 823 (m), 800 (w), 736 (m), 703 (s), 614 (m), 504 (s), 490 (m); HRMS (ES): m/z [M+H]$^+$ calcd for $C_{24}H_{34}IO_2$: 509.1373, found: 509.1355, $[\alpha]_D^{22}$ = + 8.6 (c = 1.04 in $CHCl_3$).

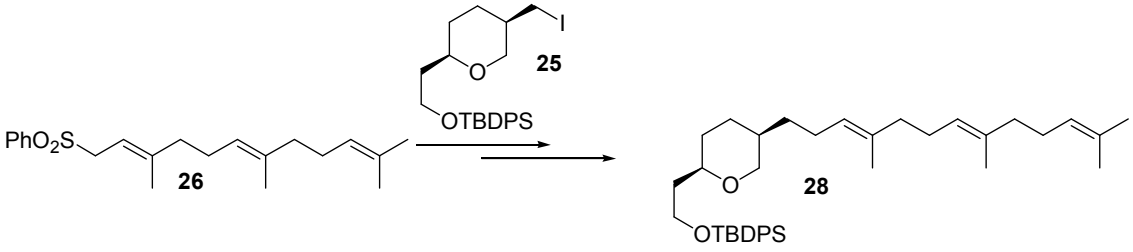
Preparation of 1-((2E,6E)-3,7,11-trimethyldodeca-2,6,10-trienylsulfonyl)benzene (26).



26

Sodium benzenesulfonic acid (581 mg, 3.54 mmol) and tetra-butyl-ammonium iodide (16 mg, 0.04 mmol) were dissolved in anhydrous DMF (22mL). After stirring for 10 min, farnesyl bromide (800 µL, 2.95 mmol) was added dropwise and the reaction mixture was stirred at RT for 3.5h. The reaction was quenched with H_2O and Et_2O and the aqueous layer was extracted two times with Et_2O. The combined organic layers were washed three times with H_2O, brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography (90:10 petroleum ether/ethyl acetate), to give the desired product **26** as a yellow oil (900 mg, 88%). The compound showed satisfactory spectra data[x]; ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.90-7.83 (m, 2H, Ar-*H*), 7.67-7.47 (m, 3H, Ar-*H*), 5.18 (td, *J* = 7.9 Hz, *J* = 1.2 Hz, 1H, alkene-*H*-CH_2SO_2Ph), 5.12-5.00 (m, 2H, alkene-*H*), 3.79 (d, *J* = 7.9 Hz, 2H, CH_2SO_2Ph), 2.19-1.89 (m, 8H, CH_2),1.66 (d, *J* = 1.0 Hz, 3H, $PhSO_2CH_2$-alkene-CH_3), 1.61-1.56 (m, 6H, CH_3), 1.30 (d, *J* = 1.2 Hz , 3H, CH_3); ^{13}C NMR (63 MHz, $CDCl_3$): δ 146.4, 138.7, 135.7, 133.5, 131.4, 128.9, 128.5, 124.2, 123.3, 110.3, 56.1, 39.7, 26.7, 26.2, 25.7, 17.7, 16.2, 16.0.

Preparation of tert-butyldiphenyl(2-((2R,5R)-5-((3E,7E)-4,8,12-trimethyltrideca-3,7,11-trienyl)tetrahydro-2H-pyran-2-yl)ethoxy)silane (28)

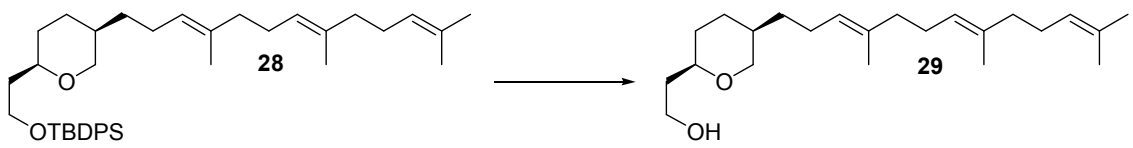


LDA (200 µL of DIPA, 710 µL of 1.9 M n-BuLi, 1.45 mL THF) was added to a cooled (-78°C) solution of the farnesyl sulfone **26** (131 mg, 0.378 mmol) in anhydrous THF (1.4 mL) and DMPU (520 µL). The resulting bright orange solution was stirred for 45-60 min at -78°C, at which point a solution of pyran **25** (160 mg, 0.315 mmol) in anhydrous THF (0.5 mL), was added dropwise. The reaction was stirred an additional 1 h at -78°C, and then the cold bath was removed and the reaction stirred for another 3-4h. The reaction mixture was then quenched with a saturated solution of ammonium chloride. The aqueous solution was extracted three times with ether, dried over magnesium sulphate,

and concentrated in *vacuo*. The resulting oil residue was purified *via* flash chromatography on silica gel (petroleum ether/ethyl acetate 90:10) to give an inseparable mixture of the desired product **27** and farnesyl sulfone **25**.

The crude mixture of sulfone (248 mg) was dissolved in anhydrous THF (3.8 mL) and $PdCl_2$(dppf) (27.7 mg, 0.04 mmol, based on the farnesyl sulfone) was added. Super Hydride (1M in THF, 1.13 mL, 1.13 mmol based on the farnesyl sulfone) was added dropwise at 10°C to the orange solution which quickly changed to red-brown. The cold bath was removed and the reaction was stirred at room temperature for 6 h, at which time it was quenched carefully at 0°C with saturated aqueous NH_4Cl solution. The resulting aqueous layer was extracted with ether three times. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in *vacuo*. The resulting oily residue was purified via flash chromatography on silica gel (98:2; petroleum ether/EtOAc) to give the desired product **28** (135 mg, 73% over two steps) as a yellow oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ 7.75-7.66 (m, 4H, Ar-*H*), 7.46-7.35 (m, 6H, Ar-*H*), 5.20-4.08 (m, 3H, alkene-*H*), 3.91-3.69 (m, 3H, C*H*$_2$O and C*H*-O), 3.65-3.51 (m, 2H, C*H*$_2$OSi), 2.10-1.80 (m, 10H, C*H*$_2$), 1.89-1.59 (m, 21H, alkene-C*H*$_3$, C*H*$_2$, C*H*), 1.09 (s, 9H, C*H*$_3$) ; ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 135.7, 135.1, 135.0, 134.2, 134.1, 131.3, 129.6, 127.7, 124.6, 124.5, 124.4, 74.5, 70.8, 60.6, 39.9 (2C), 38.8, 33.4, 30.6, 27.6, 27.5, 27.0, 26.9, 26.7, 25.9, 19.4, 17.8, 16.2 (2C); IR (film, cm^{-1}): 3071 (s), 3050 (s), 2928 (s, br), 2738 (m), 1472 (s), 1428 (s), 1384 (s), 1360 (s), 1260 (m), 1206 (m), 1189 (m), 1112 (s, br), 1007 (m), 939 (m), 900 (w), 824 (s), 736 (s), 702 (s), 614 (s), 504 (s); HRMS (ES): m/z $[M+H]^+$ calcd for $C_{39}H_{59}O_2Si$: 587.4284, found: 587.4285, $[\alpha]_D^{22}$ = + 7.4 (c = 1.08 in $CHCl_3$).

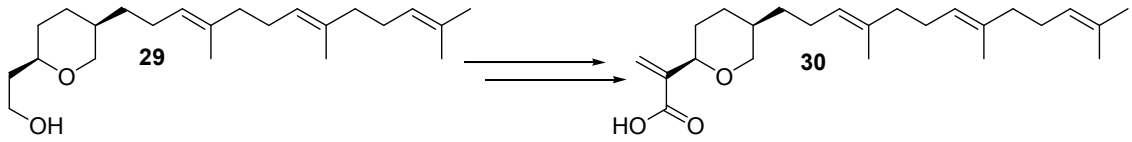
Preparation of 2-((2R,5R)-tetrahydro-5-((3E,7E)-4,8,12-trimethyltrideca-3,7,11-trienyl)-2H-pyran-2-yl)ethanol (29)



To a solution of **28** (143 mg, 0.24 mmol) in anhydrous THF (2.5 mL) was added dropwise TBAF (1M in THF, 370 µL, 0.37 mmol). The reaction was stirred at RT

for 20 h. The reaction was quenched with H_2O. The aqueous layer was extracted two times with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by flash chromatography (80:20 petroleum ether/ethyl acetate), to give the desired product **29** as colourless oil (84 g, 98%): ^{1}H NMR (250 MHz, $CDCl_3$): δ 5.14-4.99 (m, 3H, alkene-*H*), 3.80-3.67 (m, 3H, C*H*$_2$O and C*H*-O), 3.56-3.45 (m, 2H, C*H*$_2$OH), 2.94 (s, br, 1H, O*H*), 2.12-1.87 (m, 10H, C*H*$_2$), 1.82-1.31 (m, 21H, alkene-C*H*$_3$, C*H*$_2$, C*H*); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 135.2, 135.0, 131.3, 124.4 (2C), 124.3, 78.4, 71.0, 61.5, 39.8 (2C), 37.8, 33.0, 30.2, 27.4, 27.2, 26.8, 26.7, 25.9, 25.8,17.8, 16.0 (2C); IR (film, cm^{-1}): 3396 (br), 2928 (s), 2854 (s), 1450 (s), 1381 (s), 1201 (w), 1110 (m), 1065 (s), 897 (w), 863 (w), 834 (w), 741 (w), 604 (w), 538 (w), 490 (w); HRMS (ES): m/z $[M+H]^+$ calcd for $C_{23}H_{41}O_2$: 349.3107, found: 349.3113, $[\alpha]_D^{22}$ = + 13.9 (c = 1.01, $CHCl_3$).

Preparation of (+)-Rhopaloic Acid B (30)



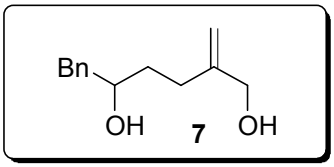
To a solution of oxalyl chloride (60 µL, 0.68 mmol) in anhydrous DCM (970 µL) was added dropwise at -78 °C a solution of DMSO (100 µL, 1.36 mmol) in anhydrous DCM (970 µL). The reaction was stirred at -78 °C for 20 min. A solution of **29** (119 mg, 0.34 mmol) in anhydrous DCM (850 µL) was added dropwise at -78 °C over 15 min period and the reaction mixture was stirred for 1h at -78 °C. Et_3N (336 µL, 2.39 mmol) was added dropwise and the reaction was stirred for another 1h at -78 °C. The cold bath was then removed and the reaction was stirred for 2h. Then reaction was quenched with brine, the aqueous layer was extracted two times with DCM. The combined organic extracts were washed with brine, dried over Na_2SO_4, filter on silica gel pad, and concentrated *in vacuo* to give the corresponding aldehyde as yellow oil that was characterized by ^{1}H NMR only (100 mg, 85% crude). ^{1}H NMR (250 MHz, $CDCl_3$): δ 9.78 (dd, *J* = 3.0 Hz, *J* = 2.0 Hz, 1H, CH_2CHO), 5.15-5.04 (m, 3H, alkene-*H*), 3.93-3.81 (m, 1H, pyran-OC*H*), 3.74 (d, br, *J* = 11.5 Hz, 1H, pyran-

OCH_2), 3.58 (dd, *J* = 11.5 Hz, *J* = 11.5 Hz, 1H, pyran-OC*H*$_2$), 2.62 (ddd, *J* = 16.5 Hz, *J* = 8.0 Hz, *J* = 3.0 Hz, 1H, C*H*$_2$CHO), 2.44 (ddd, *J* = 16.5 Hz, *J* = 5.0 Hz, *J* = 2.0 Hz, 1H, C*H*$_2$CHO), 2.13-1.93 (m, 10H, C*H*$_2$), 1.76-1.65 (m, 3H, CH_2), 1.67 (s, 3H, alkene-C*H*$_3$), 1.64-1.57 (m, 1H, pyran-C*H*), 1.60 (s, 9H, alkene-C*H*$_3$), 1.56-1.40 (m, 3H, C*H*$_2$).

The crude residue was dissolved in DCM (7.0 mL) and Eschenmoser's salt (266 mg, 1.44 mmol), Et_3N (82 µL, 0.57 mmol) were added. The reaction was stirred at RT for 24h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and the aqueous layer was extracted three times with DCM. The combined organic extracts were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. After removal of DCM in *vacuo*, pentane was added in order to precipitate remaining Eschenmoser's salt. After filtration, the α-β-unsaturated aldehyde was concentrated *in vacuo* and was obtained as a yellow oil (103 mg, 100% crude).

The crude residue was dissolved in t-BuOH/H_2O (4:1, 11.6 mL: 3 mL). To the solution was added at RT 2-methyl-2-butene (2M in THF, 36 mL, 71.9 mmol), NaH_2PO_4 (120.5 mg, 1.0 mmol), and $NaClO_2$ (113 mg, 1.00mmol).The reaction was stirred at RT for 2-3 h. After this period, brine was added and the reaction mixture extracted three times with EtOAc. The combined organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by flash chromatography (gradient starting with 90:10 and ending with 60:40 petroleum ether/Et_2O), to give the desired product **30** as a yellow oil (51 mg, 40% over three steps). The compound showed satisfactory spectra data[xi]: ^{1}H NMR (250 MHz, $CDCl_3$): δ 6.39 (s, br, 1H, HO_2C-alkene-*H*), 5.95 (t, *J* = 1.0 Hz, 1H, HO_2C-alkene-*H*), 5.17-5.04 (m, 3H, alkene-*H*), 4.21 (d, *J* = 10.5 Hz, pyran-OC*H*), 3.90 (d, *J* = 11.5 Hz, pyran-OC*H*$_2$), 3.69 (dd, *J* = 11.5 Hz, *J* = 2.0 Hz, 1H, pyran-OC*H*$_2$), 2.14-1.91 (m, 10H, C*H*$_2$), 1.82-1.65 (m, 3H, C*H*$_2$), 1.68 (s, 3H, alkene-C*H*$_3$), 1.64-1.40 (m, 4H, C*H*, C*H*$_2$), 1.60 (s, 9H, alkene-C*H*$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$): δ 169.4, 141.0, 135.6, 135.1, 131.4, 127.1, 124.5, 124.3 (2C), 76.4, 71.9, 39.9 (2C), 32.7, 30.2, 27.3 (2C), 26.9, 26.7, 25.9, 25.8, 17.8, 16.2 (2C); IR (film, cm^{-1}): 2926 (s), 2856 (s), 1694 (s), 1628 (m), 1441 (m),

1378 (w), 1286 (w), 1168 (w), 1109 (m), 1065 (m), 1041 (m); HRMS (EI): m/z $[M]^+$ calcd for $C_{24}H_{38}O_3$: 374.2821, found: 374.2811, $[\alpha]_D^{22}$ = + 56.0 (c = 0.25 in $CHCl_3$, lit.[14] $[\alpha]_D^{25}$ = + 55.0 (c = 0.23 in $CHCl_3$).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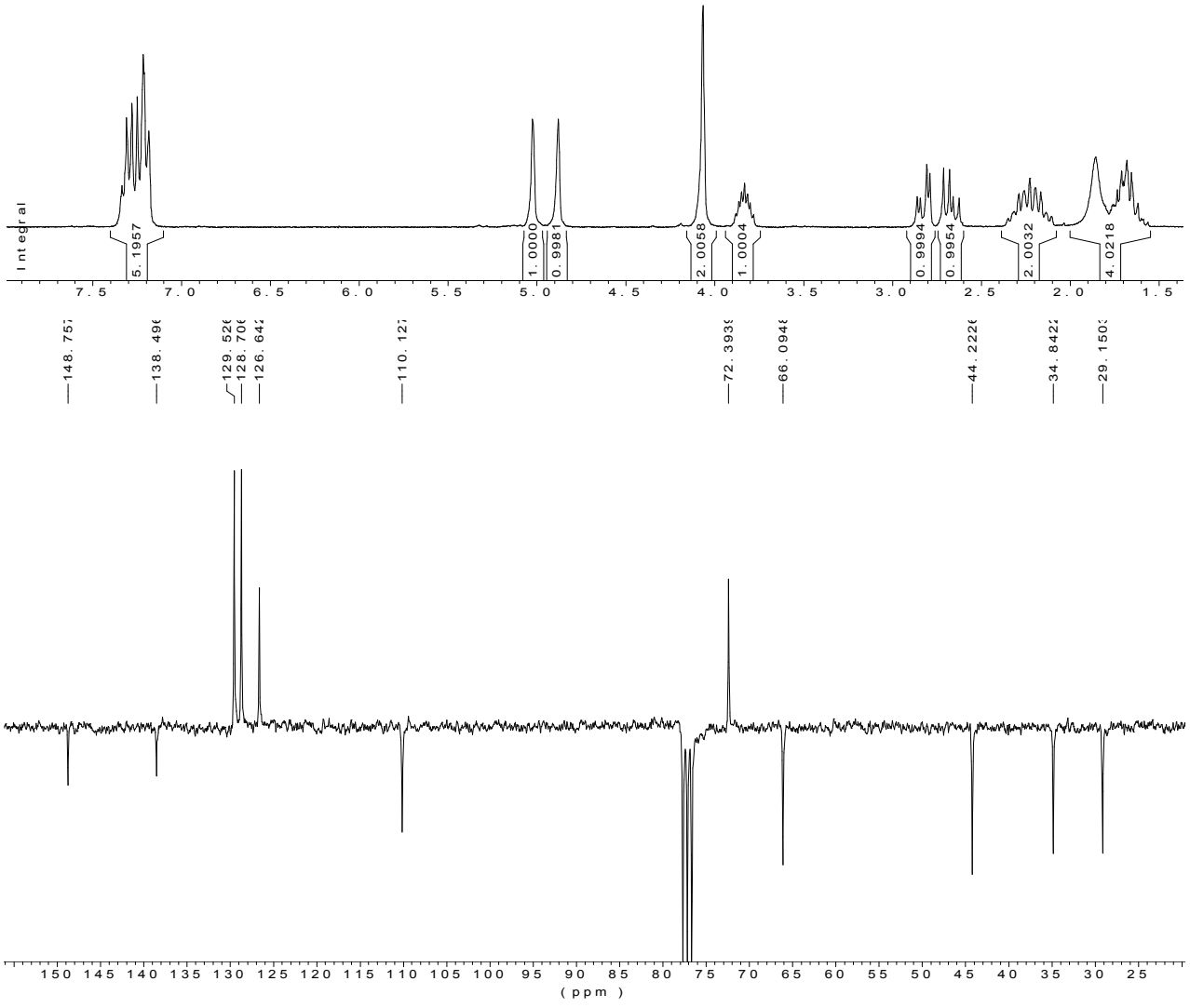
7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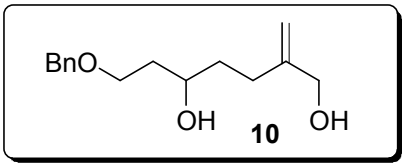
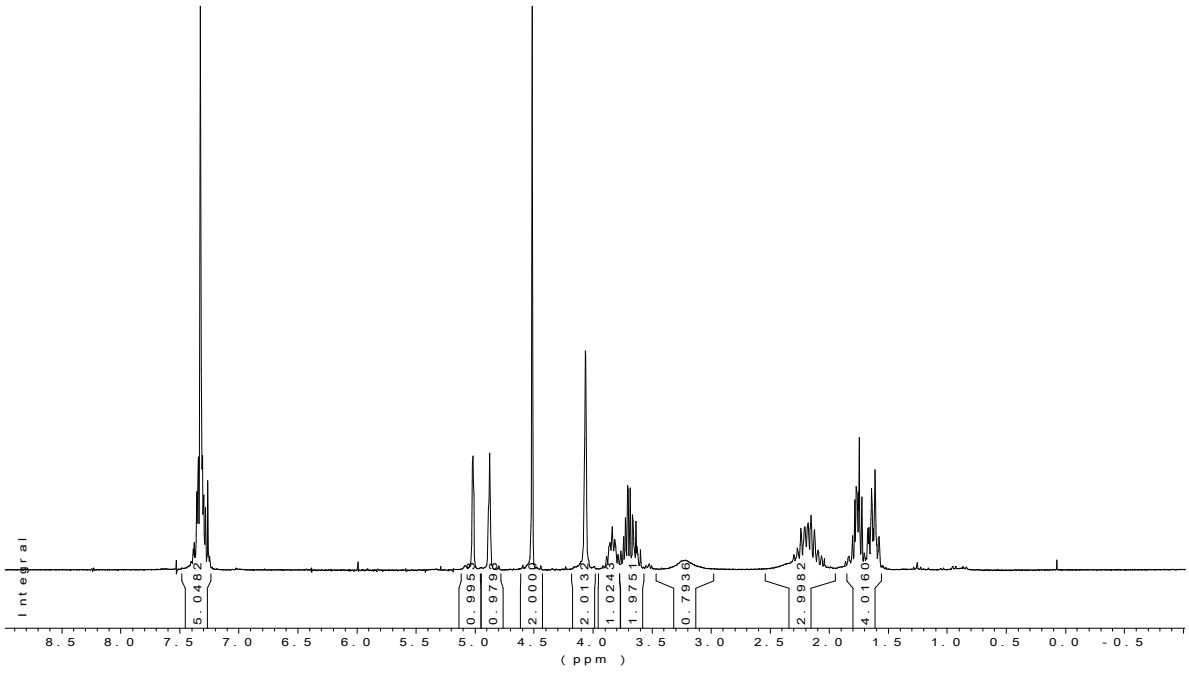
2.0058
1.0004
0.9994
0.9954
2.0032
4.0218
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5
148.75
138.49
129.52
128.70
126.64
110.12
72.393
66.094
44.222
34.842
29.150
150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25
(ppm)


BnO
OH
OH

10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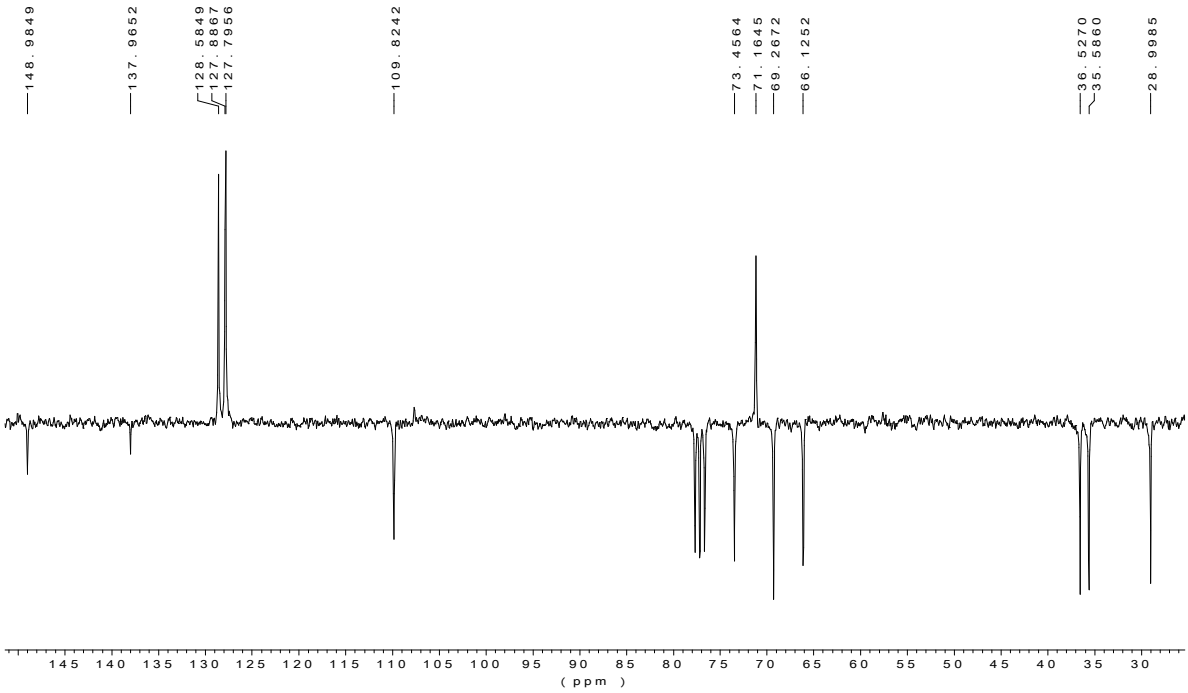
0.979
2.000
2.013
1.024
1.975
0.7936
2.9982
4.0160
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)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127.7956
109.8242
73.4564
71.1645
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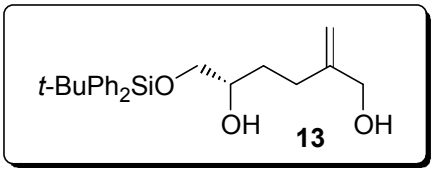
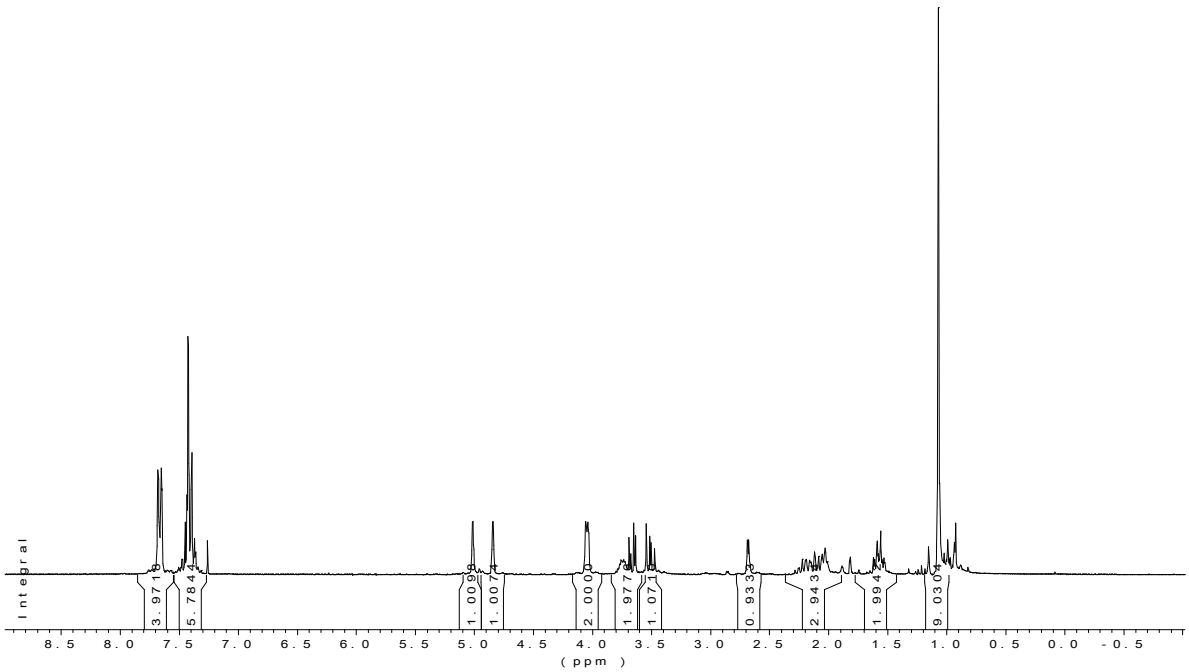
36.5270
35.5860
28.9985
145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30
(ppm)


t-BuPh2SiO
OH
OH

13


Integral
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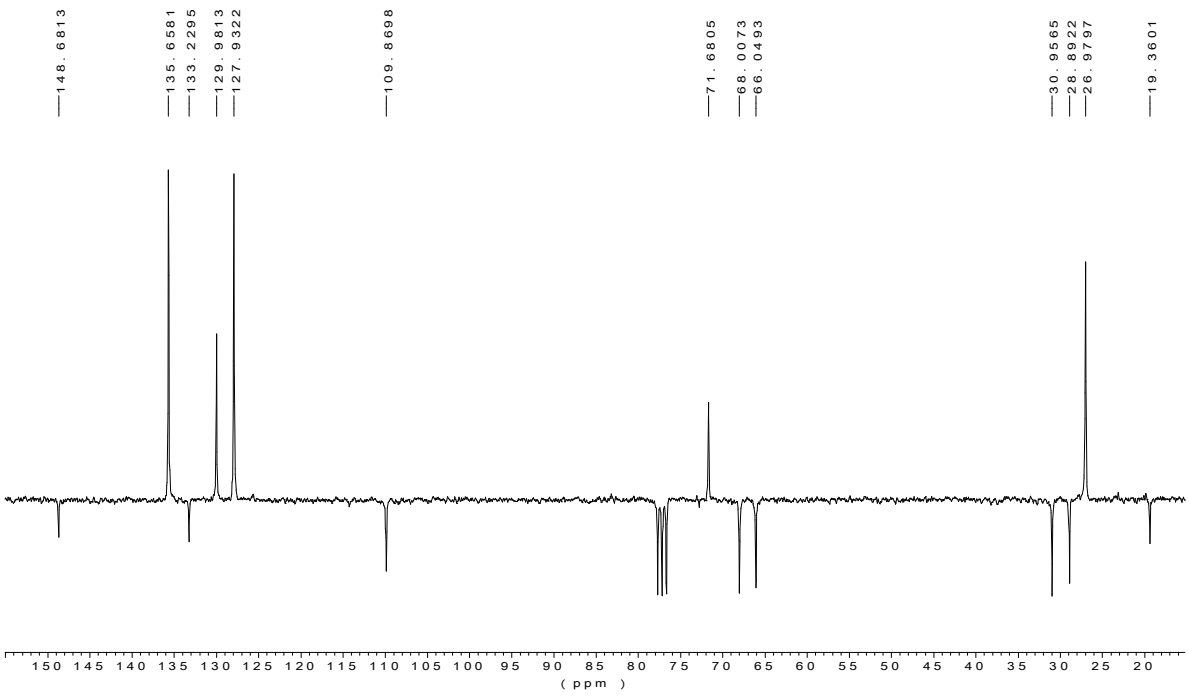
1.007
2.000
1.977
1.071
0.933
2.943
1.994
9.030
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)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129.9813
127.9322
109.8698
71.6805
68.0073
66.0493
30.9565
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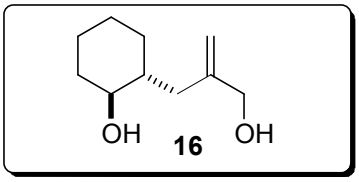
26.9797
19.3601
150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20
(ppm)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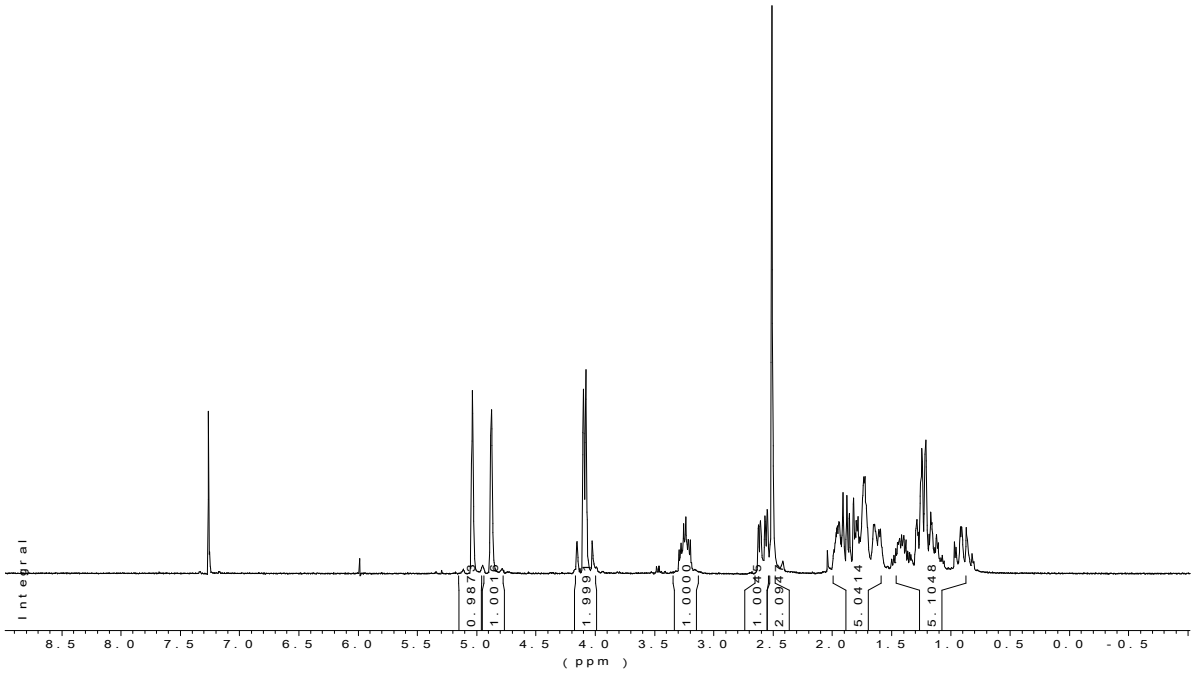
OH

16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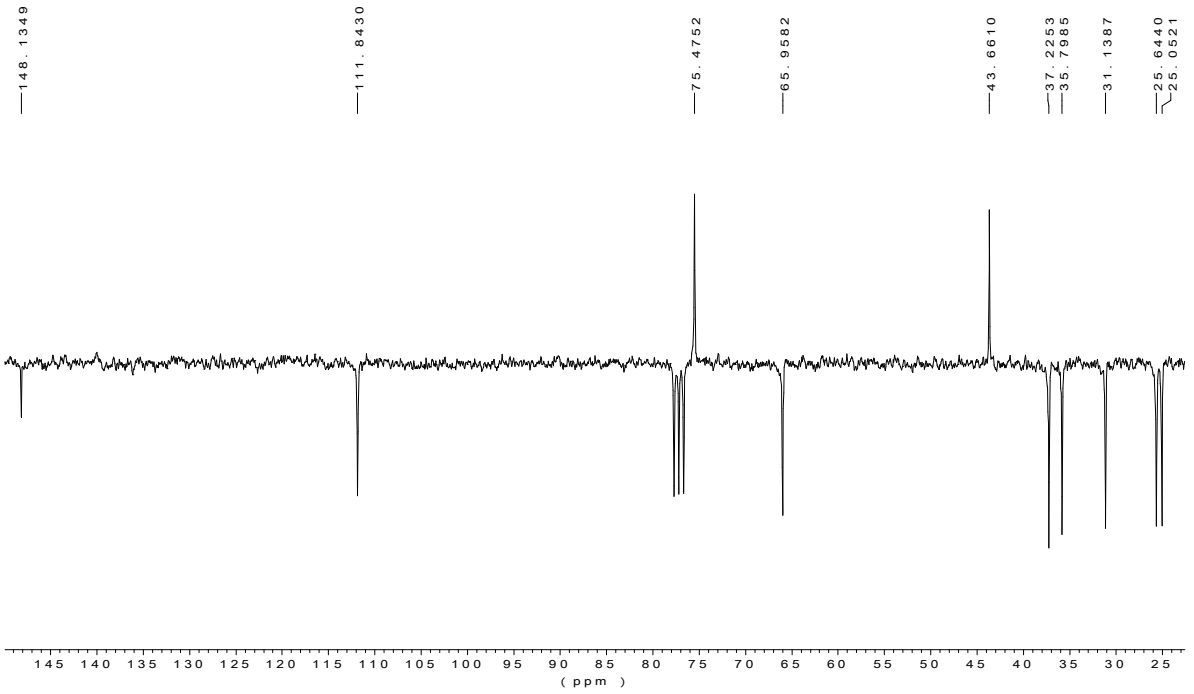
1.999
1.000
1.004
2.094
5.041
5.104
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)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43.6610
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25.6440
25.0521
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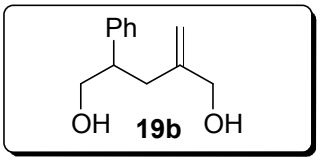
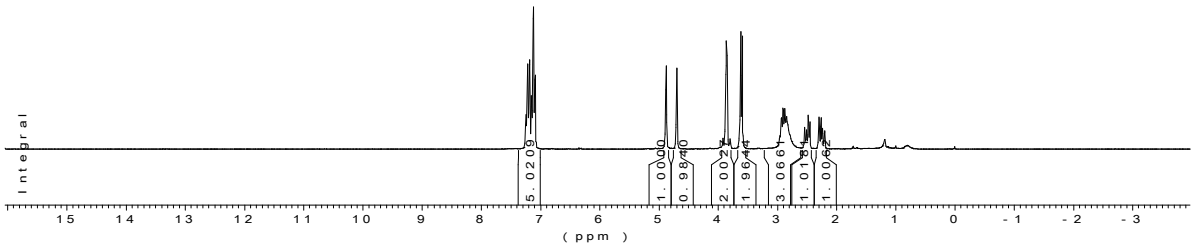
(ppm)


Ph
OH
OH

19b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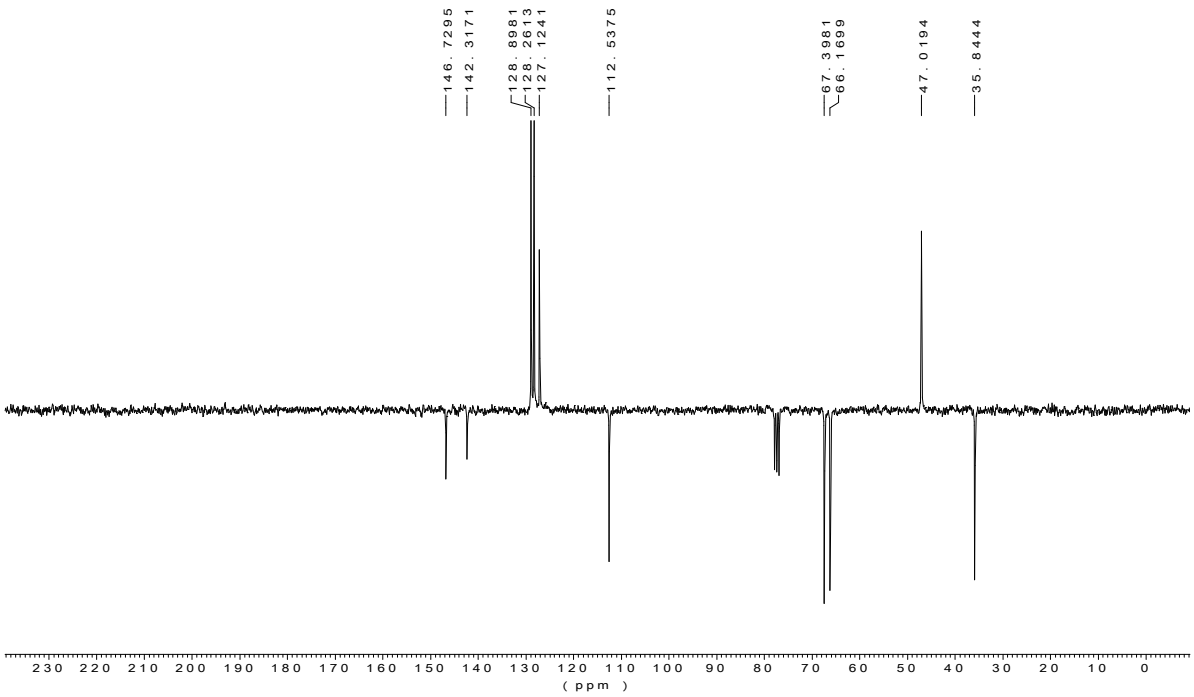
3.0667
1.0162
1.0062
15 14 13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1 -2 -3
(ppm)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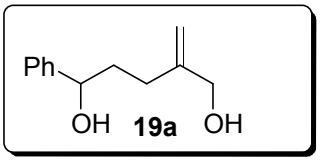
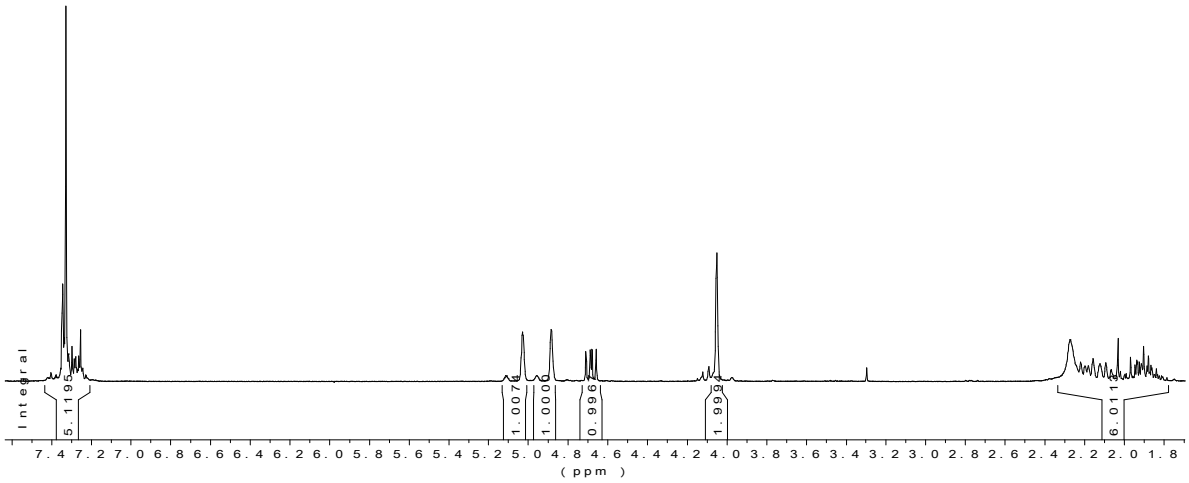
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
(ppm)


Ph
OH
OH

19a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1.000
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1.993
6.011
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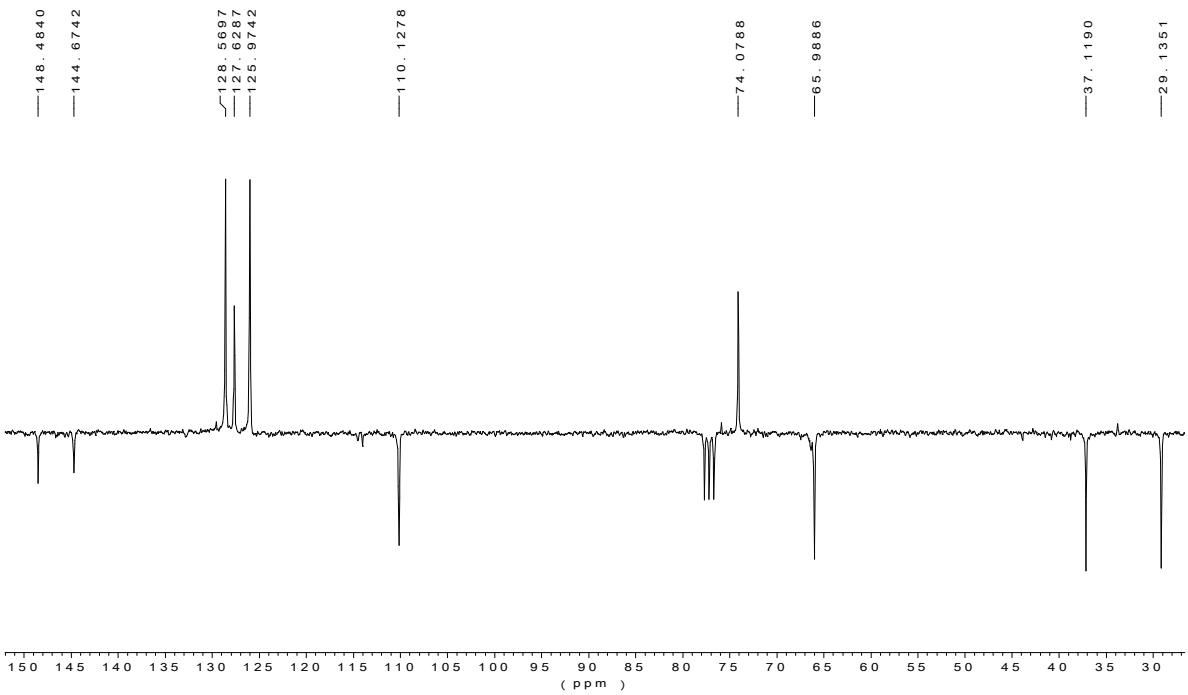
(ppm)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74.0788
65.9886
37.1190
29.1351
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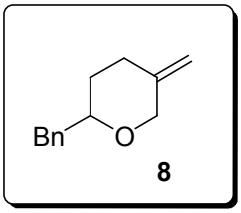
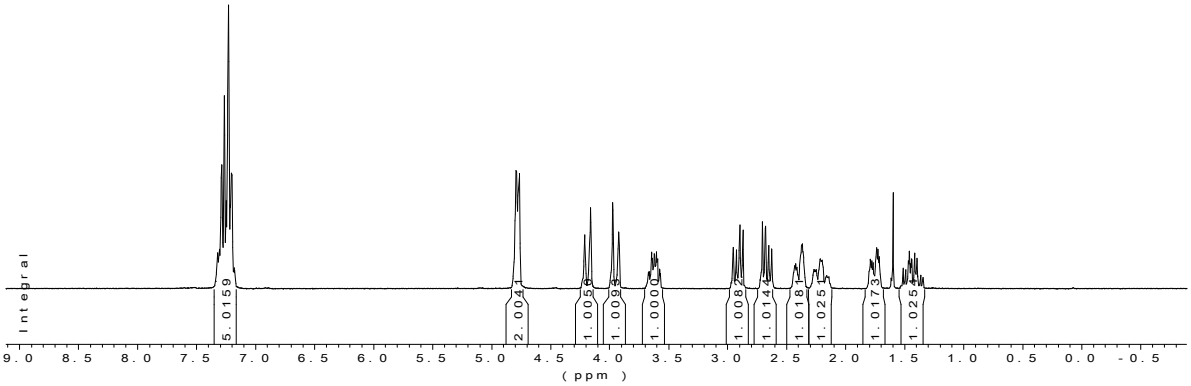
(ppm)


Bn
O

8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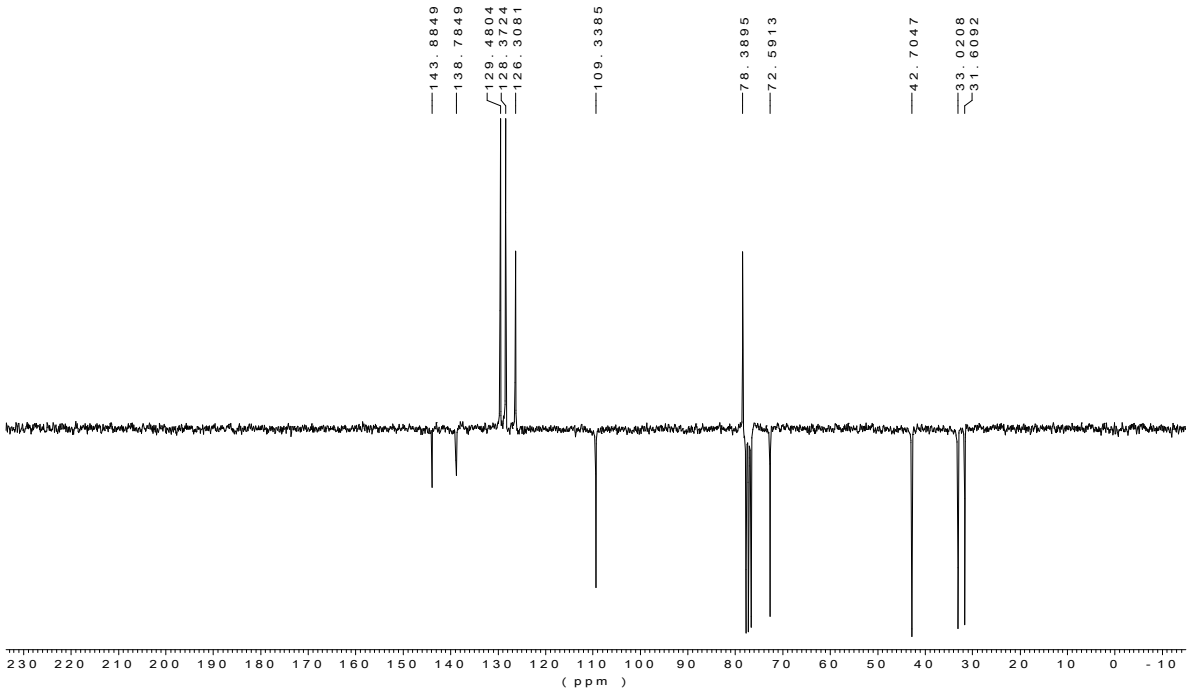
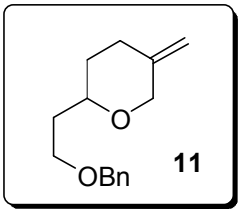
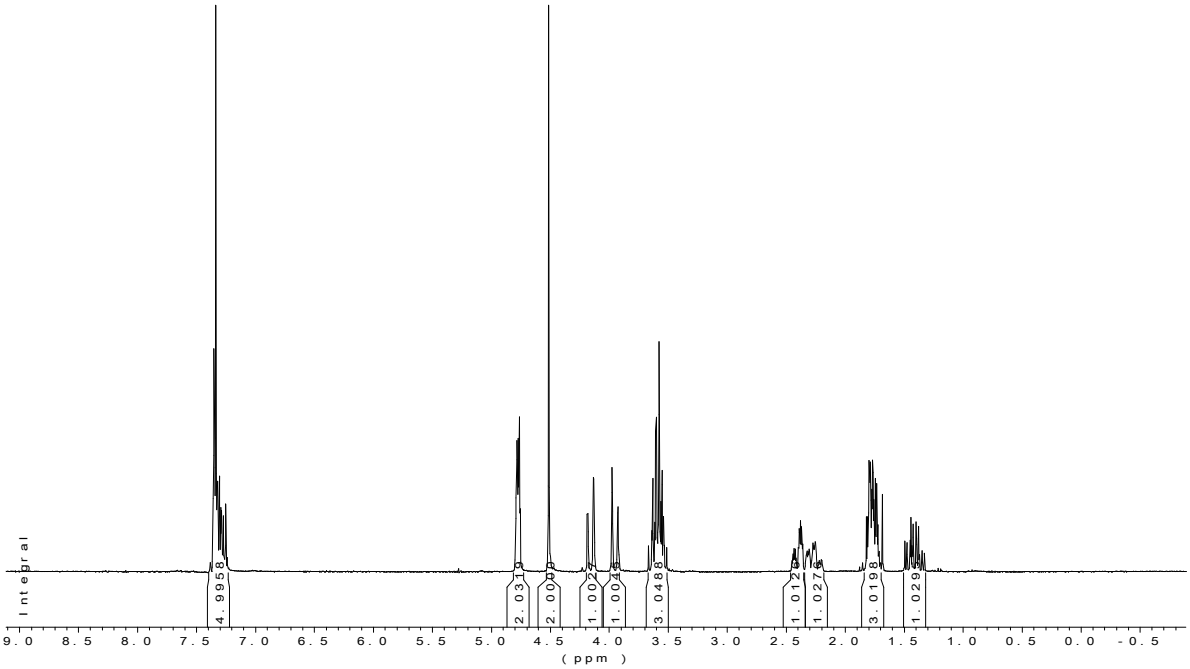
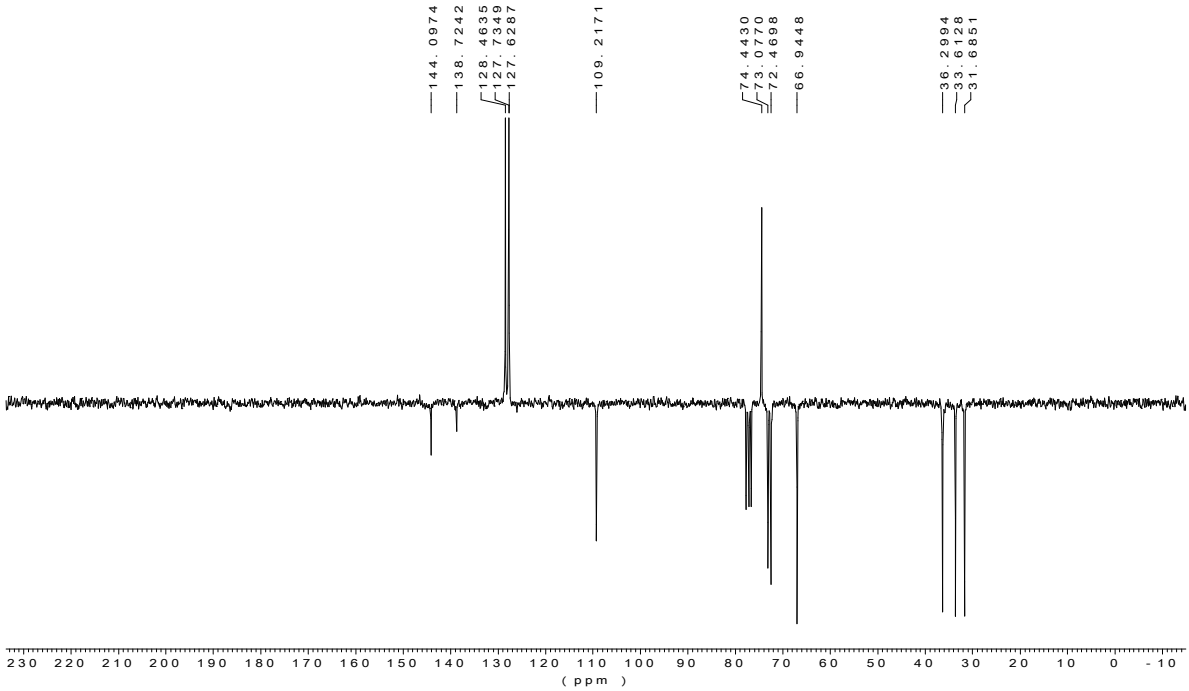
1.0091
1.0000
1.0082
1.0144
1.0187
1.0251
1.0173
1.0251
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)

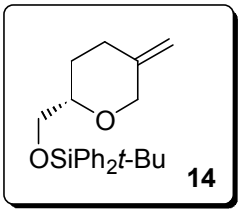

143.8849
138.7849
129.4804
128.3724
126.3081
109.3385
78.3895
72.5913
42.7047
33.0208
31.6092
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)


O
OBn

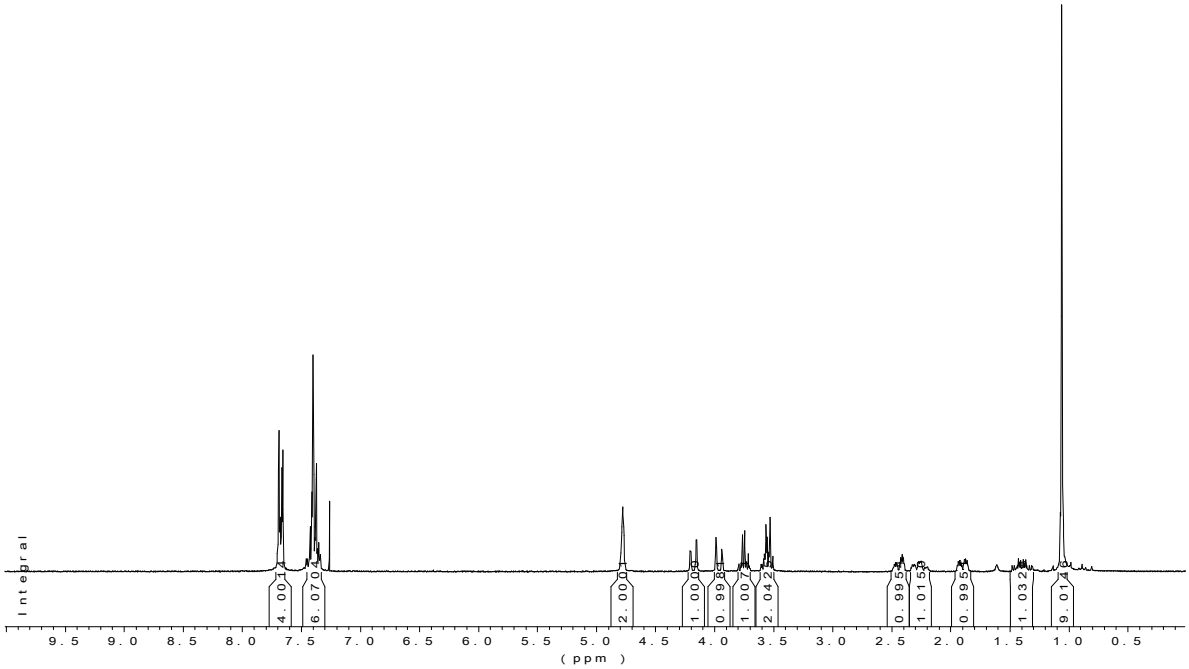
11

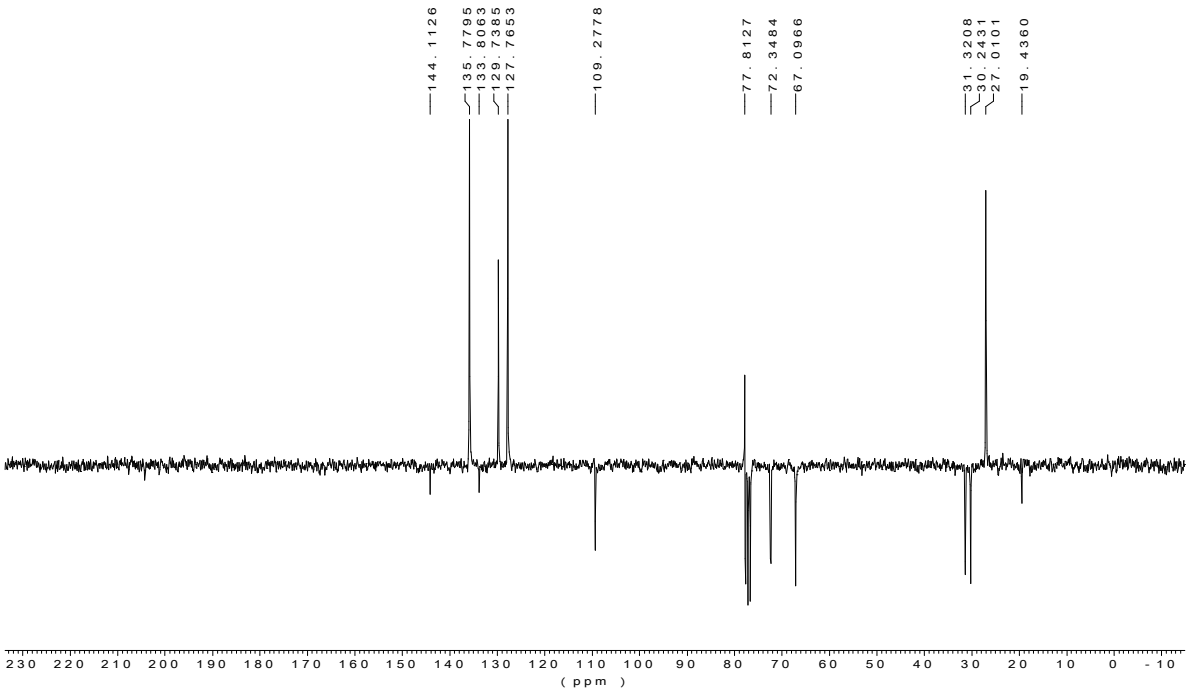

Integral
4.9958
2.0310
2.0000
1.0027
1.0043
3.0485
1.0127
1.0278
3.0198
1.0295
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)

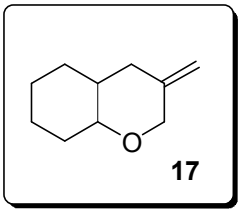

144.0974
138.7242
128.4635
127.7349
127.6287
109.2171
74.4430
73.0770
72.4698
66.9448
36.2994
33.6128
31.6851
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)


O
OSiPh2t-Bu

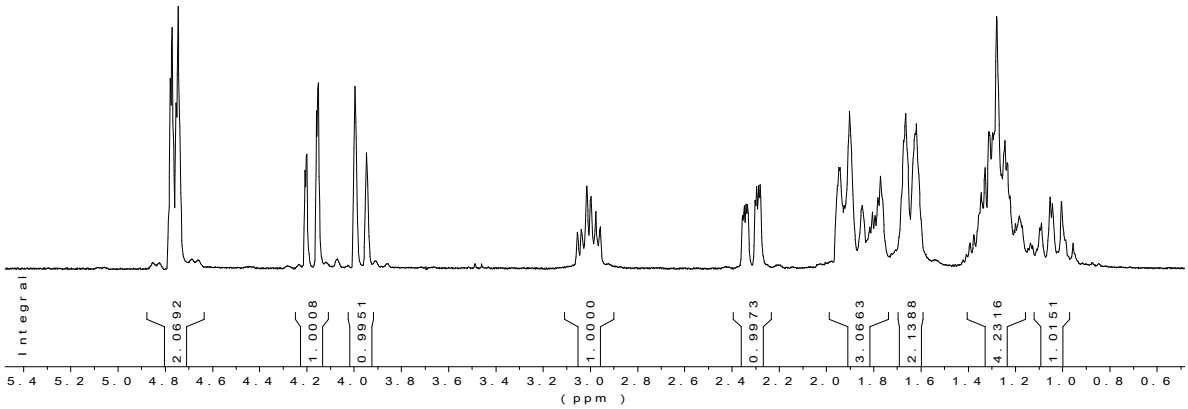
14

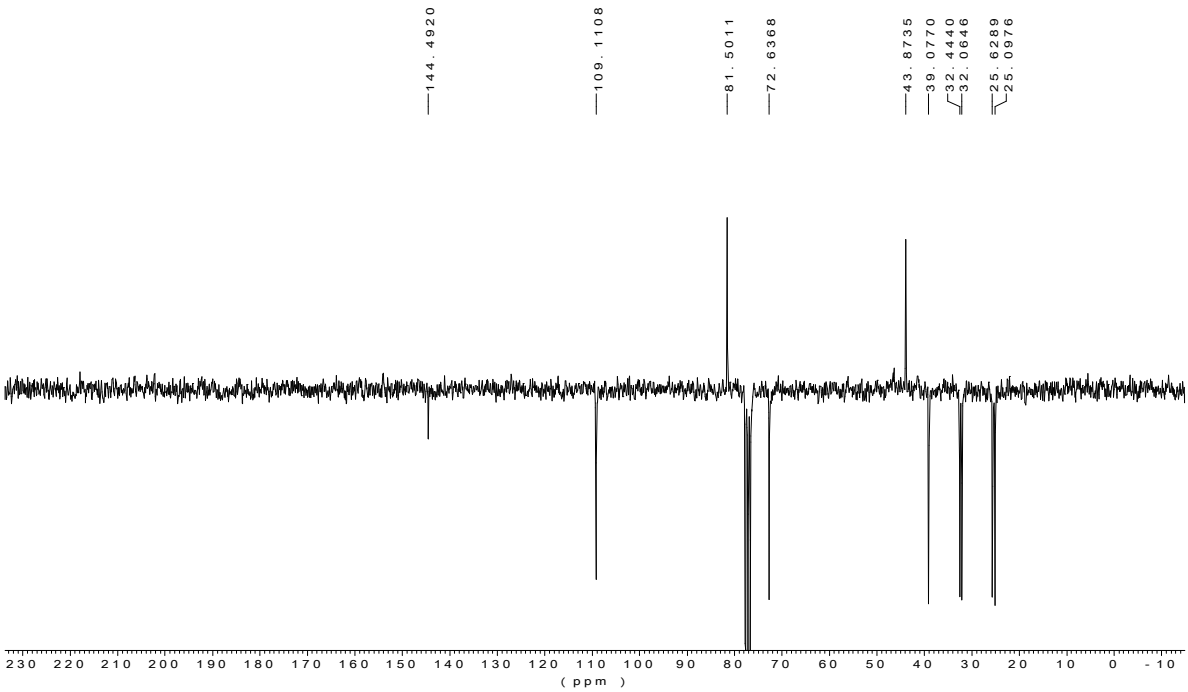

Integral
4.00
6.07
2.00
1.00
0.99
1.00
2.04
0.99
1.01
0.99
1.03
9.01
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
(ppm)

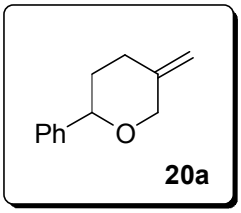

144.1126
135.7795
133.8063
129.7385
127.7653
109.2778
77.8127
72.3484
67.0966
31.3208
30.2431
27.0101
19.4360
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)


O

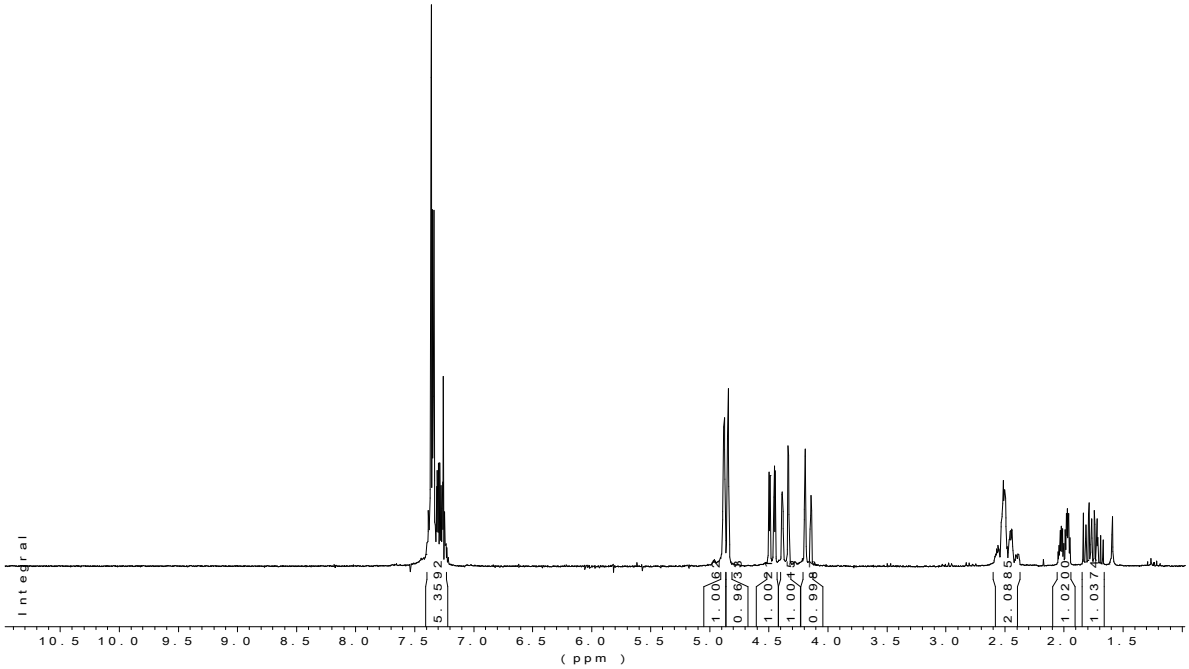
17

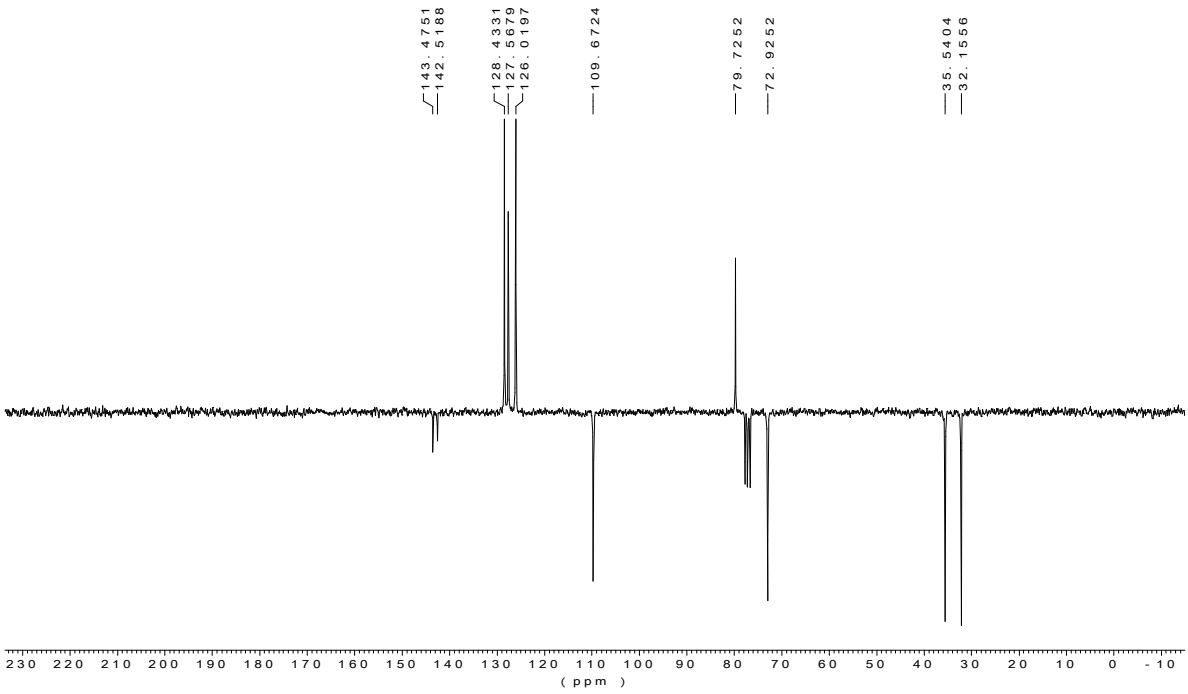

Integral
2.0892
1.0008
0.9951
1.0000
0.9973
3.0663
2.1388
4.2316
1.0151
5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6
(ppm)

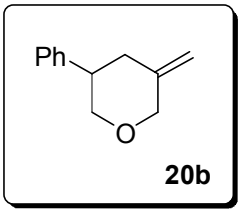

144.4920
109.1108
81.5011
72.6368
43.8735
39.0770
32.4440
32.0646
25.6289
25.0976
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)


Ph
O

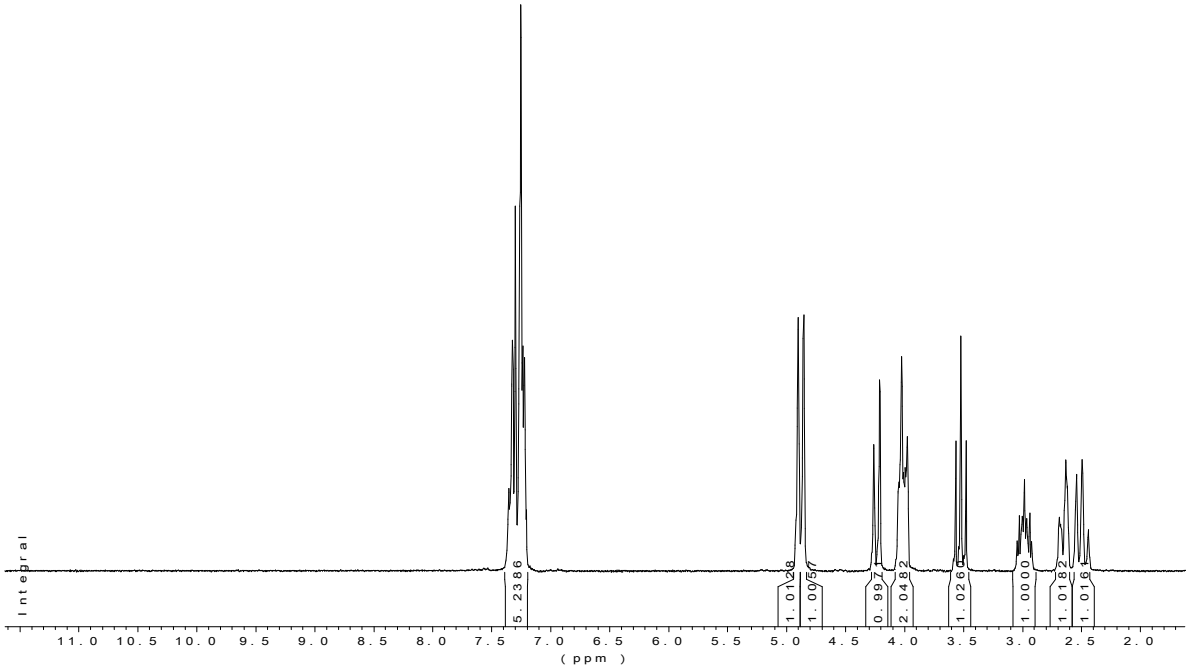
20a

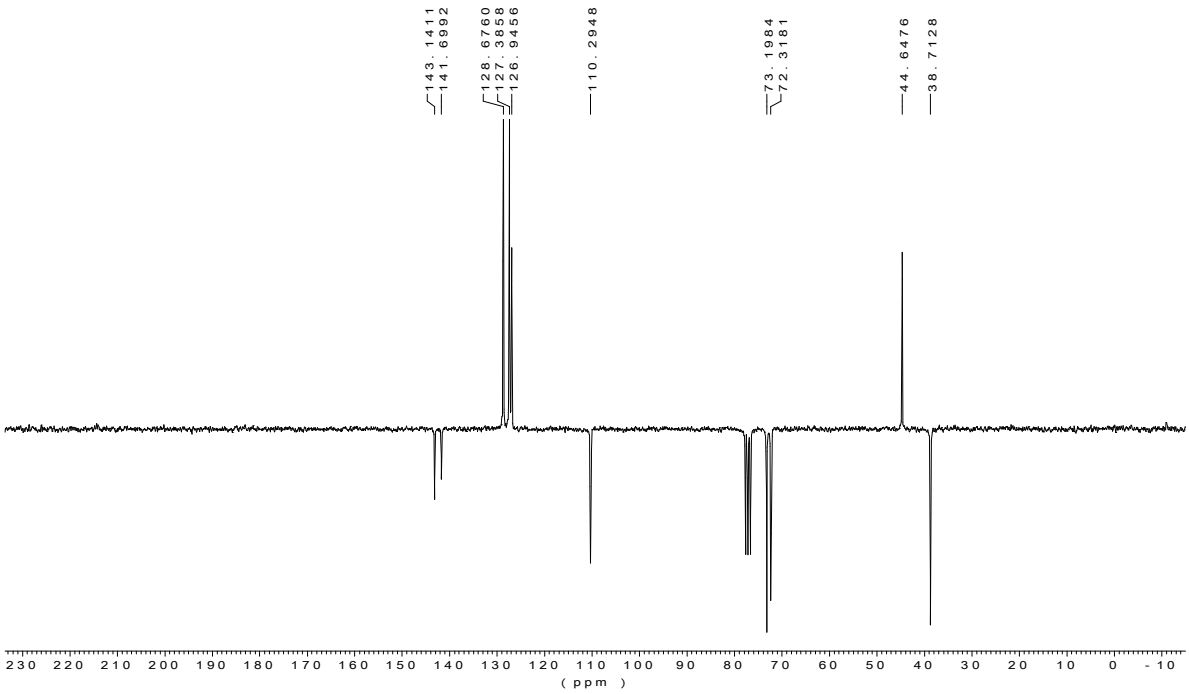

Integral
5.359
1.000
0.983
1.002
1.004
0.998
2.088
1.020
1.037
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5
(ppm)

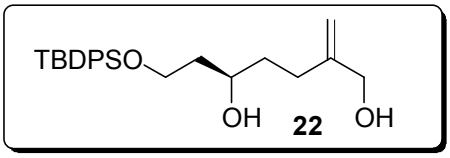

143.4751
142.5188
128.4331
127.5679
126.0197
109.6724
79.7252
72.9252
35.5404
32.1556
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)


Ph
O

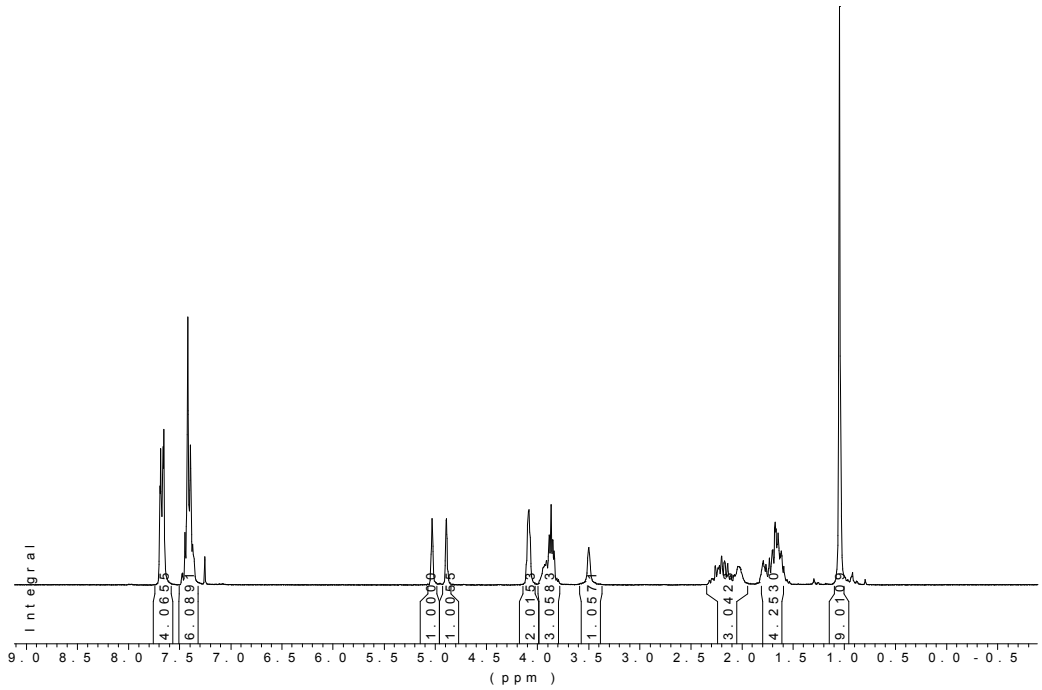
20b

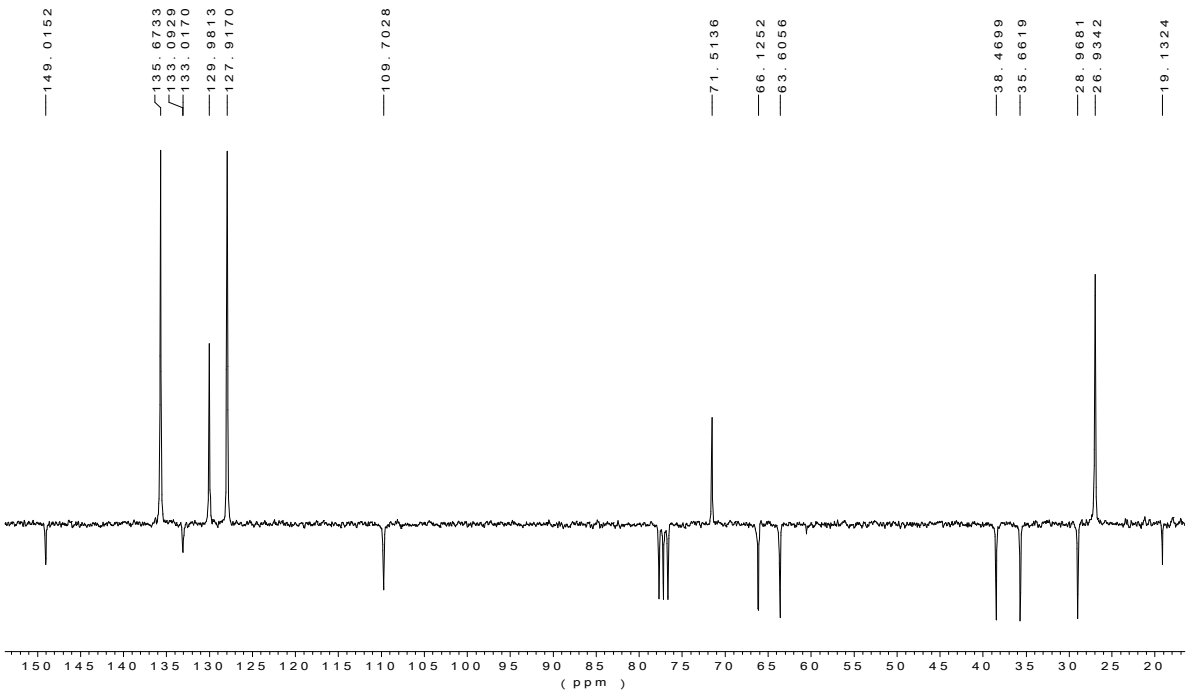

Integral
5.2386
1.0128
1.0057
0.9971
2.0482
1.0266
1.0000
1.0182
1.0161
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0
(ppm)

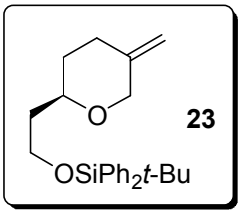

143.1411
141.6992
128.6760
127.3858
126.9456
110.2948
73.1984
72.3181
44.6476
38.7128
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)

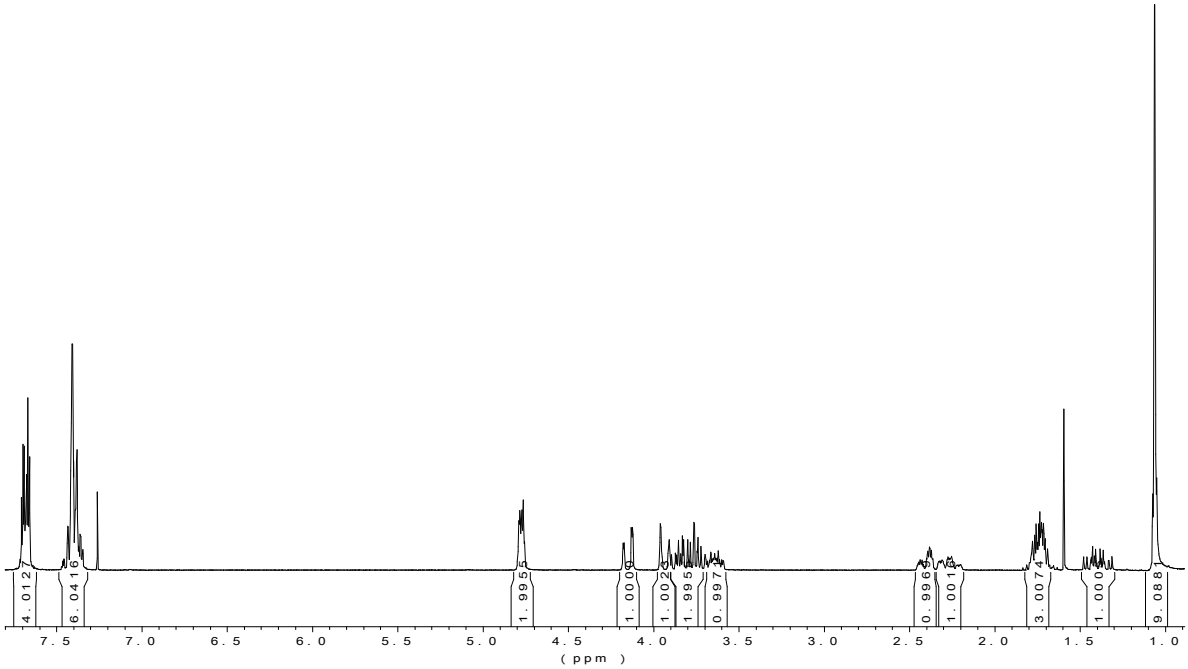

TBDPSO
OH
OH

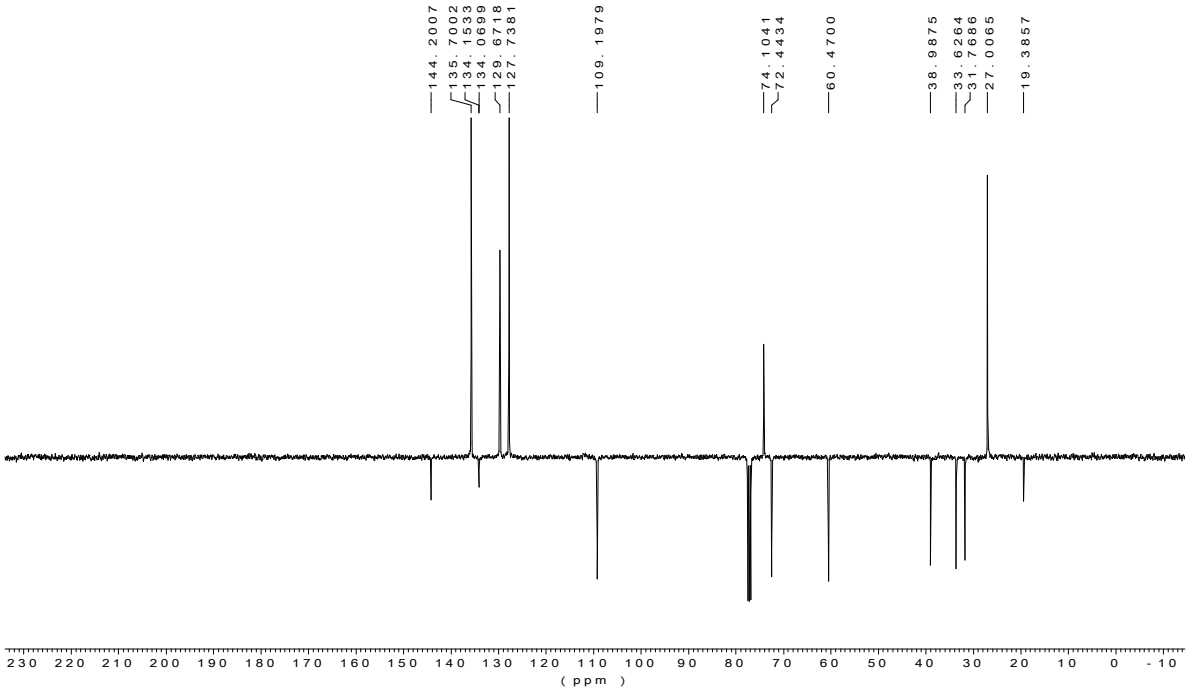
22

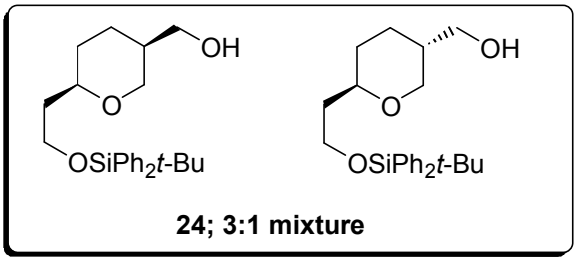

Integral
4.065
6.089
1.009
1.006
2.013
3.058
1.057
3.042
4.253
9.015
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)


149.0152
135.6733
133.0929
133.0170
129.9813
127.9170
109.7028
71.5136
66.1252
63.6056
38.4699
35.6619
28.9681
26.9342
19.1324
150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20
(ppm)

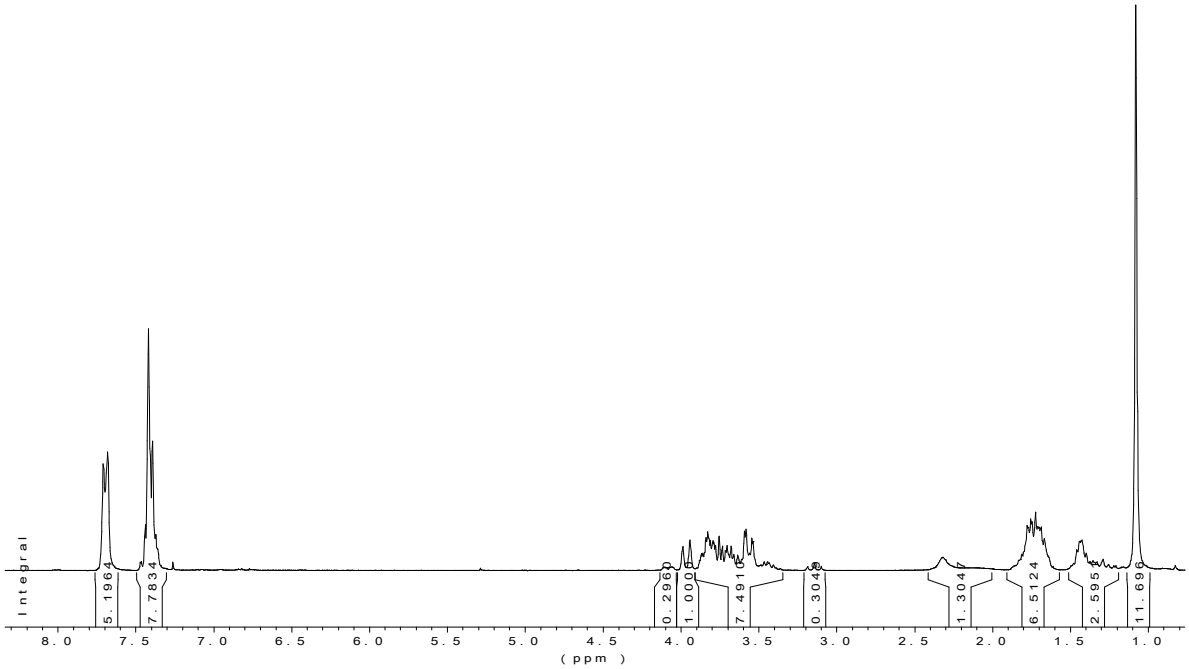

O
23
OSiPh2t-Bu

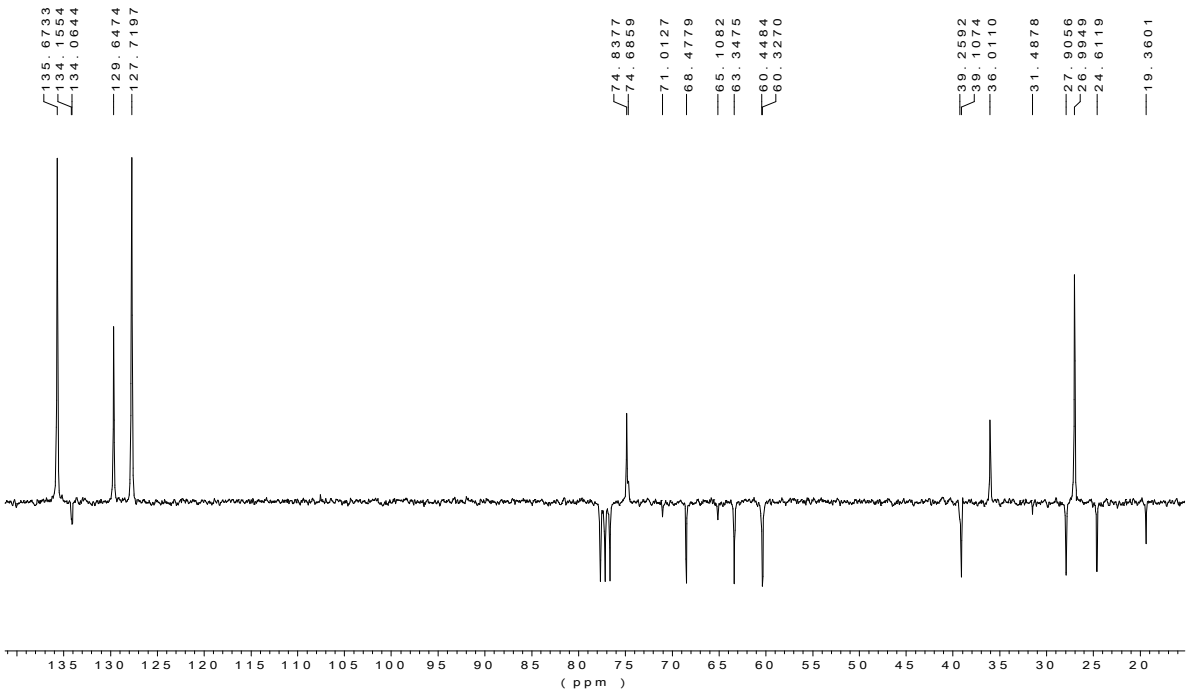

4.012
6.041
1.995
1.000
1.002
1.995
0.997
0.996
1.001
3.007
1.000
9.088
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
(ppm)

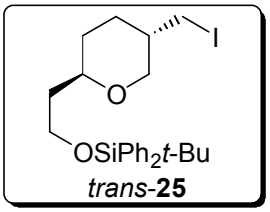

144.2007
135.7002
134.1533
134.0699
129.6718
127.7381
109.1979
74.1041
72.4434
60.4700
38.9875
33.6264
31.7686
27.0065
19.3857
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)



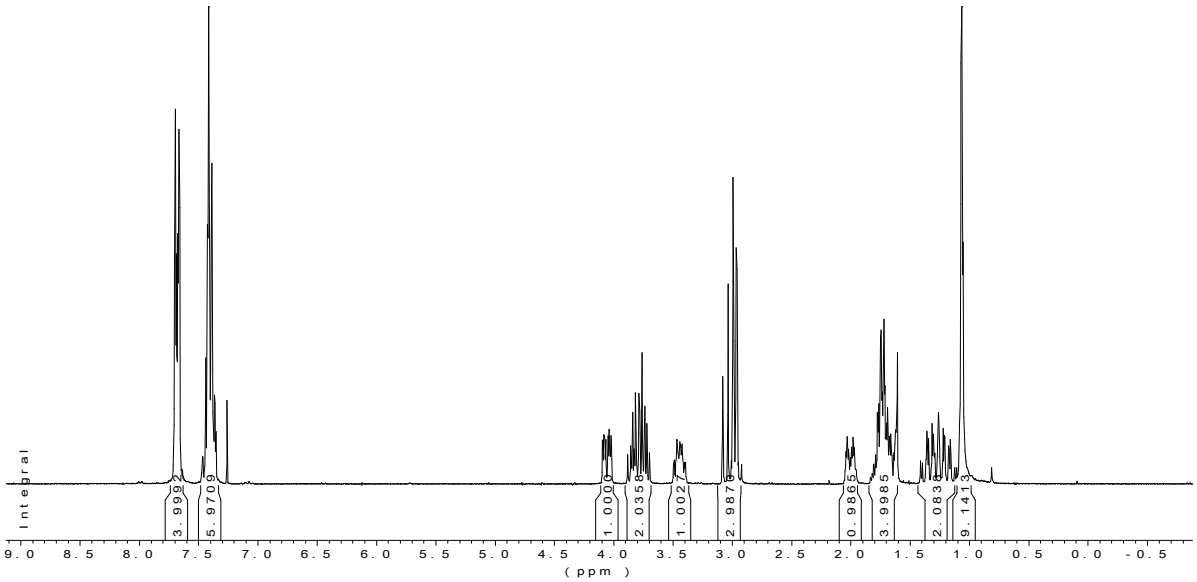
24; 3:1 mixture

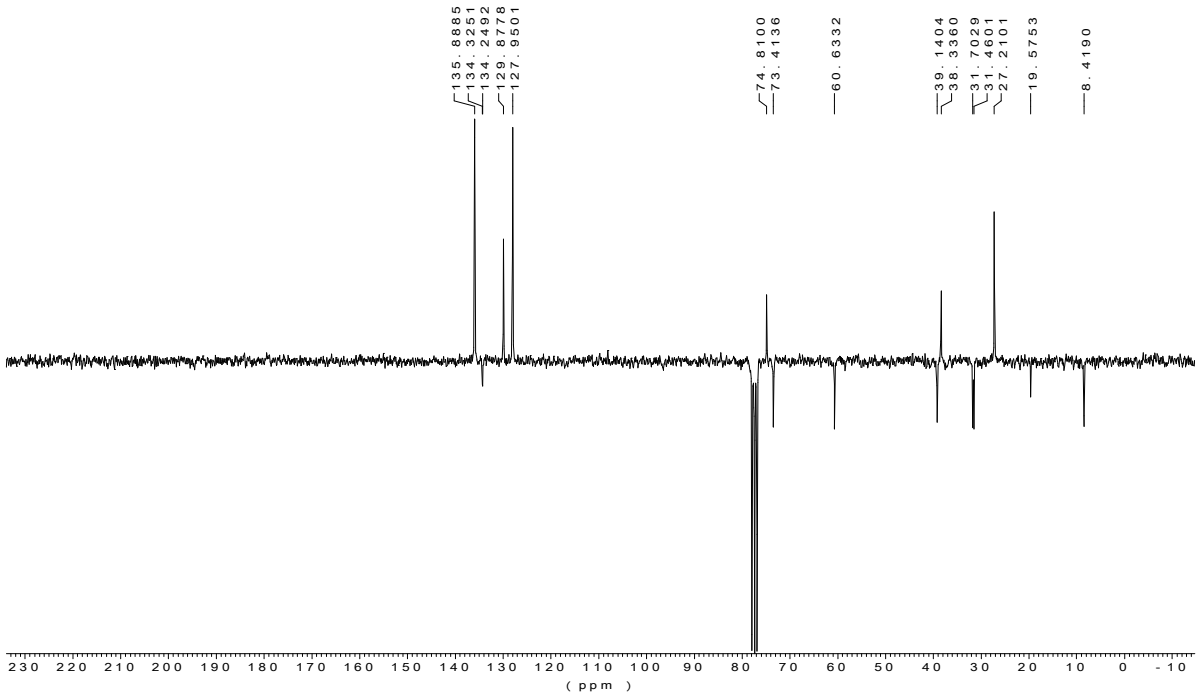


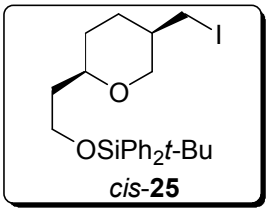



I
O
OSiPh2t-Bu

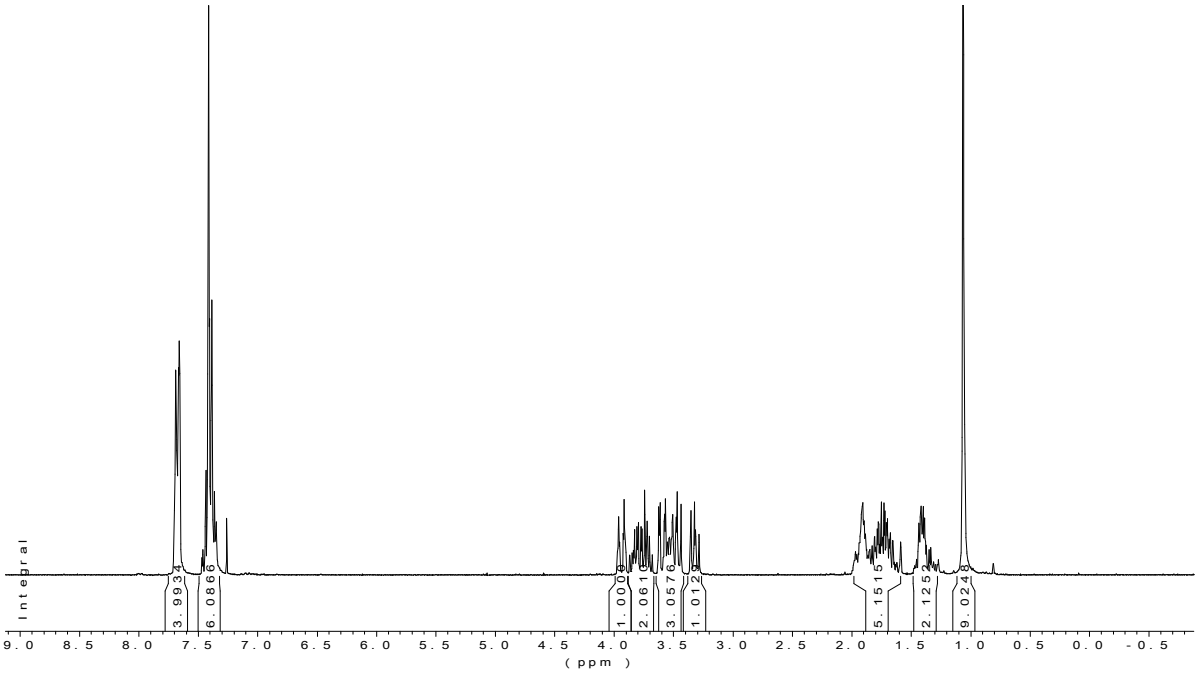
trans-**25**

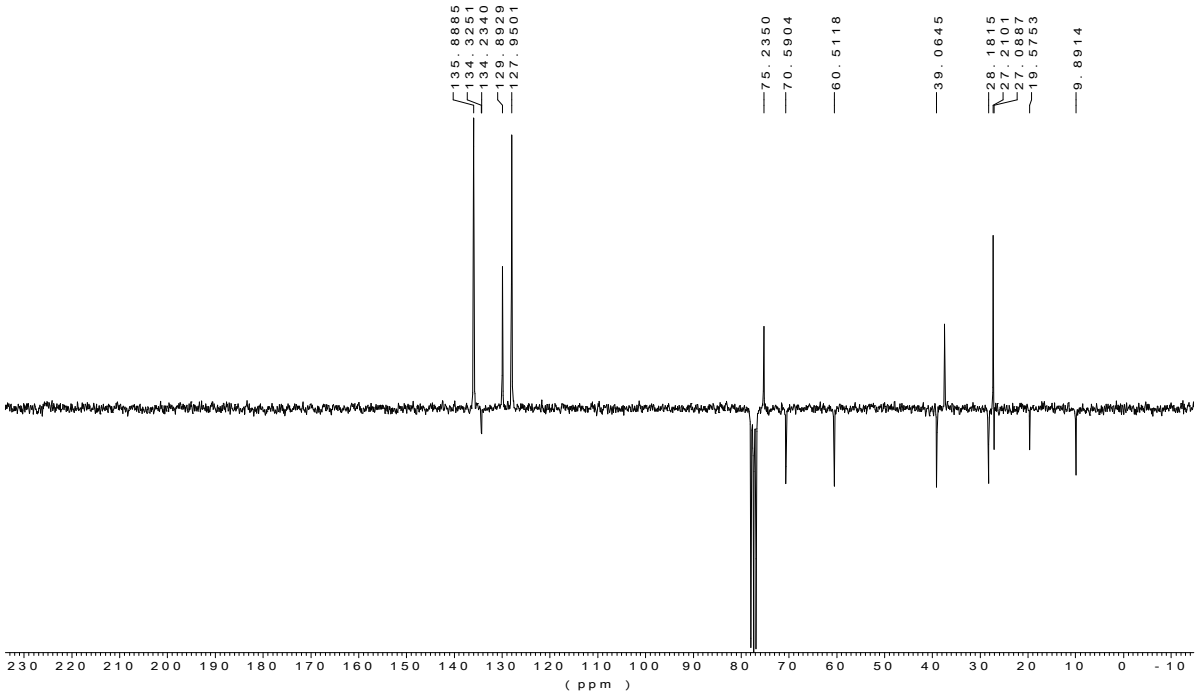

Integral
3.999
5.9709
1.000
2.0358
1.0027
2.987
0.9865
3.9985
2.083
9.141
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)

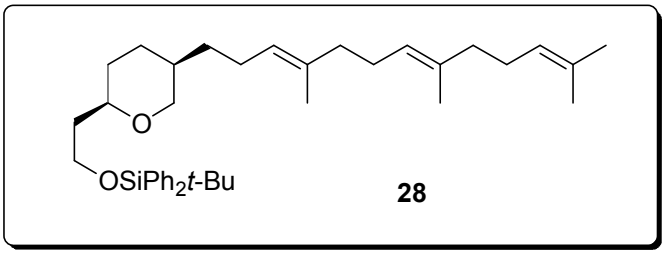

135.8885
134.3251
134.2492
129.8778
127.9501
74.8100
73.4136
60.6332
39.1404
38.3360
31.7029
31.4601
27.2101
19.5753
8.4190
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)


I
O
OSiPh2t-Bu

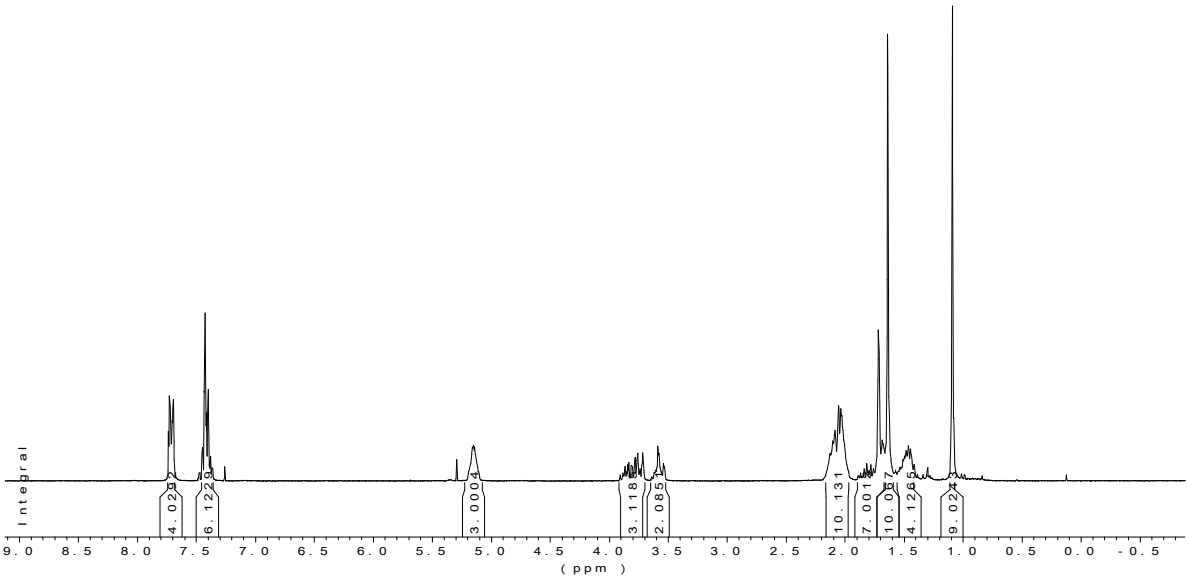
cis-**25**

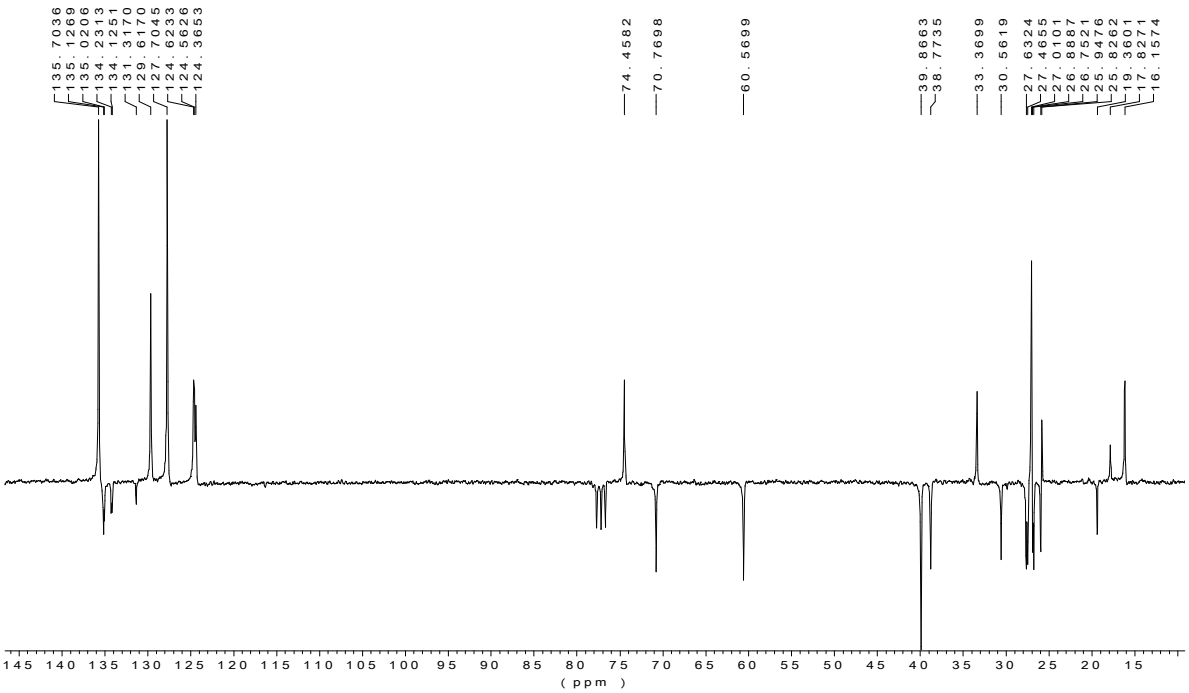

Integral
3.9934
6.0866
1.0006
2.0615
3.0576
1.0128
5.1515
2.1258
9.0248
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
(ppm)

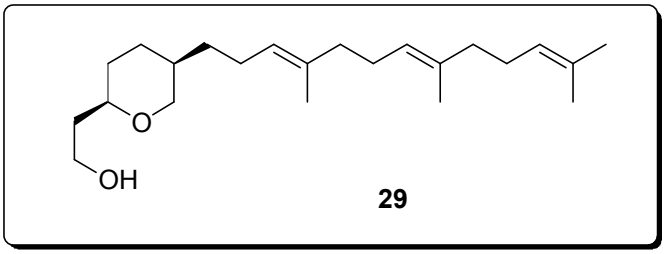

135.8885
134.3251
134.2340
129.8929
127.9501
75.2350
70.5904
60.5118
39.0645
28.1815
27.2101
27.0887
19.5753
9.8914
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
(ppm)


O
OSiPh2t-Bu

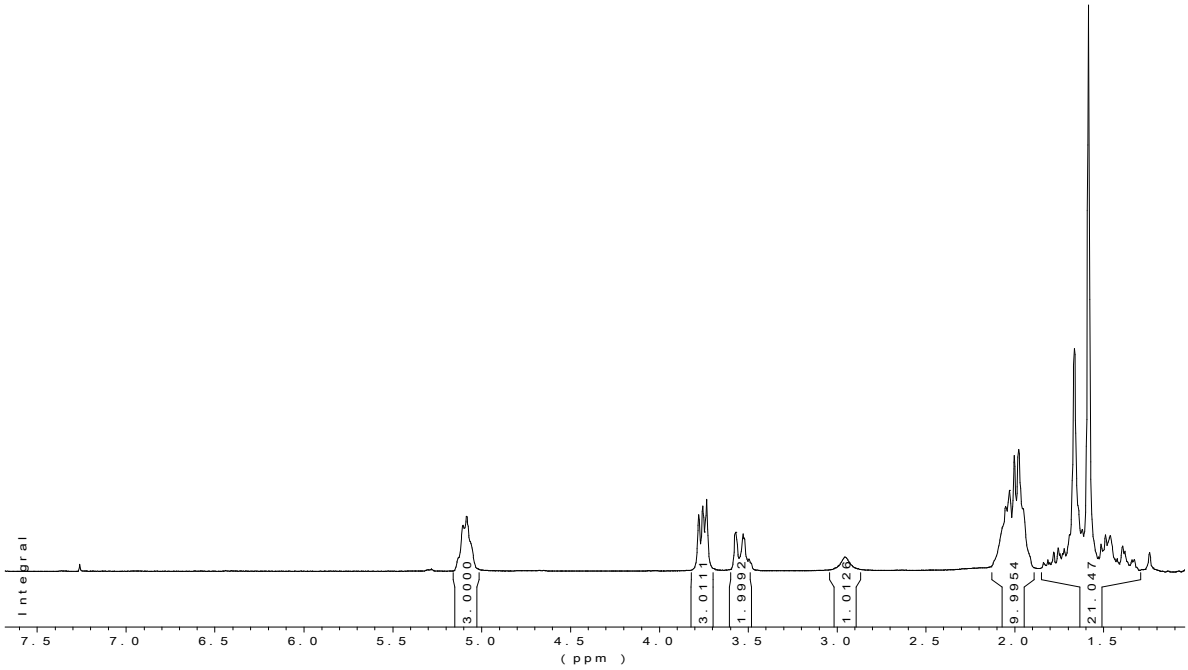
28

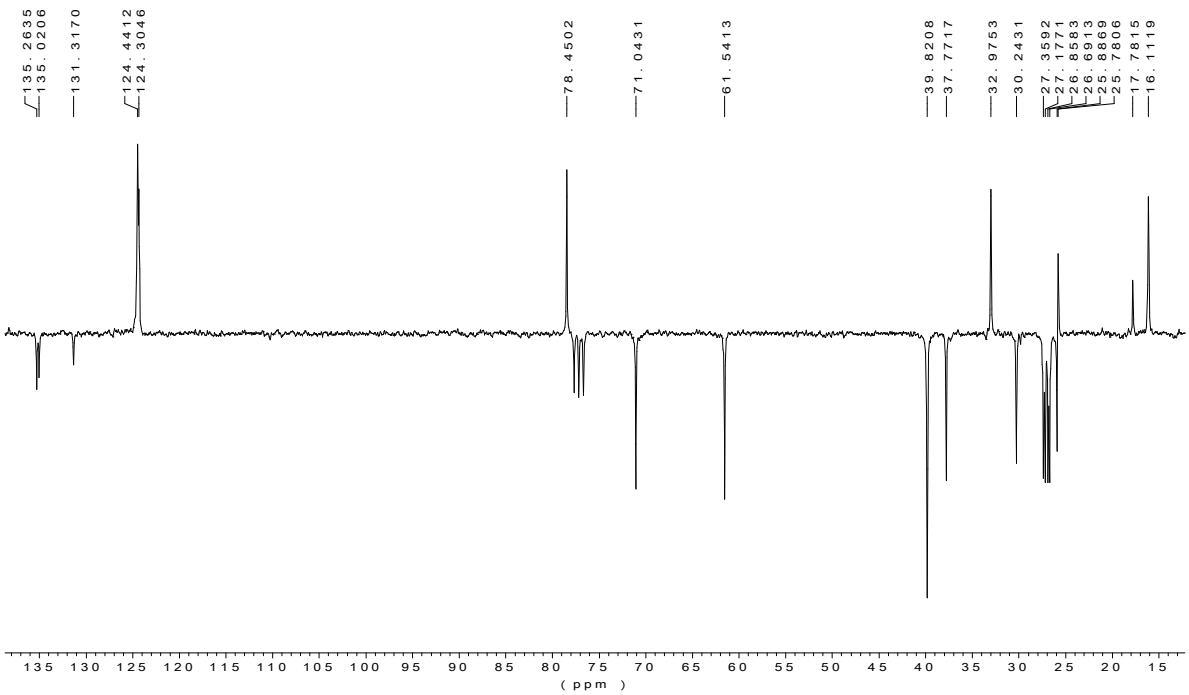

Integral
4.02
6.12
3.000
3.11
2.05
10.13
7.00
10.00
4.12
9.02
(ppm)

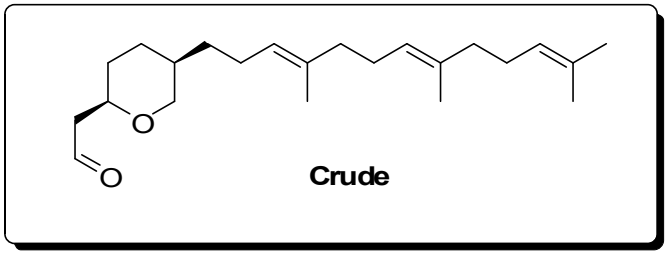

135.7036
135.1269
135.0206
134.2313
134.1251
131.3170
129.6170
127.7045
124.6233
124.5626
124.3653
74.4582
70.7698
60.5699
39.8663
38.7735
33.3699
30.5619
27.6324
27.4655
27.0101
26.8887
26.7521
25.9476
25.8262
19.3601
17.8271
16.1574
(ppm)

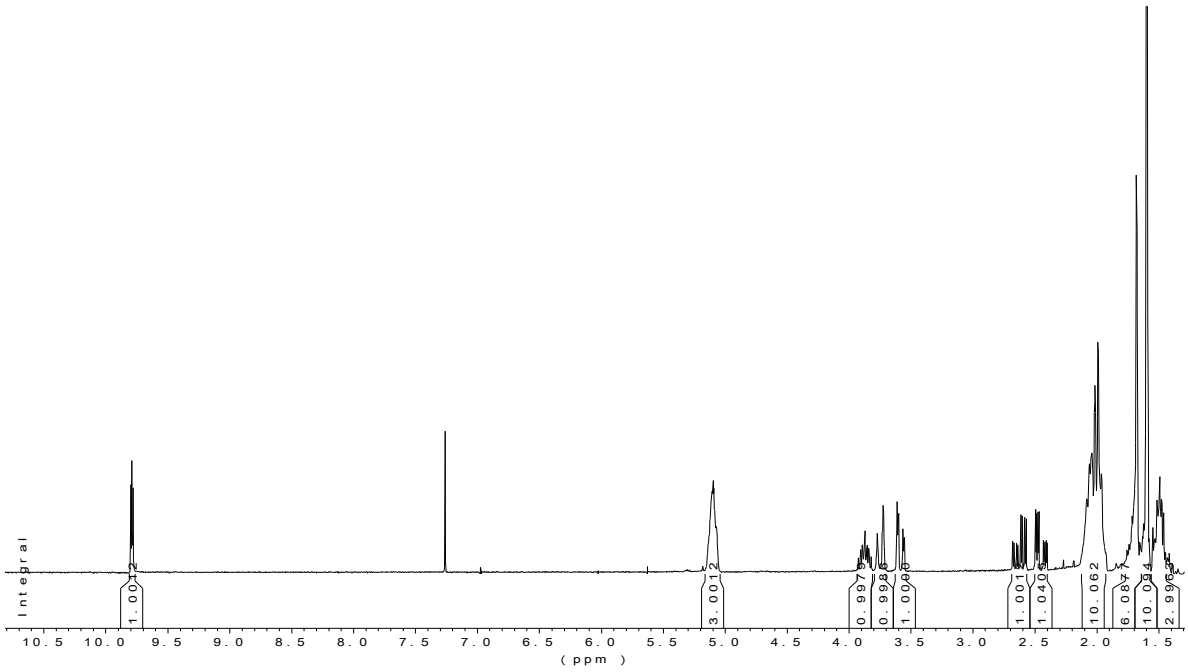

O
OH

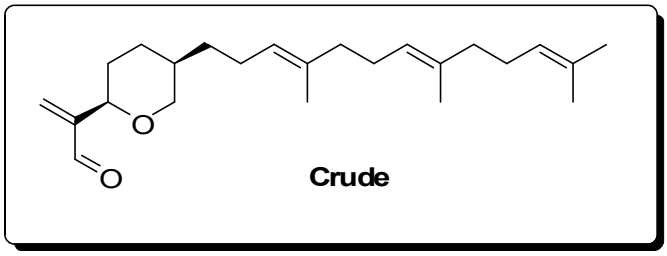
29

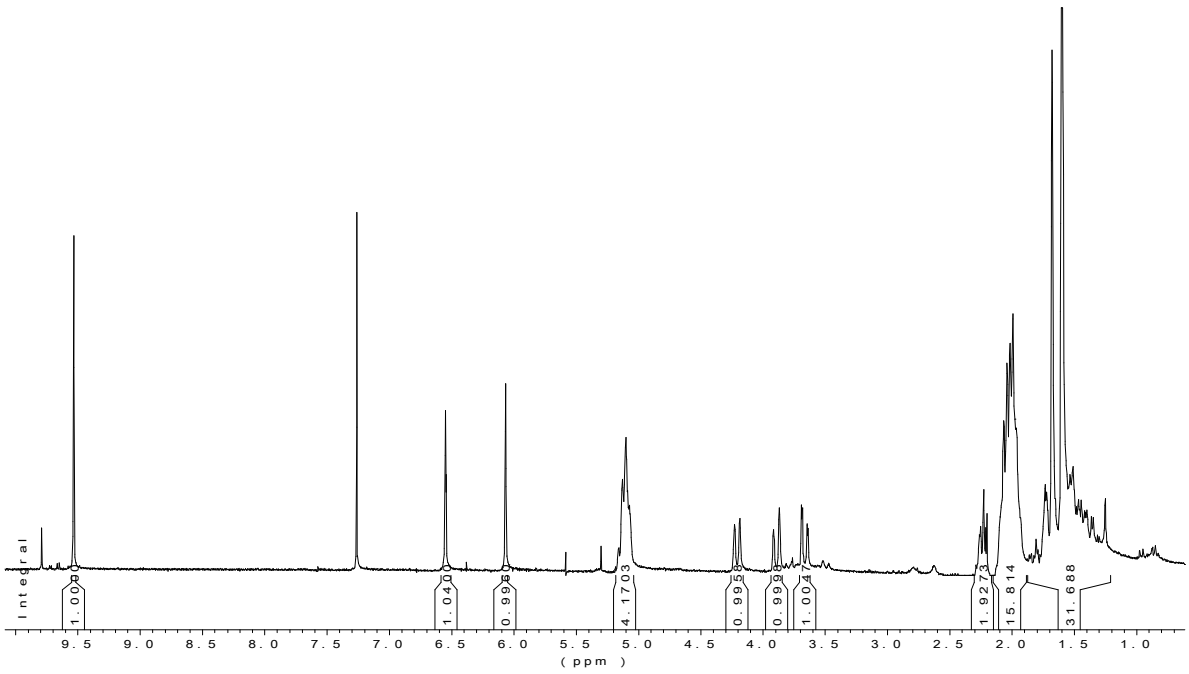

Integral
3.0000
3.0111
1.9992
1.0126
9.9954
21.047
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5
(ppm)

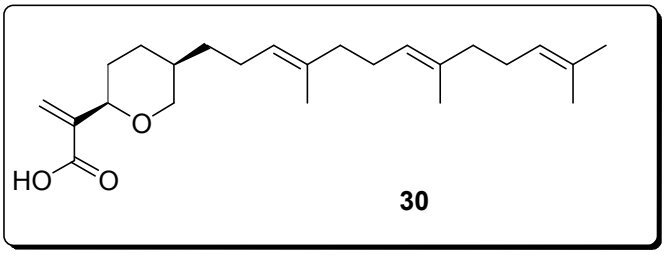

135.2635
135.0206
131.3170
124.4412
124.3046
78.4502
71.0431
61.5413
39.8208
37.7717
32.9753
30.2431
27.3592
27.1771
26.8583
26.6913
25.8869
25.7806
17.7815
16.1119
135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15
(ppm)


O
O
Crude

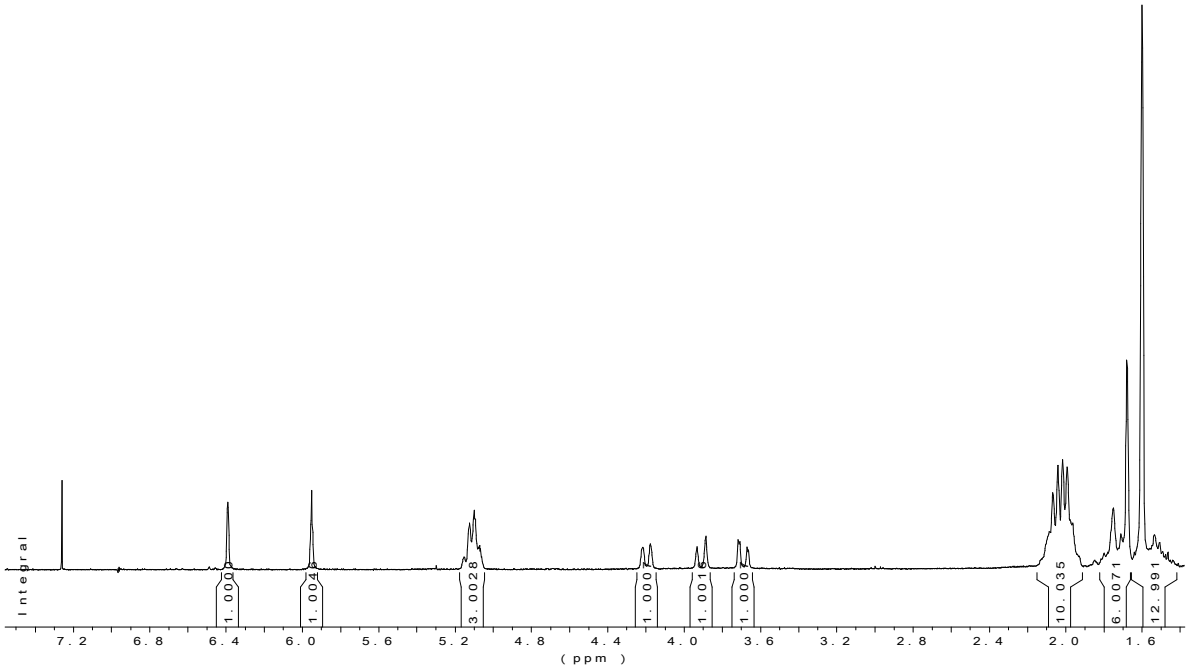

Integral
1.00
3.00
0.99
1.00
1.00
1.04
10.06
6.08
10.04
2.99
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5
(ppm)

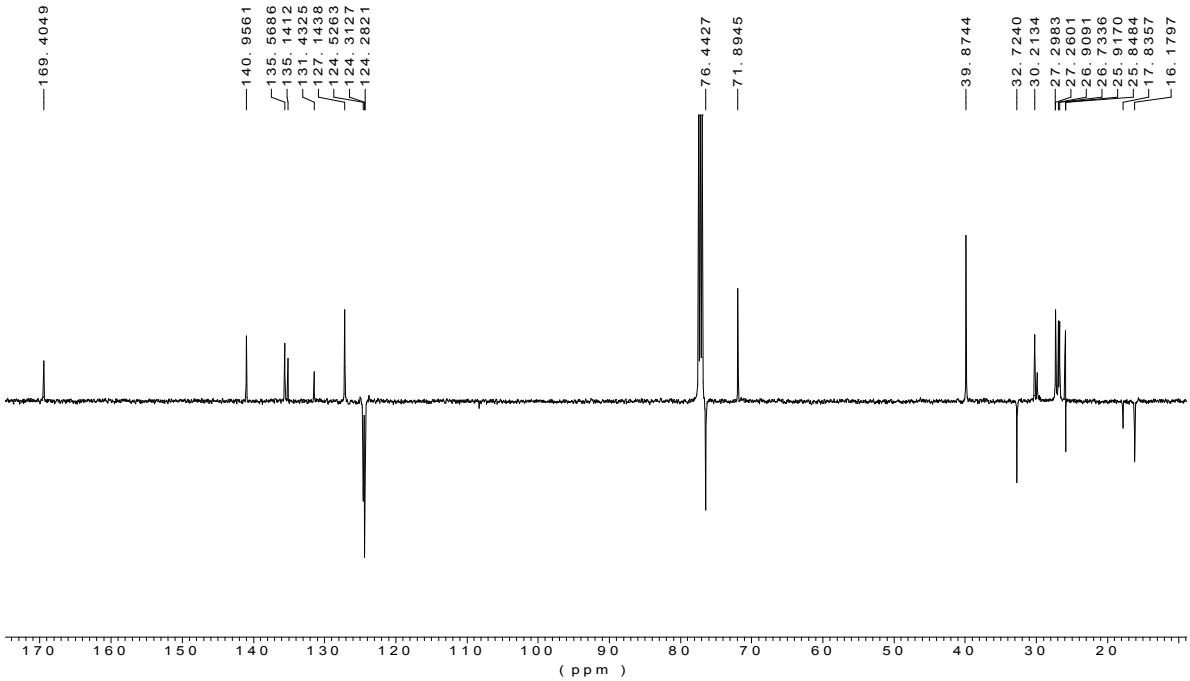

O
O
Crude

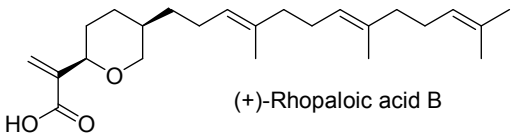

Integral
1.000
1.040
0.998
4.1709
0.995
0.999
1.004
1.927
15.814
31.688
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0
(ppm)


HO
O
O

30


Integral
1.000
1.004
3.002
1.000
1.001
1.000
10.035
6.007
12.991
7.2
6.8
6.4
6.0
5.6
5.2
4.8
4.4
4.0
3.6
3.2
2.8
2.4
2.0
1.6
(ppm)


169.4049
140.9561
135.5686
135.1412
131.4325
127.1438
124.5263
124.3127
124.2821
76.4427
71.8945
39.8744
32.7240
30.2134
27.2983
27.2601
26.9091
26.7336
25.9170
25.8484
17.8357
16.1797
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
(ppm)



(+)-Rhopaloic acid B

^{1}H Literature	^{1}H	^{13}C Literature	^{13}C
6.39 , br s, 1H	6.39 , br s, 1H	169.9	169.4
5.94 , br s, 1H	5.95 , t, 1.0 Hz 1H	141.0	141.0
5.10 m, 3H	5.17-5.04 m, 3H	135.4	135.6
4.20, d, 10.1 Hz, 1H	4.21, d, 10.1 Hz, 1H	135.0	135.1
3.91, d, 11.0 Hz, 1H	3.90, d, 11.5 Hz, 1H	131.2	131.4
3.69, dd, 11.0, 2.7 Hz, 1H	3.69, dd, 11.5, 2.0 Hz, 1H	127.0	127.1
2.07, m, 4H		124.4 (2C)	124.5
2.03, m, 2H	2.14-1.91, m, 10H	124.2	124.3 (2C)
1.99, m, 4H		76.1	76.4
1.75, m, 2H		71.7	71.9
1.73, m, 1H	1.82-1.65, m 3H	39.7 (2C)	39.9 (2C)
1.68, s, 3H	1.68, s, 3H	32.6	32.7
1.64, m, 1H	1.64-1.40, m, 4H	30.1	30.2
1.60 ,s, 9H	1.60 ,s, 9H	27.2 (2C)	27.3 (2C)
1.55, m, 2H		26.8	26.9
1.49, m, 1H		26.6	26.7
		25.8	25.9
		25.7	25.8
		17.7	17.8
		16.0 (2C)	16.2 (2C)

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