Supporting Information

Total Synthesis of (+)-Roxaticin: A Departure from Stoichiometric Chiral Reagents, Auxiliaries and Premetallated Nucleophiles in Polyketide Construction

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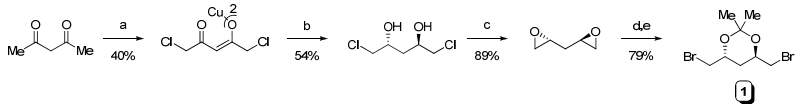
I. Graphical Summary of Prior Synthesis

Rychnovsky's Synthesis (*J. Am. Chem. Soc*. **1994**, *116*, 1753)

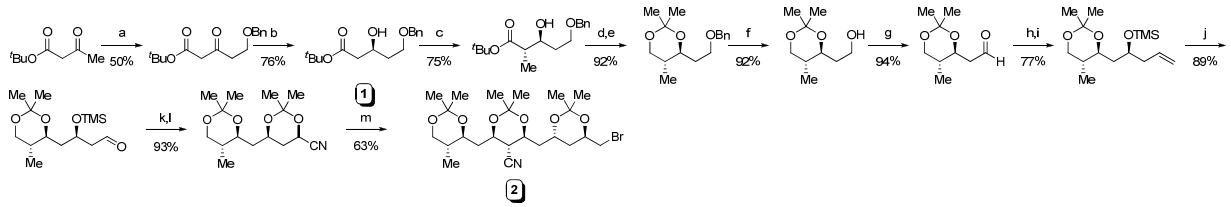
31 longest linear sequence and 51 total steps

Fragment 1



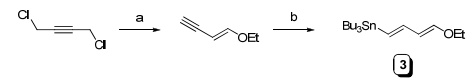
Key: (a) $AlCl_3$, $ClCH_2C(O)Cl$, 60 °C, $Cu(OAc)_2$; (b) H_3O^+, [((*S*)-BINAP)$RuCl_2$]$_2$$Et_3N$, H_2 1200 psi, 120 °C, MeOH, recrystallize; (c) KOH, Et_2O; (d) Li_2NiBr_4, 25 °C, THF; (e) 2,2-DMP, CSA, Acetone

Fragment 2



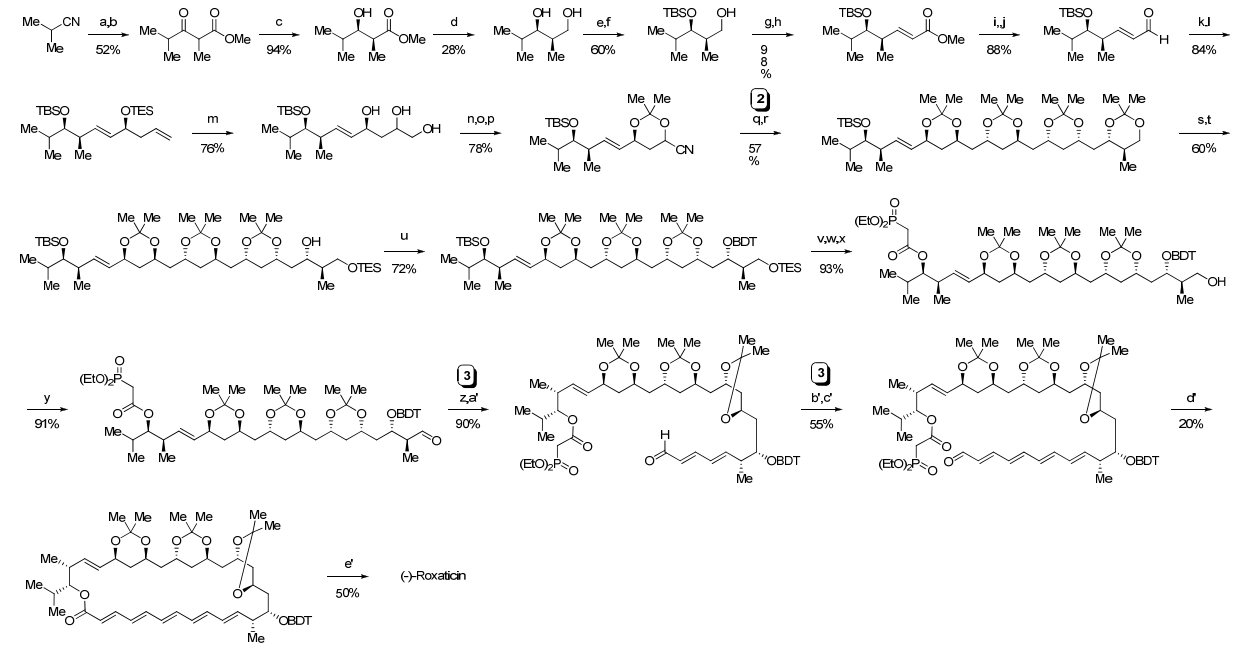
Key: (a) NaH, *n*-BuLi, chloromethyl benzyl ether; (b) H_3O^+, [((*S*)-BINAP)$RuCl_2$]$_2$$Et_3N$, H_2 1620 psi, 45 °C, MeOH; (c) LHMDS, MeI; (d) $LiAlH_4$; (e) CSA, 2,2-DMP; (f) H_2, $Pd(OH)_2/C$; (g) Swern; (h) $Ipc_2BCH_2CH{=}CH_2$, NaOH, H_2O_2; (i) BSA, CH_3CN; (j) OsO_4, NMO, $NaIO_4$; (k) TMSCN; (l) 2,2-DMP, CSA; (m) **1**, $LiNEt_2$, THF.

Fragment 3



Key: (a) KOH, EtOH, the yield is not reported; (b) Bu_3SnH, azobisisobutyronitrile, the yield is not reported

Longest Linear Sequence

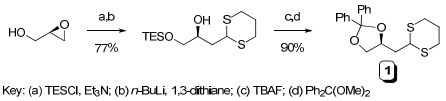


Key: (a) Zn, methyl 2-bromopropionate, THF; (b) H_3O^+; (c) (R-BINAP)$RuCl_2$, H_2, MeOH; (d) LAH_4(80%), recrystallization (35%); (e) TBSOTf; (f) Dowex H^+, MeOH; (g) Swern; (h) $Ph_3P{=}CHCO_2CH_3$, CH_3CN, reflux; (i) DIBAL-H; (j) TPAP, NMO; (k) $Ipc_2BCH_2CH{=}CH_2$, NaOH, H_2O_2; (l) TESOTf, 2,6-lutidine; (m) OsO_4, NMO, HOAc, THF, H_2O; (n) $NaIO_4$; (o) K_2CO_3, $(CH_3)_2C(OH)CN$; (p) 2,2-DMP, CSA; (q) **2**, $LiNEt_2$; (r) LiDBB, THF, MeOH; (s) TESOTf, *i*-Pr_2NEt; (t) OsO_4, *t*-BuOH, $CDCl_3$, pyridine; (u) 1,3-benzodithiolyl tetrafluoroborate, pyridine; (v) TBAF, THF; (w) $(EtO)_2P(O)CH_2CO_2H$, BOP, DMAP; (x) MeOH, NH_3; (y) Dess-Martin; (z) **3**, *n*-BuLi, $MgBr_2$, THF, -78 °C; (a') MsCl, Et_3N; (b') **3**, *n*-BuLi, $MgBr_2$, THF, -78 °C; (c') MsCl, Et_3N; (d') LiCl, DBU; (e') Dowex H^+, MeOH

Mori's Synthesis (*Tetrahedron*, **1995**, *51*, 5299 and *Tetrahedron*, **1995**, *51*, 5315)

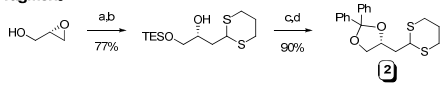
45 longest linear sequence and 71 total steps

Fragment 1



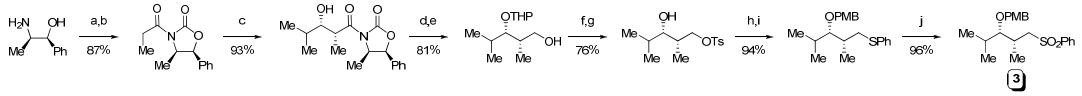
Key: (a) TESCl, Et_3N; (b) *n*-BuLi, 1,3-dithiane; (c) TBAF; (d) $Ph_2C(OMe)_2$

Fragment 2



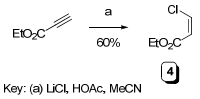
Key: (a) TESCl, Et_3N; (b) *n*-BuLi, 1,3-dithiane; (c) TBAF; (d) $Ph_2C(OMe)_2$

Fragment 3



Key: (a) diphenyl carbonate, K_2CO_3; (b) *n*-BuLi, $CH_3CH_2C(O)Cl$; (c) Bu_2BOTf, Et_3N, Me_2CHCHO; (d) DHP, PPTS; (e) $LiAlH_4$; (f) MeOH, H^+; (g) TsCl, pyridine; (h) PhSNa; (i) PMBCl, KH; (j) *m*-CPBA

Fragment 4

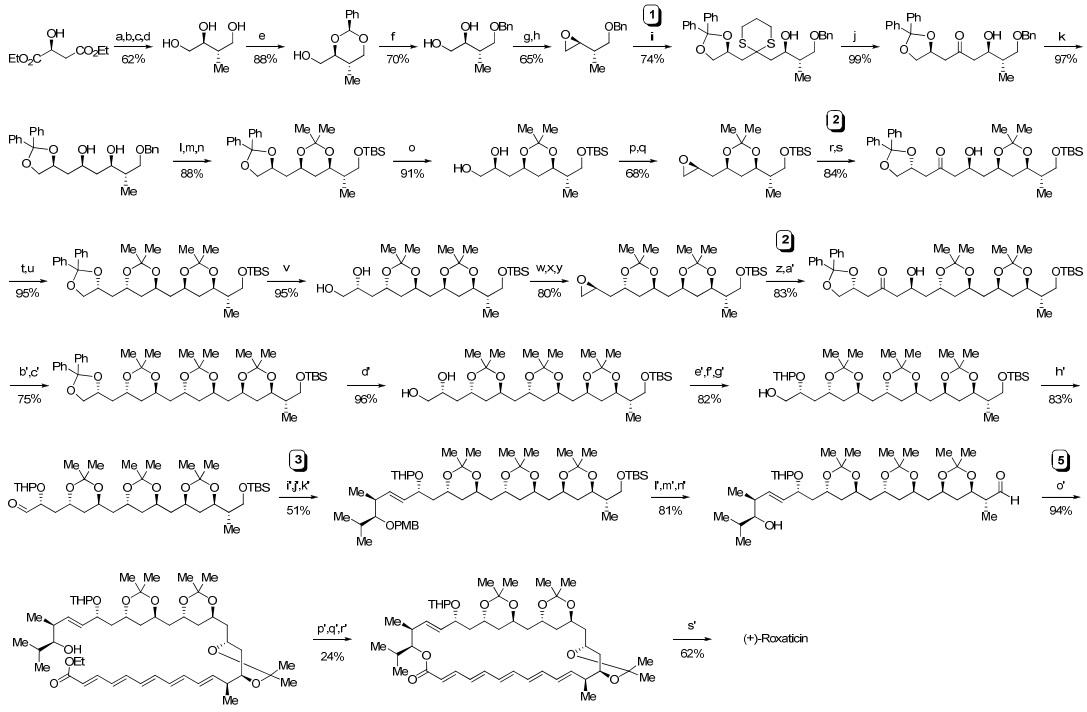


Key: (a) LiCl, HOAc, MeCN

Fragment 5

Key: (a) TBDMPSCl, imidazole; (b) MnO_2; (c) allyl triphenylphosphonium bromide, *n*-BuLi, **4**, *t*-BuOK; (d) TBAF; (e) hv, I_2; (f) PBr_3; (g) $(OEt)_3P$

Longest Linear Sequence

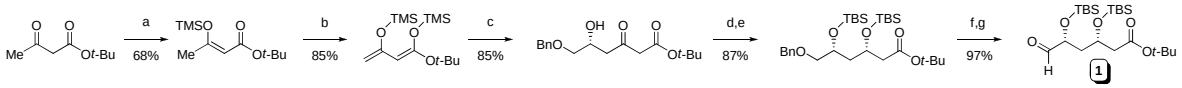


Key: (a) LDA, MeI; (b) DHP, PPTS; (c) $LiAlH_4$; (d) MeOH, H^+; (e) $PhCH(OMe)_2$, TsOH; (f) DIBAL; (g) TsCl, pyridin; (h) *t*-BuOK, Et_2O-MeOH; (i) **1**, *n*-BuLi, THF; (j) $Hg(ClO_4)_2$; (k) $NaBH_4$, Et_2BOMe; (l) $Me_2C(OMe)_2$; (m) H_2, $Pd(OH)_2$; (n) TBSCl, imidazole; (o) Li, NH_3; (p) TsCl; (q) *t*-BuOK, Et_2O-MeOH; (r) **2**, *n*-BuLi, THF; (s) MeI, $CaCO_3$; (t) $Me_4NBH(OAc)_3$; (u) $Me_2C(OMe)_2$, PPTS; (v) Li, NH_3; (w) PivCl; (x) MsCl; (y) *t*-BuOK, Et_2O-MeOH; (z) **2**, *n*-BuLi; (a') MeI, $CaCO_3$; (b') $Me_4NBH(OAc)_3$; (c') $Me_2C(OMe)_2$, PPTS; (d') Li, NH_3; (e') PivCl, pyridine; (f') DHP, PPTS; (g') $LiAlH_4$; (h') SO_3pyr; (i') **3**, n-BuLi; (j') Ac_2O, pyridine; (k') Na-Hg; (l') TBAF; (m') Dess-Martin; (n') DDQ; (o') **5**, LiN(TMS)$_2$; (p') LiOH, THF, H_2O; (q') 2,4,6-trichlorobenzoyl chloride, Et_3N; (r') DMAP, toluene; (s') Dowex 50Wx8, MeOH

Evans' Synthesis (*J. Am. Chem. Soc*. **2003**, *125*, 10899)

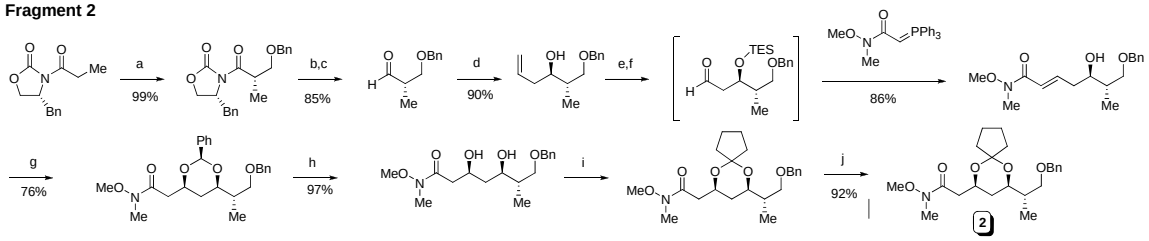
29 longest linear sequence and 52 total steps

Fragment 1



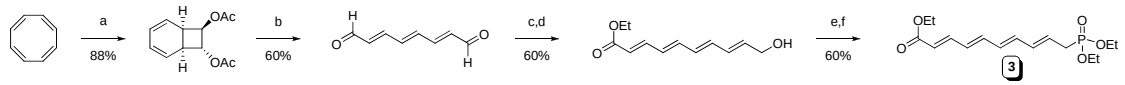
Key: (a) Et_3N, TMSCl, hexanes; (b) LDA, TMSCl, THF; (c) [Cu((S,S)-Ph-pybox)]$(SbF_6)_2$ (2 mol%), benzyloxyacetaldehyde, 99%ee; (d) Et_2BOMe, $NaBH_4$, MeOH, THF, -78 °C; (e) TBSCl, imidazole, CH_2Cl_2; (f) 2000 psi H_2, 10% Pd/C, EtOAc; (g) Dess-Martin, CH_2Cl_2

Fragment 2



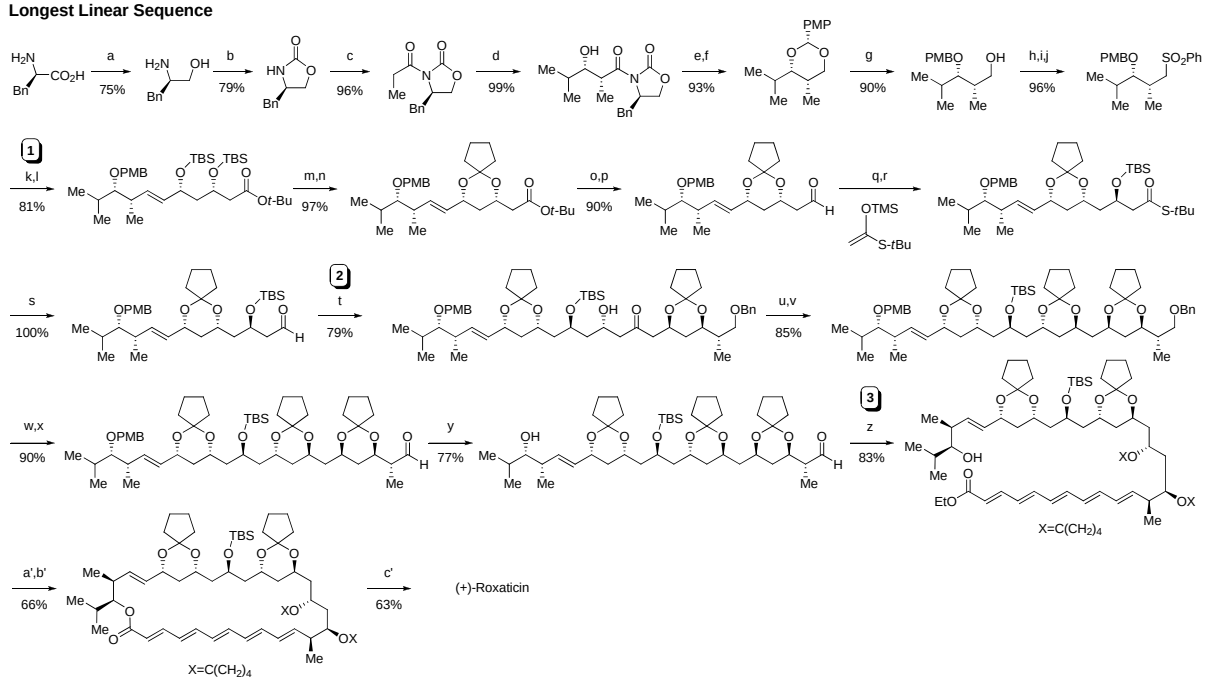
Key: (a) $TiCl_4$, NEt_3, $BnOCH_2Cl$, 0 °C, CH_2Cl_2; (b) $LiBH_4$, 0 °C, THF; (c) SO_3·pyr, DMSO, -10 °C, CH_2Cl_2; (d) allyltributyltin, $SnCl_4$, -78 °C, CH_2Cl_2; (e) TESCl, imidazole, CH_2Cl_2; (f) O_3, Ph_3P, N-MeO-N-Me(triphenylphosphoranylidene)-acetamide, TsOH, CH_2Cl_2; (g) cat. KHMDS, PhCHO, 0 °C, THF; (h) $Zn(OTf)_2$, EtSH, $NaHCO_3$, CH_2Cl_2; (i) cyclopentylidene dimethyl ketal, PPTS, CH_2Cl_2; (j) MeLi, -78 °C, THF

Fragment 3



Key: (a) $Hg(OAc)_2$, AcOH; (b) $LiAlH_4$, THF, 0 °C to rt, then O_2; (c) triethylphosphonoacetate, NaH, -78 °C to rt, THF; (d) $NaBH_4$, EtOH; (e) $SOBr_2$, 2,6-di-*tert*-butylpyridine, -20 °C, THF; (f) $(EtO)_3P$, toluene, 110 °C

Longest Linear Sequence



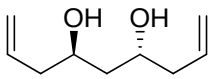
Key: (a) BF_3Et_2O, BH_3Me_2S, THF; (b) Et_2CO_3, K_2CO_3; (c) EtCOCl, BuLi, THF; (d) Bu_2BOTf, NEt_3, *i*-PrCHO, CH_2Cl_2, -78 °C, CH_2Cl_2; (e) $LiBH_4$, MeOH, THF, -78 °C; (f) cat. TsOH, *p*-MeOPhCH(OMe)$_2$, CH_2Cl_2; (g) DIBAl-H, CH_2Cl_2, -78 °C; (h) MsCl, NEt_3, CH_2Cl_2; (i) PhSLi, THF, -78 °C to 23 °C; (j) *m*-CPBA, CH_2Cl_2 $Zn(OTf)_2$; (k) *n*-BuLi, BF_3OEt_2, **1**, -78 °C, THF; (l) Na/Hg, Na_2HPO_4, -40 °C to 23 °C, MeOH; (m) HFpyr, THF; (n) cyclopentylidene dimethyl ketal, PPTS, CH_2Cl_2; (o) $LiAlH_4$, THF; (p) Dess-Martin, CH_2Cl_2; (q) BF_3OEt_2, -90 °C, toluene; (r) TBSOTf, 2,6-lutidine, -78 °C, CH_2Cl_2; (s) DIBAl-H, -78 °C, toluene; (t) BuBOTf, NEt_3, -78 °C to 100 °C, **2**, Et_2O; (u) $Me_4NBH(OAc)_3$, -25 °C, CH_3CN, AcOH; (v) cyclopentylidene dimethyl ketal, PPTS, CH_2Cl_2; (w) LiDBB, -78 °C, THF; (x) Dess-Martin, CH_2Cl_2; (y) DDQ, H_2O, CH_2Cl_2; (z) **3**, LiHMDS, -78 °C, THF; (a') LiOH, THF, H_2O, MeOH; (b') 2,4,6-trichlorobenzoyl chloride, NEt_3, DMAP, 23 °C, toluene; (c') PPTS, MeOH

II. General Methods

All reactions were run under an atmosphere of nitrogen. Tetrahydrofuran, toluene, dichloromethane were obtained from Pure-Solv MD-5 Solvent Purification System (Innovative Technology). Commercially available allyl acetate (Acros) and α-methyl allyl acetate (acetic acid 3-buten-2-yl ester, TCI) were purified by distillation prior to use. $[Ir(cod)_2Cl]$ was used as received from Strem Chemicals. Cesium carbonate was purchased from Alfa Aesar and used directly without further purification. Analytical thin-layer chromatography (TLC) was carried out using 0.2-mm commercial silica gel plates (DC-Fertigplatten Kieselgel 60 F_{254}). Infrared spectra were recorded on a Perkin-Elmer 1600 spectrometer. High-resolution mass spectra (HRMS) were obtained on a Karatos MS9 and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M+1, M or M-1) or a suitable fragment ion. Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) spectra were recorded with a Varian Gemini (400 MHz) spectrometer for $CDCl_3$ solutions and chemical shifts are reported as parts per million (ppm) relative to residual $CHCl_3$ δ_H (7.26 ppm) and $CDCl_3$ δ_C (77.0 ppm), respectively, as internal standards. Coupling constants are reported in Hertz (Hz).

III. Experimental Details and Spectral Data

(4*R*,6*R*)-Nona-1,8-diene-4,6-diol (1)



1

To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with $[Ir(cod)Cl]_2$ (1.35 g, 2.012 mmol, 5 mol%), (*R*)-Cl,MeO-BIPHEP (2.61 g, 4.008 mmol, 10 mol%), Cs_2CO_3 (5.22 g, 16.03 mmol, 40 mol%) and 4-chloro-3-nitrobenzoic acid (1.62 g, 8.016 mmol, 20 mol%) was added 1,4-dioxane (100 mL) followed by allyl acetate (43 mL, 0.401 mol, 1000 mol%). The reaction mixture was allowed to stir at 90 ^{o}C for 0.5 hr and cooled to ambient temperature. 1,3-Propanediol (3.05 g, 40.08 mmol, 100 mol%) in 1,4-dioxane (100 mL, 0.4 M) was added to the reaction mixture and the reaction mixture was allowed to stir at 90 ^{o}C for 72 hr. The reaction mixture was filtered through the pad of celite and evaporated in vacuo. Purification of the product by column chromatography (SiO_2: ethyl acetate:hexanes 1:3 to 1:1 with 0.1% TEA) provided **1** (4.36 g, 27.93 mmol, dr > 30:1) as pale yellow oil in 70% yield.

TLC (SiO_2): R_f = 0.25 (ethyl acetate:hexanes, 1:2).

$[\alpha]_D^{24}$ = –23.5 (*c* = 1.0, $CHCl_3$).

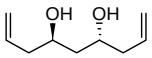
^{1}H NMR (400 MHz, $CDCl_3$): δ 5.86-5.75 (m, 2H), 5.15-5.09 (m, 4H), 4.01-3.94 (m, 2H), 2.69 (br s, 2H), 2.28-2.23 (m, 4H), 1.62 (t, *J* = 6.0 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 134.9, 118.3, 68.3, 42.2, 41.7.

FTIR (neat): υ 3346, 3076, 3005, 2978, 2936, 1827, 1641, 1433, 1335, 1230, 1131, 1071, 1046, 994, 871, 830 cm^{-1}.

HRMS (CI) Calcd. for $C_9H_{17}O_2$ $(M+H)^+$: 157.1229, Found: 157.1225.

HPLC: Enantiomeric excess was determined by HPLC analysis of bis-4-nitro-benzoate derivative of the product. (Chiralcel OD-H column, hexanes:*i*-PrOH = 95:5, 1.0 mL/min, 254 nm), t_{minor} = 17.2 min, t_{major} = 40.8 min; ee > 99%.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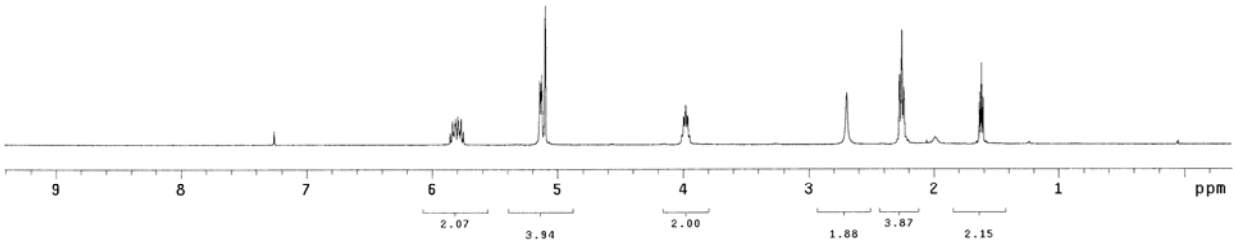
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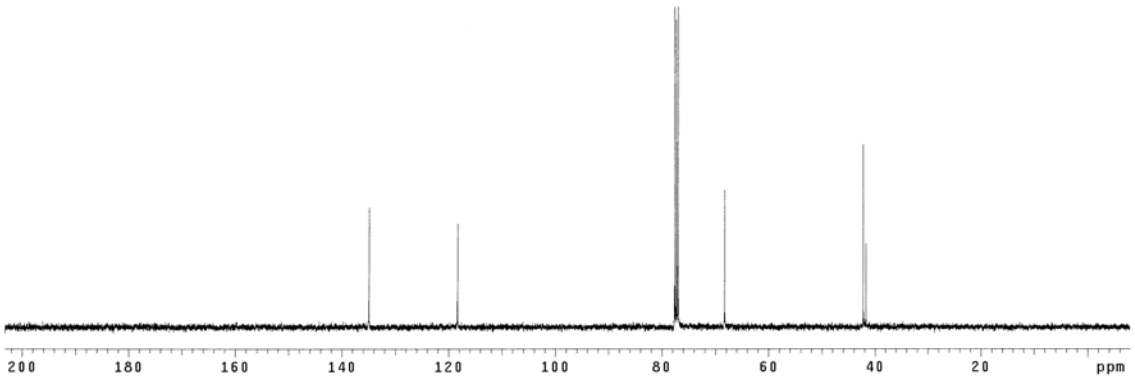
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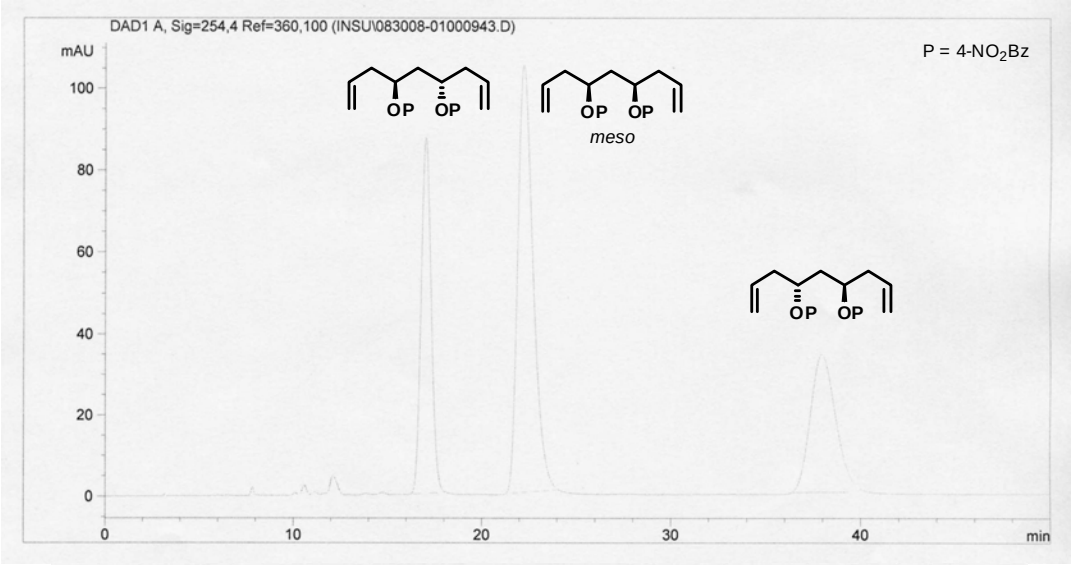

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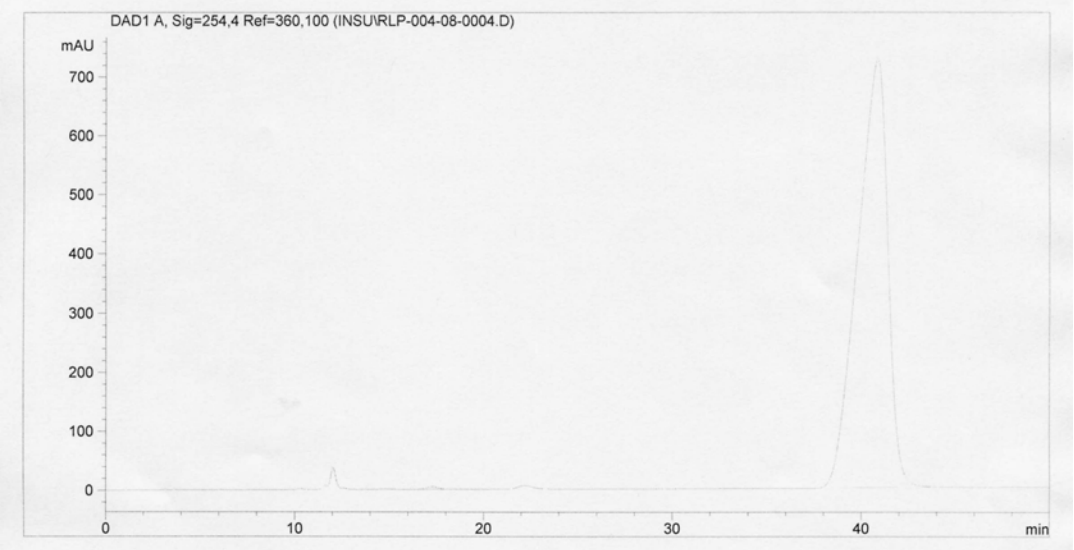

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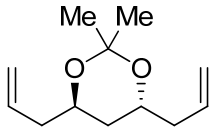
2	22.168	BB	0.7365	317.59506	5.87698	0.3908
3	40.856	BB	1.6123	8.07776e4	725.86804	99.4047

(4*R*,6*R*)-4,6-Diallyl-2,2-dimethyl-1,3-dioxane (1-1)



1-1

To a stirred solution of the diol **1** (3.5 g, 22.42 mmol, 100 mol%) in DCM (224 mL, 0.1 M) were added 2,2-dimethoxypropane (41 mL, 0.336 mol, 1500 mol%) and pyridinium *p*-toluenesulfonate (0.56 g, 2.242 mmol, 10 mol%) at ambient temperature. The reaction mixture was stirred for 1 hr and quenched with saturated aq. $NaHCO_3$ (100 mL). The aqueous layer was extracted with DCM (100 mL × 2). The combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:50 to 1:15 with 0.1% TEA) to give the acetonide **1-1** (3.99 g, 20.33 mmol) as a colorless oil in 91% yield.

TLC (SiO_2): R_f = 0.40 (ethyl acetate:hexanes, 1:20).

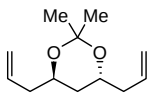
$[\alpha]_D^{24}$ = –56.0 (*c* = 1.0, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.84-5.73 (m, 2H), 5.10-5.01 (m, 4H), 3.88-3.80 (m, 2H), 2.33-2.25 (m, 2H), 2.21-2.13 (m, 2H), 1.59 (t, *J* = 7.6 Hz, 2H), 1.34 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 134.7, 117.1, 100.5, 66.4, 40.4, 37.7, 25.1.

FTIR (neat): υ 3077, 2986, 2937, 1831, 1642, 1431, 1377, 1361, 1172, 1121, 1015, 993, 911, 833, 814 cm^{-1}.

HRMS (CI) Calcd. for $C_{12}H_{21}O_2$ $[M+H]^+$: 197.1542, Found: 197.1540.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Me
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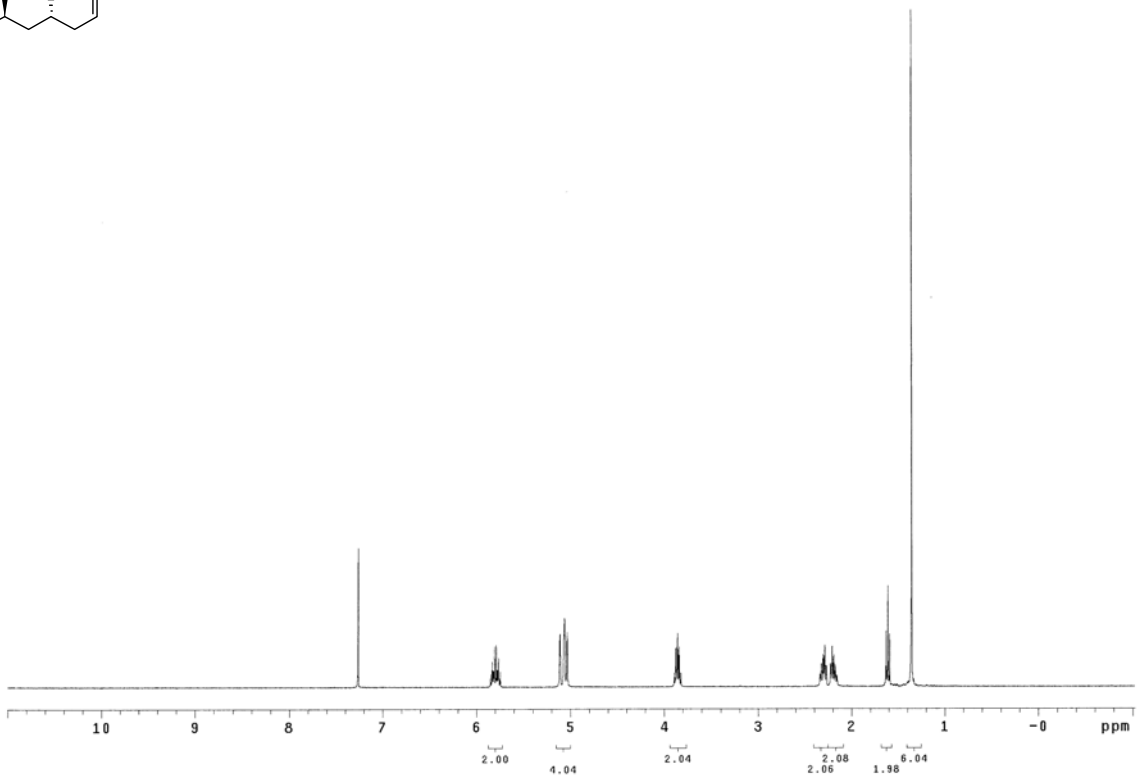
O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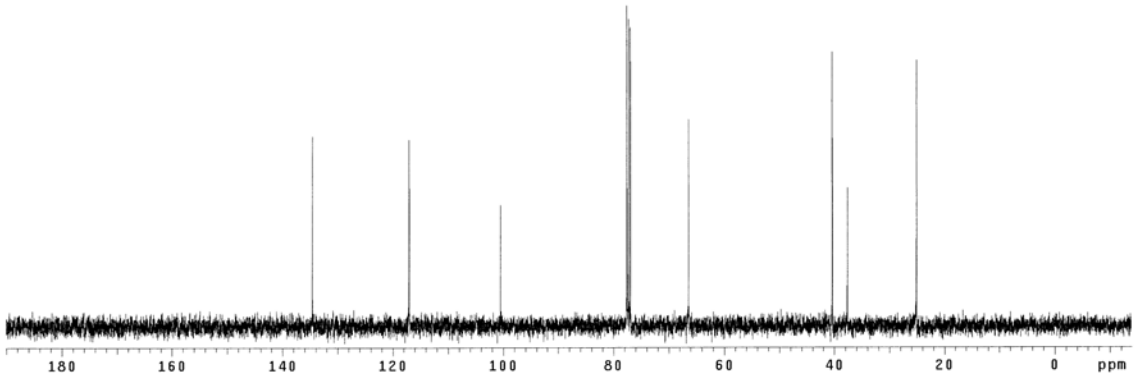
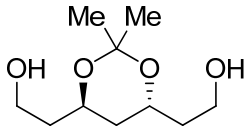
1.98
6.04


180
160
140
120
100
80
60
40
20
0
ppm

2,2'-((4*R*,6*R*)-2,2-Dimethyl-1,3-dioxane-4,6-diyl)diethanol (2)



2

To a stirred solution of the acetonide **1-1** (3.8 g, 19.36 mmol, 100 mol%) in DCM/MeOH (1:1, 130 mL, 0.15 M) was bubbled ozone at −78 °C until a blue color persisted. The excess ozone was then purged with argon for 5 min. Sodium borohydride (7.3 g, 0.194 mol, 1000 mol%) was added in one portion at – 78 °C and the resulting solution was slowly warmed to ambient temperature. The mixture was stirred for 24 hr at ambient temperature, and then quenched with H_2O (40 mL). The resulting mixture was concentrated and extracted with DCM (200 mL × 2). The combined organic extracts were dried dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:1 to ethyl acetate:methanol, 20:1 with 0.1% TEA) to give the diol **2** (3.42 g, 16.74 mmol) as a colorless oil in 86% yield.

TLC (SiO_2): R_f = 0.28 (ethyl acetate).

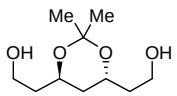
$[\alpha]_D^{25}$ = –29.0 (*c* = 1.0, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.08-4.00 (m, 2H), 3.71 (m, 4H), 2.62 (s, 2H), 1.75-1.69 (m, 4H), 1.66 (t, *J* = 7.6 Hz, 2H), 1.34 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 100.8, 66.8, 61.1, 38.3, 37.9, 25.1.

FTIR (neat): υ 3357, 2986, 2939, 2879, 2359, 1654, 1441, 1416, 1381, 1223, 1164, 1123, 1014, 974, 937, 902, 877 cm^{-1}.

HRMS (CI) Calcd. for $C_{10}H_{21}O_4$ $[M+H]^+$: 205.1440, Found: 205.1438.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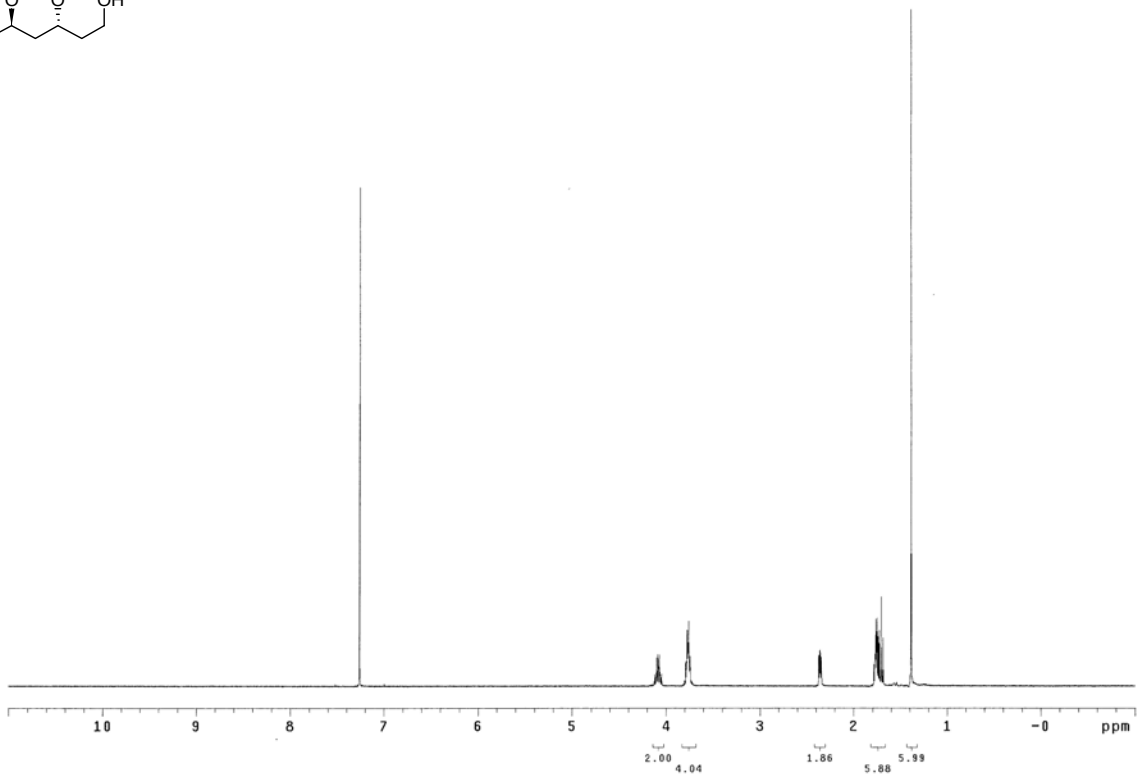
O
O
OH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6
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4
3
2
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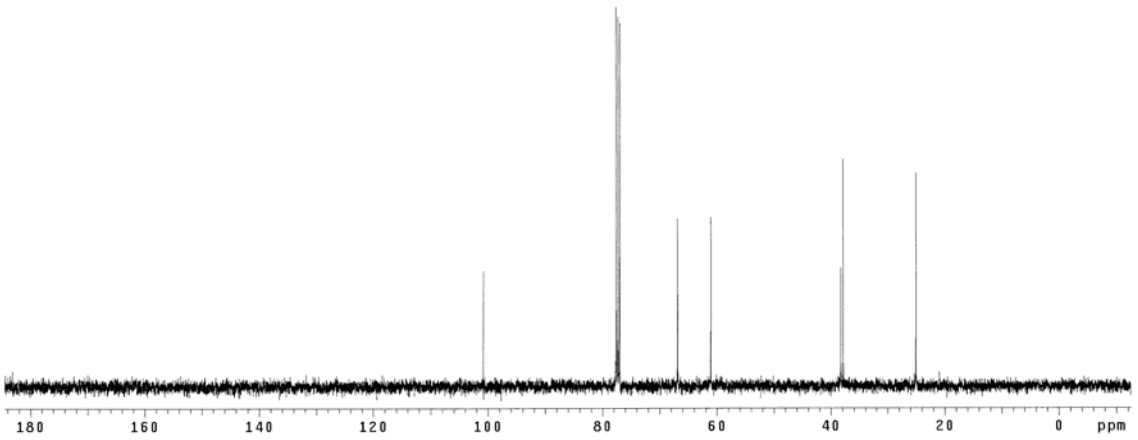
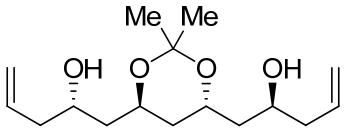
ppm
2.00
4.04
1.86
5.88
5.99


180
160
140
120
100
80
60
40
20
0
ppm

(2*S*,2'*S*)-1,1'-((4*R*,6*R*)-2,2-Dimethyl-1,3-dioxane-4,6-diyl)dipent-4-en-2-ol (2-1)



2-1

To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with $[Ir(cod)Cl]_2$ (0.58 g, 0.857 mmol, 5 mol%), (*S*)-Cl,MeO-BIPHEP (1.12 g, 1.714 mmol, 10 mol%), Cs_2CO_3 (2.23 g, 6.856 mmol, 40 mol%) and 4-chloro-3-nitrobenzoic acid (0.69 g, 3.428 mmol, 20 mol%) was added THF (43 mL) followed by allyl acetate (1.85 mL, 0.171 mol, 1000 mol%). The reaction mixture was allowed to stir at 90 ^oC for 0.5 hr and cooled to ambient temperature. The diol **2** (3.5 g, 17.14 mmol, 100 mol%) in THF (43 mL) was added to the reaction mixture and the reaction mixture was allowed to stir at 110 ^oC for 48 hr. The reaction mixture was filtered through the pad of celite and evaporated in vacuo. Purification of the product by column chromatography (SiO_2: ethyl acetate:hexanes 1:3 to 1:1 with 0.1% TEA) provided **2-1** (3.46 g, 12.17 mmol, dr > 20:1) as pale yellow oil in 71% yield.

TLC (SiO_2): R_f = 0.30 (ethyl acetate:hexanes, 1:3).

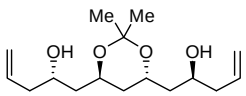
$[\alpha]_D^{24}$ = –18.0 (*c* = 1.0, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85-5.74 (m, 2H), 5.11-5.06 (m, 4H), 4.17-4.09 (m, 2H), 3.86 (br m, 2H), 2.61 (br s, 2H), 2.25-2.15 (m, 4H), 1.66-1.55 (m, 6H), 1.33 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 135.1, 118.0, 100.9, 67.9, 64.6, 42.3, 41.5, 38.0, 25.0.

FTIR (neat): υ 3415, 3075, 2985, 2938, 2917, 2850, 1837, 1717, 1640, 1433, 1380, 1222, 1163, 1129, 1081, 1035, 994, 869, 810 cm^{-1}.

HRMS (CI) Calcd. for $C_{16}H_{29}O_4$ $(M+H)^+$: 285.2066, Found: 285.2066.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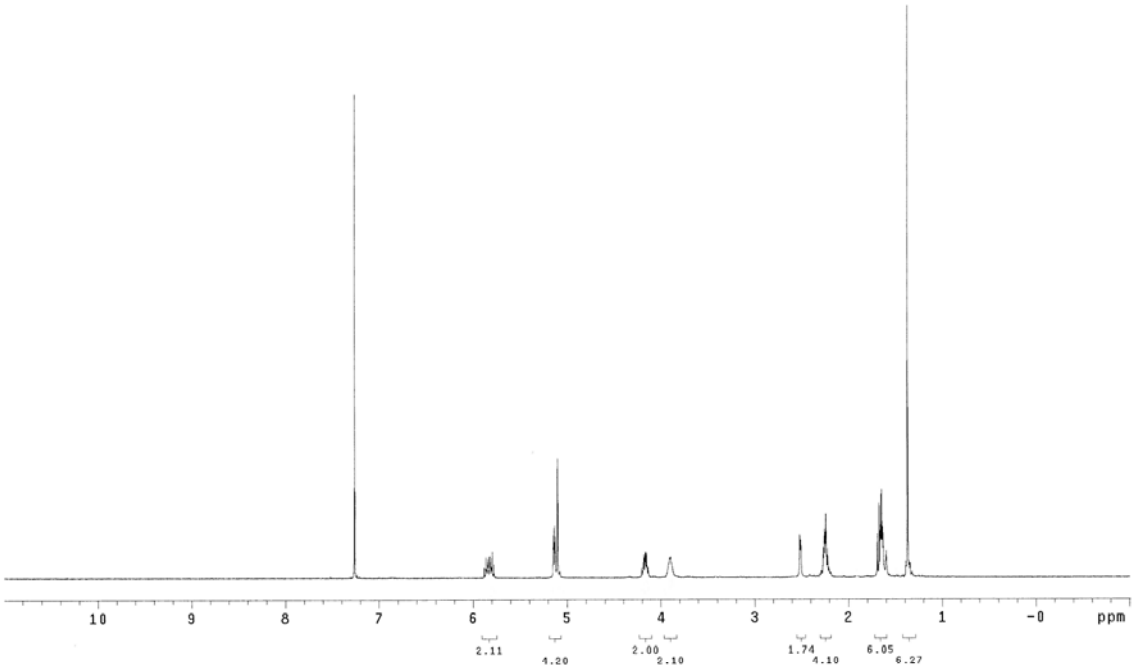
Me
OH
O
O
OH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2.00
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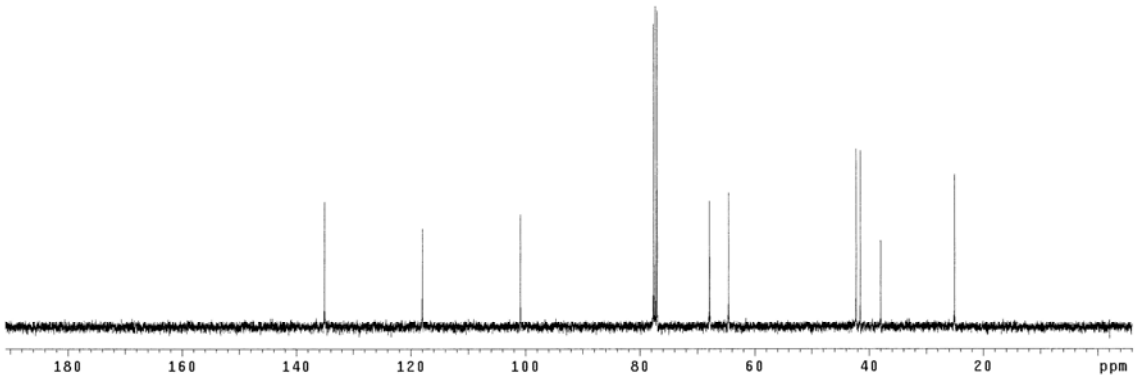
6.05
6.27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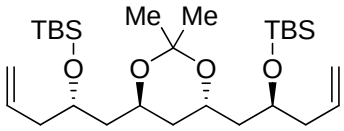
160
140
120
100
80
60
40
20
ppm

(2*S*,2'*S*)-1,1'-((4*S*,6*S*)-2,2-Dimethyl-1,3-dioxane-4,6-diyl)bis(pent-4-ene-2,1 diyl)bis(oxy)bis(*tert*-butyldimethylsilane) (2-2)



2-2

To a stirred solution of the diol **2-1** (0.49 g, 1.723 mmol, 100 mol%) in DMF (3.4 mL, 0.5 M) were added imidazole (0.47 g, 6.892 mmol, 400 mol%) and TBSCl (0.78 g, 5.169 mmol, 300 mol%) at ambient temperature. The reaction mixture was allowed to stir for 48 hr at 45 ^{o}C, and then quenched with H_2O (5 mL). The reaction mixture was extracted with EtOAc (15 mL × 2). The combined organic extracts were washed with H_2O (3 mL × 2), dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:50 to 1:30 with 0.1% TEA) to give **2-2** (0.75 g, 1.464 mmol) as a colorless oil in 85% yield.

TLC (SiO_2): R_f = 0.33 (ethyl acetate:hexanes, 1:30).

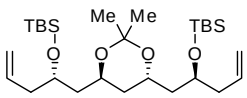
$[\alpha]_D^{26}$ = +24.0 (*c* = 0.5, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88-5.77 (m, 2H), 5.11-5.01 (m, 4H), 3.95-3.82 (m, 4H), 2.30-2.16 (m, 4H), 1.67-1.41 (m, 6H), 1.33 (s, 6H), 0.89 (s, 18H), 0.68 (s, 12H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 135.0, 127.2, 99.9, 68.8, 63.8, 44.1, 42.8, 39.3, 26.2, 25.9, 18.3, -3.7, -4.2.

FTIR (neat): υ 3078, 2989, 2945, 2929, 2882, 2856, 1641, 1472, 1462, 1434, 1377, 1253, 1223, 1168, 1112, 1061, 1003, 948, 912, 833 cm^{-1}.

HRMS (CI) Calcd. for $C_{28}H_{57}O_4Si_2$ $[M+H]^+$: 513.3795, Found: 513.3804.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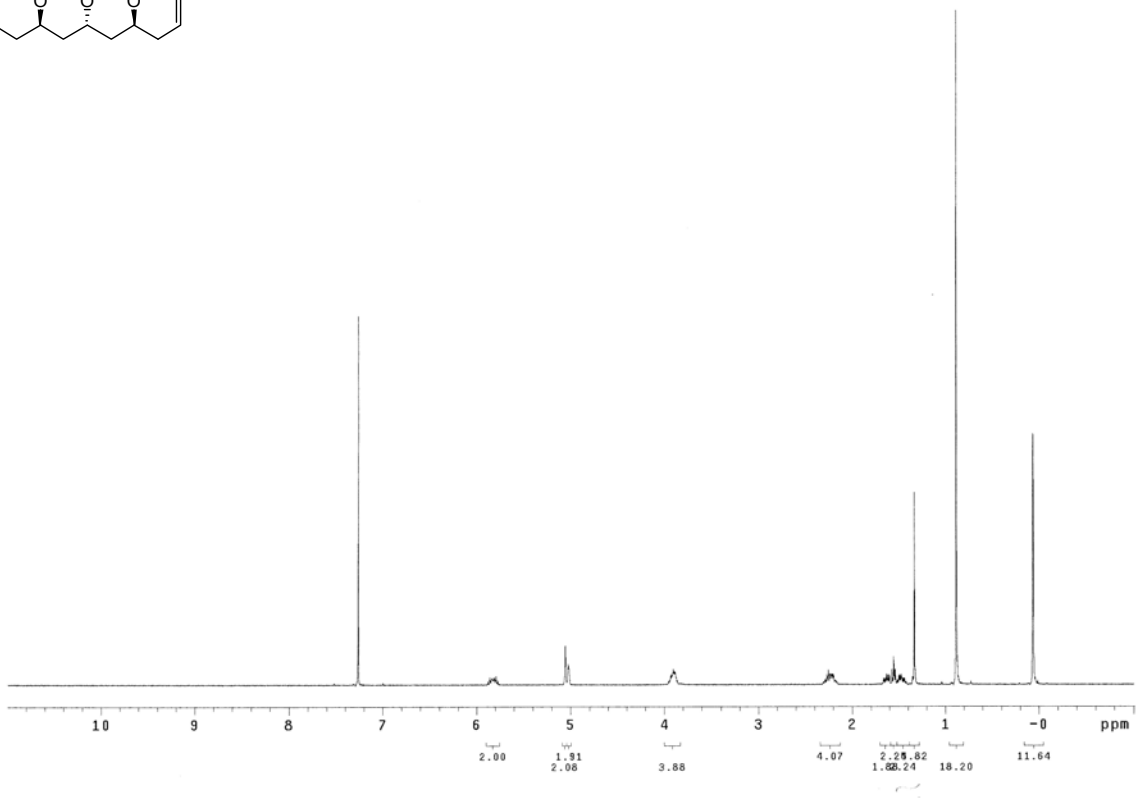
O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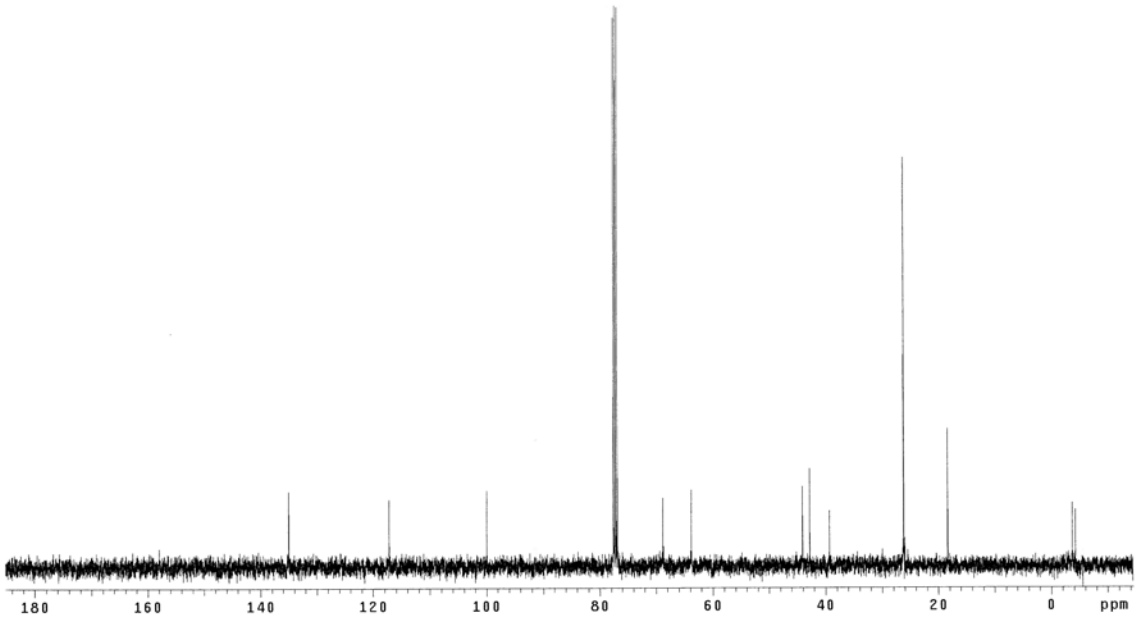
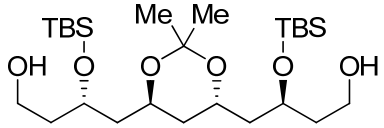
18.20
11.64


180
160
140
120
100
80
60
40
20
0
ppm

(3*S*,3'*S*)-4,4'-((4*S*,6*S*)-2,2-Dimethyl-1,3-dioxane-4,6-diyl)bis(3-(*tert*-butyldimethylsilyloxy)butan-1-ol) (2-3)



2-3

To a stirred solution of **2-2** (0.58 g, 1.132 mmol, 100 mol%) in DCM/MeOH (1:1, 57 mL, 0.02 M) was bubbled ozone at −78 °C until a blue color persisted. The excess ozone was then purged with argon for 5 min. Sodium borohydride (0.43 g, 11.32 mmol, 1000 mol%) was added in one portion at –78 °C and the resulting solution was slowly warmed to ambient temperature. The mixture was stirred for 12 hr at ambient temperature, and then quenched with H_2O (5 mL). The resulting solution was then concentrated and extracted with DCM (20 mL × 2). The combined organic extracts was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:3 to 1:1 with 0.1% TEA) to give the diol **2-3** (0.50 g, 0.962 mmol) as a colorless oil in 85% yield.

TLC (SiO_2): R_f = 0.24 (ethyl acetate:hexanes, 1:2).

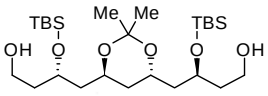
$[\alpha]_D^{26}$ = +28.0 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.01-3.93 (m, 2H), 3.90-3.71 (m, 4H), 3.70-3.65 (m, 2H), 2.40 (br s, 2H), 1.86-1.53 (m, 10H), 1.31 (s, 6H), 0.85 (s, 18H), 0.67 (s, 6H), 0.53 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 100.3, 69.1, 64.1, 59.7, 43.7, 39.4, 39.2, 26.1, 26.0, 25.7, 18.2, -4.1, -4.3.

FTIR (neat): υ 3398, 2986, 2951, 2992, 2882, 2856, 2242, 1472, 1462, 1429, 1379, 1252, 1223, 1165, 1055, 1005, 938, 909 cm^{-1}.

HRMS (CI) Calcd. for $C_{26}H_{57}O_6Si_2$ $[M+H]^+$: 521.3694, Found: 521.3691.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O
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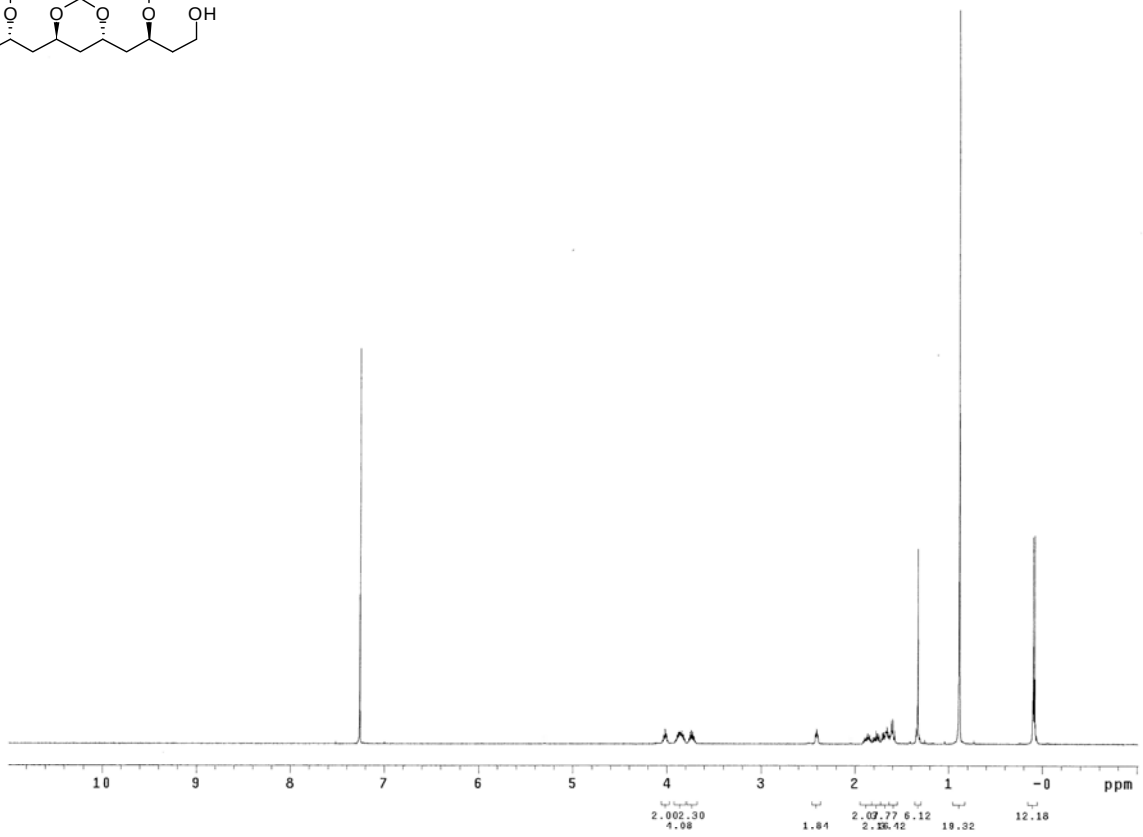
OH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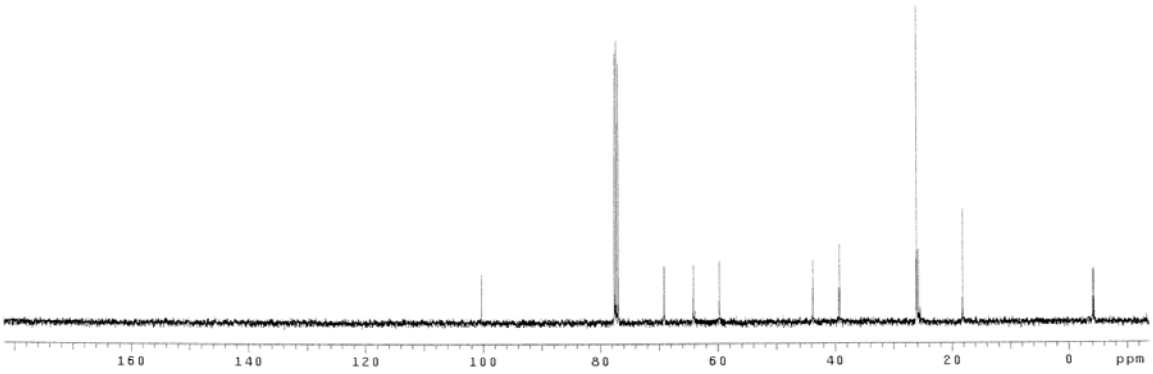
2.15 5.12
18.32
12.18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140
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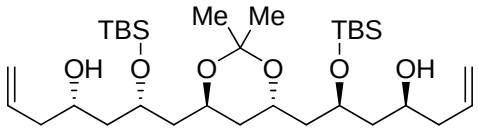
80
60
40
20
0
ppm

(4*S*,4'*S*,6*S*,6'*S*)-7,7'-((4*S*,6*S*)-2,2-Dimethyl-1,3-dioxane-4,6-diyl)bis(6-(*tert*-butyldimethylsilyloxy)hept-1-en-4-ol) (2-4)



2-4

To an oven-dried sealed tube under one atmosphere of nitrogen gas charged with $[Ir(cod)Cl]_2$ (32.2 mg, 0.048 mmol, 5 mol%), (*S*)-Cl,MeO-BIPHEP (62.5 mg, 0.096 mmol, 10 mol%), Cs_2CO_3 (0.125 g, 0.384 mmol, 40 mol%) and 4-chloro-3-nitrobenzoic acid (39 mg, 0.192 mmol, 20 mol%) was added THF (2.4 mL) followed by allyl acetate (1.04 mL, 9.599 mol, 1000 mol%). The reaction mixture was allowed to stir at 90 ^{o}C for 0.5 hr and cooled to ambient temperature. The diol **2-3** (0.5 g, 0.960 mmol, 100 mol%) in THF (2.4 mL) was added to the reaction mixture and the reaction mixture was allowed to stir at 110 ^{o}C for 48 hr, at which point the reaction mixture was evaporated onto silica gel. Purification of the product by column chromatography (SiO_2: ethyl acetate:hexanes 1:5 to 1:3 with 0.1% TEA) provided **2-4** (0.45 g, 0.749 mmol, dr > 20:1) as pale yellow oil in 78% yield.

TLC (SiO_2): R_f = 0.28 (ethyl acetate:hexanes, 1:3).

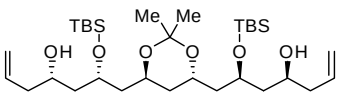
$[\alpha]_D^{26}$ = +15.0 (*c* = 0.3, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.87-5.76 (m, 2H), 5.12-5.07 (m, 4H), 3.94-3.81 (m, 6H), 2.99 (s, 2H), 2.21 (t, *J* = 6.4 Hz, 4H), 1.85-1.76 (m, 2H), 1.74-1.68 (m, 2H), 1.62-1.53 (m, 6H), 1.32 (s, 6H), 0.88 (s, 18H), 0.79 (s, 12H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 135.2, 117.7, 100.5, 70.3, 69.0, 64.4, 44.4, 43.9, 42.6, 39.8, 26.1, 25.3, 18.1, -4.0, -4.1.

FTIR (neat): υ 3432, 3075, 2948, 2928, 2856, 2030, 1720, 1641, 1472, 1462, 1429, 1379, 1359, 1251, 1223, 1165, 1115, 1063, 1003, 938, 912 cm^{-1}.

HRMS (CI) Calcd. for $C_{32}H_{65}O_6Si_2$ $(M+H)^+$: 601.4320, Found: 601.4318.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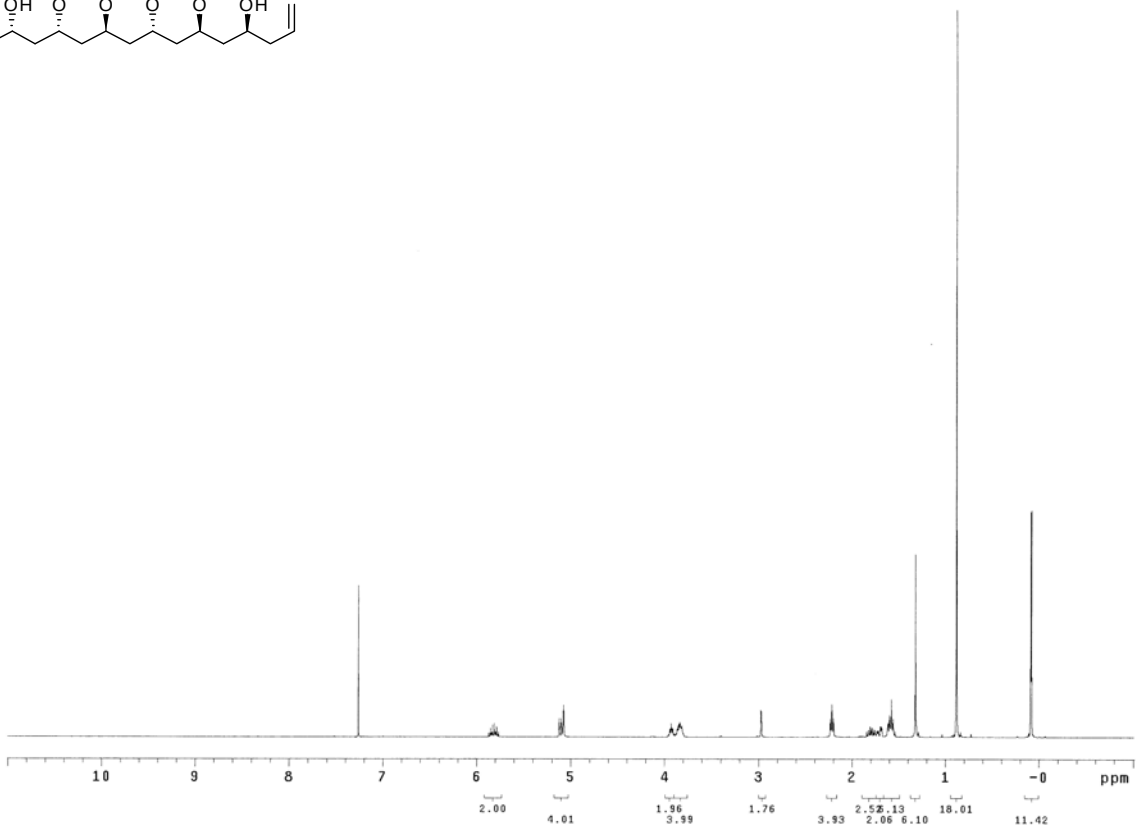
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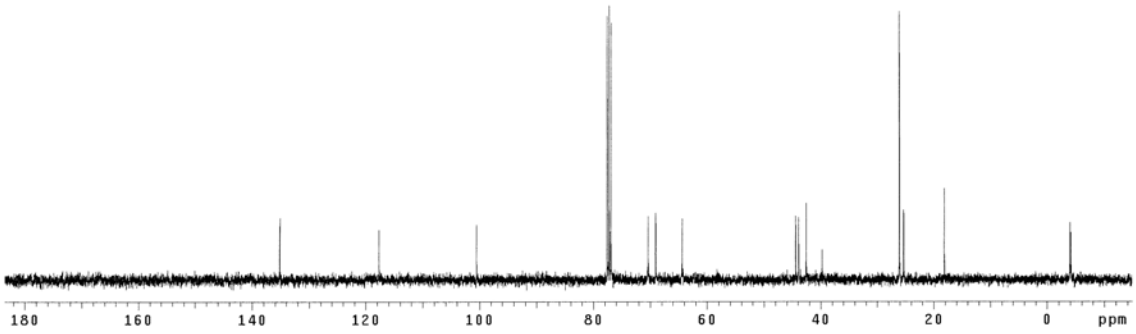
18.01
11.42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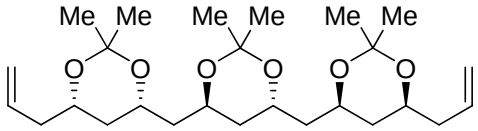
20
0
ppm

(4*S*,4'*S*,6*S*,6'*S*)-6,6'-((4*S*,6*S*)-2,2-Dimethyl-1,3-dioxane-4,6-diyl)bis(methylene)bis(4-allyl-2,2-dimethyl-1,3-dioxane) (2-5)



2-5

To a stirred solution of **2-4** (0.4 g, 0.666 mmol, 100 mol%) in methanol (6.7 mL, 0.1 M) was added *p*-toluenesulfonic acid monohydrate (12.7 mg, 0.067 mmol, 10 mol%). The reaction mixture was stirred for 1 hr at ambient temperature. TLC analysis showed complete consumption of the starting material. The reaction mixture was diluted with 2,2-dimethoxypropane (8.2 mL, 66.55 mmol, 10000 mol%) and stirred for 1 hr at ambient temperature. After concentrated in vacuo, the residue was diluted with 2,2-dimethoxypropane (4.1 mL, 33.28 mmol, 5000 mol%) and stirred for 1 hr at ambient temperature. The reaction mixture was again concentrated in vacuo. 2,2-Dimethoxypropane (4.1 mL, 33.28 mmol, 5000 mol%) was added and the reaction mixture was stirred for 1 hr at ambient temperature. The reaction mixture was diluted with EtOAc (30 mL) and washed with saturated aq. $NaHCO_3$ (15 mL) and brine (15 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:20 to 1:15 with 0.1% TEA) to give **2-5** (0.28 g, 0.619 mmol) as a colorless oil in 93% yield.

TLC (SiO_2): R_f = 0.38 (ethyl acetate:hexanes, 1:10).

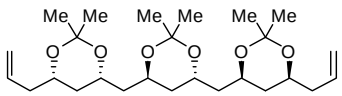
$[\alpha]_D^{26}$ = +18.5 (*c* = 0.6, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.82-5.72 (m, 2H), 5.08-5.01 (m, 4H), 4.06-3.98 (m, 4H), 3.89-3.83 (m, 2H), 2.31-2.25 (m, 2H), 2.16-2.09 (m, 2H), 1.55-1.46 (m, 8H), 1.40 (s, 6H), 1.36 (s, 6H), 1.30 (s, 6H), 1.16-1.07 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 134.1, 117.0, 100.4, 98.5, 68.7, 64.9, 62.4, 42.2, 40.8, 39.0, 36.8, 30.2, 24.4, 19.8.

FTIR (neat): υ 2989, 2941, 2907, 2860, 2239, 2106, 1736, 1642, 1460, 1431, 1373, 1350, 1223, 1199, 1143, 1111, 1024, 981, 939, 911, 881, 812 cm^{-1}.

HRMS (CI) Calcd. for $C_{26}H_{45}O_6$ $[M+H]^+$: 453.3216, Found: 453.3216.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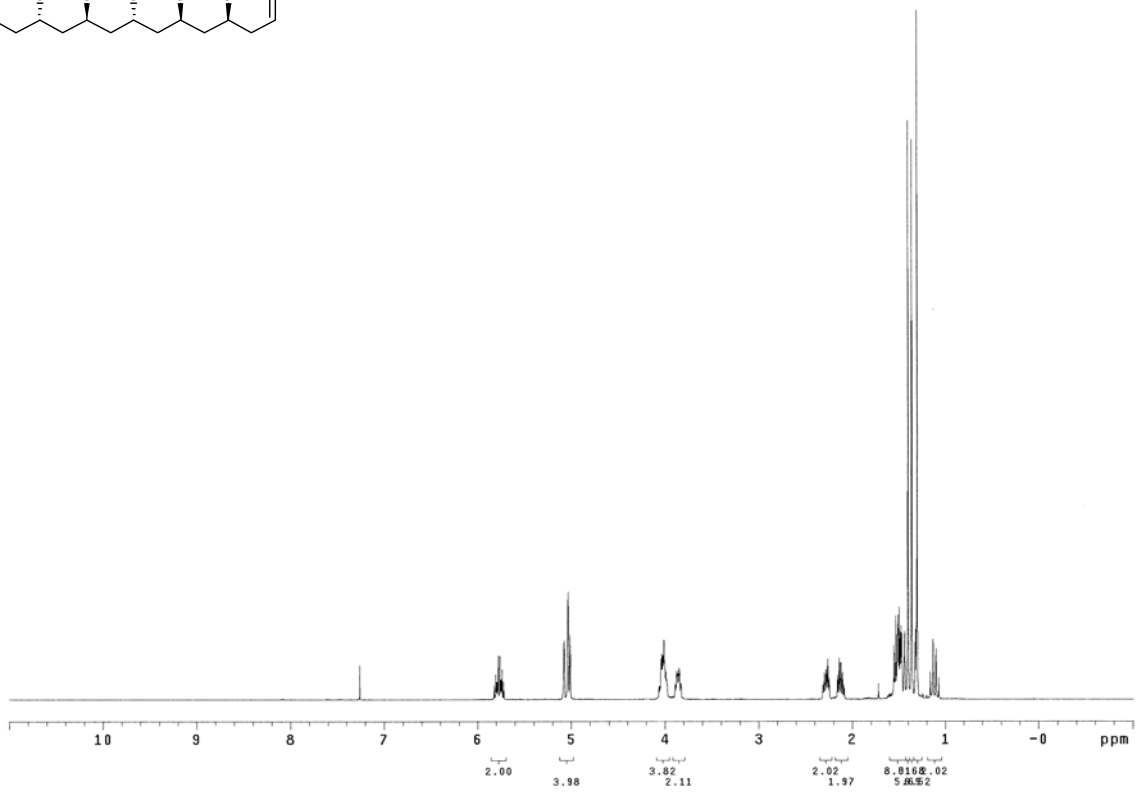
O
O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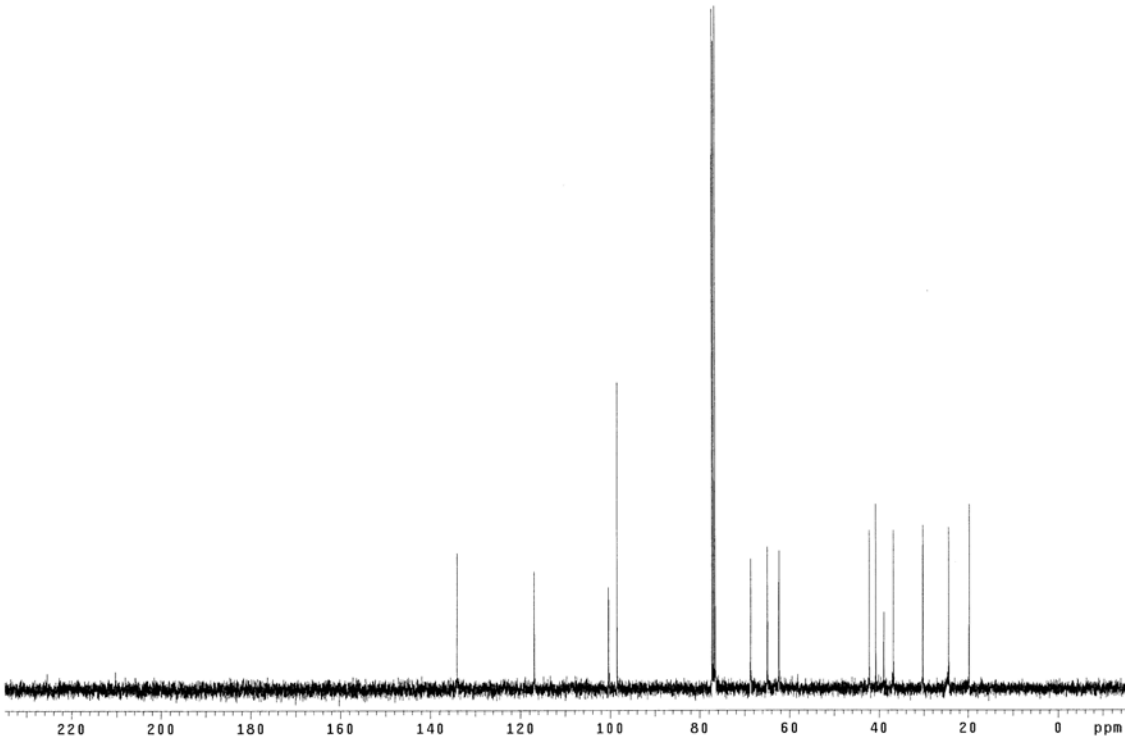
2.02
1.97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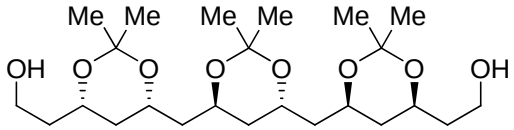
200
180
160
140
120
100
80
60
40
20
0
ppm

2,2'-(4*S*,4'*S*,6*S*,6'*S*)-6,6'-((4*S*,6*S*)-2,2-Dimethyl-1,3-dioxane-4,6-diyl)bis(methylene)bis(2,2-dimethyl-1,3-dioxane-6,4-diyl)diethanol (3)



3

To a stirred solution of **2-5** (0.15 g, 0.331 mmol, 100 mol%) in in DCM/MeOH (1:1, 17 mL, 0.02 M) was bubbled ozone at −78 °C until a blue color persisted. The excess ozone was then purged with argon for 5 min. Sodium borohydride (0.0.125 g, 3.31 mmol, 1000 mol%) was added in one portion at –78 °C and the resulting solution was warmed to ambient temperature slowly. The mixture was stirred for 12 hr at ambient temperature, and then quenched with H_2O (5 mL). The resulting mixture was concentrated and extracted with DCM (20 mL × 2). The combined organic extracts was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:1 to ethyl acetate:methanol 1:20 with 0.1% TEA) to give the diol **3** (0.119 g, 0.258 mmol) as a colorless syrup in 78% yield.

TLC (SiO_2): R_f = 0.20 (ethyl acetate:hexanes, 1:1).

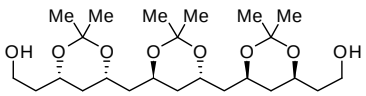
$[\alpha]_D^{26}$ = +72.5 (*c* = 0.8, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 4.13-4.02 (m, 6H), 3.81-3.74 (m, 4H), 2.55-2.52 (m, 2H), 1.74-1.70 (m, 4H), 1.58-1.50 (m, 6H), 1.44 (s, 6H), 1.43-1.38 (m, 2H), 1.37 (s, 6H), 1.30 (s, 6H), 1.32-1.24 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 100.7, 98.9, 77.5, 69.6, 65.2, 62.6, 60.9, 42.3, 39.1, 38.3, 37.3, 30.5, 24.6, 20.1.

FTIR (neat): υ 3400, 2990, 2942, 2917, 2882, 1467, 1422, 1380, 1346, 1242, 1222, 1198, 1167, 1137, 1095, 1049, 1010, 936, 910, 875, 824 cm^{-1}.

HRMS (CI) Calcd. for $C_{24}H_{45}O_8$ $[M+H]^+$: 461.3114, Found: 461.3111.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O
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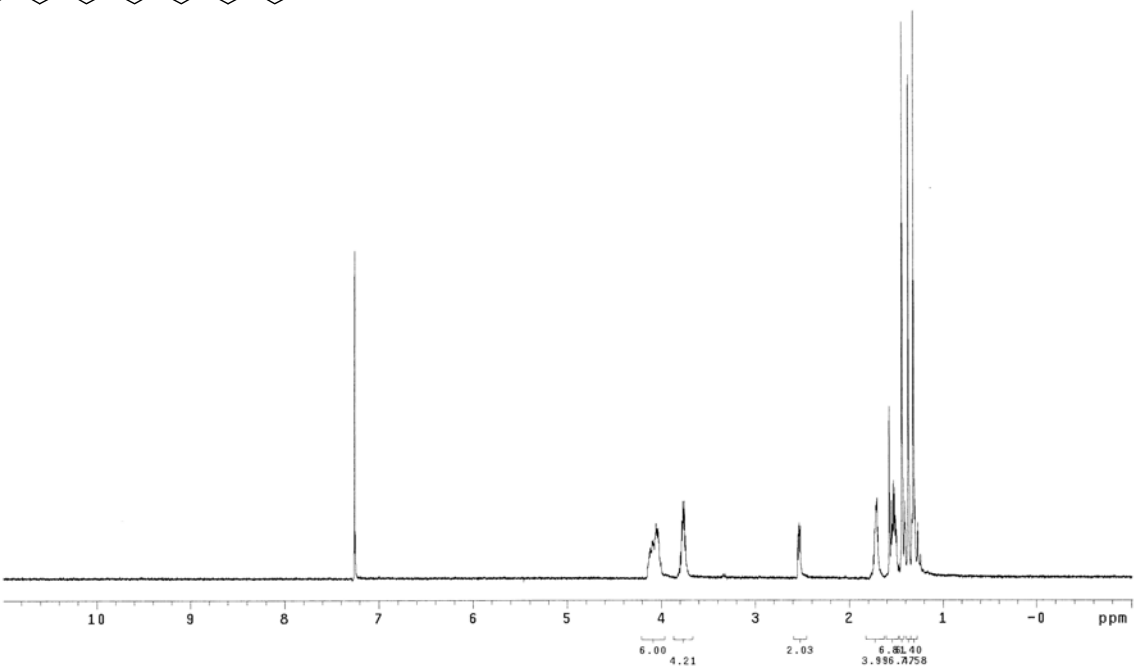
OH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-0
ppm
6.00
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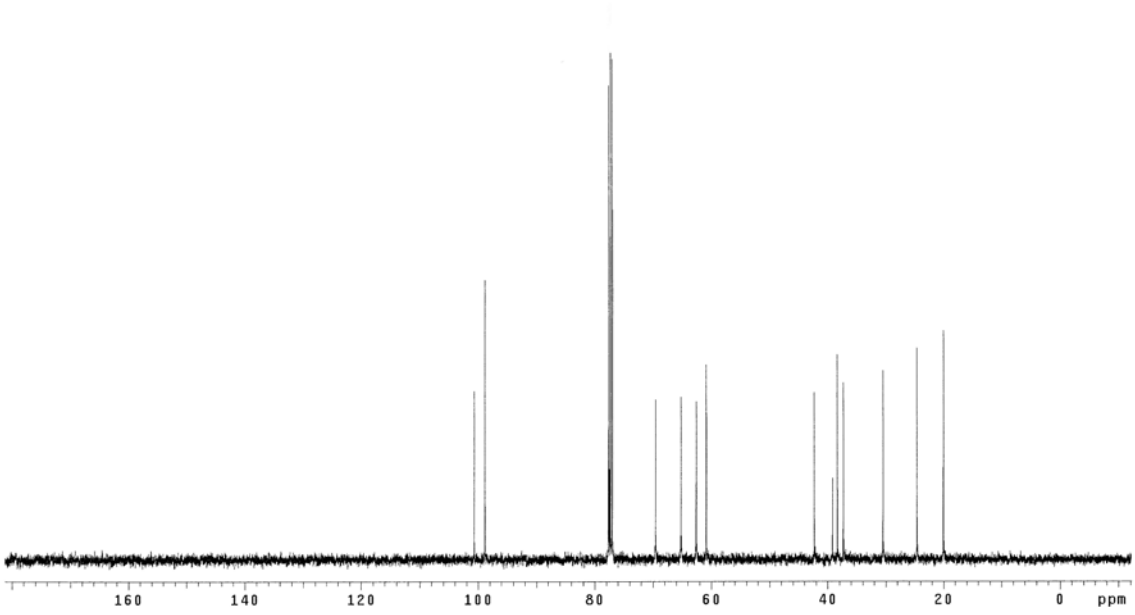
2.03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120
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80
60
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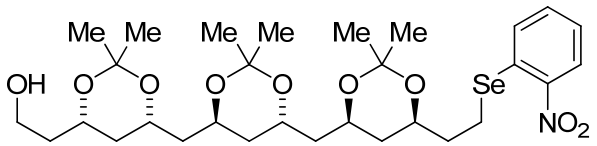
20
0
ppm

2-((4*S*,6*S*)-6-(((4*S*,6*S*)-6-(((4*R*,6*R*)-2,2-dimethyl-6-(2-(2-nitrophenylselanyl)ethyl)-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethanol (3-1)



3-1

To a stirred solution of the alcohol **3** (288 mg, 0.626 mmol, 100 mol%) in THF (3.1 mL, 0.2 M) were added 2-nitrophenyl selenocyanate (156 mg, 0.689 mmol, 110 mol%) and freshly distilled *n*-tributylphosphine (0.17 mL, 0.689 mmol, 110 mol%). The reaction mixture was stirred for 4 hr at ambient temperature and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:15 to 1:10 with 0.1% TEA) to give the selenide **3-1** (202 mg, 0.313 mmol) as a brownish oil in 50% yield and the starting diol **3** (61 mg, 0.131 mmol, 21% recovered yield). The recovered diol **3** was subjected to second round of mono-selenylation to give **3-1** (29 mg, 0.066 mmol, 10% yield).

TLC (SiO_2): R_f = 0.20 (ethyl acetate:hexanes, 1:1).

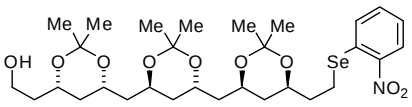
$[\alpha]_D^{26}$ = +2.47 (*c* = 1.0, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 4.16-3.88 (m, 6H), 3.82-3.68 (m, 2H), 3.10-3.03 (m, 1H), 2.97-2.90 (m, 1H), 2.56 (br s, 1H), 1.95-1.84 (m, 2H), 1.74-1.69 (m, 2H), 1.56-1.46 (m, 6H), 1.43 (s, 3H), 1.42 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 1.31 (s, 6H), 1.29-1.15 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.8, 133.6, 133.5, 129.0, 126.5, 125.3, 100.5, 98.7, 98.6, 77.2, 69.7, 68.4, 64.9, 62.4, 62.3, 61.0, 42.2, 42.1, 38.9, 38.0, 37.0, 35.1, 30.3, 30.2, 24.4, 21.5, 19.9, 19.8.

FTIR (neat): υ 2945, 1591, 1514, 1381, 1333, 1304, 1248, 1224, 1201, 1166, 1038 cm^{-1}.

HRMS (CI) Calcd. for $C_{30}H_{48}NO_9Se$ $[M+H]^+$: 646.2494, Found: 646.2497.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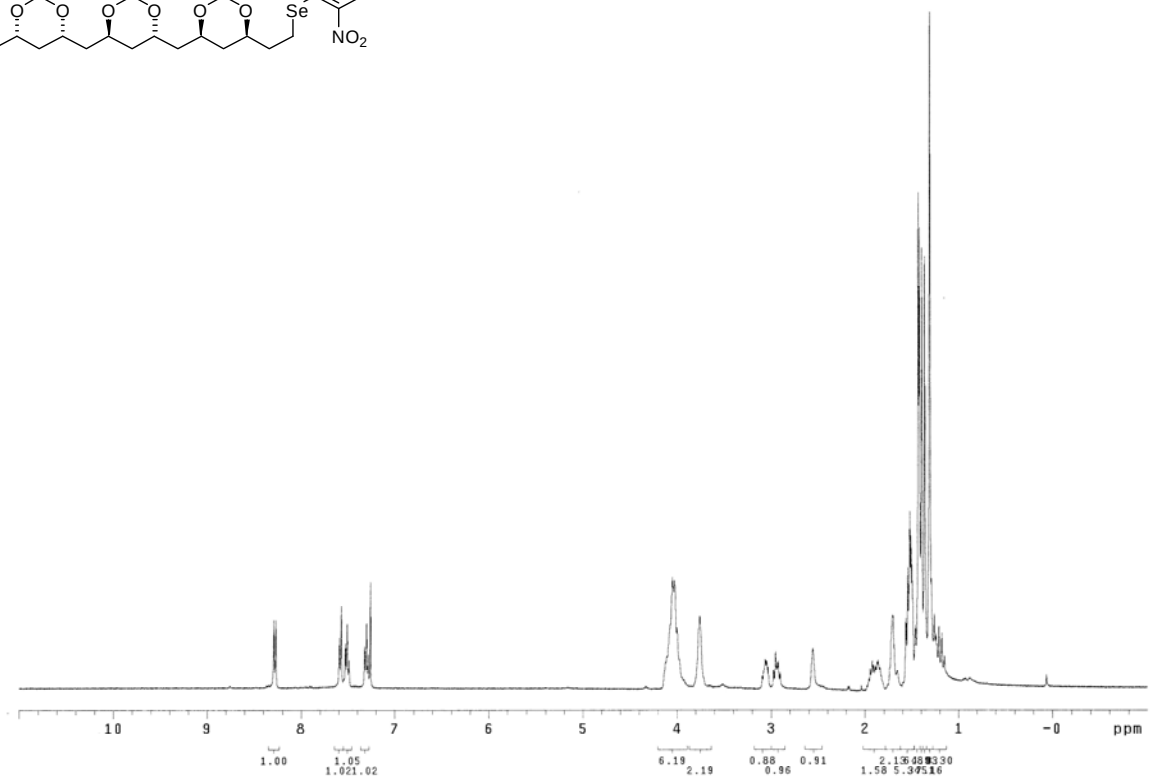
O
O
O
O
O
O
Se
NO2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4
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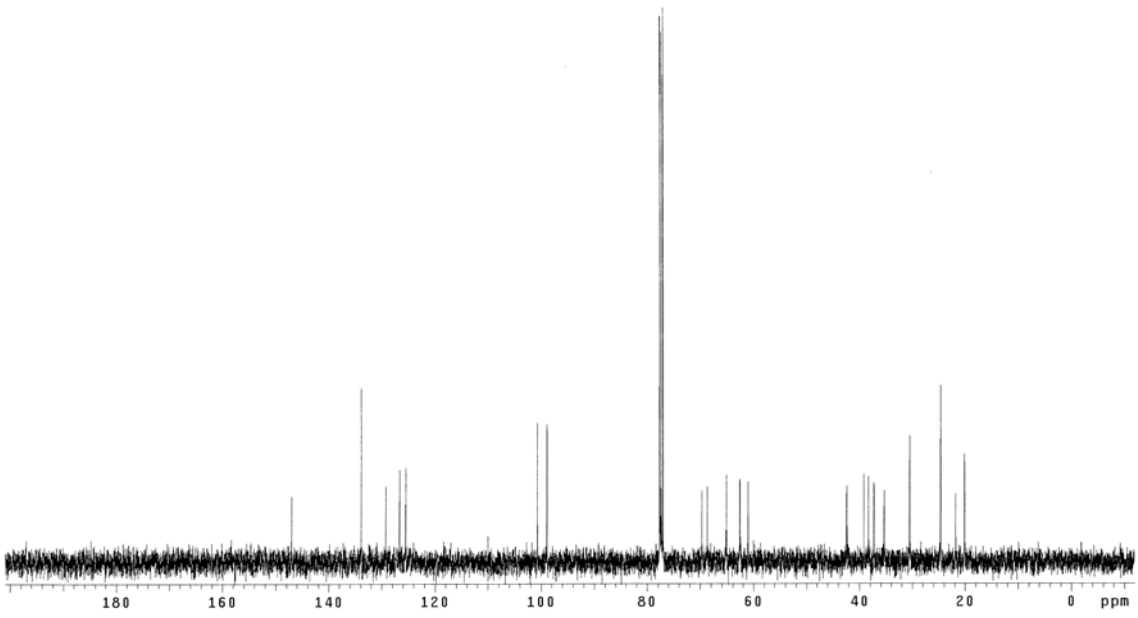
1.58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100
80
60
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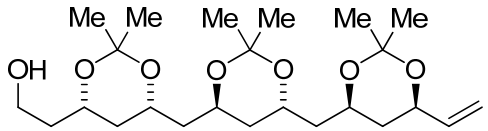
20
0
ppm

2-((4*S*,6*S*)-6-(((4*S*,6*S*)-6-(((4*R*,6*R*)-2,2-dimethyl-6-vinyl-1,3-dioxan-4-yl)methyl)-2,2 dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethanol (4)



4

To a stirred solution of the selenide **3-1** (420 mg, 0.651 mmol, 100 mol%) in THF (13 mL, 0.05 M) were added $NaHCO_3$ (164 mg, 1.953 mmol, 300 mol%) and H_2O_2 (0.71 mL, 500 mol%, 30% w/w in H_2O). The reaction mixture was stirred for 24 hr at ambient temperature and extracted with EtOAc. The combined organic extracts was washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:3 with 0.1% TEA) to give the allylic ether **4** (251 mg, 0.566 mmol) as a colorless oil in 87% yield.

TLC (SiO_2): R_f = 0.45 (ethyl acetate:hexanes, 1:1).

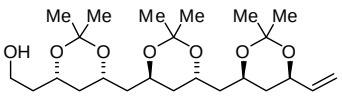
$[\alpha]_D^{26}$ = +11.3 (*c* = 0.8, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.85-5.77 (m, 1H), 5.24 (d, *J* = 17.6 Hz, 1H), 5.11 (d, *J* = 10.4 Hz, 1H), 4.37-4.33 (m, 1H), 4.14-4.01 (m, 5H), 3.78-3.75 (m, 2H), 2.55 (br s, 1H), 1.74-1.70 (m, 2H), 1.61-1.46 (m, 8H), 1.45 (s, 3H), 1.44 (s, 3H), 1.41 (s, 3H), 1.37 (s, 3H), 1.32 (s, 6H), 1.30-1.23 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7, 115.3, 100.4, 98.6, 70.3, 69.5, 64.9, 64.7, 62.3, 60.8, 42.1, 42.1, 38.9, 38.0, 37.1, 37.0, 30.3, 30.2, 24.4, 19.8, 19.7.

FTIR (neat): υ 3491, 2989, 2942, 2915, 1380, 1250, 1224, 1200, 1169, 1142, 1040, 1013, 992, 938, 916, 874, 827, 792 cm^{-1}.

HRMS (CI) Calcd. for $C_{24}H_{43}O_7$ $[M+H]^+$: 443.3009, Found: 443.3011.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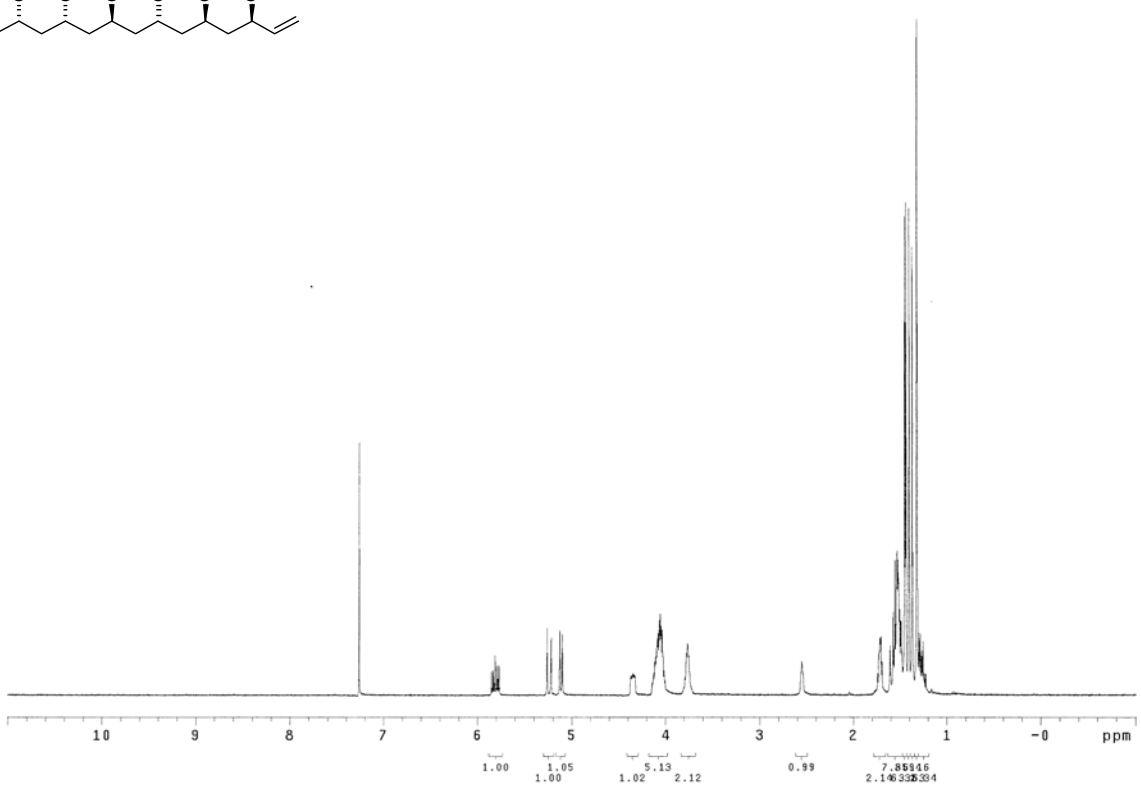
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1.00
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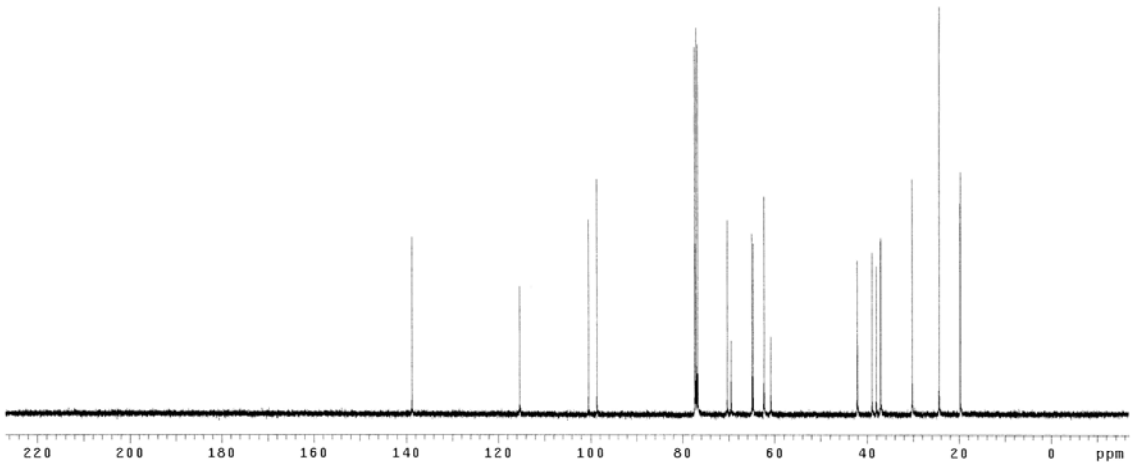
1.02
2.12
0.99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140
120
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60
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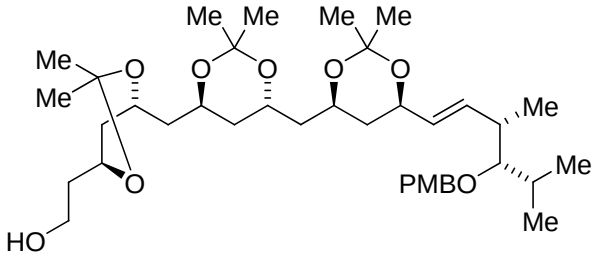
20
0
ppm

2-((4*S*,6*S*)-6-(((4*S*,6*S*)-6-(((4*R*,6*R*)-6-((3*S*,4*S*,*E*)-4-(4-methoxybenzyloxy)-3,5-dimethylhex-1-enyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)ethanol (5)



5

To a stirred solution of **4** (245 mg, 0.554 mmol, 100 mol%) and **A**[1] (413 mg, 1.662 mmol, 300 mol%) in DCM (5.5 mL, 0.1 M) was added Hoveyda-Grubbs catalyst 2nd generation (35 mg, 0.055 mmol, 10 mol%). The reaction mixture was stirred for 24 hr at 40 ^{o}C and concentrated in vacuo. Purification of the product by column chromatography (SiO_2: ethyl acetate:hexanes 1:3 with 0.1% TEA) provided **5** (195 mg, 0.29 mmol) as pale yellow oil in 53% yield.

TLC (SiO_2): R_f = 0.50 (ethyl acetate:hexanes, 1:1).

$[\alpha]_D^{26}$ = +11.0 (*c* = 1.0, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (m, 2H), 6.86 (dd, *J* = 6.8, 2.0 Hz, 2H), 5.65 (dd, *J* = 15.6, 7.6 Hz, 1H), 5.46 (dd, *J* = 15.6, 6.4 Hz, 1H), 4.47 (s, 2H), 4.36-4.27 (m, 1H), 4.14-4.02 (m, 5H), 3.80 (s, 3H), 3.80-3.74 (m, 2H), 2.96 (m, 1H), 2.54 (br s, 1H), 2.48-2.38 (m, 1H), 1.83-1.78 (m, 1H), 1.74-1.70 (m, 2H), 1.60-1.52 (m, 6H), 1.44 (s, 6H), 1.40 (s, 3H), 1.37 (s, 3H), 1.32 (s, 6H), 1.30-1.21 (m, 4H), 1.06 (d, *J* = 6.4 Hz, 3H), 0.93 (d, *J* = 6.4 Hz, 6H).

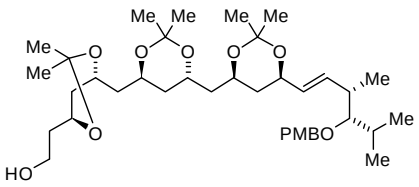
^{13}C NMR (100 MHz, $CDCl_3$): δ 158.9, 135.7, 131.1, 129.8, 129.2, 113.6, 100.4, 98.5, 98.4, 88.4, 74.7, 70.3, 69.3, 64.9, 64.7, 62.3, 60.6, 55.1, 42.1, 39.4, 38.9, 38.2, 38.0, 37.5, 37.0, 30.9, 30.2, 24.3, 20.2, 19.7, 17.7, 15.2.

FTIR (neat): υ 2997, 1979, 1674, 1514, 1382, 1215, 1037, 935, 746, 696, 667 cm^{-1}.

HRMS (CI) Calcd. for $C_{38}H_{61}O_9$ $[M-H]^+$: 661.4316, Found: 661.4323

.

[1] Burova S. A.; McDonald, F. E. *J. Am. Chem. Soc.* **2004**, *126*, 2495.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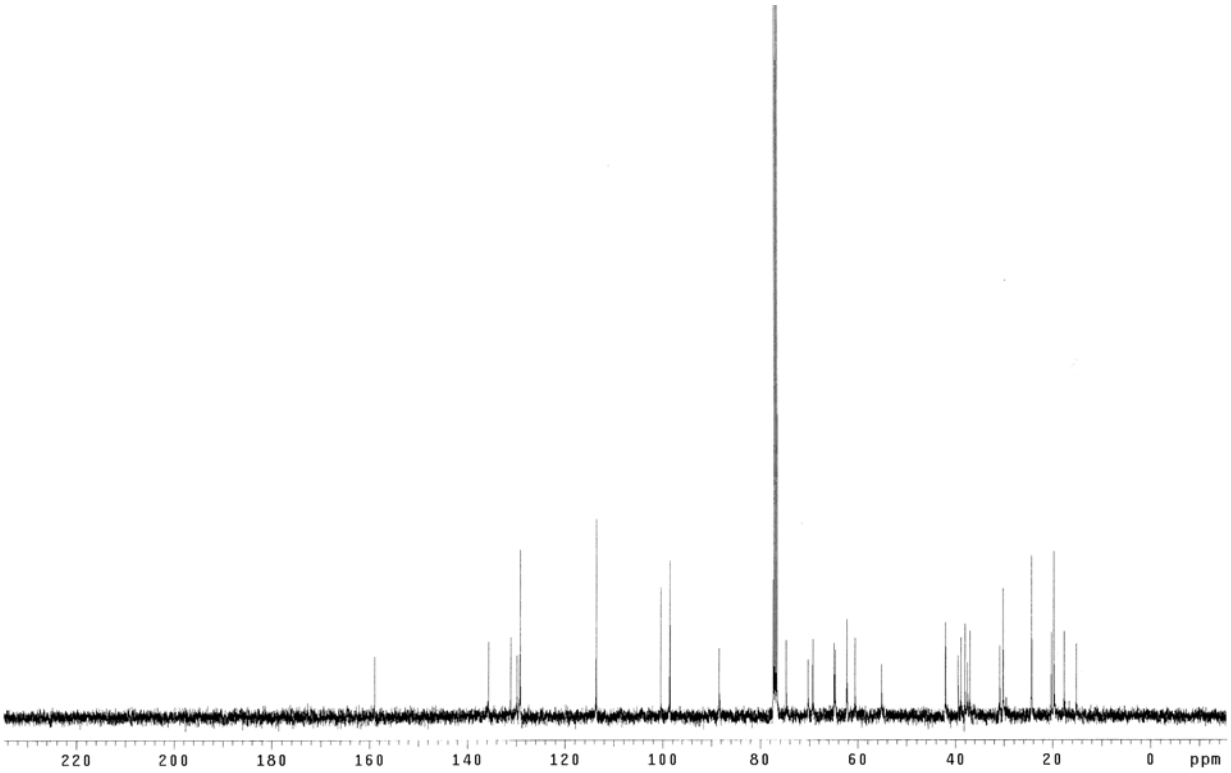
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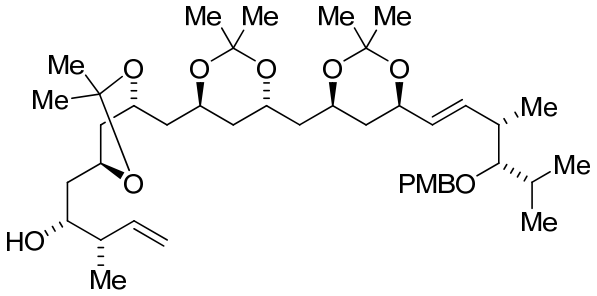
ppm

(2*R*,3*S*)-1-((4*S*,6*S*)-6-(((4*S*,6*S*)-6-(((4*R*,6*R*)-6-((3*S*,4*S*,*E*)-4-(4-methoxybenzyloxy)-3,5-dimethylhex-1-enyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-3-methylpent-4-en-2-ol (6a)



6a

An oven-dried sealed tube under one atmosphere of nitrogen gas was charged with alcohol **5** (133 mg, 0.2 mmol, 100 mol%), *(S)*-**II**[2] (20.7 mg, 0.02 mmol, 10 mol%), K_3PO_4 (43 mg, 0.20 mmol, 100 mol%). THF (0.2 mL, 1.0 M), H_2O (18 μL, 1.0 mmol, 500 mol%) and crotyl acetate (68 mg, 0.60 mmol, 300 mol%) were added and the mixture was stirred at ambient temperature for 0.5 hr. The reaction mixture was allowed to stir at 70 ^oC for 48 hr, at which point the reaction mixture was concentrated in vacuo. Purification of the residue by column chromatography (SiO_2; ethyl acetate: hexanes, 1:7 with 0.1% TEA) provided **6a** (121.9 mg, 0.17 mmol) as a yellow oil in 85% yield (14:1 dr).

TLC (SiO_2): R_f = 0.65 (ethyl acetate:hexanes, 1:3).

$[\alpha]_D^{26}$ = +98.0 (*c* = 1.0, CH_2Cl_2).

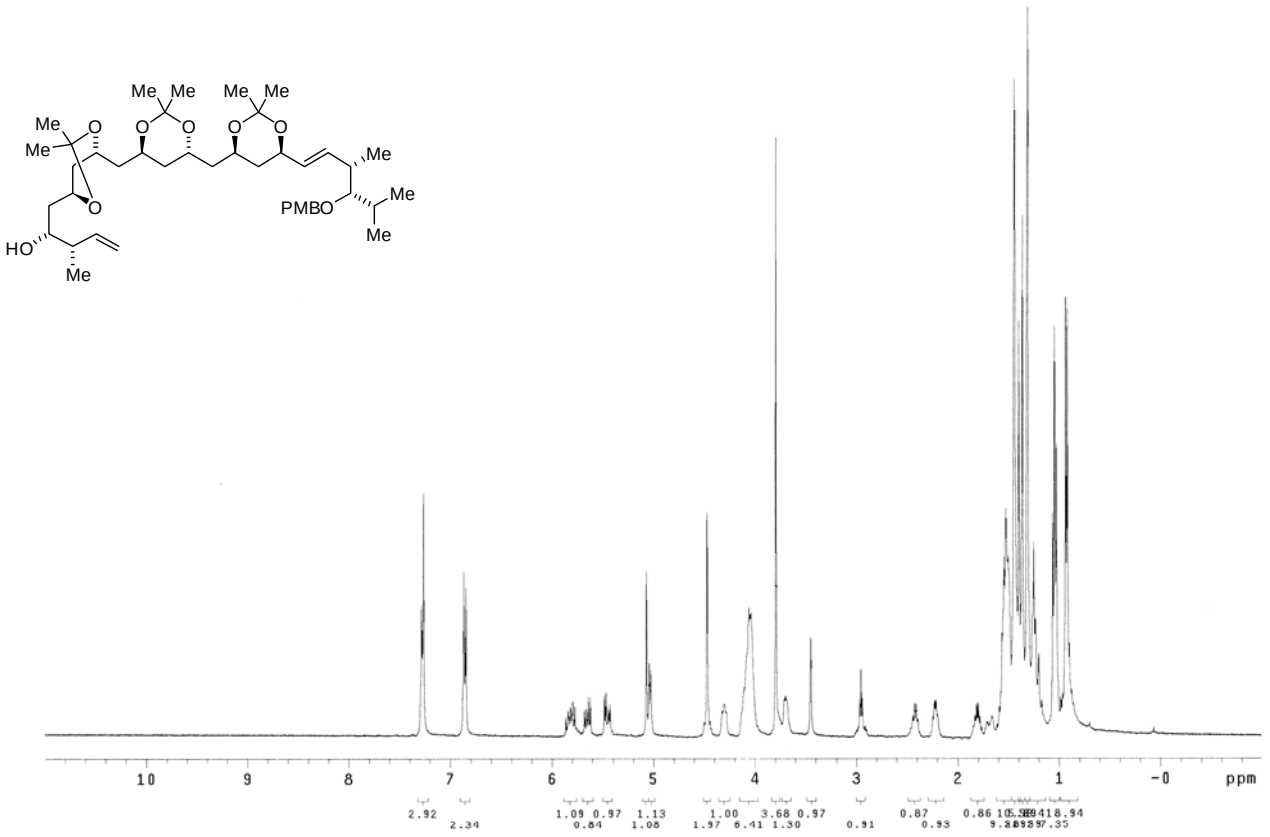
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.86-5.77 (m, 1H), 5.65 (dd, *J* = 15.2, 7.6 Hz, 1H), 5.46 (dd, *J* = 15.2, 6.4 Hz, 1H), 5.07 (s, 1H), 5.03 (d, *J* = 6.0 Hz, 1H), 4.47 (s, 2H), 4.34-4.26 (m, 1H), 4.14-3.98 (m, 5H), 3.79 (s, 3H), 3.72-3.66 (m, 1H), 3.45 (s, 1H), 2.97-2.94 (m, 1H), 2.44-2.39 (m, 1H), 2.24-2.20 (m, 1H), 1.83-1.78 (m, 1H), 1.56-1.46 (m, 8H), 1.45 (s, 3H), 1.44 (s, 3H), 1.40 (s, 3H), 1.36 (s, 3H), 1.32 (s, 6H), 1.30-1.20 (m, 4H), 1.05 (d, *J* = 7.2 Hz, 3H), 1.04 (d, *J* = 7.2 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 6H).

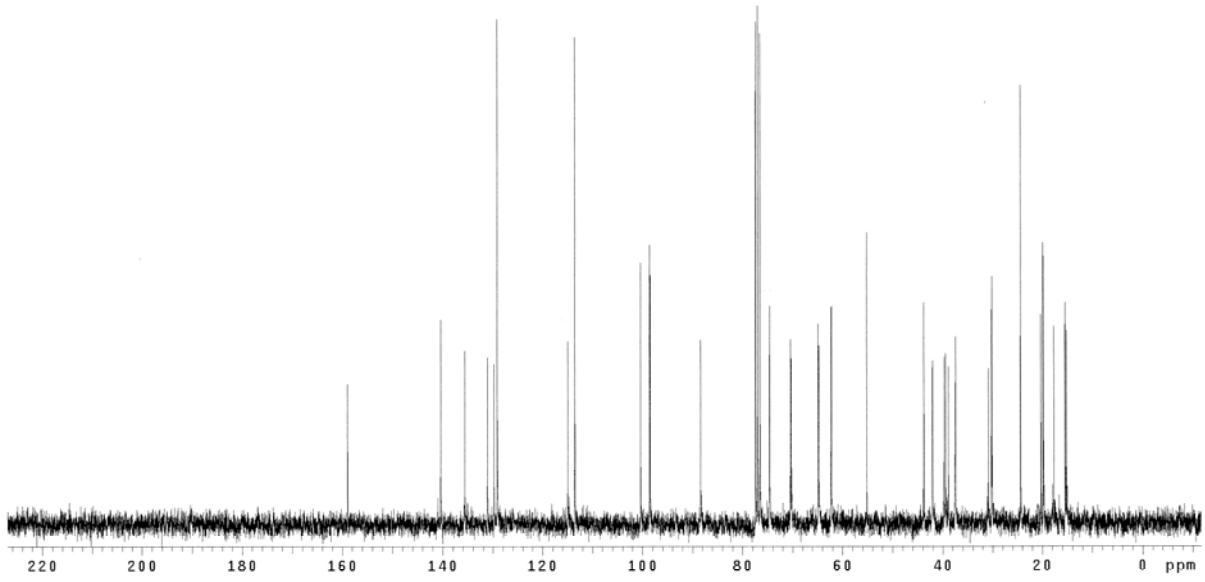
^{13}C NMR (75 MHz, $CDCl_3$): δ 158.9, 140.4, 135.7, 131.1, 129.8, 129.2, 115.0, 113.6, 100.3, 98.6, 98.5, 88.4, 74.7, 74.6, 70.4, 70.2, 64.9, 64.7, 62.3, 62.2, 55.1, 43.8, 42.1, 42.0, 39.7, 39.4, 38.9, 37.5, 37.4, 30.9, 30.2, 30.1, 24.3, 20.2, 19.8, 19.8, 17.7, 15.4, 15.2.

[2] Han, S. B.; Gao, X.; Krische, M. J. *J. Am. Chem. Soc.* **2010**,*132*, 9153.

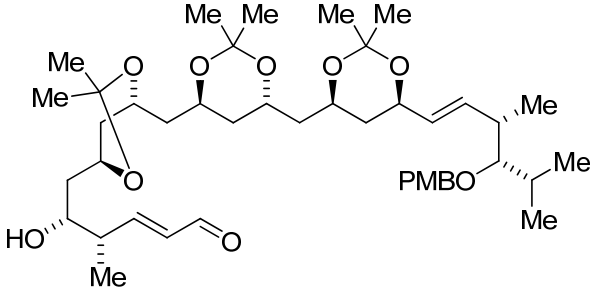
FTIR (neat): υ 3502, 2987, 2943, 1940, 1737, 1613, 1514, 1461, 1431, 1380, 1301, 1247, 1224, 1200, 1168, 1127, 1087, 1037, 980, 936, 913, 874, 823, 702 cm^{-1}.

HRMS (CI) Calcd. for $C_{42}H_{67}O_9$ $[M-H]^+$: 715.4786, Found: 715.4786





(4*S*,5*R*,*E*)-5-hydroxy-6-((4*S*,6*S*)-6-(((4*S*,6*S*)-6-(((4*R*,6*R*)-6-((3*S*,4*S*,*E*)-4-(4-methoxybenzyloxy)-3,5-dimethylhex-1-enyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-4-methylhex-2-enal (7a)



7a

To a stirred solution of **6a** (122 mg, 0.170 mmol, 100 mol%) and acrolein (48 mg, 0.85 mmol, 500 mol%) in DCE (1.7 mL, 0.1 M) was added Hoveyda-Grubbs catalyst 2nd generation (8.0 mg, 0.013 mmol, 7.5 mol%). The reaction mixture was stirred for 24 hr at 60 ^{o}C. Acrolein (48 mg, 0.85 mmol, 500 mol%) and Hoveyda-Grubbs catalyst 2nd generation (8.0 mg, 0.013 mmol, 7.5 mol%) were added and the reaction mixture was stirred for 24 hr at 60 ^{o}C. The reaction mixture was concentrated in vacuo. Purification of the product by column chromatography (SiO_2: ethyl acetate:hexanes 1:3 with 0.1% TEA) provided the starting material **6a** (37 mg, 0.051mmol, 30% recovered yield) and the product **7a** (66 mg, 0.09 mmol, 52% yield, 74% BRSM) as a pale yellow oil.

TLC (SiO_2): R_f = 0.25 (ethyl acetate:hexanes, 1:3).

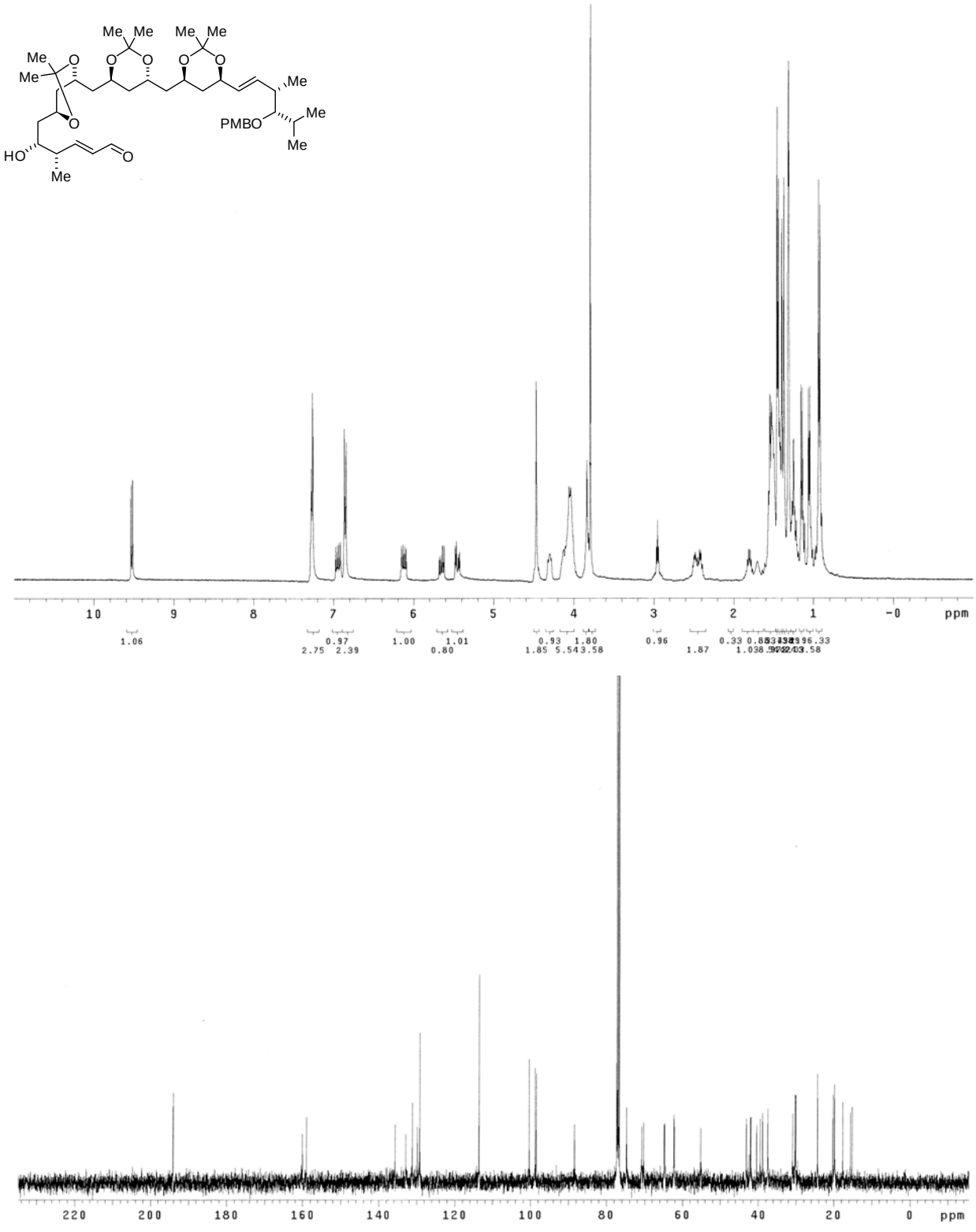
$[\alpha]_D^{26}$ = +70.0 (*c* = 1.0, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.53 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 2H), 6.94 (dd, *J* = 15.6, 8.0 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.12 (dd, *J* = 15.6, 8.0 Hz, 1H), 5.65 (dd, *J* = 15.2, 7.6 Hz, 1H), 5.45 (dd, *J* = 15.2, 6.0 Hz, 1H), 4.47 (s, 2H), 4.32-4.27 (m, 1H), 4.12-3.98 (m, 5H), 3.86-3.80 (m, 2H), 3.79 (s, 3H), 2.97-2.93 (m, 1H), 2.49-2.40 (m, 2H), 1.83-1.77 (m, 1H), 1.56-1.46 (m, 8H), 1.46 (s, 3H), 1.44 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H), 1.31 (s, 3H), 1.30 (s, 3H), 1.28-1.19 (m, 4H), 1.15 (d, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.4 Hz, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.0, 160.0, 158.9, 135.7, 132.9, 131.1, 129.8, 129.2, 113.6, 100.4, 98.8, 98.5, 88.4, 74.8, 74.7, 70.8, 70.3, 64.8, 64.7, 62.3, 62.2, 55.2, 43.2, 42.1, 41.9, 40.4, 39.4, 38.8, 37.5, 37.4, 30.9, 30.2, 30.1, 24.3, 20.2, 19.8, 19.7, 17.7, 15.6, 15.2.

FTIR (neat): υ 3508, 2987, 2940, 1690,1613, 1514, 1459, 1380, 1301, 1247, 1224, 1200, 1168, 1127, 1085, 1036, 977, 936, 874, 821, 732 cm^{-1}.

HRMS (CI) Calcd. for $C_{43}H_{67}O_{10}$ $[M-H]^+$: 743.4734, Found: 743.4738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5
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1.87
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8.58
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120
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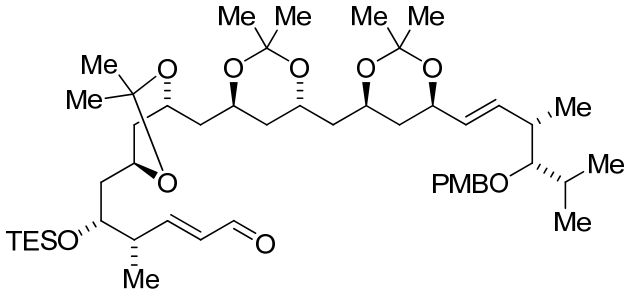
80
60
40
20
0
ppm

3*S*,4*S*,*E*)-4-(4-methoxybenzyloxy)-3,5-dimethylhex-1-enyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-4-methyl-5-(triethylsilyloxy)hex-2-enal (7b)



7b

To a stirred solution of **7a** (37 mg, 0.05 mmol, 100 mol%) in DCM (0.5 mL, 0.1 M) were added 2,6-lutidine (23 µL, 0.2 mmol, 400 mol%) and TESOTf (23 µL, 0.1 mmol, 200 mol%) at -78 ^{o}C. The reaction mixture was stirred for 2 hr at -78 ^{o}C, and then quenched with saturated aq. $NaHCO_3$ (2 mL). The reaction mixture was extracted with DCM. The combined organic extracts wase washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:20 to 1:10 with 0.1% TEA) to give **7b** (38 mg, 0.044 mmol) as a yellow oil in 87% yield.

TLC (SiO_2): R_f = 0.60 (ethyl acetate:hexanes, 1:3).

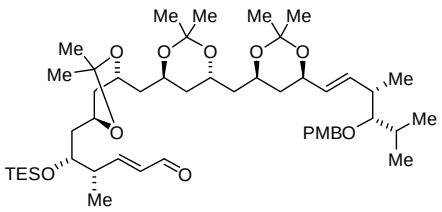
$[\alpha]_D^{26}$ = +29.0 (*c* = 1.0, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.51 (d, *J* = 8.0 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 6.90-6.85 (m, 1H), 6.86 (d, *J* = 8.0 Hz, 2H), 6.09 (dd, *J* = 15.6, 8.0 Hz, 1H), 5.65 (dd, *J* = 15.6, 8.0 Hz, 1H), 5.45 (dd, *J* = 15.2, 5.6 Hz, 1H), 4.47 (s, 2H), 4.34-4.26 (m, 1H), 4.10-3.96 (m, 4H), 3.95-3.88 (m, 1H), 3.88-3.82 (m, 1H), 3.79 (s, 3H), 2.97-2.94 (m, 1H), 2.66-2.58 (m, 1H), 2.46-2.38 (m, 1H), 1.84-1.76 (m, 1H), 1.56-1.46 (m, 8H), 1.44 (s, 3H), 1.39 (s, 6H), 1.34 (s, 3H), 1.32 (s, 6H), 1.28-1.21 (m, 4H), 1.12 (d, *J* = 6.4 Hz, 3H), 1.05 (d, *J* = 6.0 Hz, 3H), 0.98-0.92 (m, 15H), 0.63 (q, *J* = 7.6 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 193.9, 160.4, 158.9, 135.6, 132.9, 131.1, 129.8, 129.1, 113.5, 100.3, 98.4, 98.2, 88.4, 74.7, 71.5, 70.2, 65.6, 64.9, 64.7, 62.3, 55.1, 42.1, 42.0, 41.9, 41.8, 39.4, 38.9, 37.6, 37.5,30.8, 30.2, 30.1, 24.3, 20.2, 19.7, 19.6, 17.7, 15.9, 15.1, 6.8, 5.0.

FTIR (neat): υ 2987, 2950, 2912, 2876, 1693, 1613, 1514, 1460, 1379, 1301, 1246, 1224, 1199, 1169, 1128, 1083, 1034, 981, 938, 873, 854, 821, 781, 740, 726 cm^{-1}.

HRMS (CI) Calcd. for $C_{49}H_{81}O_{10}Si_1$ $[M-H]^+$: 857.5599, Found: 857.5602.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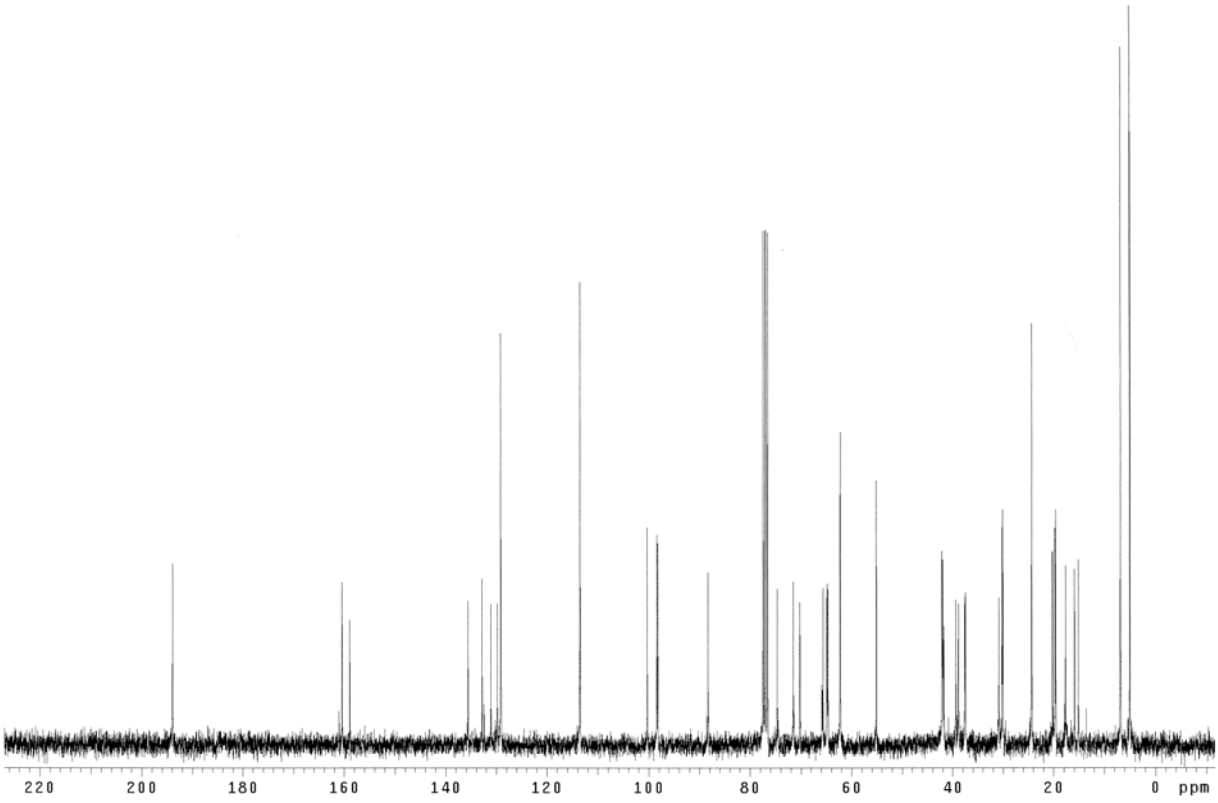
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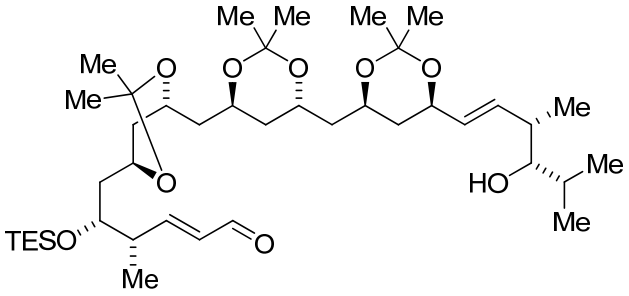
ppm

(4*S*,5*R*,*E*)-6-((4*R*,6*R*)-6-(((4*S*,6*S*)-6-(((4*R*,6*R*)-6-((3*S*,4*S*,*E*)-4-hydroxy-3,5-dimethylhex-1-enyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-4-methyl-5-(triethylsilyloxy)hex-2-enal (7c)



7c

To a stirred solution of **7b** (38 mg, 0.044 mmol, 100 mol%) in DCM/H_2O (1.4 mL/0.07 mL, 0.03M) was added DDQ (13 mg, 0.057 mmol, 130 mol%) at 0 ^oC. The reaction mixture was stirred for 2 hr at 0 ^oC, and then quenched with saturated aq. $NaHCO_3$ (0.5 mL). The reaction mixture was extracted with DCM. The combined organic extracts were washed with H_2O, dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:7 to 1:5 with 0.1% TEA) to give **7c** (28 mg, 0.037 mmol) as a colorless oil in 85% yield.

TLC (SiO_2): R_f = 0.40 (ethyl acetate:hexanes, 1:3).

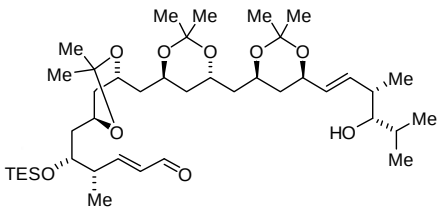
$[\alpha]_D^{26}$ = +78.0 (*c* = 1.0, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.50 (d, *J* = 7.6 Hz, 1H), 6.87 (dd, *J* = 15.6, 8.0 Hz, 1H), 6.09 (dd, *J* = 15.6, 8.0 Hz, 1H), 5.62 (dd, *J* = 15.6, 6.8 Hz, 1H), 5.48 (dd, *J* = 15.6, 6.0 Hz, 1H), 4.34-4.31 (m, 1H), 4.10-3.96 (m, 4H), 3.95-3.87 (m, 1H), 3.87-3.81 (m, 1H), 3.16-3.13 (m, 1H), 2.66-2.57 (m, 1H), 2.36-2.31 (m, 1H), 1.74-1.67 (m, 1H), 1.59-1.45 (m, 8H), 1.44 (s, 3H), 1.39 (s, 6H), 1.34 (s, 3H), 1.32 (s, 6H), 1.28-1.21 (m, 4H), 1.12 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.98-0.89 (m, 15H), 0.60 (q, *J* = 8.0 Hz, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 194.0, 160.6, 134.8, 132.9, 130.9, 100.4, 98.5, 98.3, 79.5, 71.6, 70.2, 65.7, 64.9, 64.7, 62.3, 42.2, 42.1, 41.8, 39.2, 38.9, 37.6, 30.4, 30.2, 30.1, 24.3, 19.7, 19.6, 17.0, 15.9, 13.8, 6.8, 5.0.

FTIR (neat): υ 3515, 2987, 2950, 2876, 1692, 1634, 1459, 1379, 1224, 1199, 1168, 1142, 1084, 1021, 1006, 981, 938, 913, 874, 855, 816, 781, 731 cm^{-1}.

HRMS (CI) Calcd. for $C_{41}H_{73}O_9Si_1$ $[M-H]^+$: 737.5024, Found: 737.5012.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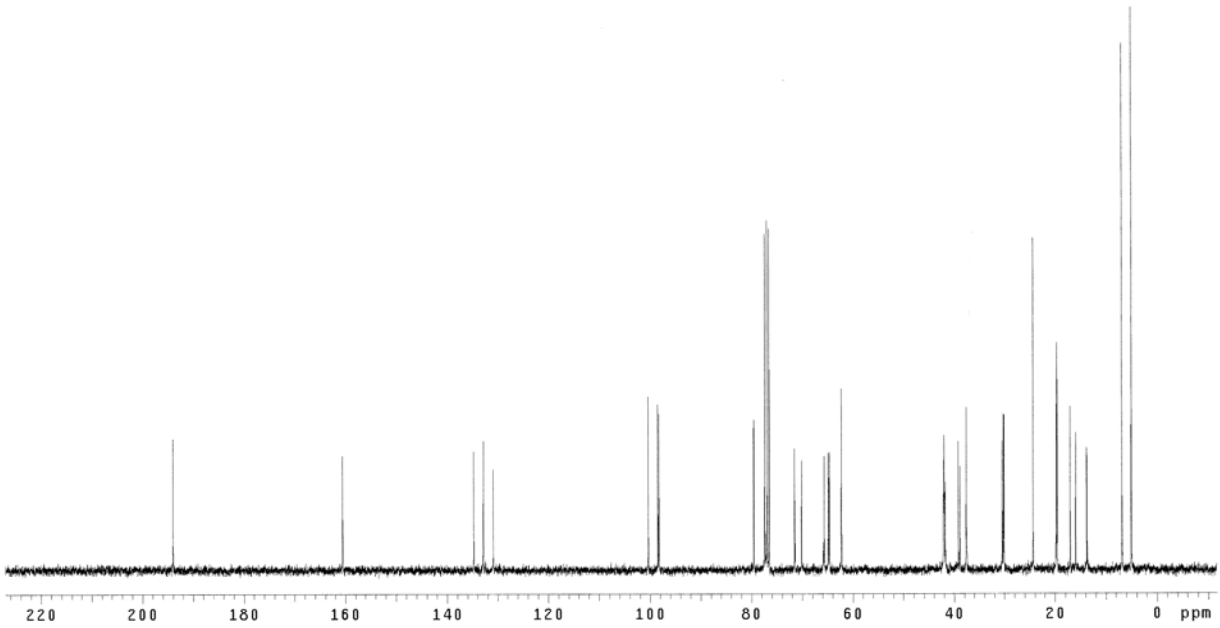
6.14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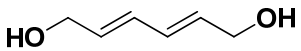
ppm

(2*E*,4*E*)-hexa-2,4-diene-1,6-diol (B-1)



B-1

Previuosly reported procedure was followed for the synthesis of **B-1**.[3] To a stirred solution of 1,6-hexadiyne (1 g, 9.08 mmol, 100 mol%) in THF (100 mL, 0.09 M) at 0 ^{o}C was added $LiAlH_4$ (1.72 g, 45.41 mmol, 500 mol%) in four portions. The reaction mixture was stirred at 0 ^{o}C for 30 min and heated to reflux for 24 h. The reaction mixture was cooled to ambeient temperature, diluted with ether (100 mL) and carefully quench with H_2O (2 mL), 15% aqueous NaOH (2 mL) and H_2O (5 mL). The suspension is filtered through celite and the residue was rinsed with ethyl acetate. The filterate is dried over $MgSO_4$, concentrated in vacuo to give the desire diol **B-1** (0.88g, 7.74 mmol) as white solid in 85 % yield.

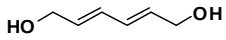
^{1}H NMR [(400 MHz, $(CD)_3CO$)]: δ 6.27-6.19 (m, 2H), 5.81-5.71 (m, 2H), 4.09 (brs, 4H), 3.78 (s, 2H).

^{13}C NMR [100 MHz,$(CD)_3CO$)]: δ 133.9, 130.2, 62.8.

FTIR (neat): υ 3484, 1726, 1712, 1242, 1030, 991, 889, 671 cm^{-1}.

HRMS (CI) Calcd. for $C_6H_{11}O_2$ $[M+H]^+$: 115.0759, Found: 115.0762.

[3]Doyle, M. P., Wang, Y., Ghorbani, P., and Bappert, E. *Org. Lett.* **2005**, *7*, 5035.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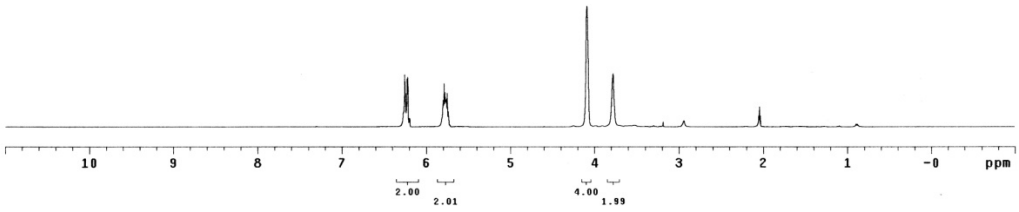
OH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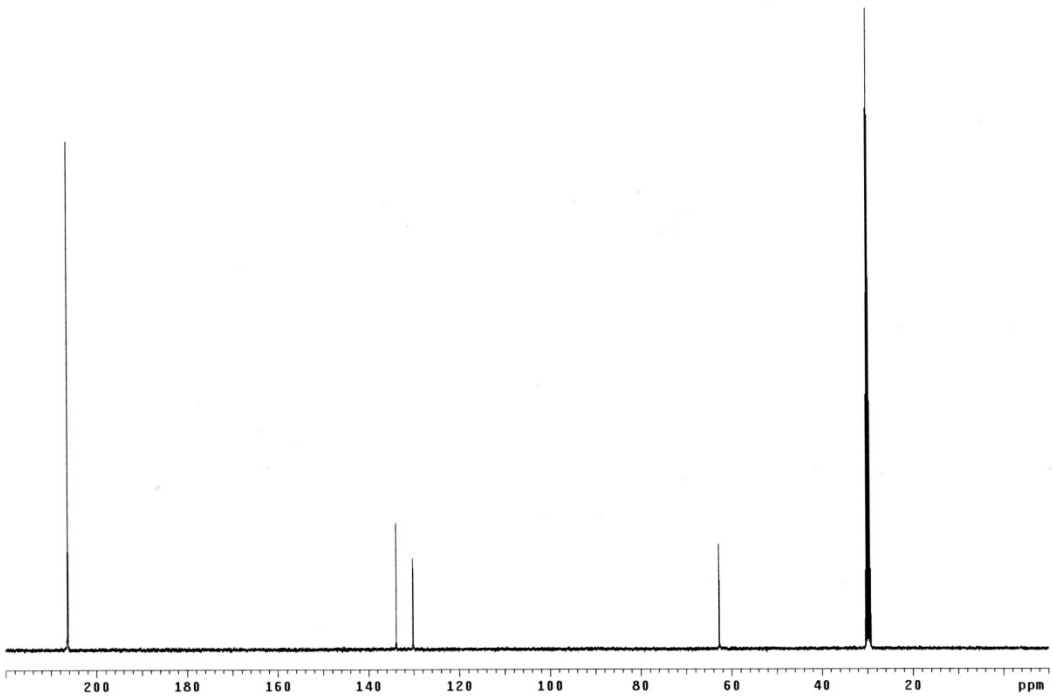
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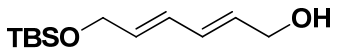
(2*E*,4*E*)-6-(tert-butyldimethylsilyloxy)hexa-2,4-dien-1-ol (B-2)



B-2

To a stirred solution of imidazole (1.23 g, 18.07 mmol, 150 mol%) in DMF (24 mL, 0.75 M) was dropwise added solution of diol **B-1** (2.05 g, 12.05 mmol, 100 mol%) in DMF (5 mL, 2.4 M) at ambient temperature. The reaction mixture was stirred for 45 min. TBSCl (1.99 g, 13.25 mmol, 110 mol%) was added to reaction mixture in one portion. The reaction mixture was stirred for 20 h at ambient temperature. H_2O (25 mL) was added to reaction mixture and the resulting solution was extracted with ether (50 mL x 3). The combined organic extracts were washed with brine (20 mL), dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:10 to 1:4) to give the mono protected diol **B-2** (1.85 g, 8.10 mmol) as a colorless liquid in 67% yield.

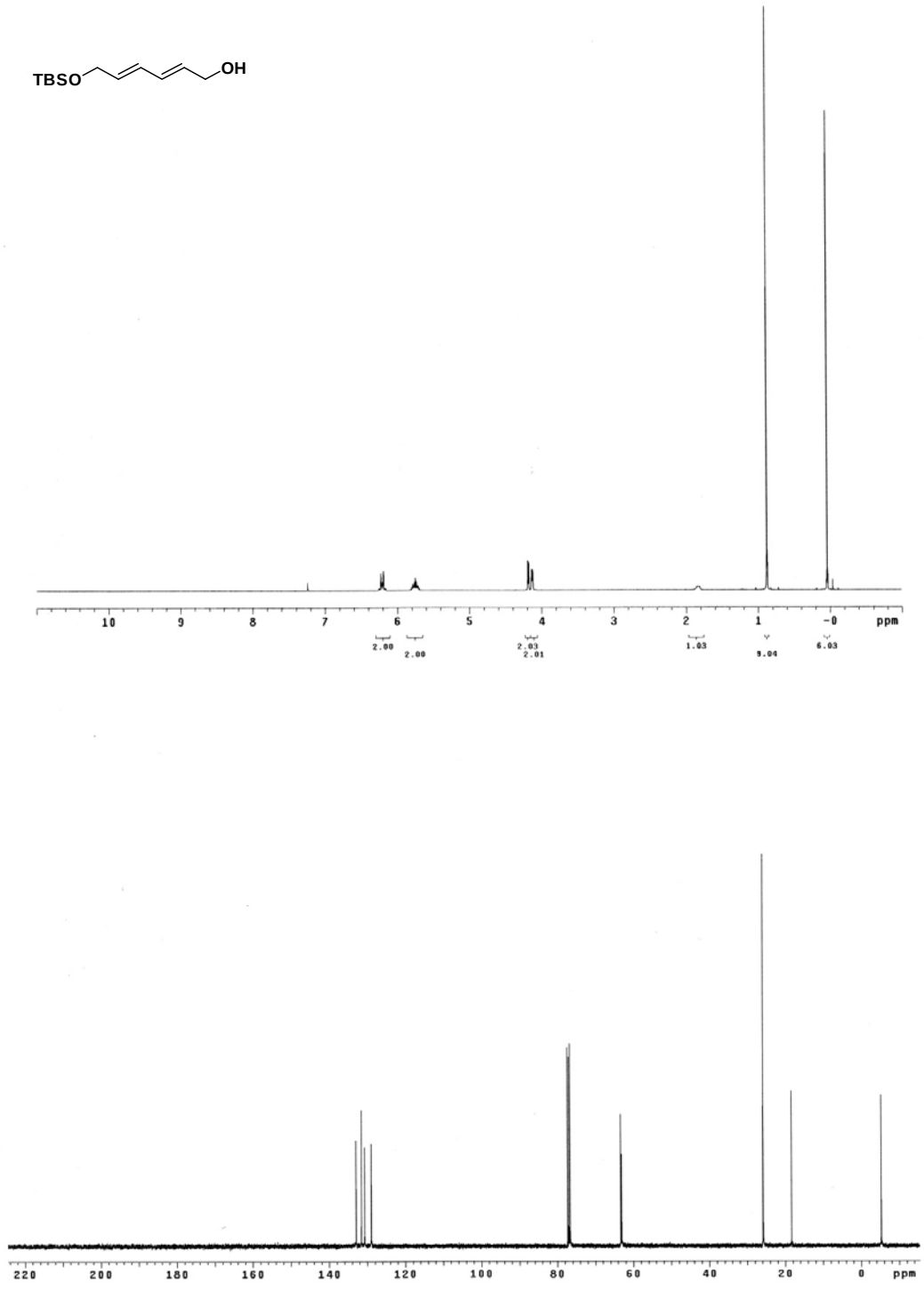
TLC (SiO_2): R_f = 0.45 (ethyl acetate:hexanes, 1:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.26-6.16 (m, 2H), 5.80-5.70 (m, 2H), 4.19 (d, *J* = 4.8 Hz, 2H), 4.13 (d, *J* = *7.0* Hz, 2H), 1.84 (br s, 1H), 0.88 (s, 9H), 0.04 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 132.9, 131.5, 130.7, 128.9, 63.3, 63.1, 25.9, 18.3, -5.3.

FTIR (neat): υ 3355, 2958, 2954, 2929, 2883, 2856, 1471, 1463, 1370, 1361, 1254, 1109, 1081, 987, 774, 672 cm^{-1}.

HRMS (CI) Calcd. for $C_{12}H_{25}O_2Si$ $[M+H]^+$: 229.1624, Found: 229.1620.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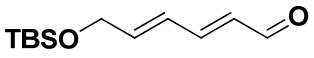
ppm

(2*E*,4*E*)-6-(tert-butyldimethylsilyloxy)hexa-2,4-dienal (B-3)



B-3

To a stirred solution of oxalyl chloride (1.2 mL, 13.79 mmol, 150 mol%) in DCM (35 mL, 0.4 M) at -78 ^{o}C was added DMSO (1 mL, 13.79 mmol, 150 mol%). The reaction mixture was allowed to stir for 20 min at -78 ^{o}C. The alcohol **B-2** (2.1 g, 9.19 mmol, 100 mol%) in DCM (12 mL, 0.75 M) was added to reaction mixture and the resulting solution was allowed to stir for 30 min at -78 ^{o}C. Triethylamine (6.4 mL, 45.97 mmol, 500 mol%) was added to the reaction mixture. The resulting solution was allowed to stir for 30 min at -78 ^{o}C, warmed to ambient temperature and stirred for 5 hr. The reaction was quenched with H_2O (40 mL) and extracted with DCM (80 mL x 3). The combined organic phase was washed with H_2O (40 mL), brine (40 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:10 with 0.1% TEA) to give the aldehyde **B-3** (1.33 g, 5.87 mmol) as a slightly yellow oil in 64% yield.

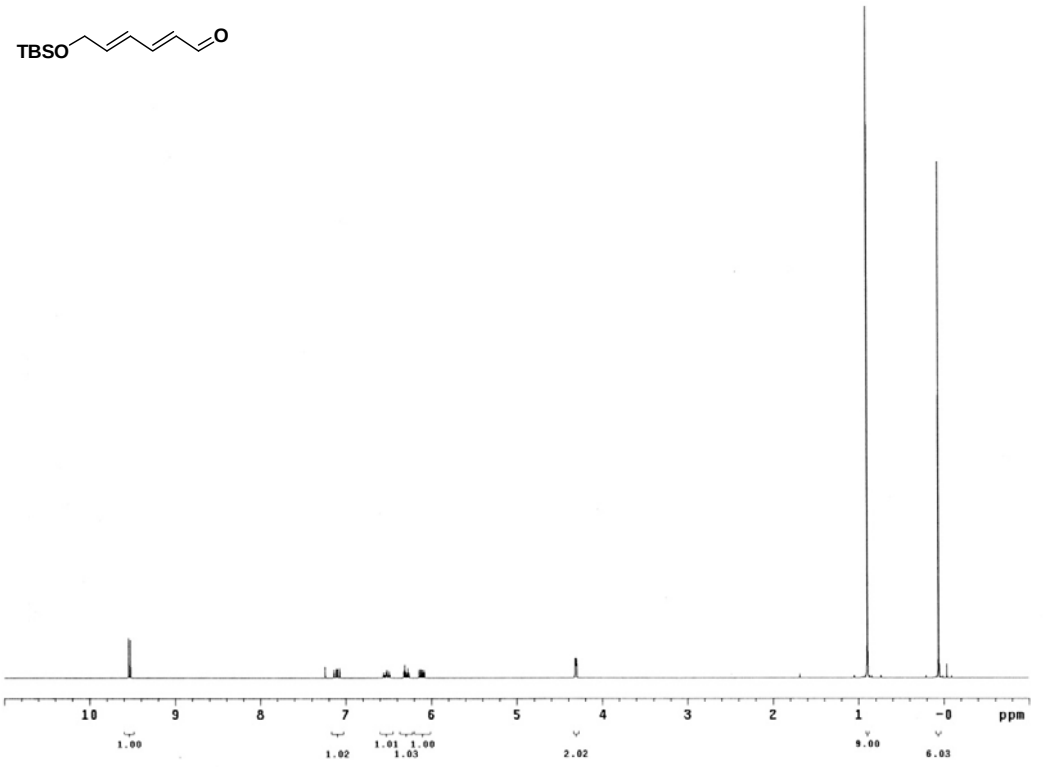
TLC (SiO_2): R_f = 0.40 (ethyl acetate:hexanes, 1:10).

^{1}H NMR (400 MHz, $CDCl_3$): δ 9.53 (d, *J* = 8.0 Hz, 1H), 7.10 (dd, *J* = 14.8, 11.2 Hz, 1H), 6.56-6.49 (m, 1H), 6.29 (dt, *J* = 14.8, 4 Hz, 1H), 6.11 (dd, *J* = 15.6, 7.6 Hz, 1H), 4.31 (dd, *J* = 4.0, 2.0 Hz, 2H), 0.89 (s, 9H), 0.06 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7, 151.6, 144.3, 131.1, 126.6, 62.7, 25.8, 25.6, -5.5.

FTIR (neat): υ 2954, 2929, 2883, 2856, 2722, 1682, 1644, 1602, 1471, 1445, 1377, 1352, 1252, 1161, 1131, 1010, 986, 960, 809, 775, 675.

HRMS (CI) Calcd. for $C_{12}H_{23}O_2Si$ $[M+H]^+$: 227.1467, Found: 227.1467.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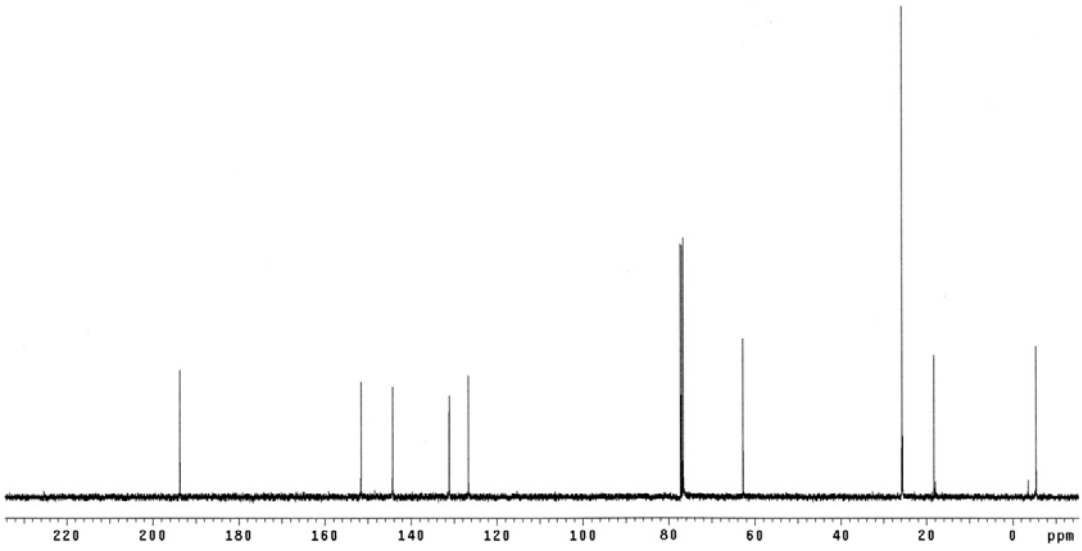
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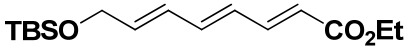
0
ppm

(2*E*,4*E*,6*E*)-ethyl 8-(tert-butyldimethylsilyloxy)octa-2,4,6-trienoate (B-4)



B-4

To a stirred solution of the triethyl phosphonoacetate (2.9 mL, 14.48 mmol, 110 mol%) in THF (66 mL, 0.22 M) was added LiHMDS (1M solution in THF, 13.8 mL, 13.82 mmol, 105 mol%) at 0 ^{o}C and the reaction mixture was stirred for 20 min. The aldehyde **B-3** (3 g, 13.16 mmol, 100 mol%) in THF (10 mL, 1.3 M) was added dropwise to reaction mixture at 0 ^{o}C. The reaction mixture was warmed to ambient temperature in 3 hr, quenched with saturated aq. NH_4Cl (50 mL) and extracted with ether (100 mL x 3). The combined organic phase was washed with H_2O (50 mL), brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: diethyl ether:hexanes, 1:20 to 1:10 with 0.1% TEA) to give the ester **B-4** (2.85 g, 9.61 mmol) as a colorless oil in 73% yield.

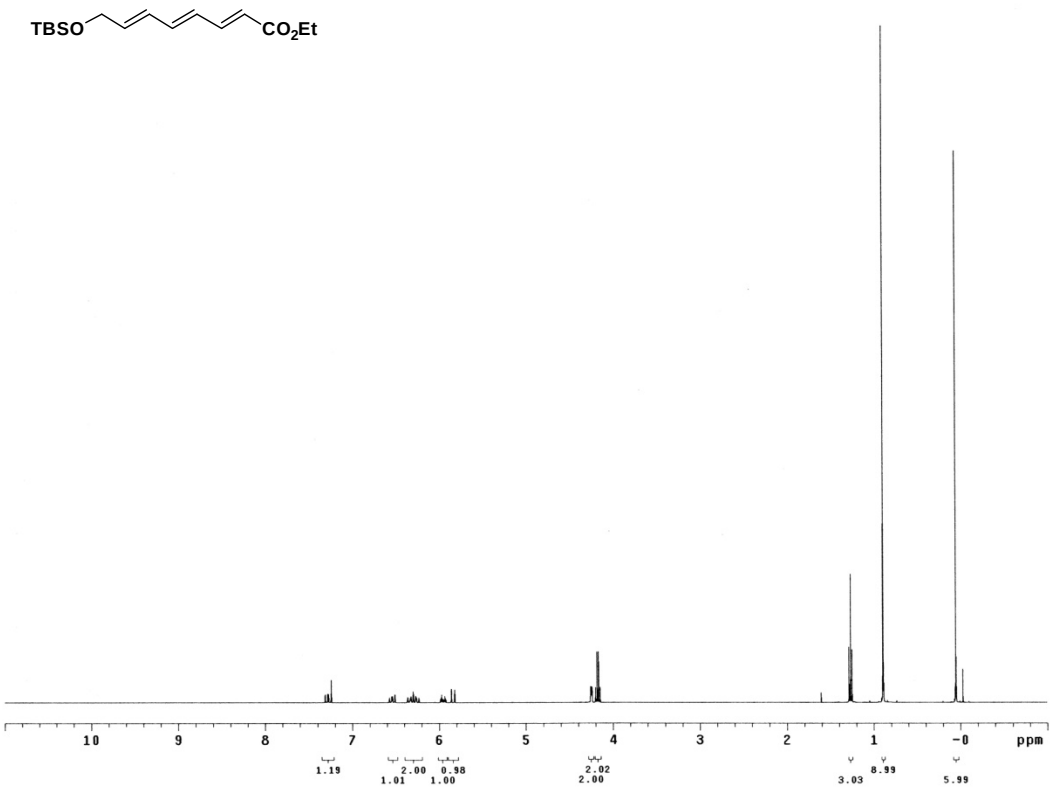
TLC (SiO_2): R_f = 0.35 (diethyl ether:hexanes, 1:10).

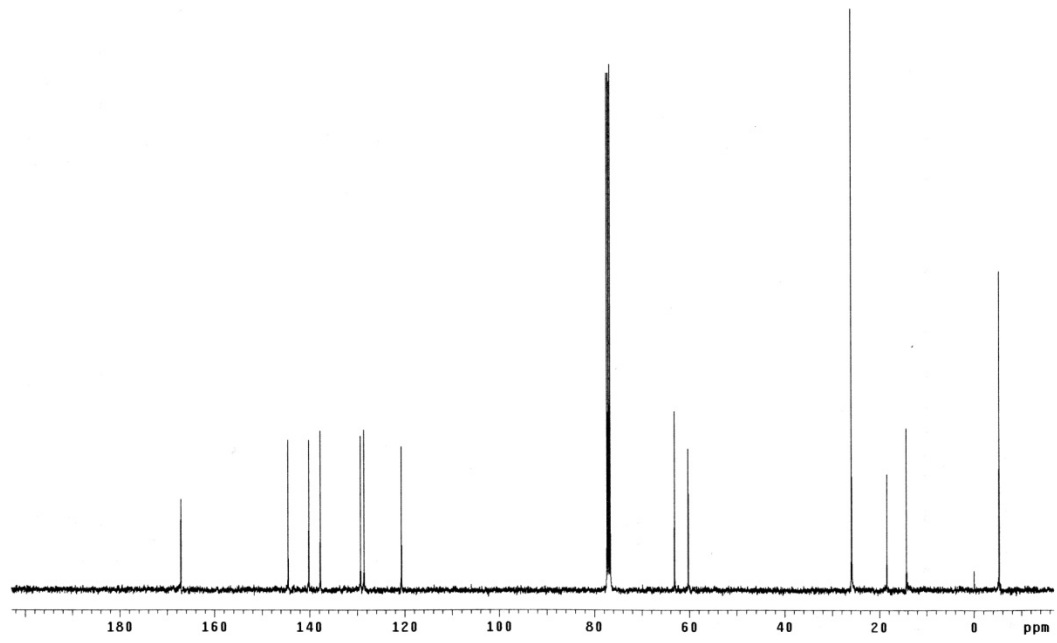
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (dd, *J* = 15.2, 11.2 Hz, 1H), 6.56 (dd, *J* = 15.2, 10.8 Hz, 1H), 6.39-6.31 (m, 1H), 6.28 (dd, *J* = 14.0, 10.4 Hz, 1H), 5.97 (dt, *J* = 15.2, 4.8, Hz, 1H), 5.86 (d, *J* = 15.2 Hz, 1H), 4.27 (d, *J* = 4.4 Hz, 2H), 4.20 (q, *J* = 7.2 Hz, 2H), 1.29 (t, *J* = 7.2 Hz, 3H), 0.92 (s, 9H), 0.08 (s, 6H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 144.5, 140.1, 137.7, 129.3, 128.5, 120.7, 63.1, 60.2, 25.9, 18.4, 14.3, -5.3.

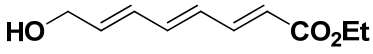
FTIR (neat): υ 2954, 2929, 2885, 2856, 1704, 1637, 1618, 1471, 1377, 1338, 1294, 1272, 1247, 1098, 1014, 977, 941, 892, 776, 744, 716, 666.

HRMS (CI) Calcd. for $C_{16}H_{29}O_3Si$ $[M+H]^+$: 297.1886, Found: 297.1890.


TBSO
CO2Et
10
9
8
7
6
5
4
3
2
1
-0
ppm
1.19
2.00
1.01
0.98
1.00
2.02
2.00
3.03
8.99
5.99


180
160
140
120
100
80
60
40
20
0
ppm

(2*E*,4*E*,6*E*)-ethyl 8-hydroxyocta-2,4,6-trienoate (B-5)



B-5

To a stirred solution of ester **B-4** (2.52 g, 8.49 mmol, 100 mol%) in THF (42 mL, 0.2 M) was added TBAF (1M solution in THF, 10.2 mL, 10.2 mmol, 120 mo%) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 1 hr and Ethyl acetate (200 mL) was added. The the organic layer was washed with H_2O (50 mL x 2), brine (50 mL) and dried (Na_2SO_4). The organic phase was concentrated in vacuo and the residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:1 with 0.1% TEA) to give the alcohol **B-5** (1.50 g, 8.32 mmol) as a white solid in 98% yield.

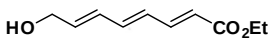
TLC (SiO_2): R_f = 0.40 (ethyl acetate:hexanes, 1:1).

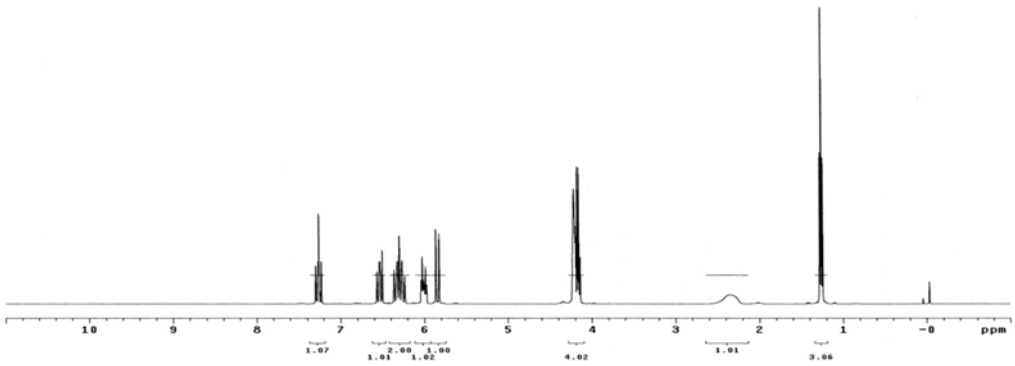
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (dd, *J* = 15.2, 11.6 Hz, 1H), 6.54 (dd, *J* = 14.8, 10.8 Hz, 1H), 6.36-6.24 (m, 2H), 6.00 (dt, *J* = 14.8, 5.6 Hz, 1H), 5.84 (d, *J* = 15.6 Hz, 1H), 4.27 (d, *J* = 4.8 Hz, 2H), 4.16 (q, *J* = 7.2 Hz, 2H), 2.35 (br s, 1H), 1.26 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.1, 144.3, 139.8, 137.1, 129.8, 129.6, 121.0, 62.7, 60.3, 14.2.

FTIR (neat): υ 3303, 3199, 3017, 2993, 2901, 2951, 1705, 1615, 1588, 1479, 1444, 1336, 1260, 1214, 1179, 1132, 1086, 967, 915, 876, 843, 814, 778, 747, 715, 692.

HRMS (CI) Calcd. for $C_{10}H_{15}O_3$ $[M+H]^+$: 183.1021, Found: 183.1025.


HO
CO2Et


10
9
8
7
6
5
4
3
2
1
0
ppm
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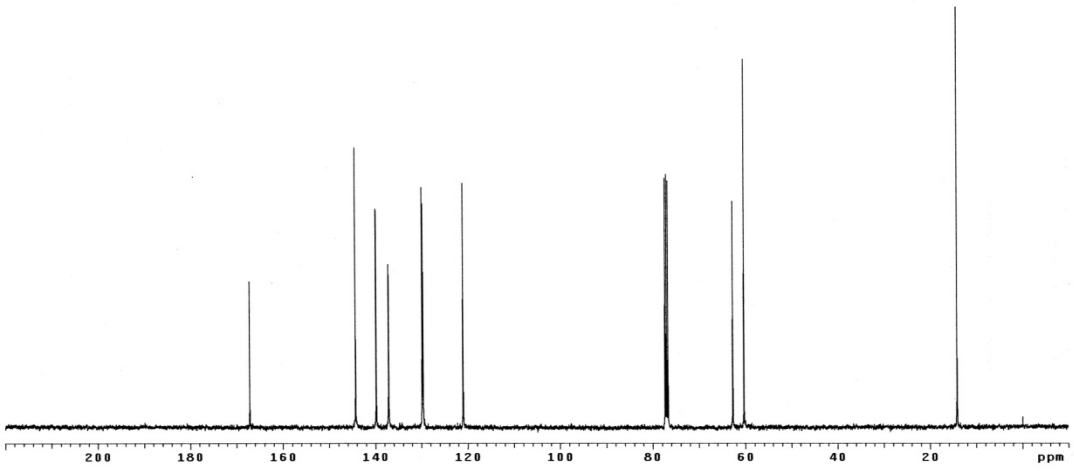
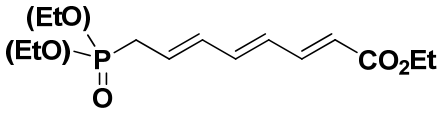
2.00
1.01
1.00
1.02
4.02
1.01
3.06


200
180
160
140
120
100
80
60
40
20
ppm

(2E,4E,6E)-ethyl 8-(diethoxyphosphoryl)octa-2,4,6-trienoate (B)



B

To a stirred solution of the alcohol **B-5** (570 mg, 3.13 mmol, 100 mol%) in DCM (11 mL, 0.3 M) was added pyridine (30 μL, 0.38 mmol, 12 mol%) followed by PBr_3 (1M solution in DCM, 4.7 mL, 4.70 mmol, 150 mol%) at 0 ^oC for 10 min. The reaction was quenched with water (20 mL) and extracted with ether (20 mL x 3). The combined organic phase was washed with water (20 mL), saturated aq. $NaHCO_3$ (30 mL), brine (30 mL), dried with Na_2SO_4, filtered and concentrated in vacuo to give allylic bromide as white semi solid which was used without any further purification.

The allylic bromide was dissolved in toluene (21 mL, 0.15 M) and triethylphosphite (1.35 mL, 7.82 mmol, 250 mol%) was added. The reaction mixture was heated at reflux for 12 hr. Ethyl acetate (21 mL) was added and the reaction mixture was washed with water (20 mL x 3) and brine (20 mL). The organic phase was dried (Na_2SO_4), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 3:1 to 5:1) to give the desire phosphonate ester **B** (662 mg, 2.189 mmol) as a light yellow semi solid in 70% yield over two steps.

TLC (SiO_2): R_f = 0.30 (ethyl acetate).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (dd, *J* = 15.2, 10.8 Hz, 1H), 6.48 (dd, *J* = 15.2, 10.4 Hz, 1H), 6.31-6.23 (m, 2H), 5.83 (d, *J* = 15.6 Hz, 1H), 5.87-5.81 (m, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 4.15-4.07 (m, 4H), 2.65 (dd, *J* = 23.2, 7.6 Hz, 2H), 1.30 (t, *J* = 7.2 Hz, 6H), 1.28 (t, *J* = 7.2 Hz, 3H).

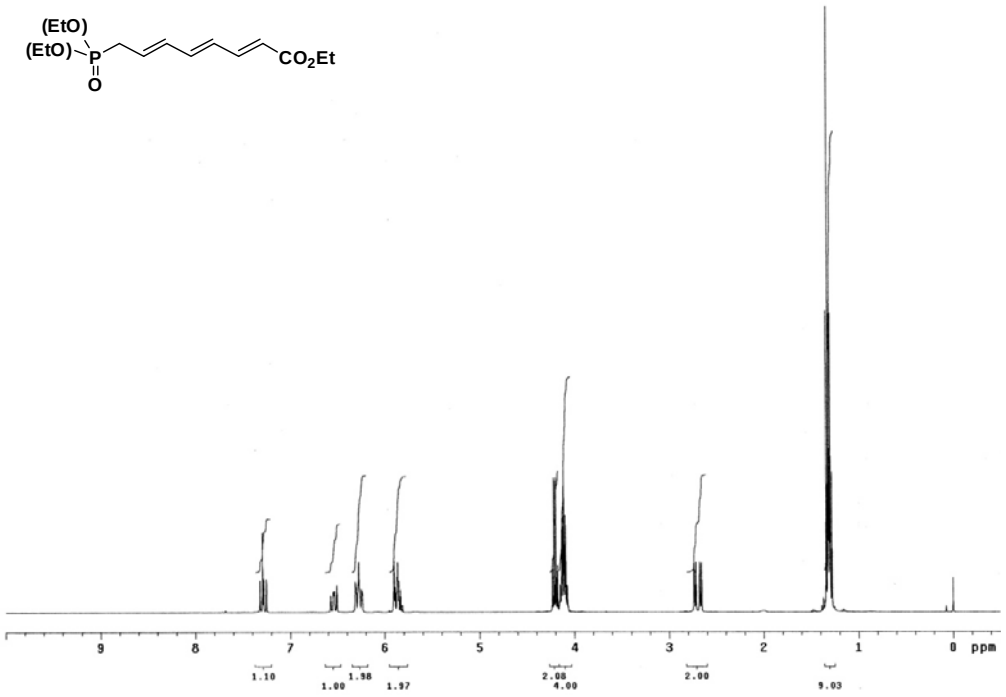
^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 144.1 (d, *J* = 12 Hz), 139.6 (d, *J* = 20.8 Hz), 134.3 (d, *J* = 59.6 Hz), 129.7 (d, *J* = 20.8 Hz), 127.2 (d, *J* = 53.6 Hz), 121.3, 62.1 (d, *J* = 26.8 Hz), 60.3, 31.9, 30.5, 16.5, 16.4, 14.3.

FTIR (neat): υ 3443, 2982, 2828, 2901, 1704, 1632, 1618, 1584, 1445, 1368, 1393, 1231, 1188, 1148, 1133, 1018, 961, 894, 844, 786, 714.

HRMS (CI) Calcd. for $C_{14}H_{24}O_5P$ $[M+H]^+$: 303.1361, Found: 303.1363.

The spectroscopic properties of this compound were consistent with the data available in the literature.[4]

[4] Lira, R.; Roush, W. R. *Org. Lett.* **2007**, 9, 533.


(EtO)
(EtO)
P
O
CO2Et
9
8
7
6
5
4
3
2
1
0 ppm
1.10
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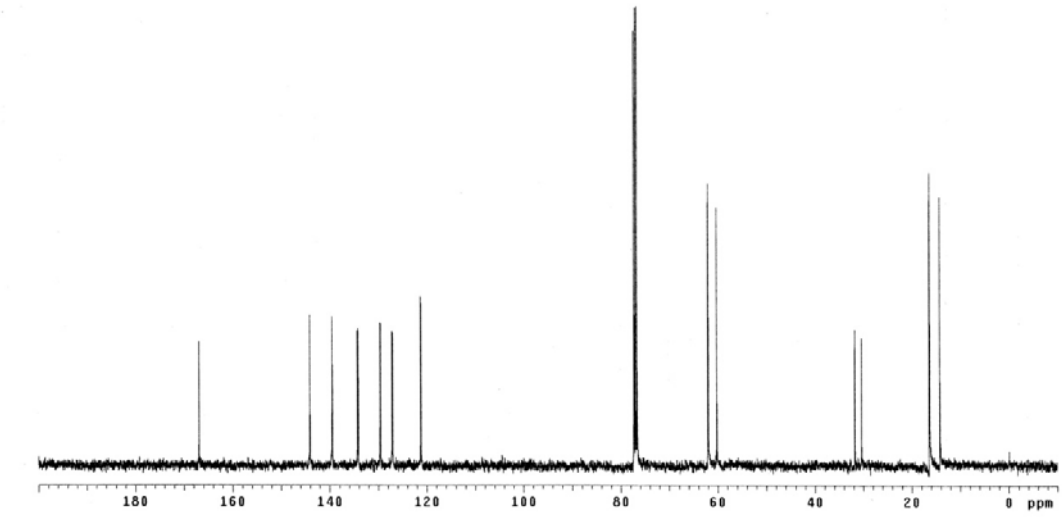
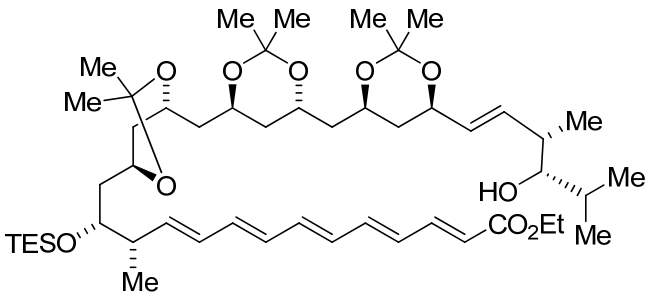
1.98
1.97
2.08
4.00
2.00
9.03


180
160
140
120
100
80
60
40
20
0 ppm

(2*E*,4*E*,6*E*,8*E*,10*E*,12*S*,13*R*)-ethyl 14-((4*R*,6*R*)-6-(((4*S*,6*S*)-6-(((4*R*,6*R*)-6-((3*S*,4*S*,*E*)-4-hydroxy-3,5-dimethylhex-1-enyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)methyl)-2,2-dimethyl-1,3-dioxan-4-yl)-12-methyl-13-(triethylsilyloxy)tetradeca-2,4,6,8,10-pentaenoate (7c-1)



7c-1

This entire experimental procedure was performed in the dark.

To a stirred solution of $EtO_2C(CH{=}CH)_3CH_2PO(OEt)_2$ **B** (34 mg, 0.111 mmol, 300 mol%) in THF (1.11 mL. 0.1 M) was added LHMDS (0.11 mL, 1.0 M in THF, 0.111 mmol, 300 mol%) at -78 ^oC. The reaction mixture was stirred for 30 min at -78 ^oC, and a solution of **7c** (28 mg, 0.037 mmol, 100 mol%) in THF (0.37 mL. 0.1 M) was added slowly -78 ^oC. The resulting solution was stirred for 30 min at -78 ^oC and gradually warmed to ambient temperature. The reaction mixture was stirred for an additional 8 hr, and then quenched with saturated aq. NH_4Cl. The resulting solution was extracted with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified by column chromatography (SiO_2: ethyl acetate:hexanes, 1:7 to 1:5 with 0.1% TEA) to give **7c-1** (59 mg, 0.067 mmol) as a yellow oil in 61% yield.

TLC (SiO_2): R_f = 0.55 (ethyl acetate:hexanes, 1:3).

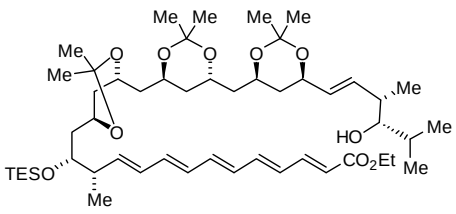
$[\alpha]_D^{26}$ = -11.0 (*c* = 1.0, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 (dd, *J* = 14.8, 11.2 Hz, 1H), 6.59 (dd, *J* = 14.4, 11.2 Hz, 1H), 6.42 (dd, *J* = 14.0, 10.4 Hz, 1H), 6.34-6.25 (m, 3H), 6.20 (dd, *J* = 14.8, 10.4 Hz, 1H), 6.07 (dd, *J* = 15.2, 10.0 Hz, 1H), 5.85 (d, *J* = 14.8 Hz, 1H), 5.74 (dd, *J* = 15.2, 8.0 Hz, 1H), 5.62 (dd, *J* = 15.6, 6.8 Hz, 1H), 5.49 (dd, *J* = 14.8, 5.2 Hz, 1H), 4.28-4.36 (m, 1H), 4.20 (q, *J* =7.2 Hz, 2H), 4.10-3.96 (m, 4H), 3.96-3.86 (m, 1H), 3.76-3.68 (m, 1H), 3.20-3.12 (m, 1H), 2.37-2.33 (m, 2H), 1.74-1.67 (m, 1H), 1.56-1.44 (m, 8H), 1.43 (s, 3H), 1.38 (s, 6H), 1.33 (s, 3H), 1.31 (s, 6H), 1.28-1.21 (m, 4H), 1.03-0.87 (m, 24H), 0.59 (q, *J* = 8.0 Hz, 6H).

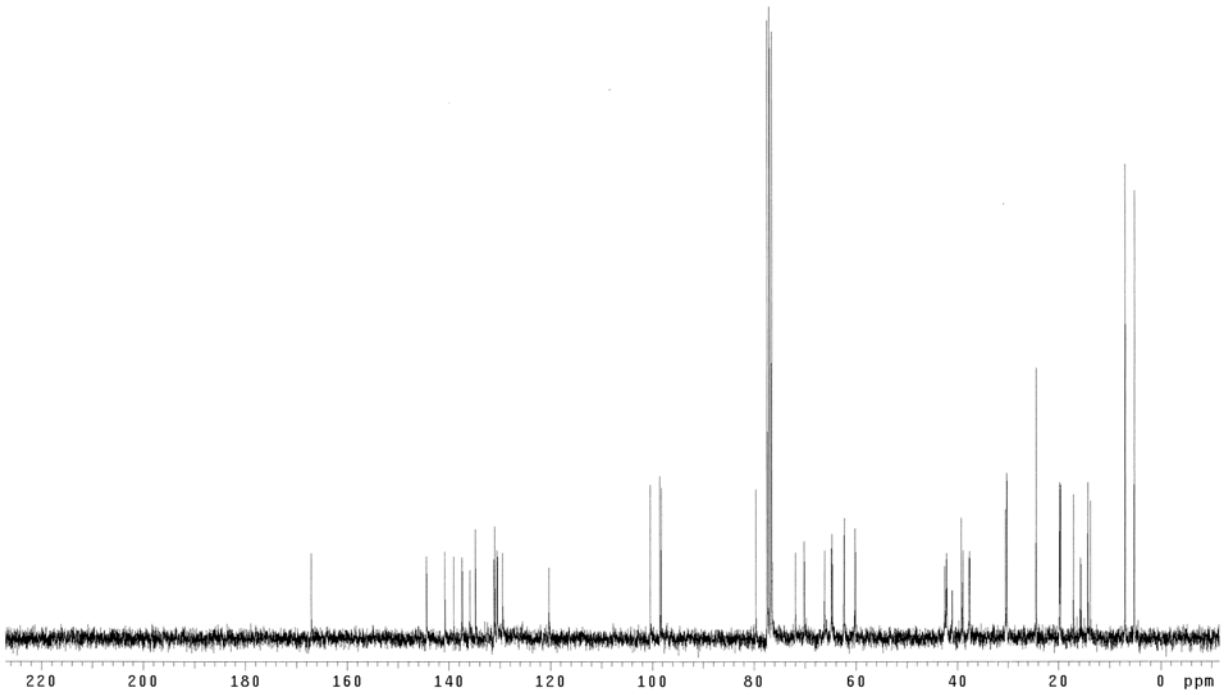
^{13}C NMR (75 MHz, $CDCl_3$): δ 167.1, 144.4, 140.8, 139.0, 137.4, 135.9, 134.8, 131.2, 131.0, 130.6, 130.5, 129.5, 120.3, 100.4, 98.6, 98.3, 79.6, 71.9, 70.2, 66.2, 64.9, 64.7, 62.4, 62.3, 60.2, 42.6, 42.3, 42.1, 41.1, 39.2, 38.9, 37.6, 30.5, 30.2, 30.1, 24.4, 19.8, 19.7,19.6, 17.1, 15.7, 14.3, 13.7, 6.9, 5.1.

FTIR (neat): υ 3510, 2952, 2875, 1708, 1622, 1578, 1459, 1379, 1300, 1248, 1224, 1199, 1168, 1128, 1007, 937, 912, 874, 817, 737 cm^{-1}.

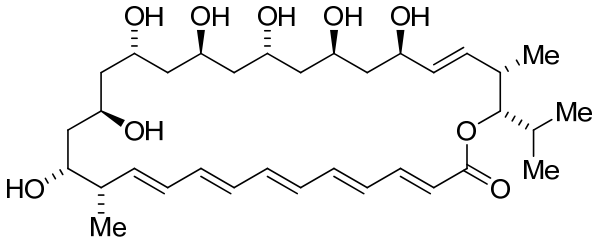
HRMS (ESI) Calcd. for $C_{51}H_{86}O_{10}Si$ $[M+Na]^+$: 909.5882, Found: 909.5880.


Me Me Me Me
Me
Me
O
O O O O
Me
HO
Me
O
TESO
CO2Et
Me
Me

10 9 8 7 6 5 4 3 2 1 -0 ppm
0.97
4.05
0.86
0.84
4.57
11.32
4.86


220 200 180 160 140 120 100 80 60 40 20 0 ppm

(3*E*,5*E*,7*E*,9*E*,11*E*,13*S*,14*R*,16*R*,18*R*,20*S*,22*S*,24*R*,26*R*,27*E*,29*S*,30*S*)-14,16,18,20,22,24,26-heptahydroxy-30-isopropyl-13,29-dimethyloxacyclotriaconta-3,5,7,9,11,27-hexaen-2-one



(+)-Roxaticin

This entire experimental procedure was performed in the dark.

To a stirred solution of **7c-1** (59 mg, 0.067 mmol, 100 mol%) in 4:1:1 THF/MeOH/H_2O (3.35 mL, 0.02 M) was added LiOH (0.34 mL, 1.0 M in H_2O, 0.335 mmol, 500 mol%) at ambient temperature. The reaction mixture was stirred for 6 hr at ambient temperature, and diluted with saturated aq. NH_4Cl. The resulting solution was extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. The resulting seco-acid was employed directly in the next reaction.

To a stirred solution of the seco-acid in THF (3.35 mL, 0.02 M) were added Et_3N (19 μL, 0.134 mmol, 200 mol%) and 2,4,6-trichlrobenzoyl chloride (16 μL, 0.101 mmol, 150 mol%). The reaction mixture was stirred for 3 hr at ambient temperature, filtered through the pad of celite and diluted with toluene (10 mL). This solution was added over a period of 8 hr using a syringe pump to a solution of 4-dimethylaminopyridine (327 mg, 2.68 mmol, 4000 mol%) in toluene (133 mL, 0.02 M) at 50 ^oC. The reaction mixture was stirred for an additional 4 hr, and toluene was removed under reduced pressure. The cloudy oil was diluted in 1:1 hexanes/ethyl acetate, filtered through a silica plug over a pad of celite and washed with 1:1 hexanes/ethyl acetate, then concentrated under reduced pressure to afford a bright yellow oil. The resulting oil was used directly in the next reaction.

A solution of protected crude roxaticin in MeOH (5 mL) was treated with Dowex 50Wx8 acidic resin (100 mg). After being stirred for 4 hr, the mixture was filtered and concentrated in vacuo. Purification by preparative reverse-phase thin-layer chromatography (RP-18, 100x100x0.25 mm, two plate, 10% H_2O/MeOH) gave **(+)-roxaticin** (12.6 mg, 0.0208 mmol, 31% yield) as a yellow solid.

$[\alpha]_D^{26}$ = +11.3 (*c* = 0.17, dioxane)[5]

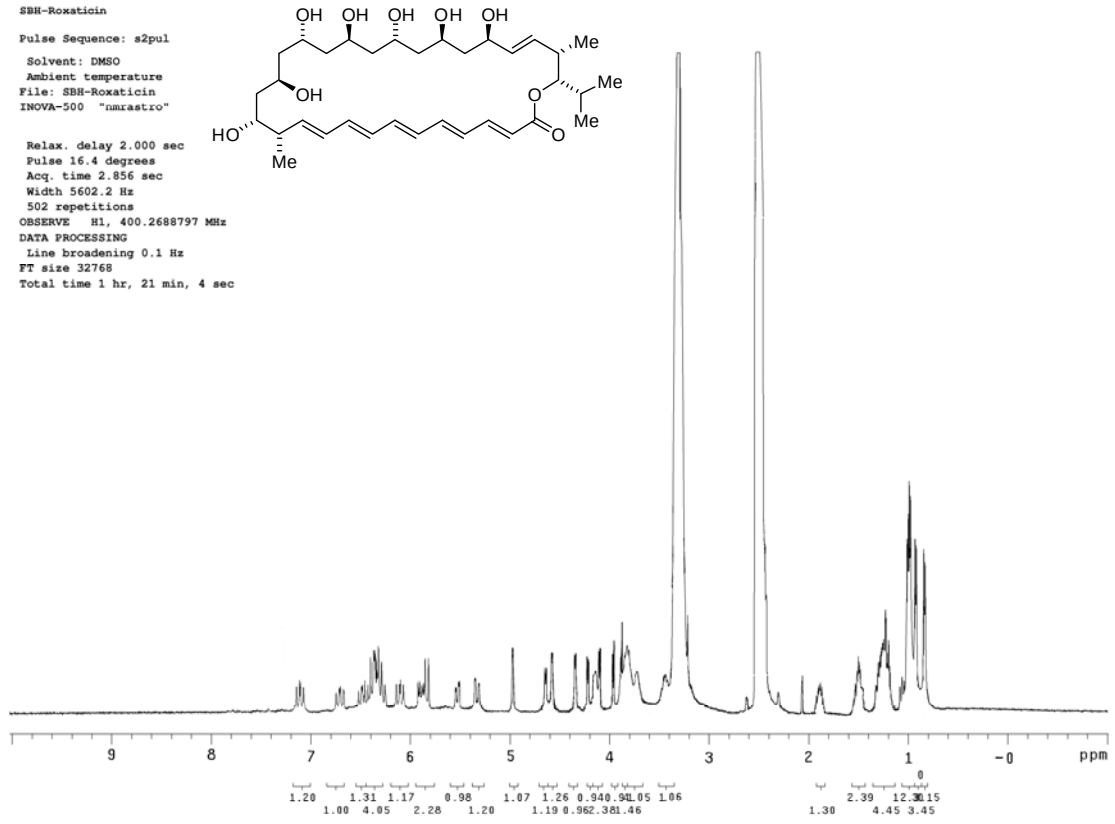
^{1}H NMR (400 MHz, DMSO- d_6): δ 7.11 (dd, *J* = 15.6, 11.6 Hz, 1H), 6.69 (dd, *J* = 15.2, 10.8 Hz, 1H), 6.47 (dd, *J* = 14.4, 11.2 Hz, 1H), 6.42-6.26 (m, 4H), 6.10 (dd, *J* = 15.2, 10.0 Hz, 1H), 5.88 (dd, *J* = 15.6, 7.2 Hz, 1H), 5.82 (d, *J* = 15.2 Hz, 1H), 5.54 (dd, *J* = 15.6, 5.1 Hz, 1H), 5.34 (dd, *J* = 16.0, 3.6 Hz, 1H), 5.01 (s, 1H), 4.65 (dd, *J* = 7.2, 2.5 Hz, 1H), 4.59 (d, *J* = 3.6 Hz, 1H), 4.36 (d, *J* = 4.0 Hz, 1H), 4.20 (d, *J* = 5.4 Hz, 1H), 4.15 (m, 1H), 4.12 (d, *J* = 5.0 Hz, 1H), 3.93 (d, *J* = 5.8 Hz, 1H), 3.84 (m, 1H), 3.98-3.72 (m, 5H), 3.42 (m, 1H), 2.55 (m, 2H), 1.86 (m 1H), 1.48 (m, 2H), 1.40-0.99 (m, 10H), 1.00 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H),

^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1, 144.6, 141.1,139.2, 137.6, 135.7, 133.1, 131.0, 130.4, 129.4, 129.1, 128.7, 120.2, 79.3, 71.0, 69.8, 67.7, 64.9, 64.3, 62.9, 62.4, 47.3, 46.7, 46.6, 44.4, 44.3, 42.6, 40.9, 35.7, 28.8, 19.7, 18.7, 13.7, 10.8.

FTIR (neat): υ 3410, 1708, 1612, 1588, 1379, 1304, 1268, 1138, 1007, 933, 910, 872, 737 cm^{-1}.

HRMS (ESI) Calcd. for $C_{41}H_{73}O_9Si_1$ $[M+Na]^+$: 629.3600, Found: 629.3663.

[5](a) $[\alpha]^{25}_D$ +8.63 (*c*=0.15, dioxane) (Maehr, H.; Yang, R.; Liu, C.-M.; Hatada, M. H.; Todaro, L. J. *J. Org. Chem.* **1989**, *54*, 3816.); (b) $[\alpha]^{25}_D$ +14 (*c*=0.13, dioxane) (Evans, D.; Connell, B. T. *J. Am.Chem. Soc.,* **2003,** *125***,** 10899.)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Solvent: DMSO
Ambient temperature
File: SBH-Roxaticin
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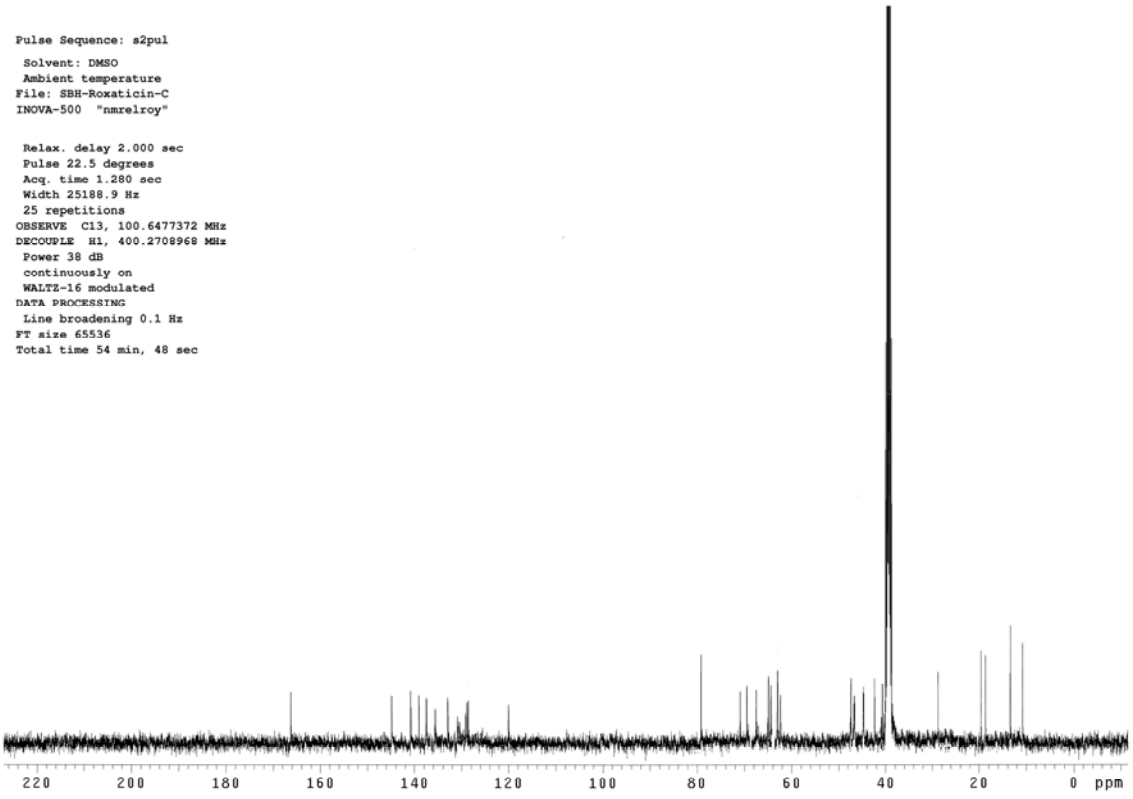
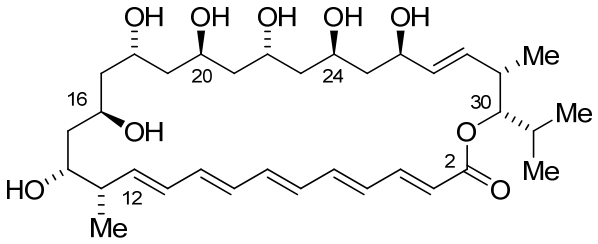
Relax. delay 2.000 sec
Pulse 16.4 degrees
Acq. time 2.856 sec
Width 5602.2 Hz
502 repetitions
OBSERVE H1, 400.2688797 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 1 hr, 21 min, 4 sec
OH
OH
OH
OH
OH
Me
Me
Me
OH
HO
Me
O
O
9
8
7
6
5
4
3
2
1
-0
ppm
1.20
1.31
1.17
0.98
1.07
1.26
0.94
0.94
1.05
1.06
1.00
4.05
2.28
1.20
1.19
0.96
2.38
1.46
1.30
2.39
12.30
3.15
4.45
3.45


Pulse Sequence: s2pul
Solvent: DMSO
Ambient temperature
File: SBH-Roxaticin-C
INOVA-500 "nmrelroy"
Relax. delay 2.000 sec
Pulse 22.5 degrees
Acq. time 1.280 sec
Width 25188.9 Hz
25 repetitions
OBSERVE C13, 100.6477372 MHz
DECOUPLE H1, 400.2708968 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 54 min, 48 sec
220
200
180
160
140
120
100
80
60
40
20
0
ppm

IV. ^{1}H NMR Comparison for Roxaticin (d_6-DMSO)



	Natural Roxaticin[6]	Krische	Rychnovsky	Mori	Evans
Me$_2$CH	0.84 (d, 6.5)	0.84 (d, 6.6)	0.83 (d, 6.1)	0.84 (d, 6.6)	0.84 (d, 6.6)
Me$_2$CH	0.93 (d, 6.5)	0.92 (d, 6.6)	0.92 (d, 7.3)	0.93 (d, 6.6)	0.92 (d, 7.0)
C$_{13}$-*Me*	0.99 (d, 6.5)	0.98 (d, 6.6)	0.97 (d, 7.3)	0.99 (d, 6.7)	0.97 (d, 6.6)
C$_{29}$-*Me*	1.01 (d, 7.5)	1.00 (d, 6.9)	1.00 (d, 6.1)	1.01 (d, 6.8)	1.00 (d, 7.0)
H$_{15,17,19,21,23,25}$	0.95–1.34, 1.16–1.34, 1.49 (m)	0.99–1.40, 1.48 (m)	1.00–1.30 (m), 1.49 (m)	1.00–1.40, 1.49 (m)	0.99–1.32, 1.48 (m)
Me$_2$C*H*	1.87 (m)	1.86 (m)	1.86 (m)	1.87 (m)	1.86 (m)
H$_{13,29}$	2.55 (m)	2.55 (m)	2.55 (m)	2.55 (m)	2.55 (m)
H$_{14,16,18,20,22,24}$	3.42, 3.71–3.89 (m)	3.42, 3.72–3.98 (m)	3.42, 3.73 (s)	3.42, 3.71–3.98 (m)	3.42, 3.83 (m)
CH*OH*	3.88 (d, 6.0)	3.84 (m)	3.83 (m)	3.87 (d, 4.6)	3.83 (m)
CH*OH*	3.94 (d, 6.0)	3.93 (d, 5.8)	3.93 (d, 6.1)	3.93 (d, 5.6)	3.93 (d, 5.9)
CH*OH*	4.13 (d, 6.0)	4.12 (d, 5.0)	4.11 (d, 4.9)	4.12 (d, 5.1)	4.11 (d, 4.4)
H$_{26}$	4.16 (m)	4.15 (m)	4.15 (m)	4.15 (m)	4.15 (m)
CH*OH*	4.22 (d, 5.0)	4.20 (d, 5.4)	4.20 (d, 4.9)	4.21 (d, 5.4)	4.20 (d, 5.9)
CH*OH*	4.38 (d, 4.5)	4.36 (d, 4.0)	4.35 (d, 3.7)	4.36 (d, 3.9)	4.36 (d, 4.4)
CH*OH*	4.60 (d, 4.0)	4.59 (d, 3.6)	4.58 (d, 3.7)	4.59 (d, 2.9)	4.59 (d, 3.7)
H$_{30}$	4.66 (dd, 7.0, 2.5)	4.65 (dd, 7.2, 2.5)	4.64 (d, 7.3)	4.66 (dd, 9.5, 2.5)	4.64 (dd, 7.0, 2.6)
CH*OH*	5.00 (d, 2.5)	5.01 (s)	4.98 (s)	4.99 (s)	4.99 (s)
H$_{28}$	5.35 (dd, 15.5, 3.0)	5.34 (dd, 16.0, 3.6)	5.34 (d, 15.9)	5.35 (dd, 16.4, 3.6)	5.33 (dd, 15.8, 3.3)
H$_{27}$	5.55 (dd, 15.5, 4.4)	5.54 (dd, 15.6, 5.1)	5.50 (dd, 15.9, 3.7)	5.55 (dd, 15.4, 5.1)	5.53 (dd, 15.5, 5.0)
H$_3$	5.83 (d, 15.5)	5.82 (d, 15.2)	5.81 (d, 14.6)	5.83 (d, 15.1)	5.82 (d, 15.0)
H$_{12}$	5.89 (dd, 15.5, 7.0)	5.88 (dd, 15.6, 7.2)	5.87 (dd, 14.6, 6.1)	5.89 (dd, 15.1, 7.3)	5.89 (dd, 15.1, 7.0)
H$_{11}$	6.12 (dd, 15.5, 10.0)	6.10 (dd, 15.2, 10.0)	6.10 (dd, 14.6, 11.0)	6.12 (dd, 15.4, 10.7)	6.10 (dd, 14.4, 11.2)
H$_9$	6.28 (dd, 15.5, 10.0)	6.26–6.42 (m)	6.25–6.41 (m)	6.25–6.43 (m)	6.26–6.41 (m)
H$_7$	6.33 (dd, 14.5, 10.0)	6.26–6.42 (m)	6.25–6.41 (m)	6.25–6.43 (m)	6.26–6.41 (m)
H$_{10}$	6.36 (dd, 15.0, 10.0)	6.26–6.42 (m)	6.25–6.41 (m)	6.25–6.43 (m)	6.26–6.41 (m)
H$_5$	6.40 (dd, 15.0, 11.0)	6.26–6.42 (m)	6.25–6.41 (m)	6.25–6.43 (m)	6.26–6.41 (m)
H$_8$	6.48 (dd, 14.5, 10.0)	6.47 (dd, 14.4, 11.2)	6.47 (dd, 14.6, 11.0)	6.48 (dd, 15.1, 10.7)	6.47 (dd, 14.4, 11.2)
H$_6$	6.70 (dd, 15.0, 10.0)	6.69 (dd, 15.2, 10.8)	6.69 (dd, 14.6, 11.0)	6.70 (dd, 14.4, 11.2)	6.70 (dd, 14.4, 11.2)
H$_4$	7.13 (dd, 15.5, 11.0)	7.11 (dd, 15.6, 11.6)	7.11 (dd, 15.9, 12.2)	7.12 (dd, 15.4, 11.7)	7.11 (dd, 15.5, 11.7)