Exploration of ω-Side Chain Addition Strategies for the Syntheses of Isocarbacyclin and 15*R*-16-(*m*-tolyl)-17,18,19,20-tetranorisocarbacyclin Supporting Information

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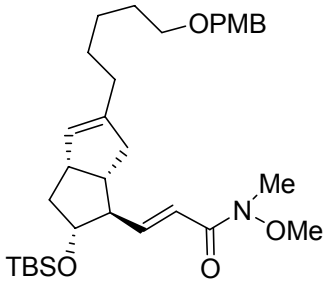
General Experimental

All reactions were carried out in oven or flame-dried glassware under an argon atmosphere, unless otherwise stated. Anhydrous tetrahydrofuran (THF) and diethyl ether (Et_2O) were freshly distilled from sodium / benzophenone under argon. All other solvents were HPLC grade. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) with E. Merck silica gel 60-F254 plates. Flash column chromatography was performed with Merck silica gel (0.04-0.63 μm, 240-400 mesh) under high pressure. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise stated. NMR spectra were recorded on either a Bruker Avance DPX 400 MHz or 600 MHz spectrometer. Unless otherwise stated, all NMR spectra were measured in $CDCl_3$ solutions and referenced to the residual $CHCl_3$ signal (^1H, $\delta = 7.26$; ^{13}C, $\delta = 77.0$). All ^1H and ^{13}C NMR shifts are given in ppm (for ^1H NMR: s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet; br s = broad signal; for ^{13}C NMR: p = primary, s = secondary, t = tertiary, q = quaternary). Coupling constants *J* are given in Hz; assignments of proton resonances were confirmed, when possible, by selective homonuclear decoupling experiments or by correlated spectroscopy.

(*E*)-3-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)-*N*-methoxy-*N*-methylacrylamide, 7



7

A suspension of NaH (0.043 g, 1.08 mmol) in anhydrous THF (5 mL) was stirred for 30 minutes at 0 °C. Diethyl 2-(methoxy(methyl)amino)-2-oxoethylphosphonate (0.258 g, 1.08 mmol) in anhydrous THF (4 mL) was added dropwise and the solution was stirred for a further 45 minutes at 0 °C. (1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalene-1-carbaldehyde, **9** (0.300 g, 0.635 mmol) in anhydrous THF (5 mL) was then added and allowed to stir overnight warming to ambient temperature. The reaction was quenched by the addition of saturated aq. NH_4Cl solution (10 mL) and was extracted with Et2O (5 x 10 mL) Combined organic layers were washed with H_2O (1 x 10 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* Crude product was purified by flash column chromatography using using hexanes:ethyl (3:1) as the mobile phase to afford (*E*)-3-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)-*N*-methoxy-*N*-methylacrylamide, **7**, as a pale yellow oil (0.307 g, 87 %).

$C_{32}H_{51}NO_5Si$ **M_r** = 557.84

^{1}H NMR (400 MHz, $CDCl_3$) 7.25 (2H, d, *J* 8.3, Ar*H*), 6.87 (2H, d, *J* 8.8, Ar*H*), 6.45 (1H, dd, *J* 15.1, 9.2, vinylic in chain), 6.45 (1H, d, J 15.1, vinylic in chain), 5.25 (1H, s, vinylic in ring), 4.42 (2H, s, CH_2Ar), 3.87 (1H, ddd, *J* 9.3, 9.3, 7.1, C*H*OTBS), 3.80 (3H, s, ArOCH_3), 3.68 (3H, s, NOCH_3), 3.43 (2H, dd, *J* 6.8, 6.6, alkyl CH_2), 3.24 (3H, s, NCH_3), 3.00 (1H, d, *J* 7.6, C*H*CH$_2$CHOTBS), 2.47-2.35 (2H, m, (2H, m, C*H*HC*H*C*H*CHOTBS), 2.29-2.16 (2H, m, C*H*HCHOTBS, C*H*CHOTBS), 2.05-1.92 (3H, m, alkyl CH_2, CH*H*CHCHCHOTBS), 1.60 (2H, dddd, *J* 7.3, 7.1, 6.8, 6.8, alkyl CH_2), 1.48-1.23 (5H, m, 2 x alkyl CH2, CH*H*CHOTBS), 0.84 (9H, s, SiC(CH_3)$_3$), 0.01 (3H, s, SiCH_3), 0.00 (3H, s, SiCH_3)

^{13}C-NMR (100 MHz, $CDCl_3$) 166.8 (q), 159.1 (q), 149.2 (t), 141.7 (q), 130.8 (q), 129.2 (t), 127.7 (t), 119.6 (t), 113.7 (t), 77.8 (t), 72.5 (s), 70.1 (s), 61.6 (p), 58.1 (t), 55.2 (p), 45.7 (t), 43.5 (t), 41.0 (s), 39.9 (s), 32.4 (p), 30.9 (s), 29.6 (s), 27.6 (s), 26.1 (s), 25.8 (p), 18.0 (q), -4.6 (p), -4.6 (p)

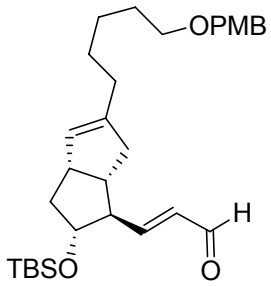
IR (Si, Film) $\tilde{\upsilon}_{max}$ = 2932, 2856, 1665, 1636, 1614, 1586, 1513, 1463, 1443, 1383, 1037, 863

HRMS (200 °C 70 eV): *m/z* calcd for $C_{28}O_{42}O_5NSi$ (M+ - C_4H_9): 500.2582; found 500.2583

Optical Rotation: $[\alpha]_D^{20} = -2.7$ (c = 0.93, $CHCl_3$)

***R*$_f$** (3:1 Hex/EtOAc) = 0.23

(*E*)-3-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)acrylaldehyde, 8



8

A solution of (*E*)-3-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)-*N*-methoxy-*N*-methylacrylamide, **7**, in anhydrous THF (5 mL) was stirred at -78 °C for 40 minutes. DIBAL-H (1.5 M, toluene, 0.86 mL, 3 eq.) was added dropwise and stirred at this temperature for 1.5 hours. The reaction was quenched by the addition of saturated aq. NH_4Cl solution (10 mL) where a Na/K-tartrate solution (20 mL) was added and allowed to warm to ambient temperature overnight. Extraction was carried out with CH_2Cl_2 (5 x 10 mL) and the combined organic layers were washed with H_2O (1 x 15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* Crude product was purified by flash column chromatography using using hexanes:ethyl (5:1) as the mobile phase to afford (*E*)-3-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)acrylaldehyde, **8**, as a pale yellow oil (0.213 g, 100 %).

$C_{30}H_{46}O_4Si$ **M_r** = 498.77

^{1}H NMR (400 MHz, $CDCl_3$) 9.53 (1H, d, *J* 7.8, C*H*O), 7.26 (2H, d, *J* 8.6, Ar*H*), 6.87 (2H, d, *J* 8.6, Ar*H*), 6.77 (1H, dd, *J* 15.7, 7.8, vinylic in chain), 6.17 (1H, ddd, *J* 15.7, 7.8, 0.7, vinylic in chain), 5.27 (1H, d, *J* 1.3, vinylic in ring), 4.43 (2H, s, CH_2Ar), 3.87 (1H, ddd, *J* 9.3, 9.3, 7.1, C*H*OTBS), 3.80 (3H, s, OCH_3), 3.43 (2H, dd, *J* 6.8, 6.6, alkyl CH_2), 3.09-2.99 (1H, m, C*H*CH_2CHOTBS), 2.51-2.31 (3H, m, C*H*HC*H*C*H*CHOTBS), 2.26 (1H, ddd, *J* 12.3, 8.8, 7.0, C*H*HCHOTBS), 2.05-1.93 (3H, m, alkyl CH_2, CH*H*CHCHCHOTBS), 1.61 (2H, dddd, *J* 7.3, 7.1, 6.8, 6.8, alkyl CH_2), 1.49-1.23 (5H, m, 2 x alkyl CH_2, CH*H*CHOTBS), 0.85 (9H, s, SiC(CH_3)$_3$), 0.02 (3H, s, SiCH_3), 0.00 (3H, s, SiCH_3)

^{13}C-NMR (100 MHz, $CDCl_3$) 193.9 (t), 160.0 (t), 159.1 (q), 141.8 (q), 133.5 (t), 130.8 (q), 129.2 (t), 127.5 (t), 113.8 (t), 77.5 (t), 72.5 (s), 70.1 (s), 58.1 (t), 55.3 (p), 45.8 (t), 43.1 (t), 41.0 (s), 39.9 (s), 30.9 (s), 29.6 (s), 27.6 (s), 26.1 (s), 25.7 (p), 18.0 (q), -4.4 (p), -4.7 (p)

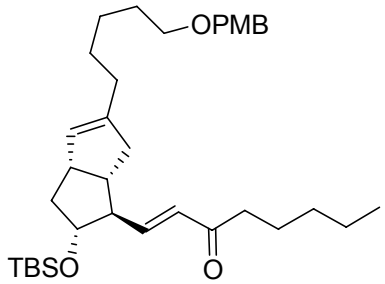
IR (Si, Film) $\tilde{\upsilon}_{max}$ = 2928, 2856, 1691, 1653, 1616, 1559, 1513, 1457, 1362, 1249, 1113, 863

HRMS (150 °C 70 eV): *m/z* calcd for $C_{30}H_{46}O_4Si$: 498.3165; found 498.3151

Optical Rotation: $[\alpha]_D^{20}$ = + 13.5 (c = 0.24, $CHCl_3$)

***R*$_f$** (5:1 Hex/EtOAc) = 0.35

(*E*)-1-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)oct-1-en-3-one, 13



13

To the solution of (*E*)-3-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)-*N*-methoxy-*N*-

methylacrylamide, **7**, (0.416 g, 0.746 mmol) in anhydrous THF (25 mL) at -78 °C was added pentyl magnesium bromide (2.0 M, 1.12 mL, 2.24 mmol). The solution was stirred at -78°C for 1 hour and allowed to warm to 0 °C. H_2O (10 mL) was added and extracted with CH_2Cl_2 (5 x 10 mL) and the combined organic layers were washed with H_2O (1 x 15 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Crude product was purified by flash column chromatography using using hexanes:ethyl (10:1) as the mobile phase to afford (*E*)-1-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)oct-1-en-3-one, **13**, as a clear oil (0.398 g, 94 %).

$C_{35}H_{56}O_4Si$ **M_r** = 568.90

^{1}H NMR (400 MHz, $CDCl_3$) 7.26 (2H, d, *J* 8.8, Ar*H*), 6.87 (2H, d, *J* 8.6, Ar*H*), 6.73 (1H, dd *J* 15.8, 8.2, vinylic in chain), 6.14 (1H, dd, *J* 15.8, 1.0, vinylic in chain), 5.25 (1H, d *J* 1.3, vinylic in ring), 4.43 (2H, s, C*H*$_2$Ar), 3.84 (1H, ddd, *J* 9.6, 9.6, 7.1, C*H*OTBS), 3.80 (3H, s, OC*H*$_3$), 3.43 (2H, dd, *J* 6.8, 6.6, alkyl C*H*$_2$), 3.01 (1H, ddd, *J* 8.8, 8.3, 7.8, C*H*CH$_2$CHOTBS), 2.52 (2H, dd, *J* 7.6, 7.3, O=CC*H*$_2$), 2.48 (2H, m, C*H*HC*H*CHCHOTBS), 2.24 (1H, ddd, *J* 12.2, 8.8, 7.0, C*H*HCHOTBS), 2.16 (1H, ddd, *J* 9.3, 8.8, 8.6, TBSOCHC*H*), 2.05-1.91 (3H, m, CH*H*CHCHCHOTBS, alkyl C*H*$_2$), 1.67-1.55 (4H, m, 2 x C*H*$_2$), 1.48-1.22 (9H, m, CH*H*CHOTBS, 4 x alkyl C*H*$_2$), 0.89 (3H, dd, *J* 7.1, 6.8, C*H*$_3$), 0.85 (9H, s, SiC(C*H*$_3$)$_3$), 0.01 (3H, s, SiC*H*$_3$), 0.00 (3H, s, SiC*H*$_3$)

^{13}C-NMR (100 MHz, $CDCl_3$) 200.6 (q), 159.1 (q), 148.4 (t), 141.8 (q), 130.9 (t), 130.8 (q), 129.2 (t), 127.6 (t), 113.7 (t), 77.5 (t), 72.5 (s), 70.1 (s), 57.8 (t), 55.3 (p), 45.7 (t), 43.1 (t), 40.9 (s), 40.1 (s), 39.9 (s), 31.5 (s), 30.9 (s), 29.6 (s), 27.6 (s), 26.1 (s), 25.7 (p), 24.0 (s), 22.5 (s), 18.0 (q), 13.9 (p), -4.5 (p), -4.7 (p)

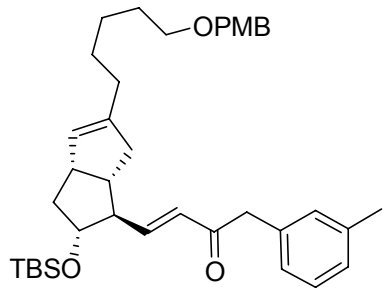
IR (Si, Film) $\tilde{\upsilon}_{max}$ = 2929, 2857, 1735, 1696, 1672, 1586, 1560, 1513, 1463, 1361, 1248, 980

HRMS (150 °C 70 eV): *m/z* calcd for $C_{31}O_{47}O_4Si$ (M+ - C_4H_9): 511.3244; found 511.3233

Optical Rotation: $[\alpha]_D^{20}$ = + 1.3 (c = 0.69, $CHCl_3$)

***R*$_f$** (5:1 Hex/EtOAc) = 0.34

(*E*)-4-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)-1-*m*-tolylbut-3-en-2-one, 14



14

To the solution of (*E*)-3-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)-*N*-methoxy-*N*-methylacrylamide, **7**, (0.100 g, 0.180 mmol) in anhydrous THF (2 mL) at -78 °C was added (3-methylbenzyl)magnesium bromide (0.74 M, 0.730 mL, 0.54 mmol). The solution was stirred at -78°C for 1 hour and allowed to warm to 0 °C. H_2O (2 mL) was added and extracted with CH_2Cl_2 (5 x 2 mL) and the combined organic layers were washed with H_2O (1 x 2 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Crude product was purified by flash column chromatography using using hexanes:ethyl (10:1) as the mobile phase to afford (*E*)-4-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)-1-*m*-tolylbut-3-en-2-one, **14**, as a clear oil (0.098 g, 90 %).

$C_{38}H_{54}O_4Si$ **M_r** = 602.92

^{1}H NMR (400 MHz, $CDCl_3$) 7.26 (2H, d, *J* 8.6, Ar*H*), 7.20 (1H, t, J 7.6, Ar*H*), 7.05 (1H, d, *J* 7.6, Ar*H*), 7.03-6.97 (2H, m, Ar*H*), 6.88 (2H, d, *J* 8.8, Ar*H*), 6.82 (1H, dd *J* 15.7, 8.6, vinylic in chain), 6.20 (1H, dd, *J* 15.7, 0.8, vinylic in chain), 5.24 (1H, s, vinylic in ring), 4.43 (2H, s, CH_2Ar), 3.82 (1H, overlapping ddd, *J* 9.6, 9.6, 7.1, C*H*OTBS), 3.80 (3H, s, OCH_3), 3.78 (2H, bs, O=CCH_2), 3.44 (2H, dd, *J* 6.8, 6.6, alkyl CH_2), 3.05-2.95 (1H, m, C*H*CH$_2$CHOTBS), 2.46-2.28 (2H, C*H*HC*H*CHCHOTBS), 2.33 (3H, s, ArCH_3), 2.22 (1H, ddd, *J* 12.3, 8.7, 7.1, C*H*HCHOTBS), 2.14 (1H, ddd, *J* 9.3, 9.1, 9.1, TBSOCHC*H*), 1.99 (2H, dd, *J* 7.3, 6.6, alkyl CH_2) 1.91 (1H, d, *J* 15.2, CH*H*CHCHCHOTBS), 1.60 (2H, dddd, 7.3, 7.1, 6.8, 6.8, alkyl CH_2), 1.47-1.16 (5H, m, 2 x alkyl CH_2, CH*H*CHOTBS), 0.82 (9H, s, SiC(CH_3)$_3$), -0.02 (3H, s, SiCH_3), -0.06 (3H, s, SiCH_3)

^{13}C-NMR (100 MHz, $CDCl_3$) 197.3 (q), 159.1 (q), 149.6 (t), 141.8 (q), 138.2 (q), 134.4 (q), 130.8 (q), 130.2 (t), 130.0 (t), 129.2 (t), 128.5 (t), 127.6 (t), 127.6 (t), 126.5 (t), 113.7 (t), 77.5 (t), 72.5 (s), 70.1 (s), 57.9 (t), 55.3 (p), 47.6 (s), 45.8 (t), 43.2 (t), 41.0 (s), 39.9 (s), 30.9 (s), 29.7 (s), 27.6 (s), 26.1 (s), 25.7 (p), 21.3 (p), 18.0 (q), -4.6 (p), -4.8 (p)

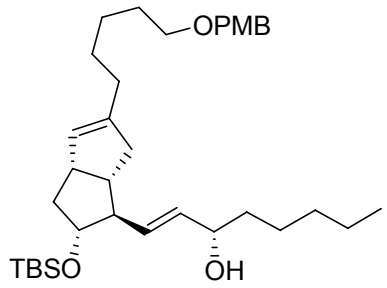
IR (Si, Film) $\tilde{\upsilon}_{max}$ = 2928, 2856, 1699, 1607, 1513, 1463, 1361, 1257, 1169, 1113, 1035, 836

HRMS (170 °C 70 eV): *m/z* calcd for $C_{38}H_{54}O_4Si$: 602.3791; found 602.3777

Optical Rotation: $[\alpha]_D^{20}$ = + 9.6 (c = 0.19, $CHCl_3$)

***R*$_f$** (3:1 Hex/EtOAc) = 0.44

(*S*,*E*)-1-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)oct-1-en-3-ol, 21



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Method 1: (*R*)-CBS Reduction

(*E*)-1-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)oct-1-en-3-one, **13** (0.199 g, 0.350 mmol) and (*R*)-2-methyl-CBS-oxazoborilidine* (1.0 M in toluene, 0.18 mL, 0.180 mmol) in toluene (3 mL) was stirred at -78 °C for 30 minutes. Catecholborane (1.0 M in toluene, 1.4 mL, 1.40 mmol) was added dropwise, via syringe pump, over 6 hours. The reaction was stirred at -78 °C for 14 h at which time methanol (3 mL) was added to quench the remaining hydride. The reaction was warmed to ambient temperature, extracted with Et_2O (5 x 4 mL) and combined organic layers were washed with NaOH (1 M, 5 mL), and brine (5 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* Crude product was purified by flash column chromatography using using hexanes:ethyl (10:1) as the mobile phase to afford a 9:1 mixture of (*S*,*E*)-1-

((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)oct-1-en-3-ol and (*R*,*E*)-1-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)oct-1-en-3-ol, respectively, as a clear oil (0.191 g, 96 %).

* Same procedure was followed, when using the (*R*)-2-*n*-butyl-CBS-oxazoborilidine as catalyst to afford a 10:1 mixture of (*S*,*E*)-1-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)oct-1-en-3-ol and (*R*,*E*)-1-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)oct-1-en-3-ol, respectively (92%).

Method 2: (*S*)-BINAL-H Reduction

A dry Schlenk flask equipped equipped with a rubber septum was flame-dried and placed under an argon atmosphere. A solution of $LiAlH_4$ (1M in THF, 0.704 mL, 0.704 mmol, 4 equiv) was added via syringe at room temperature, then a solution of absolute EtOH (0.032 g, 0.704 mmol, 4 equiv) in dry THF (0.5 mL) was added dropwise via cannula over a period of *ca*. 10 min with stirring. Subsequently a THF solution of *bis*(*S*)-naphthol (0.202 g, 0.704 mmol, 4 equiv in 1.5 mL of dry THF) was added dropwise, and the resulting mixture was stirred for an additional 30 min at rt and used for the asymmetric reduction. The (*S*)-BINAL-H reagent thus formed in THF was a homogeneous, milky mixture, which did not separate any precipitate; this mixture was cooled to –100°C and a solution of (*E*)-1-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)oct-1-en-3-one, **13**, (0.100 g, 0.176 mmol, 1.0 equiv) in dry THF (2 mL) was added dropwise via cannula. After stirring for 2 h at the same temperature, the asymmetric reduction was completed. Excess BINAL-H was destroyed by addition of methanol (0.2 mL) at –78°C and the mixture, followed by $KHSO_4$ (5% in water, 0.5 mL) and was warmed to r.t. Et_2O (3 mL) were added; extracted with Et_2O (5 x 1 mL) where combined organic layers were washed with water (1 x 1 mL) and brine (1 x 2 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* Crude product was purified by flash column chromatography using using hexanes:ethyl (10:1) as the mobile phase to afford (*S*,*E*)-1-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)oct-1-en-3-ol as a clear oil (0.91 g, 91 %).

Method 3: Seebach's Alkylation Method

Catalysts **17**, **18** and **19** were prepared, as described by J. L. von der Bussche-Hünnefeld, D. Seebach, *Tetrahedron*, **1992**, *48*, 5719.

A 1.0 M zinc chloride solution in Et_2O (20 mL, 20.00 mmol) was diluted with Et_2O (10 mL) and pentyl magnesium bromide (2.0 M in Et_2O, 19.1 mL, 40 mmol) was then added dropwise. The resulting suspension was stirred at room temperature for 2 h. then treated with 3.6 mL of 1,4-dioxane (freshly distilled from sodium metal) and stirred for an additional 45 minutes. Subsequent filtration under an argon atmosphere (Schlenk filter) yielded a clear 0.41 M solution of dipentyl zinc reagent **20**. An aliquot of the dipentyl zinc solution (0.49 mL, 0.20 mmol) was then added to a previously prepared solution of 0.02 g of spirotitanate **17** (0.02 mmol) (or 2.0 mmol of **18** or **19**), followed by $Ti(OCHMe_2)_4$ (0.031 mL, 0.12 mmol) in toluene (0.5 mL). The mixture was stirred at -78 °C for 1 h., where a solution of (*E*)-3-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)acrylaldehyde, **8**, (0.05 g, 0.10 mmol) in toluene (0.5 mL) was added dropwise, and the reaction temperature raised to -30 °C. The reaction was kept at this temperature for a further 14 hours where it was quenched by the addition of a saturated solution of NH_4Cl (1 mL) and Et_2O (3 mL), extracted with Et_2O (5 x 1 mL) where combined organic layers were washed with water (1 x 1 mL) and brine (1 x 2 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo.* Pentane was added to the resulting oil to recover the diol ligand. Crude product was purified by flash column chromatography using using hexanes:ethyl (10:1) as the mobile phase to afford (*S*,*E*)-1-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)oct-1-en-3-ol, **21** as a clear oil (0.047 g, 82 %).

$C_{35}H_{58}O_4Si$ **M_r** = 570.92

^{1}H NMR (400 MHz, $CDCl_3$) 7.26 (2H, d, *J* 8.6, Ar*H*), 6.88 (2H, d, *J* 8.6, Ar*H*), 5.59-5.48 (1H, overlapping dd, *J* 15.4, 4.3, *H*C=CH), 5.59-5.48 (1H, overlapping dd, *J* 15.4, 5.3, HC=C*H*), 5.24 (1H, d, *J* 1.3, vinylic in ring), 4.43 (2H, s, OCH_2Ar), 4.10-4.03 (1H, m, HC=CHC*H*OH), 3.80 (3H, s, ArOCH_3), 3.73 (1H, ddd, *J* 9.8, 9.5, 6.8, C*H*OTBS), 3.43 (2H, dd, *J* 6.8, 6.6, , alkyl CH_2), 2.94 (1H, dddd, *J* 8.6, 8.6, 8.5, 1.8, C*H*CH_2CHOTBS), 2.40 (1H, dd, *J* 16.6, 9.0, HC=CC*H*H), 2.25 (1H, dddd, *J* 9.5, 9.5, 8.9, 1.8, , *H*CHCHC=CH), 2.18 (1H,

ddd, *J* 12.2, 8.8, 7.0, C*H*HCHOTBS), 2.04-1.93 (4H, m, *H*CHC=CH, HC=CCH*H*, alkyl CH_2), 1.61 (2H, dddd, *J* 7.3, 7.1, 6.8, 6.8, alkyl CH_2), 1.59-1.57 (1H, m, O*H*), 1.56-1.24 (15H, m, 7 x alkyl CH_2, CH*H*CHOTBS), 0.93-0.84 (3H, m, alkyl CH_3), 0.86 (9H, s, SiC(CH_3)$_3$), 0.02 (6H, s, Si(CH_3)$_2$)

^{13}C-NMR (100 MHz, $CDCl_3$) 159.1 (q), 141.8 (q), 134.1 (t), 133.1 (t), 130.8 (q), 129.2 (t), 127.8 (t), 113.8 (t), 77.8 (t), 73.1 (t), 72.5 (s), 70.1 (s), 57.3 (t), 55.3 (p), 45.4 (t), 43.2 (t), 40.7 (s), 39.9 (s), 37.3 (s), 31.8 (s), 31.0 (s), 29.6 (s), 27.6 (s), 26.1 (s), 25.9 (p), 25.3 (p), 22.6 (s), 18.1 (q), 14.0 (p), -4.4 (p), -4.6 (p)

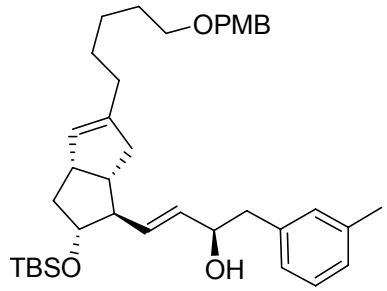
IR (Si, Film) $\tilde{\upsilon}_{max}$ = 3437, 2930, 2857, 1613, 1587, 1513, 1463, 1360, 1302, 1249, 1172

HRMS (140 °C 50 eV): *m/z* calcd for $C_{35}H_{58}O_4Si$: 570.4104; found 570.4394

Optical Rotation: $[\alpha]_D^{20} = -3.3$ (c = 0.48, acetone)

***R*$_f$** (3:1 Hex/EtOAc) = 0.37

(*R*,*E*)-4-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)-1-*m*-tolylbut-3-en-2-ol



Method 1: (*S*)-CBS Reduction

(*E*)-4-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)-1-*m*-tolylbut-3-en-2-one, **14** (0.045 g, 0.075 mmol) and (*S*)-2-methyl-CBS-oxazoborilidine* (1.0 M in toluene, 0.09 mL, 0.090 mmol) in toluene (2 mL) was stirred at -78 °C for 30 minutes. Catecholborane (1.0 M in toluene, 0.18 mL, 0.180 mmol) was added dropwise, via syringe pump, over 12 hours. The reaction was stirred at -78 °C for 14 h at which time methanol (2 mL) was added to quench the remaining hydride.

The reaction was warmed to ambient temperature, extracted with Et_2O (5 x 2 mL) and combined organic layers were washed with NaOH (1 M, 2 mL), and brine (2 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Crude product was purified by flash column chromatography using using hexanes:ethyl (3:1) as the mobile phase to afford a 6:1 mixture of (*R*,*E*)-4-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)-1-*m*-tolylbut-3-en-2-ol and (*S*,*E*)-4-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)-1-*m*-tolylbut-3-en-2-ol, respectively, as a clear oil (0.043 g, 95 %).

* Same procedure was followed, when using the (*S*)-2-*n*-butyl-CBS-oxazoborilidine as catalyst to afford a 7:1 mixture of (*R*,*E*)-4-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)-1-*m*-tolylbut-3-en-2-ol and (*S*,*E*)-4-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)-1-*m*-tolylbut-3-en-2-ol, respectively (86%).

Method 2: (*R*)-BINAL-H Reduction

A dry Schlenk flask equipped equipped with a rubber septum was flame-dried and placed under an argon atmosphere. A solution of $LiAlH_4$ (1M in THF, 0.300 mL, 0.300 mmol, 4 equiv) was added via syringe at room temperature, then a solution of absolute EtOH (0.014 g, 0.300 mmol, 4 equiv) in dry THF (0.3 mL) was added dropwise via cannula over a period of *ca*. 10 min with stirring. Subsequently a THF solution of *bis*(*R*)-naphthol (0.086 g, 0.300 mmol, 4 equiv in 1 mL of dry THF) was added dropwise, and the resulting mixture was stirred for an additional 30 min at rt and used for the asymmetric reduction. The (*R*)-BINAL-H reagent formed in THF was a homogeneous, milky mixture, which did not separate any precipitate; this mixture was cooled to –100°C and a solution of (*E*)-4-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)-1-*m*-tolylbut-3-en-2-one, **14**, (0.045 g, 0.075 mmol, 1.0 equiv) in dry THF (2 mL) was added dropwise via cannula. After stirring for 2 h at the same temperature, the asymmetric reduction was completed. Excess BINAL-H was destroyed by addition of methanol (0.2 mL) at –78°C and the mixture, followed by $KHSO_4$ (5% in water, 0.5 mL) and was warmed to r.t. Et_2O (2 mL) were added; extracted with Et_20 (5 x 1 mL) where combined

organic layers were washed with water (1 x 1 mL) and brine (1 x 2 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Crude product was purified by flash column chromatography using using hexanes:ethyl (3:1) as the mobile phase to afford an 8:1 mixture of (*R*,*E*)-4-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)-1-*m*-tolylbut-3-en-2-ol and (*S*,*E*)-4-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)-1-*m*-tolylbut-3-en-2-ol, respectively, as a clear oil (0.041 g, 90 %).

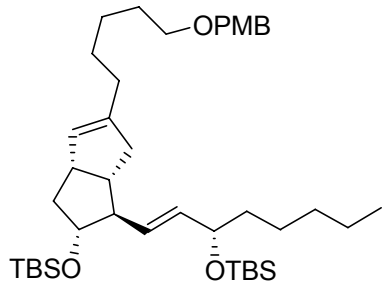
$C_{38}H_{56}O_4Si$ **M_r** = 604.93

^{1}H NMR (400 MHz, $CDCl_3$) 7.26 (2H, d, *J* 8.6, Ar*H*), 7.18 (1H, dd, *J* 7.6, 7.4, Ar*H*), 7.08-7.01 (3H, m, Ar*H*), 6.88 (2H, d, *J* 8.6, Ar*H*), 5.65-5.54 (1H, overlapping dd, *J* 15.3, *H*C=CH), 5.65-5.54 (1H, overlapping dd, *J* 15.3, HC=C*H*), 5.24 (1H, d, *J* 1.3, vinylic in ring), 4.43 (2H, s, OCH_2Ar), 4.37-4.30 (1H, m, HC=CHC*H*OH), 3.80 (3H, s, ArOCH_3), 3.74 (1H, ddd, *J* 9.6, 9.6, 7.1, C*H*OTBS), 3.44 (2H, dd, *J* 6.8, 6.8, alkyl CH_2), 2.98-2.90 (1H, m, C*H*CH_2CHOTBS), 2.85 (1H, ddd, *J* 13.3, 13.3, 4.4, CHOHC*H*HArCH_3), 2.71 (1H, dd, *J* 13.3, 8.3, CHOHC*H*HArCH_3), 2.47-2.36 (1H, m, HC=CC*H*H), 2.34m(3H, s, ArCH_3), 2.29 (1H, ddd, *J* 8.8, 8.8, 8.7, *H*CHCHC=CH), 2.18 (1H, ddd, *J* 12.3, 8.8, 7.0, C*H*HCHOTBS), 2.06-1.93 (4H, m, *H*CHC=CH, HC=CCH*H*, alkyl CH_2), 1.61 (2H, dddd, *J* 7.3, 7.1, 6.8, 6.6, alkyl CH_2), 1.47-1.23 (8H, m, 3 x alkyl CH_2, CH*H*CHOTBS, O*H*), 0.86 (9H, s, SiC(CH_3)$_3$), 0.02 (6H, s, Si(CH_3)$_2$)

HRMS (150 °C 70 eV): *m/z* calcd for $C_{38}H_{56}O_4Si$: 604.3948; found 604.3957

***R*$_f$** (3:1 Hex/EtOAc) = 0.38

tert-butyl((_S_,_E_)-1-((1_R_,2_R_,3_aS_,6_aS_)-2-(_tert_-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3_a_,6,6_a_-hexahydropentalen-1-yl)oct-1-en-3-yloxy)dimethylsilane, 15



15

$C_{41}H_{72}O_4Si_2$ **M_r** = 685.18

To a solution of (*S*,*E*)-1-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)oct-1-en-3-ol (0.200 g, 0.350 mmol) and imizadole (0.060 g, 0.875 mmol) in anhydrous DMF (2 mL), TBSCl (0.63 g, 0.420 mmol) in anhydrous DMF (1 mL) was dropwise added and stirred for 14 h. H_2O (3 mL) and Et_2O (5 mL) were added, extracted with Et_2O (5 x 3 mL). Combined organic layers were washed with H_2O (1 x 2 mL), brine (1 x 2 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Crude product was purified by flash column chromatography using using hexanes:ethyl acetate (5:1) as the mobile phase to afford *tert*-butyl((*S*,*E*)-1-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)oct-1-en-3-yloxy)dimethylsilane, **15**, as a pale yellow oil (0.239 g, 100 %).

^{1}H NMR (600 MHz, $CDCl_3$) 7.26 (2H, d, *J* 8.5, Ar*H*), 6.88 (2H, d, *J* 8.5, Ar*H*), 5.52-5.44 (1H, overlapping dd, *J* 15.4, *H*C=CH), 5.52-5.44 (1H, overlapping dd, *J* 15.4, HC=C*H*), 5.23 (1H, d, *J* 1.5, vinylic in ring), 4.43 (2H, s, OCH_2Ar), 4.06 (1H, ddd, *J* 6.2, 6.2, 4.7, HC=CHC*H*OTBS), 3.80 (3H, s, ArOCH_3), 3.74 (1H, ddd, *J* 9.4, 7.0, 7.0, C*H*OTBS), 3.44 (2H, dd, *J* 6.8, 6.6, alkyl CH_2), 2.97-2.88 (1H, m, C*H*CH_2CHOTBS), 2.39 (1H, dd, *J* 16.3, 8.6, HC=CC*H*H), 2.23 (1H, dddd, *J* 9.4, 9.4, 8.8, 1.7, *H*CHCHC=CH), 2.18 (1H, ddd, *J* 12.2, 8.8, 6.9, C*H*HCHOTBS), 2.04-1.93 (4H, m, *H*CHC=CH, HC=CCH*H*, alkyl CH_2), 1.61 (2H, dddd, *J* 7.5, 7.3, 6.8, 6.8, alkyl CH_2), 1.53-1.38 (4H, m, 2 x alkyl CH_2), 1.38-1.22 (9H, 4 x CH_2, CH*H*CHOTBS), 0.90-0.88 (3H, m, alkyl CH_3), 0.89 (9H, s, SiC(CH_3)$_3$), 0.86 (9H, s, SiC(CH_3)$_3$), 0.04 (3H, s, SiCH_3), 0.02 (9H, s, SiCH_3, Si(CH_3)$_2$)

^{13}C-NMR (100 MHz, $CDCl_3$) 159.6 (q), 141.8 (q), 134.3 (t), 130.9 (t), 130.8 (q), 129.2 (t), 127.8 (t), 113.7 (t), 78.0 (t), 73.3 (t), 72.5 (s), 70.2 (s), 57.0 (t), 55.3 (p), 45.3 (t), 43.3 (t), 40.8 (s), 40.0 (s), 38.7 (s), 31.8 (s), 31.0 (s), 29.6 (s), 27.6 (s), 26.1 (s), 25.9 (p), 25.9 (p), 25.2 (s), 22.6 (s), 18.3 (q), 18.1 (q), 14.0 (p), -4.2 (p), -4.5 (p), -4.6 (p), -4.7 (p)

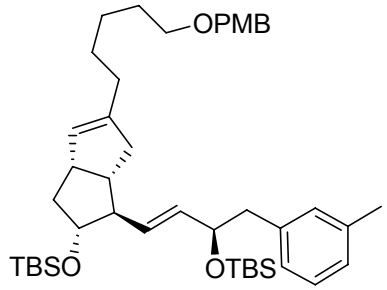
IR (Si, Film) $\tilde{\upsilon}_{max}$ = 2930, 2857, 1608, 1514, 1462, 1255, 1113, 835, 775

HRMS (150 °C 60 eV): *m/z* calcd for $C_{41}H_{72}O_4Si_2$: 684.4969; found 684.4957

Optical Rotation: $[\alpha]_D^{20} = -1.1$ (c = 0.3, acetone)

***R*$_f$** (10:1 Hex/EtOAc) = 0.52

<u>*tert*-butyl((2*R*,3*R*,3*aS*,6*aS*)-3-((*R*,*E*)-3-(*tert*-butyldimethylsilyloxy)-4-*m*-tolylbut-1-enyl)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,4,6*a*-hexahydropentalen-2-yloxy)dimethylsilane, 16</u>



16

$C_{44}H_{70}O_4Si_2$ **M_r** = 719.20

To a solution of (*R*,*E*)-4-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)-1-*m*-tolylbut-3-en-2-ol (0.067 g, 0.111 mmol) and imizadole (0.019 g, 0.278 mmol) in anhydrous DMF (0.5 mL), TBSCl (0.020 g, 0.133 mmol) in anhydrous DMF (0.5 mL) was dropwise added and stirred for 14 h. H_2O (1 mL) and Et_2O (2 mL) were added, extracted with Et_2O (5 x 1 mL). Combined organic layers were washed with H_2O (1 x 1 mL), brine (1 x 1 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Crude product was purified by flash column chromatography using using hexanes:ethyl acetate (5:1) as the mobile phase to afford *tert*-butyl((2*R*,3*R*,3*aS*,6*aS*)-3-((*R*,*E*)-3-(*tert*-butyldimethylsilyloxy)-4-*m*-tolylbut-1-enyl)-5-(5-(4-

methoxybenzyloxy)pentyl)-1,2,3,3*a*,4,6*a*-hexahydropentalen-2-yloxy)dimethylsilane, **16**, as a pale yellow oil (0.077 g, 96 %).

^{1}H NMR (400 MHz, $CDCl_3$) 7.26 (2H, d, *J* 8.6; ArH), 7.14 (1H, dd, *J* 7.6, 7.3, ArH), 7.02-6.95 (3H, m, ArH), 6.88 (2H, d, *J* 8.6, ArH), 5.56-5.42 (1H, overlapping dd, *J* 15.3, 6.3, *H*C=CH), 5.56-5.42 (1H, overlapping dd, *J* 15.3, 6.9, HC=C*H*), 5.23 (1H, d, *J* 1.3, vinylic in ring), 4.43 (2H, s, OCH_2Ar), 4.22 (1H, ddd, *J* 7.6, 5.9, 5.4, HC=CHC*H*OTBS), 3.80 (3H, s, ArOCH_3), 3.72 (1H, ddd, *J* 9.6, 9.5, 6.8, C*H*OTBS), 3.44 (2H, *J* 6.8, 6.6, alkyl CH_2), 3.01-2.88 (1H, m, C*H*CH_2CHOTBS), 2.77-2.64 (1H, overlapping dd, *J* 13.1, 4.5, *H*HCArCH_3), 2.77-2.64 (1H, overlapping dd, *J* 13.0, 7.7, H*H*CArCH_3), 2.39 (1H, dd, *J* 15.7, 8.8, HC=CC*H*H), 2.31 (3H, s, ArCH_3), 2.25 (1H, dddd, *J* 9.1, 8.8, 8.5, 2.0, *H*CHCHC=CH), 2.20-2.14 (1H, m, C*H*HCHOTBS), 2.05-1.91 (4H, m, *H*CHC=CH, HC=CCH*H*, alkyl CH_2), 1.61 (2H, dddd, *J* 7.3, 7.3, 6.8, 6.6, alkyl CH_2), 1.48-1.29 (6H, m, 3 x alkyl CH_2), 1.29-1.22 (1H, m, CH*H*CHOTBS), 0.86 (9H, s, SiC(CH_3)$_3$), 0.80 (9H, s, SiC(CH_3)$_3$), 0.02 (6H, s, Si(CH_3)$_2$), -0.14 (3H, s, SiCH_3), -0.22 (3H, s, SiCH_3)

^{13}C-NMR (100 MHz, $CDCl_3$) 159.1 (q), 141.9 (q), 139.0 (q), 137.3 (q), 134.4 (t), 131.9 (t), 130.9 (t), 130.8 (q), 129.2 (t), 127.8 (t), 127.8 (t), 126.9 (t), 126.6 (t), 113.8 (t), 77.8 (t), 75.3 (t), 72.5 (s), 70.2 (s), 57.3 (t), 55.3 (p), 45.4 (t), 45.3 (s), 43.2 (t), 40.8 (s), 40.1 (s), 31.0 (s), 29.6 (s), 27.6 (s), 26.1 (s), 25.9 (p), 25.8 (p), 21.3 (p), 18.2 (q), 18.1 (q), -4.4 (p), -4.6 (p), -4.6 (p), -5.1 (p)

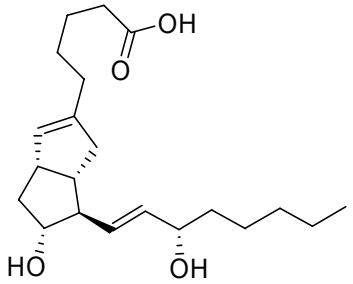
IR (Si, Film) $\tilde{\upsilon}_{max}$ = 2929, 2856, 1714, 1610, 1513, 1462, 1360, 1249, 1112, 835

HRMS (160 °C 70 eV): *m/z* calcd for $C_{44}H_{70}O_4Si_2$: 718.4813; found 718.4801

Optical Rotation: $[\alpha]_D^{20}$ = + 1.4 (c = 0.66, acetone)

R_f (10:1 Hex/EtOAc) = 0.39

5-((3*aS*,5*R*,6*R*,6*aS*)-5-hydroxy-6-((*S*,*E*)-3-hydroxyoct-1-enyl)-1,3*a*,4,5,6,6*a*-hexahydropentalen-2-yl)pentanoic acid (Isocarbacyclin), 2



Isocarbacyclin (2)

$C_{21}H_{34}O_4$ **M_r** = 350.25

^{1}H NMR (600 MHz, $CDCl_3$) 5.56 (1H, dd, *J* 15.3, 7.2, vinylic in chain), 5.50 (1H, dd, *J* 15.3, 8.4, vinylic in chain), 5.29 (1H, d, *J* 1.4, vinylic in ring), 5.23-3.26 (1H, broad s, COO*H*), 4.06 (1H, ddd, *J* 6.9, 6.7, 6.7, HC=CHC(OH)*H*), 3.76 (1H, ddd, *J* 9.6, 7.2, 7.1, *H*COH), 3.00 (1H, ddd, *J* 8.8, 8.6, 2.1, C*H*CH_2CHOH), 2.42-2.25 (5H, m, alkyl CH_2, C*H*CHCHOH, C*H*HCHCH, C*H*HCHOH), 2.06 (2H, dd, *J* 7.2, 6.9, alkyl CH_2), 1.99 (1H, bd, *J* 15.7, CH*H*CHCH), 1.92 (1H, ddd, *J* 9.5, 9.2, 8.8, C*H*CHOH), 1.70-1.54 (3H, m, alkyl CH_2, HC=CHC(OH)HC*H*H), 1.52-1.44 (3H, m, alkyl CH_2, HC=CHC(OH)HCH*H*), 1.40-1.23 (7H, m, 3 x alkyl CH_2, CH*H*CHOH), 0.89 (3H, t, *J* 7.0, CH_3)

^{13}C-NMR (100 MHz, $CDCl_3$) 178.1 (q), 141.1 (q), 135.6 (t), 133.0 (t), 128.9 (t), 77.3 (t), 73.3 (t), 58.0 (t), 45.6 (t), 44.3 (t), 39.5 (s), 39.2 (s), 37.0 (s), 33.7 (s), 31.7 (s), 30.3 (s), 26.9 (s), 25.2 (s), 24.3 (s), 22.6 (s), 14.0 (p)

IR (Si, Film) $\tilde{\upsilon}_{max}$ = 3369, 2927, 2857, 1707, 1653, 1560, 1540, 1507, 1457, 1261, 1088, 970

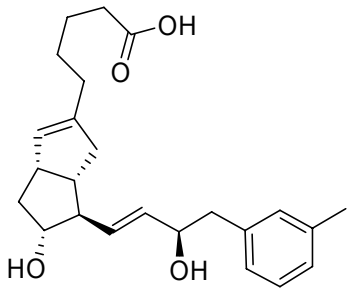
HRMS (170 °C 70 eV): *m/z* calcd for $C_{21}H_{34}O_4$: 350.2457; found 350.2432

Optical Rotation: $[\alpha]_D^{20}$ = + 11.8 (c = 0.46, CH_2Cl_2)

***R*$_f$** (EtOAc/1% AcOH) = 0.33

^{1}H, ^{13}C NMR and optical rotation were concurrent with literature values for Isocarbacyclin. See T. Ishikawa; H. Ishii; K. Shimizu; H. Nakao; J. Urano; T. Kudo; S. Saito, *J. Org. Chem.* **2004**, *69,* 8133.

5-((3*aS*,5*R*,6*R*,6*aS*)-5-hydroxy-6-((*R*,*E*)-3-hydroxy-4-*m*-tolylbut-1-enyl)-1,3*a*,4,5,6,6*a*-hexahydropentalen-2-yl)pentanoic acid (15*R*-TIC), 3



15*R*-TIC (3)

$C_{24}H_{32}O_4$ **M_r** = 384.23

^{1}H NMR (600 MHz, $CDCl_3$) 7.20 (1H, dd, *J* 7.6, 7.5, Ar*H*), 7.05 (1H, d, *J* 7.6, Ar*H*), 7.02 (1H, s, Ar*H*), 7.00 (1H, d, *J* 7.5, Ar*H*), 5.61 (1H, ddd, *J* 15.4, 6.7, 0.7, vinylic in chain), 5.44 (1H, ddd, *J* 15.4, 8.7, 0.7, vinylic in chain), 5.28 (1H, d, *J* 3.3, vinylic in ring), 4.35 (1H, ddd, *J* 6.6, 6.5, 6.4, HC=CHC(OH)*H*), 3.63 (1H, ddd, *J* 9.5, 7.0, 6.9, *H*COH), 2.98 (1H, ddd, *J* 9.0, 8.9, 8.9, C*H*CH_2CHOH), 2.86 (1H, dd, *J* 13.3, 7.2, C*H*HAr), 2.79 (1H, dd, *J* 13.3, 6.3, CH*H*Ar), 2.42-2.34 (2H, m, CH_2COOH), 2.33 (3H, s, CH_3), 2.31-2.27 (2H, m, C*H*CHCHOH, C*H*HCHCH), 2.26 (1H, ddd, *J* 12.5, 8.8, 7.1, C*H*HCHOH), 2.08-1.94 (3H, m, alkyl CH_2, CH*H*CHCH), 1.89 (1H, ddd, *J* 9.4, 9.3, 9.2, C*H*CHOH), 1.70-1.58 (2H, m, alkyl CH_2), 1.54-1.45 (2H, m, alkyl CH_2), 1.39-1.18 (3H, CH*H*CHO*H*, HC=CHCO*H*)

^{13}C-NMR (100 MHz, $CDCl_3$) 178.3 (q), 141.3 (q), 138.2 (q), 137.8 (q), 134.3 (t), 132.9 (t), 130.4 (t), 128.5 (t), 128.3 (t), 127.4 (t), 126.6 (t), 76.9 (s), 73.7 (t), 58.1 (t), 45.6 (t), 44.3 (t), 44.3 (t), 39.5 (s), 39.3 (s), 33.5 (s), 30.5 (s), 27.0 (s), 24.4 (s), 21.4 (p)

IR (Si, Film) $\tilde{\upsilon}_{max}$ = 3401, 2917, 2849, 1701, 1653, 1560, 1540, 1507, 1457, 1261, 1092, 1020

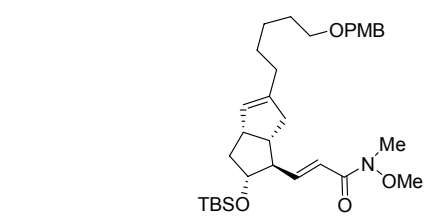
HRMS (170 °C 70 eV): *m/z* calcd for $C_{24}H_{32}O_4$: 384.2301; found 384.2287

***R*$_f$** (EtOAc/1% AcOH) = 0.52

^{1}H, ^{13}C NMR and optical rotation were concurrent with literature values for 15*R*-TIC. See M. Suzuki; K. Kato; R. Noyori; Y. Watanabe; H. Takechi,; K. Matsumura; B. Långström; Y. Watanabe, *Angew. Chem. Int. Ed. Engl.* **1996**, *35,* 334.

* Care must be taken on deprotection of the C15 TBS ether (in 0.5N HCl media) due to the acid labile nature of this position, which can ultimately lead to the elimination of H_2O, to give the corresponding conjugated system.

^{1}H and ^{13}C NMR: (*E*)-3-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)-*N*-methoxy-*N*-methylacrylamide (7)



(*E*)-3-((1*R*,2*R*,3a*S*,6a*S*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3a,6,6a-hexahydropentalen-1-yl)-*N*-methoxy-*N*-methylacrylamide (7)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EXPNO                      1
PROCNO                     1

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Time                  18.48
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PROBHD    5 mm BBO BB-1H
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8278.146 Hz
FIDRES            0.126314 Hz
AQ                3.9584243 sec
RG                    101.6
DW                   60.400 usec
DE                    6.00 usec
TE                     300.0 K
D1                1.00000000 sec

======== CHANNEL f1 ========
NUC1                      1H
P1                     8.75 usec
PL1                   -3.00 dB
SFO1           400.1324710 MHz

F2 - Processing parameters
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SF                400.1300097 MHz
WDW                         EM
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LB                        0.30 Hz
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PC                        1.00
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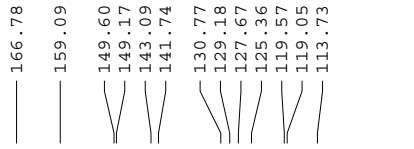


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Current Data Parameters
NAME                  NAS423
EXPNO                      2
PROCNO                     1

F2 - Acquisition Parameters
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Time                  19.34
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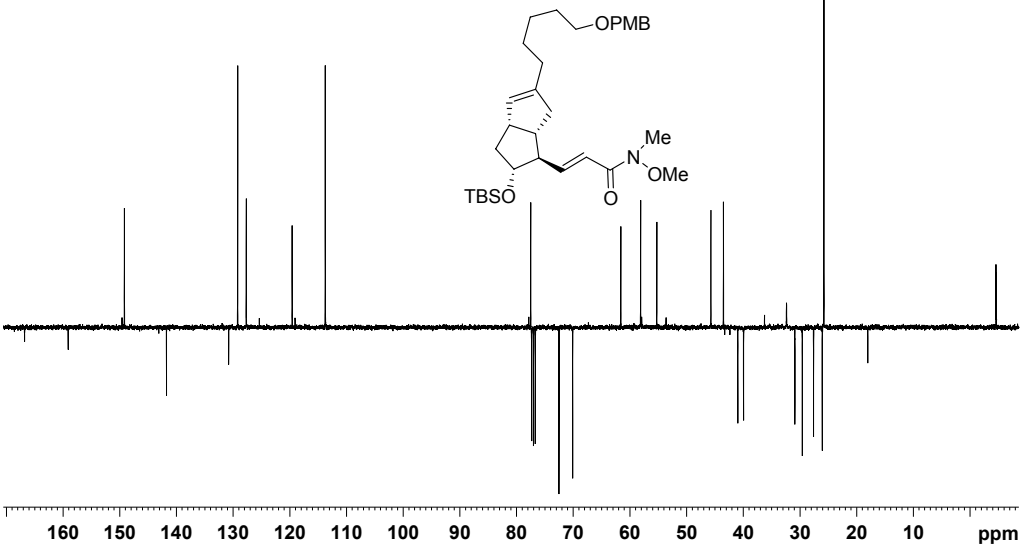
PULPROG                jmod
TD                    65536
SOLVENT               CDCl3
NS                       800
DS                        2
SWH               25062.656 Hz
FIDRES            0.382426 Hz
AQ                1.3074932 sec
RG                     6502
DW                   19.950 usec
DE                    6.00 usec
TE                     300.0 K
CNST2             145.0000000
CNST11              1.0000000
D1                2.00000000 sec
d13               0.00000300 sec
d20               0.00689655 sec
DELTA             0.00001311 sec

======== CHANNEL f1 ========
NUC1                      13C
P1                    10.30 usec
p2                    20.60 usec
PL1                    -1.00 dB
SFO1           100.6232933 MHz

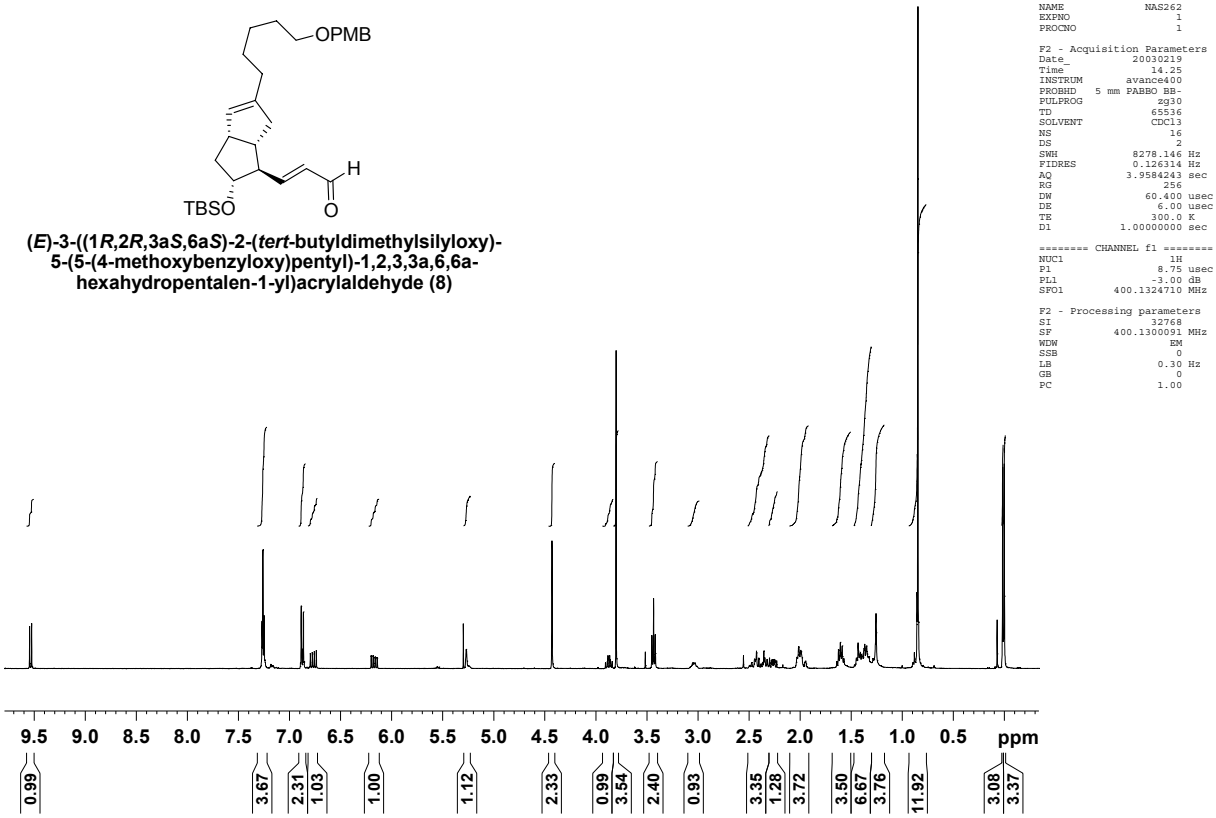
======== CHANNEL f2 ========
CPDPRG2                waltz16
NUC2                      1H
PCPD2                100.00 usec
PL2                   -3.00 dB
PL12                  16.00 dB
SFO2           400.1316005 MHz

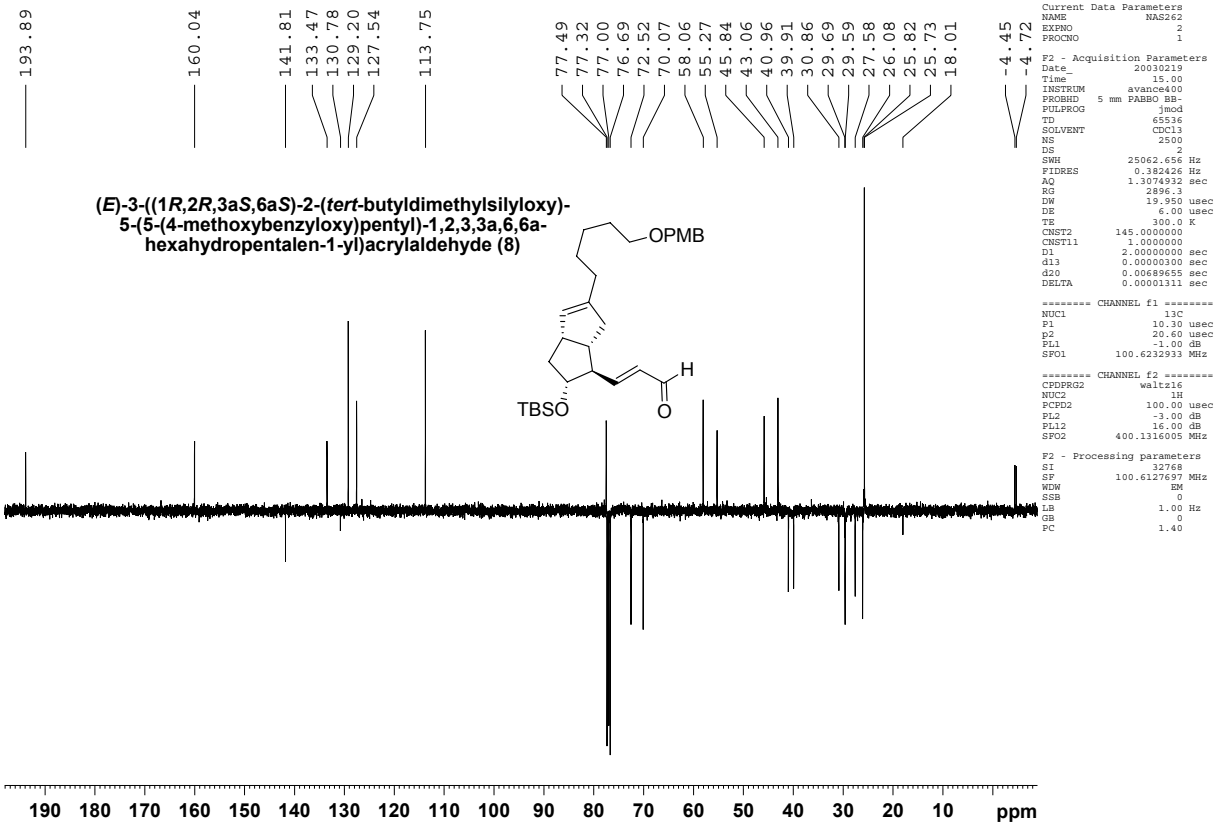
F2 - Processing parameters
SI                       32768
SF                100.6127717 MHz
WDW                         EM
SSB                          0
LB                        1.00 Hz
GB                           0
PC                        1.40
```

(*E*)-3-((1*R*,2*R*,3a*S*,6a*S*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3a,6,6a-hexahydropentalen-1-yl)-*N*-methoxy-*N*-methylacrylamide (7)

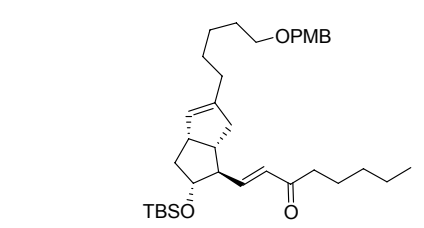


^{1}H and ^{13}C NMR: (*E*)-3-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)acrylaldehyde (8)





^{1}H and ^{13}C NMR: (*E*)-1-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)oct-1-en-3-one (13)



(*E*)-1-((1*R*,2*R*,3a*S*,6a*S*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3a,6,6a-hexahydropentalen-1-yl)oct-1-en-3-one (13)


```
Current Data Parameters
NAME                  NAS433
EXPNO                      1
PROCNO                     1

F2 - Acquisition Parameters
Date_              20050124
Time                  22.59
INSTRUM           avance400
PROBHD    5 mm BBO BB-1H
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                        16
DS                         2
SWH                8278.146 Hz
FIDRES            0.126314 Hz
AQ                 3.9584243 sec
RG                       114
DW                    60.400 usec
DE                     6.00 usec
TE                    300.0 K
D1                 1.00000000 sec

======== CHANNEL f1 ========
NUC1                       1H
P1                      8.75 usec
PL1                    -3.00 dB
SFO1           400.1324710 MHz

F2 - Processing parameters
SI                        32768
SF                400.1300094 MHz
WDW                          no
SSB                           0
LB                         0.00 Hz
GB                            0
PC                         1.00
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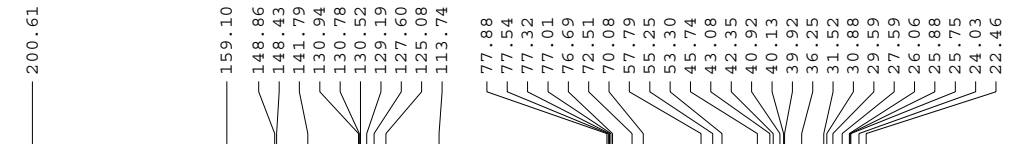
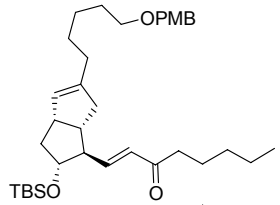


(*E*)-1-((1*R*,2*R*,3a*S*,6a*S*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3a,6,6a-hexahydropentalen-1-yl)oct-1-en-3-one (13)

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Current Data Parameters
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EXPNO                      2
PROCNO                     1

F2 - Acquisition Parameters
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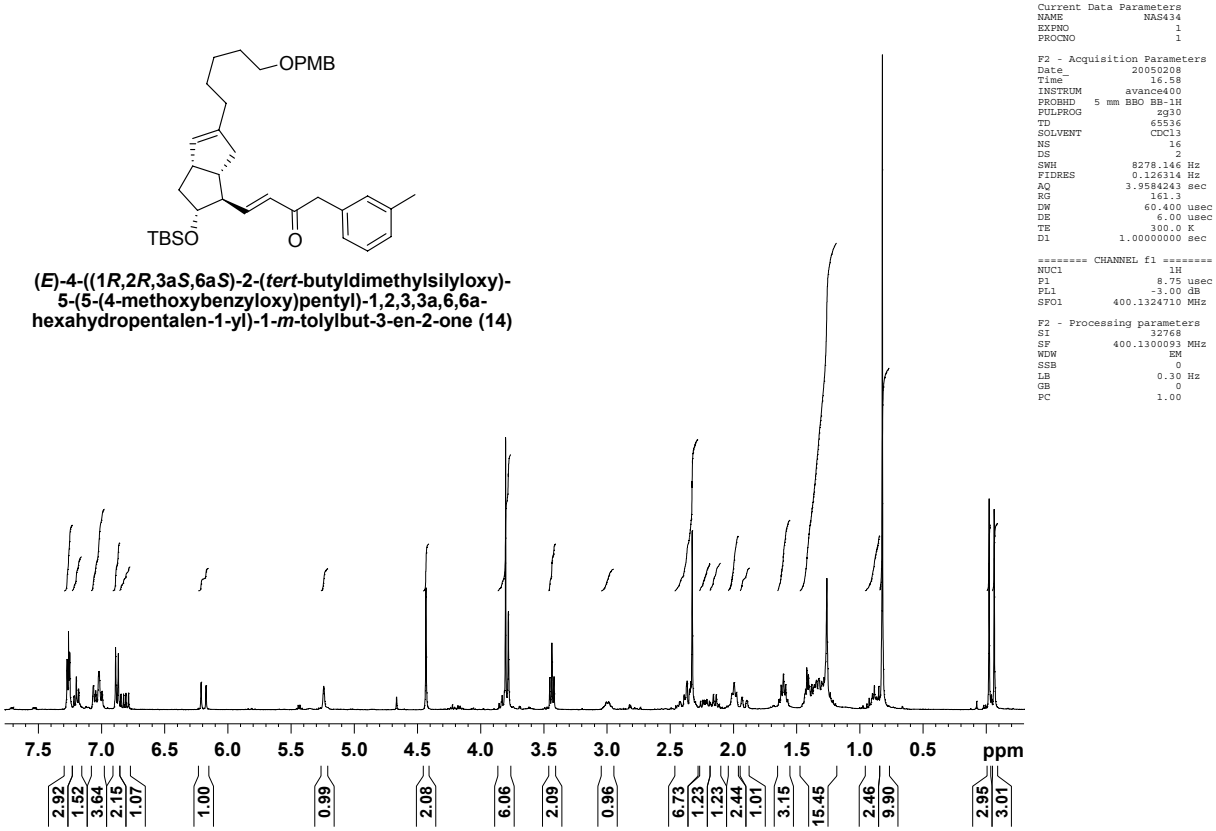
Time                  23.45
INSTRUM           avance400
PROBHD    5 mm BBO BB-1H
PULPROG               jmod
TD                    65536
SOLVENT               CDCl3
NS                      800
DS                         2
SWH               25062.656 Hz
FIDRES            0.382426 Hz
AQ                 1.3074932 sec
RG                    5792.6
DW                   19.950 usec
DE                     6.00 usec
TE                    300.0 K
CNST2             145.0000000
CNST11              1.0000000
D1                 2.00000000 sec
d13                0.00000300 sec
d20                0.00689655 sec
DELTA              0.00001311 sec

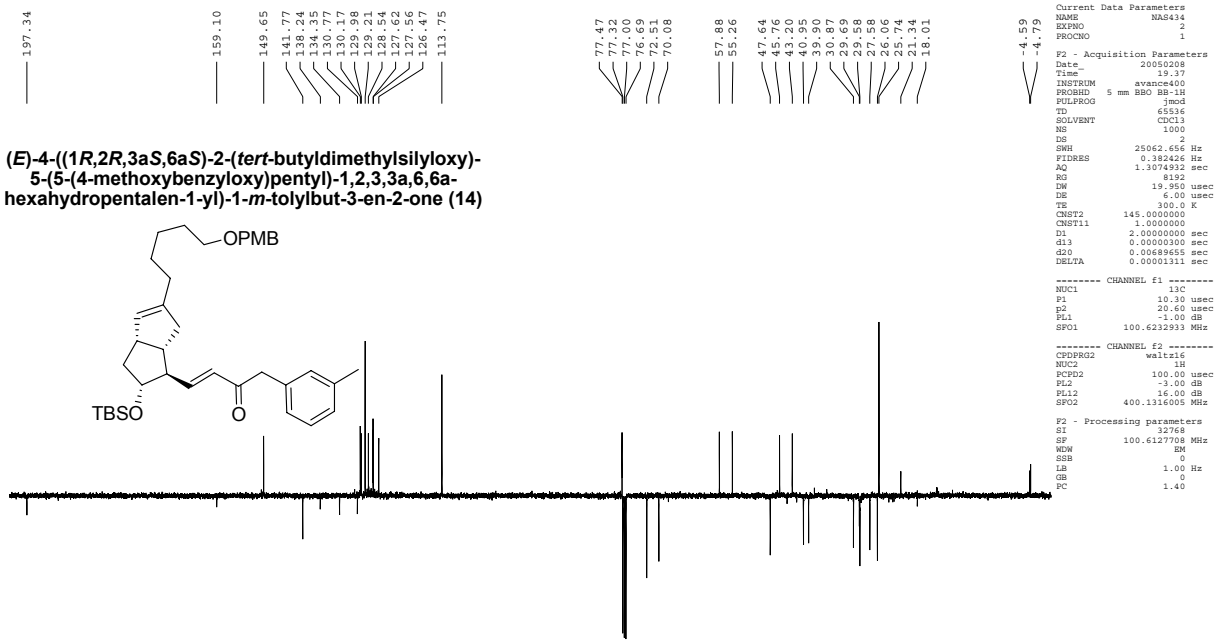
======== CHANNEL f1 ========
NUC1                      13C
P1                    10.30 usec
p2                    20.60 usec
PL1                    -1.00 dB
SFO1           100.6232933 MHz

======== CHANNEL f2 ========
CPDPRG2              waltz16
NUC2                       1H
PCPD2                100.00 usec
PL2                    -3.00 dB
PL12                   16.00 dB
SFO2           400.1316005 MHz

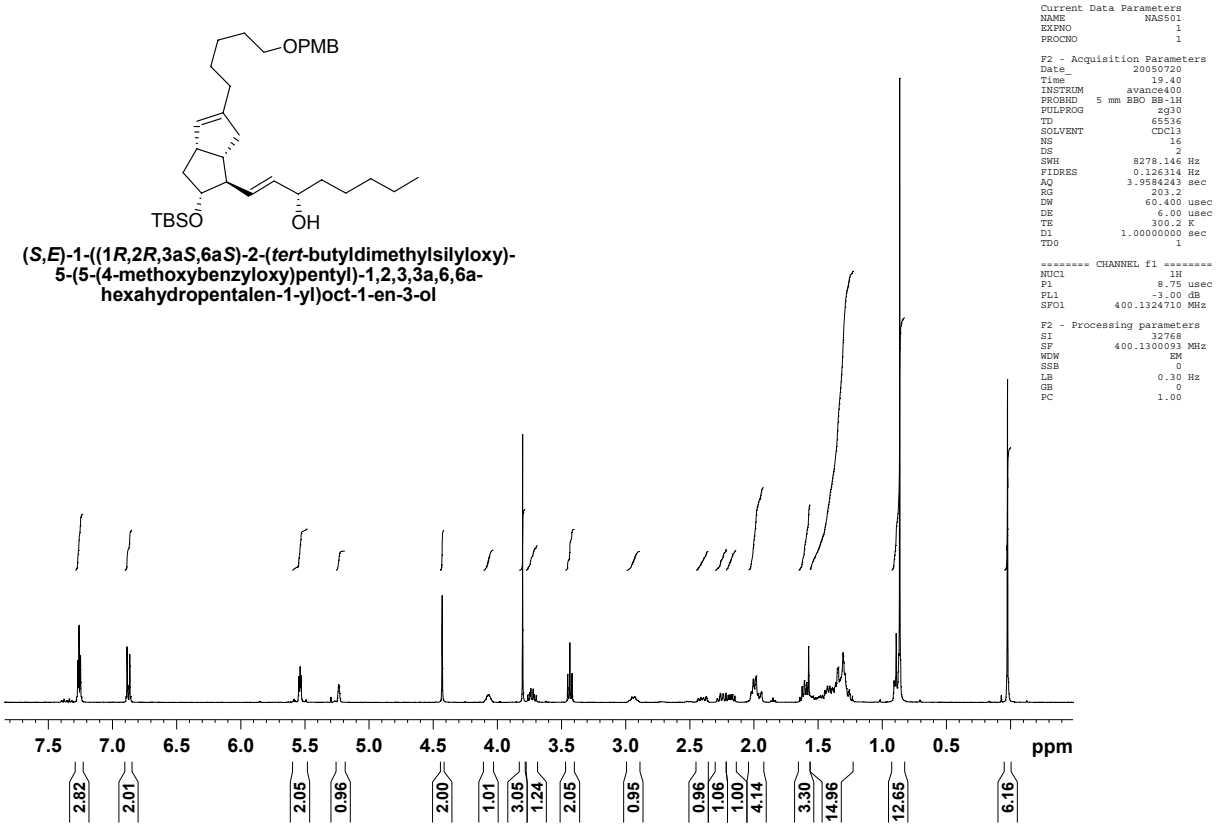
F2 - Processing parameters
SI                        32768
SF                100.6127707 MHz
WDW                          EM
SSB                           0
LB                         1.00 Hz
GB                            0
PC                         1.40
```

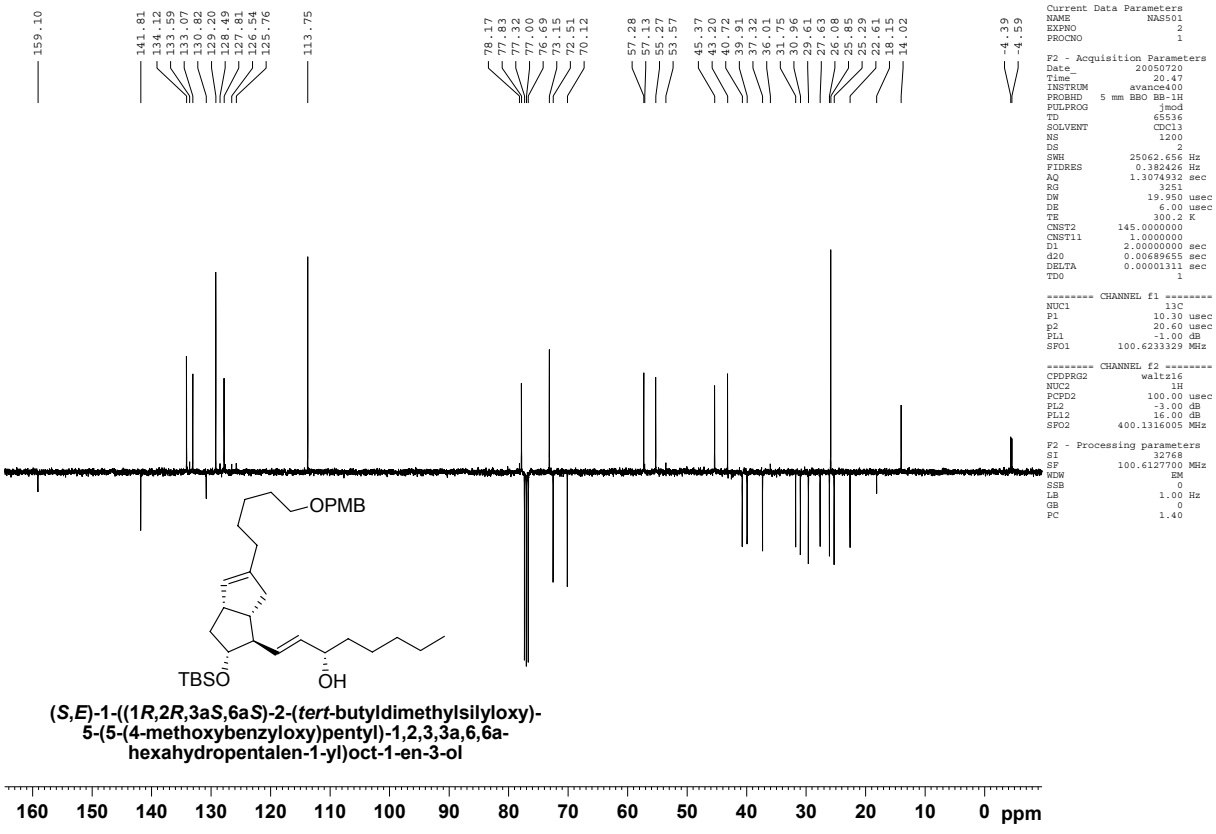
^{1}H and ^{13}C NMR: (*E*)-4-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)-1-*m*-tolylbut-3-en-2-one (14)



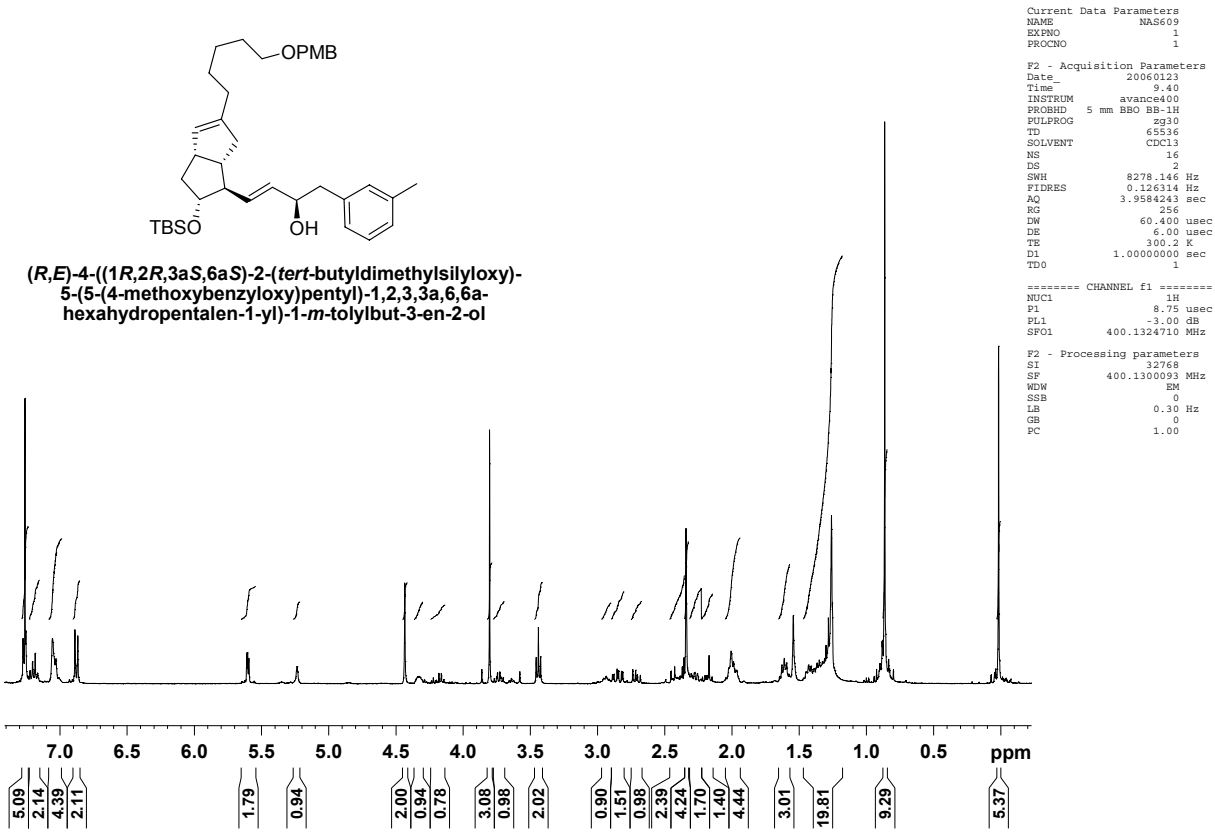


^{1}H and ^{13}C NMR: (S,E)-1-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)oct-1-en-3-ol





^{1}H NMR: (*R*,*E*)-4-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3a,6,6a-hexahydropentalen-1-yl)-1-*m*-tolylbut-3-en-2-ol

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Current Data Parameters
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EXPNO                      1
PROCNO                     1

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Time                   9.40
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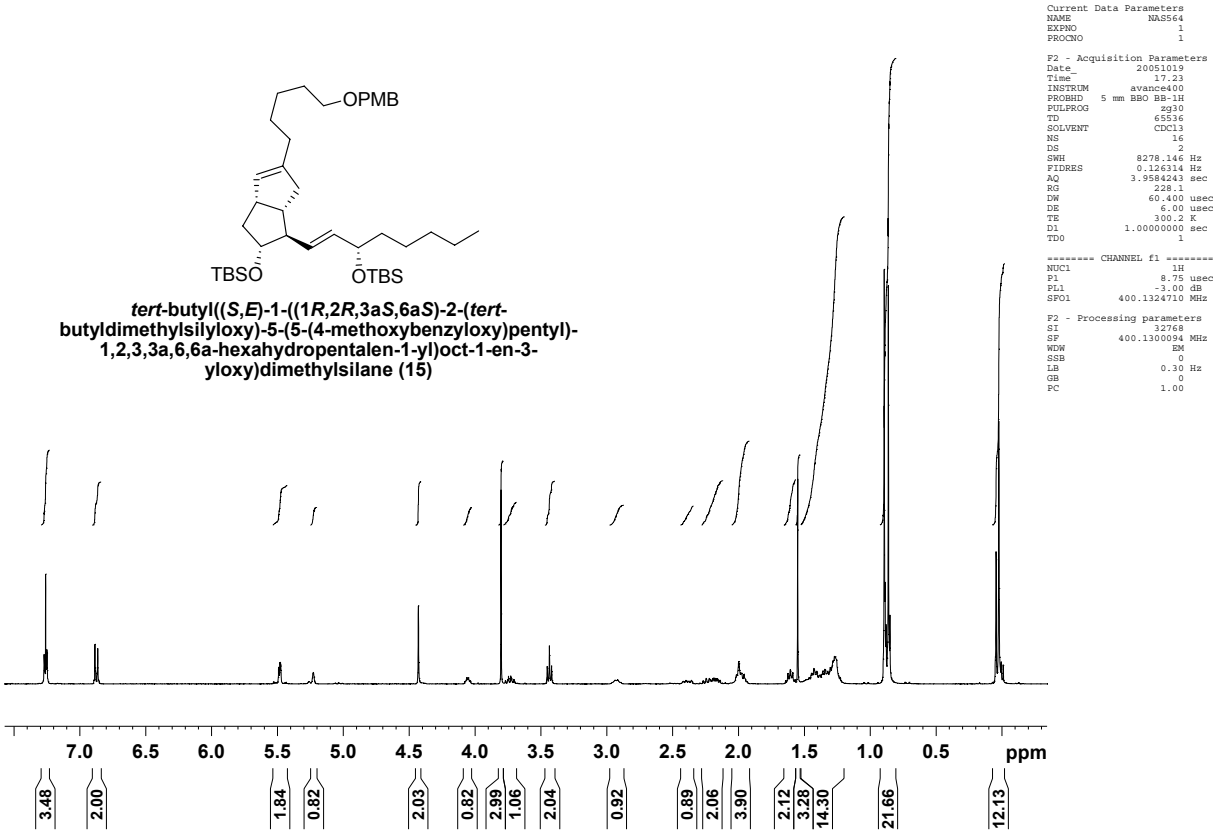
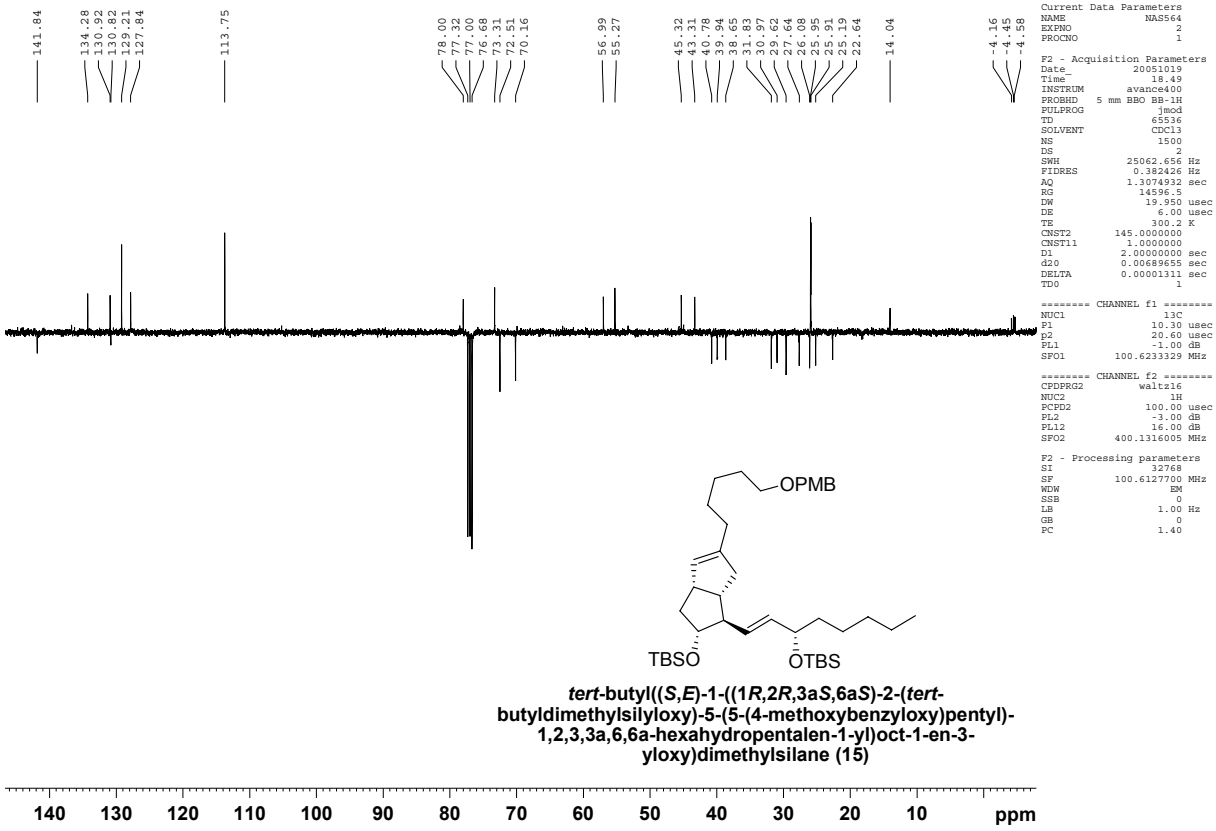
PULPROG                zg30
TD                    65536
SOLVENT               CDCl3
NS                       16
DS                        2
SWH                8278.146 Hz
FIDRES            0.126314 Hz
AQ                3.9584243 sec
RG                      256
DW                   60.400 usec
DE                    6.00 usec
TE                   300.2 K
D1              1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                     8.75 usec
PL1                   -3.00 dB
SFO1          400.1324710 MHz

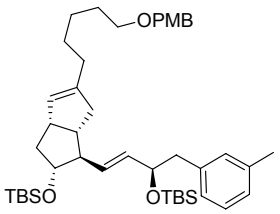
F2 - Processing parameters
SI                     32768
SF            400.1300093 MHz
WDW                       EM
SSB                        0
LB                      0.30 Hz
GB                         0
PC                      1.00
```

^{1}H and ^{13}C NMR: *tert*-butyl((*S*,*E*)-1-((1*R*,2*R*,3*aS*,6*aS*)-2-(*tert*-butyldimethylsilyloxy)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-1-yl)oct-1-en-3-yloxy)dimethylsilane (15)

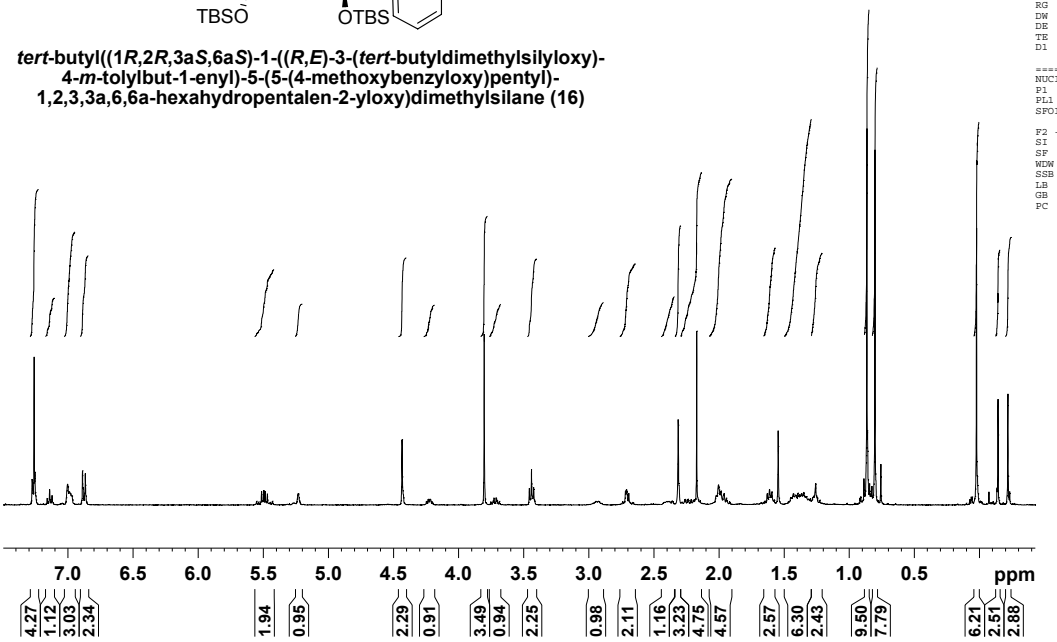




^{1}H and ^{13}C NMR: *tert*-butyl((1*R*,2*R*,3*aS*,6*aS*)-1-((*R*,*E*)-3-(*tert*-butyldimethylsilyloxy)-4-*m*-tolylbut-1-enyl)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3*a*,6,6*a*-hexahydropentalen-2-yloxy)dimethylsilane (16)



***tert*-butyl((1*R*,2*R*,3a*S*,6a*S*)-1-((*R*,*E*)-3-(*tert*-butyldimethylsilyloxy)-4-*m*-tolylbut-1-enyl)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3a,6,6a-hexahydropentalen-2-yloxy)dimethylsilane (16)**

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PROCNO                  1

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PULPROG              zg30
TD                  65536
SOLVENT             CDCl3
NS                     16
DS                      2
SWH             8278.146 Hz
FIDRES          0.126314 Hz
AQ              3.9584243 sec
RG                  456.1
DW                 60.400 usec
DE                  6.00 usec
TE                 300.0 K
D1              1.00000000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                   8.75 usec
PL1                 -3.00 dB
SFO1          400.1324710 MHz

F2 - Processing parameters
SI                    32768
SF            400.1300093 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
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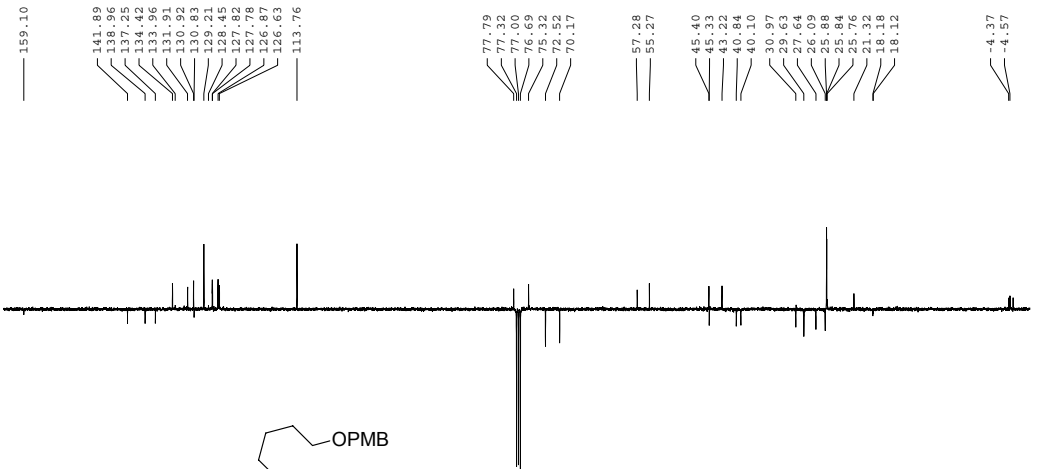


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Current Data Parameters
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PROCNO                  1

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Time                13.07
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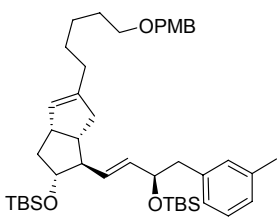
PULPROG             jmod
TD                  65536
SOLVENT             CDCl3
NS                   3741
DS                      2
SWH            25062.656 Hz
FIDRES          0.382426 Hz
AQ              1.3074932 sec
RG                  16384
DW                 19.950 usec
DE                  6.00 usec
TE                 300.0 K
CNST2         145.0000000
CNST11          1.0000000
D1              2.00000000 sec
d13             0.00000300 sec
d20             0.00689655 sec
DELTA           0.00001311 sec

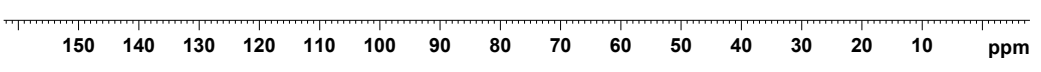
======== CHANNEL f1 ========
NUC1                  13C
P1                  10.30 usec
p2                  20.60 usec
PL1                 -1.00 dB
SFO1          100.6232933 MHz

======== CHANNEL f2 ========
CPDPRG2           waltz16
NUC2                   1H
PCPD2              100.00 usec
PL2                 -3.00 dB
PL12                16.00 dB
SFO2          400.1316005 MHz

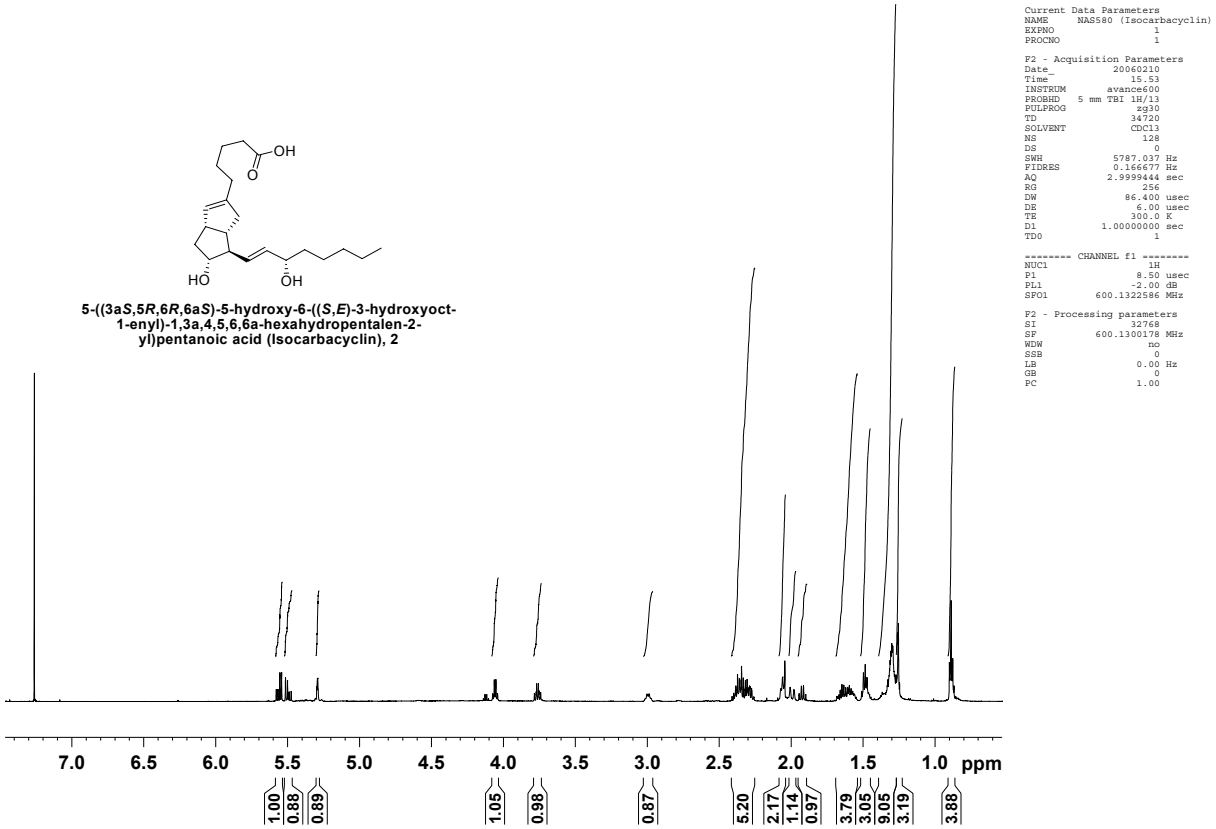
F2 - Processing parameters
SI                    32768
SF            100.6127696 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40
```



***tert*-butyl((1*R*,2*R*,3a*S*,6a*S*)-1-((*R*,*E*)-3-(*tert*-butyldimethylsilyloxy)-4-*m*-tolylbut-1-enyl)-5-(5-(4-methoxybenzyloxy)pentyl)-1,2,3,3a,6,6a-hexahydropentalen-2-yloxy)dimethylsilane (16)**



^{1}H and ^{13}C NMR: 5-((3*aS*,5*R*,6*R*,6*aS*)-5-hydroxy-6-((*S*,*E*)-3-hydroxyoct-1-enyl)-1,3*a*,4,5,6,6*a*-hexahydropentalen-2-yl)pentanoic acid (Isocarbacyclin), 2

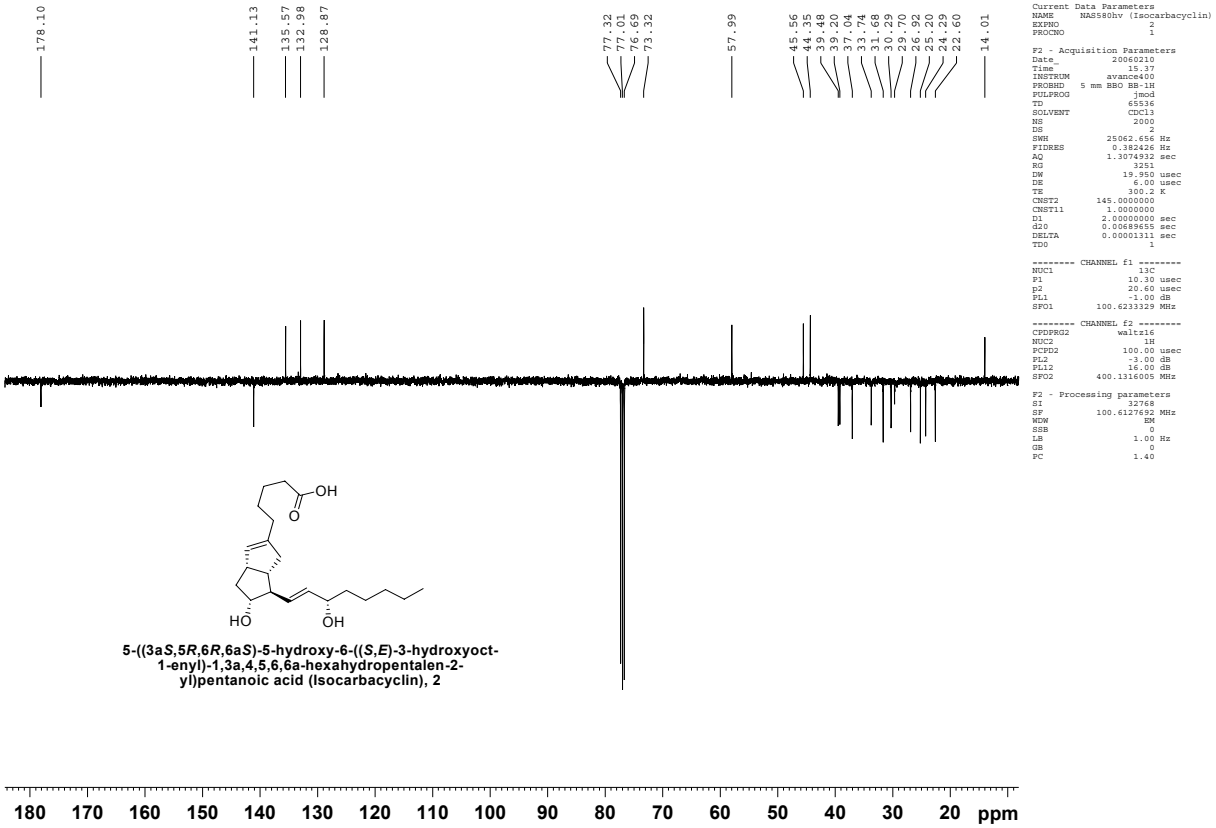



```
Current Data Parameters
NAME      NAS580 (Isocarbacyclin)
EXPNO                1
PROCNO               1

F2 - Acquisition Parameters
Date_          20060210
Time              15.53
INSTRUM       avance600
PROBHD  5 mm TBI 1H/13
PULPROG           zg30
TD               34720
SOLVENT          CDCl3
NS                 128
DS                   0
SWH           5787.037 Hz
FIDRES        0.166677 Hz
AQ            2.9999444 sec
RG                 256
DW              86.400 usec
DE               6.00 usec
TE              300.0 K
D1           1.00000000 sec
TD0                  1

======== CHANNEL f1 ========
NUC1                1H
P1                8.50 usec
PL1              -2.00 dB
SFO1       600.1322586 MHz

F2 - Processing parameters
SI                32768
SF         600.1300178 MHz
WDW                  no
SSB                   0
LB                 0.00 Hz
GB                    0
PC                 1.00
```




```
Current Data Parameters
NAME      NAS580hv (Isocarbacyclin)
EXPNO                2
PROCNO               1

F2 - Acquisition Parameters
Date_          20060210
Time              15.37
INSTRUM       avance400
PROBHD  5 mm BBO BB-1H
PULPROG           jmod
TD               65536
SOLVENT          CDCl3
NS                2000
DS                   2
SWH           25062.656 Hz
FIDRES        0.382426 Hz
AQ            1.3074932 sec
RG                3251
DW              19.950 usec
DE               6.00 usec
TE              300.2 K
CNST2        145.0000000
CNST11         1.0000000
D1           2.00000000 sec
d20          0.00689655 sec
DELTA        0.00001311 sec
TD0                  1

======== CHANNEL f1 ========
NUC1                13C
P1                10.30 usec
p2                20.60 usec
PL1               -1.00 dB
SFO1       100.6233329 MHz

======== CHANNEL f2 ========
CPDPRG2          waltz16
NUC2                1H
PCPD2           100.00 usec
PL2               -3.00 dB
PL12              16.00 dB
SFO2       400.1316005 MHz

F2 - Processing parameters
SI                32768
SF         100.6127692 MHz
WDW                  EM
SSB                   0
LB                 1.00 Hz
GB                    0
PC                 1.40
```

^{1}H and ^{13}C NMR: 5-((3*aS*,5*R*,6*R*,6*aS*)-5-hydroxy-6-((*R*,*E*)-3-hydroxy-4-*m*-tolylbut-1-enyl)-1,3*a*,4,5,6,6*a*-hexahydropentalen-2-yl)pentanoic acid (15*R*-TIC), 3