Total Synthesis of RK-397

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SUPPORTING INFORMATION

General Experimental

^1H, ^{13}C and ^{31}P NMR spectra were recorded on Varian Unity-400 (400 MHz ^1H, 100 MHz ^{13}C, 162 MHz ^{31}P), Unity-500 (500 MHz ^1H, 125 MHz ^{13}C, 202 MHz ^{31}P) and Varian Unity Inova 500 (500 MHz ^1H) spectrometers in deuterochloroform unless otherwise stated. Data are reported in the following order: chemical shift in ppm (δ); multiplicities are indicated (br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet)); coupling constants, *J*, are reported in hertz (Hz); integration is provided; and assignment is indicated. ^1H and ^{13}C NMR assignments are corroborated by 2D experiments (HETCOR and COSY). Spectra are available on request from denmark@scs.uiuc.edu. Mass spectrometry was performed by the University of Illinois Mass Spectrometry Center. Electron impact (EI) spectra were performed on a Micromass 70-VSE spectrometer, chemical ionization (CI) spectra were obtained on a Micromass 70-VSE spectrometer using methane as the carrier gas, field ionization (FI) spectra were obtained from Micromass 70-VSE spectrometer, electrospray ionization (ESI) spectra were obtained from Micromass Q-TOF spectrometer. Data are reported in the form of *m*/*z* (intensity relative to base peak = 100). Infrared spectra (IR) were recorded on a Mattson Galaxy 5020 spectrophotometer. Peaks are reported in cm^{-1} with indicated intensities: s (strong, 67 – 100% absorption), m (medium, 34 – 66%), w (weak, 0 – 33%). UV/Vis spectrum was obtained from HP8453 spectrophotometer. Optical rotations were measured on a Jasco DIP-360 digital polarimeter and are reported in the standard format for [α]. The CD spectrum was obtained with Jasco J-720 spectropolarimeter. Elemental analyses were performed by the University of Illinois Microanalytical Service Laboratory.

Analytical thin-layer chromatography was performed on Merck silica gel plates with F-254 indicator. Visualization was accomplished by UV light, iodine, potassium permanganate solution ($KMnO_4$), phosphomolybdic acid stain(PMA), *p*-anisaldehyde stain or dinitrophenylhydrazine (DNP) solution. Column chromatography was performed by the method of Still[1] with 32-63 mm silica gel (Merck). Bulb-to-bulb distillations were performed on a Büchi GKR-50 Kugelrohr and boiling points (bp) correspond to uncorrected, air bath temperatures. Analytical supercritical fluid chromatography (SFC) was performed on a Berger Instruments packed-column SFC with built in photometric detector. Analytical columns used were Daicel Chiralpak AD and AS, Chiralcel OJ and OD and Regis (*R*,*R*)-Welk-01. Analytical and preparative HPLC were performed on Rainin Model SD 200 equipped with UV absorbance detector (Model UV 1) at a wavelength of 360 nm. The products were analyzed and purified on Vydac C-18 (analytical column, 250 x 4.6 mm; preparative column, 250 x 22 mm). Products were eluted with 40/60 to 20/80 water/methanol with flow rates of 1 mL/min for analytical and 8 mL/min for preparative runs. Melting points (mp) were determined in sealed capillary tubes on a Thomas-Hoover melting point apparatus and are corrected.

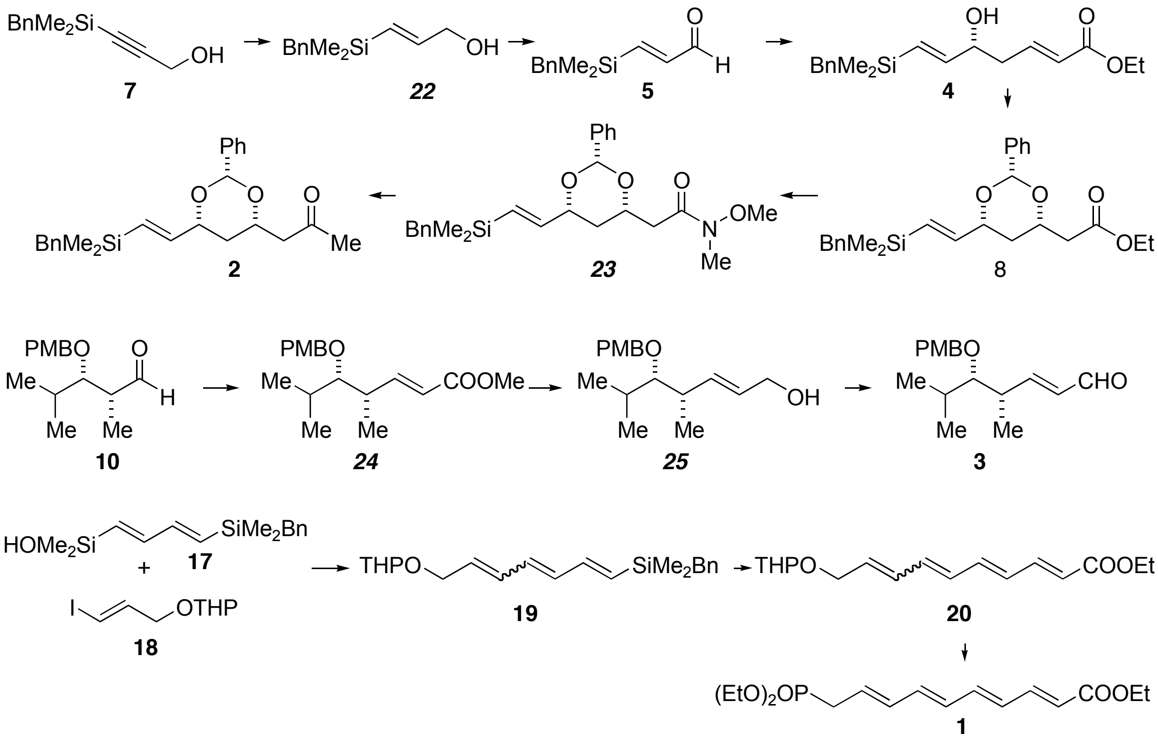
All reactions were performed in oven (140 °C) and/or flame-dried glassware under an atmosphere of dry argon, unless otherwise stated. All reaction temperatures correspond to internal temperatures measured by Teflon-coated thermocouples unless otherwise noted. Solvents for extraction and chromatography were technical grade and distilled from the indicated drying agents: dichloromethane (CH_2Cl_2), pentane, hexane: $CaCl_2$; ethyl acetate (EtOAc): K_2CO_3; acetone and methanol (MeOH) were reagent grade. *n*-Butyllithium was titrated according to the method of Gilman.[2] “Brine” refers to a saturated solution of NaCl. Polymer-bound piperidine (200 – 400 mesh, 3.0 mmol/g loading, 1% cross-lined with divinylbenzene) was purchased from Aldrich and used as received.

Literature Preparations

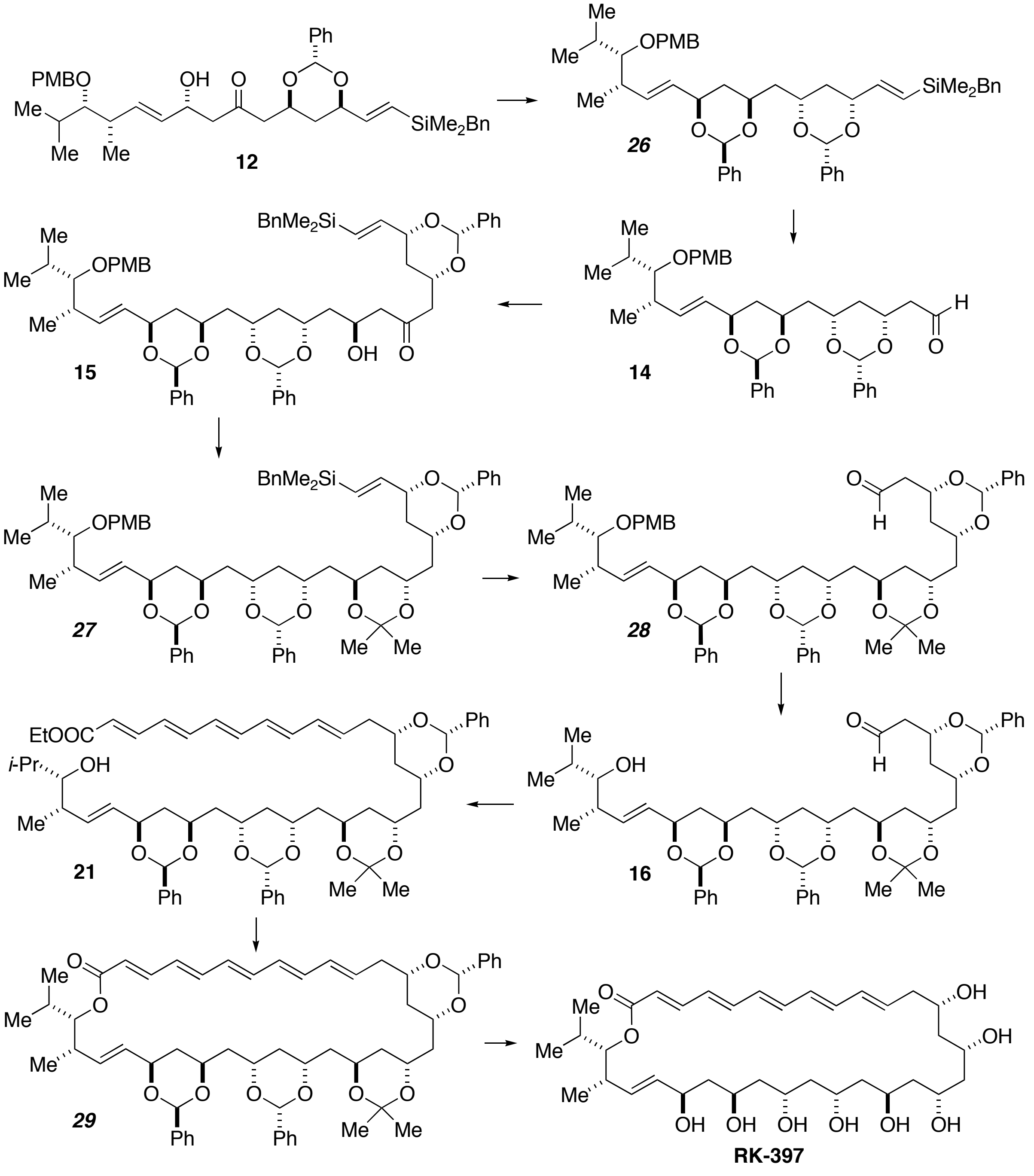
The following compounds were prepared by literature methods: 3-benzyldimethylsilylpropargyl alcohol (**7**)[3], 1-*tert*-butylsilyloxy-1-ethoxy-1,3-butadiene (**6**)[4], (2*R*,3*R*)-3-*p*-methoxybenzyloxy-2,4-dimethylpentanal (**10**)[5], 1-dimethylhydroxylsilyl-4-benzyldimethylsilyl-1,3-butadiene (**17**)[6], 3-iodo-1-tetrahydropyranyloxy-2-propene (**18**)[7], ethyl 3-iodoacrylate[8].

Tetraenephosphonate **1** was prepared from THP ether **20** according to the procedure described by Mori et al.[9]

Scheme 1. Synthesis of RK-397. Characterized compounds not appearing in the text are shown in bold italic type.

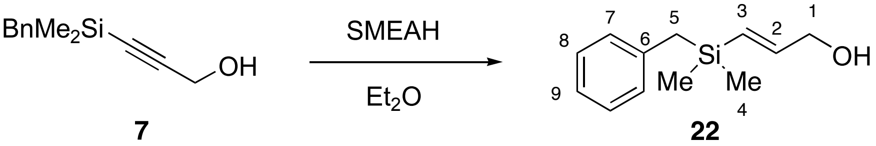


Scheme 2. Synthesis of RK-397 (continued).



Experimental Procedures

(*E*)-3-Benzyldimethylsilyl-2-propen-1-ol (22)



To a 500-mL 3-neck flask equipped with a 250-mL, pressure-equalized addition funnel, a septum (pierced with thermocouple probe), a gas inlet and a magnetic stir bar were placed sodium methoxyethoxyaluminium hydride (40.8 mL, 136 mmol, 1.25 equiv) and ether (100 mL). The solution was cooled to 0 ºC using an ice bath. To the solution was added solution of **7** (22.3 g, 109 mmol) in 30 mL of ether dropwise over 1 h maintaining the internal temperature below 5 ºC. After the addition, the reaction mixture was warmed to rt and was stirred for 1 h. The reaction mixture was cooled to 0 ºC using an ice bath. The reaction mixture was carefully quenched with 1.8 M H_2SO_4 (200 mL) maintaining the internal temperature below 10 ºC. The biphasic mixture was transferred to a 1-L separatory funnel, and the phases were separated. The aqueous layer was extracted with pentane (2 x 200 mL). The combined organic layers were washed with saturated $NaHCO_3$ (2 x 100 mL) and with brine (100 mL). The solution was dried over Na_2SO_4 and was concentrated under reduced pressure. The residue was distilled to afford 16.6 g (80.6 mmol, 74%) of **22** as a clear, colorless oil.

<u>Data for **22**</u>:

<u>bp</u>: 125 ºC (0.5 mmHg)

<u>^{1}H NMR</u>: (500 MHz, $CDCl_3$)

7.22 (t, *J* = 7.5, 2 H, 2 x HC(8)); 7.07 (t, *J* = 7.5, 1 H, HC(9)); 6.99 (d, *J* = 7.0, 2 H, 2 x HC(7)); 6.16 (dt, *J* = 18.5, 4.3, 1 H, HC(2)); 5.92 (dt, *J* = 18.5, 1.8, 1 H, HC(3)); 4.18 (m, 2 H, $H_2C(1)$), 2.14 (s, 2 H, $H_2C(5)$); 1.36 (t, *J* = 6.0, 1 H, HO); 0.06 (s, 6 H, 2 x $H_3C(4)$)

<u>^{13}C NMR</u>: (126 MHz, $CDCl_3$)

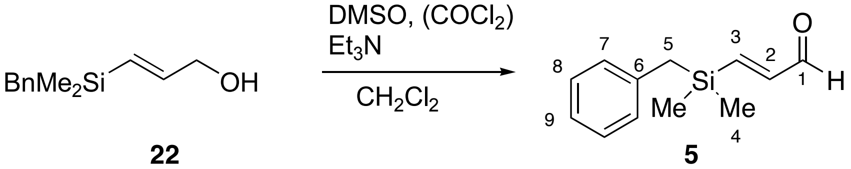
146.02 (C(2)); 139.83 (C(6)); 128.22 (2 x C(8)); 128.11 (2 x C(7)); 127.30 (C(3));

124.00 (C9)); 65.42 (C(1)); 25.37 C(5)); -3.50 (C4))

IR:	(neat)
	3368 (br, s); 3081 (m); 3024 (m); 2955(s); 2917(s); 1618 (m); 1600 (m); 1492 (s); 1451(m); 1407 (w); 1248 (m); 1207 (m); 1154 (m); 1057 (m)
MS:	(FI)
	206 (100, M^+); 170 (12); 156 (10); 126 (10); 115 (10); 114 (13); 60 (17)
TLC:	R_f 0.28 (hexane/EtOAc, 1/1) [silica gel, $KMnO_4$]
Analysis:	$C_{12}H_{18}OSi$ (206.36)

Calcd:	C, 69.84%;	H, 8.39%
Found:	C, 69.67%;	H, 8.54%

(*E*)-3-Dimethylsilyl-2-propenal (5)



In a 500-mL, Schlenk flask were placed oxalyl chloride (10.2 mL, 117 mmol, 1.5 equiv) and dichloromethane (200 mL). The solution was cooled to –70 °C (internal temperature) using an isopropanol/dry ice bath. To the solution was added dimethyl sulfoxide (13.8 mL, 194 mmol, 2.5 equiv) dropwise maintaining internal temperature below –50 °C over 20 min. The reaction mixture was stirred for 10 min. To the reaction mixture was added solution of **22** (16.0 g, 77.7 mmol) in 50 mL of dichloromethane dropwise over 20 min maintaining internal temperature below –50 °C. The reaction mixture was stirred for 20 min. To the reaction mixture was added triethylamine (38.0 mL, 272 mmol, 3.5 equiv) dropwise over 30 min maintaining internal temperature below –30 °C. The reaction mixture was stirred for 30 min at –70 ^{O}C and for 1 h after warming to 0 °C. To the reaction mixture was added 100 mL of water and 100 mL of pentane. The biphasic solution was transferred to a 1-L separatory funnel. The organic layer was successively washed with 1 M HCl (100 mL), water (100 mL), saturated $NaHCO_3$ (100 mL) and brine (100 mL). The solution was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting oil was distilled under vacuum to afford 13.1 g (64.1 mmol, 83%) of **5** as a clear, pale-yellow oil.

Data for **5**:

bp: 108 °C (0.5 mm Hg)

^{1}H NMR: (500 MHz, $CDCl_3$)
9.49 (d, *J* = 8.0, 1 H, HC(1)); 7.23 (t, *J* = 7.5, 2 H, 2 x HC(8)); 7.11 (t, *J* = 7.0, 1 H, HC(9)); 6.99 (d, *J* = 7.0, 2 H, 2 x HC(7));)); 7.14 (d, *J* = 19.0, 1 H, HC(3)); 6.48 (dd, *J* = 18.5, 7.5, 1 H, HC(2); 2.23 (s, 2 H, $H_2C(5)$); 0.16 (s, 6 H, 2 x $H_3C(4)$)

^{13}C NMR: (126 MHz, $CDCl_3$)
194.53 (C(1)); 156.63 (C(3)); 144.87 (C(2)); 138.44 (C(6)); 128.38 (2 x C(8)); 128.13 (2 x C(7)); 124.53 (C(9)); 24.90 (C(5)); -4.01 (2 x C(4))

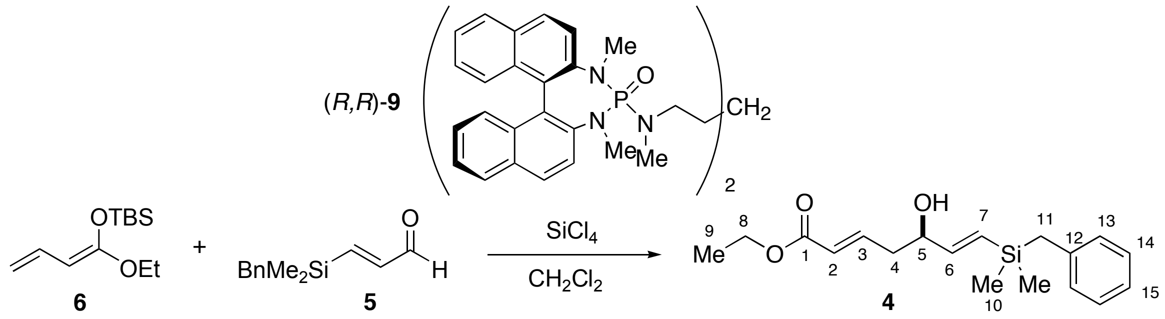
IR: (neat)
3059 (w); 3024 (m); 2958(m); 2798(m); 1692 (s); 1599 (m); 1493 (m); 1452(m); 1407 (w); 1251 (m); 1206 (m); 1157 (m); 1085 (m)

MS: (FI)
204 (100, M^+)

TLC: R_f 0.25 (hexane/EtOAc, 5/1) [silica gel, $KMnO_4$]

Analysis: $C_{12}H_{16}OSi$ (204.34)
Calcd: C, 70.53%; H ,7.89%
Found: C, 70.25%; H, 8.04%

(5*R*)-Ethyl 7-benzyldimethylsilyl-5-hydroxy-hepta-2,6-dienoate (4)



In a 100-mL Schlenk flask were placed phosphoramide (*R,R*)-**9** (220 mg, 0.26 mmol, 0.015 equiv), dichloromethane (50 mL), aldehyde **5** (3.72 g, 18.2 mmol) and diisopropylethylamine (0.65 mL, 3.64 mmol, 0.20 equiv). The solution was cooled to –70 ºC (internal temperature measured by thermocouple) using an isopropanol/dry ice bath. To the reaction mixture was added silicon tetrachloride (2.29 mL, 20.0 mmol, 1.1 equiv) followed by ketene acetal **6** (5.00 g, 21.8 mmol, 1.2 equiv) dropwise over 20 min maintaining the internal temperature below –68 ºC. The reaction mixture was stirred at –70 ºC for 3 hrs. Then the reaction mixture was transferred via cannula into a vigorously stirring saturated aqueous $NaHCO_3$ solution (200 mL) at 0 ºC (bath temperature). The resulting mixture was stirred vigorously for 3 h at rt. The solution was filtered through a layer of Celite, and the filtrate was transferred into a 500-mL separatory funnel. The aqueous layer was extracted with dichloromethane (2 x 100 mL), and the combined organic layers were washed with brine (100 mL). The organic solution was dried over Na_2SO_4 and concentrated under reduced pressure to give 8.7 g of a crude oil. The crude product was chromatographed (silica gel, hexane/EtOAc 3/1, 60 mm) to afford 4.35 g (13.7 mmol, 75%) of **4** as a clear, colorless oil.

Data for **4**:

^{1}H NMR: (500 MHz, $CDCl_3$)

7.20 (t, *J* = 7.7, 2 H, 2 x HC(14)); 7.06 (t, *J* = 7.3, 1 H, HC(15)); 6.98 (d, *J* = 7.1, 2 H, 2 x HC(13)); 6.94 (dd, *J* = 15.6, 7.5, 1 H, HC(3)); 6.01 (dd, *J* = 18.8, 5.2, 1 H, HC(6)); 5.90 (dd, *J* = 15.8, 1.5, 1 H, HC(2); 5.87 (dd, *J* = 18.9, 1.2, 1 H, HC(7)); 4.22 (qd, *J* = 5.6, 1.1, 1 H, HC(5)); 4.19 (q, *J* = 7.2, 2 H, $H_2C(8)$); 2.34-

2.46 (m, 2 H, $H_2C(4)$); 2.14 (s, 2 H, $H_2C(11)$); 1.60 (d, *J* = 4.5, 1 H, HO); 1.28 (t, *J* = 7.1, 3 H, $H_3C(9)$); 0.06 (s, 6 H, 2 x $H_3C(10)$)

^{13}C NMR: (126 MHz, $CDCl_3$)

166.24 (C(1)); 148.18 (C(6)); 144.54 (C(3)); 139.58 (C(12)); 128.12 (2 x C(13)); 128.08 (C(7)); 128.03 (2 x C(14)); 123.97 (C(15)); 123.87 (C(2)); 72.74 (C(5)); 60.23 (C(8)); 39.54 (C(4)); 25.78 (C(11)); 14.16 (C(9)); -3.53 (2 x C(10))

IR: (neat)

3437 (br, m); 3060 (w); 3024 (m); 2982 (m); 2956(m); 2898(m); 1720 (s); 1655 (m); 1619 (w); 1600 (m); 1493 (m); 1452(m); 1396 (w); 1369 (m); 1316 (m); 1249 (m); 1207 (m); 1157 (m); 1096 (m); 1042 (m)

MS: (FI)

319 (100, M^+); 227 (55)

Opt. Rot.: $[\alpha]_D^{24}$ –5.79 (c = 0.36, EtOH)

TLC: R_f 0.08 (hexane/EtOAc, 5/1) [silica gel, $KMnO_4$]

SFC: (Chiralpak-AD, 3.0 mL/min, 4.0% MeOH, 125 bar);

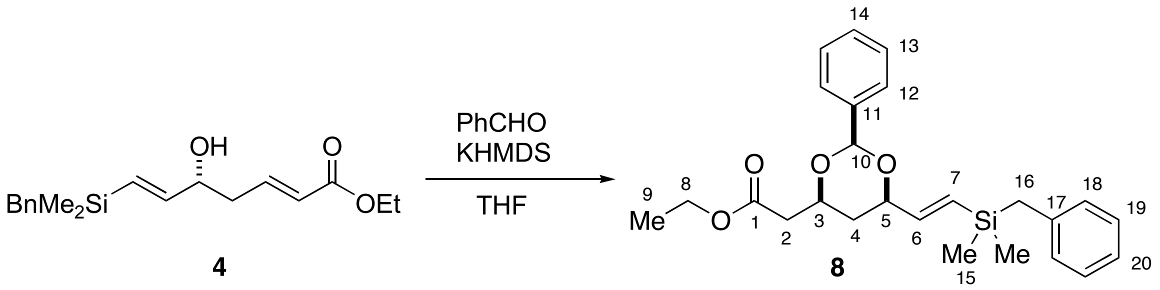
(5*R*)-**4**: 5.31 min (98.1%); (5*S*)-**4**: 5.74 min (1.9%)

Analysis: $C_{18}H_{26}O_3Si$ (318.48)

Calcd: C, 67.88%; H, 8.23%

Found: C, 67.59%; H, 8.41%

(2'*R*, 4'*S*, 6'*R*)-Ethyl (2'-phenyl-6'-(2-benzyldimethylsilylethenyl)-[1,3]dioxan-4'-yl)-acetate (8)



In a 500-mL Schlenk flask were placed **4** (3.41 g, 10.7 mmol), benzaldehyde (1.23 mL, 11.8 mmol, 1.1 equiv) and THF (100 mL). The solution was cooled to 0 ºC (internal temperature monitored by thermocouple) using ice bath. To the solution was added 0.5 M KHMDS in THF (2.13 mL, 1.07 mmol, 0.1 equiv) in one portion. The reaction mixture turned dark yellow and the internal temperature rose to 5 ºC. The reaction mixture was stirred for 20 min at 0 ºC. To the reaction mixture were added benzaldehyde (1.23 mL, 11.8 mmol, 1.1 equiv) and 0.5 M KHMDS in THF (2.13 mL, 1.07 mmol, 0.1 equiv). The reaction mixture was stirred for 20min at 0ºC. The addition and stirring sequence was repeated one more time before the reaction mixture was quenched with cold (0 ºC, bath temperature) pH 7 phosphate buffer (100 mL). The biphasic mixture was poured into a 500-mL separatory funnel and was extracted with pentane (200 mL). The organic layer was washed with brine (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Most of the remaining benzaldehyde was removed under vacuum with stirring. The resulting crude oil was chromatographed (silica gel, hexanes/EtOAc 9/1, 60 mm) to afford 3.38 g (7.96 mmol, 74%) of **8** as a pale-yellow oil.

Data for **8**:

^{1}H NMR: (500 MHz, $CDCl_3$)

7.52 (d, *J* = 6.7, 2 H, 2 x HC(12)); 7.33 – 7.38 (m, 3 H, HC(14), 2 x HC(13)); 7.20 (t, *J* = 7.6, 2 H, 2 x HC(19)); 7.07 (t, *J* = 7.4, 1 H, HC(20)); 6.98 (d, *J* = 7.2, 2 H, 2 x HC(18)); 6.07 (dd, *J* = 19.0, 4.6, 1 H, HC(6)); 5.94 (dd, J = 19.1, 1.2, 1 H, HC(7); 5.62 (s, 1 H, HC(10));4.32 – 4.40 (m, 2 H, HC(3), HC(5)); 4.18 (q, *J* = 7.2, 2 H, $H_2C(8)$); 2.64 (ABX, J_{AB} = 5.7, 2 H, $H_2C(2)$); 2.13 (s, 2 H, $H_2C(16)$); 1.78 (dt, *J* = 13.0, 7.3, 1 H, $H_{eq}C(4)$); 1.53 (q, *J* = 11.4, 1 H, $H_{ax}C(4)$); 1.28 (t, *J* = 7.1, 3 H, $H_3C(9)$); 0.05 (s, 6 H, 2 x $H_3C(15)$)

^{13}C NMR: (126 MHz, $CDCl_3$)

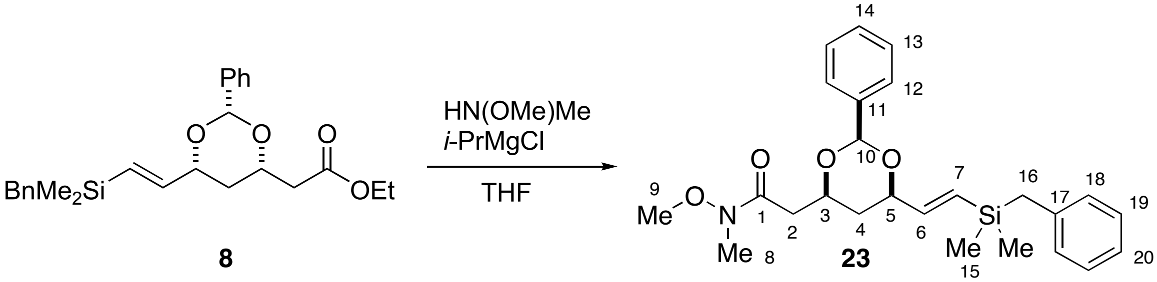
170.61 (C(1)); 145.69 (C(6)); 139.62 (C(17)); 138.19 (C(11)); 128.64 (C(14)); 128.14 (C7)); 128.08 (2 x C(13)); 128.05 (2 x (C(18)); 128.00 (2 x C(19)); 126.10 (C(12)); 123.91 (C(20)); 100.42 (C(10)); 78.22 (C(5)); 72.97 (C(3)); 60.50 (C(8)); 40.75 (C(2)); 36.00 (C(4)); 25.71 (C(16)); 14.06 (C(9)); -3.71, -3.66 (2 x C(15))

IR: (neat)

3061 (w); 3024 (m); 2981 (m); 2957(m); 2897(m); 1736 (s); 1623 (m); 1600 (m); 1493 (m); 1452(m); 1401 (m); 1373 (m); 1339 (m); 1314 (m); 1250(m); 1206 (m); 1158 (m); 1112 (m); 1097 (m); 1056 (m)

MS:	(FI)
	425 (52, M$^+$); 424 (27); 423 (31); 422 (18); 351 (19); 335 (88); 333 (47); 317 (43); 316 (35); 291 (38); 290 (97); 243 (38); 220 (92); 219 (29); 190 (67); 128 (27); 106 (100); 91 (45)
Opt. Rot.:	$[\alpha]^{24}_D$ + 15.3 (c = 0.57, EtOH)
TLC:	R_f 0.33 (pentane /ether 9/1) [silica gel, $KMnO_4$]
Analysis:	Calc for $C_{25}H_{32}O_4Si$ (424.60)
	Calcd: C, 70.72%; H, 7.60%
	Found: C, 70.73%; H, 7.52%

(2'*R*, 4'*S*, 6'*R*)-*N,O*-Dimethyl (2'-phenyl-6'-(2-benzyldimethylsilylethenyl)-[1,3]dioxan-4'-yl)-acetamide (23)



In a 50-mL Schlenk flask were placed **8** (2.20 g, 5.18 mmol), *N,O*-dimethylhydroxylamine hydrochloride (758 mg, 7.77 mmol, 1.5 equiv) and THF (11 mL). The reaction mixture was cooled to –20 °C (internal temperature monitored by thermocouple) using NaCl/ice bath. To the reaction mixture was added 2 M solution of isopropylmagnesium chloride in THF (7.77 mL, 15.5, 3 equiv) dropwise over 30 min maintaining internal temperature below –10 °C. The reaction mixture was stirred at –20 °C for 20 min and was quenched with saturated aqueous NH_4Cl solution (20 mL). The reaction mixture was poured into a 250-mL separatory funnel and extracted with pentane (100 mL). The organic phase was washed with brine (25 mL), dried over Na_2SO_4 and concentrated. The resulting oil was chromatographed (silica gel, hexane/EtOAc 2/1, 50 mm) to afford 1.98 g (4.50 mmol, 87%) of **23** as a clear, colorless oil.

Data for **23**:

^{1}H NMR: (500 MHz, $CDCl_3$)

7.53 (dd, *J* = 8.0, 1.4, 2 H, 2 x HC(12)); 7.32 – 7.38 (m, 3 H, HC(14), 2 x HC(13)); 7.21 (t, *J* = 7.7, 2 H, 2 x HC(19)); 7.07 (t, *J* = 7.5, 1 H, HC(20)); 6.99 (d, *J* = 7.1, 2 H, 2 x HC(18)); 6.09 (dd, *J* = 19.1, 4.7, 1 H, HC(6)); 5.95 (dd, *J* = 18.9, 1.3, 1 H, HC(7)); 5.64 (s, 1 H, HC(10)); 4.38 – 4.46 (m, 2 H, HC(3), HC(5)); 3.68 (s, 3 H, $H_3C(9)$); 3.20 (s, 3 H, $H_3C(8)$); 2.79 (ABX, J_{AB} = 15.6, 2 H, $H_2C(2)$); 2.14 (s, 2 H, $H_2C(16)$); 1.90 (dt, *J* = 13.2, 2.4, 1 H, $H_{eq}C(4)$); 1.52 (q, *J* = 12.4, 1 H, $H_{ax}C(4)$); 0.05, 0.04 (s, 6 H, 2 x $H_3C(15)$)

^{13}C NMR: (126 MHz, $CDCl_3$)

171.24 (C(1)); 145.90 (C(6)); 139.78 (C(17)); 138.43 (C(11)); 128.73 (C(7)); 128.24 (2 x C(18)); 128.17 (2 x C(13), 2 x C(19)); 128.09 (C(14)); 126.24 (2 x C(12)); 123.97 (C(20)); 100.70 (C(10)); 78.46 (C(5)); 73.40 (C(3)); 61.37 (C(9)); 38.08 (C(2)); 36.53 (C(4)); 31.93 (C(8)); 25.81 (C(16)); -3.63, -3.60 (2 x C(15))

IR: (neat)

3060 (w); 3024 (m); 2998 (m); 2956(m); 2916 (m); 2894(m); 1664 (s); 1623 (s); 1600 (m); 1493 (m); 1452(m); 1413 (m); 1388 (m); 1336 (m); 1313 (w); 1248(m); 1208 (m); 1176 (m); 1128 (m); 1097 (m); 1056 (m); 1027 (m)

MS: (FI)

440 (3, M^+); 437 (14); 436 (43); 434 (11); 423 (22); 422 (67); 420 (13); 409 (31); 408 (100); 381 (23); 380 (77); 366 (28)

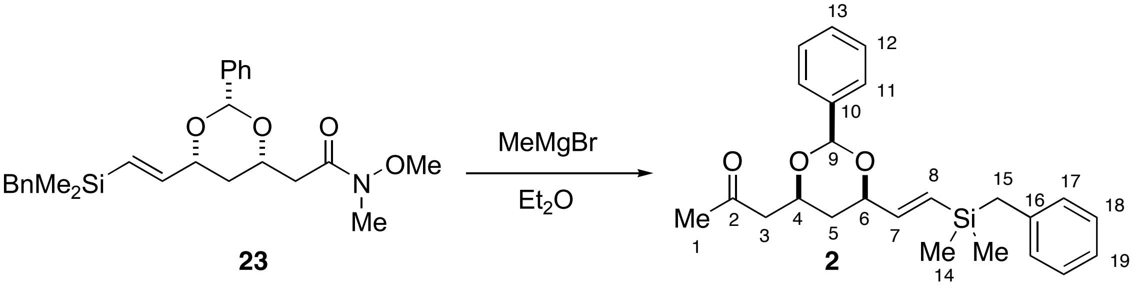
Opt. Rot.: $[\alpha]_D^{24}$ + 12.5 (c = 0.50, EtOH)

TLC: R_f 0.08 (hexane/EtOAc 2/1) [silica gel, $KMnO_4$]

Analysis: Calc for $C_{25}H_{33}NO_4Si$ (439.62)

Calcd:	C, 68.30%;	H, 7.57%;	N, 3.19%
Found:	C, 68.28%;	H, 7.61%;	N, 3.29%

(2'*R*, 4'*S*, 6'*R*)-3-(2'-Phenyl-6'-(2-benzyldimethylsilylethenyl)-[1,3]dioxan-4'-yl)-propan-2-one (2)



In a 100-mL Schlenk flask were placed **23** (1.49 g, 3.39 mmol) and ether (20 mL). The reaction mixture was cooled to 0 °C in an ice bath. To the solution was added a 3 M solution of methylmagnesium bromide in ether (1.69 mL, 5.08 mmol, 1.5 equiv) dropwise over 1 min. The reaction mixture was allowed to warm to rt and was stirred for 10 h. The reaction was quenched with saturated aqueous NH_4Cl solution (10 mL) and was poured into a 125-mL separatory funnel, and the biphasic mixture was extracted with pentane (80 mL). The organic phase was washed with brine (20 mL), dried over Na_2SO_4 and concentrated. The resulting oil was chromatographed (silica gel, hexanes/EtOAc 3/1, 50 mm) to afford 1.20 g (3.04 mmol, 90%) of **2** as a clear, colorless oil.

Data for **2**:

^{1}H NMR: (500 MHz, $CDCl_3$)

7.51 (dd, *J* = 7.8, 1.5, 2 H, 2 x HC(11)); 7.32 – 7.38 (m, 3 H, HC(13), 2 x HC(12)); 7.20 (t, *J* = 7.7, 2 H, 2 x HC(18)); 7.07 (t, *J* = 7.3, 1 H, HC(19)); 6.99 (d, *J* = 7.3, 2 H, 2 x HC(17)); 6.07 (dd, *J* = 18.9, 4.5, 1 H, HC(7)); 5.94 (dd, *J* = 18.8, 12, 1 H, HC(8)); 5.61 (s, 1 H, HC(9)); 4.32 – 4.40 (m, 2 H, HC(4), HC(6)); 2.75 (ABX, J_{AB} = 16.4, J_{AX} = 7.0, J_{BX} = 5.7, 2 H, $H_2C(3)$); 2.22 (s, 3 H, $H_3C(1)$); 2.13 (s, 2 H, $H_2C(15)$); 1.78 (dt, J = 13.1, 2.5, 1 H, $H_{eq}C(5)$); 1.47 (dt, *J* = 13.0, 11.3, 1 H, $H_{ax}C(5)$); 0.05, 0.04 (s, 6 H, 2 x $H_3C(14)$)

^{13}C NMR: (126 MHz, $CDCl_3$)

206.25 (C(2)); 145.67 (C(8)); 139.59 (C(16)); 138.19 (C(10)); 128.63 (C(13));

128.18 (C(7)); 128.11 (2 x C(17)); 128.05 (2 x C(12)); 127.97 (2 x C(18)); 126.02 (2 x C(11)); 123.89 (C(19)); 100.39 (C(9)); 78.38 (C(6)); 76.26 (C(4)); 49.15 (C(3)); 36.15 (C(5)); 31.00 (C(1)); 25.68 (C(15)); -3.72, -3.68 (2 x C(14))

IR: (neat)

3060 (w); 3025 (m); 2999 (m); 2958(m); 2916 (m); 1716 (s); 1623 (m); 1600 (m); 1494 (m); 1452(m); 1403 (m); 1337 (m); 1316 (w); 1248(m); 1208 (m); 1159 (m); 1133 (m); 1099 (m); 1055 (m); 1027 (m)

MS: (FI)

394 (100, M$^+$); 306 (15); 305 (50); 304 (21); 303 (80); 270 (17); 204 (11); 161 (17); 152 (12); 115 (12); 114 13), 113 (14); 106 (11)

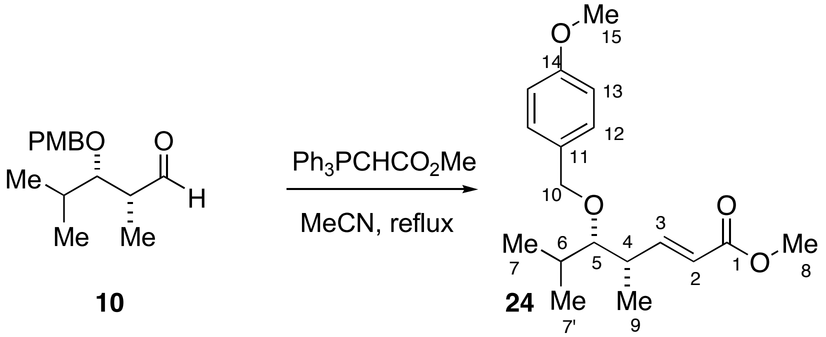
Opt. Rot.: $[\alpha]_D^{24}$ + 4.9 (c = 0.85, EtOH)

TLC: R_f 0.28 (hexanes/EtOAc 3/1) [silica gel, KMnO$_4$]

Analysis: Calc for $C_{24}H_{30}O_3Si$ (394.58)

Calcd:	C, 73.05%;	H, 7.66%
Found:	C, 72.96%;	H, 7.87%

(4*S*, 5*S*)-Methyl 4,6-dimethyl-5-(4-methoxyphenylmethoxy)-2-heptenoate (24)



In a 250-mL flask were placed **10** (4.43 g, 17.7 mmol), methyl triphenylphosphanylideneacetate (8.88 g, 26.6, 1.5 equiv) and acetonitrile (100 mL). The flask was fitted with a reflux condenser and was immersed into an oil bath. The mixture was heated to 90 °C (bath temperature) for 24 hrs. The reaction mixture was cooled to rt and was placed under reduced pressure (20 mmHg) to remove most of the acetonitrile. The resulting solid/oil mixture was chromatographed (silica gel, hexanes/EtOAc 9/1, 60 mm) to afford 4.86 g (15.9 mmol, 90%)

of **24** as a clear, colorless oil.

Data for **24**:

^{1}H NMR: (500 MHz, $CDCl_3$)
7.27 (d, *J* = 8.5, 2 H, 2 x HC(12)); 7.02 (dd, *J* = 15.9, 8.1, 1 H, HC(3)); 6.88 (d, *J* = 8.6, 2 H, 2 x HC(13)); 5.86 (dd, *J* = 15.6, 1.2, 1 H, HC(2)); 4.48 (s, 2 H, $H_2C(10)$); 3.84 (s, 3 H, $H_3C(15)$); 3.74 (s, 3 H, $H_3C(8)$); 3.08 (t, *J* = 5.6, 1 H, HC(5)); 2.62 (sextd, *J* = 6.6, 1.0, 1 H, HC(4)); 1.82 (sext, *J* = 6.8, 1 H, HC(6)); 1.12 (d, *J* = 6.6, 3 H, $H_3C(9)$); 0.96 (d, *J* = 6.9, 3 H, $H_3C(7)$); 0.95 (d, *J* = 6.6, 3 H, $H_3C(7')$)

^{13}C NMR: (126 MHz, $CDCl_3$)
167.11 (C(1)); 159.08 (C(14)); 152.69 (C(3)); 130.72 (C(11)); 129.29 (C(12)); 119.93 (C(2)); 113.64 (C(13)); 87.35 (C(5)); 74.77 (C(10)); 55.14 (C(15)); 51.36 (C(8)); 39.70 (C(4)); 31.19 (C(6)); 20.17 (C(7)); 17.48 (C(7')); 14.58 (C(9))

IR: (neat)
2961 (m); 2909(m); 2874 (m); 2838 (m); 1723 (s); 1655 (m); 1613 (m); 1586 (m); 1514 (m); 1464(m); 1436 (m); 1383 (w); 1364 (w); 1336 (m); 1301 (m); 1249 (s); 1194 (m); 1175 (m); 1137 (w); 1110 (m); 1063 (m); 1036 (m); 1012 (m)

MS: (FI)
307 (20); 306 (100, M^+); 276 (15)

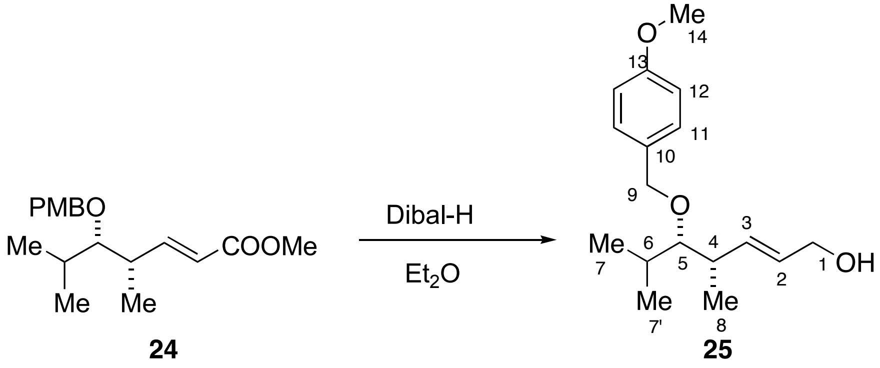
Opt. Rot.: $[\alpha]_D^{24}$ + 5.0 (c = 0.90, EtOH)

TLC: R_f 0.18 (hexanes/EtOAc 9/1) [silica gel, $KMnO_4$]

Analysis: Calc for $C_{14}H_{26}O_4$ (306.40)

Calcd:	C, 70.56%;	H, 8.55%
Found:	C, 70.57%;	H, 8.52%

(4*S*, 5*S*)-4,6-Dimethyl-5-(4-methoxy-phenylmethoxy)-2-hepten-1-ol (25)



In a 250-mL, three-neck flask equipped with a 50-mL pressure-equalizing addition funnel, a septum pierced with thermocouple temperature probe and a gas inlet were placed **24** (4.33 g, 14.1 mmol) and ether (90 mL). The solution was cooled to –74 °C (internal temperature) using isopropanol/dry ice bath. The addition funnel was charged with 1 M solution of diisobutylaluminum hydride in hexanes (42.3 mL, 42.3 mmol, 3 equiv). The solution of diisobutylaluminum hydride was added dropwise over 30 min maintaining temperature below -65 °C. The reaction mixture was stirred for 30 min at –74 °C, allowed to warm to 0 °C and was stirred for 1 h at 0 °C. At this temperature, the reaction mixture was carefully quenched with 10% v/v aqueous acetic acid (100 mL) maintaining internal temperature below 10 °C. The resulting clear solution was poured into a 500-mL separatory funnel. The aqueous layer was extracted with ether (2 x 100 mL), and the combined organic layers were washed with water (50 mL), saturated aqueous $NaHCO_3$ solution (2 x 50 mL) and brine (50 mL). The extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting clear oil was chromatographed (silica gel, hexanes/EtOAc 2/1, 60 mm) to afford **25** (3.80 g, 13.6 mmol, 97%) as clear colorless oil.

Data for **25**:

^{1}H NMR: (500 MHz, $CDCl_3$)

7.28 (d, *J* = 8.5, 2 H, 2 x HC(11)); 6.87 (d, *J* = 8.6, 2 H, 2 x HC(12)); 5.64 – 5.68 (m, 2 H, HC(2), HC(3)); 4.50 (s, 2 H, $H_2C(9)$); 4.09 (td, *J* = 4.9, 2.2, 2 H, $H_2C(1)$); 3.80 (s, 3 H, $H_3C(14)$); 2.98 (t, *J* = 5.8, 1 H, HC(5)); 2.46 (sext, *J* = 6.5, 1 H, HC(4)); 1.84 (sext, J = 6.7, 1 H, HC(6)); 1.23 (t, J = 7.5, 1 H, HO); 1.07 (d, J = 6.8, 3 H, $H_3C(8)$); 0.96 (d, J = 6.8, 3 H, $H_3C(7)$); 0.95 (d, J = 6.8, 3 H, $H_3C(7')$)

^{13}C NMR: (126 MHz, $CDCl_3$)

159.05 (C(13)); 136.61 (C(3)); 130.21 (C(10)); 129.23 (2 x C(11)); 128.10 (C(2)); 113.67 (2 x C(12)); 88.34 (C(5)); 74.86 (C(9)); 63.77 (C(1)); 55.24 (C(14)); 39.59 (C(4)); 30.95 (C(6)); 20.41 (C(7)); 17.51 (C(7')); 15.68 (C(9))

IR: (neat)

3392 (br, m); 2961 (s); 2871 (m); 1723 (s); 1689 (w); 1613 (m); 1587 (m); 1514 (s); 1464 (m); 1422 (m); 1383 (m); 1364 (m); 1351 (m); 1302 (m); 1249 (s); 1173 (m); 1110 (m); 1037 (m); 1012 (m)

MS: (EI, 70eV, 170°C)

278 (0.3, M^+); 206 (2); 122 (10); 121 (100); 91 (3); 78 (5); 77 (4)

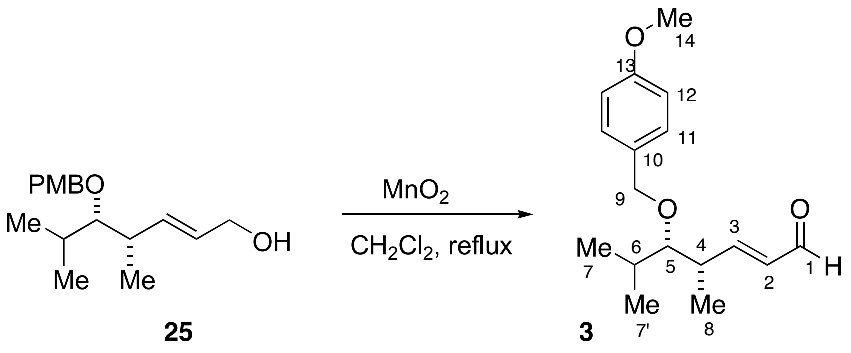
Opt. Rot.: $[\alpha]_D^{24}$ + 4.9 (c = 0.85, EtOH)

TLC: R_f 0.18 (hexanes/EtOAc 2/1) [silica gel, short UV]

Analysis: Calc for $C_{17}H_{26}O_3$ (278.39)

Calcd:	C, 73.34%;	H, 9.41%
Found:	C, 73.27%;	H, 9.26%

(4*S*, 5*S*)-4,6-Dimethyl-5-(4-methoxyphenylmethoxy)-2-heptenal (3)



In a 250-mL round bottom flask were placed **25** (8.07 g, 28.7 mmol), dichloromethane (80 mL) and manganese (IV) oxide (22.5 g, 259 mmol, 9.0 equiv). The flask was fitted with a reflux condenser and the reaction mixture was heated to reflux under argon for 36 h. The reaction mixture was cooled to rt and was filtered through a pad of silica gel (60 mm x 2 cm). The silica gel was washed with dichloromethane (200 mL) and ethyl acetate (200 mL). The combined filtrates were concentrated under reduced pressure. The resulting brown oil was chromatographed (silica gel, hexanes/EtOAc 5/1, 60 mm) to afford 5.58 g (20.2 mmol, 70%) of **3** as a pale yellow oil along with 2.30 g (8.27 mmol, 29%) of recovered **25**.

Data for **3**:

^{1}H NMR: (500 MHz, $CDCl_3$)
9.47 (d, *J* = 8.0, 1 H, HC(1)); 7.25 (d, *J* = 8.5, 2 H, 2 x HC(11)); 6.88 (d, *J* = 8.6, 2 H, 2 x HC(12)); 6.83 (dd, *J* = 15.8, 7.8, 1 H, HC(3)); 6.12 (dd, *J* = 15.5, 8.0, 1 H, HC(2)); 4.50 (AB, 2 H, $H_2C(9)$); 3.81 (s, 3 H, $H_3C(14)$); 3.13 (t, *J* = 5.5, 1 H, HC(5)); 2.74 (sext, *J* = 6.2, 1 H, HC(4)); 1.84 (sext, *J* = 6.8, 1 H, HC(6)); 1.15 (d, *J* = 6.5, 3 H, $H_3C(9)$); 0.97 (d, *J* = 6.5, 3 H, $H_3C(7)$); 0.97 (d, *J* = 6.6, 3 H, $H_3C(7')$

^{13}C NMR: (126 MHz, $CDCl_3$)
194.45 (C(1)); 162.28 (C(3)); 159.49 (C(13)); 132.02 (C(2)); 130.82 (C(10)); 129.61 (2 x C(11)); 114.02 (2 x C(12)); 87.39 (C(5)); 74.93 (C(9)); 55.48 (C(14)); 40.26 (C(4)); 31.56 (C(6)); 20.44 (C(7)); 18.16 (C(7')); 14.41 (C(9)

IR: (neat)
2962 (m); 2873 (m); 2837 (m); 2731 (w); 1686 (s); 1612 (m); 1586 (m); 1514 (m); 1466(m); 1421 (w); 1384 (m); 1364 (m); 1350 (m); 1302 (m); 1248 (m); 1173 (m); 1112 (m); 1059 (m); 1036 (m)

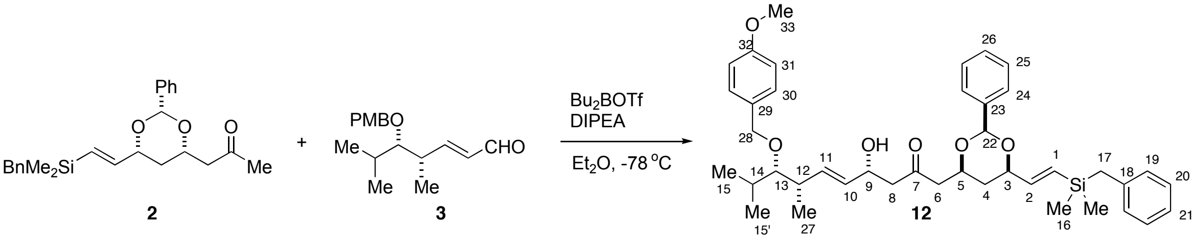
MS: (FI)
277 (20); 276 (100, M^+)

Opt. Rot.: $[\alpha]_D^{24}$ + 19.6 (c = 0.45, EtOH)

TLC: R_f 0.18 (hexanes/EtOAc 5/1) [silica gel, *p*-anisaldehyde]

Analysis: Calc for $C_{17}H_{26}O_3$ (276.37)
Calcd: C, 73.88%; H, 8.75%
Found: C, 73.52%; H, 8.72%

(7*S*, 9*S*, 2'*R*, 4'*S*, 6'*R*) 1-(6'-(2-benzyldimethylsilyl-ethenyl)-2'-phenyl-[1,3]-dioxan-4'-yl)-7,9-dimethyl-6-hydroxy-8-(4-methoxy-phenylmethoxy)-5-nonen-2-one (12)



In a 50-mL Schlenk flask were placed **2** (592 mg, 1.50 mmol, 1.2 equiv) and ether (7 mL). The solution was cooled to –72 °C (internal temperature) using a dry ice/isopropanol bath. To the solution was added diisopropylethylamine (0.32 mL, 1.80 mmol, 1.44 equiv) followed by a 1.0 M solution of dibutylboron triflate in dichloromethane (1.65 mL, 1.65 mmol, 1.32 equiv). The reaction mixture was stirred at –72 °C for 15 min before the addition of **3** (345 mg, 1.25 mmol) whereupon the reaction mixture was stirred for 7 h. To the reaction mixture was added a 6/1 MeOH/pH 7 phosphate buffer solution (10 mL). The reaction mixture was warmed to 0 °C using an ice bath. To the reaction mixture was added a 3/1 MeOH/30% H_2O_2 solution (10 mL) dropwise. The resulting emulsion was stirred for 1 h and was poured into a 125-mL separatory funnel. The whole mixture was extracted with ethyl acetate (3 x 50 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ solution (25 mL) and brine (25 mL). The extracts were dried over Na_2SO_4 and were concentrated under reduced pressure. The resulting clear oil was chromatographed (silica gel, hexanes/EtOAc 5/1 to 3/1, 40 mm) to afford 715 mg (1.07 mmol, 85%) of **12** as a clear, colorless oil.

Data for **12**:

^{1}H NMR: (500 MHz, $CDCl_3$)

7.49 (dd, *J* = 7.7, 1.8, 2 H, 2 x HC(24)); 7.32 – 7.38 (m, 3 H, HC(26), 2 x HC(25)); 7.27 (d, *J* = 7.5, 2 H, 2 x HC(30)); 7.20 (t, *J* = 7.6, 2 H, 2 x HC(20)); 7.07 (t, *J* = 7.3, 1 H, HC(21)); 6.99 (dd, *J* = 7.3, 1.3, 2 H, 2 x HC(19)); 6.86 (d, *J* = 8.5, 2 H, 2 x HC(31)) ; 6.06 (dd, *J* = 18.9, 4.5, 1 H, HC(2)); 5.92 (dd, *J* = 19.1, 1.3, 1 H, HC(1)); 5.67 (ddd, *J* =15.5, 8.0, 1.0, 1 H, HC(11)); 5.59 (s, 1 H, HC(22)); 5.46 (ddd, *J* = 15.5, 6.3, 0.8, 1 H, HC(10)); 4.52 – 4.57 (m, 1 H, HC(9)); 4.48 (s, 2 H, H$_2$C(28)); 4.35 – 4.41 (m, 2 H, HC(3), HC(5)); 3.79 (s, 3 H, H$_3$C(33)); 2.95 (t, *J* = 5.8, HC(13)); 2.75 (d, *J* = 3.7, HO); 2.73 (ABX, J_{AB} = 16.3, J_{AX} = 7.3, J_{BX} = 5.4, 2 H, H$_2$C(6)); 2.67 (ABX, J_{AB} = 11.5, J_{AX} = 5.9, J_{BX} = 3.1, 2 H, H$_2$C(8)); 2.41 (sext, *J* = 6.9, 1 H, HC(12)); 2.13 (s, 2 H, H$_3$C(17)); 1.79 (sext, *J* = 6.8, 1 H, HC(14)); 1.75 (dt, *J* = 12.9, 2.4, 1 H, H$_{eq}$C(4)); 1.47 (dt, *J* = 13.2, 11.2, 1 H, H$_{ax}$C(4)); 1.05 (d, *J* = 6.8, 3 H, H$_3$C(27)); 0.94 (d, *J* = 8.3, 3 H, H$_3$C(15)); 0.92 (d, *J* = 8.3, 3 H, H$_3$C(15’)); 0.04, 0.04 (s, 6 H, 2 x H$_3$C(14))

^{13}C NMR: (126 MHz, CDCl$_3$)

208.73 (C(7)); 159.00 (C(32)); 145.56 (C(2)); 139.71 (C(18)); 138.13 (C(23)); 135.63 (C(11)); 131.17 (C(29)); 129.73 (C(10)); 129.17 (C(30)); 128.55 (C(26)); 128.31 (C(1)); 128.22 (2 x C(19), 2 x C(25)); 128.09 (2 x C(20)); 126.12 (2 x C(24)); 123.99 (C(21)); 113.65 (C(31)); 100.59 (C(22)); 88.25 (C(13)); 78.37 (C(3)); 74.86 (C(9)); 72.72 (C(5)); 68.33 (C(28)); 55.24 (C(33)); 50.50 (C(8)); 49.30 (C(6)); 39.61 (C(12)); 36.28 (C(4)); 30.97 (C(14)); 25.81 (C(17)); 20.41, 17.44 (C(15), C(15’)); 15.70 (C(27)); -3.57, -3.60 (2 x C(16))

IR: (neat)

3480 (br, m); 3061 (m); 3025 (m); 2959(s); 2872 (m); 1714 (s); 1614 (m); 1601 (m); 1589 (m); 1514 (s); 1494 (m); 1454(m); 1384 (m); 1338 (m); 1302 (s); 1248 (m); 1209 (m); 1174 (m); 1030 (m)

MS: (HR ESI)

Calcd: 693.3587 (for C$_{41}$H$_{54}$O$_6$Si + Na)

Found: 693.3603

Opt. Rot.: $[\alpha]_D^{24}$ +8.5 (c = 0.45, EtOH)

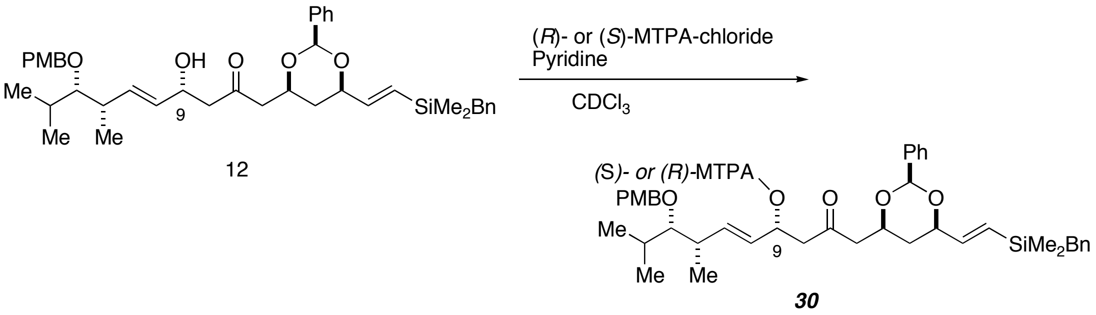
TLC: R_f 0.09 (hexane/EtOAc 3/1) [silica gel, *p*-anisaldehyde]

Analysis: Calc for C$_{41}$H$_{54}$O$_6$Si (670.95)

Calcd: C, 73.39%; H, 8.11%

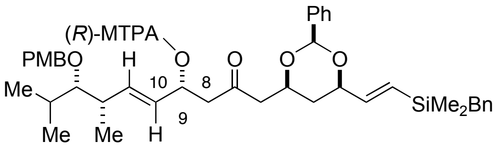
Found: C, 73.33%; H, 7.97%

Determination of Configuration at C(9) in Aldol Adduct 12, (C(27) in RK-397).



In an NMR tube was placed a solution of **12** (5.0 mg, 0.0075 mmol) in $CDCl_3$ (0.75 mL). To the solution was added sequentially pyridine (0.02 mL) and (*R*)- or (*S*)-α-methoxy-α-trifluoromethylphenylacetyl chloride (2.8 μL, 0.015 mmol, 2.0 equiv). The reaction mixture was thoroughly mixed and was let stand for 2 h at rt. The crude Mosher ester **30** was analyzed by NMR and found to be of *R* configuration.

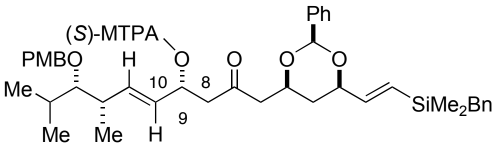
From (*R*)-MTPA-**30**:



δ $H_2C(8)$ = 2.70 ppm

δ HC(10) = 5.48 ppm

From (*S*)-MTPA-**30**:



δ $H_2C(8)$ = 2.77 ppm

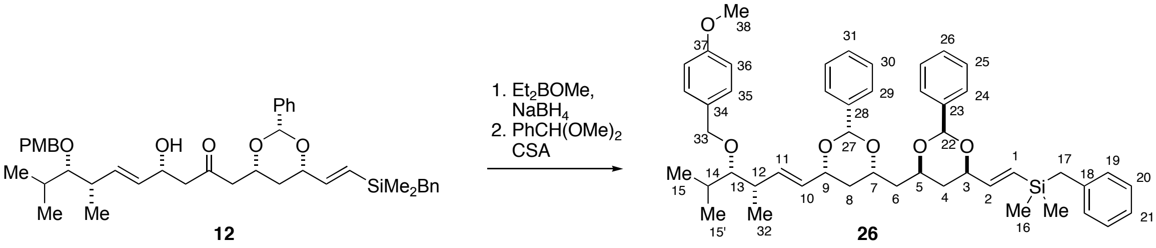
δ HC(10) = 5.35 ppm

Difference in chemical shifts:

$\Delta\delta_{SR}$ $H_2C(8)$ = + 0.07 ppm

$\Delta\delta_{SR}$ HC(9) = - 0.13 ppm

Bisbenzylidene Silane 26



In a 50-mL Schlenk flask were placed **12** (2.85 g, 4.25 mmol), tetrahydrofuran (20 mL) and methanol (4.3 mL). The reaction mixture was cooled to –72 ºC (internal temperature) using dry ice/isopropanol bath. To the solution was added dropwise diethylmethoxyborane (0.693 mL, 5.10 mmol, 1.2 equiv), and the reaction mixture was stirred for 15 min at –72 ºC. To the solution was added sodium borohydride (193 mg, 5.10 mmol, 1.2 equiv) and the mixture was stirred for 4 h at –72 ºC. The reaction mixture was quenched with acetic acid (6 mL) in one portion and the mixture was allowed to warm to rt and then was transferred to a 125-mL separatory funnel. The solution was extracted with ethyl acetate (2 x 25 mL) and the combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (20 mL) and brine (20 mL). The extracts were dried over Na_2SO_4 and were concentrated under reduced pressure to afford a crude diol (3.10 g). In a 100-mL round bottom flask were placed the crude diol (3.10 g), dichloromethane (25 mL), benzaldehyde dimethyl acetal (2.54 mL, 17.0 mmol, 4.0 equiv) and *dl*-camphorsulfonic acid (148 mg, 0.64 mmol, 0.15 equiv). The reaction mixture was stirred at rt for 16 h and was quenched with saturated aqueous $NaHCO_3$ solution (30 mL). The biphasic mixture was transferred to a 125-mL separatory funnel and the aqueous layer was extracted with dichloromethane (20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (20 mL) and brine (20 mL). The solution was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was chromatographed (silica gel, hexanes/ether 9/1, 60 mm) to afford 2.79 g (3.80 mmol, 86%) of **26** as a clear, colorless oil.

Data for **26**:

^{1}H NMR: (500 MHz, $CDCl_3$)

7.55 (dd, *J* = 8.3, 1.5, 2 H, 2 x HC(24) or HC(29)); 7.53 (dd, *J* = 8.1, 1.3, 2 H, 2 x

HC(24) or HC(29)); 7.34 – 7.40 (m, 6 H, HC(26), 2 x HC(25), HC(31), 2 x HC(30)); 7.27 (d, *J* = 7.3, 2 H, 2 x HC(35)); 7.19 (t, *J* = 7.6, 2 H, 2 x HC(20)); 7.06 (t, *J* = 7.4, 1 H, HC(21)); 6.98 (d, *J* = 6.8, 2 H, 2 x HC(19)); 6.83 (d, *J* = 8.6, 2 H, 2 x HC(36)) ; 6.07 (dd, *J* = 19.0, 4.8, 1 H, HC(2)); 5.91 (dd, *J* = 19.0, 1.4, 1 H, HC(1)); 5.76 (dd, 15.7, 7.9, 1 H, HC(11)); 5.61 (s, 1 H, HC(22) or HC(27)); 5.61 (s, 1 H, HC(22) or HC(27)); 5.59 (dd, *J* = 16.7, 6.9,, 1 H, HC(10)); 4.48 (AB, J_{ab} = 10.8, 2 H, $H_2C(33)$); 4.31 – 4.36 (m, 2 H, HC(3), HC(9)); 4.20 – 4.23 (m, 2 H, HC(5), HC(7)); 3.78 (s, 3 H, $H_3C(38)$); 2.98 (t, *J* = 5.8, HC(13)); 2.45 (sext, *J* = 6.7, 1 H, HC(12)); 2.13 (s, 2 H, $H_3C(17)$); 1.83 (sext, *J* = 6.7, 1 H, HC(14)); 1.81 (m, 2 H, $H_2C(6)$) 1.66 (dt, *J* = 13.2, 2.5, 1 H, $H_{eq}C(4)$ or $H_{eq}C(8)$); 1.63 (dt, *J* = 13.2, 2.6, 1 H, $H_{eq}C(4)$ or $H_{eq}C(8)$); 1.54 (dt, *J* = 13.5, 11.2, 1 H, $H_{ax}C(4)$ or $H_{ax}C(8)$); 1.49 (dt, *J* = 13.5, 11.2, 1 H, $H_{ax}C(4)$ or $H_{ax}C(8)$); 1.07 (d, *J* = 6.8, 3 H, $H_3C(32)$); 0.95 (d, *J* = 6.6, 3 H, $H_3C(15)$); 0.94 (d, *J* = 6.9, 3 H, $H_3C(15')$); 0.04 (s, 6 H, 2 x $H_3C(14)$)

^{13}C NMR: (126 MHz, $CDCl_3$)

158.94 (C(37)); 146.08 (C(2)); 139.67 (C(18)); 138.76, 138.66 (C(23), C(27)); 135.93 (C(11)); 131.07 (C(34)); 129.20 (2 x C(35)); 128.81 (C(10)); 128.62, 128.55 (C(26), C(31)); 128.15 (2 x C(25) or C(30)); 128.11 (2 x C(19)); 128.10 (2 x C(25) or C(30)); 128.01 (2 x C(20)); 127.97 (C(1)); 126.15 (2 x C(24), 2 x C(29)); 123.92 (C(21)); 113.57 (2 x C(31)); 100.38, 100.33 (C(22), C(27)); 88.23 (C(13)); 78.47 (C(3)); 77.15 (C(9)); 74.78 (C(33)); 72.36, 72.33 (C(5), C(7)); 55.09 (C(38)); 42.42 (C(6)); 39.44 (C(12)); 37.49, 36.94 (C(4), C(8)); 30.91 (C(14)); 25.77 (C(17)); 20.20, 17.78 (C(15), C(15')); 15.04 (C(32)); -3.61, -3.66 (2 x C(16))

IR: ($CHCl_3$)

3154 (w); 3066 (m); 3027 (m); 2959(s); 2916 (m); 2873 (m); 2838 (m); 2250 (m); 1794 (w); 1613 (m); 1600 (m); 1587 (w); 1514 (s); 1493 (m); 1453 (m); 1429 (w); 1408 (m); 1386 (m); 1339 (m); 1302 (m); 1248(s); 1210 (m); 1174 (m); 1121 (m); 1095 (m); 1057 (m); 1029 (s); 1010 (s)

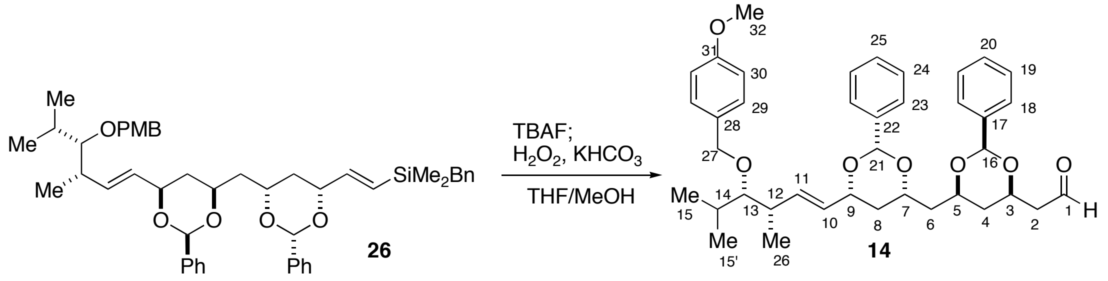
MS: (HR ESI)
Calcd: 783.4057 (for $C_{48}H_{60}O_6Si + Na$)
Found: 783.4059

Opt. Rot.: $[\alpha]_D^{24}$ + 62.4 (c = 1.05, EtOH)

TLC: R_f 0.07 (hexane/EtOAc 9/1) [silica gel, *p*-anisaldehyde]

Analysis: Calc for $C_{48}H_{60}O_6Si$
Calcd: C, 75.75%; H, 7.95%
Found: C, 75.79%; H, 8.02%

Bisbenzylidene Aldehyde 14



In a 100-mL round bottom flask were placed **26** (751 mg, 0.99 mmol) and tetrahydrofuran (14 mL). The solution was cooled to 0 °C (bath temperature) using an ice bath. To the solution was added a 1.0 M solution of TBAF (1.08 mL, 1.08 mmol, 1.1 equiv) dropwise over 10 min. The reaction mixture was stirred for 15 min at 0 °C. To the reaction mixture were added 30% H_2O_2 solution (4.24 mL, 23.8 mmol, 24 equiv), methanol (10 mL) and $KHCO_3$ (495 mg, 4.95 mmol, 5.0 equiv). The reaction mixture was warmed to rt and stirred for 18 h. To the reaction mixture was added water (40 mL) and the resulting emulsion was stirred for 30 min. The reaction mixture was diluted with ethyl acetate (20 mL) and transferred to a 250-mL separatory funnel. The aqueous layer was extracted with ethyl acetate (2 x 50 mL) and the combined organic extracts were washed with 30% aqueous $Na_2S_2O_3$ solution (3 x 30 mL) and with brine (30 mL). The combined extracts were dried over $MgSO_4$ and concentrated. The resulting clear oil was chromatographed (silica gel, hexanes/ether 1/1, 30 mm) to afford **14** (457 mg, 0.73 mmol, 73%) as white foamy solid.

Data for **14**:

mp: 101 – 103 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

9.85 (t, *J* = 1.9, 1 H, HC(1)); 7.52 (dd, *J* = 8.0, 1.6, 2 H, 2 x HC(18) or HC(23)); 7.49 (dd, *J* = 7.9, 1.5, 2 H, 2 x HC(18) or HC(23)); 7.39 – 7.27 (m, 6 H, HC(20), 2 x HC(19), HC(25), 2 x HC(24)); 7.26 (d, *J* = 8.3, 2 H, 2 x HC(29)); 6.84 (d, *J* = 8.8, 2 H, 2 x HC(30)) ; 5.76 (dd, *J* = 15.6, 8.0, 1 H, HC(11)); 5.61 (s, 1 H, HC(16) or HC(21)); 5.60 (s, 1 H, HC(16) or HC(21)); 5.59 (dd, *J* = 16.4, 6.9,, 1 H, HC(10)); 4.48 (AB, J_{ab} = 10.6, 2 H, $H_2C(27)$); 4.45 – 4.41 (m, 1 H, HC(9)); 4.34 – 4.31 (m, 1 H, HC(3) or HC(5) or HC(7)); 4.26 – 4.18 (m, 2 H, HC(3) or HC(5) or HC(7)); 3.78 (s, 3 H, $H_3C(32)$); 2.98 (t, *J* = 5.8, HC(13)); 2.71 (ABXd, J_{ax} = 7.4, J_{bx} = 5.1, J_{ab} = 16.9, *J* = 2.0, 2 H, $H_2C(2)$); 2.44 (sext, *J* = 6.8, 1 H, HC(12)); 1.83 (sext, *J* = 6.6, 1 H, HC(14)); 1.82 – 1.80 (m, 2 H, $H_2C(6)$) 1.71 (dt, *J* = 13.0, 2.5, 1 H, $H_{eq}C(4)$ or $H_{eq}C(8)$); 1.62 (dt, *J* = 13.2, 2.6, 1 H, $H_{eq}C(4)$ or $H_{eq}C(8)$); 1.57 – 1.43 (m, 2 H, $H_{ax}C(4)$, $H_{ax}C(8)$); 1.06 (d, *J* = 6.9, 3 H, $H_3C(26)$); 0.95 (d, *J* = 6.6, 3 H, $H_3C(15)$); 0.94 (d, *J* = 6.8, 3 H, $H_3C(15')$)

^{13}C NMR: (126 MHz, $CDCl_3$)

200.37 (C(1)); 159.03 (C(31)); 138.74, 138.31 (C(22), C(17)); 136.11 (C(11)); 131.18 (C(28)); 129.30 (2 x C(29)); 128.82 (C(10)); 128.67 (C(20), C(25)); 128.24, 128.20 (2 x C(19), 2 x C(24)); 126.19, 126.02 (2 x C(18), 2 x C(23)); 113.66 (2 x C(30)); 100.59, 100.46 (C(16), C(21)); 88.35 (C(13)); 77.25 (C(9)); 74.87 (C(27)); 72.45, 72.33, 71.81 (C(3), C(5), C(7)); 55.23 (C(32)); 49.30 (C(2)); 42.37 (C(6)); 39.54 (C(12)); 37.53, 37.00 (C(4), C(8)); 30.99 (C(14)); 20.26, 17.81 (C(15), C(15')); 15.12 (C(32))

IR: (CH_2Cl_2)

3051 (m); 2960(s); 2911 (m); 2869 (m); 1726 (w); 1612 (m); 1600 (m); 1514 (m); 1458 (m); 1344 (m); 1266 (m); 1244(m); 1110 (m); 1058 (m); 1028 (m); 1007 (m)

MS: (FD)

630 (15); 629 (47); 628 (100, M^+); 627 (12); 556 (17); 435 (14); 122 (10); 121 (69); 105 (22)

Opt. Rot.: $[\alpha]_D^{24}$ + 81.3 (c =0.45 , EtOH)

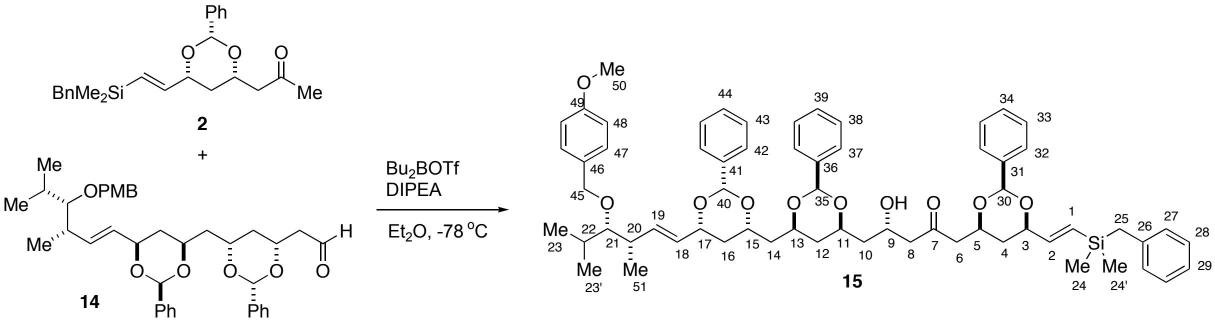
TLC: R_f 0.12 (hexane/Ether 1/1) [silica gel, *p*-anisaldehyde]

Analysis: Calc for $C_{39}H_{48}O_7$ (628.79)

Calcd: C, 74.49%; H, 7.69%

Found: C, 74.55%; H, 7.67%

Aldol Product 15



In a 100-mL Schlenk flask were placed **2** (1.07 g, 2.71 mmol, 1.2 equiv) and ether (10 mL). The solution was cooled to –72 °C (internal temperature) using a dry ice/isopropanol bath. To the reaction mixture were added diisopropylethylamine (0.583 mL, 3.25 mmol, 1.44 equiv) followed by a 1.0 M solution of dibutylboron triflate (2.98 mL, 2.98 mmol, 1.32 equiv) dropwise. The reaction mixture was stirred for 20 min before the addition of solution of **14** (1.42 g, 2.26 mmol) in dichloromethane (7 mL + 2 mL rinse) dropwise over 1 h whereupon the reaction mixture was stirred for 8 h. To the reaction mixture was added a 6/1 mixture MeOH/pH 7 phosphate buffer solution (35 mL). The resulting emulsion was allowed to warm to 0 °C using an ice bath. To the reaction mixture was added dropwise a 3/1 mixture of MeOH/30% H_2O_2 solution (32 mL). The reaction mixture was stirred for 30 min and was poured into a 250-mL separatory funnel. The solution was diluted with ethyl acetate (100 mL) and was washed with water (20 mL), saturated aqueous $NaHCO_3$ solution (20 mL) and brine (20 mL). The solution was dried over Na_2SO_4 and was concentrated under reduced pressure. The resulting clear oil was chromatographed (silica gel, hexanes/EtOAc 5/1 to 2/1, 50 mm) to afford 2.03 g (1.98 mmol, 88%) of **15** as white foam.

Data for **15**:

mp: 52 – 53 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

7.53 – 7.46 (m, 6 H, 2 x HC(32), 2 x HC(37), 2 x HC(42)); 7.38 – 7.30 (m, 9 H, HC(34), 2 x HC(33), HC(39), 2 x HC(38), HC(44), 2 x HC(43)); 7.26 (d, *J* = 7.3, 2 H, 2 x HC(47)); 7.20 (t, *J* = 7.7, 2 H, 2 x HC(28)); 7.07 (t, *J* = 7.3, 1 H, HC(29)); 6.98 (d, *J* = 7.6, 2 H, 2 x HC(27)); 6.84 (d, *J* = 8.6, 2 H, 2 x HC(48) ; 6.05 (dd, *J* = 18.9, 4.5, 1 H, HC(2)); 5.93 (d, *J* = 18.8, 1 H, HC(1)); 5.77 (dd, 15.7, 8.1, 1 H, HC(19)); 5.60, 5.58, 5.54 (3 x s, 3 x 1 H, HC(30), HC35), HC(40)); 5.59 (dd, *J* = 15.4, 6.4,, 1 H, HC(18)); 4.48 (AB, J_{ab} = 10.7, 2 H, $H_2C(45)$); 4.44 – 4.30 (m, 4 H, HC(3), HC(5), HC(9), HC(17)); 4.19 – 4.17 (m, 2 H, HC(11), HC(13) or HC(15)); 4.11 – 4.08 (m, 1 H, HC(11) or HC(13) or HC(15)); 3.78 (s, 3 H, $H_3C(50)$); 3.17 (d, *J* = 3.9, 1 H, OH); 2.98 (t, *J* = 5.8, HC(21)); 2.72 (ABX, J_{ax} = 7.5, J_{bx} = 5.2, J_{ab} = 16.2, 2 H, $H_2C(6)$); 2.66 (ABX, J_{ax} = 3.2, J_{bx} = 9.0, J_{ab} = 17.3, 2 H, $H_2C(8)$) 2.45 (sext, *J* = 6.8, 1 H, HC(20)); 2.13 (s, 2 H, $H_3C(25)$); 1.82 (sext, *J* = 6.5, 1 H, HC(22)); 1.82 – 1.67 (m, 7 H, $H_2C(10)$, $H_2C(14)$, $H_{eq}C(4)$, $H_{eq}C(12)$, $H_{eq}C(16)$); 1.57 – 1.43 (m, 3 H, $H_{ax}C(4)$, $H_{ax}C(12)$, $H_{ax}C(16)$); 1.06 (d, *J* = 6.6, 3 H, $H_3C(51)$); 0.95 (d, *J* = 6.3, 3 H, $H_3C(23)$); 0.94 (d, *J* = 6.6, 3 H, $H_3C(23')$); 0.04 (s, 6 H, 2 x $H_3C(24)$)

^{13}C NMR: (126 MHz, $CDCl_3$)

208.27 (C(7)); 158.97 (C(49)); 145.55 (C(2)); 139.69 (C(26)); 138.73, 138.66, 138.06 (C(31), C(36), C(41)); 136.02 (C(19)); 131.12 (C(46)); 129.26 (2 x C(47)); 128.85 (C(18)); 128.63, 128.58, 128.51, 128.19, 128.16, 128.14 (C(34), C(39), HC(44),2 x C(33), 2 x C(38), 2 x C(43), 2 x C(27), 2 x C(28), C(1)); 126.13, 126.11, 125.97 (2 x C(32), 2 x C(37), 2 x C(42)); 123.98 (C(29)); 113.62 (2 x C(48)); 100.62, 100.37 (C(30), C(35), C(40)); 88.33 (C(21)); 78.34 (C(3)); 77.24 (C(17)); 74.85 (C(45)); 73.50, 72.83, 72.55, 72.42 (C(5), C(11), C(13), C(15)); 64.15 (C(9)); 55.21 (C(50)); 50.86 (C(8)); 49.13 (C(6)); 42.44, 42.04 (C(10), C(14)); 39.52 (C(20)); 37.57, 37.35, 36.25 (C(4), C(12), C(16)); 30.98 (C(22)); 25.80 (C(25)); 20.27, 17.81 (C(23), C(23')); 15.13 (C(51)); -3.57, -3.61 (2 x C(24))

<u>IR</u>: (CH_2Cl_2)

3522 (br, m); 3034 (m); 2955(s); 2914 (m); 2872 (m); 1712 (m); 1613 (m); 1514 (m); 1494 (m); 1453 (m); 1408 (m); 1338 (m); 1248 (m); 1212(m); 1174 (m); 1111 (m); 1057 (m); 1012 (m)

<u>MS</u>: (FD)

1024 (23); 1023 (54, M^+); 1022 (77); 1021 (21); 931 (11); 122 (12); 121 (100); 106 (14)

<u>Opt. Rot.</u>: $[\alpha]_D^{24}$ + 45.3 (c =0.40 , EtOH)

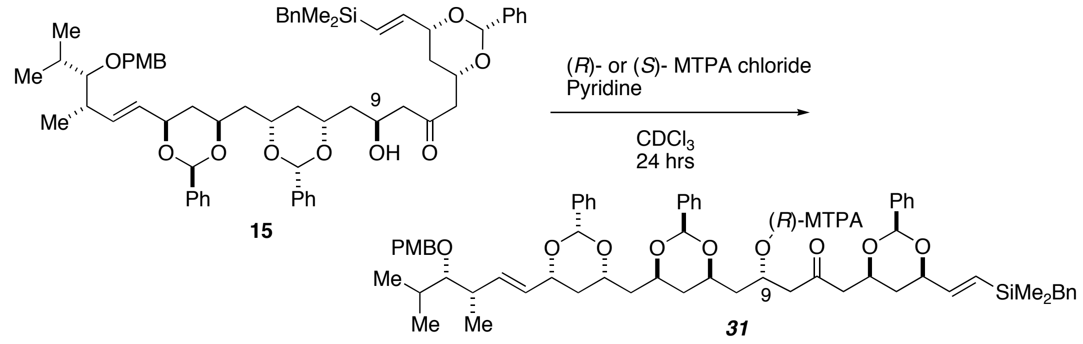
<u>TLC</u>: R_f 0.30 (hexane/EtOAc 1/1) [silica gel, *p*-anisaldehyde]

<u>Analysis</u>: Calc for $C_{63}H_{78}O_{10}Si$ (1023.37)

Calcd: C, 73.94%; H, 7.68%

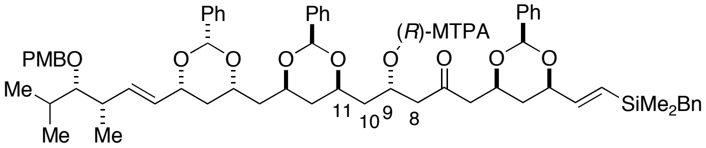
Found: C, 73.92%; H, 7.86%

Determination of Configuration at C(9) in Aldol Adduct 15, (C(19) in RK-397).



In an NMR tube was placed a solution of **15** (4.1 mg, 0.0039 mmol) in $CDCl_3$ (0.75 mL). To the solution was added sequentially pyridine (0.02 mL) and (*R*)- or (*S*)-α-mehoxy-α-trifluoromethyl-phenylacetyl chloride (5.6 μL, 0.031 mmol, 8.0 equiv). The reaction mixture was thoroughly mixed and was let stand for 24 h at rt. The crude Mosher ester **31** was analyzed by NMR and found to be of *S* configuration.

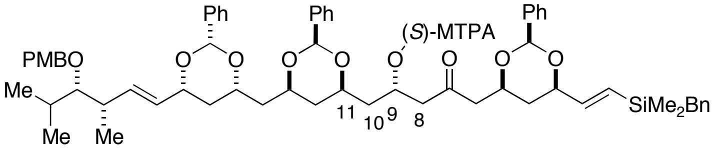
From (*R*)-MTPA-**31**



δ $H_2C(8)$ = 2.86 ppm

δ $H_2C(11)$ = 3.80 ppm

From (*S*)-MTPA-**31**



δ $H_2C(8)$ = 2.90 ppm

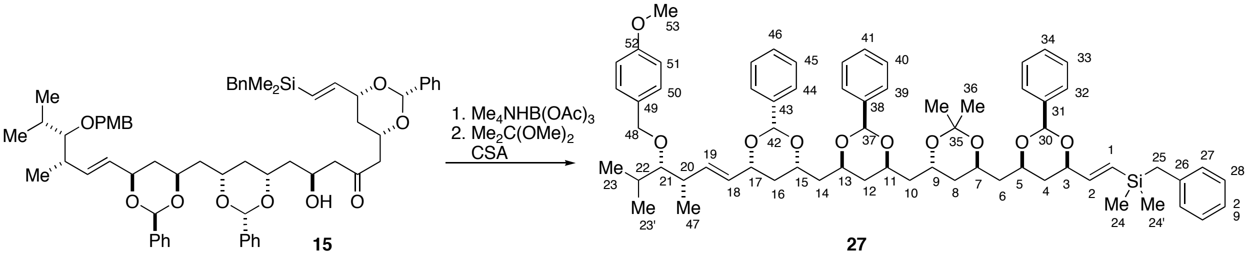
δ $H_2C(11)$ = 3.62 ppm

Difference in chemical shifts:

$\Delta\delta_{SR}$ $H_2C(18)$ = + 0.04 ppm

$\Delta\delta_{SR}$ HC(21) = - 0.18 ppm

Acetonide 27



In a 100-mL, round-bottom flask were placed **15** (1.34 g, 1.31 mmol), acetonitrile (7 mL) and acetic acid (7 mL). The solution was cooled to 0 °C (bath temperature) using an ice bath. To the solution was added tetramethylammonium triacetoxyborohydride (1.72 g, 6.55 mmol, 5.0 equiv), and the reaction mixture was stirred at 0 °C for 10 h. The reaction was quenched with saturated aqueous sodium potassium tartrate (50 mL) and the mixture was transferred to a 125-mL separatory funnel and then was extracted with dichloromethane (2 x 30 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (20 mL) and brine (20 mL), then was dried over Na_2SO_4 and concentrated under reduced pressure to afford a crude diol (1.89 g). In a 100-mL, round-bottom flask were placed the crude diol (1.89 g), dichloromethane (60 mL), 2,2-dimethoxypropane (1.59 mL, 13.1 mmol, 10.0 equiv) and *dl*-camphorsulfonic acid (5 mg). The solution was stirred at rt for 6 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (30 mL) and the biphasic mixture was transferred to a 250-mL separatory funnel. The aqueous layer was extracted with dichloromethane (30 mL) and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (30 mL) and brine (30 mL). The extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was chromatographed (silica gel, hexane/EtOAc 9/1 to 5/1, 50 mm) to afford 1.21 g (1.14 mmol, 87%) of **27** as white foam.

Data for **27**:

mp: 61 - 62 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

7.53 – 7.50 (m, 6 H, 2 x HC(32), 2 x HC(39), 2 x HC(44)); 7.39 – 7.30 (m, 9 H, HC(34), 2 x HC(33), HC(41), 2 x HC(40), HC(46), 2 x HC(45)); 7.27 (d, *J* = 7.1, 2 H, 2 x HC(50)); 7.20 (t, *J* = 7.6, 2 H, 2 x HC(28)); 7.06 (t, *J* = 7.5, 1 H, HC(29)); 6.98 (d, *J* = 7.1, 2 H, 2 x HC(27)); 6.83 (d, *J* = 8.6, 2 H, 2 x HC(51); 6.08 (dd, *J* = 19.0, 4.6, 1 H, HC(2)); 5.92 (dd, *J* = 18.8, 1.2, 1 H, HC(1)); 5.77 (dd, *J* = 15.6, 7.8, 1 H, HC(19)); 5.60, 5.57, 5.56 (3 x s, 3 x 1 H, HC(30), HC37), HC(42)); 5.56 (dd, *J* = 18.4, 6.5,, 1 H, HC(18)); 4.48 (AB, J_{ab} = 10.7, 2 H, H$_2$C(48)); 4.36 – 4.30 (m, 2 H, HC(3), HC(17)); 4.25 – 3.98 (m, 6 H, HC(5), HC(7), HC(9), HC(11), HC(13), HC(15)); 3.78 (s, 3 H, H$_3$C(53)); 2.98 (t, *J* = 5.7, HC(21)); 2.45 (sext, *J* = 6.3, 1 H, HC(20)); 2.13 (s, 2 H, H$_3$C(25)); 1.83 (sext, *J* = 6.5, 1 H, HC(22)); 2.05 – 1.99, 1.82 – 1.34 (m, 14 H, H$_2$C(4), H$_2$C(6), HC(8), H$_2$C(10), H$_2$C(12), H$_2$C(14), H$_2$C(16)); 1.38 (s, 3 H, H$_3$C(36)); 1.37 (s, 3 H, H$_3$C(36')); 1.07 (d, *J* = 6.6, 3 H, H$_3$C(47)); 0.95 (d, *J* = 6.6, 3 H, H$_3$C(23)); 0.94 (d, *J* = 6.8, 3 H, H$_3$C(23')); 0.05 (s, 6 H, 2 x H$_3$C(24))

^{13}C NMR: (126 MHz, CDCl$_3$)

158.98 (C(52)); 146.12 (C(2)); 139.76 (C(26)); 138.90, 138.77, 138.54 (C(31), C(38), C(43)); 136.01 (C(19)); 131.13 (C(49)); 129.26 (2 x C(50)); 128.87 (C(18)); 128.65, 128.58, 128.51, 128.21, 128.16, 128.05 (C(34), C(41), HC(46),2 x C(33), 2 x C(40), 2 x C(45), 2 x C(27), 2 x C(28), C(1)); 126.16, 126.14, 125.83 (2 x C(32), 2 x C(39), 2 x C(44)); 123.96 (C(29)); 113.96 (2 x C(51)); 100.48, 100.42, 100.37, 100.13 (C(30), C(35), C(37), C(42)); 88.31 (C(21)); 78..52 (C(3)); 77.26 (C(17)); 74.83 (C(48)); 73.23, 73.04, 72.49 (C(5), C(11), C(13), C(15)); 62.84, 62.38 (C(7), C(9)); 55.17 (C(53)); 42.48, 41.82, 41.64 (C(6), C(10), C(14)); 39.49 (C(20)); 38.59, 37.74, 37.56, 36.24 (C(4), C(8), C(12), C(16)); 30.95 (C(22)); 25.83 (C(25)); 24.68, 24.60 (2 x C(36)); 20.24, 17.79 (C(23), C(23')); 15.10 (C(47)); -3.57, -3.63 (2 x C(24))

IR: (CHCl$_3$)

3061 (w); 3025 (m); 2953(s); 2911 (m); 2869 (m); 1612 (m); 1514 (m); 1493 (m); 1452 (m); 1380 (m); 1341 (m); 1248 (m); 1224(m); 1119 (m); 1058 (m); 1028 (m); 1012 (m)

MS: (HR ESI)

Calcd: 1087.5731 (for $C_{66}H_{84}O_{10}Si$ + Na)

Found: 1087.5765

Opt. Rot.: $[\alpha]_D^{24}$ + 67.7 (c =0.60 , EtOH)

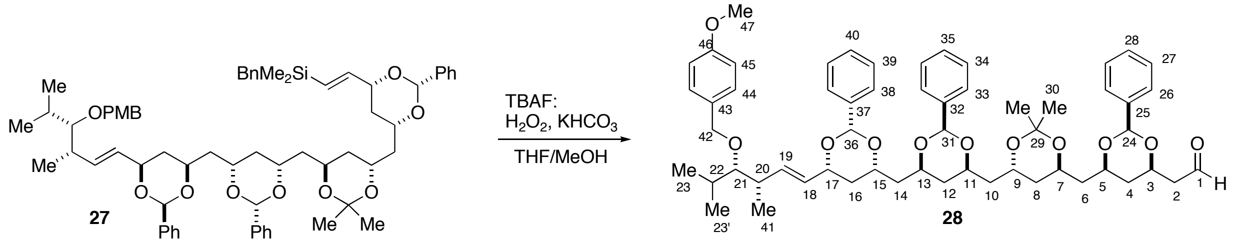
TLC: R_f 0.12 (hexane/EtOAc, 5/1) [silica gel, *p*-anisaldehyde]

Analysis: Calc for $C_{66}H_{84}O_{10}Si$ (1065.45)

Calcd: C, 74.40%; H, 7.95%

Found: C, 74.18%; H, 7.86%

Acetonide Aldehyde 28



In a 10-mL Schlenk flask were placed **27** (200 mg, 019 mmol) and tetrahydrofuran (2 mL). The solution was cooled to 0 °C (bath temperature) using an ice bath. To the solution was added dropwise a 1.0 M solution of TBAF in THF (0.21 mL, 0.21 mmol, 1.1 equiv). The solution was stirred for 15 min at 0 °C. To the solution was sequentially added 30% H_2O_2 solution (0.36 mL, 4.51 mmol, 24 equiv), methanol (1.5 mL) and $KHCO_3$ (94 mg, 0.94 mmol, 5 equiv). The reaction mixture was allowed to warm to rt and was stirred for 20 h. To the mixture was added water (4 mL) and the resulting emulsion was stirred for 10 min, then was diluted with ethyl acetate (5 mL) and transferred to a 60-mL separatory funnel. The aqueous layer was extracted with ethyl acetate (2 x 15 mL) and the combined organic layers were washed with 30% aqueous $Na_2S_2O_3$ solution (3 x15 mL) and with brine (10 mL). The combined extracts were dried over $MgSO_4$ and concentrated. The resulting clear oil was chromatographed (silica gel, hexanes/EtOAc, 30 mm) to afford152 mg (0.16 mmol, 86%) of **28** as white foam.

Data for **28**:

mp: 77 - 78 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

9.86 (t, *J* = 1.8, 1 H, HC(1)); 7.53 – 7.45 (m, 6 H, 2 x HC(26), 2 x HC(33), 2 x

HC(38)); 7.39 – 7.31 (m, 9 H, HC(28), 2 x HC(27), HC(35), 2 x HC(34), HC(40), 2 x HC(39)); 7.27 (d, J = 9.0, 2 H, 2 x HC(44)); 6.84 (d, J = 8.6, 2 H, 2 x HC(45); 5.77 (dd, 15.8, 8.0, 1 H, HC(19)); 5.60, 5.57, 5.56 (3 x s, 3 x 1 H, HC(24), HC(31), HC(36)); 5.61 – 5.53 (m, 1 H, HC(18)); 4.49 (AB, J_{ab} = 10.8, 2 H, $H_2C(42)$); 4.42 – 4.37 (m, 1 H, HC(3)); 4.37 – 4.33 (m, 1 H, HC(17)); 4.26 – 3.99 (m, 6 H, HC(5), HC(7), HC(9), HC(11), HC(13), HC(15)); 3.78 (s, 3 H, $H_3C(47)$); 2.98 (t, J = 5.8, HC(21)); 2.72 (ABXd, J_{ax} = 7.4, J_{bx} = 5.1, J_{ab} = 16.9, J = 2.3, 2 H, $H_2C(2)$); 2.45 (sext, J = 6.7, 1 H, HC(20)); 1.83 (sext, J = 8.5, 1 H, HC(22)); 2.04 – 1.97, 1.82 – 1.39 (m, 14 H, $H_2C(4)$, $H_2C(6)$, HC(8), $H_2C(10)$, $H_2C(12)$, $H_2C(14)$, $H_2C(16)$); 1.37 (s, 3 H, $H_3C(30)$); 1.36 (s, 3 H, $H_3C(30')$); 1.07 (d, J = 6.6, 3 H, $H_3C(41)$); 0.95 (d, J = 6.6, 3 H, $H_3C(23)$); 0.94 (d, J = 6.9, 3 H, $H_3C(23')$)

^{13}C NMR: (126 MHz, $CDCl_3$)

200.39 (C(1)); 159.02 (C(46)); 138.92, 138.80, 138.17 (C(25), C(32), C(37)); 136.06 (C(19)); 131.18 (C(43)); 129.30 (2 x C(44)); 128.90 (C(18)); 128.79, 128.62, 128.55 (C(28), C(35), C(40)); 128.22, 128.19 (2 x C(27), 2 x C(34), 2 x C(39)); 126.19, 125.98, 125.86 (2 x C(26), 2 x C(33), 2 x C(38)); 113.66 (2 x C(45)); 100.71, 100.45, 100.16 (C(24), C(29), C(31), C(36)); 88.36 (C(21)); 77.26 (C(17)); 74.87 (C(42)); 73.29, 73.05, 72.53, 72.52 (C(5), C(11), C(13), C(15)); 71.85 (C(3)); 62.79, 62.40 (C(7), C(9)); 55.22 (C(47)); 49.34 (C(2)); 42.51, 41.82, 41.50 (C(6), C(10), C(14)); 39.54 (C(20)); 38.61, 37.76, 37.60, 36.16 (C(4), C(8), C(12), C(16)); 30.98 (C(22)); 24.65, 24.59 (2 x C(30)); 20.27, 17.79 (C(23), C(23')); 15.14 (C(41))

IR: ($CHCl_3$)

3061 (w); 3025 (m); 2953(s); 2911 (m); 2869 (m); 1612 (m); 1514 (m); 1493 (m); 1452 (m); 1380 (m); 1341 (m); 1248 (m); 1224(m); 1119 (m); 1058 (m); 1028 (m); 1012 (m)

MS: (FD)

934 (10); 933 (31); 932 (40, M^+); 904 (10); 122 (26); 121 (100)

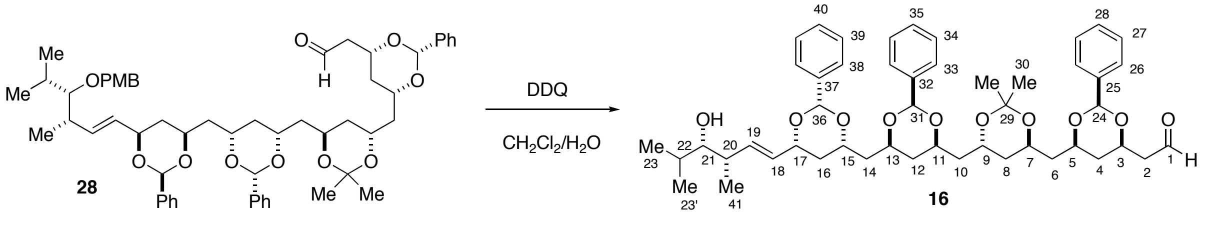
Opt. Rot.: $[\alpha]_D^{24}$ + 44.1 (c =0.45 , EtOH)

TLC: R_f 0.20 (hexane/EtOAc 2/1) [silica gel, *p*-anisaldehyde]

Analysis: Calc for $C_{57}H_{72}O_{11}$ (933.17)

Calcd:	C, 73.36%;	H, 7.78%
Found:	C, 73.15%;	H, 7.86%

Hydroxy Aldehyde 16



In a 100-mL Schlenk flask were placed **28** (136 mg, 0.15 mmol), dichloromethane (7 mL) and water (0.35 mL). To the solution was added DDQ (36 mg, 0.16 mmol, 1.1 equiv) in one portion and the reaction mixture was stirred for 25 min at rt. To the reaction mixture was added another portion of DDQ (5 mg, 0.02 mmol, 0.1 equiv) and the mixture was stirred for an additional 25 min at rt. To the reaction mixture was added saturated aqueous $NaHCO_3$ solution (8 mL). The biphasic mixture was stirred for 15 min and was transferred to a 60-mL separatory funnel. The aqueous layer was extracted with dichloromethane (2 x 15 mL) and the combined organic layer was washed with brine (10 mL). The organic extracts dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was chromatographed (silica gel, hexane/EtOAc 3/1 to 1/1, 20 mm) to afford 107 mg (0.13 mmol, 90%) of **16** as white foam.

Data for **16**:

mp: 74 - 75 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

9.86 (s, 1 H, HC(1)); 7.55 – 7.46 (m, 6 H, 2 x HC(26), 2 x HC(33), 2 x HC(38)); 7.40 – 7.33 (m, 9 H, HC(28), 2 x HC(27), HC(35), 2 x HC(34), HC(40), 2 x HC(39)); 5.73 (dd, *J* = 15.7, 7.3, 1 H, HC(19)); 5.63 (dd, *J* = 15.5, 5.8, 1 H, HC(18)); 5.62, 5.58, 5.57 (3 x s, 3 x 1 H, HC(24), HC(31), HC(36)); 4.43 – 4.36 (m, 2 H, HC(3), HC(17)); 4.28 – 4.02 (m, 6 H, HC(5), HC(7), HC(9), HC(11), HC(13), HC(15)); 3.76 (t, *J* = 6.3, 1 H , OH); 3.17 (td, *J* = 5.3, 4.9, 1 H, HC(21));

2.72 (ABXd, J_{ax} = 7.4, J_{bx} = 4.2, J_{ab} = 16.9, J = 2.0, 2 H, $H_2C(2)$); 2.38 (sext, J = 6.5, 1 H, HC(20)); 2.04 – 1.97, 1.86 – 1.39 (m, 15 H, HC(22), $H_2C(4)$, $H_2C(6)$, HC(8), $H_2C(10)$, $H_2C(12)$, $H_2C(14)$, $H_2C(16)$); 1.39 (s, 3 H, $H_3C(30)$); 1.37 (s, 3 H, $H_3C(30')$); 1.04 (d, J = 6.6, 3 H, $H_3C(41)$); 0.93 (d, J = 7.3, 3 H, $H_3C(23)$); 0.92 (d, J = 7.5, 3 H, $H_3C(23')$)

^{13}C NMR: (126 MHz, $CDCl_3$)

200.37 (C(1)); 138.88, 138.67, 138.14 (C(25), C(32), C(37)); 135.07 (C(19)); 130.00 (C(18)); 128.75, 128.64, 128.52 (C(28), C(35), C(40)); 128.18, 128.16 (2 x C(27), 2 x C(34), 2 x C(39)); 126.16, 125.95, 125.83 (2 x C(26), 2 x C(33), 2 x C(38)); 100.66, 100.47, 100.40, 100.12 (C(24), C(29), C(31), C(36)); 79.56 (C(21)); 77.13 (C(17)); 73.26, 73.01, 72.49 (C(5), C(11), C(13), C(15)); 71.81 (C(3)); 62.76, 62.36 (C(7), C(9)); 49.29 (C(2)); 42.45, 41.79, 41.46 (C(6), C(10), C(14)); 39.35 (C(20)); 38.57, 37.71, 37.63, 36.12 (C(4), C(8), C(12), C(16)); 30.47 (C(22)); 24.62, 24.55 (2 x C(30)); 19.62, 16.96 (C(23), C(23')); 13.92 (C(41))

IR: (CH_2Cl_2)

3584 (br, w); 3053 (w); 2952(s); 1726(m); 1458 (m); 1381 (m); 1343 (m); 1265 (s); 1224 (m); 1113 (m); 1059 (m); 1011 (m)

MS: (FD)

814 (22); 813 (45); 812 (55, M^+); 811 (15); 799 (22); 798 (55); 797 (100); 740 (33); 739 (49)

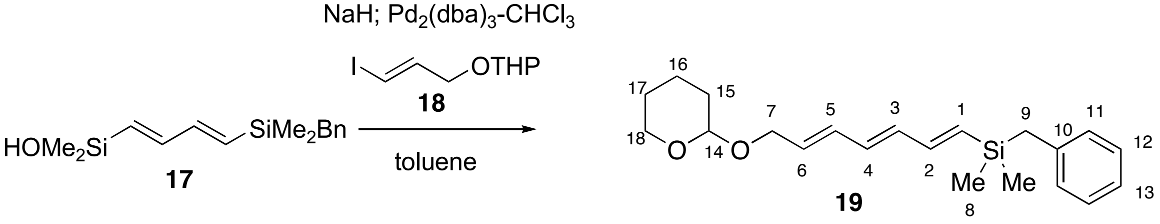
Opt. Rot.: $[\alpha]_D^{24}$ + 29.7 (c =0.17, EtOH)

TLC: R_f 0.28 (hexane/EtOAc, 1/1) [silica gel, *p*-anisaldehyde]

Analysis: Calc for $C_{49}H_{64}O_{10}$ (813.03)

Calcd:	C, 72.39%;	H, 7.93%
Found:	C, 72.18%;	H, 8.01%

1-Benzyldimethylsilyl-7-(tetrahydropyan-2-yloxy)-1,3,5-heptatriene (19)



To a 10-mL Schlenk flask were placed washed sodium hydride (40 mg, 1.69 mmol, 1.4 equiv) and toluene (0.5 mL). To this suspension was added solution of **17** (501 mg, 1.81 mmol, 1.5 equiv) in toluene (2.5 mL) dropwise over 5 min, and the reaction mixture was stirred for 15 min at rt. To the solution was sequentially added **18** (328 mg, 1.21 mmol) and tris(dibenzylideneacetone)dipalladium(0) chloroform adduct (62.6 mg, 0.061 mmol, 0.05 equiv). The reaction mixture was stirred for 6 h and then was passed through a pad of silica gel (60 mm x 2 cm). The silica gel was washed with ethyl acetate (3 x 20 mL), and the filtrate was concentrated under reduced pressure. The crude oil was chromatographed (silica gel, hexane/EtOAc 9/1, 30 mm) to afford 319 mg (0.93 mmol, 77%) of **19** as a yellow oil. An analytically pure sample was obtained by further chromatography (silica gel, hexanes/ether 15/1, 30 mm) followed by bulb-to-bulb distillation (ABT 165 °C at 0.1 mmHg).

Data for **19**:

bp: 165 °C (ABT, 0.1 mmHg)

^{1}H NMR: (500 MHz, CDCl$_3$)

7.21 (t, J = 7.6, 2 H, 2 x HC(12)); 7.07 (t, J = 7.3, 1 H, HC(13)); 6.99 (d, J = 7.3, 2 H, 2 x HC(11))); 6.54 – 6.49 (m, 1 H, HC(2)); 6.32 – 6.27 (m, 1 H, HC(3)); 6.24 – 6.22 (m, 2 H, HC(4), HC(5));5.87 – 5.82 (m, 2 H, HC(1), HC(6)); 4.66 (t, J = 3.6, 1 H, HC(14)); 4.18 (ABX, J_{ab} = 13.4, J_{ax} = 5.9, J_{bx} = 6.8, 2 H, H$_2$C(7)); 3.90 – 3.86 (m, 1 H, H$_{eq}$C(18)); 3.54-3.50 (m, 1 H, H$_{ax}$C(18)); 2.15 (s, 2 H, H$_2$C(9)); 1.88 – 1.82 (m, 1 H, H$_{eq}$C(15)); 1.76 – 1.72 (m, 1 H, H$_{ax}$C(15)); 1.64 – 1.53 (m, 4 H, H$_2$C(16), H$_2$C(17)); 0.06 (s, 6 H, 2 x H$_3$C(8))

^{13}C NMR: (126 MHz, $CDCl_3$)

144.88 (C(2)); 139 87 (C(10)); 135.40 (C(4)); 132.79 (C(5)); 132.60 (C(1)); 132.33 (C(3)); 130.79 (C(6)); 128.23 (2 x C(11)); 128.11 (2 x C(12)); 123.97 (C(13)); 97.87 (C(14)); 67.24 (C(7)); 62.18 (C(18)); 30.56 (C(15)); 26.00 (C(17)); 25.40 (C(9)); 19.40 (C(16)); -3.47 (2 x C(8))

IR: (neat)

3081 (w); 3059 (m); 3024 (m); 2947(s); 1727(w); 1686 (m); 1642 (w); 1600 (m); 1560 (m); 1493 (m); 1452 (m); 1441 (m); 1406 (m); 1350 (m); 1322 (m); 1284 (m); 1248 (m); 1203 (m); 1183 (m); 1155 (m); 1119 (m); 1078 (m); 1055 (m); 1024 (s); 1006 (s)

MS: (EI, 70eV)

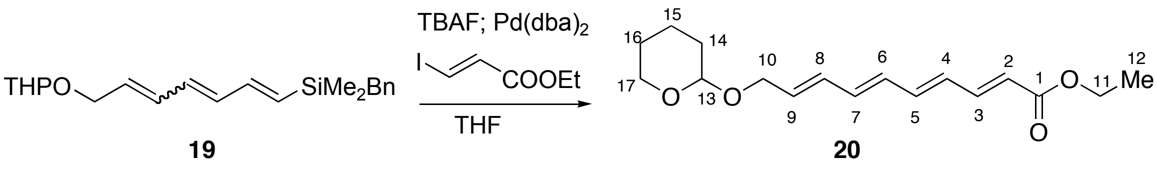
342 (2, M^+); 251 (11); 149 (22); 91 (12); 85 (100); 75 (29); 59 (11); 57 (17)

TLC: R_f 0.05 (hexane/EtOAc, 9/1) [silica gel, *p*-anisaldehyde]

Analysis: $C_{21}H_{30}O_2Si$ (342.55)

Calcd:	C, 73.63%;	H, 8.83%
Found:	C, 73.62%;	H, 9.11%

Ethyl 10-(Tetrahydropyran-2-yl)-2,4,6,8-tetraenoate (20)



In a 10-mL Schlenk flask was placed **19** (360 mg, 1.05 mmol, 1.2 equiv) and tetrahydrofuran (3 mL). The solution was cooled to 0 ºC (bath temperature) using an ice bath. To the solution was added dropwise a 1.0 M solution of TBAF in THF (2.10 mL, 2.10 mmol, 2.4 equiv) and the solution was stirred for 15 min at 0 ºC. To the solution was added sequentially ethyl 3-iodoacrylate (198 mg, 0.88 mmol) and bis(dibenzylieneacetone)palladium(0) (23.1 mg, 0.044 mmol, 0.05 equiv). The reaction mixture was allowed to warm to rt and was stirred for 7 h. The reaction mixture was passed through a pad of silica gel (60 mm x 2 cm) and the silica gel was washed with ethyl acetate (3 x 20 mL). The filtrate was concentrated under reduced pressure. The resulting crude oil was chromatographed (silica gel, hexanes/EtOAc 7/1, 30 mm) to afford **20** (204 mg, 0.70 mmol, 79%) as yellow powder. An analytically pure sample was obtained by recrystallization of **20** (60 mg) from refluxing hexanes/ether 3/1 (20 mL).

Data for **20**:

mp: 59 - 60 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

7.31 (dd, J = 15.3, 11.4, 1 H, HC(3)); 6.58 (dd, J = 14.7, 11.0, 1 H, HC(5)); 6.44 – 6.27 (m, 4 H, HC(4), HC(6), HC(7), HC(8)); 5.92 (dt, J = 14.4, 6.0, HC(9)); 5.87 (d, J = 15.1, 1 H, HC(2)); 4.65 (t, J = 3.7, 1 H, HC(13)); 4.19 (ABX, J_{ab} = 13.9, J_{ax} = 6.0, J_{bx} = 6.6, 2 H, $H_2C(10)$); 4.20 (q, J = 7.1, 2 H, $H_2C(11)$); 3.89 – 3.85 (m, 1 H, $H_{eq}C(17)$); 3.54 - 3.50 (m, 1 H, $H_{ax}C(17)$); 1.86 – 1.82 (m, 1 H, $H_{eq}C(14)$); 1.77 – 1.71 (m, 1 H, $H_{ax}C(14)$); 1.65 – 1.52 (m, 4 H, $H_2C(15)$, $H_2C(16)$); 1.30 (t, J = 7.1, 3 H, $H_3C(12)$)

^{13}C NMR: (126 MHz, $CDCl_3$)

167.11 (C(1)); 144.28 (C(3)); 140.44 (C(5)); 136.28 (C(4)); 132.54 (C(6)); 131.86 (C(9)); 131.82 (C(7)); 130.16 (C(8)); 120.81 (C(2)); 97.97 (C(13)); 67.07 (C(10)); 62.19 (C(17)); 60.25 (C(11)); 30.53(C(14)); 25.37(C(15) or C(16)); 19.34 (C(15) or C(16)); 14.27 (C(12))

IR: (neat)

2944(s); 2872 (m); 1702(s); 1654 (m); 1624 (m); 1599 (m); 1466 (m); 1368 (m); 1340 (m); 1302 (m); 1261 (m); 1201 (m); 1127 (m); 1077 (m); 1008 (m)

MS: (EI, 70eV)

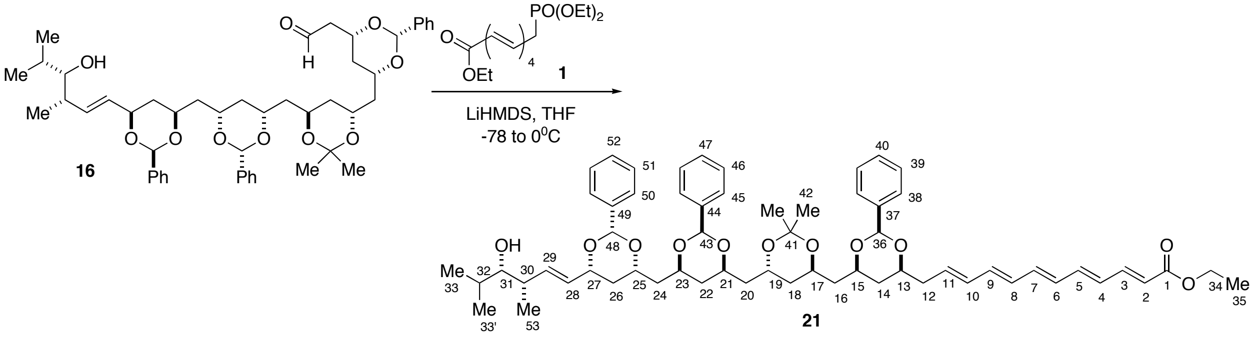
292 (0.3, M^+); 208 (19); 191 (11); 117 (24); 91 (12); 85 (100); 67 (13); 57 (17)

TLC: R_f 0.08 (hexane/EtOAc, 7/1) [silica gel, *p*-anisaldehyde]

Analysis: $C_{17}H_{24}O_4$ (292.37)

Calcd:	C, 69.84%;	H, 8.27%
Found:	C, 69.73%;	H, 8.33%

Ethyl Pentaenoate 21



In a 50-mL Schlenk flask was placed **1** (59 mg, 0.18 mmol, 2.5 equiv) and tetrahydrofuran (15 mL). The solution was cooled to –72 °C (internal temperature) using a dry ice/isopropanol bath. To the solution was added dropwise a 0.2 M solution of LiHMDS in THF (0.9 mL, 0.18 mmol, 2.5 equiv). The dark blue solution was stirred for 15 min before the addition of a solution of **16** (58 mg, 0.072 mmol) in tetrahydrofuran (5 mL). The reaction mixture was stirred at –72 °C for 15 min, then was allowed to warm to 0 °C using an ice bath and was stirred for 45 min at 0 °C. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution (20 mL). The biphasic mixture was transferred to a 125-mL separatory funnel. The aqueous layer was extracted with ether (2 x 20 mL) and the combined organic layers were washed with brine (20 mL). The extracts were dried over Na_2SO_4 and then were concentrated under reduced pressure. The resulting crude oil was chromatographed (silica gel, hexanes/EtOAc 3/1, 20 mm) to afford 54.7 mg (0.055 mmol, 77%) of **21** as yellow solid.

Data for **21**:

mp: 88 - 90 °C

^{1}H NMR: (500 MHz, C_6D_6)

7.75 – 7.69 (m, 6 H, 2 x HC(38), 2 x HC(45), 2 x HC(50)); 7.52 (dd, *J* = 15.2, 11.5, 1H, HC(3)); 7.23 – 7.10 (m, 9 H, HC(40), 2 x HC(39), HC(47), 2 x HC(46), HC(52), 2 x HC(51); 6.23 – 5.93 (m, 8 H, HC(2), HC(4), HC(5), HC(6), HC(7), HC(8), HC(9), HC(10)); 5.83 (dt, *J* = 14.5, 7.4, 1 H, HC(11)); 5.65 (dd, *J* = 15.6, 7.6, 1 H, HC(29)); 5.57 (dd, *J* = 15.7, 5.2, 1 H, HC(28)); 5.54, 5.54, 5.45 (3 x s, 3 x 1 H, HC(36), HC(43), HC(48)); 4.09 (q, *J* = 7.0, 2 H, $H_2C(34)$); 4.33 – 4.27, 4.28 – 3.86 (m, 7 H, HC(15), HC(17), HC(19), HC(21), HC(23), HC(25), HC(27)); 3.61 – 3.56 (m, 1 H , HC(13)); 2.95 (m, 1 H, HC(31)); 2.46 – 2.25(m, 2 H, $H_2C(12)$); 2.23 (sext, *J* = 7.1, 1 H, HC(30)); 2.13 – 2.07, 1.72 – 1.10 (m, 15 H, HC(32), $H_2C(14)$, $H_2C(16)$, HC(18), $H_2C(20)$, $H_2C(22)$, $H_2C(24)$, $H_2C(26)$); 1.46 (s, 3 H, $H_3C(30)$); 1.42 (s, 3 H, $H_3C(30')$); 1.07 (d, *J* = 5.7, 1 H, OH); 1.02 (d, *J* = 7.1, 3 H, $H_3C(53)$); 1.02 (t, *J* = 7.1, 3 H, $H_3C(35)$); 0.91 (d, *J* = 6.9, 3 H, $H_3C(33)$); 0.80 (d, *J* = 6.8, 3 H, $H_3C(33')$)

^{13}C NMR: (126 MHz, C_6D_6)

166.76 (C(1)); 144.58 (C(3)); 140.76 (C(11)); 140.05, 139.85, 139.69 (C(37), C(44), C(49)); 137.23, 135.53, 133.33, 132.07, 132.04, 131.55, 130.15 (C(4), C(5), C(6), C(7), C(8), C(9), C(10)); 134.79 (C(29)); 130.36 (C(28)); 128.86, 128.81, 128.29, 126.94, 126.73, 126.71 (C(40), C(47), C(52), 2 x C(39), 2 x C(46), 2 x C(51), 2 x C(38), 2 x C(45), 2 x C(50)); 121.15 (C(2)); 101.25, 101.22, 100.42, 99.29 (C(36), C(41), C(43), C(48)); 79.47 (C(31)); 77.10 (C(27)); 76.37 (C(13)); 73.60, 73.26, 72.70, 72.62 (C(15), C(21), C(23), C25)); 63.13, 62.63 (C(17), C(19)); 60.13 (C(34)); 43.21, 42.52, 42.22 (C(16), C(20), C(24)); 40.16 (C(30)); 39.83 (C(12)); 38.99, 38.19, 38.03, 36.40 (C(14), C(18), C(22), C(26)); 30.85 (C(32)); 25.00, 24.94 (2 x C(42)); 19.88, 16.70 (C(33), C(33')); 14.95 (C(53)); 14.31 (C(35))

IR: (CH_2Cl_2)

3524 (br, w); 3019 (m); 2982 (m); 2947(s); 2916 (m); 2872 (m); 1706(s); 1622 (m); 1579 (m); 1454 (m); 1429 (w); 1408 (m); 1378 (m); 1343 (m); 1309 (m); 1224 (m); 1128 (s); 1058 (m); 1011 (s)

MS: (HR-ESI)

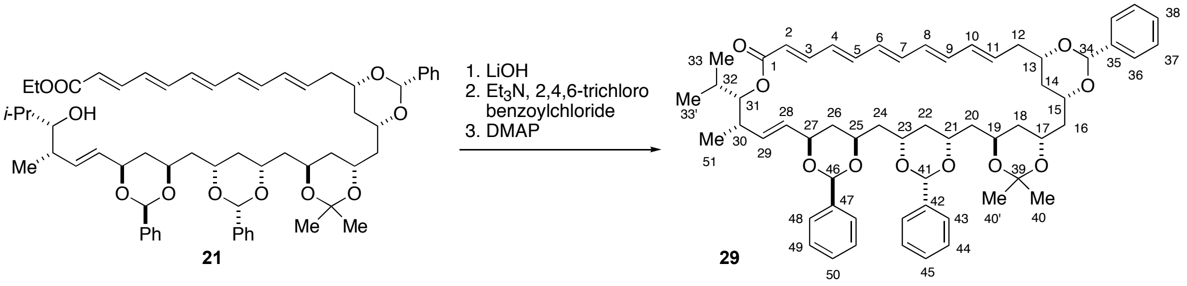
Calcd: 1009.5442 (for $C_{61}H_{78}O_{11}$ + Na)

Found: 1009.5452

Opt. Rot.: $[\alpha]_D^{24}$ + 19.0 (c = 0.05, EtOH)

TLC: R_f 0.48 (hexane/EtOAc, 1/1) [silica gel, *p*-anisaldehyde]

Macrolactone 29



In a 25-mL, round-bottom flask was placed sequentially **21** (14 mg, 0.014 mmol), tetrahydrofuran (2 mL), methanol (0.5 mL), water (0.5 mL) and a 1.0 M aqueous LiOH (1.0 mL, 1.0 mmol). The solution was stirred for 16 h at rt, then was quenched by the addition of 1 mL of water. The reaction mixture was transferred to a 60-mL separatory funnel and extracted with ethyl acetate (3 x 15 mL). The combined extracts were washed with brine (15 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the crude acid as pale yellow oil. The crude acid was placed in a 100-mL Schlenk flask together with a 0.04 M solution of triethylamine in THF(3.5 mL, 0.14 mmol, 10.0 equiv) followed by 0.04 M solution of 2,4,6-trichlorobenzoyl chloride in THF (2.45 mL, 0.10 mmol, 7.0 equiv), and the reaction mixture was stirred at rt for 1 h. The volatile materials were removed under vacuum (0.5 mmHg) and the residue was dissolved in toluene (50 mL). In a 250-mL, 3-neck flask were placed 4-dimethylaminopyridine (30 mg) and toluene (125 mL), to which was added dropwise over 8h the solution of the activated anhydride in toluene using a cannula. The resulting reaction mixture was stirred for additional 12 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and was transferred to a 500-mL separatory funnel. The aqueous layer was extracted with ether (100 mL) and the combined organic extracts were washed with brine (50 mL). The extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude oil was chromatographed (silica gel, hexanes/EtOAc 4/1, 20 mm) to afford 9.3 mg (0.010 mmol, 71%) of **29** as pale yellow powder.

Data for **29**:

mp: 83 - 85 °C (dec.)

^{1}H NMR: (500 MHz, C_6D_6)

7.78 – 7.64 (m, 6 H, 2 x HC(36), 2 x HC(43), 2 x HC(48)); 7.60 (dd, *J* = 15.2, 10.8, 1H, HC(3)); 7.26 – 7.10 (m, 9 H, HC(38), 2 x HC(37), HC(45), 2 x HC(44), HC(50), 2 x HC(49)); 6.10 – 5.90 (m, 8 H, HC(2), HC(4), HC(5), HC(6), HC(7), HC(8), HC(9), HC(10)); 5.56 – 5.36 (m, 3 H, HC(29), HC(28), HC(11)); 5.53, 5.46, 5.46 (3 x s, 3 x 1 H, HC(34), HC(41), HC(46)); 5.09 (dd, *J* = 9.8, 3.0, 1 H, HC(31)); 4.19 – 3.79 (m, 7 H, HC(15), HC(17), HC(19), HC(21), HC(23), HC(25), HC(27)); 3.52 – 3.48 (m, 1 H , HC(13)); 2.65 – 2.62 (m, 1 H, $H_2C(12)$); 2.52 – 2.49 (m, 1 H, HC(30)); 2.30 – 2.21 (m, 1 H, $H_2C(12)$); 1.72 – 0.92 (m, 15 H, HC(32), $H_2C(14)$, $H_2C(16)$, HC(18), $H_2C(20)$, $H_2C(22)$, $H_2C(24)$, $H_2C(26)$); 1.40 (s, 3 H, $H_3C(30)$); 1.39 (s, 3 H, $H_3C(30')$); 1.50 (d, *J* = 7.1, 3 H, $H_3C(53)$); 1.01 (d, *J* = 6.6, 3 H, $H_3C(33)$); 0.70 (d, *J* = 6.8, 3 H, $H_3C(33')$)

^{13}C NMR: (126 MHz, C_6D_6)

166.80 (C(1)); 145.59 (C(3)); 141.09 (C(11)); 140.14, 140.05, 139.69 (C(35), C(42), C(47)); 137.84, 137.18, 135.01, 134.65, 132.07, 132.02, 131.67, 130.72, 130.62 (C(4), C(5), C(6), C(7), C(8), C(9), C(10), C(29), C(28)); 129.96, 129.87, 129.28, 128.81, 128.76, 128.51, 127.50, 127.19, 126.77, 126.75, 125.65 (C(38), C(45), C(50), 2 x C(37), 2 x C(44), 2 x C(49), 2 x C(36), 2 x C(43), 2 x C(48)); 121.25 (C(2)); 101.34, 101.29, 100.91, 100.10 (C(34), C(39), C(41), C(46)); 80.07 (C(31)); 75.56, 75.24, 74.48, 73.33, 71.91, 71.86 (C(13), C(15), C(21), C(23), C25), C(27)); 63.22, 61.12 (C(17), C(19)); 44.16, 43.58, 41.89 (C(16), C(20), C(24)); 39.57 (C(12)); 36.52 (C(30)); 40.00, 39.22, 35.67 (C(14), C(18), C(22), C(26)); 29.75 (C(32)); 25.79, 25.61 (2 x C(40)); 20.01, 18.69 (C(33), C(33')); 11.05 (C(51))

IR: (CH_2Cl_2)

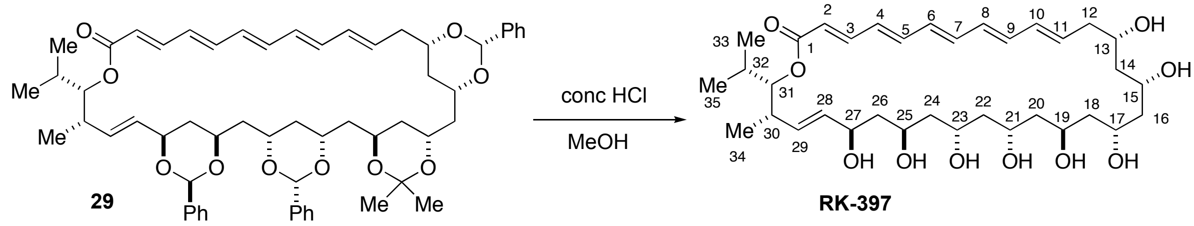
2916 (s); 1702 (m); 1619 (m); 1578 (m); 1379 (m); 1344 (m); 1224 (m); 1125 (s); 1010 (s)

MS: (HR-ESI)
Calcd: 963.5023 (for $C_{59}H_{72}O_{10}$ + Na)
Found: 963.5028

Opt. Rot.: $[\alpha]_D^{24}$ + 44.9 (c = 0.085, EtOH)

TLC: R_f 0.55 (hexane/EtOAc, 1/1) [silica gel, *p*-anisaldehyde]

RK-397



In a 25-mL, round-bottom flask were placed methanol (2 mL) and conc. HCl (0.05 mL, 0.6 mmol). To the solution was added dropwise a solution of **29** (9.3 mg, 0.010 mmol) in methanol (5 mL). The reaction solution was stirred for 5 h, then was neutralized using polymer-bound piperidine (400 mg, ca. 1.2 mmol). The polymer was removed by filtration and the filtrate was concentrated under reduced pressure. The resulting crude solid was chromatographed (silica gel, EtOAc/MeOH 4/1, 10 mm) to afford RK-397 and partially deprotected macrolactone. The partially deprotected macrolactone was resubjected under the reaction conditions described above to afford ca. 7 mg of RK-397 combined. After silica gel chromatography, the synthetic RK-397 was further purified by reversed-phase preparative HPLC (Vydac C-18 250 x 22 mm, 60/40 to 80/20 MeOH/H_2O over 45 min, flow 8 mL/min, UV detector at 360 nm; retention time 43 min). The HPLC purification was repeated twice to obtain pure synthetic RK-397 (6.0 mg, 0.0094 mmol, 93%) as yellow powder.

Comparison of Natural and Synthetic RK-397:

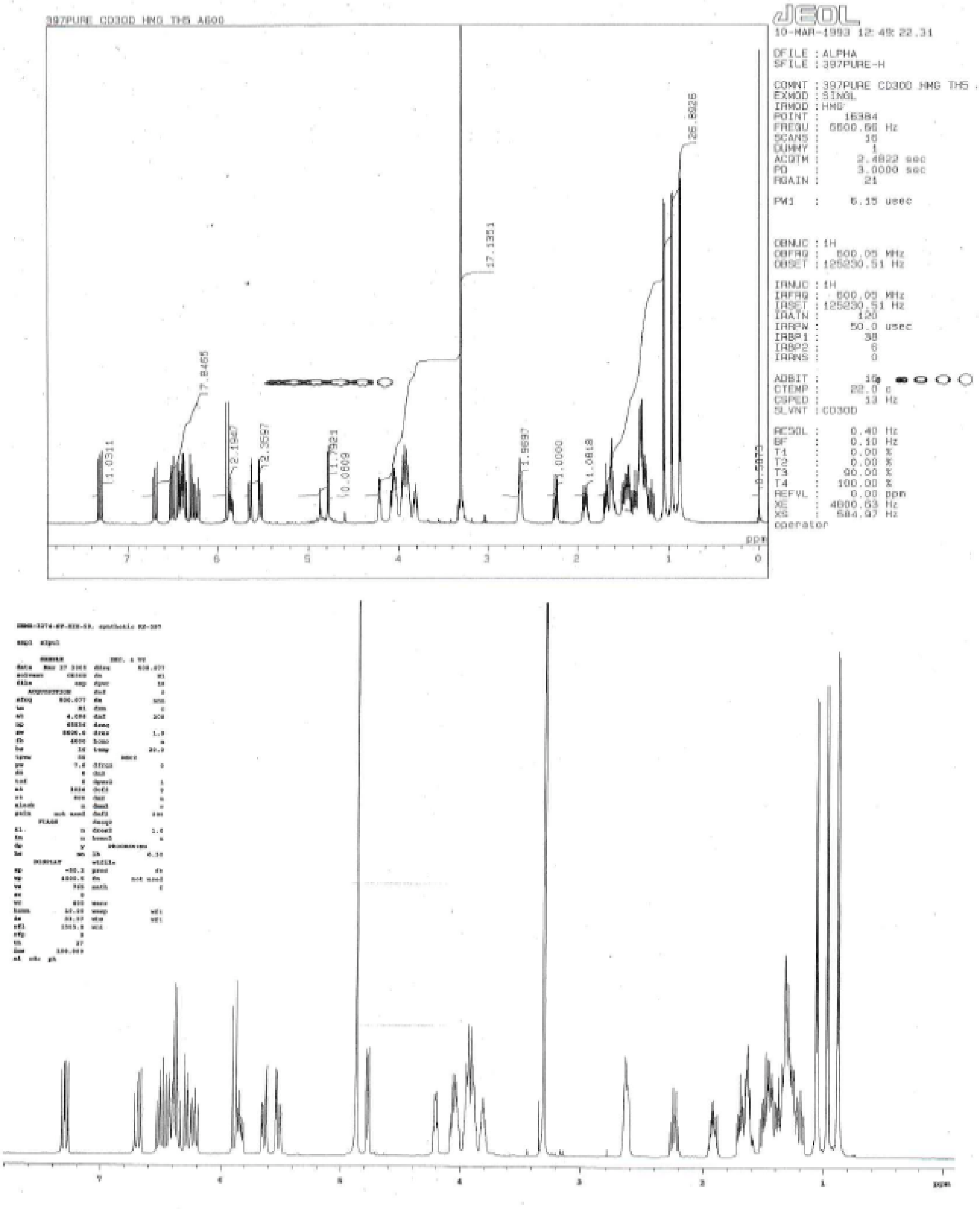


Figure 1. ^{1}H NMR spectra of RK-397 (top: natural RK-397 from RIKEN; bottom: synthetic RK-397 from UIUC)

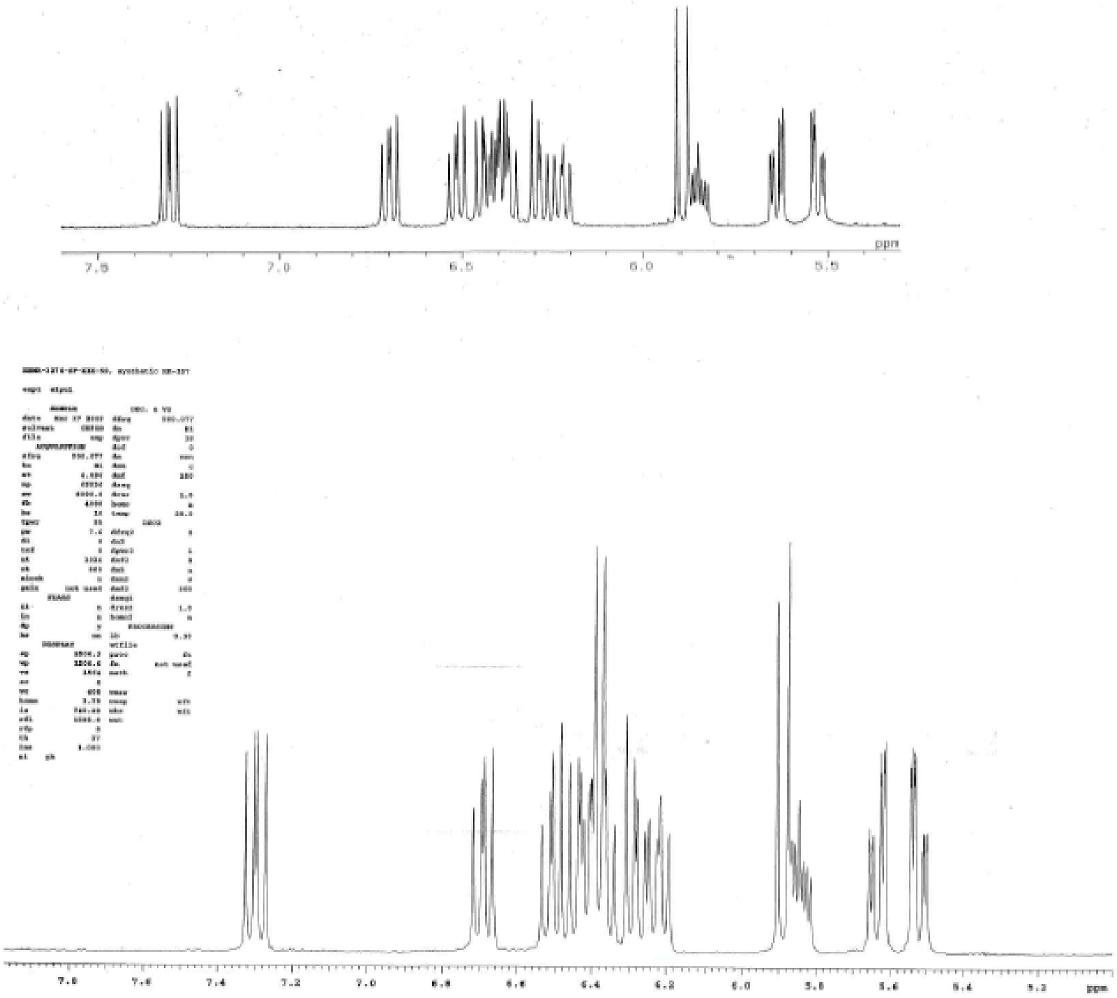
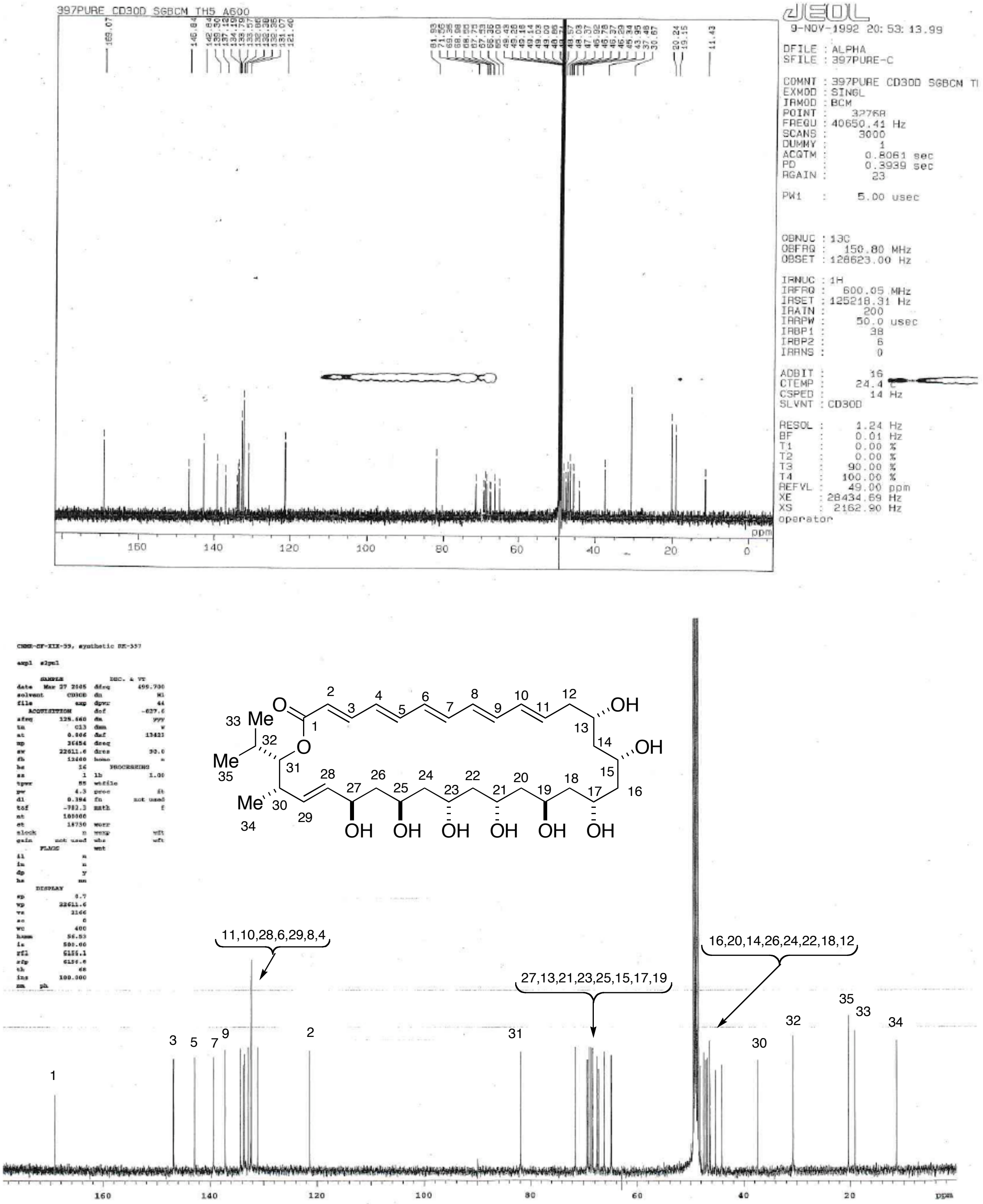


Figure 2. ^{1}H NMR spectra of RK-397: 5.2 – 7.9 ppm (top: natural RK-397 from RIKEN; bottom: synthetic RK-397 from UIUC)



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 9-NOV-1992 20:53:13.99

DFILE : ALPHA
SFILE : 397PURE-C

COMNT : 397PURE CD3OD SGBCM TI
EXMOD : SINGL
IRMOD : BCM
POINT :    32768
FREQU : 40650.41 Hz
SCANS :     3000
DUMMY :        1
ACQTM :      0.8061 sec
PD    :      0.3939 sec
RGAIN :       23

PW1   :     5.00 usec


OBNUC : 13C
OBFRQ :   150.80 MHz
OBSET : 128623.00 Hz

IRNUC : 1H
IRFRQ :   600.05 MHz
IRSET : 125218.31 Hz
IRAIN :      200
IRRPW :     50.0 usec
IRBP1 :       38
IRBP2 :        6
IRRNS :        0

ADBIT :       16
CTEMP :     24.4 c
CSPED :       14 Hz
SLVNT : CD3OD

RESOL :     1.24 Hz
BF    :     0.01 Hz
T1    :     0.00 %
T2    :     0.00 %
T3    :    90.00 %
T4    :   100.00 %
REFVL :    49.00 ppm
XE    : 28434.69 Hz
XS    :  2162.90 Hz
operator
```

Figure 3. ^{13}C spectra of RK-397 (top: natural RK-397 from RIKEN; bottom: synthetic RK-397 from UIUC)

I. NMR Spectroscopic Properties:

^{13}CNMR (Natural at 150 MHz; Synthetic at 125 MHz)

Carbon No.	Natural (ppm)	Synthetic (ppm)	Difference (ppm)
1	169.07	169.10	+0.03
2	121.40	121.44	+0.04
3	146.84	146.90	+0.06
4	131.07	131.16	+0.09
5	142.84	142.89	+0.15
6	132.86	132.92	+0.06
7	139.30	139.37	+0.07
8	132.38	132.38	0
9	137.12	137.20	+0.08
10	133.79	133.77	-0.02
11	134.19	134.31	+0.12
12	43.95	44.11	+0.16
13	69.35	69.22	-0.13
14	46.92	47.14	+0.22
15	67.53	67.34	-0.19
16	48.03	48.11	+0.08
17	66.36	66.25	-0.11
18	45.34	45.32	-0.02
19	65.09	64.94	-0.15
20	47.37	47.50	+0.13
21	68.98	68.87	-0.11
22	46.29	46.32	+0.03
23	68.55	68.45	-0.10
24	46.37	46.36	-0.01
25	67.75	67.61	-0.14
26	46.78	46.86	+0.08
27	71.56	71.46	-0.10
28	133.57	133.55	-0.02
29	132.35	132.38	+0.03
30	37.48	37.43	-0.05
31	81.93	81.88	-0.05
32	30.67	30.70	+0.03
33	19.15	19.11	-0.04
34	11.43	11.34	-0.09
35	20.24	20.27	+0.03

^{1}HNMR (Natural at 600 MHz; Synthetic at 500 MHz)

Carbon No.	Natural (ppm)	Synthetic (ppm)
1	--	--
2	5.89 (d, 14.9)	5.89 (d, 15.1)
3	7.30 (dd, 14.9, 11.7)	7.30 (dd, 14.9, 11.5)
4	6.44 (dd, 14.9, 11.7)	6.43 (dd, 14.7, 11.6)
5	6.70 (dd, 14.9, 11.3)	6.69 (dd, 14.6, 11.0)
6	6.37 (dd, 14.9, 11.3)	6.37 (dd, 15.2, 11.0)
7	6.51 (dd, 14.9, 10.9)	6.51 (dd, 14.7, 11.0)
8	6.29 (dd, 14.9, 10.9)	6.28 (dd, 14.8, 10.9)
9	6.40 (dd, 14.9, 10.9)	6.40 (dd, 15.2, 10.8)
10	6.22 (dd, 14.9, 10.1)	6.22 (dd, 14.9, 10.8)
11	5.85 (ddd, 14.9, 10.1, 5.3)	5.85 (ddd, 15.4, 10.3, 5.6)
12	2.63 (m); 2.24 (ddd, 13.7, 10.1, 10.0)	2.62 (m); 2.24 (m)
13	3.96 (m)	3.92 (m)
14	1.68 – 1.59 (m)	1.68 – 1.58 (m)
15	3.82 (m)	3.80 (m)
16	1.70 (ddd, 13.7, 8.2, 4.8) 1.38 (ddd, 13.7, 8.9, 4.4)	1.69 (ddd, 13.7, 8.6, 5.2) 1.37 (ddd, 13.4, 8.8, 4.6)
17	3.89 (m)	3.92 (m)
18	1.46 (ddd, 14.1, 9.6, 3.2) 1.20 (ddd, 14.1, 10.1, 2.4)	1.46 (m) 1.19 (ddd, 14.2, 10.5, 2.7)
19	4.07 (m)	4.05 (m)
20	1.33 (m), 1.27 (m)	1.32 (m), 1.29 (m)
21	3.94 (m)	3.92 (m)
22	1.33 (m), 1.25 (m)	1.32 (m), 1.27 (m)
23	4.04 (m)	4.05 (m)
24	1.44 (ddd, 14.1, 10.1, 8.4) 1.33 (m)	1.43 (m) 1.32 (m)
25	3.91 (m)	3.92 (m)
26	1.50 (ddd,14.1, 10.1, 8.4) 1.31 (m)	1.50 (ddd, 13.9, 9.5, 8.3) 1.32 (m)
27	4.22 (m)	4.21 (m)
28	5.53 (ddd, 15.7, 4.8, 1.6)	5.52 (ddd, 15.6, 4.2, 1.2)
29	5.64 (ddd, 15.7, 5.2, 1.2)	5.63 (ddd, 15.6, 5.2, 1.0)
30	2.64 (m)	2.64 (m)
31	4.78 (dd, 10.0, 2.6)	4.78 (dd, 9.9, 2.6)
32	1.92 (dqq, 10.0, 6.9, 6.8)	1.92 (m)
33	0.98 (d, 6.9)	0.97 (d, 6.6)
34	1.06 (d, 6.9)	1.06 (d, 7.0)
35	0.88 (d, 6.8)	0.88 (d, 6.6)

II. Physicochemical properties

Property	Natural	Synthetic
Appearance	Yellow powder	Yellow powder
Mp	157-163 ºC (dec.)	159 – 160 ºC (dec.)
Spec. Opt. Rot.	-21º (c = 0.3, MeOH)	-21.7 ºC (c = 0.30, MeOH
HRMS	Found: 637.3930 (M+H) Calcd: 637.3951 (for $C_{35}H_{57}O_{10}$) [FAB]	Found: 637.3957 (M + H) Calcd: 637.3952 (for $C_{35}H_{57}O_{10}$) [ESI]
UV λ_{max} (nm)	260, 360	260, 365
IR	3350, 2900, 1420, 1250, 1105	3368 (s, br), 2939 (m), 1706 (m), 1616 (m), 1577 (m), 1420 (m), 1371 (m), 1324 (m), 1265 (w), 1237 (w), 1126 (s), 1087 (m), 1011 (m)
TLC	0.45 (silica gel, $CHCl_3$/MeOH 2/1)	0.41 (silica gel, $CHCl_3$/MeOH 2/1)
HPLC	Senshu Pak ODS-H 80/20 MeOH/H_2O flow = 6.0 mL/min detector 200-400 nm array t_R = 28 min	Vydac C-18 60/40 – 80/20 MeOH/H_2O flow = 8.0 mL/min detector 360 nm t_R = 43 min
CD		negative Cotton effect peak at 210 nm (10 mdeg) trough at 257 nm (-7 mdeg) (0.5 μM in MeOH)

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