Supporting Information

Formal Synthesis of Premisakinolide A and C(19)–C(32) of Swinholide A via Site-Selective C–H Allylation and Crotylation of Unprotected Diols

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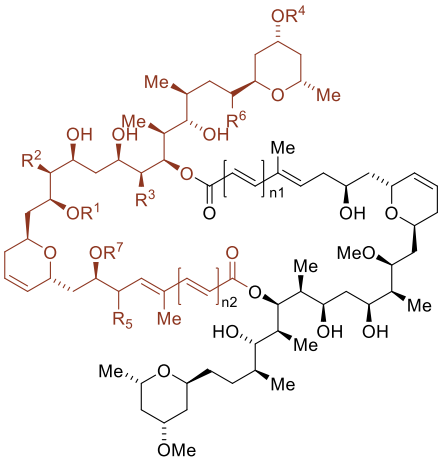
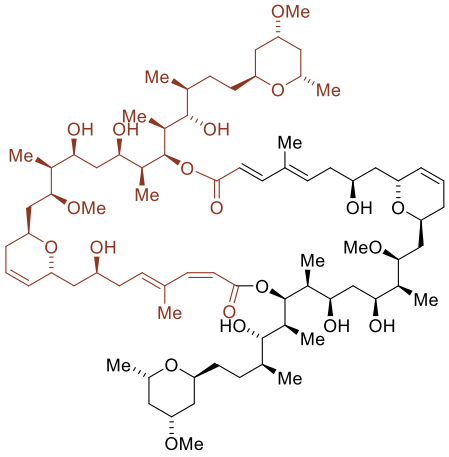
Contents:

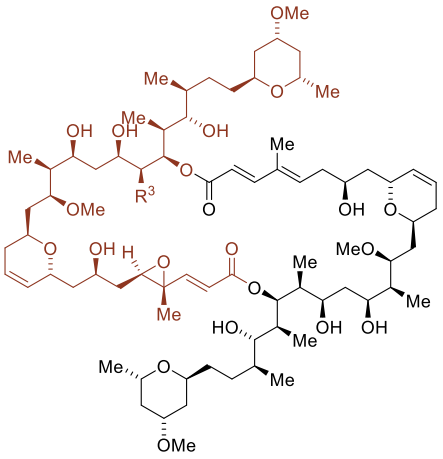
Figure S1. Swinholide A and Congeners.



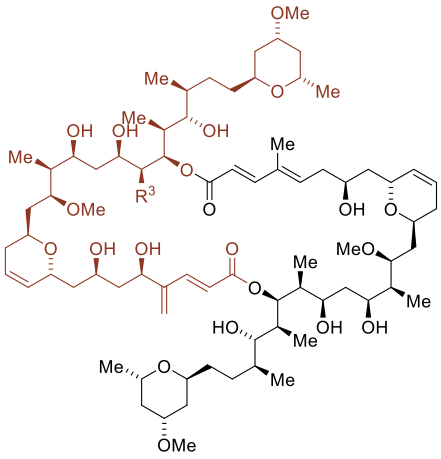


swinholide A, $R^1 = R^2 = R^3 = R^4 = Me$, $R^5 = R^6 = R^7 = H$, n1 = n2 = 1
swinholide B, $R^1 = R^3 = R^4 = Me$, $R^2 = R^5 = R^6 = R^7 = H$, n1 = n2 = 1
swinholide C, $R^1 = R^2 = R^3 = Me$, $R^4 = R^5 = R^6 = R^7 = H$, n1 = n2 = 1
swinholide D, $R^1 = R^5 = R^6 = R^7 = H$, $R^2 = R^3 = R^4 = Me$, n1 = n2 = 1
swinholide E, $R^1 = R^2 = R^3 = R^4 = Me$, $R^5 = OH$, $R^6 = R^7 = H$, n1 = n2 = 1
swinholide G, $R^1 = R^2 = R^4 = Me$, $R^3 = R^5 = R^6 = R^7 = H$, n1 = n2 = 1
swinholide H, $R^1 = R^2 = R^3 = R^4 = R^7 = Me$, $R^5 = R^6 = H$, n1 = n2 = 1
swinhilide I, $R^1 = R^2 = R^3 = R^4 = Me$, $R^5 = R^7 = H$, $R^6 = OH$, n1 = n2 = 1
misakinolide A = bistheonellide A, $R^1 = R^2 = R^3 = R^4 = Me$, $R^5 = R^6 = R^7 = H$, n1 = n2 = 0
bistheonellide B, $R^1 = R^3 = R^4 = Me$, $R^2 = R^5 = R^6 = R^7 = H$, n1 = n2 = 0
bistheonellide C, $R^2 = R^3 = R^4 = Me$, $R^2 = R^5 = R^6 = R^7 = H$, n1 = n2 = 0
hurghadolide A, $R^1 = R^2 = R^3 = R^4 = Me$, $R^5 = R^7 = H$, n1 = 1, n2 = 0

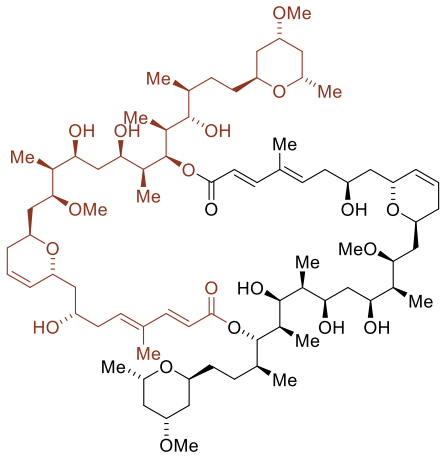
swinholide F



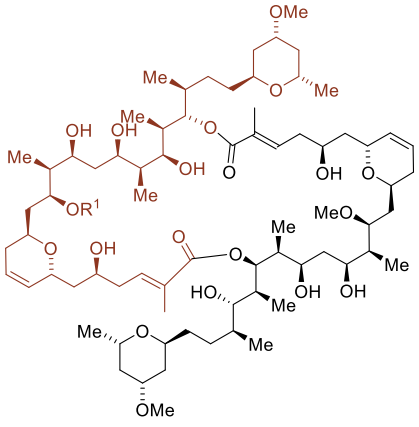
swinholide J



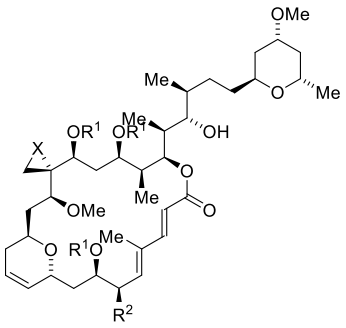
swinholide K



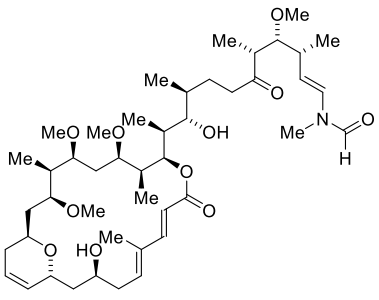
isoswinholide A



isobistheoneliide



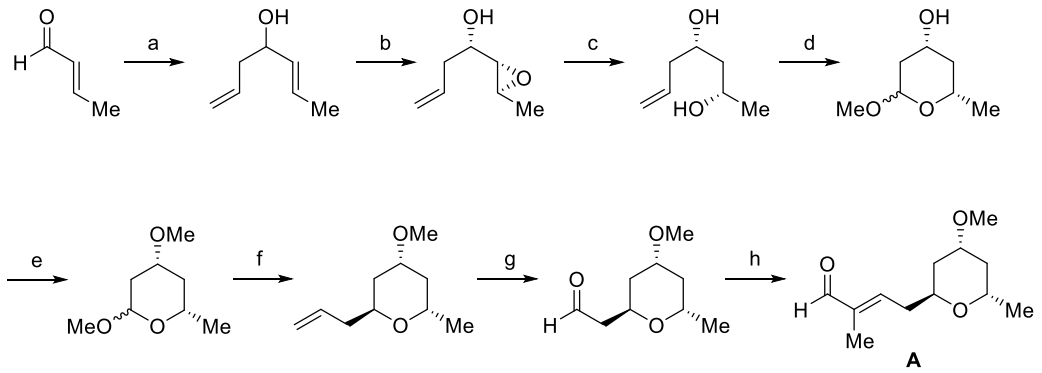
hemiswinholide A, $R^1 = R^2 = H$, $X = H_2$
lobophorolide, $R^1 = Me$, $R^2 = OH$, $X = O$



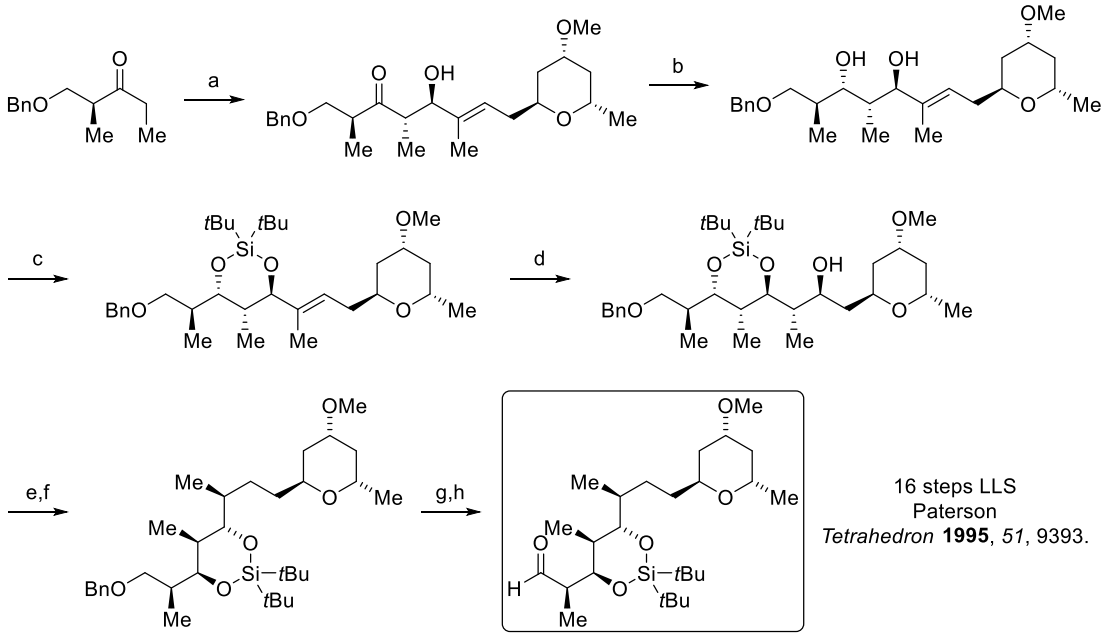
scytophycin C

Summaries of Previous Syntheses

A. Paterson, I; Cumming, J. G.; Ward, R. A.; Lamboley, S. *Tetrahedron* **1995**, *51*, 9393.



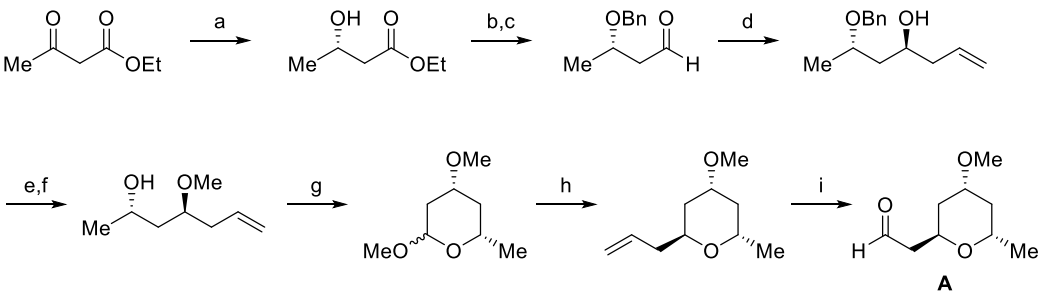
(a) allyl bromide, Zn, DMF; (b) (+)-DIPT, $Ti(OiPr)_4$, *t*BuOOH, 4A, MS, CH_2Cl_2, then DMS; (c) Red-Al, THF; (d) O_3, MeOH, then DMS, 1M HCl; (e) NaH, MeI, THF; (f) allyl-TMS, Me_3SiOTf, MeCN; (g) O_3, CH_2Cl_2, MeOH, $NaHCO_3$, then DMS; (h) $Ph_3P{=}C(Me)CHO$, toluene.



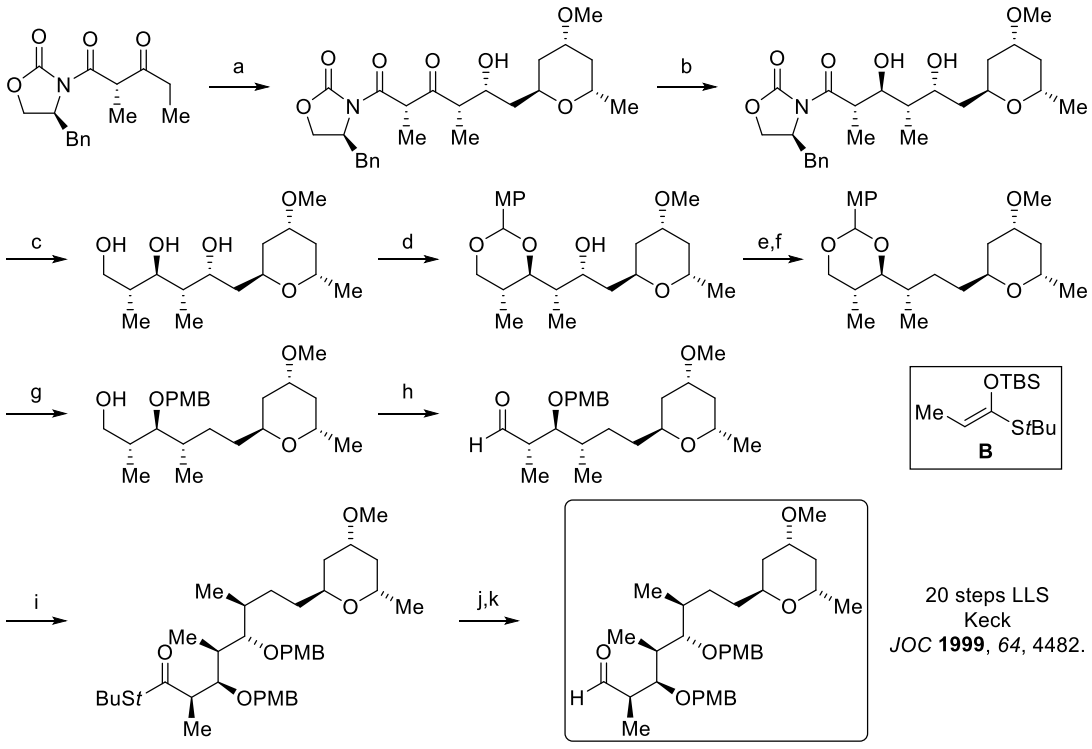
16 steps LLS
Paterson
Tetrahedron **1995**, *51*, 9393.

(a) $(c\text{-}C_6H_{11})_2BCl$, Et_3N, Et_2O, then **A**, then H_2O_2, pH7 buffer, MeOH; (b) $Me_4NBH(OAc)_3$, AcOH, MeCN; (c) $tBu_2Si(OTf)_2$, 2,6-lutidine, CH_2Cl_2; (d) Thexylborane, THF, then H_2O_2/NaOH; (e) $(Imid)_2C{=}S$, THF; (f) nBu_3SnH, toluene; (g) H_2, Pd/C, EtOH; (h) $(COCl)_2$, DMSO, CH_2Cl_2, then Et_3N.

B. Keck, G. E.; Lundquist, G. D. *J. Org. Chem.* **1999**, *64*, 4482.

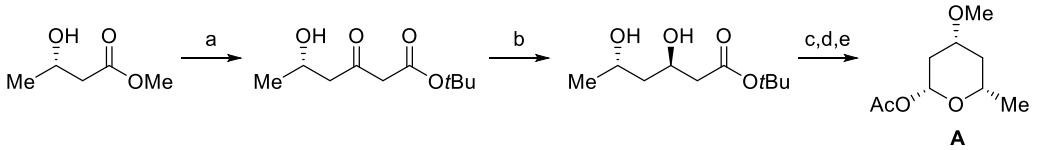


(a) RuBINAP, H_2; (b) $CCl_3C(NH)OBn$, H^+; (c) DIBAL, CH_2Cl_2; (d) $TiCl_4$, then allyl-$Sn(Ph)_3$; (e) KH, MeI; (f) Li/NH_3; (g) O_3, MeOH, then DMS, 1M HCl; (h) allyl-TMS, TMSOTf; (i) O_3, CH_2Cl_2, then PPh_3.

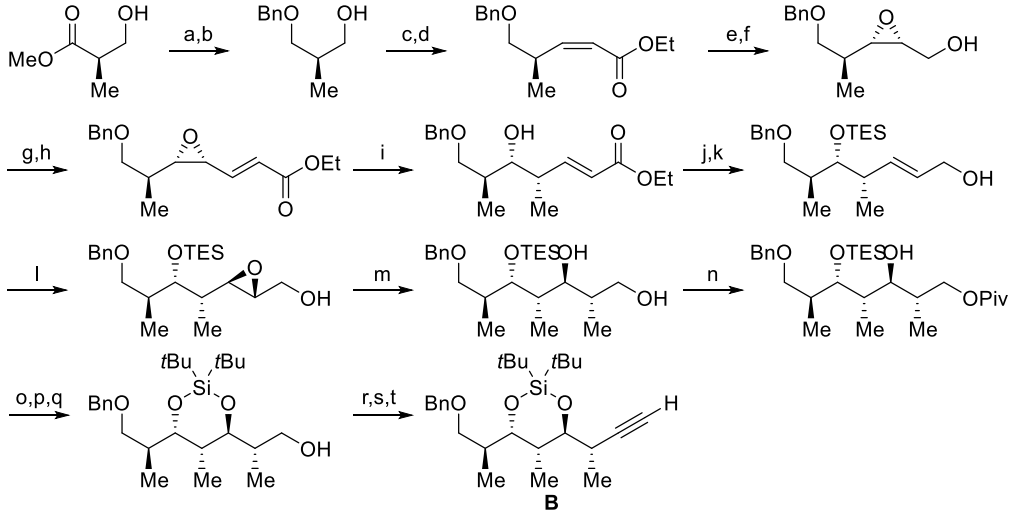


(a) **A**, $TiCl_4$, *i*Pr_2NEt; (b) $Me_4NBH(OAc)_3$; (c) $LiBH_4$, Et_2O; (d) PMBOMe, DDQ; (e) TCDI, THF; (f) Bu_3SnH, toluene; (g) DIBAL, CH_2Cl_2; (h) Dess-Martin periodinane, CH_2Cl_2; (i) **B**, $BF.OEt_2$, CH_2Cl_2; (j) $Cl_3CC(NH)OPMB$, CSA; (k) DIBAL.

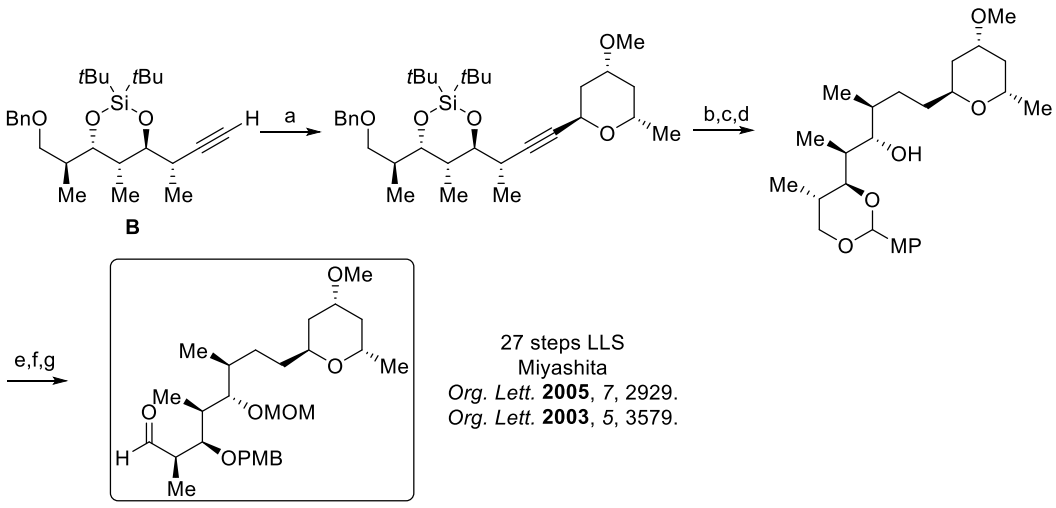
C. Nakamura, R.; Tanino, K.; Miyashita, M. *Org. Lett.* **2005**, *7*, 2929.



(a) CH_3CO_2tBu, LDA, THF; (b) $Me_4NBH(OAc)_3$, AcOH, CH_3CN; (c) PPTS, $ClCH_2CH_2Cl$; (d) MeI, Ag_2O, MS 4A, Et_2O, CH_2Cl_2; (e) DIBAL, CH_2Cl_2, then pyridine, DMAP, $(CH_3CO)_2O$.



(a) $BnOC(=NH)CCl_3$, TfOH, CH_2Cl_2; (b) $LiAlH_4$, THF; (c) DMSO, $(COCl)_2$, CH_2Cl_2, then Et_3N; (d) di-*o*-tolyl ethoxycarbonyl-methyl phosphate, NaH, THF; (e) DIBAL, THF; (f) *m*-CPBA, CH_2Cl_2; (g) DMSO, $(COCl)_2$, CH_2Cl_2, then Et_3N; (h) triethyl phosphonoacetate, NaH, THF; (i) $(CH_3)_3Al$, CH_2Cl_2, then H_2O; (j) TESCl, DMAP, imidazole, CH_2Cl_2; (k) DIBAL, THF; (l) *m*-CPBA, CH_2Cl_2; (m) Me_3CuLi, Et_2O; (n) *t*-BuCOCl, pyridine, Ch_2Cl_2; (o) TBAF, THF; (p) $tBu_2Si(OTf)_2$, 2,6-lutidine, CH_2Cl_2; (q) DIBAL, THF; (r) DMSO, $(COCl)_2$, CH_2Cl_2, then Et_3N; (s) Ph_3P, CBr_4, pyridine, CH_2Cl_2; (t) BuLi, THF.

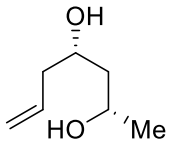


27 steps LLS
Miyashita
Org. Lett. **2005**, *7*, 2929.
Org. Lett. **2003**, *5*, 3579.

(a) BuLi, Me_2AlOTf, then **A**, CH_2Cl_2; (b) H_2, $Pd(OH)_2/C$, AcOEt; (c) HF-Py, THF; (d) 4-$MeOC_6H_4CH(OMe)_2$, CSA, DMF; (e) MOMCl, iPr_2NEt, $ClCH_2CH_2Cl$; (f) DIBAL, CH_2Cl_2; (g) Dess-Martin periodinane, CH_2Cl_2.

General Considerations.

Tetrahydrofuran (THF), diethyl ether (Et_2O) and 1,4-dioxane were distilled from sodium/benzophenone, and dichloromethane (CH_2Cl_2) and dichloroethane (DCE) were distilled from calcium hydride under a nitrogen atmosphere. Triethylamine (Et_3N) was distilled prior to use. ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz with a Varian Gemini spectrometer. Chemical shifts are reported as parts per million (ppm) from trimethylsilane (TMS) or ppm relative to the deuteriochloroform ($CDCl_3$), 7.26 ppm for ^1H NMR and 77.16 ppm for ^{13}C NMR, respectively. Infrared spectra were recorded on a Thermo Nicolet 380 spectrometer. Specific rotations were measured using an Atago AP-300 automatic polarimeter and are reported as the average value of three measurements. Analytical thin layer chromatography (TLC) was performed on TLC silica gel plates (250 μm) precoated with a fluorescent indicator. Standard flash column chromatography procedures were followed using 40–63 μm silica gel. Visualization was effected with *p*-anisaldehyde solution.



(2*S*,4*S*)-Hept-6-ene-2,4-diol (2).

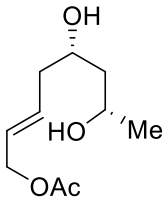
To a sealed tube under an argon atmosphere charged with (*S*)-butane-1,3-diol **1** (1.0 g, 11.10 mmol, 100 mol%), $[Ir(cod)Cl]_2$ (186 mg, 0.278 mmol, 2.5 mol%), (*S*)-Cl,MeO-BIPHEP (362 mg, 0.555 mmol, 5 mol%), Cs_2CO_3 (723 mg, 2.22 mmol, 20 mol%) and 4-Cl-3-NO_2-BzOH (224 mg, 1.11 mmol, 10 mol%) was added freshly distilled THF (56 mL) and allyl acetate (12.0 mL, 111.0 mmol, 1000 mol%). The septum was quickly replaced with a screw cap and the reaction mixture was allowed to stir in an oil bath at 100 °C for 40 h. The reaction mixture was allowed to cool to ambient temperature, and evaporated onto silica gel. Purification by flash column chromatography (hexanes/EtOAc = 3:1 to 1:1) provided title compound **2** (1.07 g, 8.22 mmol, dr = >20:1) as a yellow oil in 74% yield, then (CH_2Cl_2/Et_2O = 3:1) provided the preformed catalyst (195 mg, 0.180 mmol) as a light yellow solid in 33% yield.

To a sealed tube under an argon atmosphere charged with (*S*)-butane-1,3-diol **1** (324 mg, 3.60 mmol, 100 mol%), recovered preformed catalyst (195 mg, 0.180 mmol, 5 mol%), and Cs_2CO_3 (235 mg, 0.720 mmol, 20 mol%) was added freshly distilled THF (18 mL) and allyl acetate (3.9 mL, 36.0 mmol, 1000 mol%). The septum was quickly replaced with a screw cap and the reaction mixture was allowed to stir in an oil bath at 100 °C for 40 h. The reaction mixture was allowed to cool to ambient temperature, and evaporated onto silica gel. Purification by flash column chromatography (hexanes/EtOAc = 3:1 to 1:1) provided title compound **2** (335 mg, 2.57 mmol, dr = >20:1) as a yellow oil in 71% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.29–5.75 (m, 1H), 5.18–5.13 (m, 1H), 5.13–5.08 (m, 1H), 4.23–4.08 (m, 1H), 4.04–3.93 (m, 1H), 2.75 (br s, 2H), 2.30–2.21 (m, 2H), 1.62–1.57 (m, 2H), 1.22 (d, J = 6.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 134.8, 118.2, 68.3, 65.4, 43.7, 42.1, 23.6.

Data is consistent with that reported in the literature.[a]



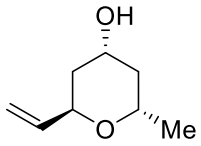
(5*S*,7*S*,*E*)-5,7-Dihydroxyoct-2-en-1-yl Acetate (3).

To a sealed tube under an argon atmosphere charged with diol **2** (1.42 g, 10.91 mmol, 100 mol%) and *cis*-1,4-diacetoxy-2-butene (7.5 g, 43.64 mmol, 400 mol%) was added freshly distilled CH_2Cl_2 (61 mL). The Grubbs second generation catalyst [$Cl_2(PCy_3)$(IMes)Ru=CHPh] (278 mg, 0.33 mmol, 3 mol%) was added in one portion. The septum was quickly replaced with a screw cap, and the reaction mixture was allowed to stir in an oil bath at 50 °C for 20 h. The reaction mixture was allowed to cool to ambient temperature, and was evaporated onto silica gel. Purification by flash column chromatography (hexanes/EtOAc = 3:2 to 1:2) provided title compound **3** (1.83 g, 9.05 mmol, *E:Z* = 5:1) as a brown oil in 83% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82–5.58 (m, 2H), 4.51 (dd, *J* = 6.2, 0.9 Hz, 2H), 4.17–4.05 (m, 1H), 4.01–3.91 (m, 1H), 2.98 (br s, 2H), 2.29–2.21 (m, 2H), 2.04 (s, 3H), 1.67–1.49 (m, 2H), 1.21 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, mixture of *E*- and *Z* isomer) δ 171.3, 171.1, 132.0, 131.0, 127.2, 126.2, 68.4, 68.2, 65.3, 65.1, 60.6, 43.9, 43.7, 40.5, 35.7, 23.6, 21.1.

Data is consistent with that reported in the literature.[a]



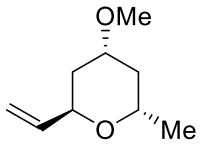
(2*S*,4*R*,6*R*)-2-Methyl-6-vinyltetrahydro-2H-pyran-4-ol (4).

To a round bottomed flask under an argon atmosphere charged with $Pd_2(dba)_3$-$CHCl_3$ (163 mg, 0.157 mmol, 3 mol%) and (*R*,*R*)-DACH-Phenyl Trost ligand (326 mg, 0.472 mmol, 9 mol%) was added freshly distilled CH_2Cl_2 (87 mL). The mixture was allowed to stir at ambient temperature for 30 minutes, during which time the color of the solution changed from purple to orange. The orange solution was cannulated to a round bottomed flask charged with a solution of acetate **3** (1.06 g, 5.24 mmol, 100 mol%) and Et_3N (1.5 mL, 10.48 mmol, 200 mol%) in CH_2Cl_2 (262 mL). The reaction mixture was allowed to stir at ambient temperature for 24 h. The reaction mixture was evaporated onto silica gel. Purification by flash column chromatography (hexanes/EtOAc = 4:1 to 1:1) provided title compound **4** (672 mg, 4.73 mmol, dr = 4:1) as a colorless oil in 90% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (ddd, *J* = 17.9, 10.6, 4.1 Hz, 1H), 5.26–5.22 (m, 1H), 5.22–5.17 (m, 1H), 4.65–4.54 (m, 1H), 3.93 (ddd, *J* = 15.4, 10.9, 4.5 Hz, 1H), 3.80–3.67 (m, 1H), 2.12–2.00 (m, 1H), 1.96–1.87 (m, 1H), 1.75–1.53 (m, 2H), 1.27–1.16 (m, 1H), 1.20 (d, *J* = 6.2 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 116.6, 73.2, 65.8, 64.5, 43.3, 37.3, 21.9.

Data is consistent with that reported in the literature.[a]



(2*S*,4*R*,6*R*)-4-Methoxy-2-methyl-6-vinyltetrahydro-2H-pyran (5).

To a round bottomed flask under an argon atmosphere charged with alcohol **4** (170 mg, 1.20 mmol, 100 mol%) was added freshly distilled THF (4 mL). The reaction mixture was cooled to 0 °C, and ^{t}BuOK (201 mg, 1.79 mmol, 150 mol%) was added in one portion at 0 °C. After stirring at 0 °C for 10 min, MeI (0.15 mL, 2.39 mmol, 200 mol%) was added slowly. The reaction mixture was gradually warmed to ambient temperature, and allowed to stir for additional 18 h. The mixture was quenched with H_2O and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (pentane/Et_2O = 6:1). Combined fractions were evaporated at 40 °C (750–800 mbar) to around 5% of solvents with product. Then Ar was bubbled through the solution to remove the rest of solvents to furnish title compound **5** (161 mg, 1.03 mmol) as a colorless liquid in 86%.*

* (2*S*,4*R*,6*R*)-4-Methoxy-2-methyl-6-vinyltetrahydro-2H-pyran **5** is volatile.

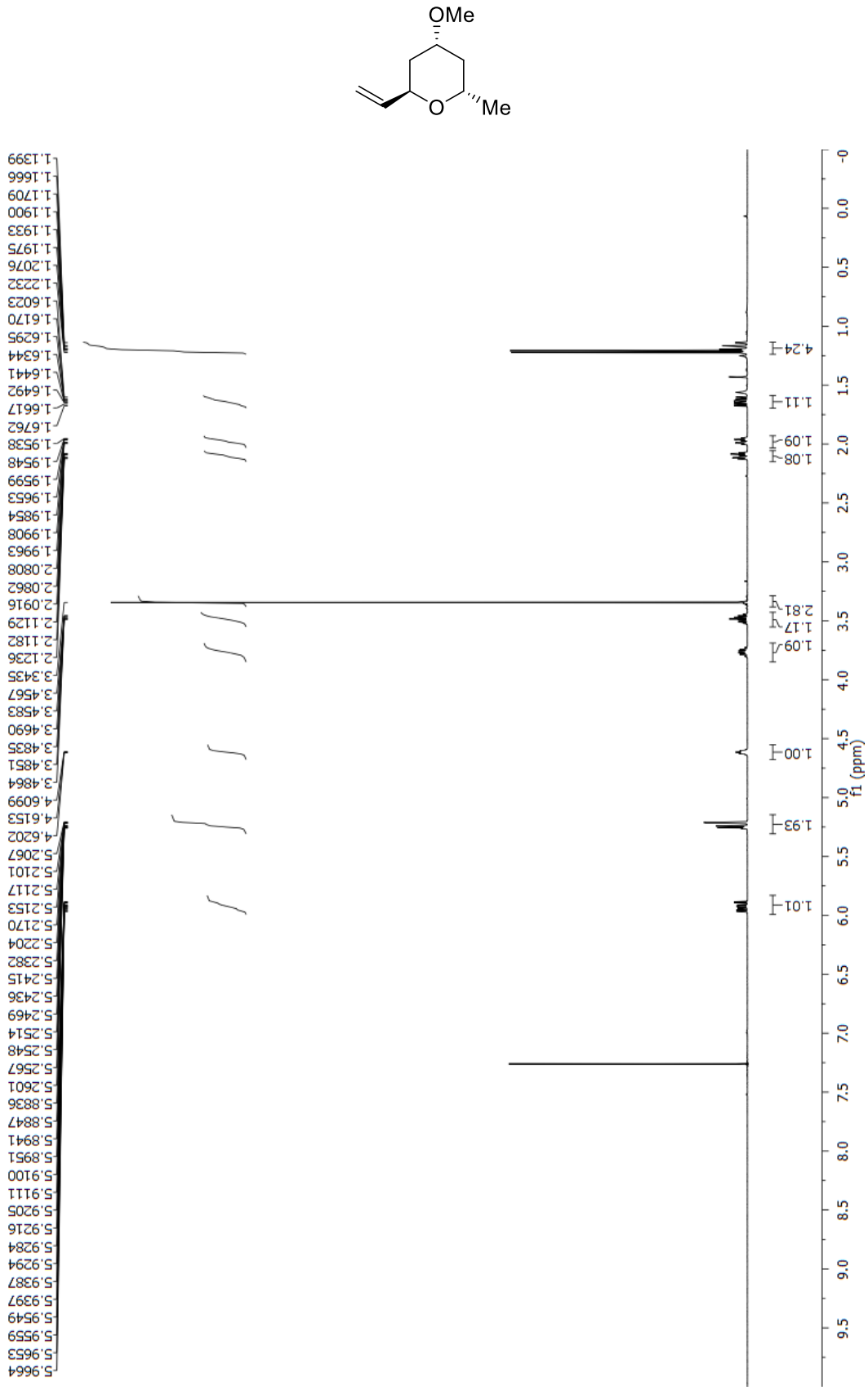
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 (ddd, *J* = 17.9, 10.6, 4.1 Hz, 1H), 5.25 (ddd, *J* = 5.2, 2.1, 1.4 Hz, 1H), 5.21 (ddd, *J* = 3.5, 1.4, 1.4 Hz, 1H), 4.65–4.58 (m, 1H), 3.81–3.72 (m, 1H), 3.53–3.44 (m, 1H), 3.34 (s, 3H), 2.10 (dddd, *J* = 12.8, 4.3, 2.2, 2.2 Hz, 1H), 1.98 (dddd, *J* = 12.4, 4.4, 2.2, 2.2 Hz, 1H), 1.64 (ddd, *J* = 16.8, 10.9, 5.9 Hz, 1H), 1.22 (d, *J* = 2.2 Hz, 3H), 1.24–1.13 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 116.3, 72.9, 72.7, 65.8, 55.2, 39.3, 33.9, 21.8.

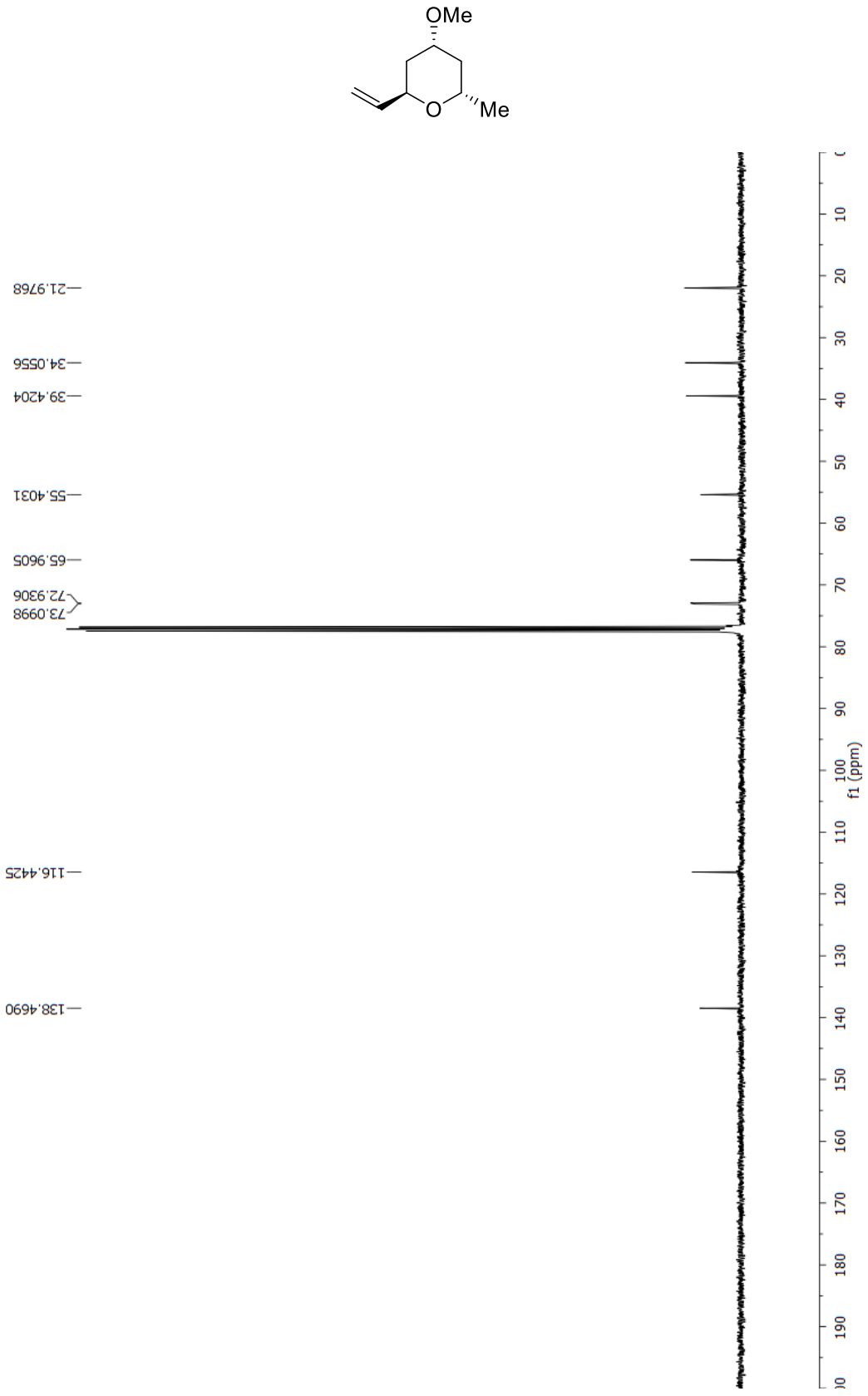
IR (neat) 2932, 1378, 1154, 1107, 1081, 917 cm^{-1}.

HRMS (ESI+) calcd. for $C_9H_{16}O_2Na$ $[M+Na]^+$ 179.1043, found 179.1040.

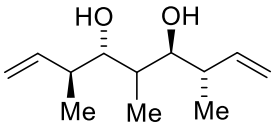
$[\alpha]_D^{25}$ = –68.05 ° (c = 0.72, $CHCl_3$).



^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of Compound **5**



^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of Compound **5**



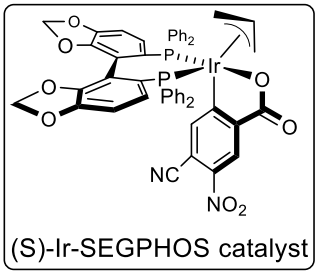
(3*S*,4*S*,6*S*,7*S*)-3,5,7-Trimethylnona-1,8-diene-4,6-diol (7).

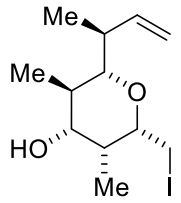
A sealed tube under an atmosphere of argon was charged with 2-methyl-1,3-propanediol **6** (1.26 g, 13.97 mmol, 100 mol%), (*S*)-Ir-SEGPHOS catalyst (360 mg, 0.35 mmol, 2.5 mol%), K_2CO_3 (3.9 g, 27.94 mmol, 200 mol%), H_2O (1 mL, 55.87 mmol, 400 mol%) and THF (14 mL). Freshly distilled crotyl acetate (8.0 g, 69.84 mmol, 500 mol%) was added and the mixture was sparged with Ar for 2 min. The reaction was heated to 70 °C for 7 d. The reaction mixture was cooled to ambient temperature and evaporated onto silica gel. The resulting residue was subjected to flash column chromatography (hexanes/EtOAc = 4:1) to furnish title compound **7** (1.41 g, 7.12 mmol, dr = 6:1) as a colorless viscous oil which solidified on standing in 51%. The major diastereomer could be separated by flash column chromatography.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85–5.73 (m, 2H), 5.15–5.09 (m, 4H), 3.65 (d, *J* = 9.6 Hz, 1H), 3.39–3.37 (m, 1H), 2.80 (s, 1H), 2.54 (d, *J* = 4.0 Hz, 1H), 2.46–2.40 (m, 1H), 2.31–2.25 (m, 1H), 1.89–1.86 (m, 1H), 1.03 (d, *J* = 7.2 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 1H), 0.94 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 141.0, 116.5, 116.0, 79.3, 73.9, 42.3, 42.0, 34.8, 17.2, 16.5, 10.7.

Data is consistent with that reported in the literature.[b]





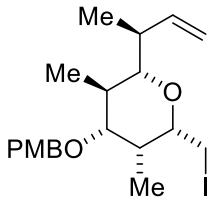
(2*S*,3*R*,4*R*,5*R*,6*S*)-2-{(*S*)-But-3-en-2-yl}-6-(iodomethyl)-3,5-dimethyltetrahydro-2H-pyran-4-ol (S1).

A solution of diol **7** (1.24 g, 6.25 mmol, 100 mol%) and $NaHCO_3$ (1.3 g, 15.62 mmol, 250 mol%) in MeCN (125 mL) was cooled to –20 °C. To this solution was added iodine (4.80 g, 18.75 mmol, 300 mol%) in one portion. The reaction was stirred at –20 °C for 1 h. The reaction mixture was warmed to 0 °C and was allowed to stir at 0 °C for 6 h. Saturated aqueous $Na_2S_2O_3$ was added and the reaction mixture was allowed to stir until the solution became colorless. The reaction mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and evaporated onto silica gel. The residue was subjected to flash column chromatography (hexanes/EtOAc = 20:1 to 10:1) to afford title compound **S1** (1.52 g, 4.69 mmol, dr = >20:1) as a colorless oil in 75%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87–5.78 (m, 1H), 5.02–4.97 (m, 2H), 3.54–3.50 (m, 1H), 3.40 (dd, *J* = 10.8, 4.8 Hz, 1H), 3.25 (dd, *J* = 10.0, 7.6 Hz, 1H), 3.08 (dd, *J* = 10.0, 6.0 Hz, 1H), 2.88 (dd, *J* = 10.0, 2.0 Hz, 1H), 2.44–2.37 (m, 1H), 2.19–2.13 (m, 1H), 1.56-1.49 (m, 2H), 1.16 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.80 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.2, 115.2, 85.1, 78.7, 76.4, 39.9, 38.2, 34.6, 18.8, 12.2, 6.2, 4.6.

Data is consistent with that reported in the literature.[b]



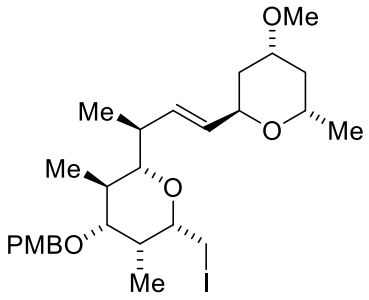
(2*S*,3*R*,4*R*,5*R*,6*S*)-2-{(*S*)-But-3-en-2-yl}-6-(iodomethyl)-4-{(4-methoxybenzyl)oxy}-3,5-dimethyltetrahydro-2H-pyran (8).

A solution of alcohol **S1** (285 mg, 0.879 mmol, 100 mol%) and freshly prepared PMB-imidate (1.24 g, 4.40 mmol, 500 mol%) in Et_2O (2.9 mL) was heated to 30 °C. To this solution was added camphorsulfonic acid (41 mg, 0.18 mmol, 20 mol%) in one portion. The reaction was stirred at 30 °C for 20 h. Saturated aqueous $NaHCO_3$ was added and the reaction mixture was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and evaporated onto silica gel. The residue was purified by flash column chromatography (hexanes/EtOAc = 40:1) to afford title compound (309 mg, 0.69 mmol) as a colorless oil in 79%.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28–7.26 (m, 2H), 6.89–6.86 (m, 2H), 5.81 (dt, *J* = 18.0, 9.2 Hz, 1H), 4.99–4.95 (m, 2H), 4.56 (d, *J* = 11.2 Hz, 1H), 4.28 (d, *J* = 11.2 Hz, 1H), 3.81 (s, 3H), 3.47 (ddd, *J* = 8.0, 6.0, 2.0 Hz, 1H), 3.27 (dd, *J* = 10.0, 8.0 Hz, 1H), 3.11 (dd, *J* = 10.0, 6.4 Hz, 2H), 2.87 (dd, *J* = 10.4, 2.0 Hz, 1H), 2.43–2.32 (m, 2H), 1.70–1.60 (m, 1H), 1.15 (d, *J* = 7.2 Hz, 3H), 0.86 (d, *J* = 6.4 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 139.2, 130.5, 129.4, 115.2, 113.8, 85.4, 82.9, 78.6, 69.7, 55.3, 39.9, 33.8, 32.2, 18.7, 12.6, 6.6, 4.9.

Data is consistent with that reported in the literature.[b]



(2*S*,3*R*,4*R*,5*R*,6*S*)-2-(Iodomethyl)-6-[(*S*,*E*)-4-{(2*R*,4*R*,6*S*)-4-methoxy-6-methyltetrahydro-2H-pyran-2-yl}but-3-en-2-yl]-4-{(4-methoxybenzyl)oxy}-3,5-dimethyltetrahydro-2H-pyran (9).

To a flask under an argon atmosphere charged with pyran **5** (64.9 mg, 0.416 mmol, 100 mol%) and iodoether **8** (925 mg, 2.08 mmol, 500 mol%) was added freshly distilled DCE (2.1 mL). Hoveyda-Grubbs second generation catalyst (52.1 mg, 0.0832 mmol, 20 mol%) was added to the solution in one portion. The flask equipped with reflux condenser was heated at 80 °C for 3 d. The reaction mixture was evaporated onto silica gel. The residue was purified by flash column chromatography (hexanes/EtOAc = 50:1) to recover iodoether **8** (538 mg, 1.21 mmol, 290 mol%) as a colorless oil, and (hexanes/EtOAc = 10:1 to 4:1) to provide title compound **9** (123.1 mg, 0.215 mmol) as a brown oil in 52%.

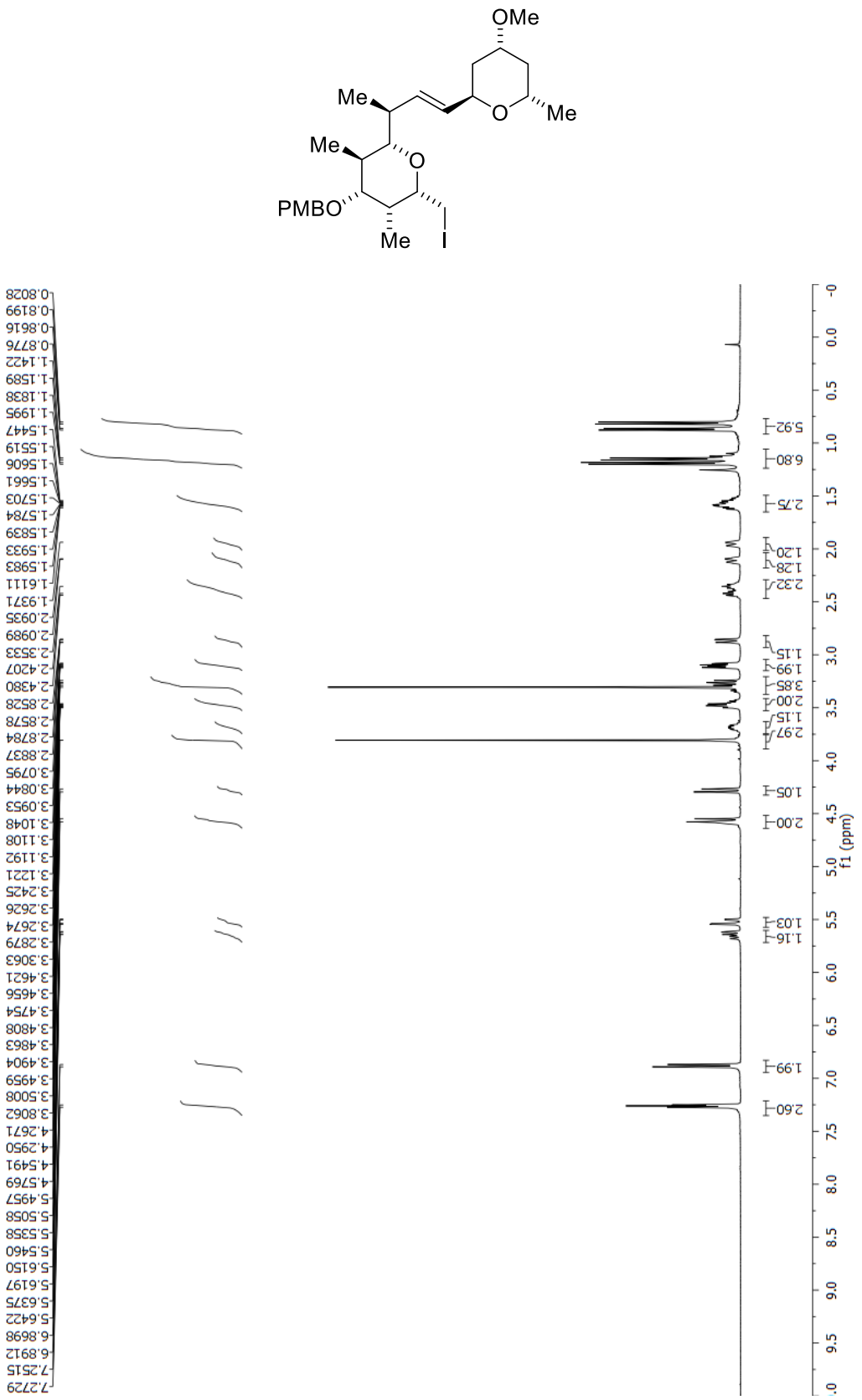
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.65 (ddd, *J* = 16.0, 9.0, 1.6 Hz, 1H), 5.52 (dd, *J* = 16.1, 4.1 Hz, 1H), 4.62–4.55 (m, 1H), 4.56 (d, *J* = 11.2 Hz, 1H), 4.26 (d, *J* = 11.1 Hz, 1H), 3.81 (s, 3H), 3.68 (dddd, *J* = 16.9, 8.4, 8.4, 2.2 Hz, 1H), 3.52–3.43 (m, 2H), 3.31 (s, 3H), 3.27 (dd, *J* = 10.0, 8.1 Hz, 1H), 3.14–3.08 (m, 2H), 2.87 (dd, *J* = 10.2, 1.9 Hz, 1H), 2.47–2.27 (m, 2H), 2.14–2.07 (m, 1H), 1.98–1.90 (m, 1H), 1.65–1.47 (m, 2H), 1.19 (d, *J* = 6.2 Hz, 3H), 1.15 (d, *J* = 6.9 Hz, 3H), 1.14–1.09 (m, 1H), 0.87 (d, *J* = 6.4 Hz, 3H), 0.81 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 133.1, 131.1, 130.6, 129.5, 114.0, 85.8, 82.9, 78.8, 73.2, 72.5, 69.9, 65.8, 55.4, 55.4, 39.6, 38.9, 34.2, 34.0, 33.8, 22.1, 19.3, 12.7, 6.5, 5.1.

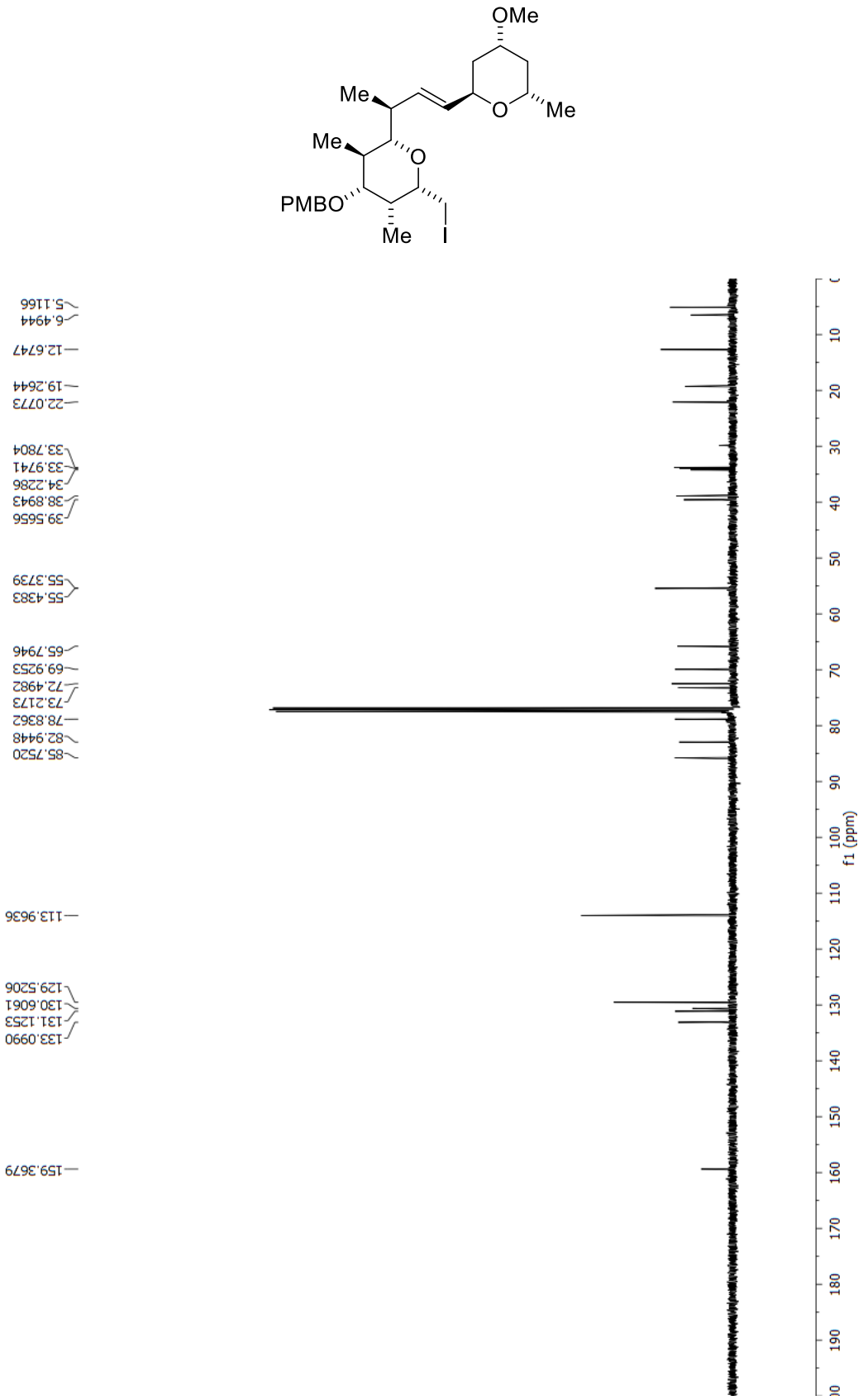
IR (neat) 2968, 2930, 1513, 1246, 1082, 1022, 971 cm^{-1}.

HRMS (CI+) calcd. for $C_{27}H_{41}O_5I$ $[M]^+$ 572.1999, found 572.1980.

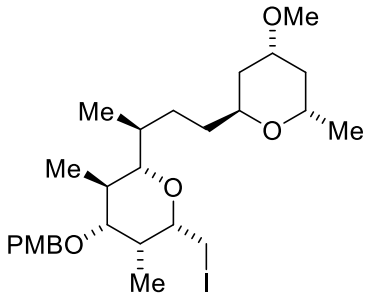
$[\alpha]_D^{25}$ = +31.16 ° (c = 0.46, $CHCl_3$).



^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of Compound **9**



^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of Compound **9**



(2*S*,3*R*,4*R*,5*R*,6*S*)-2-Iodomethyl)-6-[(*S*)-4-{(2*S*,4*R*,6*S*)-4-methoxy-6-methyltetrahydro-2H-pyran-2-yl}butan-2-yl]-4-{(4-methoxybenzyl)oxy}-3,5-dimethyltetrahydro-2H-pyran (S2).

To a round bottomed flask under an argon atmosphere charged with alkene **9** (25.0 mg, 0.0437 mmol, 100 mol%) and tosylhydrazide (40.7 mg, 0.218 mmol, 500 mol%) was added DME (2.2 mL) and the solution was heated to 95 °C. A solution of NaOAc (1.0 M in H_2O, 0.2 mL, 0.218 mmol, 500 mol%) was added in three portion over a period of 2 h. The reaction mixture was stirred for 12 h at 95 °C. More NaOAc (1.0 M in H_2O, 0.1 mL, 0.109 mmol, 250 mol%) was added, and the mixture was stirred for additional 6 h at 95 °C. The reaction mixture was cooled to ambient temperature, H_2O was added, and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and evaporated onto silica gel. The residue was purified by flash column chromatography (hexanes/EtOAc = 4:1) to afford title compound **S2** (20.0 mg, 0.348 mmol) as a colorless oil in 80%.

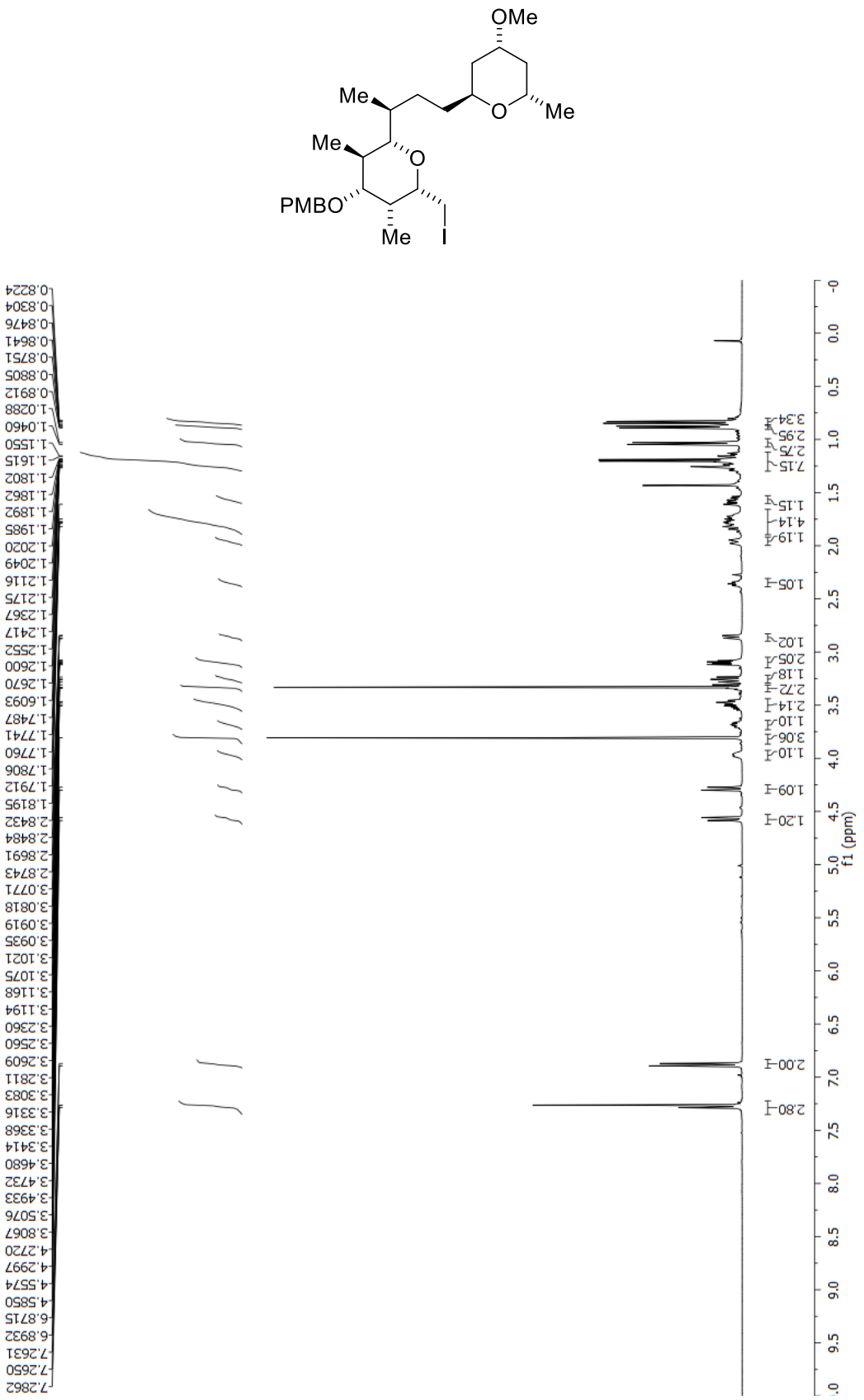
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 4.57 (d, *J* = 11.0 Hz, 1H), 4.29 (d, *J* = 11.1 Hz, 1H), 4.00–3.94 (m, 1H), 3.81 (s, 3H), 3.72–3.64 (m, 1H), 3.55–3.42 (m, 2H), 3.33 (s, 3H), 3.26 (dd, *J* = 10.0, 8.0 Hz, 1H), 3.14–3.07 (m, 2H), 2.86 (dd, *J* = 10.3, 2.1 Hz, 1H), 2.40–2.31 (m, 1H), 1.99–1.93 (m, 1H), 1.88–1.67 (m, 4H), 1.61–1.53 (m, 1H), 1.30–1.14 (m, 3H), 1.20 (d, *J* = 6.3 Hz, 3H), 1.04 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 6.4 Hz, 3H), 0.84 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 130.6, 129.5, 113.9, 87.0, 83.3, 78.9, 73.4, 71.7, 69.9, 64.8, 55.4, 55.4, 38.8, 35.0, 34.1, 33.1, 32.7, 29.7, 24.9, 22.0, 17.9, 13.0, 6.8, 5.1.

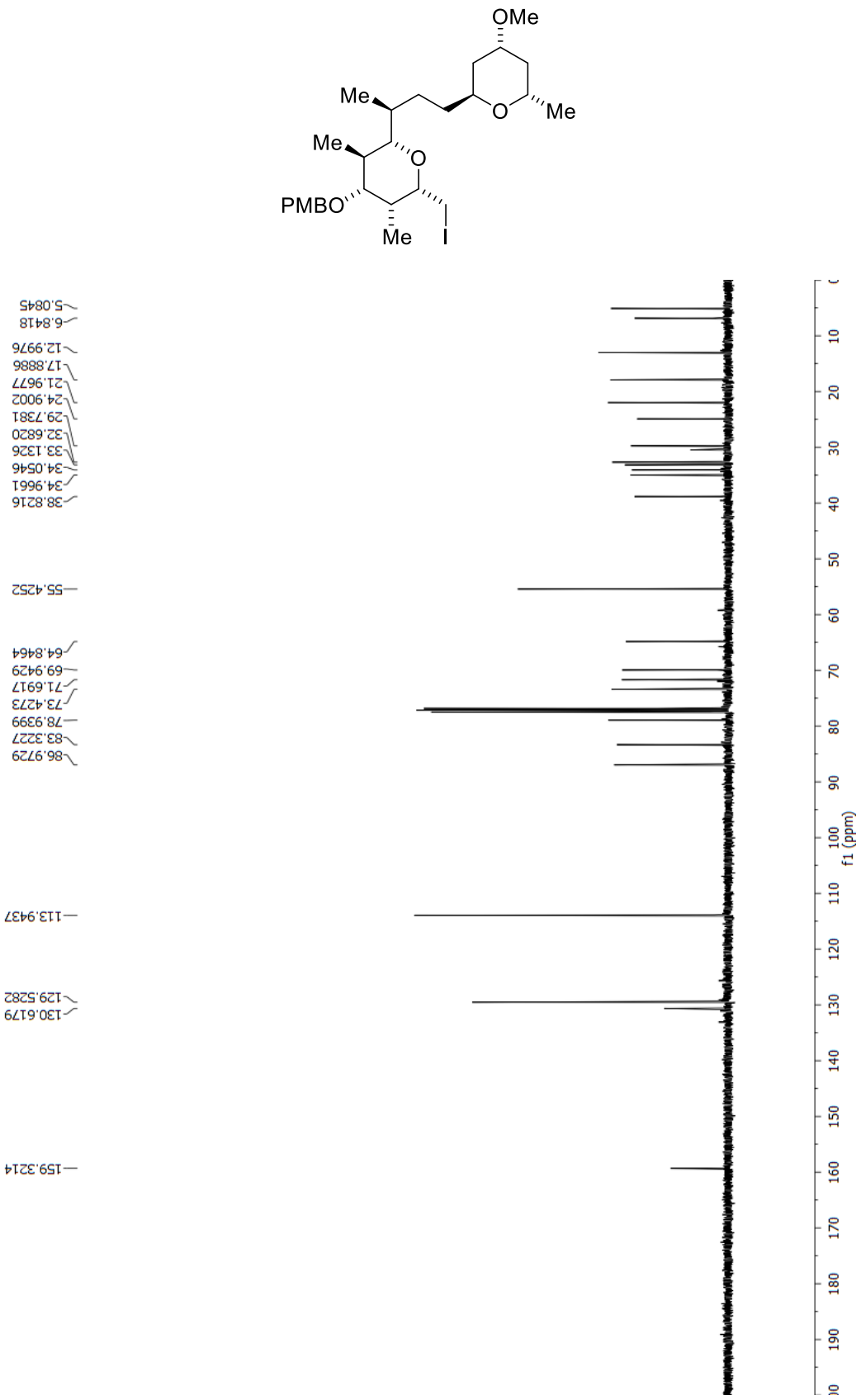
IR (neat) 2933, 1513, 1248, 1082, 1026 cm^{-1}.

HRMS (ESI+) calcd. for $C_{27}H_{43}O_5INa$ $[M+Na]^+$ 597.2047, found 597.2048.

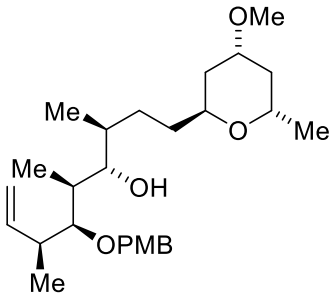
$[\alpha]_D^{25}$ = +9.10 ° (c = 0.43, $CHCl_3$).



^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of Compound **S2**



^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of Compound **S2**



(3*S*,4*S*,5*S*,6*S*,7*S*)-1-{(2*S*,4*R*,6*S*)-4-Methoxy-6-methyltetrahydro-2H-pyran-2-yl}-6-{(4-methoxybenzyl)oxy}-3,5,7-trimethylnon-8-en-4-ol (10).

To a solution of iodoether **S2** (19.7 mg, 0.0343 mmol, 100 mol%) in EtOH (0.34 mL) was added Zn dust (33.6 mg, 0.515 mmol, 1500 mol%) and NH_4Cl (18.3 mg, 0.343 mmol, 1000 mol%). The mixture was allowed to stir at 80 °C for 6 h. The reaction mixture was filtered through a short plug of silica gel and washed with EtOAc, and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes/EtOAc = 4:1) to provide title compound **10** (12.6 mg, 0.0281 mmol) as a colorless oil in 82%.

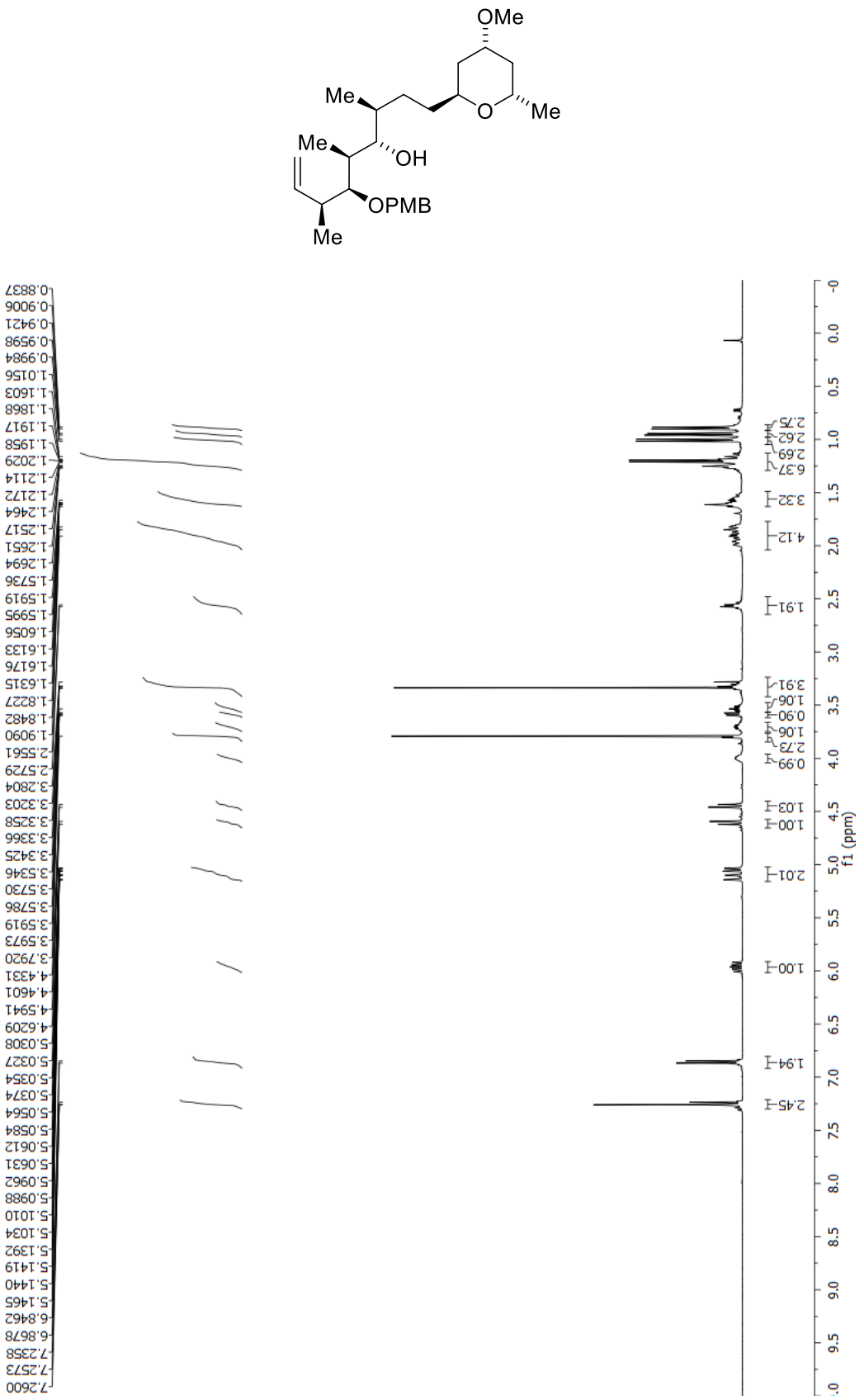
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.96 (ddd, *J* = 17.2, 10.3, 7.9 Hz, 1H), 5.16–5.02 (m, 2H), 4.61 (d, *J* = 10.7 Hz, 1H), 4.45 (d, *J* = 10.8 Hz, 1H), 4.03–3.96 (m, 1H), 3.79 (s, 3H), 3.75–3.65 (m, 1H), 3.59 (dd, *J* = 7.5, 2.2 Hz, 1H), 3.56–3.49 (m, 1H), 3.34 (s, 3H), 3.36–3.28 (m, 1H), 2.62–2.54 (m, 2H), 2.01–1.77 (m, 4H), 1.65–1.50 (m, 3H), 1.30–1.12 (m, 3H), 1.20 (d, *J* = 6.2 Hz, 3H), 1.01 (d, *J* = 6.9 Hz, 3H), 0.95 (d, *J* = 7.1 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 142.0, 130.6, 129.5, 114.5, 113.7, 83.2, 78.9, 73.3, 7.30, 72.0, 64.6, 55.3, 55.3, 40.9, 38.7, 36.4, 35.1, 34.9, 29.2, 26.3, 21.8, 17.4, 16.8, 11.7.

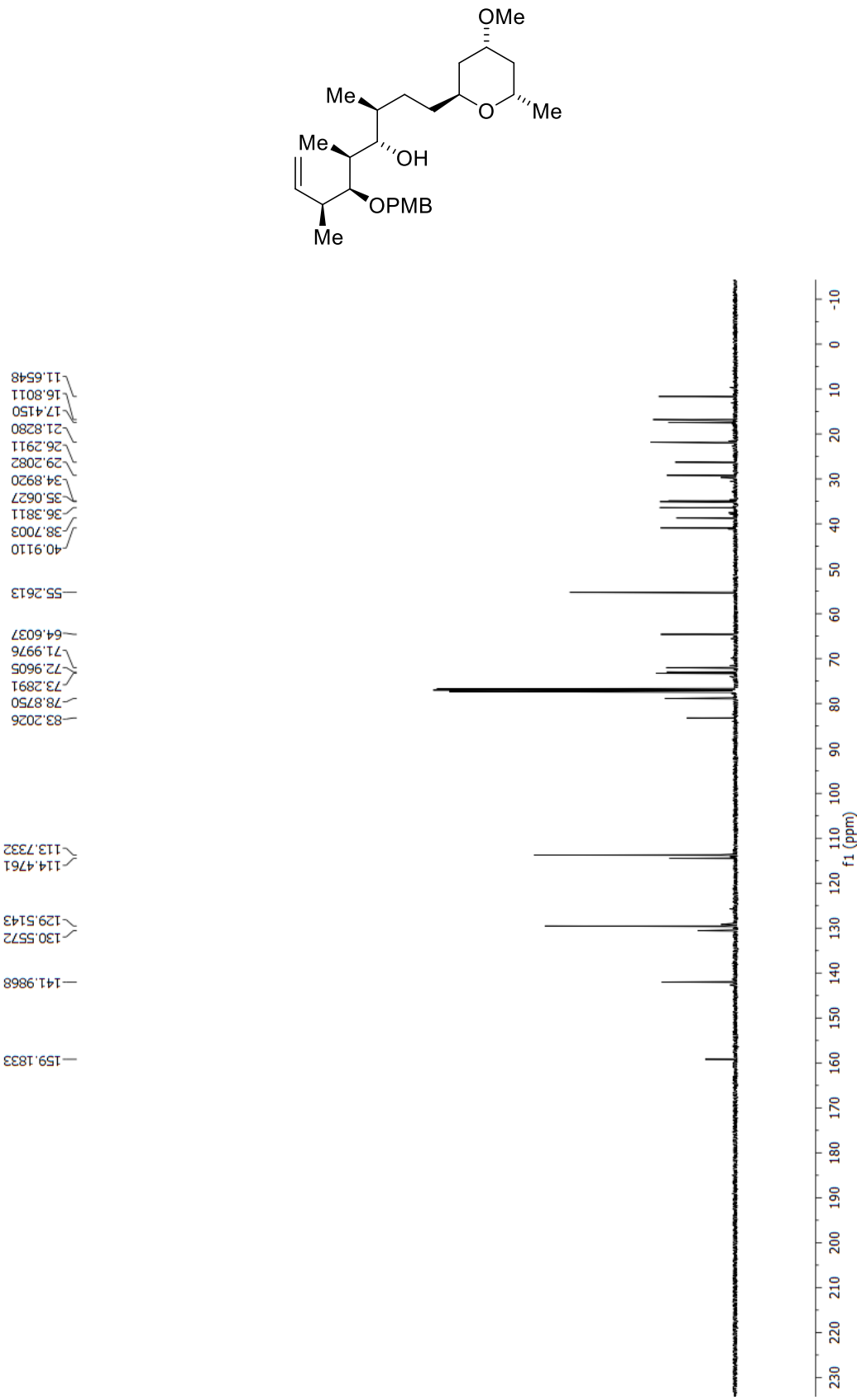
IR (neat) 2923, 1514, 1248, 1081, 1035 cm^{-1}.

HRMS (ESI+) calcd. for $C_{27}H_{44}O_5Na$ $[M+Na]^+$ 471.3081, found 471.3081.

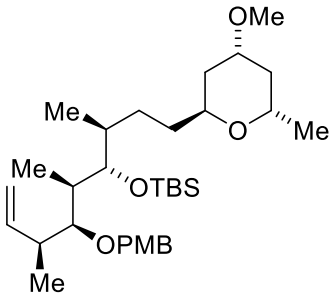
$[\alpha]_D^{25}$ = –13.33 ° (c = 0.25, $CHCl_3$).



^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of Compound **10**



^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of Compound **10**



***tert*-Butyl[{(3*S*,4*S*,5*R*,6*S*,7*S*)-1-{(2*S*,4*R*,6*S*)-4-methoxy-6-methyltetrahydro-2H-pyran-2-yl}-6-{(4-methoxybenzyl)oxy}-3,5,7-trimethylnon-8-en-4-yl}oxy]dimethylsilane (S3).**

Alcohol **10** (6.0 mg, 0.0134 mmol, 100 mol%) was dissolved in CH_2Cl_2 (0.13 mL). Et_3N (11 μL, 0.0804 mmol, 600 mol%) was added and the reaction was cooled to 0 °C. TBSOTf (7 μL, 0.0402 mmol, 300 mol%) was added and the reaction mixture was stirred at ambient temperature for 20 h. The reaction was quenched with H_2O, and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes/EtOAc = 12:1) to provide title compound **S3** (6.9 mg, 0.0122 mmol) as a colorless oil in 91%.

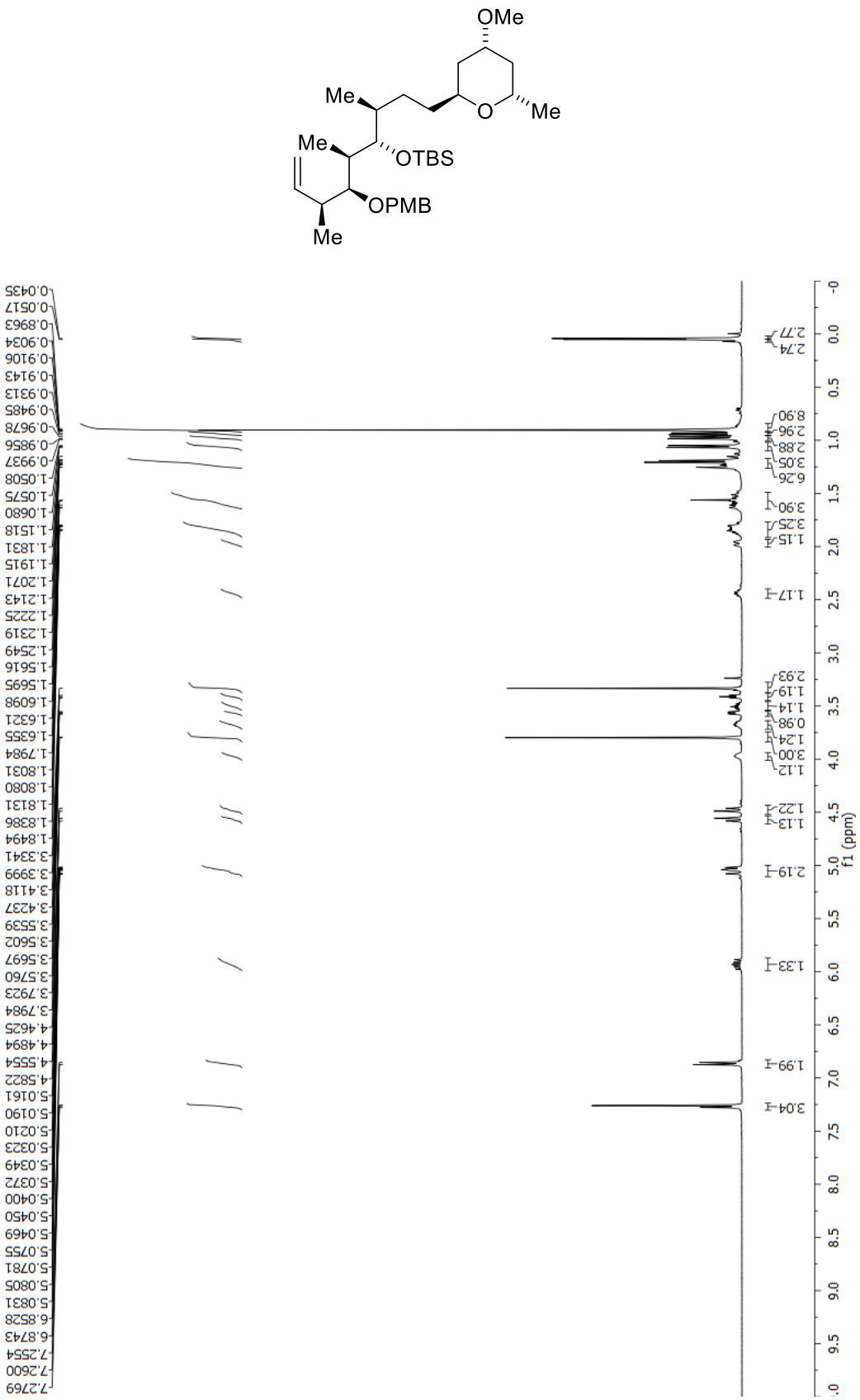
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 5.93 (ddd, *J* = 17.2, 10.3, 8.0 Hz, 1H), 5.11–5.00 (m, 2H), 4.57 (d, *J* = 10.7 Hz, 1H), 4.48 (d, *J* = 10.7 Hz, 1H), 4.02–3.93 (m, 1H), 3.80 (s, 3H), 3.72–3.63 (m, 1H), 3.56 (dd, *J* = 6.3, 2.5 Hz, 1H), 3.54–3.46 (m, 1H), 3.41 (dd, *J* = 4.8, 4.8 Hz, 1H), 3.33 (s, 3H), 2.49–2.39 (m, 1H), 2.02–1.93 (m, 1H), 1.92–1.75 (m, 3H), 1.69–1.45 (m, 3H), 1.34–1.11 (m, 3H), 1.20 (d, *J* = 6.3 Hz, 3H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.98 (d, *J* = 7.1 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.90 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 141.5, 131.7, 128.9, 114.7, 113.8, 83.7, 78.9, 74.0, 73.5, 72.4, 64.7, 55.4, 55.4, 42.1, 41.7, 39.0, 36.0, 34.9, 30.1, 27.8, 26.4, 22.0, 18.7, 18.1, 17.7, 11.8, –3.2, –3.9.

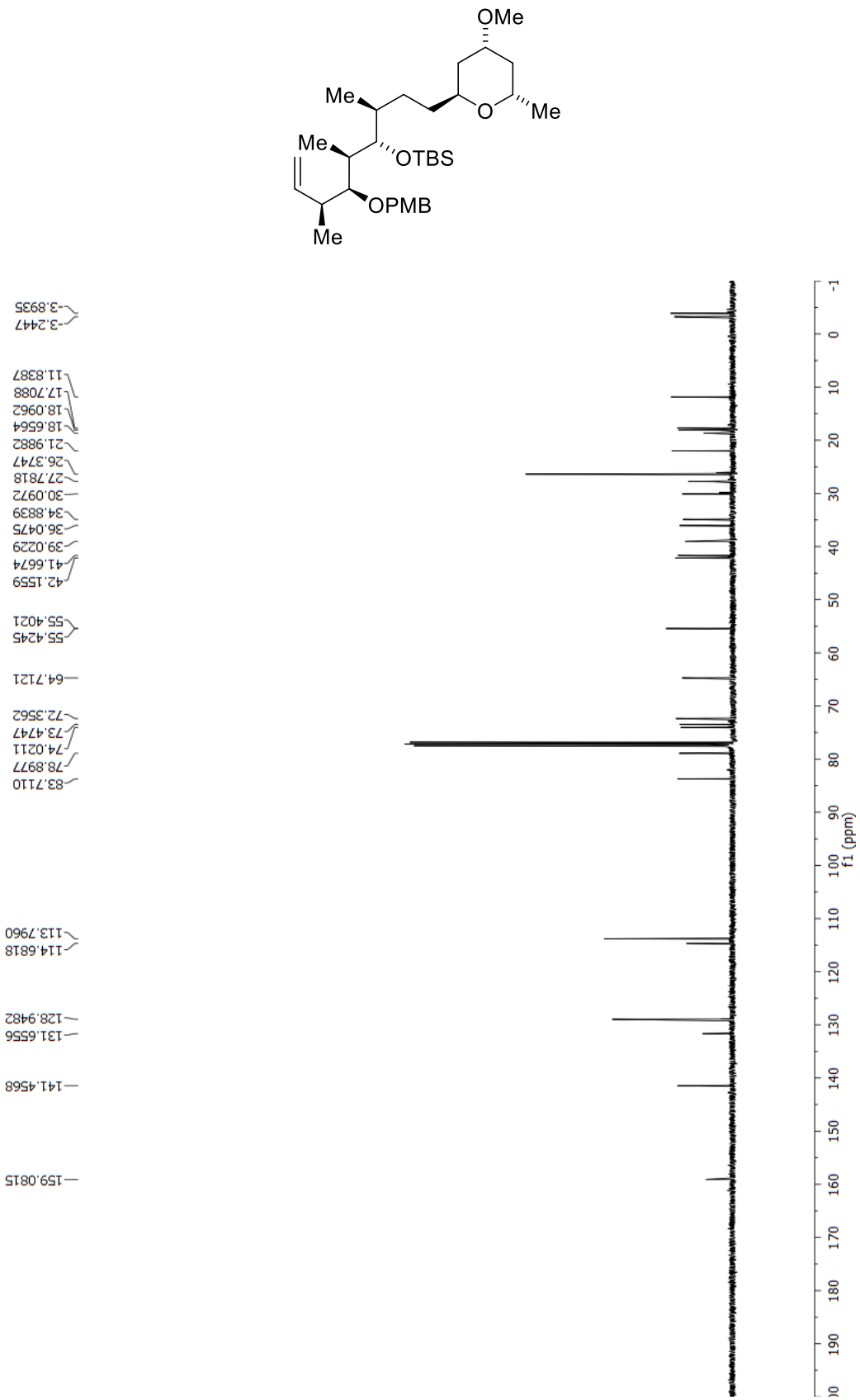
IR (neat) 2932, 2857, 1514, 1248, 1084, 1039 cm^{-1}.

HRMS (ESI+) calcd. for $C_{33}H_{58}O_5SiNa$ $[M+Na]^+$ 585.3946, found 585.3942.

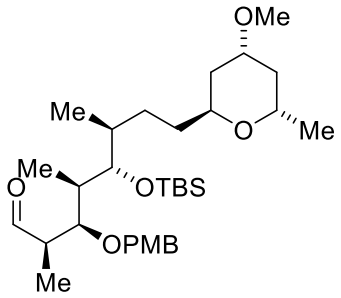
$[\alpha]_D^{25}$ = –11.90 ° (c = 0.14, $CHCl_3$).



^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of Compound **S3**



^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of Compound **S3**



(2*R*,3*R*,4*R*,5*S*,6*S*)-5-{(*tert*-Butyldimethylsilyl)oxy}-8-{(2*S*,4*R*,6*S*)-4-methoxy-6-methyltetrahydro-2H-pyran-2-yl}-3-{(4-methoxybenzyl)oxy}-2,4,6-trimethyloctanal (11).

The alkene **S3** (6.0 mg, 0.0107 mmol, 100 mol%) was dissolved in 1,4-dioxane (0.4 mL) and H_2O (0.14 mL). NMO (3.8 mg, 0.0321 mmol, 300 mol%) and OsO_4 solution in dioxane (1 mg/1 mL dioxane, 0.14 mL, 0.00054 mmol, 5 mol%) were added. The reaction mixture was stirred for 15 h, then $NaIO_4$ (11.4 mg, 0.0535 mmol, 500 mol%) was added in one portion. The reaction mixture was stirred at ambient temperature for additional 2 h. The reaction mixture was diluted with pH 7 buffer solution, and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes/EtOAc = 5:1) to provide title compound **11** (4.8 mg, 0.00856 mmol) as a colorless oil in 80%.

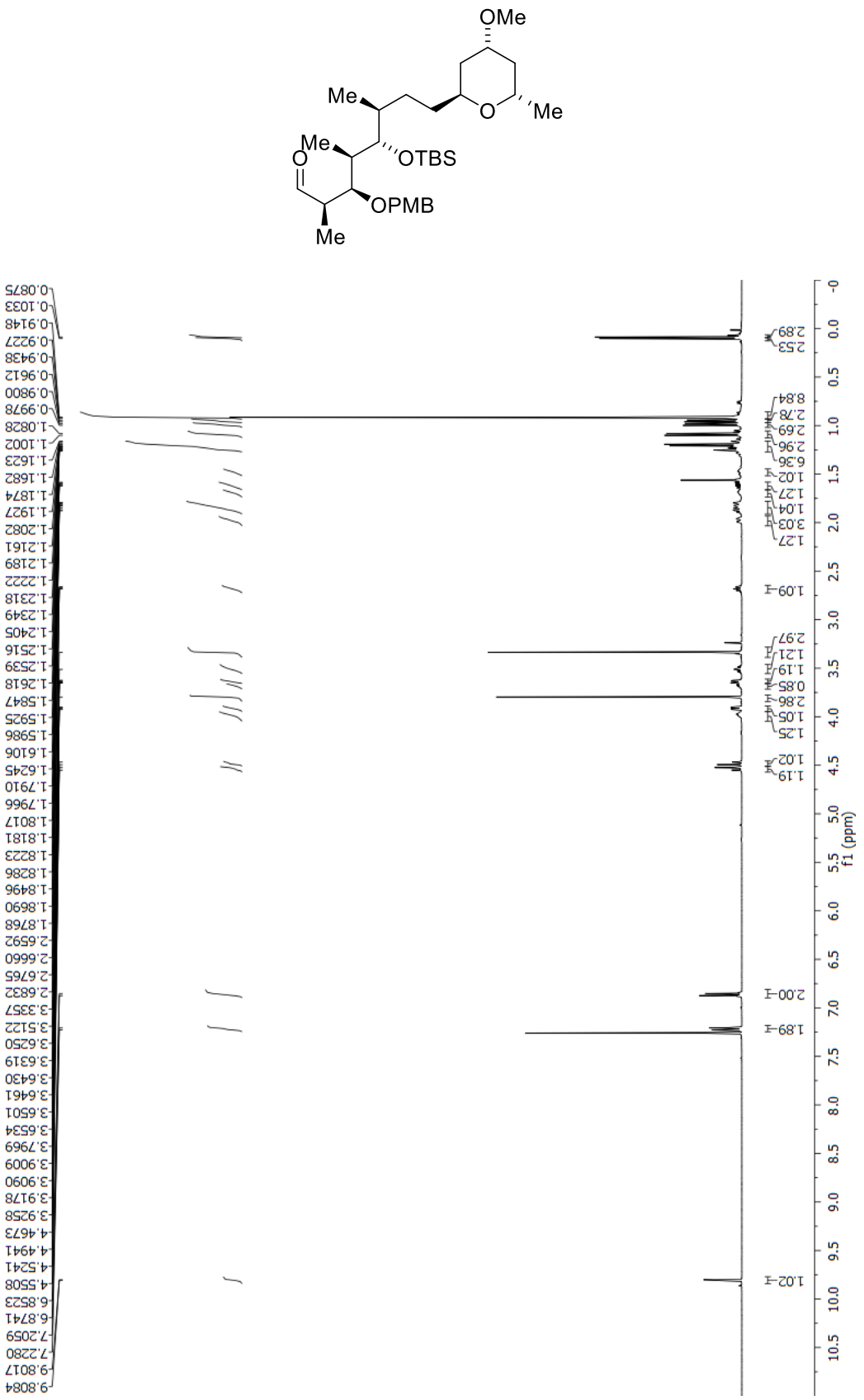
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (d, *J* = 2.7 Hz, 1H), 7.21 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.54 (d, *J* = 10.7 Hz, 1H), 4.48 (d, *J* = 10.7 Hz, 1H), 4.01–3.94 (m, 1H), 3.91 (dd, *J* = 6.7, 3.2 Hz, 1H), 3.80 (s, 3H), 3.71–3.65 (m, 1H), 3.64 (dd, *J* = 7.2, 2.8 Hz, 1H), 3.55–3.46 (m, 1H), 3.34 (s, 3H), 2.68 (ddd, *J* = 6.9, 6.9 Hz, 1H), 2.01–1.93 (m, 1H), 1.91–1.76 (m, 3H), 1.72–1.65 (m, 1H), 1.64–1.58 (m, 1H), 1.52–1.43 (m, 1H), 1.30–1.12 (m, 3H), 1.20 (d, *J* = 6.2 Hz, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.99 (d, *J* = 7.1 Hz, 3H), 0.95 (d, *J* = 7.0 Hz, 3H), 0.91 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 204.8, 159.1, 130.6, 128.8, 113.7, 80.8, 79.0, 73.8, 73.3, 71.9, 64.6, 55.3, 55.3, 50.3, 41.1, 38.7, 36.7, 34.8, 30.0, 27.5, 26.3, 21.8, 18.6, 16.8, 11.8, 11.6, –3.3, –3.8.

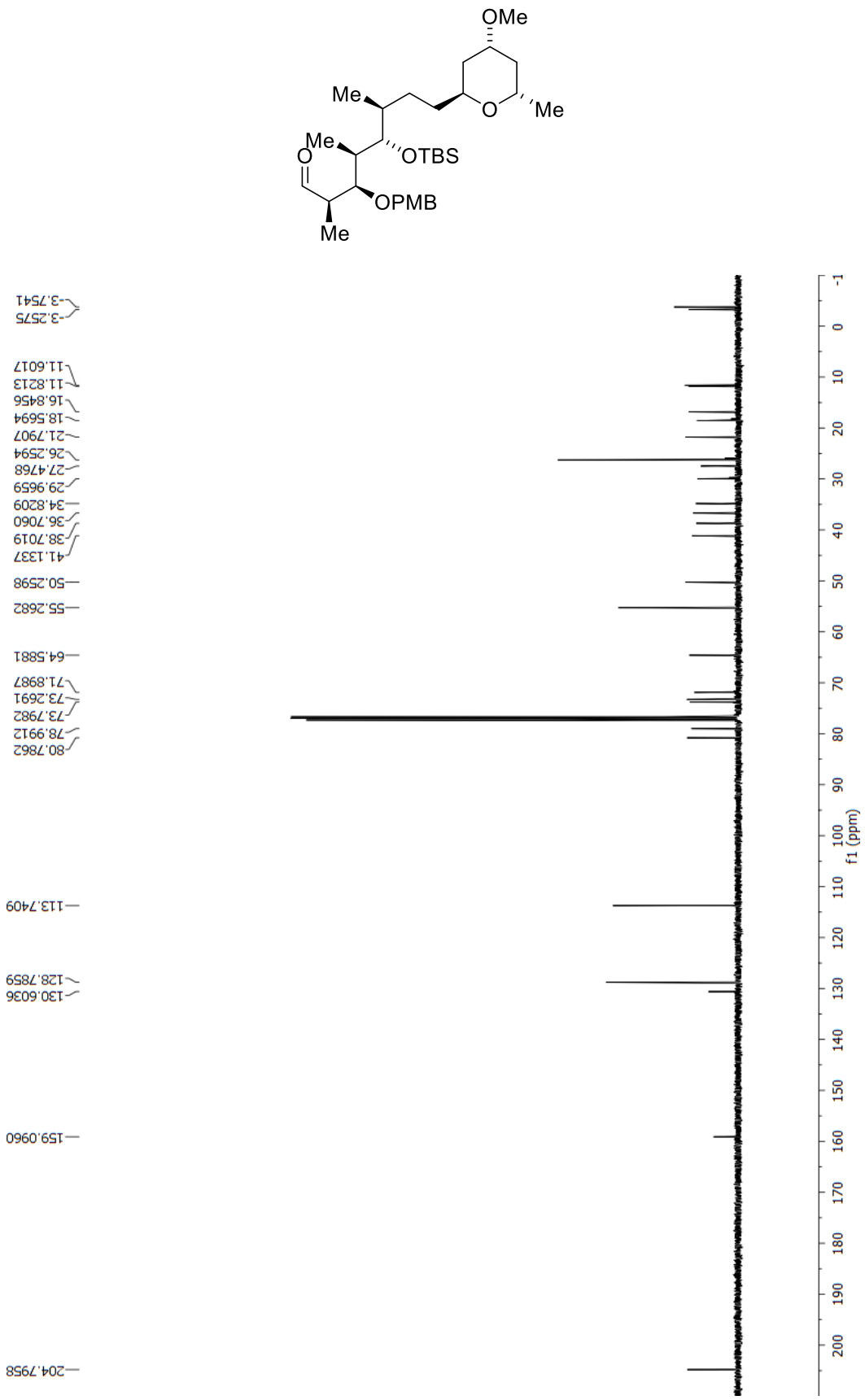
IR (neat) 2931, 2856, 1724, 1514, 1249, 1036 cm^{-1}.

HRMS (ESI+) calcd. for $C_{32}H_{56}O_6SiNa$ $[M+Na]^+$ 587.3738, found 587.3737.

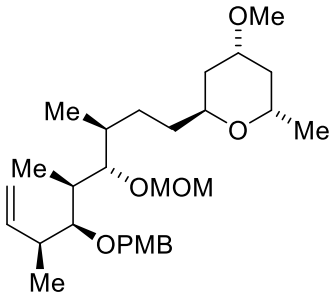
$[\alpha]_D^{25}$ = –36.88 ° (c = 0.47, $CHCl_3$).



^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of Compound **11**



^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of Compound **11**



(2*S*,4*R*,6*S*)-4-Methoxy-2-[(3*S*,4*S*,5*R*,6*S*,7*S*)-6-{(4-methoxybenzyl)oxy}-4-(methoxymethoxy)-3,5,7-trimethylnon-8-en-1-yl]-6-methyltetrahydro-2H-pyran (S4).

To a solution of alcohol **10** (6.1 mg, 0.0136 mmol, 100 mol%) in DCE (0.1 mL) was added $^{i}Pr_2NEt$ (19 μL, 0.109 mmol, 800 mol%). MOMCl (2.1 M in toluene, 50 μL, 0.109 mmol, 800 mol%) was added and the reaction mixture was stirred at 60 °C for 4 h. The reaction was quenched with H_2O, and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes/EtOAc = 4:1) to provide title compound **S4** (6.1 mg, 0.0124 mmol) as a colorless oil in 91%.

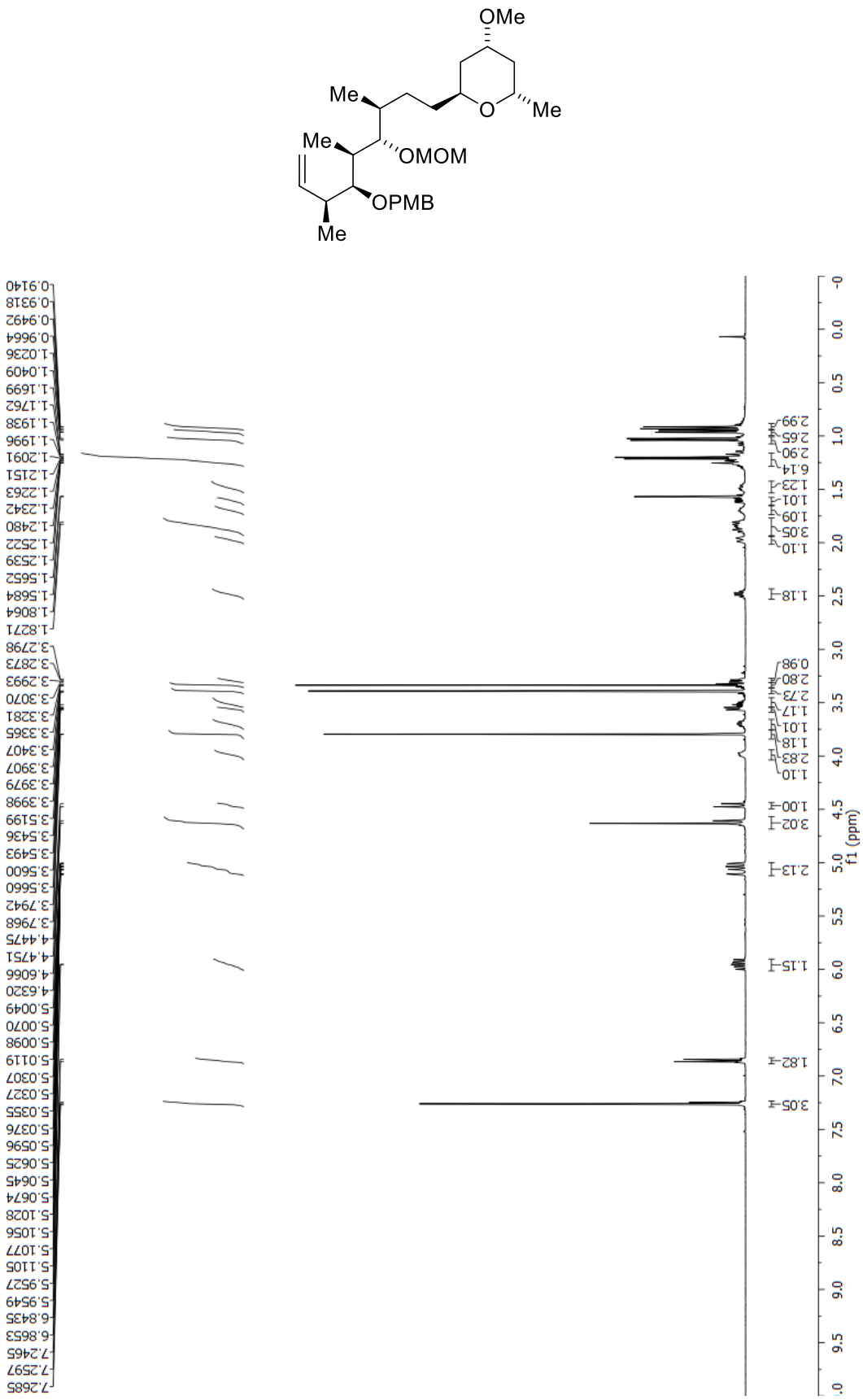
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.95 (ddd, *J* = 17.3, 10.3, 7.8 Hz, 1H), 5.12–4.99 (m, 2H), 4.63 (s, 3H), 4.62 (d, *J* = 11.0 Hz, 1H), 4.46 (d, *J* = 11.0 Hz, 1H), 4.02–3.95 (m, 1H), 3.79 (s, 3H), 3.75–3.64 (m, 1H), 3.55 (dd, *J* = 6.6, 2.3 Hz, 1H), 3.54–3.46 (m, 1H), 3.39 (s, 3H), 3.34 (s, 3H), 3.29 (dd, *J* = 7.8, 3.0 Hz, 1H), 2.55–2.42 (m, 1H), 2.01–1.93 (m, 1H), 1.92–1.79 (m, 3H), 1.76–1.65 (m, 1H), 1.63–1.57 (m, 1H), 1.52–1.42 (m, 1H), 1.30–1.13 (m, 1H), 1.21 (d, *J* = 6.2 Hz, 3H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.96 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 142.0, 131.8, 128.7, 114.2, 113.6, 98.5, 87.2, 82.3, 73.3, 73.2, 71.9, 64.7, 55.8, 55.3, 55.3, 42.0, 38.7, 38.6, 34.8, 34.6, 29.7, 26.7, 21.8, 17.5, 17.3, 11.3.

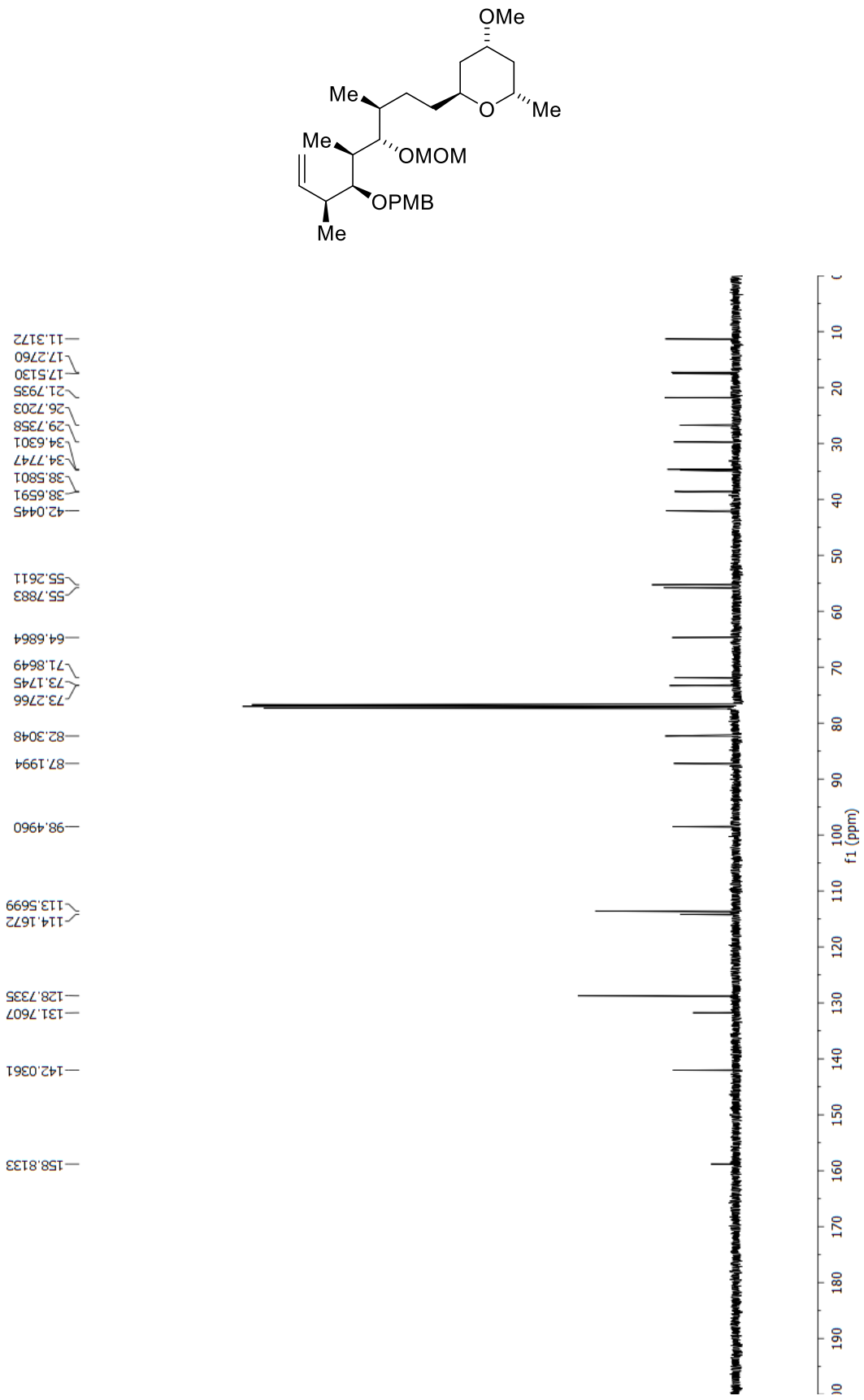
IR (neat) 2926, 1514, 1247, 1086, 1036 cm^{-1}.

HRMS (ESI+) calcd. for $C_{29}H_{48}O_6Na$ $[M+Na]^+$ 515.3343, found 515.3335.

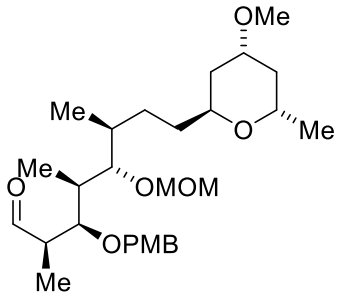
$[\alpha]_D^{25}$ = –37.26 ° (c = 0.17, $CHCl_3$).



^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of Compound **S4**



^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of Compound **S4**



(2*R*,3*R*,4*R*,5*S*,6*S*)-8-{(2*S*,4*R*,6*S*)-4-Methoxy-6-methyltetrahydro-2H-pyran-2-yl}-3-{(4-methoxybenzyl)oxy}-5-(methoxymethoxy)-2,4,6-trimethyloctanal (12).

The alkene **S4** (2.8 mg, 0.00568 mmol, 100 mol%) was dissolved in 1,4-dioxane (0.2 mL) and H_2O (0.1 mL). NMO (2.0 mg, 0.0170 mmol, 300 mol%) and OsO_4 solution in dioxane (1 mg/1 mL dioxane, 0.07 mL, 0.00028 mmol, 5 mol%) were added. The reaction mixture was stirred for 15 h, then $NaIO_4$ (6.1 mg, 0.0284 mmol, 500 mol%) was added in one portion. The reaction mixture was stirred at ambient temperature for additional 2 h. The reaction mixture was diluted with pH 7 buffer solution, and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexanes/EtOAc = 4:1) to provide title compound **12** (2.3 mg, 0.00465 mmol) as a colorless oil in 82%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (d, *J* = 2.6 Hz, 1H), 7.22 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.69 (d, *J* = 6.6 Hz, 1H), 4.66 (d, *J* = 6.6 Hz, 1H), 4.55 (d, *J* = 11.0 Hz, 1H), 4.48 (d, *J* = 11.0 Hz, 1H), 4.04 (dd, *J* = 7.9, 1.8 Hz, 1H), 4.02–3.94 (m, 1H), 3.79 (s, 3H), 3.75–3.64 (m, 1H), 3.56–3.48 (m, 1H), 3.41 (s, 3H), 3.37–3.32 (m, 1H), 3.34 (s, 3H), 2.79–2.67 (m, 1H), 2.02–1.91 (m, 1H), 1.90–1.67 (m, 4H), 1.66–1.56 (m, 1H), 1.51–1.39 (m, 1H), 1.31–1.16 (m, 3H), 1.21 (d, *J* = 6.3 Hz, 3H), 1.07 (d, *J* = 7.0 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 7.1 Hz, 3H).

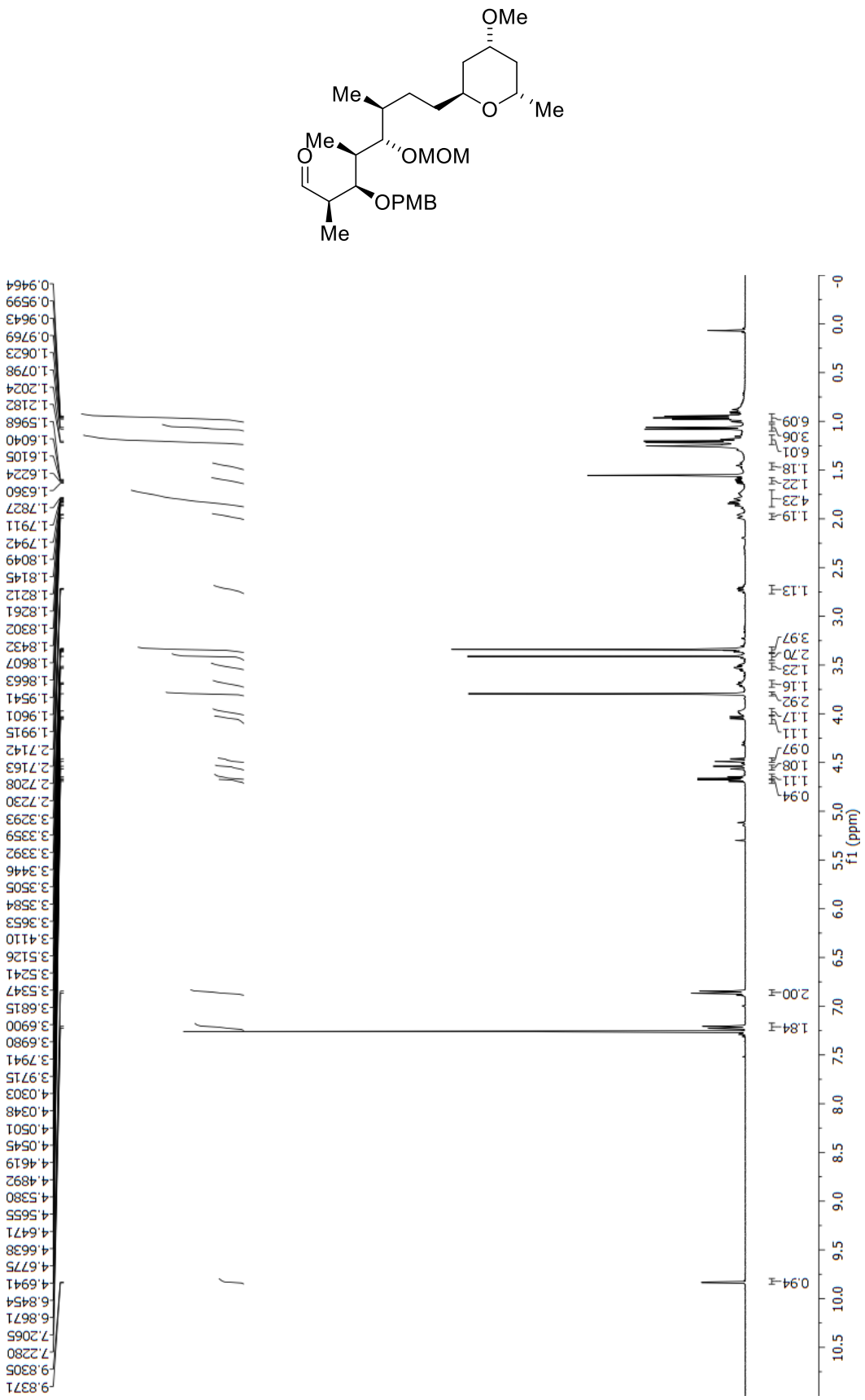
^{13}C NMR (100 MHz, $CDCl_3$) δ 205.0, 159.2, 131.0, 129.0, 113.9, 99.9, 87.4, 80.1, 73.4, 71.7, 64.9, 56.0, 55.4, 55.4, 50.5, 39.0, 38.7, 35.1, 34.9, 29.9, 29.8, 26.4, 21.9, 17.4, 11.9, 11.1.

IR (neat) 2972, 1514, 1247, 1097, 1036 cm^{-1}.

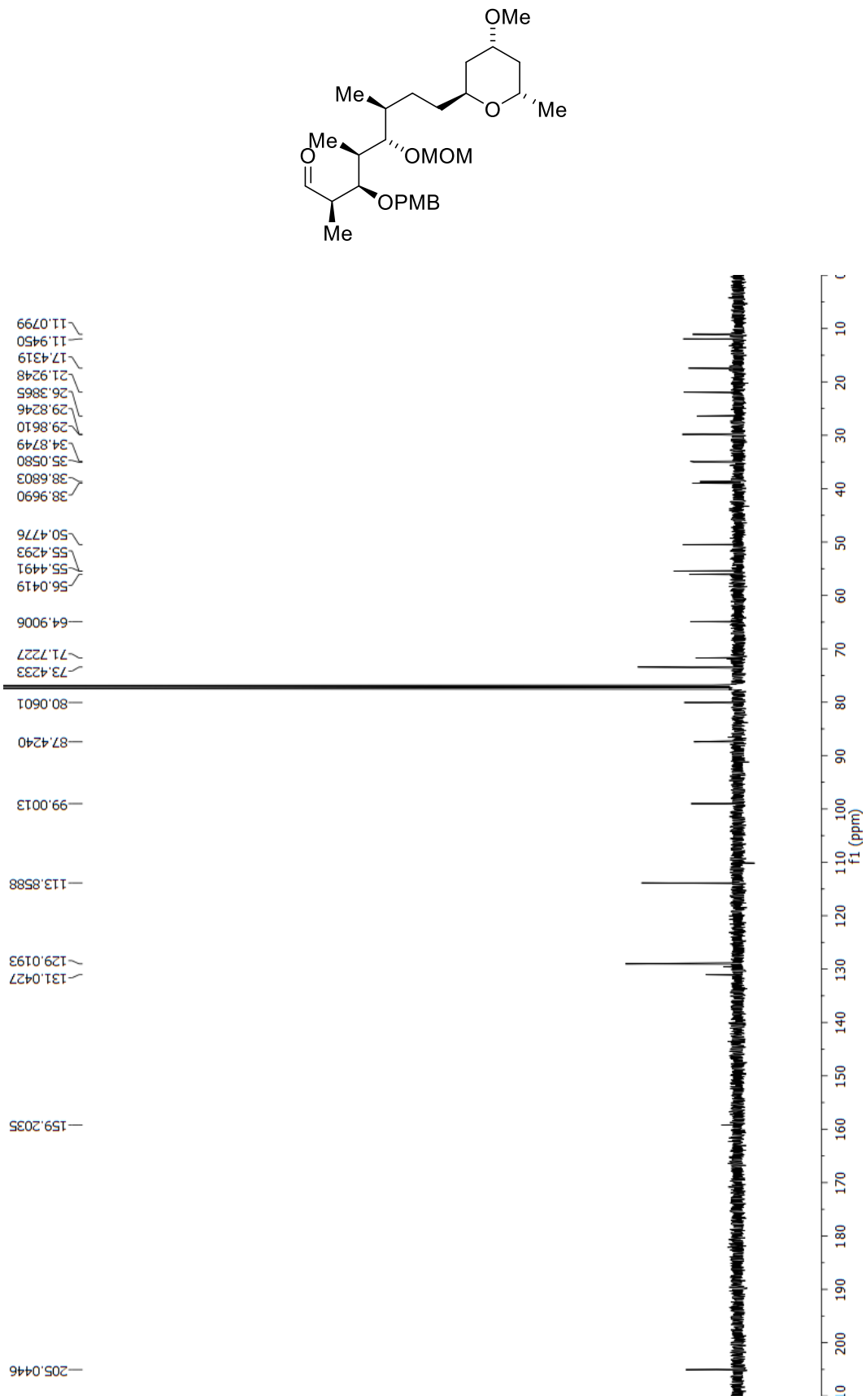
HRMS (ESI+) calcd. for $C_{28}H_{46}O_7Na$ $[M+Na]^+$ 517.3136, found 517.3142.

$[\alpha]_D^{25}$ = –13.03 ° (c = 0.23, $CHCl_3$).

Data is consistent with that reported in the literature.[c]



^{1}H NMR (400 MHz, $CDCl_3$) Spectrum of Compound **12**



^{13}C NMR (100 MHz, $CDCl_3$) Spectrum of Compound **12**

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a) Shin, I; Wang, G.; Krische, M. J. *Chem. Eur. J.* **2014**, *20*, 13382.

b) Gao, X.; Woo, S. K.; Krische, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 4223.

c) Nakamura, R.; Tanino, K.; Miyashita, M. *Org. Lett.* **2005**, *7*, 2929.