Supplementary Material (ESI) for Chemical Communications

Short Synthesis of the C_{16}-C_{28} Polyketide Fragment of Apoptolidin A Aglycone

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Detailed procedures, new compound characterizations

General remarks

Reagents were purchased from commercial suppliers (Fluka, Aldrich or Merck) and used without further purification. All solvents for extraction, chromatography and reactions requiring anhydrous conditions were distilled prior to use: THF and Et_2O from Na and benzophenone; DMF, CH_2Cl_2, and toluene from CaH_2. Solvent after reactions and extractions were evaporated in a rotatory evaporator under reduced pressure.

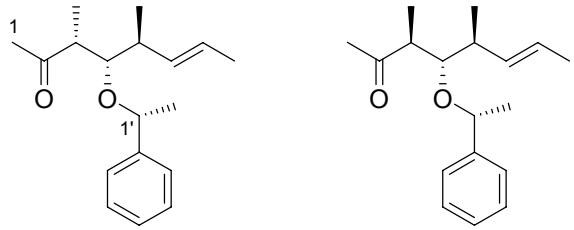
Liquid/solid flash chromatography (FC): columns of silica gel (0.040-0.63 μm, silica gel *60*,240-400 mesh). Thin layer chromatography (TLC) for reaction monitoring; detection by UV light, *Pancaldi* reagent ($(NH_4)_6MoO_4$, $Ce(SO_4)_2$, H_2SO_4, H_2O), or $KMnO_4$.

IR Spectra: spectrometer; υ in cm^{-1}. ^{1}H-NMR Spectra: 400 MHz spectrometer; δ(H) in ppm rel. to internal Me_4Si (= 0.00 ppm) or to the solvent's residual ^{1}H-signal ($CHCl_3$, δ(H) 7.26; C_6HD_5, δ(H) 7.16) as internal reference. ^{13}C-NMR Spectra: same instruments as above (101.61MHz); δ(C) in ppm rel. to internal Me_4Si (= 0.00 ppm) or to solvents ^{13}C-signal ($CDCl_3$, δ(C) 77.16; C_6D_6, δ(C) 128.06) as internal reference; coupling constants *J* in Hz (±0.5 Hz). Ms, chemical ionization (NH_3) mode m/z amu [% relative base peak (100%)]

The NMR spectra were recorded on Bruker DPX-400 FT, Bruker ARX-400 FT and Bruker DRX-400 FT spectrometers. The mass spectra were recorded on a Nermag R 10-10C in chemical ionization mode. The microanalyses were performed by the Ilse Beetz Laboratory,

Kronach (Germany). The IR spectra were recorded on Perkin Elmer Paragon 1000 FT-IR spectrometer. The chromatography separations in liquid phase were realized by flash chromatography (SiO_2, Merck n°9385).

4:1 Mixture of (3*S*,4*S*,5*S*,6*E*) and (3*R*,4*S*,5*S*,6*E*)-3,5-dimethyl-4-(1'-(*R*)-(1'-phenylethoxy))oct-6-en-2-one (6 : 3-epimer of 6)

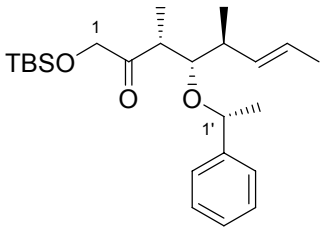


6 **3-epimer of 6**

In a two-necked round-bottom flask were placed anhydrous CH_2Cl_2 (24 mL) and 0.5 M $(CF_3SO_2)NH$ in CH_2Cl_2 (10.62 mL, 5.31 mmol, 0.3 eq.) under an Ar atmosphere. After freezing (-196 °C) dry SO_2 (48 mL) was transferred. The system was pressurized with Ar and allowed to warm to –78 °C. After stirring at –78 °C for 30 min, a solution of ((1*R*)-1-{[(1*E*,3*E*)-2-methylpenta-1,3-dienyl]oxy}ethyl)benzene **4** (3.62 g, 17.9 mmol)[17] and 2-triethylsilyloxybut-2-ene **5** (*E*/*Z* = 1/1) (10.0 g, 53.8 mmol, 3.0 eq.)[28] in CH_2Cl_2 (24 mL) was slowly added over 2 h. After stirring at –78 °C overnight, the solvents were evaporated. The residual oil was dissolved in CH_3CN (150 mL). Isopropanol (45 mL) and Et_3N (550 µL) were added and the mixture was heated at 80 °C for 45 min. After cooling, the reaction was quenched by water (20 mL) and Et_2O (200 mL) was added. The aqueous layer was extracted with Et_2O (150 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was concentrated under reduced pressure. The crude product was purified by flash chromatography (pentane/EtOAc, 10:1) to afford a 4:1 mixture of diastereoisomers **6** (3.48 g, 12.7 mmol, 71%) as a colourless oil. Data for the major diastereoisomer **6**: R_f = 0.29 (pentane/EtOAc, 5:1); IR (film) ν = 2970, 1710, 1455, 1355, 1180, 1080, 975, 760, 700; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 0.91 (d, 3H, J = 7.1 Hz, CH_3-C(3)), 1.11 (d, 3H, J = 6.8 Hz, CH_3-C(5)), 1.44 (d, 3H, J = 6.5 Hz, CH_3-C(1')), 1.68 (d, 3H, J = 4.5 Hz, H_3-C(8)), 1.89 (s, 3H, CH_3(1)), 2.40 (qdm, 1H, J = 6.8, 4.3 Hz, H-C(5)), 2.61 (qd, 1H, J = 7.1, 6.5 Hz, H-C(3)), 3.57 (dd, 1H, J = 6.5, 4.3 Hz, H-C(4)), 4.50 (q, 1H, J = 6.5 Hz, H-C(1')), 5.40-5.49 (m, 2H,

H-C(6) + H-C(7)), 7.27-7.34 (m, 5H, arom.); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ= 12.9 (CH_3-C(3)), 17.5 (CH_3-C(5)), 18.0 (C(8)), 23.3 (C(1)), 29.0 (C(2')), 40.5 (C(5)), 50.0 (C(3)), 78.3 (C(1')), 80.7 (C(4)), 125.6 (C(7)), 127.4, 128.2 (arom.), 132.9 (C(6)), 143.6 (arom.), 211.6 (C(2)); HRMS (MALDI) calcd for $C_{18}H_{26}O_2$: 274.1933, found 274.1954.

(3*R*,4*S*,5*S*,6*E*)-1-[(*tert*-Butyl)-dimethylsilyloxy]-3,5-dimethyl-4-(1'-(*R*)-1'-phenylethoxy)oct-6-en-2-one (7)



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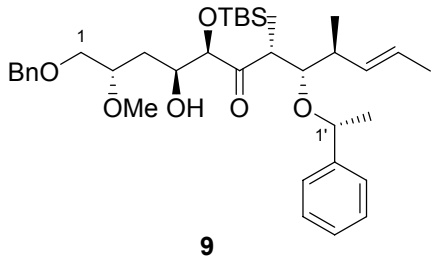
To a stirred solution of ketone **6** (4:1 mixture of diastereoisomers) (3.0 g, 10.95 mmol) in dry CH_2Cl_2 (30 mL) were added at 0 °C, Et_3N (1.92 mL, 13.69 mmol, 1.25 eq.) followed by TBSOTf (3.12 mL, 13.69 mmol, 1.25 eq.). After stirring for 30 min at this temperature, *m*CPBA (2.97 g, 70%, 12.04 mmol, 1.1 eq.) was added portion-wise over 10 min (exothermic reaction). The reaction was stirred at 0 °C for 1 h and then was quenched with sat. aq. solution of Na_2SO_3 (40 mL) and CH_2Cl_2 (100 mL). The aqueous layer was extracted with CH_2Cl_2 (40 mL, 3 times). The combined organic layers were washed with sat. aq. solution of $NaHCO_3$ (20 mL, 2 times), brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (pentane/Et_2O, 10:1) afforded the pure major diastereoisomer **7** (3.31 g, 8.2 mmol, 75% from 4:1 mixture of diastereoisomers **6**) as a colourless oil: R_f = 0.63 (pentane/Et_2O 3:1); $[\alpha]_D^{21}$ = +26.0 (c = 0.53, $CHCl_3$), IR (film) ν = 2930, 2360, 1715, 1655, 1560, 1455, 1255, 1080, 1005, 840, 780, 670, 670, ^{1}H NMR ($CDCl_3$, 400 MHz) δ= 0.02, 0.03 (2s, 6H, $Si(CH_3)_2$), 0.90 (d, 3H, J = 7.0 Hz, CH_3-C(3)), 0.94 (s, 9H, $SiC(CH_3)_3$), 1.10 (d, 3H, J = 7.0 Hz, CH_3-C(5)), 1.40 (d, 3H, J = 6.4 Hz, CH_3-C(1')), 1.70 (d, 3H, J = 5.1 Hz, H_3-C(8)), 2.30-2.36 (m,1 H, H-C(5)), 2.90 (dq, 1H, J = 7.0, 7.0 Hz, H-C(3)), 3.70 (dd, 1H, J = 7.0, 3.8 Hz, H-C(4)), 3.80 (d, 1H, J = 17.9 Hz, Hb-C(1)), 4.00 (d, 1H, J = 17.9 Hz, Ha-C(1)), 4.51 (q, 1H, J = 6.4 Hz, H-C(1')), 5.41-5.50 (m, 2H, H-C(6) + H-C(7)),

7.28-7.33 (m, 5H, arom.); ^{13}C NMR ($CDCl_3$, 100.61MHz) $\delta = -5.6$, -5.5 ($Si(CH_3)_2$), 13.0 (CH_3-C(3)), 17.9 (CH_3-C(5)), 18.0 (C(8)), 18.1 ($SiC(CH_3)_3$), 23.3 (C(2')), 25.7 ($SiC(CH_3)_3$), 41.0 (C(5)), 44.6 (C(3)), 68.0 (C(1)), 78.0 (C(1')), 80.2 (C(4)), 125.4 (C(7)), 127, 127.5, 128.3 (arom.), 133.2 (C(6)), 143.7 (arom.), 212.6 (C(2)); HRMS (MALDI) calcd. for $C_{24}H_{40}O_3SiNa$: 427.2644, found 427.2673; Anal. Calc. for $C_{24}H_{40}O_3Si$: C 71.23%; H 9.96%; O 11.86%; Si 6.94%, Found: C 71.26%, H 9.99%.

(2*S*,4*S*,5*R*,7*R*,8*S*,9*S*,10*E*)-1-Benzyloxy-5-[(*tert*-butyl)-dimethylsilyloxy]-2-methoxy-4-hydroxy-7,9-dimethyl-8-(1'-(*R*)-1'-(phenylethoxy)dodec-10-en-6-one (9)

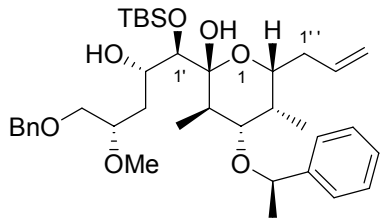


9

To a stirred solution of ketone **7** (2.8 g, 6.9 mmol) in dry THF (30 mL) was slowly added sodium *bis*(trimethylsilyl)amide (1.4 g, 7.6 mmol, 1.1 eq.) at –78 °C. The solution was stirred at this temperature for 30 min and Me_3SiCl (1.1 ml, 8.3 mmol , 1.2 eq.) was added dropwise. The reaction mixture was allowed to warm to room temperature. After 2 h, the reaction mixture was quenched with sat. aq. solution of $NaHCO_3$ (10 mL) and Et_2O (20 mL) was added. The aqueous layer was extracted with Et_2O (10 mL, 3 times). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. To a stirred solution of aldehyde **8** (2.87 g, 13.8 mmol, 2.0 eq.)[29] and silyl enol ether prepared as mentioned above (100%) in CH_2Cl_2 (50 mL) was added $BF_3.Et_2O$ (1.76 mL, 13.9 mmol, 2.0 eq.) at –78 °C. After 1 h, the reaction mixture was quenched by adding sat. aq. solution of $NaHCO_3$ (15 mL) and was diluted with CH_2Cl_2 (30 mL). The reaction mixture was warmed to room temperature and the aqueous layer was extracted CH_2Cl_2 (20 mL, 3 times). The organic extracts were washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography (pentane/Et_2O, 3:1) afforded ketone **9** (3.1 g, 5.0 mmol, 73%) as a colourless oil: R_f = 0.32 (pentane/ Et_2O 1:1); $[\alpha]_D^{22} = -28.2$ (*c* = 1.00, $CHCl_3$); IR (film): ν = 3477 (br), 3030 (w), 2959 (s), 2930 (s), 2857 (s), 1722

(m), 1454 (m), 1255 (m), 1082 (m), 909 (s), 733 (m); ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 0.20, 0.30 (2s, 6H, $Si(CH_3)_2$), 1.08 (s, 9H, $Si(CH_3)_3$), 1.20 (d, J = 7.1 Hz, 3H, CH_3-C(7)), 1.32 (d, J = 7.1 Hz, 3H, CH_3-C(9)), 1.47 (d, J = 6.8 Hz, 3H, CH_3-C(1')), 1.75 (dd, J = 7.1, 1.8 Hz, 3H, H_3-C(12)), 1.90-2.04 (m, 2H, H_2-C(3)), 2.48-2.56 (m, 1H, H-C(9)), 2.66 (d, J = 10.3 Hz, OH-C(4)), 3.41 (s, 3H, OCH_3), 3.44-3.56 (m, 3H, H-C(7) + H_2-C(1)), 3.80-3.86 (m, 2H, H-C(2) + H-C(8)), 4.42 (s, 2H, CH_2Ph), 4.46-4.58 (m, 2H, H-C(5) + H-(C4)), 4.62 (q, 1H, J = 6.8 Hz, H-(C1')), 5.58-5.68 (m, 1H, H-C(11)), 5.80-5.88 (m, 1H, H-C(10)), 7.18-7.44 (m, 10H, arom.); ^{13}C-NMR (75 MHz, $CDCl_3$) δ = –4.4, –3.9 ($Si(CH_3)_2$), 14.7 (CH_3-C(7)), 18.4 (CH_3-C(12)), 18.9 (Si<u>C</u>$(CH_3)_3$), 19.7 (CH_3-C(9)), 23.6 (CH_3-C(2')), 26.3 (SiC(<u>C</u>$H_3)_3$), 38.2 (C(3)), 42.2 (C(9)), 45.9 (C(7)), 58.3 (OCH_3), 69.8 (C(1)), 72.8 (C(4)), 73.5 (C(2)), 77.5 (CH_2Ph), 78.6 (C(1')), 81.9 (C(5)), 82.2 (C(8)), 125.9 (C(11)), 127.0, 127.8, 127.9, 127.95, 128.8 (arom.), 133.9 (C(10)), 144.8 (arom.), 213.6 (C(6)); HR-MS (ESI) $C_{36}H_{56}O_6SiNa$: calcd 635.3744; found 635.3750 $[M+Na]^+$; Anal. Calc. for $C_{36}H_{56}O_6Si$: C 70.55%; H 9.21%; Found: C 70.42%, H 9.10%.

(2*R*,3*R*,4*S*,5*R*,6*R*,1'*R*,2'*S*,4'*S*)-2-{[(1'-*tert*-Butyl)-dimethylsilyloxy]-2'-acetoxy-5'-benzyloxy-4'-methoxy-pentyl}-4-((*R*)-1-phenylethoxy)-6-allyl-2-hydroxy-3,5-dimethyl-2,3,5,6-tetrahydro-4*H*-pyran (10)



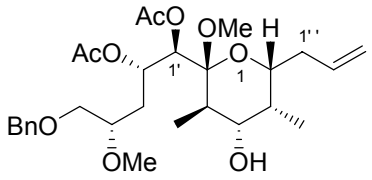
10

$NaHCO_3$ (5.0 g, 59.5 mmol, 36 eq.) was added to a solution of ketone **9** (1.0 g, 1.63 mmol) in CH_2Cl_2 (80 mL). After cooling to –78 °C, ozone was bubbled until a blue colour persisted. Excess ozone was purged by a stream of oxygen, and Me_2S (240 µl, 3.26 mmol, 2.0 eq.) was added. The reaction was allowed to warm to room temperature over 1 h and was filtered through a pad of Celite. After concentration under reduced pressure, the residue was dissolved in CH_2Cl_2 (5 mL), filtered through a pad of silica gel (3 cm high, elution with pentane/Et_2O, 3:1 (5 mL, 3 times)), and concentrated under reduced pressure to afford the corresponding crude aldehyde.

To a solution of (+)-*B*-methoxydiisopinocampheylborane (2.37 g, 7.5 mmol) in Et_2O (6 mL) at 0 °C was added drop-wise over 20 min allylmagnesium bromide (1 M in Et_2O, 7.4 mL, 7.4 mmol). The cooling bath was removed and the mixture was stirred 3 h at room temperature. After concentration under reduced pressure, the residue was dissolved in dry pentane (4 mL), solids were removed by filtration on a pad of Celite and washed with pentane (2 mL, 3 times). The pentane solution was filled up to 10 mL. 1 mL of this solution was concentrated under reduced pressure to determine the concentration (0.70 M).

An aliquot of the above allylation reagent (2.8 mL, 1.95 mmol, 1.2 eq., pre-cooled to –78 °C) was transferred through a cannula to a stirred solution of the crude aldehyde, prepared as mentioned above, in Et_2O (20 mL) at –78 °C. The reaction mixture was stirred for 1 h at –78 °C, quenched with MeOH (2 mL) and then allowed to warm to room temperature. The mixture was concentrated under reduced pressure, redissolved in a 1:1 mixture of THF/H_2O (10 mL) and $NaBO_3.4H_2O$ (5.0 g, 3.2 mmol, 2.0 eq.) was added. After 12 h of stirring at room temperature, the reaction was diluted with EtOAc (10 mL), the aqueous layer was extracted with EtOAc (5 mL, 3 times) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash chromatography (pentane/Et_2O, 2:1) afforded alkene **10** (3.1 g, 5.0 mmol, 78% over two steps) as a colourless oil: R_f = 0.44 (pentane/ Et_2O 1:1); $[\alpha]_D^{22}$ = +63.5 (*c* = 1.00, $CHCl_3$); IR (film): ν = 3417 (br), 3065 (w), 2929 (s), 2858 (m), 1722 (m), 1454 (m), 1259 (m), 1098 (m), 908 (s), 733 (m); ^{1}H-NMR (400 MHz, C_6D_6) δ = 0.03, 0.10 (2s, 6H, $Si(CH_3)_2$), 0.99 (s, 9H, $Si(CH_3)_3$), 1.18 (d, *J* = 7.1 Hz, 3H, CH_3-C(5)), 1.32 (d, *J* = 6.9 Hz, 3H, CH_3-C(3)), 1.41 (d, *J* = 6.9 Hz, 3H, Ph(CH)C<u>H</u>$_3$), 2.22-2.28 (m, 3H, H-C(5) + Hb-C(1'') + Hb-C(3')), 2.38-2.54 (m, 3H, H-C(3) + Ha-C(3') + Ha-C(1'')), 3.22 (s, 3H, OCH_3), 3.40-3.44 (m, 1H, H-C(4')), 3.49-3.58 (m, 2H, H-C(4) + Hb-C(5')), 3.65 (dd, 1H, *J* = 10.6, 5.3 Hz, Ha-C(5')), 3.98 (d, 1H, *J* = 3.5 Hz, H-C(1')), 4.09-4.13 (m, 1H, H-C(6)), 4.22-4.28 (m, 1H, H-C(2')), 4.26 (s, 2H, C<u>H</u>$_2$Ph), 4.45 (q, 1H, *J* = 7.1 Hz, PhC<u>H</u>(Me)), 4.98 (d, 1H, *J* = 1.6 Hz, OH-C(2')), 5.01-5.12 (m, 2H, H_2-C(3'')), 5.73-5.84 (m, 1H, H-C(2'')), 5.80-5.88 (m, 1H, H-C(10)), 7.05-7.35 (m, 10H, arom.); ^{13}C-NMR (75 MHz, $CDCl_3$) δ = –4.1, –3.7 ($Si(CH_3)_2$), 5.5 (CH_3-C(5)), 13.5 (CH_3-C(3)), 18.4 (Si<u>C</u>$(CH_3)_3$), 25.2 (PhCH<u>C</u>H_3), 26.3 (SiC(<u>C</u>$H_3)_3$), 34.1 (C(5)), 34.9 (C(3)), 35.5 (C(3')), 37.9 (C(1'')), 57.9 (OCH_3), 69.9 (C(6)), 72.6 (C(5')), 72.8 (C(2')), 73.1 (C(1')), 73.5 (Ph(<u>C</u>H)CH_3 + CH_2Ph), 77.1 (C(4)), 79.9 (C(4')), 102.7 (C(2)), 116.7 (C(3'')), 127.6, 127.8, 128.1, 128.5 (arom.), 136.0 (C(2'')), 144.4 (2 x arom.); HR-MS (ESI) $C_{37}H_{58}O_7SiNa$: calcd 665.3850; found 665.3858 $[M+Na]^+$.

(2*R*,3*R*,4*S*,5*R*,6*R*,1'*R*,2'*S*,4'*S*)-2-[1',2'-Diacetoxy-5'-benzyloxy-4'-methoxy-pentyl]-4-hydroxy-6-allyl-2-methoxy-3,5-dimethyl-2,3,5,6-tetrahydro-4*H*-pyran (11)

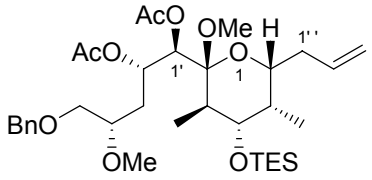


11

Alkene **11** (1.2 g, 1.87 mmol) was dissolved in 25 ml of HCl (0.2 N in MeOH) and was heated to 50 °C for 3 h. Then, the solvent was removed under reduced pressure. The residue was taken up in toluene (20 mL) and the solvent was evaporated. The crude product was dried under high vacuum for 30 min and was dissolved in 15 ml of pyridine. Ac_2O (1.75 µL, 3.74 mmol, 10.0 eq.) was added to the reaction mixture at 0 °C. After stirring at 0 °C for 2 h, the cooling bath was removed and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with water (30 mL) and Et_2O was added (30 mL). The two layers were separated and the aqueous layer was extracted with Et_2O (30 mL, 3 times). The combined organic layers were washed with brine (20 mL), dried with $MgSO_4$, concentrated and the residue was distilled (azeotropic distillation) with toluene (3x 20 mL). The crude product was purified by flash chromatography (pentane/Et_2O 1:2) to yield diacetate **11** (810 mg, 1.55 mmol, 83%) as a colourless oil: R_f = 0.22 (pentane/Et_2O 1:3); $[\alpha]_D^{22}$ = +24.2 (*c* = 1.00, $CHCl_3$); IR (film) ν = 3465 (br), 3067 (w), 3029 (w), 2979 (s), 2945 (s), 2897 (s), 1736 (s), 1371 (s), 1230 (s), 1096(s), 1047 (s), 1023 (s), 911 (s), 733 (s); ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.89 (d, *J* = 7.4 Hz, 3H, CH_3-C(5)), 1.16 (d, *J* = 6.6 Hz, 3H, CH_3-C(3)), 1.50 (d, *J* = 5.8 Hz, 1H, OH), 1.64-1.76 (m, 2H, H-C(3') + H-C(5)), 1.85-1.95 (m, 1H, H-C(3)), 2.03-2.16 (m, 2H, H_2-C(1'')), 2.06, 2.11 (2s, 6H, OAc), 2.28-2.36 (m, 1H, H-C(3')), 3.09, 3.41 (2s, 9H, OCH_3), 3.28-3.33 (m, 1H, H-C(4')), 3.45-3.53 (m, 2H, H_2-C(5')), 3.63-3.67 (m, 1H, H-C(6)), 3.72-3.79 (m, 1H, H-C(4)), 4.56 (s, 2H, C$\underline{H_2}$Ph), 5.04-5.12 (m, 3H, H-C(1') + H_2-C(3'')), 5.44-5.50 (m, 1H, H-C(2')), 5.75-5.86 (m, 1H, H-C(2'')), 7.28-7.39 (m, 5H, arom.); ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ = 4.7 (5-CH_3), 10.7 (3-CH_3), 21.0 (2 x OAc), 35.8 (C(3')), 36.6 (C(3)), 36.8 (C(1'')), 37.2 (C(5)), 47.9 (2-OCH_3), 58.2 (OCH_3), 68.8 (C(2')), 71.8 (C(6)), 72.0 (C(5')), 72.6 (C(1')), 72.8 (CH_2Ph), 73.4 (C(4)), 76.6 (C(4')), 100.6

(C(2)), 117.2 (C(3'')), 127.6, 128.4 (arom.), 134.6 (C(2'')), 138.2 (arom.), 168.9, 170.1 (2 x OAc); HR-MS (ESI) $C_{28}H_{42}O_9Na$: calcd 545.2727; found 545.2728 $[M+Na]^+$.

(2*R*,3*R*,4*S*,5*R*,6*R*,1'*R*,2'*S*,4'*S*)-2-[1',2'-Diacetoxy-5'-benzyloxy-4'-methoxypentyl]-4-triethylsilyloxy-6-allyl-2-methoxy-3,5-dimethyl-2,3,5,6-tetrahydro-4*H*-pyran (12)



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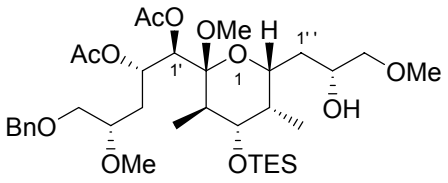
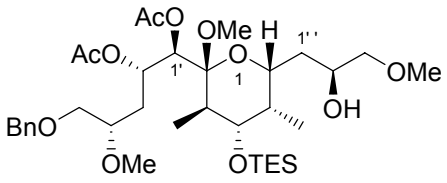
Diacetate **11** (900 mg, 1.72 mmol) was dissolved in CH_2Cl_2 (70 mL). Imidazole (585 mg, 8.6 mmol, 5.0 eq.) and Et_3SiCl (865 µL, 5.16 mmol, 2.0 eq.) were added at room temperature. After 2 h stirring, Et_2O (100 mL) and sat. aq. $NaHCO_3$ (100 mL) were added. The two layers were separated and the aqueous layer was extracted with Et_2O (50 mL, 3 times). The combined organic layers were dried with $MgSO_4$, concentrated and the residue was purified by flash chromatography (pentane/Et_2O 1:1) to yield silyl ether **12** (1.0 g, 1.58 mmol, 92%) as a colourless oil: R_f = 0.62 (pentane/Et_2O 1:2); $[\alpha]_D^{21}$ = +33.7 (*c* = 1.00, $CHCl_3$); IR (film) ν = 3067 (w), 2951 (s), 2877 (s), 1747 (s), 1370 (s), 1227 (s), 1100(s), 1075 (s), 1028 (s), 850 (s), 741 (s); ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.52 (q, *J* = 8.0 Hz, 6H, SiC<u>H</u>$_2$CH$_3$), 0.79 (d, *J* = 6.8 Hz, 3H, CH_3-C(5)), 0.88 (t, *J* = 7.6 Hz, 9H, SiCH$_2$C<u>H</u>$_3$), 0.99 (d, *J* = 6.0 Hz, 3H, CH_3-C(3)), 1.59-1.69 (m, 2H, H-C(3') + H-C(5)), 1.74-1.79 (m, 1H, H-C(3)), 1.94, 2.01 (2s, 6H, OAc), 1.95-2.02 (m, 2H, H_2-C(1'')), 2.17-2.26 (m, 1H, H-C(3')), 3.02, 3.32 (2s, 9H, OCH_3), 3.18-3.26 (m, 1H, H-C(4')), 3.36-3.44 (m, 2H, H_2-C(5')), 3.49-3.54 (m, 1H, H-C(6)), 3.66 (dd, *J* = 10.4, 4.8 Hz, 1H, H-C(4)), 4.47 (s, 2H, C<u>H</u>$_2$Ph), 4.93-5.03 (m, 3H, H-C(1') + H_2-C(3'')), 5.34-5.39 (m, 1H, H-C(2')), 5.67-5.78 (m, 1H, H-C(2'')), 7.18-7.27 (m, 5H, arom.); ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ = 5.0 (Si<u>C</u>H$_2$CH$_3$), 5.0 (5-CH_3), 6.8 (SiCH$_2$<u>C</u>H$_3$), 11.0 (3-CH_3), 20.8 (2 x OAc), 35.5 (C(3')), 36.7 (C(3)), 36.9 (C(1'')), 38.4 (C(5)), 47.7 (2-OCH_3), 58.0 (OCH_3), 68.9 (C(2')), 71.6 (C(6)), 72.0 (C(5')), 72.9 (C(1')), 73.0 (C(4)), 73.3 (CH_2Ph), 76.6 (C(4')), 100.7 (C(2)), 116.9 (C(3'')), 127.3, 127.4, 128.3 (arom.), 134.8 (C(2'')), 138.2 (arom.), 169.7, 169.9 (2 x OAc); HR-MS (ESI) $C_{34}H_{56}O_9SiNa$: calcd 659.3591; found 659.3593 $[M+Na]^+$; Anal. Calc. for $C_{34}H_{56}O_9Si$: C 64.12%; H 8.86%; Found: C 63.96%, H 8.96%.

(2*R*,3*R*,4*S*,5*R*,6*R*,1'*R*,2'*S*,4'*S*,2''*R*)-2-[1',2'-Diacetoxy-5'-benzyloxy-4'-methoxy-pentyl]-4-triethylsilyloxy-6-[2''-hydroxy-3''-methoxypropyl]-2-methoxy-3,5-dimethyl-2,3,5,6-tetrahydro-4*H*-pyran (13) and (2*R*,3*R*,4*S*,5*R*,6*R*,1'*R*,2'*S*,4'*S*,2''*S*)-2-[1',2'-Diacetoxy-5'-benzyloxy-4'-methoxy-pentyl]-4-triethylsilyloxy-6-[2''-hydroxy-3''-methoxypropyl]-2-methoxy-3,5-dimethyl-2,3,5,6-tetrahydro-4*H*-pyran (2''-epimer of 13)



13



2''-epimer of 13

To a stirred suspension of $(DHQD)_2PYR$ (334 mg, 0.38 mmol, 1.0 eq.), $K_3Fe(CN)_6$ (1.25 g, 3.8 mmol, 10 eq.) and K_2CO_3 (105 mg, 0.76 mmol, 2.0 eq.) in t-BuOH-H_2O (1:1, 20 mL) was added $K_2OsO_4.2H_2O$ (7 mg, 0.019 mmol, 0.05 eq.) at 0 °C. The solution was stirred for 2 h and poured on to a t-BuOH-H_2O (1:1, 2 mL) solution of alkene **12** (240 mg, 0.38 mmol) at 0 °C. The mixture was stirred for 6 h at 0 °C. A saturated aqueous solution of Na_2SO_3 (15 mL) was added and the crude material was extracted with EtOAc (30 mL, 3 times). The combined organic extracts were dried (Na_2SO_4) and concentrated to afford the crude diol, which was used immediately in the next step. The crude diol was dissolved in DMF (2 mL) and MeI (472 µL, 7.6 mmol, 20 eq.) followed by Ag_2O (175 mg, 0.76 mmol, 2.0 eq.) were added. The reaction mixture was stirred at room temperature for 20 h and then filtered through Celite. The Celite pad was washed with Et_2O (20 mL). The combined filtrate was washed with H_2O (10 mL, twice), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (pentane/Et_2O 1:2) to yield alcohol **13** (177 mg, 0.26 mmol, 68%, 2 steps) and its 2''-epimer (39 mg). Data for alcohol **13**: colourless oil, R_f = 0.24 (pentane/Et_2O 1:2); $[\alpha]_D^{21}$ = +42.6 (*c* = 0.85, $CHCl_3$), lit. $[\alpha]_D^{24}$ = +45.1 (*c* = 0.85, $CHCl_3$);[6c] IR (film) ν = 3472 (bs), 3063 (w), 2951 (s), 2912 (s), 2878 (s), 1746 (s), 1457 (s), 1371 (s), 1228 (s), 1100(s), 1075 (s), 850 (s), 745 (s); ^{1}H-NMR (400 MHz, C_6D_6) δ = 0.59 (q, *J* = 8.1 Hz, 6H, SiC$\underline{H}_2$CH$_3$), 0.99 (t, *J* = 7.9 Hz, 9H, SiCH$_2$C$\underline{H}_3$), 1.17 (d, *J* = 7.2 Hz, 3H, CH$_3$-C(5)), 1.25-1.34 (m, 1H, Hb-C(1'')), 1.52 (d, *J* = 6.5 Hz, 3H, CH$_3$-C(3)), 1.61-1.70 (m, 1H,

Ha-C(1’’)), 1.73-1.82 (m, 1H, H-C(5)), 1.76, 1.79 (2s, 6H, OAc), 1.89-1.98 (m, 1H, Hb-C(3’)), 2.18-2.33 (m, 2H, H-C(3) + Ha-C(3’)), 2.93 (dd, *J* = 8.8, 8.0 Hz, 1H, Hb-C(3’’)), 3.03-3.07 (m, 1H, Ha-C(3’’)), 3.02, 3.33, 3.36 (3s, 9H, OCH_3), 3.34-3.46 (m, 3H, H_2-C(5’) + H-C(4’)), 4.01-4.07 (m, 1H, H-C(2’’)), 4.09 (dd, *J* = 10.2, 4.8 Hz, 1H, H-C(4)), 4.27-4.36 (m, 3H, H-C(6) + CH_2Ph), 5.49 (d, *J* = 5.3 Hz, 1H, H-C(1’)), 5.91-5.98 (m, 1H, H-C(2’)), 7.06-7.30 (m, 5H, arom.); ^{13}C-NMR (100.6 MHz, C_6D_6) δ = 5.4 (SiCH_2CH_3), 5.8 (5-CH_3), 7.2 ($SiCH_2CH_3$), 11.8 (3-CH_3), 20.55, 20.60 (2x OAc), 36.8, 36.9 ((C(1’’)+ C(3’)), 37.6 (C(3)), 40.3 (C(5)), 48.1 (2-OCH_3), 58.1, 58.6 (2 x OCH_3), 66.7 (C(2’’)), 68.1 (C(6)), 69.3 (C(2’)), 72.6 (C(5’)), 73.4 (CH_2Ph), 73.6, 73.7 (C(4), + C(1’)), 77.1 (C(4’)), 77.7 (C(3’’)), 101.4 (C(2)), 127.6, 127.7, 128.5 (arom.), 139.1 (arom.), 169.4, 169.7 (2 x OAc); HR-MS (ESI) $C_{35}H_{60}O_{11}SiNa$: calcd 707.3803; found 707.3806 $[M+Na]^+$; Anal. Calc. for $C_{35}H_{60}O_{11}Si$: C 61.37%; H 8.83%; Found: C 61.36%, H 8.75%.

Data for the 2’’-epimer of **13**: colourless oil, R_f = 0.23 (pentane/Et_2O 1:2); ^{1}H-NMR (400 MHz, C_6D_6) δ = 0.61 (q, *J* = 7.6 Hz, 6H, $SiCH_2CH_3$), 1.00 (t, *J* = 8.0 Hz, 9H, $SiCH_2CH_3$), 1.16 (d, *J* = 6.8 Hz, 3H, CH_3-C(5)), 1.26-1.37 (m, 1H, Hb-C(1’’)), 1.51 (d, *J* = 6.8 Hz, 3H, CH_3-C(3)), 1.58-1.65 (m, 1H, Ha-C(1’’)), 1.73-1.82 (m, 1H, H-C(5)), 1.74, 1.76 (2s, 6H, OAc), 1.88-1.96 (m, 1H, Hb-C(3’)), 2.22-2.34 (m, 2H, H-C(3) + Ha-C(3’)), 3.09 (dd, *J* = 8.8, 4.8 Hz, 1H, Hb-C(3’’)), 3.18-3.22 (m, 1H, Ha-C(3’’)), 3.05, 3.23, 3.34 (3s, 9H, OCH_3), 3.32-3.45 (m, 3H, H_2-C(5’) + H-C(4’)), 3.86-3.94 (m, 1H, H-C(2’’)), 4.03-4.11 (m, 2H, H-C(4) + H-C(6)), 4.31 (dd, *J* = 15.2, 12.0 Hz, 2H, CH_2Ph), 5.46 (d, *J* = 5.6 Hz, 1H, H-C(1’)), 5.93-5.98 (m, 1H, H-C(2’)), 7.06-7.28 (m, 5H, arom.); HR-MS (ESI) $C_{35}H_{60}O_{11}SiNa$: calcd 707.3803; found 707.3804 $[M+Na]^+$

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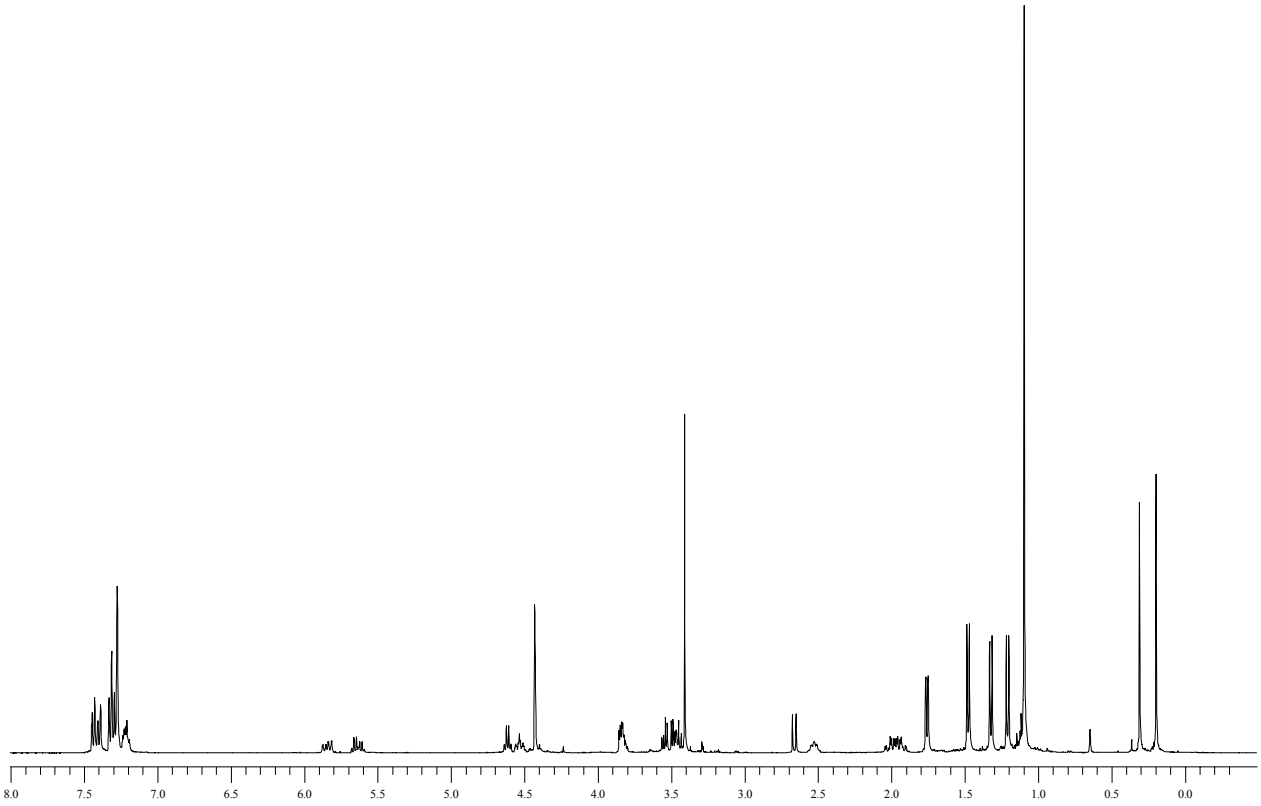
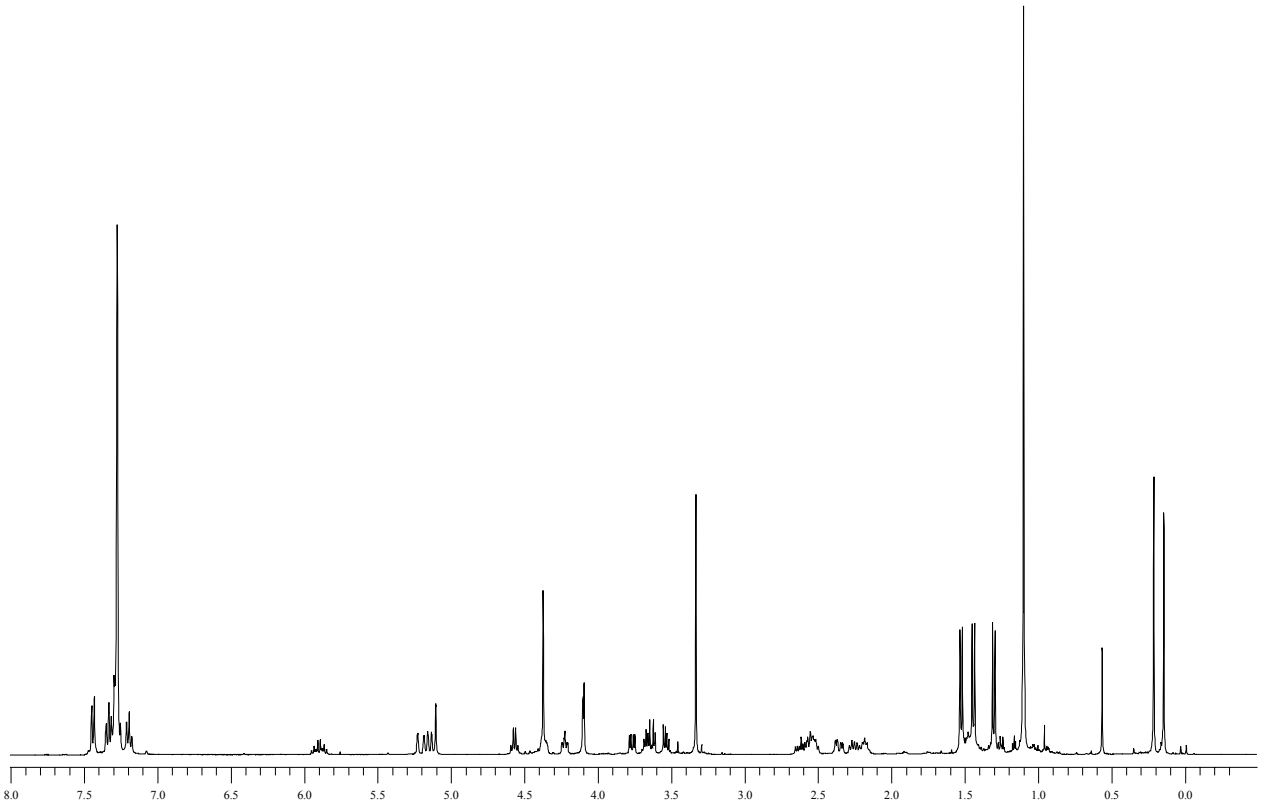
^{1}H NMR spectrum: Ketone 9



Alkene 10



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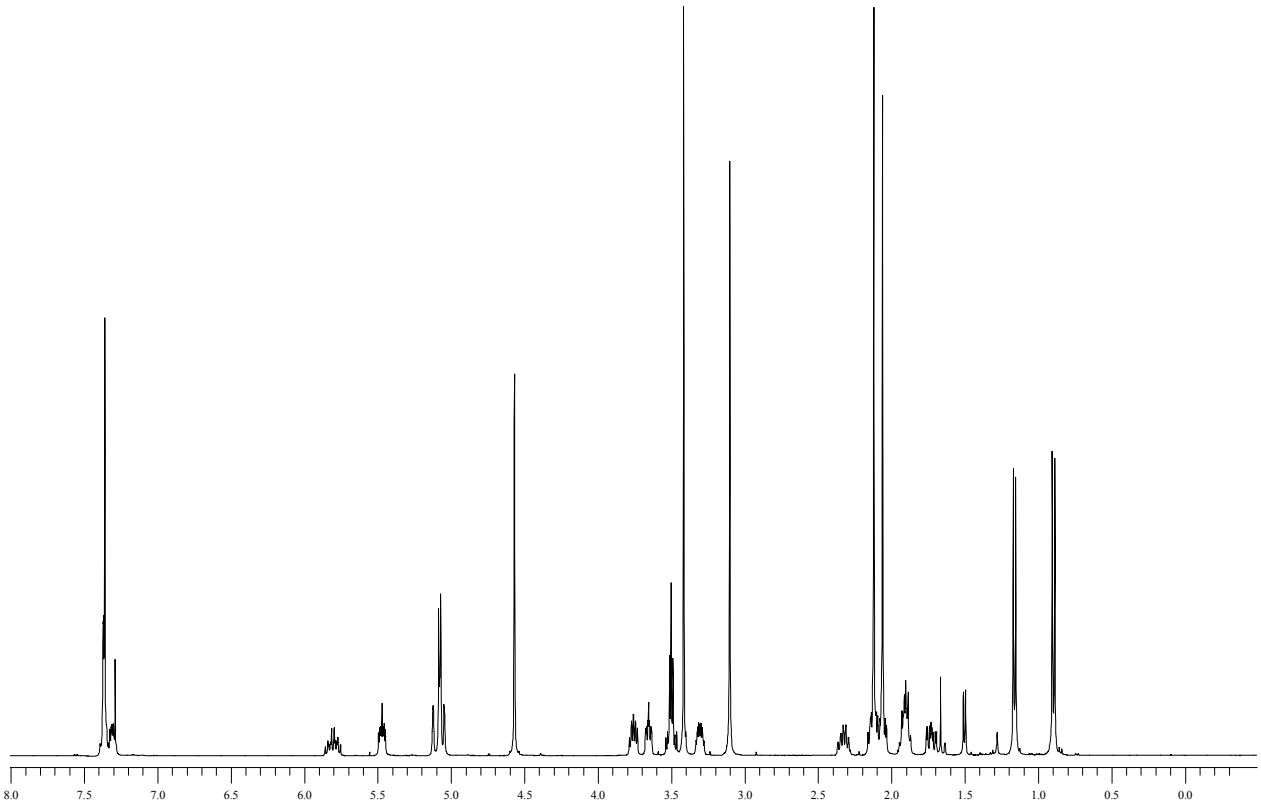

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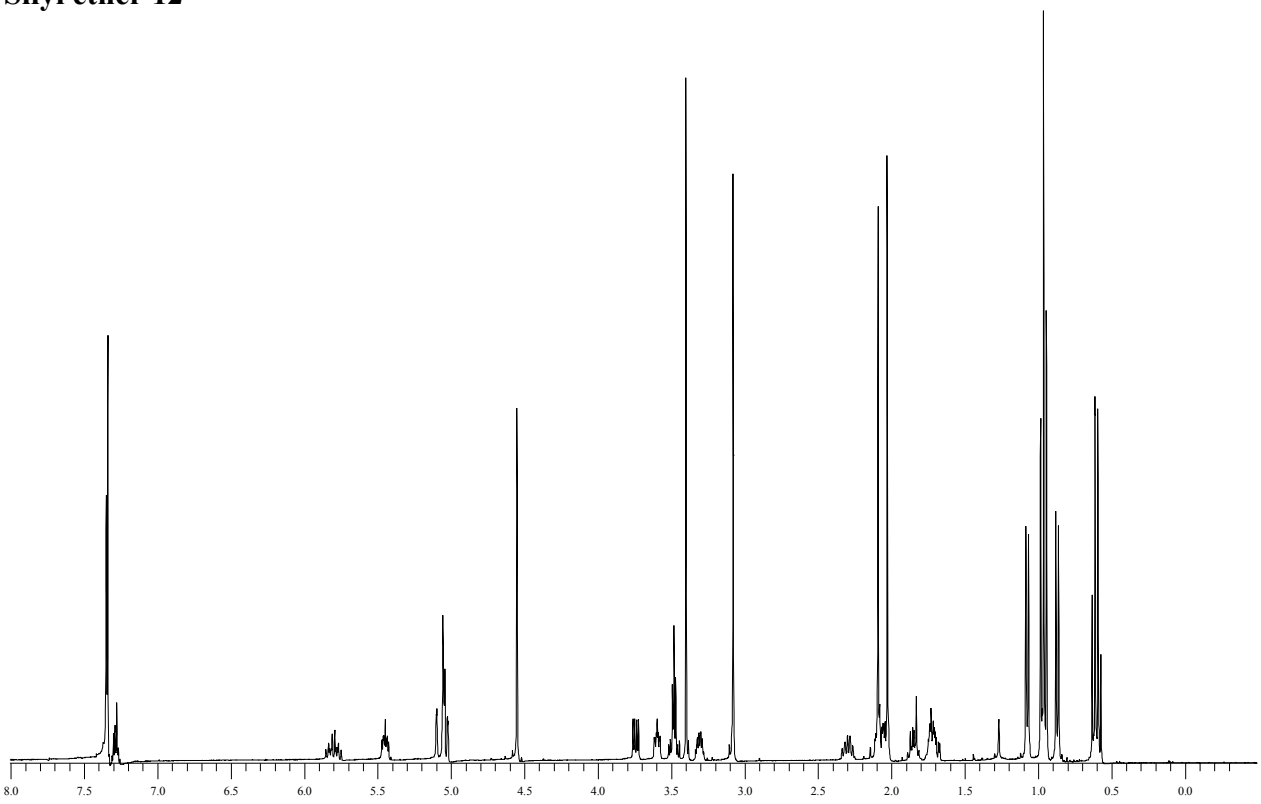

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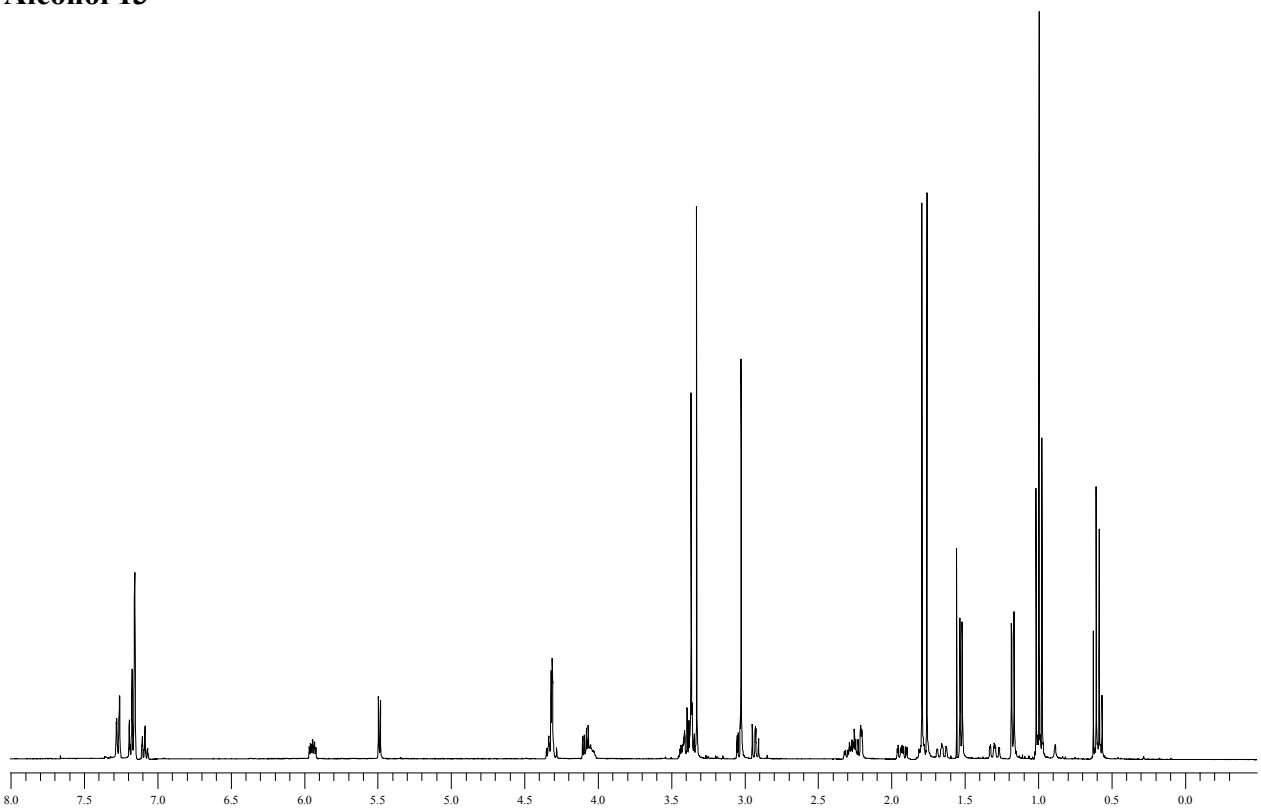

2''-epimer of alcohol 13