Stereochemically Versatile Synthesis of the C1–C12 Fragment of Tedanolide C

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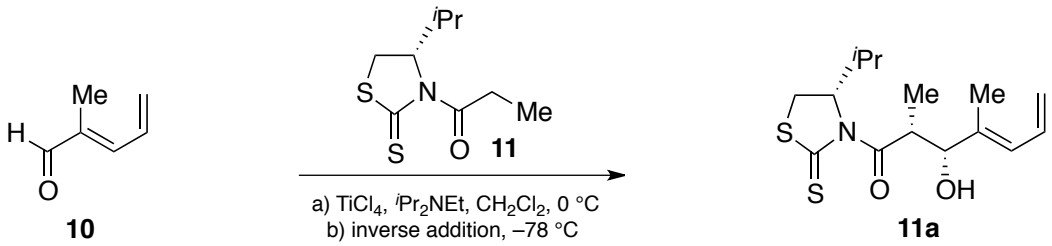
Supporting Information

General Information. Oxygen- or moisture-sensitive reactions were carried out in flame-dried or oven-dried glassware sealed with rubber septa under a positive pressure of dry nitrogen. Similarly sensitive liquids and solutions were transferred by gas-tight syringe or cannula. Unless indicated otherwise, reagents and solvents were purchased and used without purification. Ether, THF, and CH_2Cl_2 were purified by passage through a bed of activated alumina.[1] Analytical TLC was performed with 0.25 mm silica gel 60 plates with 254 nm fluorescent indicator from SiliCycle. Plates were visualized under UV light and treatment with either acidic *p*-anisaldehyde stain or aqueous ceric ammonium molybdate solution followed by gentle heating. The term flash chromatography refers to preparative silica gel column chromatography as described by Still and co-workers.[2] Automated chromatography was accomplished using an Isco Combiflash System Sg 100c. Silica gel 60, 230–240 mesh, was purchased from SiliCycle (R10030B). Analytical high performance liquid chromatography (HPLC) was carried out on an Agilent 1100 chromatograph equipped with a variable wavelength detector. ^{1}H NMR spectra were recorded on a Brüker Avance 500 (500 MHz) spectrometer and are reported in ppm using tetramethylsilane (0.00 ppm) or solvent ($CDCl_3$: 7.24 ppm; acetone-d_6: 2.04 ppm) as an internal standard. Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hz; integration). Proton-decoupled ^{13}C NMR spectra were recorded at 125 MHz and are reported in ppm using solvent as an internal standard ($CDCl_3$: 77.00 ppm, acetone-d_6: 206.00 ppm). Infrared spectra were recorded as thin films on NaCl plates on a Perkin-Elmer 710 Series Fourier transform spectrometer (FTIR). Melting points were determined with a Laboratory Devices Mel-Temp II apparatus equipped with an Fluke Model 51 K/J thermocouple and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter using the sodium (589, D line) lamp and are reported as follows: $[\alpha]_\lambda^{T\,^\circ C}$ (c = g/100 mL, solvent). Combustion analyses were performed by Atlantic Microlab, Norcross, Georgia. High Resolution mass spectra (HRMS) were recorded at the Nebraska Center for Mass Spectrometry or at the University of Hawaii, Manoa.

(1) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

(2) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem* **1978**, *43*, 2923.

Preparation of Aldol Adduct 11a[3]

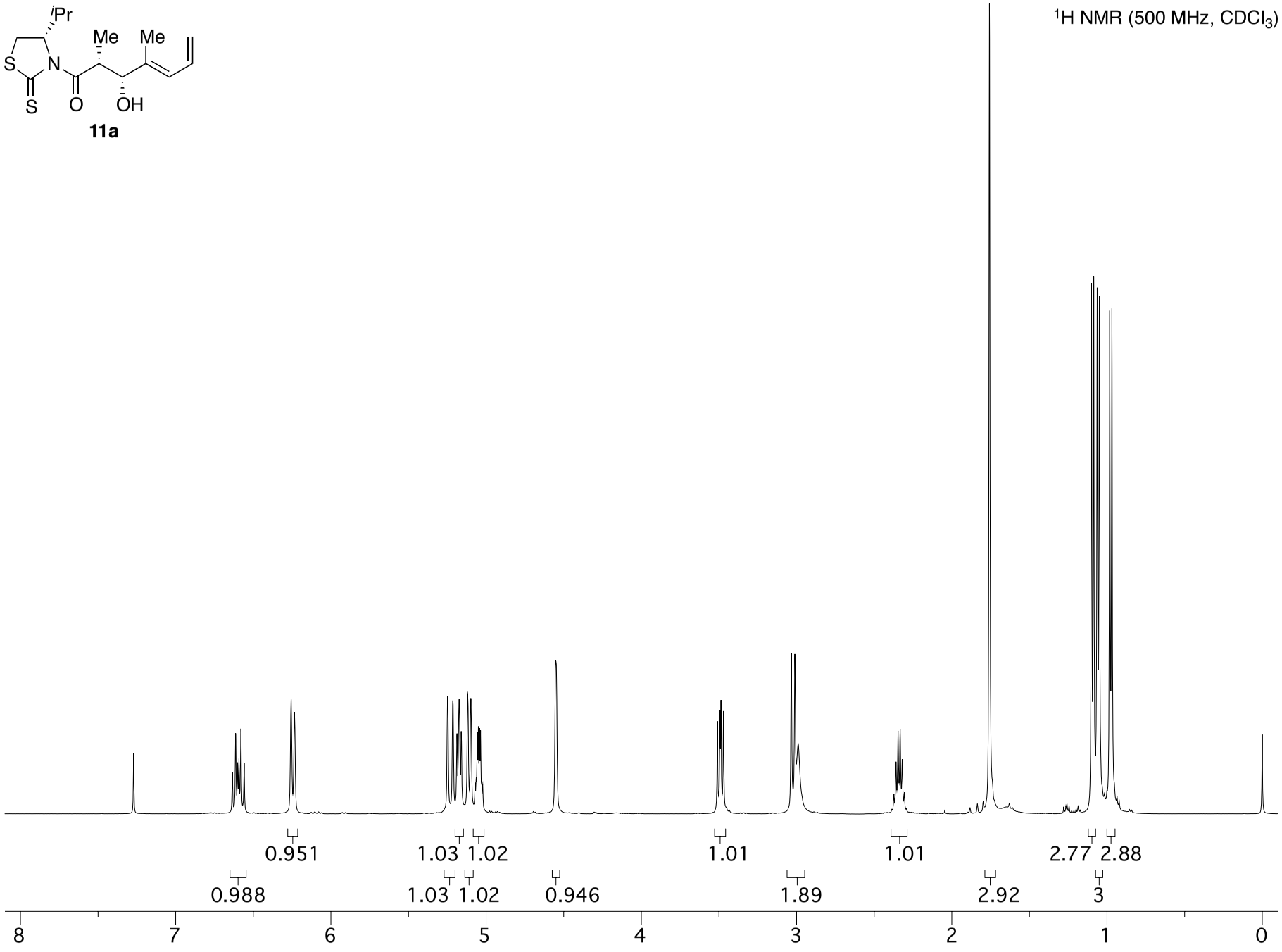


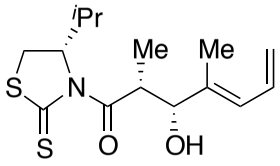
To a yellow solution of *N*-propionyl thiazolidinethione **11**[4] (2.37 g, 10.92 mmol, 1.05 equiv) in CH_2Cl_2 (60 mL) under argon atmosphere at 0 °C was added $TiCl_4$ (1.20 mL, 10.92 mmol, 1.05 equiv) dropwise *via* syringe. After 10 min, $^iPr_2NEt$ (1.99 mL, 11.44 mmol, 1.10 equiv) was added dropwise to the viscous orange solution. The resulting blood-red titanium enolate solution was stirred at 0 °C for 45 min and then cooled to –78 °C. A solution of aldehyde **10**[5] (1.00 g, 10.40 mmol, 1 equiv) in CH_2Cl_2 (15 mL) was added dropwise, with an additional rinse of CH_2Cl_2 (5 mL) to complete the transfer. After stirring at –78 °C for 2 h, the reaction mixture warmed to 0 °C for 30 min and then quenched by pouring into a rapidly stirring biphasic mixture of CH_2Cl_2 (60 mL) and half-saturated NH_4Cl (120 mL). After stirring for 45 min, the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (4 x 15 mL). The combined yellow organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield a viscous yellow-orange oil. The product was purified *via* automated silica column chromatography (0→30% EtOAc/hexanes, 110 g column; TLC R_f = 0.41 in 20% EtOAc/hexanes, UV and anisaldehyde stain) to provide diastereomerically pure aldol adduct **11a** (2.72 g, 80% yield) as a highly viscous yellow oil. This material degrades during storage and should be protected immediately: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.60 (ddd, *J* = 16.8, 10.6, 10.6 Hz, 1H), 6.25 (d, *J* = 11.0 Hz, 1H), 5.23 (d, *J* = 16.8 Hz, 1H), 5.17 (dd, *J* = 7.1, 6.8 Hz, 1H), 5.11 (d, *J* = 10.2 Hz, 1H), 5.05 (qd, *J* = 7.0, 3.4 Hz, 1H), 4.55 (d, *J* = 1.5 Hz, 1H), 3.49 (dd, *J* = 11.5, 8.2 Hz, 1H), 3.02 (d, *J* = 11.5 Hz, 1H), 2.99 (br s, 1H), 2.34 (dqq, *J* = 6.9, 6.8, 6.7 Hz, 1H), 1.76 (s, 3H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.1, 178.0, 136.5, 132.4, 126.2, 117.2, 74.7, 71.9, 40.7, 30.8, 29.8, 19.1, 17.5, 14.0, 10.7 ppm; IR (film) 3500, 2964, 2874, 2360, 2342, 1693, 1456, 1372, 1315, 1279, 1254, 1155, 1092 1036, 987, 908, 876, 841, 668 cm^{-1}; $[\alpha]_D^{24}$ = +308.1° (*c* = 1.00, $CHCl_3$); HRMS (EI): Exact mass calcd for $C_{15}H_{23}NO_2S_2$ $[M]^+$: 313.1170; Found: 313.1161.

(3) This procedure was adapted from: Crimmins, M. T.; Slade, D. J. *Org. Lett.* **2006**, *8*, 2191–2194.

(4) (a) Ferstl, E. M.; Venkatesan, H.; Ambhaikar, N. B.; Snyder, J. P.; Liotta, D. C. *Synthesis* **2002**, *14*, 2075–2083; (b) Galvez, E.; Urpi, F. *Org. Synth.* **2009**, *86*, 70–80.

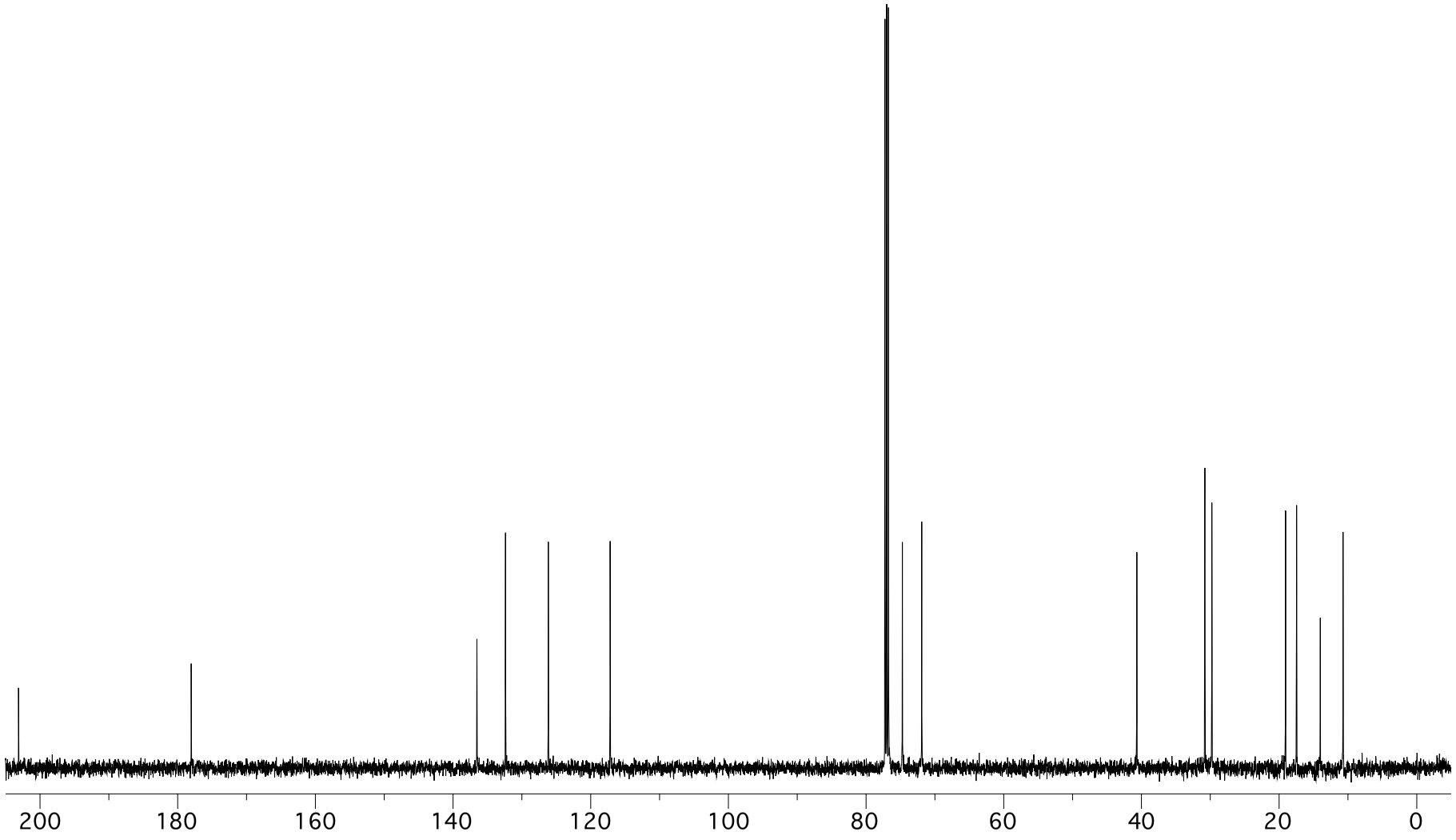
(5) Prepared in one step from 3-ethoxymethacrolein and vinylmagesium bromide: Spangler, C. W.; McCoy, R. K.; Karavakis, A. A. *J. Chem. Soc., Perkin Trans. 1* **1986**, *7*, 1203–1207.


iPr
Me
Me
S
N
S
O
OH
11a
^{1}H NMR (500 MHz, $CDCl_3$)
0.951
1.03
1.02
1.01
1.01
2.77
2.88
0.988
1.03
1.02
0.946
1.89
2.92
3
8
7
6
5
4
3
2
1
0

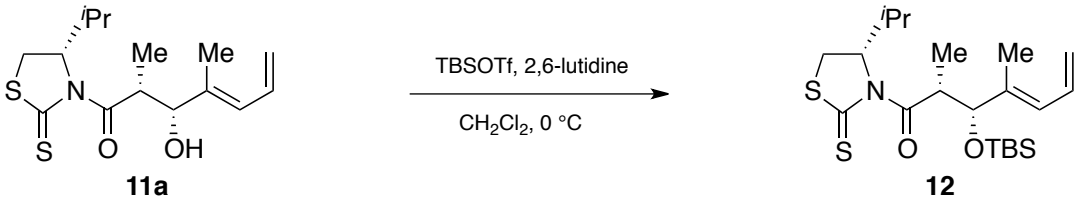


11a

^{13}C NMR (125 MHz, $CDCl_3$)

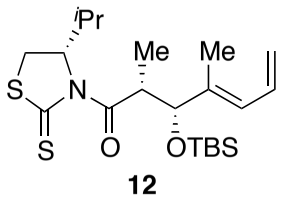


Preparation of Protected Aldol Adduct 12



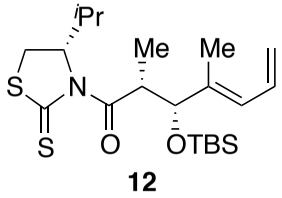
11a **12**

To a solution of aldol adduct **11a** (2.160 g, 6.905 mmol, 1 equiv) in CH_2Cl_2 (13.8 mL) at 0 °C was added 2,6-lutidine (1.04 mL, 8.977 mmol, 1.3 equiv) followed by TBSOTf (1.90 mL, 0.383 mmol, 1.2 equiv) dropwise. The reaction mixture was stirred at 0 °C for 30 min then quenched with 1 *M* HCl (29 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield a yellow oil. The product was purified *via* automated silica column chromatography (0→20% EtOAc/hexanes, 110 g column; TLC R_f = 0.71 in 20% EtOAc/hexanes, UV and anisaldehyde stain) to provide TBS-protected aldol product **12** (2.585 g, 88% yield) as a clear yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.48 (ddd, *J* = 16.9, 10.5, 10.5 Hz, 1H), 5.94 (d, *J* = 10.9 Hz, 1H), 5.23 (ddd, *J* = 8.7, 5.2, 1.1 Hz, 1H), 5.17-5.11 (m, 2H), 5.05 (dd, *J* = 10.2, 1.6 Hz, 1H), 4.35 (d, *J* = 9.1 Hz, 1H), 3.40 (dd, *J* = 11.5, 8.8 Hz, 1H), 2.89 (dd, *J* = 11.5, 1.2 Hz, 1H), 2.14-2.05 (m, 1H), 1.75 (s, 3H), 1.23 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.85 (d, *J* = 7.0 Hz, 3H), 0.07 (s, 3H), –0.02 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.5, 175.9, 138.5, 132.5, 128.6, 117.0, 80.1, 71.4, 42.9, 30.6, 28.2, 25.8, 19.0, 18.2, 16.7, 15.3, 11.9, –4.7, –5.1 ppm; IR (film) 2960, 2930, 2857, 1693, 1471, 1362, 1316, 1251, 1156, 1071, 1018, 910, 880, 839, 776, 663, 562 cm^{-1}; $[\alpha]_D^{25}$ = +199.1° (*c* = 1.00, $CHCl_3$); HRMS (EI): Exact mass calcd for $C_{21}H_{37}NO_2S_2Si$ $[M]^+$: 427.2035; Found: 427.2051.



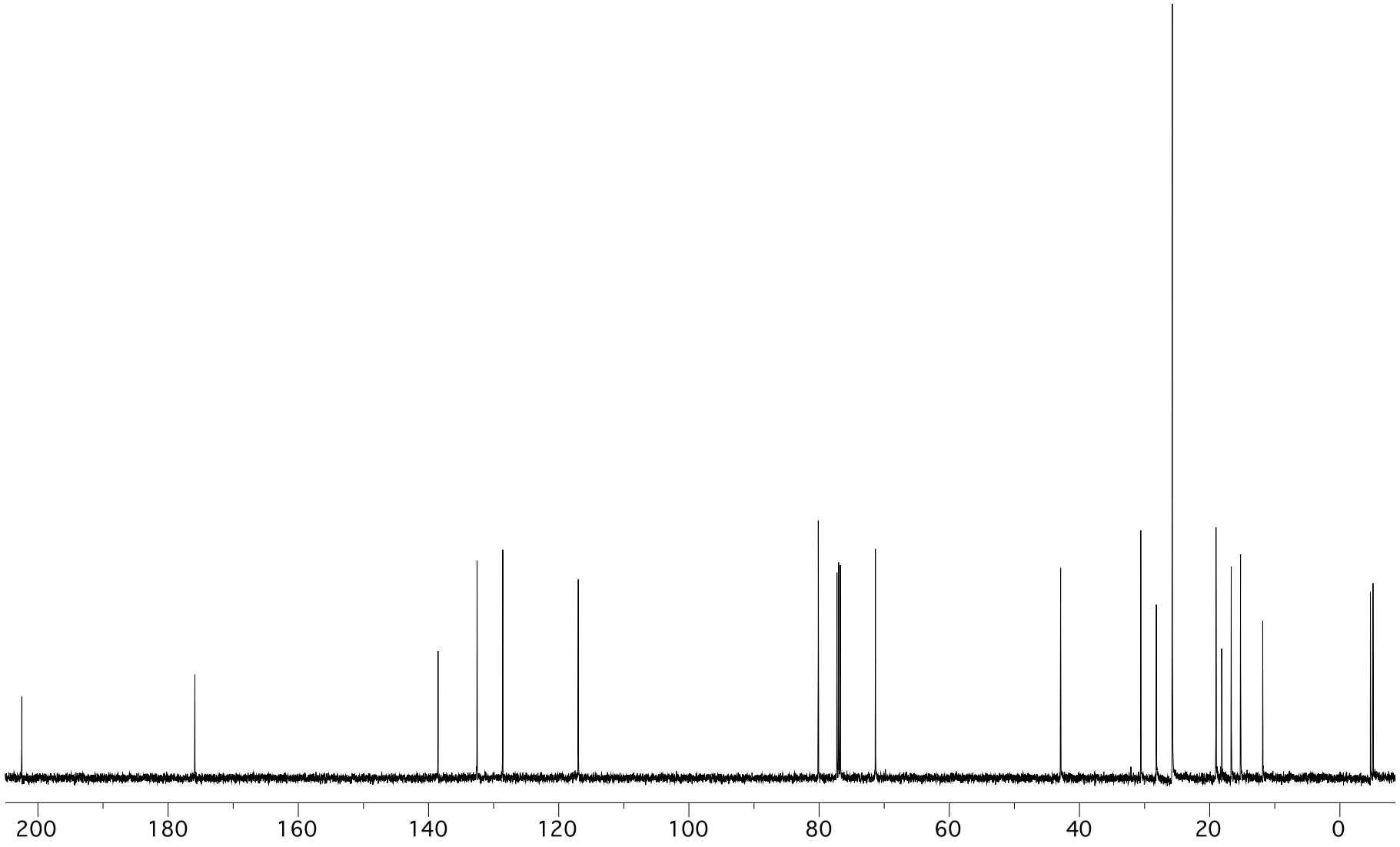
12

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

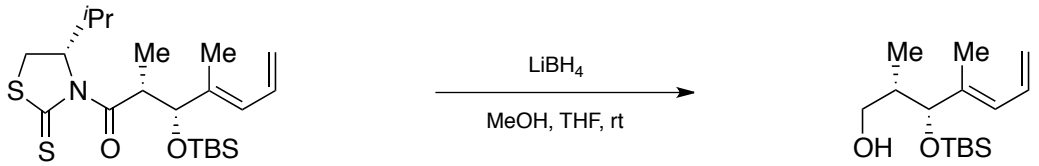


12

^{13}C NMR (125 MHz, $CDCl_3$)

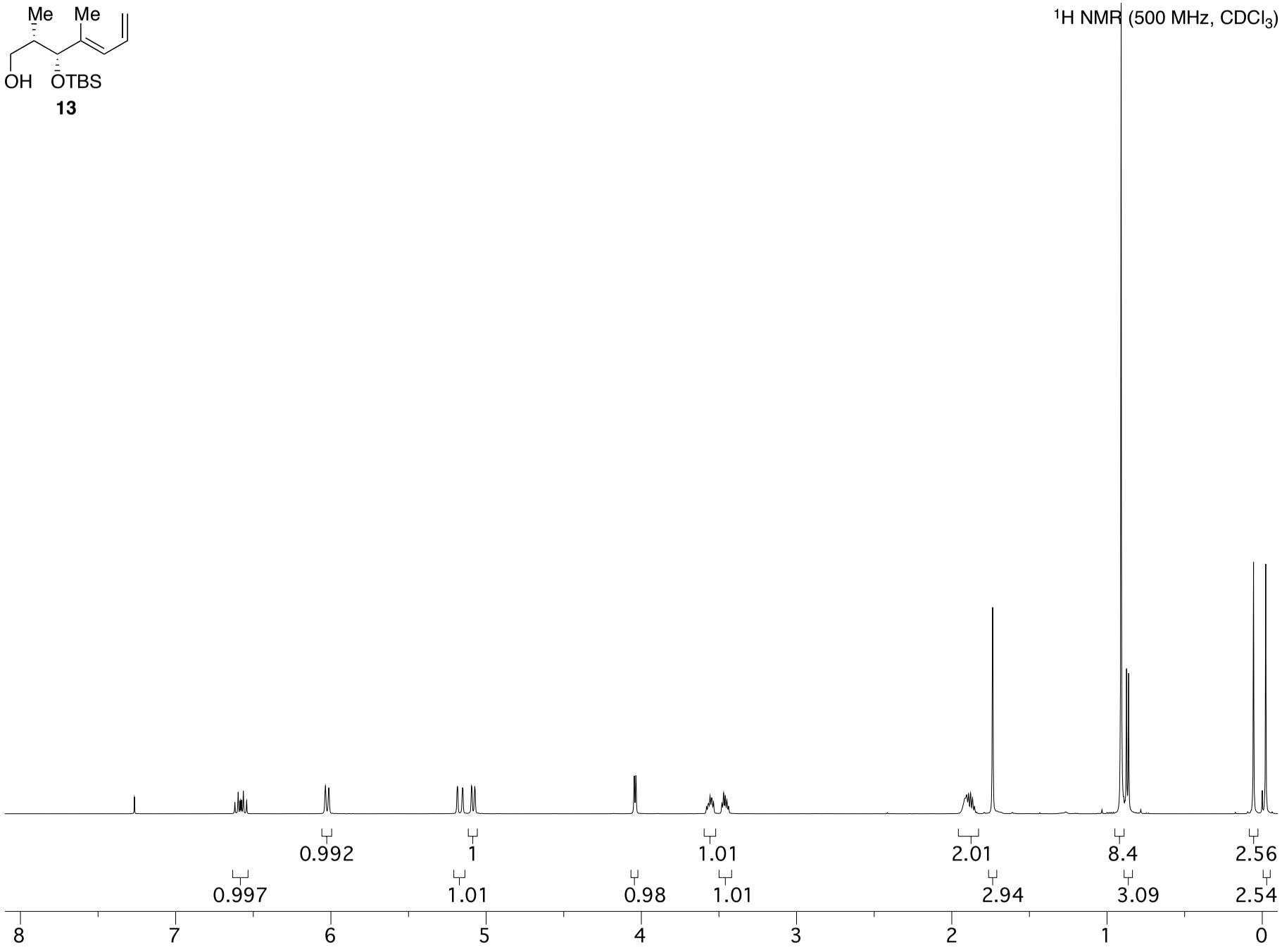


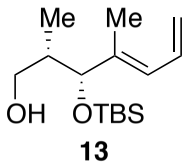
Preparation of Model Hydroformylation Substrate 13



12 **13**

To a stirring solution of TBS-protected aldol adduct **12** (2.89 g, 6.75 mmol, 1 equiv) in THF (34 mL) and methanol (0.81 mL, 20.13 mmol, 3.0 equiv) was added lithium borohydride (440 mg, 20.13 mmol, 3.0 equiv). The color slowly faded from bright yellow to an almost imperceptible yellow. After one hour, the reaction was quenched with saturated aqueous Rochelle's salt (50 mL) and stirred rapidly overnight. The resulting biphasic solution was separated and extracted with ether (3 x 50 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield a white solid and an oily residue. This material was purified *via* automated silica column chromatography (0→20% EtOAc/Hexanes; 110 g column with sample loaded on Celite in the headspace of column; TLC R_f = 0.41 in 20% EtOAc/hexanes, UV and anisaldehyde stain) to provide primary alcohol **13** (1.624 g, 89% yield) as a clear colorless oil.: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.58 (ddd, *J* = 16.8, 10.6, 10.6 Hz, 1H), 6.02 (d, *J* = 11.0 Hz, 1H), 5.17 (dd, *J* = 16.8, 1.3 Hz, 1H), 5.08 (d, *J* = 10.2 Hz, 1H), 4.04 (d, *J* = 5.4 Hz, 1H), 3.56 (ddd, *J* = 10.7, 5.6, 5.6 Hz, 1H), 3.46 (ddd, *J* = 10.7, 5.3, 5.3 Hz, 1H), 1.92 (br. s, 1H), 1.94-1.84 (m, 1H), 1.74 (s, 3H), 0.91 (s, 9H), 0.87 (d, *J* = 6.9 Hz, 3H), 0.06 (s, 3H), –0.02 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.3, 132.5, 126.6, 116.5, 79.2, 65.9, 39.9, 25.8, 18.2, 13.4, 12.0, –4.7, –5.3 ppm; IR (film) 3350, 2957, 2929, 2858, 1472, 1463, 1380, 1361, 1252, 1108, 1006, 987, 905, 865, 838, 775, 676 cm^{-1}; $[\alpha]_D^{24}$ = +12.9° (*c* = 1.00, $CHCl_3$); HRMS (EI): Exact mass calcd for $C_{15}H_{30}O_2Si$ $[M]^+$: 270.2015; Found: 270.2008.


Me
Me
OH
OTBS
13
^{1}H NMR (500 MHz, $CDCl_3$)
0.997
0.992
1.01
1
0.98
1.01
1.01
2.94
2.01
3.09
8.4
2.54
2.56
8
7
6
5
4
3
2
1
0



13

^{13}C NMR (125 MHz, $CDCl_3$)

General Procedure for Hydroformylation

A 4:1 molar ratio of bidentate ligand to rhodium catalyst was prepared by adding Binaphos (11.7 mg, 0.0152 mmol) and $Rh(acac)(CO)_2$ (1.0 mg, 0.0038 mmol) to a 1 dram vial containing a stir bar. Benzene or toluene (1.0 mL, freeze-pump-thaw degassed) was added and stirred magnetically for one minute or less. The bulk of the resulting yellow solution was rapidly transferred *via* pipette (without rinsing) to another 1 dram vial containing the conjugated diene substrate and a stir bar. This reaction vial was quickly placed in a stainless steel pressure vessel (Parr Instrument Company) which was immediately charged with Syngas (CO/H_2, 1:1 v/v, 300 atm), purging three times, and the reaction was stirred at 30–35 °C. To evaluate the hydroformylation progress, the CO/H_2 pressure was released and a small aliquot was concentrated *in vacuo* and analyzed by ^{1}HNMR for percent conversion, branched:linear selectivity, and diastereoselectivity. Upon completion, the residue in the vial was transferred to a 10 mL rbf with appropriate solvent (~1 mL) and was treated with $NaBH_4$ or $MeTi(O^iPr)_3$ according to the specific procedures below. In general, attempts to purify the intermediate aldehyde by silica gel chromatography led to partial epimerization. Fortunately, $NaBH_4$ or $MeTi(O^iPr)_3$ could be added to the crude reaction mixtures, so intermediate aldehyde isolation and purification is unnecessary.

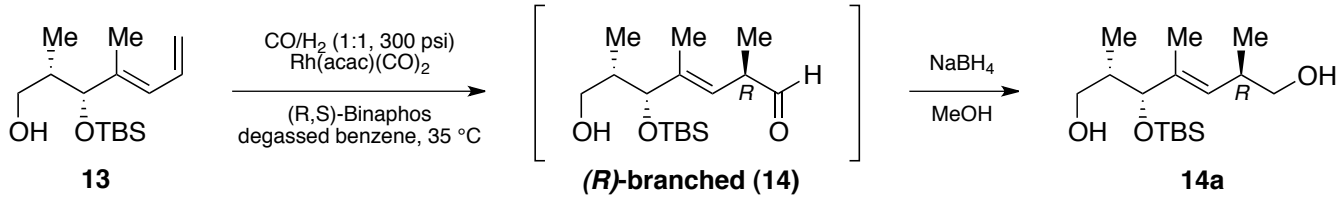
Safety Warning: *Precautions should be taken for working with compressed flammable gasses. The carbon monoxide in Syngas presents an extreme hazard. It is a colorless, odorless and tasteless toxic gas. Inhalation of carbon monoxide can cause headache, dizziness, mental dullness, weakness, sleepiness, nausea, vomiting, unconsciousness and death. These hydroformylation reactions should be conducted in a ventilated fume hood and a CO detector should be monitored to ensure a safe laboratory environment.*

Preparation of $MeTi(O^iPr)_3$

Following the general procedure of Reetz,[6] A vial containing a solution of $ClTi(O^iPr)_3$ (477.8 μL, 2 mmol) in Et_2O (1 mL) was cooled to –40 °C. MeLi (1.13 mL at 1.6 *M* in Et_2O, 1.8 mmol) was added with stirring and the bath was allowed to warm to rt. After 2.5 hours the vial was centrifuged at high speed for 4 min to settle the precipitated LiCl. The yellow supernatant was assumed to be 0.84 M in $MeTi(O^iPr)_3$ and was used immediately.

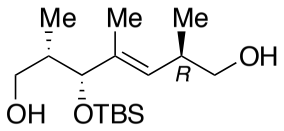
(6) Reetz, M. T.; Westermann, J.; Steinbach, R.; Wenderoth, B.; Peter, R.; Ostarek, R.; Maus, S. *Chem. Ber. Recl.* **1985,** *118*, 1421–1440.

(*R*)-Hydroformylated/Reduced Model System 14a



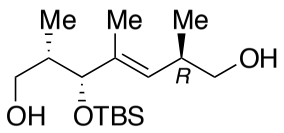
13 ***(R)*-branched (14)** **14a**

Model substrate diene **13** (31.1 mg, 0.115 mmol) was subjected to the general hydroformylation conditions using (*R*,*S*)-Binaphos in degassed benzene (0.2 mL) with 100 psi syngas at 35 °C for 113 h. The crude aldehyde product was diluted with EtOAc (1 mL) and methanol (20 drops) and $NaBH_4$ (~ 5 mg) was added. The reaction was stirred at room temperature for 10 min and was then quenched by adding saturated aqueous Rochelle's salt (1 mL) and stirred overnight. The aqueous phase was further diluted with water (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield the reduced product (100% conversion, branched/linear = 94:6, *R*/*S* = 93:7) as a yellow oil. An analytical sample was obtained *via* automated silica column chromatography (0→50% EtOAc/hexanes, 10 g column; TLC R_f = 0.35 in 40% EtOAc/hexanes, anisaldehyde stain) to provide pure (*R*)-hydroformylated/reduced model system **14a** as a single observable isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.17 (d, *J* = 9.6 Hz, 1H), 3.95 (d, *J* = 5.6 Hz, 1H), 3.53 (dd, *J* = 10.7, 6.8 Hz, 1H), 3.46 (dd, *J* = 9.6, 5.9 Hz, 1H), 3.44 (dd, *J* = 10.6, 5.4 Hz, 1H), 3.40 (dd, *J* = 10.4, 7.5 Hz, 1H), 2.69-2.60 (m, 1H), 2.09 (br. s, 1H), 1.88-1.80 (m, 1H), 1.64 (d, *J* = 1.2 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.04 (s, 3H), –0.03 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.2, 128.8, 79.4, 67.7, 65.8, 39.6, 35.1, 25.8, 18.1, 16.8, 13.4, 12.3, –4.5, –5.2 ppm; IR (film) 3336, 2956, 2929, 2857, 1472, 1451, 1251, 1028, 870, 837, 774, 673 cm^{-1}; $[\alpha]_D^{24}$ = +33.9° (*c* = 1.00, $CHCl_3$); HRMS (EI): Exact mass calcd for $C_{16}H_{34}O_3SiNa$ $[M+Na]^+$: 325.2175; Found: 325.2184.



14a

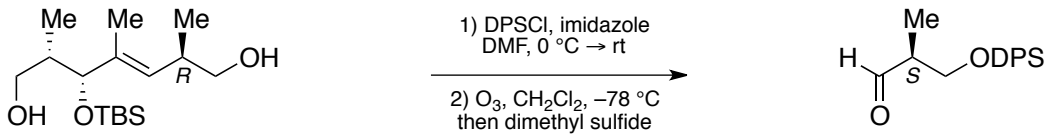
^{1}H NMR (500 MHz, $CDCl_3$)



14a

^{13}C NMR (125 MHz, $CDCl_3$)

Proof of Hydroformylation Stereochemistry by Formation of Aldehyde 14b



14a **14b**

To a solution of diol **14a** (78.8 mg, 0.2605 mmol, 1 equiv: from hydroformylation using (*R*,*S*)-Binaphos) and imidazole (88.7 mg, 1.3023 mmol, 5.0 equiv) in DMF (1.0 mL) at 0 °C was added *tert*-butyldiphenylsilyl chloride (DPS-Cl, 0.147 mL, 0.573 mmol, 2.2 equiv). The reaction was immediately warmed to rt. After stirring for 1 h, an additional volume of DPS-Cl (50 μL) was added and the reaction was stirred overnight. The reaction was diluted with water (5 mL), pentane (5 mL) and Et_2O (5 mL) and the layers were separated. The aqueous layer was extracted with pentane (3 x 5 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield a clear oil. The crude material was purified *via* automated silica column chromatography (0→5% Et_2O/hexanes, 10 g column; TLC R_f = 0.76 in 5% Et_2O/hexanes, UV and anisaldehyde stain) to provide the disilylated intermediate (187.2 mg, 92%) as a clear oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67-7.61 (m, 8H), 7.44-7.31 (m, 12H), 5.13 (d, *J* = 9.5 Hz, 1H), 3.94 (d, *J* = 5.9 Hz, 1H), 3.49 (ap. ddd, *J* = 9.8, 5.5, 4.3 Hz, 2H), 3.36 (ap. ddd, *J* = 9.9, 6.8, 3.1 Hz, 2H), 2.60-2.44 (m, 1H), 1.78-1.58 (m, 1H), 1.40 (d, *J* = 1.1 Hz, 3H), 1.05 (s, 9H), 1.04 (s, 9H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H), 0.84 (s, 9H), –0.03 (s, 3H), –0.11 (s, 3H) ppm.

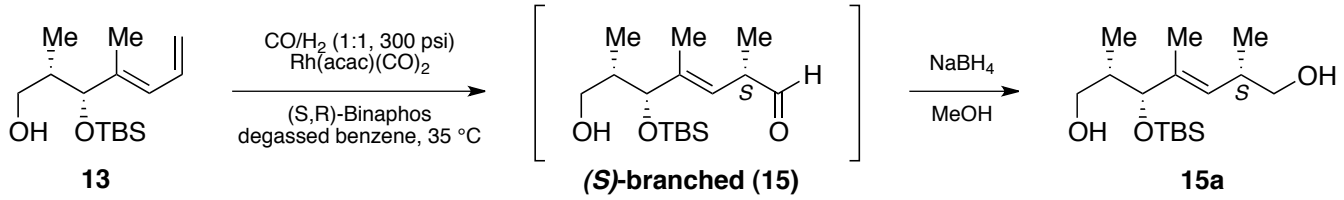
Ozonolysis was accomplished by bubbling a stream of ozone through a solution of disilylated intermediate (181.3 mg, 0.2326 mmol) in CH_2Cl_2 (~ 3 mL) at –78 °C for exactly 1 min. (After 30 s, the solution had turned a light blue color). Oxygen gas was bubbled through the solution for an additional 2–3 min followed by nitrogen gas for 5 min. Dimethyl sulfide (~ 10 drops) was added and the solution was stirred rapidly overnight while the dry ice/acetone bath was allowed to gradually warm to rt. The aldehyde product was concentrated gingerly and purified *via* automated silica column chromatography (0→10% Et_2O/hexanes, 35 g column; TLC R_f = 0.15 in straight hexanes, 2,4-DNP stain) to provide known aldehyde **14b** (59.9 mg, 79% yield) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (d, *J* = 1.6 Hz, 1H), 7.67-7.62 (m, 4H), 7.48-7.35 (m, 6H), 3.90 (dd, *J* = 10.3, 5.1 Hz, 1H), 3.84 (dd, *J* = 10.3, 6.3 Hz, 1H), 2.63-2.50 (m, 1H), 1.10 (d, *J* = 7.0 Hz, 3H), 1.04 (s, 9H) ppm; $[\alpha]_D^{24}$ = +26.4° (*c* = 1.50, $CHCl_3$).

The published optical rotation for (*R*)-3-(*tert*-butyldiphenylsilyloxy)-2-methylpropanal is $[\alpha]_D^{20}$ = –24.7° (*c* = 1.50, $CHCl_3$).[7] The published optical rotation for the (*S*) enantiomer is $[\alpha]_D$ = +20° (*c* = 1.00, $CHCl_3$).[8]

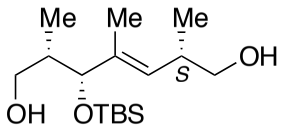
(7) Johns, B. A.; Grant, C. M.; Marshall, J. A. *Org. Synth.* **2002**, *79*, 59.

(8) Wasicak, J. T.; Donaldson, W. A. *Tetrahedron: Asymmetry* **1998**, *9*, 133–140.

(*S*)-Hydroformylated/Reduced Model System 15a

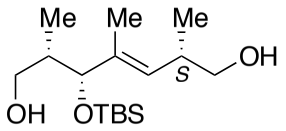


Model substrate diene **13** (32.7 mg, 0.121 mmol) was subjected to the general hydroformylation conditions using (*S*,*R*)-Binaphos in degassed benzene (0.2 mL) with 100 psi syngas at 35 °C for 113 h. The crude aldehyde product was diluted with EtOAc (1 mL) and methanol (20 drops) and $NaBH_4$ (~ 5 mg) was added. The reaction was stirred at room temperature for 10 min and was then quenched by adding saturated aqueous Rochelle's salt (1 mL) and stirred overnight. The aqueous phase was further diluted with water (10 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield the reduced product (100% conversion, branched/linear = 92:8, *R*/*S* = 6:94) as a yellow oil. An analytical sample was obtained *via* automated silica column chromatography (0→50% EtOAc/hexanes, 10 g column; TLC R_f = 0.24 in 40% EtOAc/hexanes, anisaldehyde stain) to provide pure (*S*)-hydroformylated/reduced model system **15a** as a single observable isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.08 (d, *J* = 9.7 Hz, 1H), 3.69 (d, *J* = 8.3 Hz, 1H), 3.53 (dd, *J* = 10.1, 4.9 Hz, 1H), 3.41 (dd, *J* = 11.5, 3.5 Hz, 1H), 3.36 (dd, *J* = 11.5, 7.5 Hz, 1H), 3.24 (dd, *J* = 9.8, 9.8 Hz, 1H), 3.20 (br. s, 2H), 2.70-2.60 (m, 1H), 1.86-1.77 (m, 1H), 1.64 (d, *J* = 1.1 Hz, 3H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.872 (s, 9H), 0.869 (d, *J* = 5.1 Hz, 3H), 0.02 (s, 3H), –0.03 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.7, 129.6, 83.1, 67.9, 65.7, 40.3, 34.8, 25.8, 18.1, 16.2, 14.4, 12.3, –4.5, –5.1 ppm; IR (film) 3342, 2956, 2929, 2858, 1472, 1462, 1250, 1065, 1036, 874, 836, 774, 670 cm^{-1}; $[\alpha]_D^{24}$ = –17.0° (*c* = 1.00, $CHCl_3$); HRMS (EI): Exact mass calcd for $C_{16}H_{34}O_3SiNa$ $[M+Na]^+$: 325.2175; Found: 325.2173.



15a

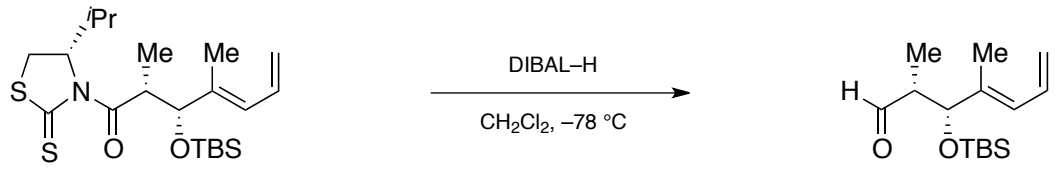
^{1}H NMR (500 MHz, $CDCl_3$)



15a

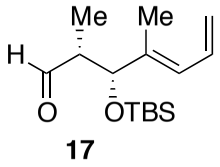
^{13}C NMR (125 MHz, $CDCl_3$)

Preparation of Aldehyde 17



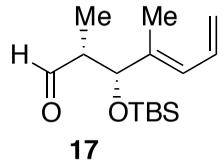
12 **17**

To a solution TBS-protected aldol adduct **12** (1.971 g, 4.608 mmol, 1.0 equiv) in CH_2Cl_2 (46 mL) at –78 ºC was added DIBAL-H (1.0 M in CH_2Cl_2; 9.2159 mL, 9.2159 mmol, 2.0 equiv) dropwise *via* syringe. The color rapidly faded to pale yellow, and the reaction mixture was stirred at –78 ºC for 60 min until no starting material remained by TLC. The reaction was quenched by addition of methanol (16 mL) and was then warmed to room temperature. Saturated aqueous Rochelle's salt (60 mL) was added and the biphasic mixture was stirred until two clear layers formed. The aqueous phase was extracted with CH_2Cl_2 (3 x 30 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield a clear oil. The product was purified *via* automated silica column chromatography (10→30% CH_2Cl_2/hexanes, 110 g column; TLC R_f = 0.72 in 20% EtOAc/hexanes, UV and anisaldehyde stain) to provide aldehyde **17** (1.1213 g, 91% yield) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.68 (d, *J* = 1.6 Hz, 1H), 6.54 (ddd, *J* = 16.8, 10.9, 10.3 Hz, 1H), 6.05 (d, *J* = 11.0 Hz, 1H), 5.18 (dd, *J* = 16.8, 1.5 Hz, 1H), 5.10 (dd, *J* = 10.2, 1.5 Hz, 1H), 4.39 (d, *J* = 5.1 Hz, 1H), 2.51 (ddq, *J* = 6.9, 5.1, 1.6 Hz, 1H), 1.71 (s, 3H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 3H), –0.02 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.4, 137.5, 132.2, 127.2, 117.3, 76.8, 50.9, 25.7, 18.1, 13.2, 8.4, –4.6, –5.3 ppm; IR (film) 2956, 2930, 2858, 2712, 1726, 1472, 1389, 1253, 1142, 1110, 1071, 1034, 1006, 988, 907, 838, 776, 680 cm^{-1}; $[\alpha]_D^{24}$ = +19.3° (*c* = 1.00, $CHCl_3$); HRMS (EI): Exact mass calcd for $C_{15}H_{28}O_2Si$ $[M]^+$: 268.1859; Found: 268.1852.



17

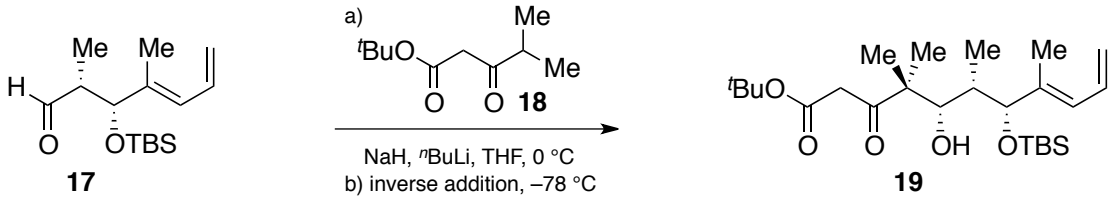
^{1}H NMR (500 MHz, $CDCl_3$)



17

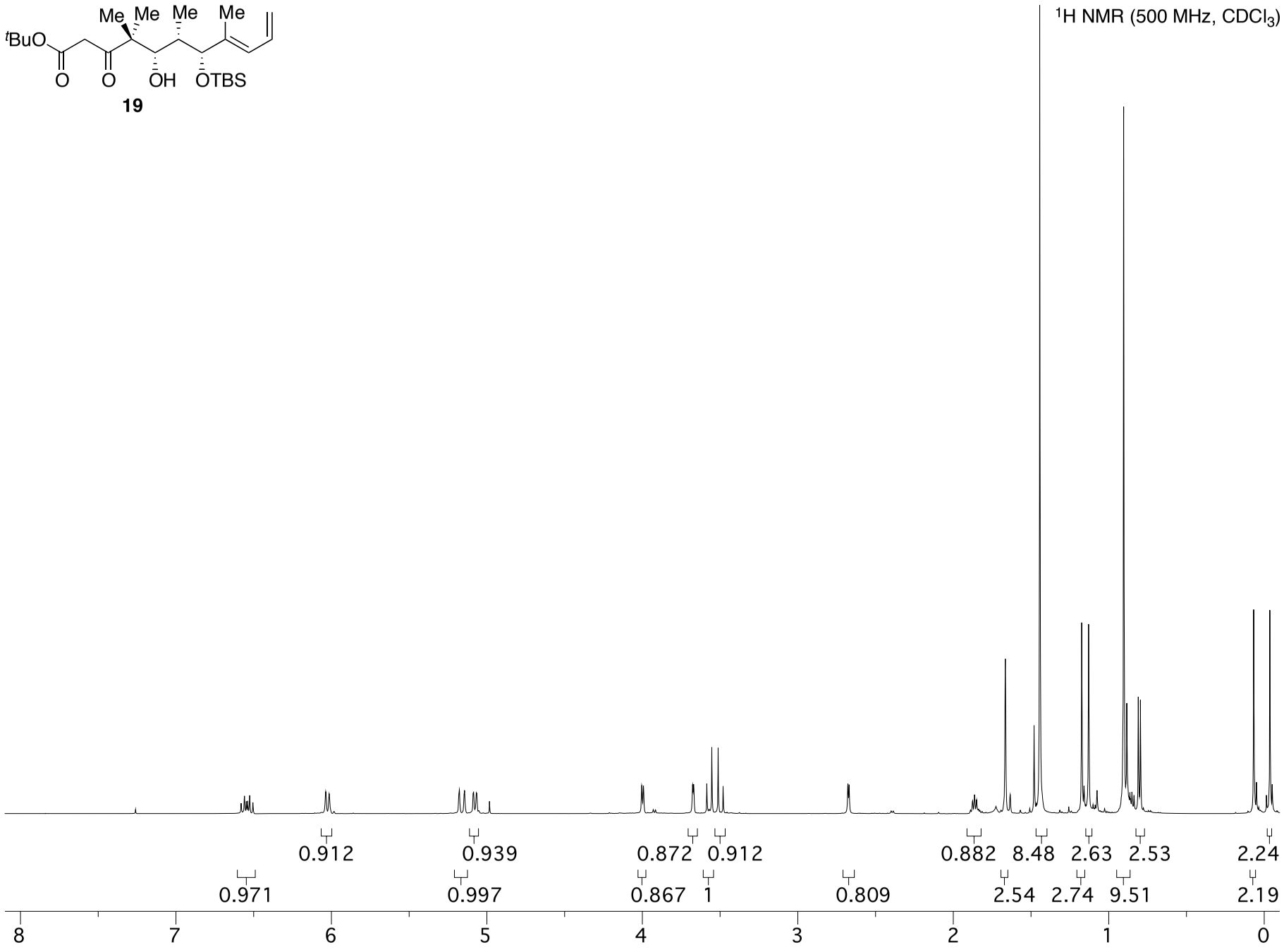
^{13}C NMR (125 MHz, $CDCl_3$)

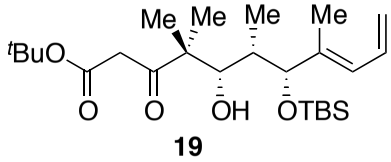
Preparation of β-Hydroxy Ketone 19



A suspension of NaH (60% dispersion in mineral oil; 788 mg, 19.7 mmol, 4.5 equiv) in THF (44 mL) was cooled to 0 ºC. A solution of *t*-butyl β-keto ester **18**[9] (2.48 mL, 13.14 mmol, 3 equiv) in THF (18 mL plus a 4 mL wash) was added dropwise *via* cannula. After 15 min, *n*-BuLi (1.91 *M* in hexanes; 6.88 mL, 13.14 mmol, 3 equiv) was added and the solution gradually took a bright yellow color. The yellow solution was stirred at 0 ºC for 18 min and then cooled to –78 ºC. A solution of aldehyde **17** (1.176 g, 4.380 mmol, 1 equiv) in THF (17 mL plus a 2.5 mL wash) was added dropwise *via* cannula. The resulting peachy-pink solution was stirred at –78 ºC for 1 h and then quenched with saturated NH_4Cl (30 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield a clear oil. Although the minor diastereomer was never isolated, the absence of significant impurity/isomer peaks in the NMR of the unpurified material indicated a diastereomer ratio ≥ 10:1. The product was purified *via* automated silica column chromatography (0→20% EtOAc/hexanes, 110 g column; TLC R_f = 0.50 in 20% EtOAc/hexanes, UV and anisaldehyde or 2,4-DNP stain) to provide diastereomerically pure β-hydroxy ketone **19** (1.3682 g, 69% yield) as a clear colorless oil. This material exists as an approximately 10:1 mixture of keto:enol forms in $CDCl_3$ solution: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.54 (ddd, *J* = 16.8, 10.6, 10.6 Hz, 1H), 6.03 (d, *J* = 11.0 Hz, 1H), 5.16 (dd, *J* = 16.8, 1.7 Hz, 1H), 5.08 (dd, *J* = 10.1, 1.6 Hz, 1H), [4.98 (s, enol)], 4.00 (d, *J* = 5.5 Hz, 1H), [3.92 (d, *J* = 7.0 Hz, enol)], 3.67 (d, *J* = 3.4 Hz, 1H), 3.57 (d, *J* = 16.0 Hz, 1H), 3.50 (d, *J* = 16.0 Hz, 1H), 2.67 (d, *J* = 4.0 Hz, 1H), [2.39 (d, *J* = 6.7 Hz, enol)] 1.89-1.84 (m, 1H), 1.67 (s, 3H), 1.44 (s, 9H), 1.17 (s, 3H), 1.13 (s, 3H), 0.90 (s, 9H), 0.80 (d, *J* = 6.9 Hz, 3H), 0.07 (s, 3H), –0.04 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.3, 167.2, 138.2, 132.3, 127.3, 116.8, 82.3, 81.5, 78.5, 52.3, 47.5, 37.2, 28.3, 28.0, 25.9, 22.7, 20.8, 18.1, 13.3, 8.3, –4.7, –5.2 ppm; IR (film) 3447, 2955, 2931, 2858, 1733, 1717, 1705, 1473, 1458, 1393, 1369, 1319, 1254, 1154, 1066, 1006, 837, 776 cm^{-1}; $[\alpha]_D^{24}$ = –10.7° (*c* = 1.00, $CHCl_3$); HRMS (EI): Exact mass calcd for $C_{25}H_{46}O_5Si$ $[M]^+$: 454.3115; Found: 454.3100.

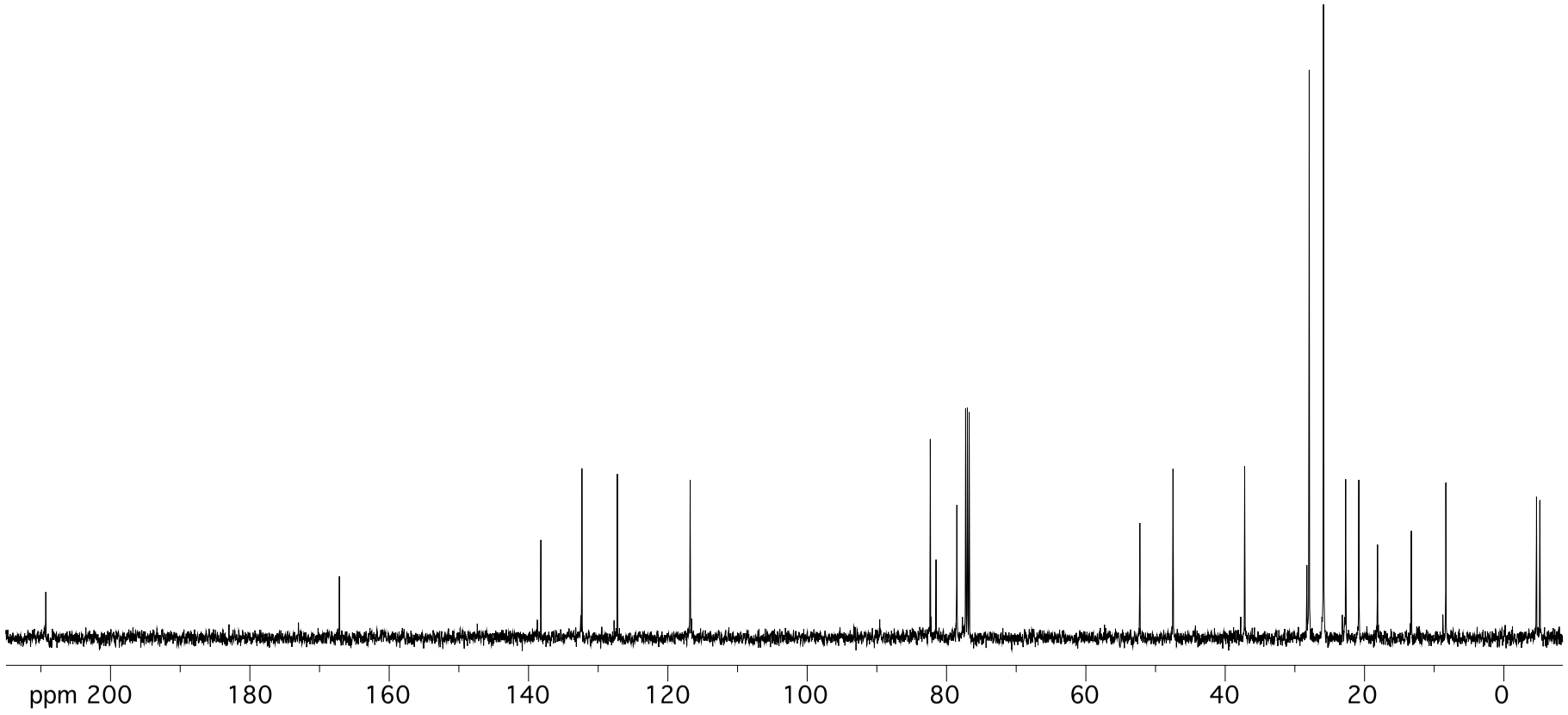
(9) (a) Meyer, W. L.; Brannon, M. J.; da G. Burgos, C.; Goodwin, T. E.; Howard, R. W. *J. Org. Chem*. **1985**, *50*, 438–447. (b) Oikawa,Y.; Yoshioka, T.; Sugano, K.; Yonemitsu O. *Org. Synth.* **1985**, *63*, 198.(c) Sørenson, U. S.; Falch, E.; Krogsgaard-Larsen, P. *J. Org. Chem.* **2000**, *65*, 1003–1007.


Me Me Me Me
tBuO
O O OH OTBS
19
1H NMR (500 MHz, CDCl3)
0.912
0.939
0.872
0.912
0.882
8.48
2.63
2.53
2.24
0.971
0.997
0.867
1
0.809
2.54
2.74
9.51
2.19
8
7
6
5
4
3
2
1
0

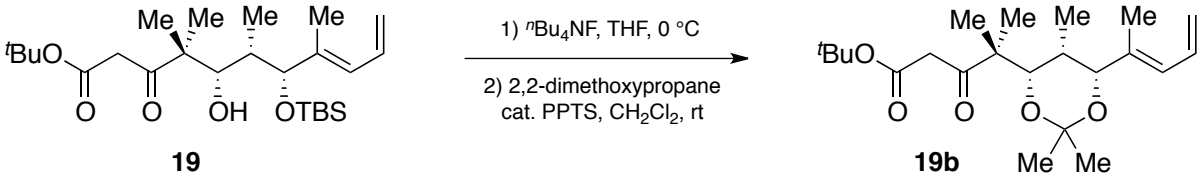


19

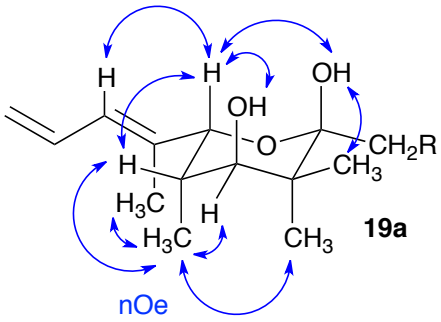
^{13}C NMR (125 MHz, $CDCl_3$)



Proof of Stereochemistry by Formation of Acetonide 19b



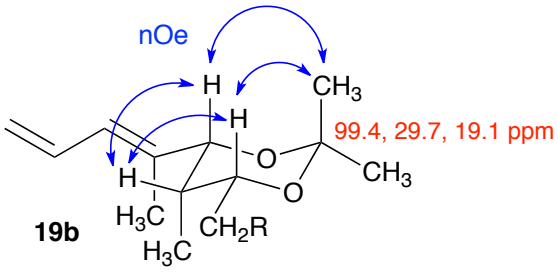
To a solution of β-hydroxy ketone **19** (140.8 mg,0.31 mmol, 1 equiv) in THF (3.1 mL) at 0 °C was added TBAF (1.584 mL of a 1.0 M solution in THF, 1.548 mmol, 5 equiv) dropwise *via* syringe. The resulting pale yellow solution was stirred for 30 min at 0 °C and was then warmed to rt and stirred for 5h. The reaction was quenched by the addition of water (6 mL) and was extracted with CH_2Cl_2 (3 x 6 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield an interconverting mixture of acyclic keto alcohol and cyclic hemiacetal as a clear oil. The product mixture was purified *via* automated silica column chromatography (0→30% EtOAc/hexanes, 10 g column; TLC R_f = 0.44 (keto alcohol) and 0.15 (lactol) in 20% EtOAc/hexanes, UV) to provide deprotected intermediate **19a** (47.1 mg, 45% yield) as a clear colorless oil. The equilibrium mixture of products strongly favors the lactol form in $CDCl_3$ solution: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.62 (ddd, *J* = 16.8, 11.0, 10.4 Hz, 1H), 6.17 (d, *J* = 11.4 Hz, 1H), 5.97 (s, 1H), 5.12 (dd, *J* = 16.8, 1.7 Hz, 1H), 5.02 (dd, *J* = 10.3, 1.8 Hz, 1H), 4.74 (br. s, 1H), 4.03 (d, *J* = 10.5 Hz, 1H), 3.35 (dd, *J* = 10.5, 2.2 Hz, 1H), 2.57 (d, *J* = 14.6 Hz, 1H), 2.52 (d, *J* = 14.6 Hz, 1H), 2.20-2.13 (m, 1H), 1.69 (s, 3H), 1.48 (s, 9H), 1.15 (s, 3H), 1.02 (s, 3H), 0.84 (d, *J* = 7.7 Hz, 3H). ppm



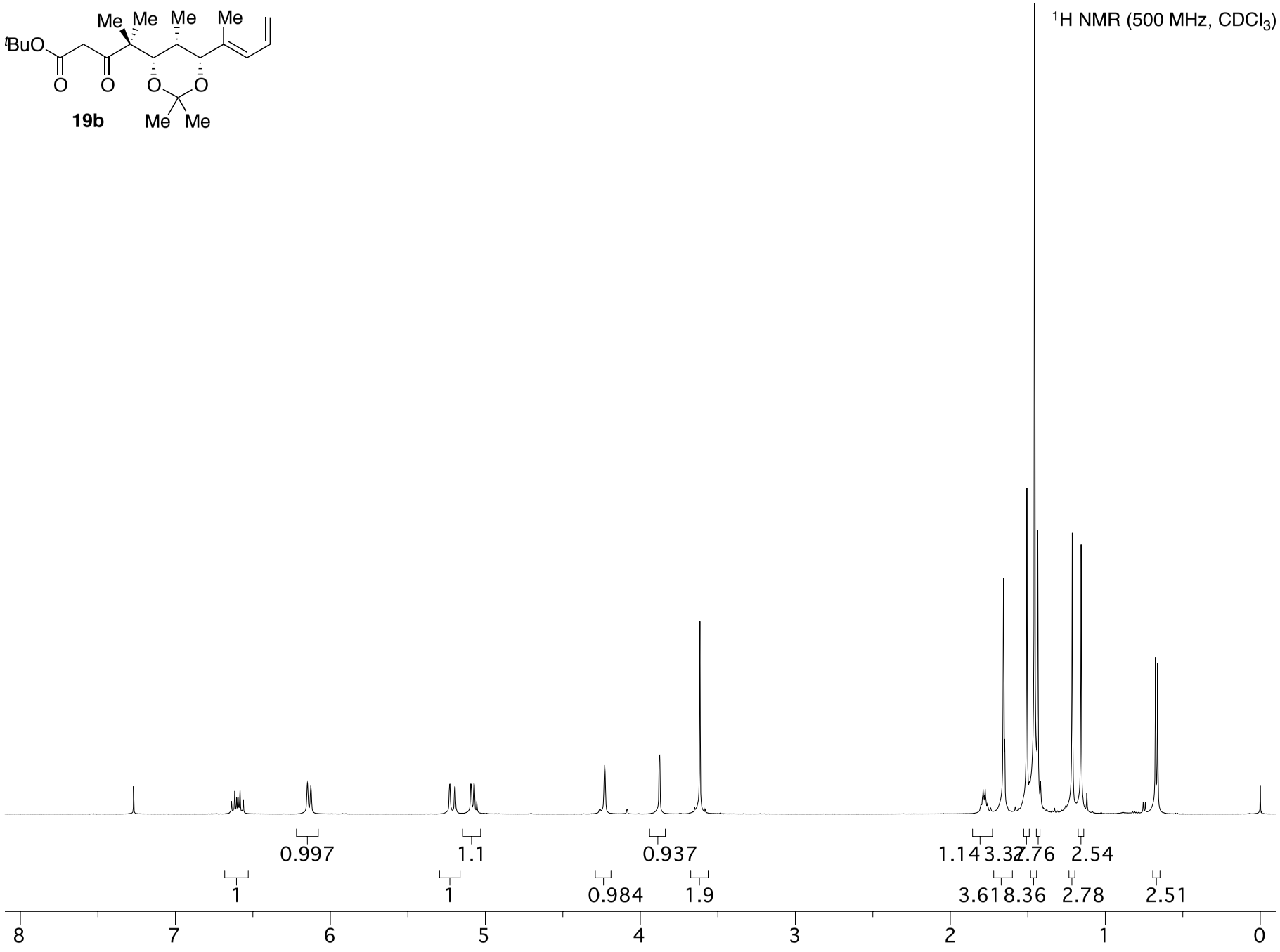
The entire amount of intermediate lactol **19a** (47.1 mg, 0.138 mmol, 1 equiv) was dissolved in CH_2Cl_2 (1.4 mL) and 2,2-dimethyoxypropane (1.0 mL, 7.99 mmol, 58 equiv) and a catalytic amount of PPTS (approximately 10 mg) was added. After 2 h at rt, the reaction was quenched with aqueous $NaHCO_3$ (5 mL) and was extracted with CH_2Cl_2 (2 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield a clear oil. The product was purified *via* automated silica column chromatography (0→15% EtOAc/hexanes, 10 g column; TLC R_f = 0.72 in 20% EtOAc/hexanes, UV) to provide acetonide **19b** (34.5 mg, 66% yield) as a clear colorless oil. This material exists as an approximately 15:1 mixture of keto:enol forms in $CDCl_3$ solution: ^{1}H NMR (500 MHz, $CDCl_3$) δ [12.59 (s, enol)], 6.60 (ddd, *J* = 16.8, 10.6, 10.6 Hz, 1H), 6.14 (d, *J* = 11.1 Hz, 1H), 5.21 (d, *J* = 16.7 Hz, 1H), 5.08 (d, *J* = 10.1 Hz, 1H), [5.06 (s, enol)], 4.23 (s, 1H), 3.88 (d, *J* = 1.5 Hz, 1H), 3.62 (s, 2H), 1.78 (dq, *J* = 6.8, 1.5 Hz, 1H), 1.66 (s, 3H), 1.51 (s, 3H), 1.46 (s, 9H), 1.44 (s, 3H), 1.21 (s, 3H), 1.16 (s, 3H), 0.67 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.6, 167.6, 135.4, 132.4, 124.8, 116.7, 99.4, 81.0, 79.5, 76.9, 51.1, 48.6, 32.2, 29.7, 28.0, 23.1, 20.6, 19.1, 13.8, 6.1 ppm; IR (film) 3084, 2981, 2937,

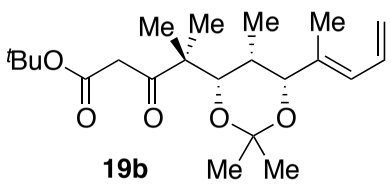
2875, 1739, 1704, 1652, 1601, 1458, 1392, 1381, 1368, 1316, 1257, 1201, 1169, 1145, 1121, 1106, 1053, 1013, 990, 910, 868, 838, 761, 654 cm^{-1}; $[\alpha]_D^{24} = -11.1°$ (c = 1.00, CH_2Cl_2); HRMS (FAB): Exact mass calcd for $C_{22}H_{36}O_5Na$ $[M+Na]^+$: 403.2460; Found: 403.2460.

The nOe data for cyclic compounds **19a** and **19b** support the relative stereochemical assignments. The chemical shifts of 99.4, 29.7, and 19.1 ppm for the acetonide carbons furthermore indicate a *syn* relationship between the oxygen substituents at C5 and C7.[10]



(10) (a) Rychnovsky, S. D.; Skalitzky, D. J. *Tetrahedron Lett*. **1990**, *31*, 945–948. (b) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett*. **1990**, *31*, 7099-7100. (c) Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. *Acc. Chem. Res*. **1998**, *31*, 9–17.


tBuO
Me
Me
Me
Me
O
O
O
O
Me
Me
19b
^{1}H NMR (500 MHz, $CDCl_3$)
0.997
1.1
0.937
1.14
3.32
2.76
2.54
1
1
0.984
1.9
3.61
8.36
2.78
2.51
8
7
6
5
4
3
2
1
0

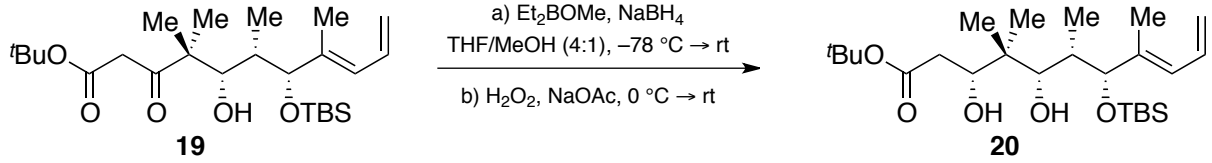


19b

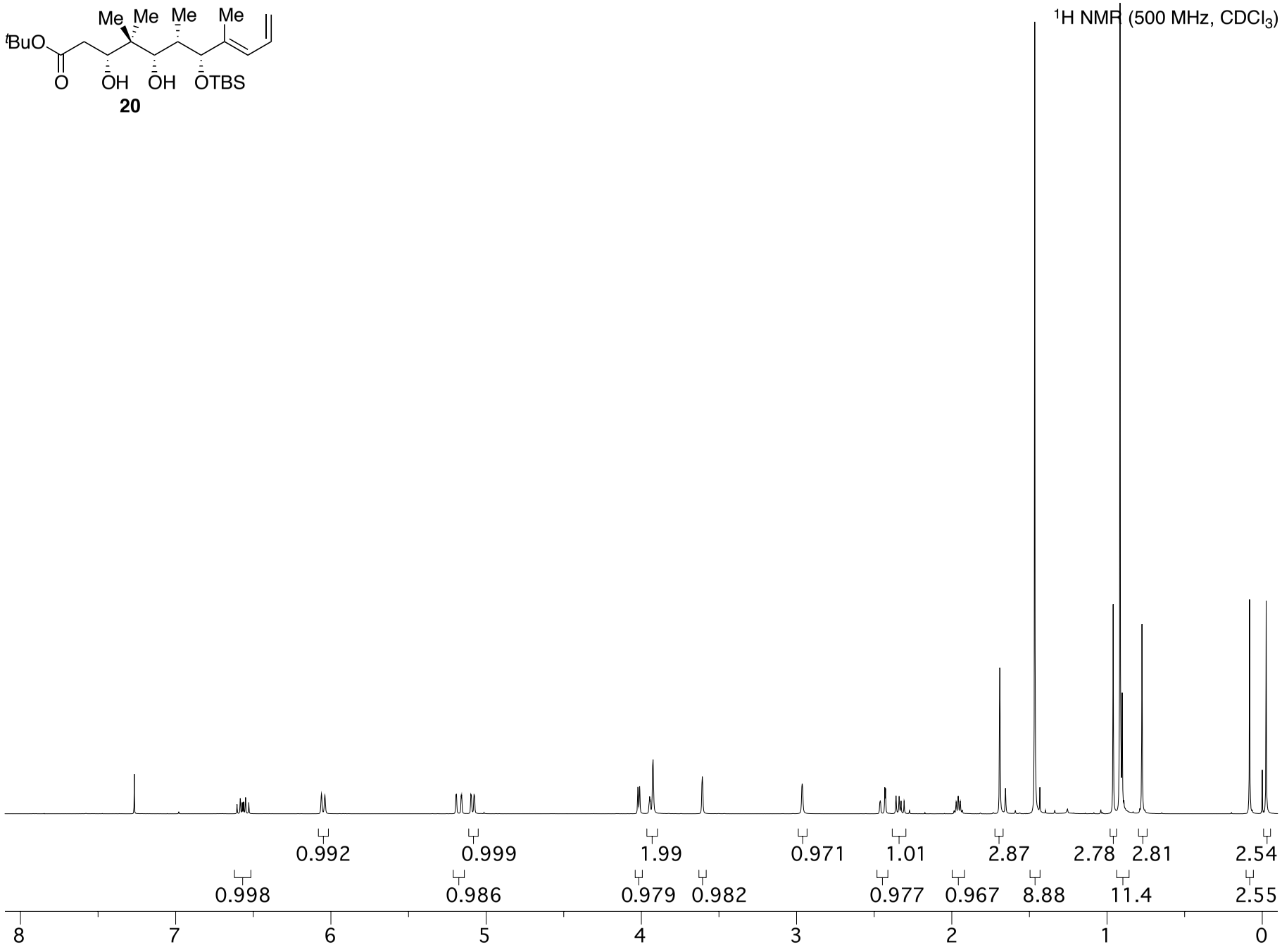
^{13}C NMR (125 MHz, $CDCl_3$)

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

Preparation of Diol 20



To a solution of β-hydroxy ketone **19** (74.3 mg, 0.1634 mmol, 1 equiv) in THF (0.82 mL) and MeOH (205 μL) was added Et_2BOMe (25.8 μL, 0.1961 mmol, 1.2 equiv) dropwise. The reaction mixture was cooled to –78 °C and the septum was briefly removed to add $NaBH_4$ (12.4 mg, 0.3268 mmol, 2.0 equiv) in one portion. The reaction was stirred at –78 °C for 30 min and then at rt for another 90 min. The reaction was diluted with THF (1.6 mL), quenched with distilled H_2O (0.8 mL) and stirred under open atmosphere for 4 h. Sodium acetate (26.8 mg, 0.3268 mmol, 2 equiv) was added in one portion, the reaction mixture was cooled to 0 °C, and 30% hydrogen peroxide (212 μL) was added dropwise *via* syringe. After 10 minutes at 0 °C, the mixture was warmed to room temperature and stirred for an additional 150 minutes. The oxidative workup was terminated by addition of sat. aq. $Na_2S_2O_3$ (4 mL) at 0 °C. After stirring for 5 min, the mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (6 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield a clear oil. The product was purified *via* automated silica column chromatography (0→20% Et_2O/hexanes, 10 g column of SiliCycle Ultra Pure Silica Gel 60; TLC R_f = 0.49 in 20% EtOAc/hexanes, UV and anisaldehyde stain) to provide diol **20** (56.7 mg, 76% yield) as a single observable diastereoisomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.57 (ddd, *J* = 16.8, 10.9, 10.3 Hz, 1H), 6.05 (d, *J* = 11.1 Hz, 1H), 5.18 (dd, *J* = 16.8, 1.8 Hz, 1H), 5.09 (dd, *J* = 10.1, 1.7 Hz, 1H), 4.02 (d, *J* = 5.6 Hz, 1H), 3.95-3.92 (m, 2H), 3.61 (s, 1H), 2.96 (s, 1H), 2.44 (dd, *J* = 17.1, 2.5 Hz, 1H), 2.33 (dd, *J* = 16.1, 10.0 Hz, 1H), 1.95 (dq, *J* = 6.9, 5.6 Hz, 1H), 1.69 (s, 3H), 1.47 (s, 9H), 0.96 (s, 3H), 0.92 (s, 9H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.77 (s, 3H), 0.08 (s, 3H), –0.03 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 138.5, 132.5, 127.1, 116.6, 82.6, 81.1, 79.7, 76.2, 41.1, 37.5, 37.3, 28.1, 25.9, 21.3, 18.2, 16.6, 13.3, 8.8, –4.6, –5.1 ppm; IR (film) 2957, 2930, 2885, 2857, 1712, 1472, 1392, 1369, 1315, 1254, 1153, 1096, 1056, 1005, 988, 910, 866, 837, 775 cm^{-1}; $[\alpha]_D^{24}$ = +33.0° (*c* = 1.00, $CHCl_3$); HRMS (FAB): Exact mass calcd for $C_{25}H_{48}O_5SiNa$ $[M+Na]^+$: 479.3169; Found: 479.3186.


Me Me Me Me
tBuO
O OH OH OTBS
20
1H NMR (500 MHz, CDCl3)
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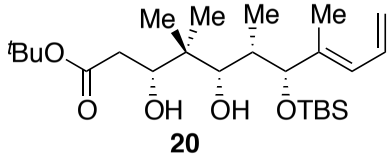
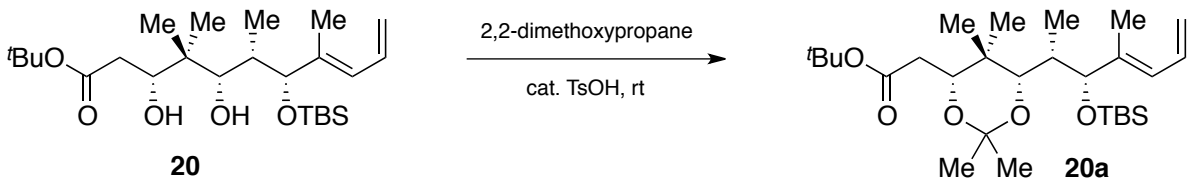
0.998 0.986 0.979 0.982 0.977 0.967 8.88 11.4 2.55
8 7 6 5 4 3 2 1 0



20

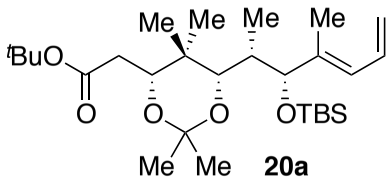
^{13}C NMR (125 MHz, $CDCl_3$)

Proof of Stereochemistry by Formation of Acetonide 20a



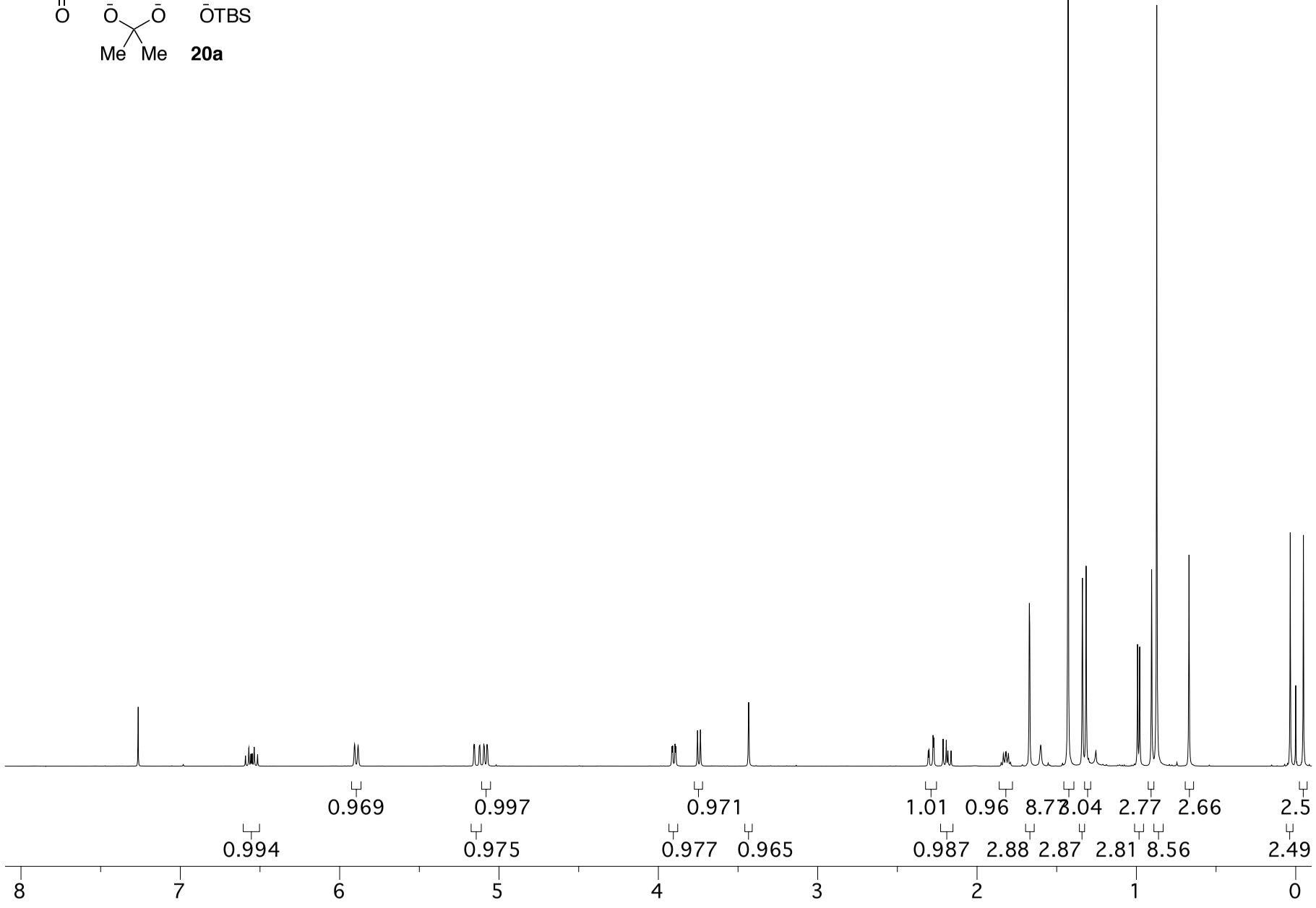
To diol **20** (22.7 mg, 0.0497 mmol, 1 equiv) was added an excess of 2,2-dimethyoxypropane (1.0 mL, 7.99 mmol, 160 equiv) and a catalytic amount of TsOH (approximately 5 mg) was added. After 30 min at rt, the reaction was quenched with aqueous $NaHCO_3$ (10 mL) and was extracted with Et_2O (4 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield acetonide **20a** (24.7 mg, 97% yield) as clear colorless oil that required no further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.55 (ddd, *J* = 16.9, 10.5, 10.5 Hz, 1H), 5.90 (d, *J* = 11.0 Hz, 1H), 5.14 (dd, *J* = 16.9, 1.8 Hz, 1H), 5.08 (dd, *J* = 10.1, 1.6 Hz, 1H), 3.90 (dd, *J* = 9.9, 2.5 Hz, 1H), 3.74 (d, *J* = 9.1 Hz, 1H), 3.43 (s, 1H), 2.29 (dd, *J* = 15.1, 2.5 Hz, 1H), 2.19 (dd, *J* = 15.1, 9.9 Hz, 1H), 1.82 (dq, *J* = 9.1, 6.7 Hz, 1H), 1.67 (s, 3H), 1.43 (s, 9H), 1.34 (s, 3H), 1.32 (s, 3H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.90 (s, 3H), 0.87 (s, 9H), 0.67 (s, 3H), 0.03 (s, 3H), -0.05 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 139.4, 132.4, 128.9, 116.7, 98.3, 82.7, 80.4, 75.9, 75.6, 36.5, 36.4, 36.0, 29.8, 28.1, 25.9, 21.3, 19.4, 18.2, 15.0, 11.8, 11.6, –4.6, –5.1 ppm; IR (film) 2960, 2930, 2894, 2857, 1736, 1472, 1390, 1379, 1367, 1312, 1252, 1201, 1169, 1152, 1112, 1057, 1022, 974, 911, 862, 837, 775 cm^{-1}; $[\alpha]_D^{24}$ = –29.9° (*c* = 1.00, $CHCl_3$); HRMS (FAB): Exact mass calcd for $C_{28}H_{52}O_5SiNa$ $[M+Na]^+$: 519.3482; Found: 519.3480.

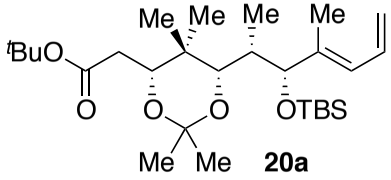
The chemical shifts of 98.3, 29.8, and 19.4 ppm for the acetonide carbons indicate a *syn* relationship between the oxygen substituents at C3 and C5.[7]



20a

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

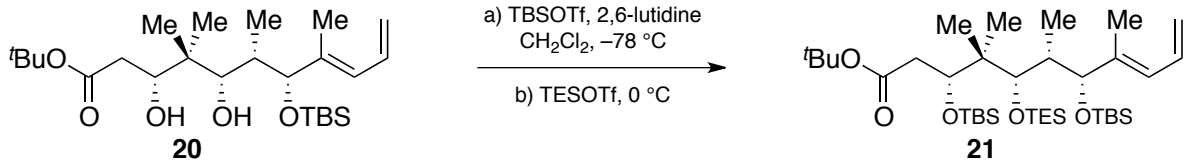




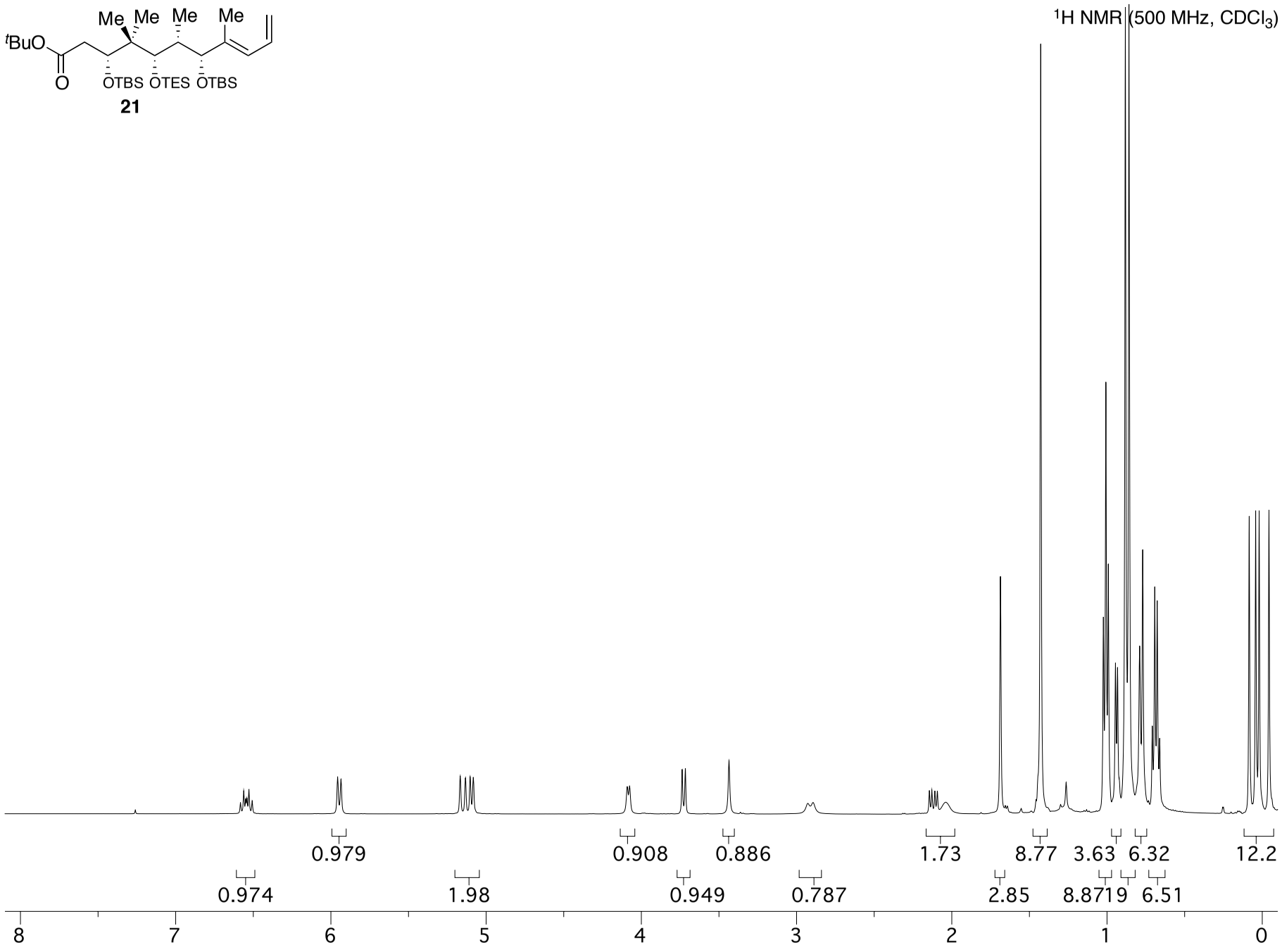
20a

^{13}C NMR (125 MHz, $CDCl_3$)

Preparation of Fully Protected Hydroformylation Substrate 21



To a stirring solution of diol **20** (321.7 mg, 0.7044 mmol, 1 equiv) in CH_2Cl_2 (7.0 mL) was added 2,6-lutidine (0.164 mL, 1.409 mmol, 2.0 equiv). The flask was cooled to –78 °C and TBSOTf (0.194 mL, 0.8452 mmol, 1.2 equiv) was added dropwise *via* syringe. The progress of this first protection was monitored by TLC and additional volumes of both 2,6-lutidine (40 μL) and TBSOTf (50 μL) were added after 1.5 h, 2.5 h, and 4h. After 4.5 h, the solution was warmed to 0 °C and 2,6-lutidine (0.245 mL, 2.113 mmol, 3.0 equiv) was added, followed by TESOTf (0.239 mL, 1.057 mmol, 1.5 equiv). After a further hour at 0 °C, the reaction was quenched by addition of 0.5 *M* HCl (2 mL) and was extracted with hexanes (5 x 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residual oil was redissolved in hexanes and flushed through a filter pipette of neutral alumina (Brockman Activity I, 80–200 mesh, Fisher Scientific). The extremely non-polar product was purified *via* automated silica column chromatography (0→5% Et_2O/hexanes, 10 g column; TLC R_f = 0.80 in 10% EtOAc/hexanes, UV visualization) to provide fully protected compound **21** (475.6 mg, 98% yield) as a clear colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.54 (ddd, *J* = 16.9, 10.5, 10.5 Hz, 1H), 5.95 (d, *J* = 10.8 Hz, 1H), 5.15 (d, *J* = 16.8 Hz, 1H), 5.09 (d, *J* = 10.2 Hz, 1H), 4.08 (d, *J* = 7.5 Hz, 1H), 3.73 (d, *J* = 10.3 Hz, 1H), 3.44 (s, 1H), 2.91 (br. d, *J* = 17.0 Hz, 1H), 2.12 (dd, *J* = 17.6, 8.1 Hz, 1H), 2.04 (br. s, 1H), 1.69 (s, 3H), 1.43 (s, 9H), 1.01 (t, *J* = 7.9 Hz, 9H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.88 (s, 9H), 0.86 (s, 9H), 0.79 (s, 3H), 0.77 (s, 3H), 0.68 (q, *J* = 7.9 Hz, 6H), 0.08 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H), –0.04 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 50 °C) δ 172.1, 140.3, 132.5, 129.2, 116.8, 82.3, 79.8, 77.2, 73.6, 44.3, 40.8, 38.0, 28.3, 26.4, 25.9, 24.6, 20.2, 18.5, 18.3, 12.0, 7.3, 6.2, –3.8, –4.49, –4.54, –4.9 ppm; IR (film) 2956, 2930, 2881, 2858, 1734, 1473, 1389, 1368, 1301, 1251, 1158, 1104, 1005, 960, 836, 775, 741, 616 cm^{-1}; $[\alpha]_D^{20}$ = –1.8° (*c* = 1.00, CH_2Cl_2); HRMS (ESI): Exact mass calcd for $C_{37}H_{76}O_5Si_3Na$ $[M+Na]^+$: 707.4898; Found: 707.4885.


Me Me Me Me
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O
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21
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0.908
0.886
1.73
8.77
3.63
6.32
12.2
0.974
1.98
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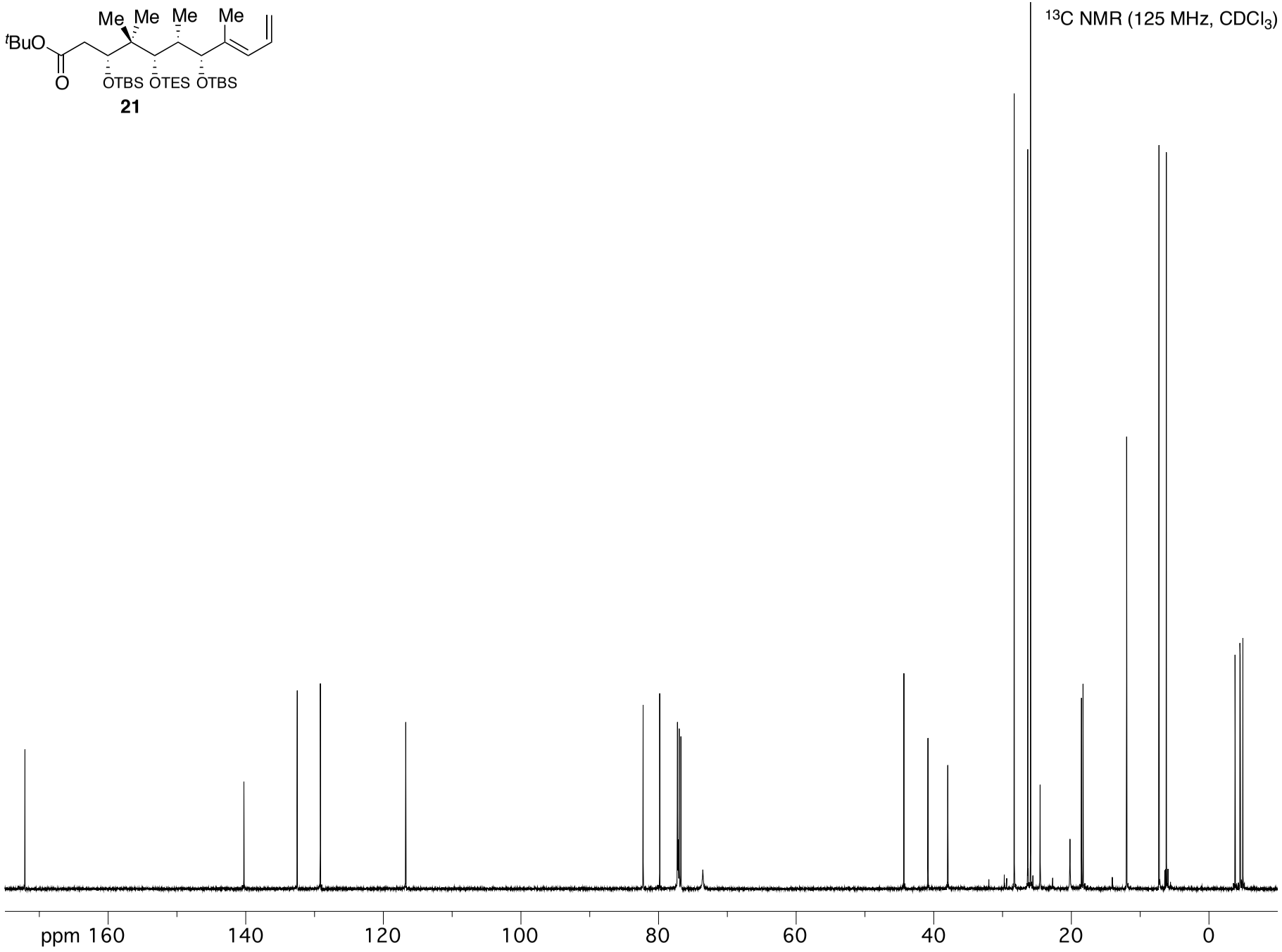
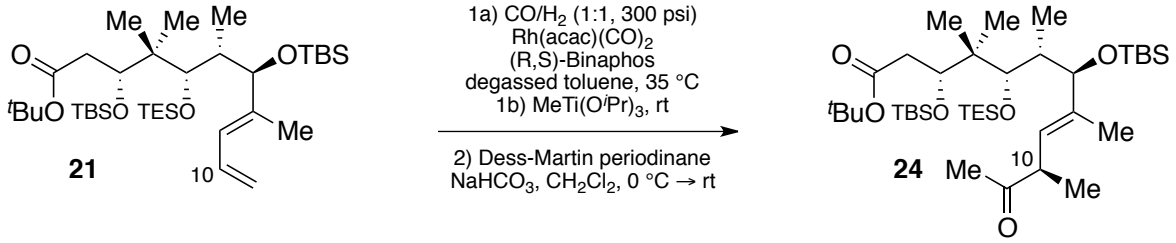
2.85
8.8719
6.51
8
7
6
5
4
3
2
1
0

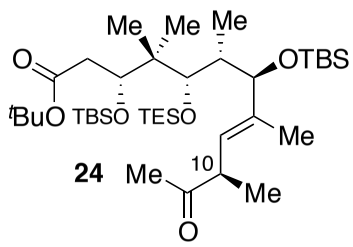

Me Me Me Me
tBuO
O
OTBS OTES OTBS
21
13C NMR (125 MHz, CDCl3)
ppm 160
140
120
100
80
60
40
20
0

(*R*)-Methyl Ketone 24

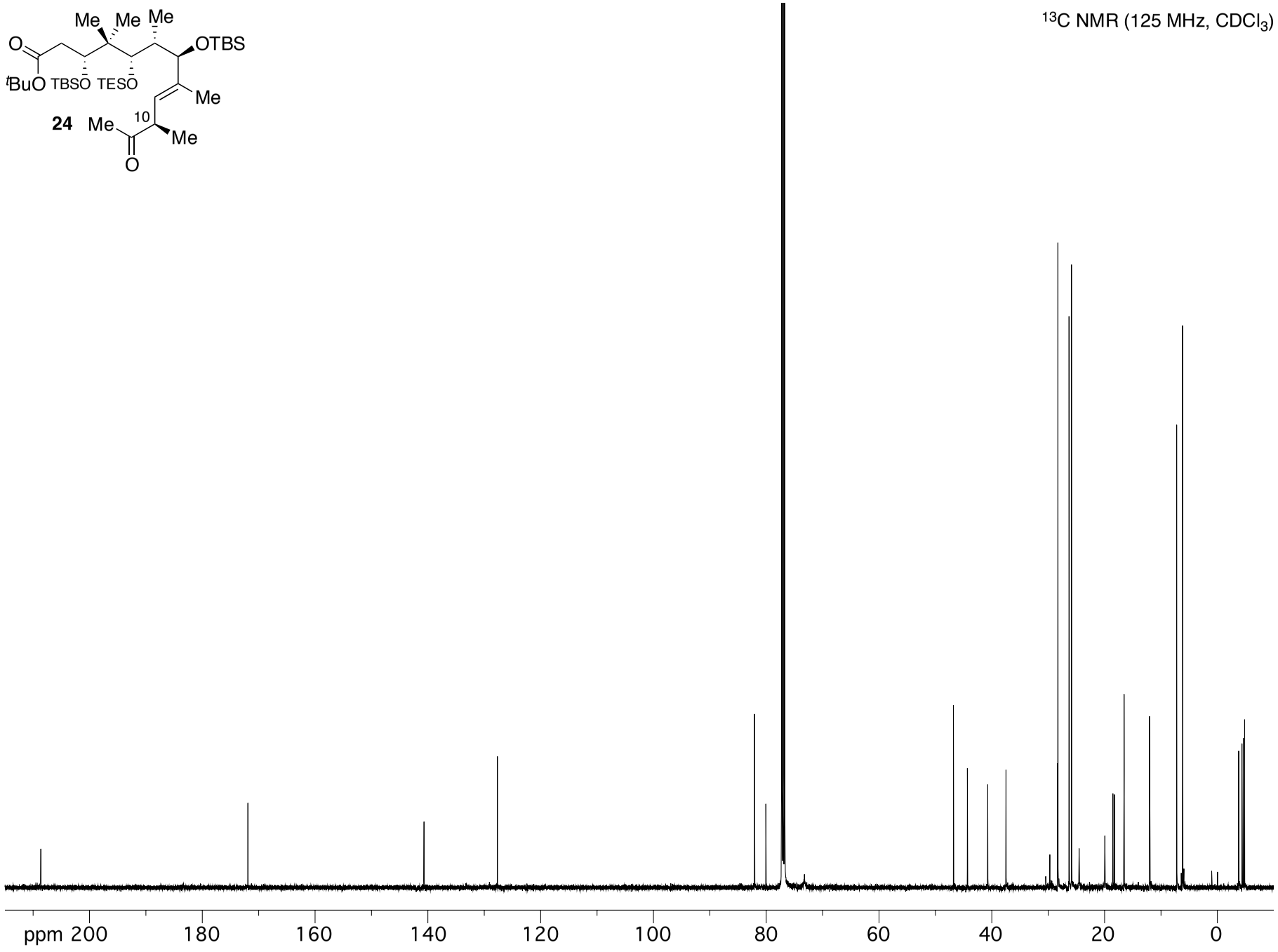


Substrate diene **21** (46.7 mg, 0.0682 mmol, 1 equiv) was subjected to the general hydroformylation conditions using (*R,S*)-BINAPHOS in degassed toluene (1.0 mL) with 300 psi syngas at 30–35 °C for 288 hours. After release of the pressure, the vial was capped with a septum and flushed with nitrogen. This reaction mixture was cannulated through an Ar-flushed Pasteur pipette filled with alumina (neutral, Brockman Activity I, 80–200 mesh) into an Ar-blanketed 25 mL round bottom flask containing a stir bar using 2.5 mL degassed toluene. After this process was complete, the flask was capped and cooled to 0 °C. A yellow solution of $MeTi(O^iPr)_3$ (0.3 mL, 0.252 mmol, 3.7 equiv) prepared according to the general procedure, was added by syringe. After 100 min, a second addition of $MeTi(O^iPr)_3$ (0.3 mL, 0.252 mmol, 3.7 equiv) was made. After another 90 min, the reaction was quenched by pouring into a stirring mixture of 1 *N* HCl and Et_2O (about 5 mL each). The aqueous layer was extracted with Et_2O (5 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield a clear oil. The product was purified *via* automated silica column chromatography (0→7% EtOAc/hexanes, 10 g column; TLC R_f = 0.41 in 10% EtOAc/hexanes, anisaldehyde stain) to provide the methyl carbinol intermediate (38.2 mg, 77%) as a mixture of C11 epimers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.22 (d, 1H, *J* = 9.6 Hz), 4.10 (d, 1H, *J* = 7.9 Hz), 3.72-3.60 (m, 2H), 3.45 (s, 1H), 2.92 (d, 1H, *J* = 17.7 Hz), 2.56-2.42 (m, 1H), 2.14 (dd, 1H, *J* = 17.6, 8.4 Hz), 2.02 (s, 1H), 1.60 (s, 3H), 1.43 (s, 9H), 1.20 (d, 3H, 6.3 Hz), 1.04 (d, 3H, *J* = 6.7 Hz), 1.00 (t, 9H, *J* = 7.8 Hz), 0.92 (d, 3H, *J* = 6.7 Hz), 0.89 (s, 9H), 0.86 (s, 9H), 0.79 (s, 6H), 0.67 (q, 6H, *J* = 7.8 Hz), 0.09 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), –0.01 (s, 3H) ppm.

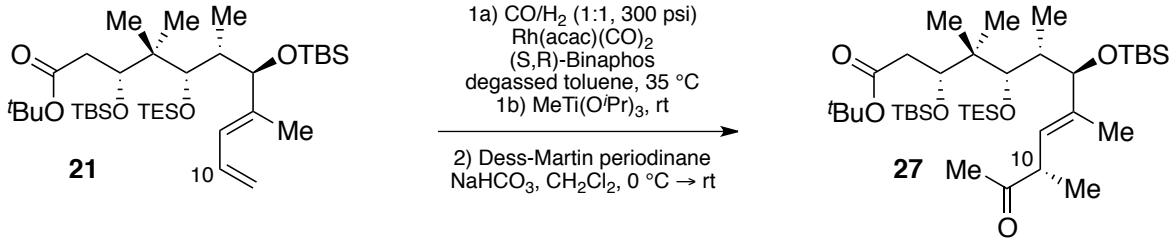
To this methyl carbinol intermediate (18.5 mg, 0.0253 mmol, 1 equiv) in CH_2Cl_2 (5.5 mL) was added sodium bicarbonate (74.4 mg, 0.885 mmol, 35 equiv) in one portion. The solution was cooled to 0 °C, Dess-Martin periodinane (35.4 mg, 0.0835 mmol, 3.3 equiv) was added in one portion, and the reaction was allowed to stir for 100 min. The reaction was quenched by the sequential addition of saturated aqueous $NaHCO_3$ (2.5 mL) and saturated aqueous $Na_2S_2O_3$ (2.5 mL). The mixture was diluted with water (10 mL) and Et_2O (25 mL). The aqueous layer was extracted with Et_2O (5 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was purified *via* automated silica column chromatography (0→45% CH_2Cl_2/hexanes, 4 g column; TLC R_f = 0.54 in 20% EtOAc/hexanes, anisaldehyde stain) to provide methyl ketone **24** (16.1 mg, 87%) as a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.19 (d, *J* = 9.6 Hz, 1H), 4.09 (d, *J* = 7.8 Hz, 1H), 3.68 (d, *J* = 10.4 Hz, 1H), 3.45 (qd, *J* = 8.1, 6.9 Hz, 1H), 3.41 (s, 1H), 2.87 (br. d, *J* = 14.0 Hz, 1H), 2.14 (s, 3H), 2.12 (dd, *J* = 17.5, 8.2 Hz, 1H), 2.10-1.98 (m, 1H), 1.67 (d, *J* = 1.1 Hz, 3H), 1.43 (s, 9H), 1.17 (d, *J* = 6.7 Hz, 3H), 0.99 (t, *J* = 7.9 Hz, 9H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.88 (s, 9H), 0.86 (s, 9H), 0.79 (s, 3H), 0.77 (s, 3H), 0.65 (q, *J* = 7.9 Hz, 6H), 0.09 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H), –0.06 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.6, 171.9, 127.7, 82.1, 80.1, 73.2, 46.8, 44.3, 40.7, 37.5, 29.7, 28.33, 28.28, 26.3, 25.9, 24.5, 20.0, 18.5, 18.3, 16.5, 12.1, 12.0, 7.2, 6.2, –3.8, –4.4, –4.6, –4.8 ppm; IR (film) 2956, 2931, 2882, 2858, 1734, 1721, 1472, 1462, 1382, 1368, 1301, 1286, 1251, 1158, 1123, 1080, 1006, 973, 955, 940, 900, 870, 836, 813, 776, 740, 671 cm^{-1}; $[\alpha]_D^{20}$ = –64.8° (*c* = 1.00, CH_2Cl_2); HRMS (ESI): Exact mass calcd for $C_{39}H_{80}O_6Si_3$ $[M+Na]^+$: 751.5160; Found: 751.5141.



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

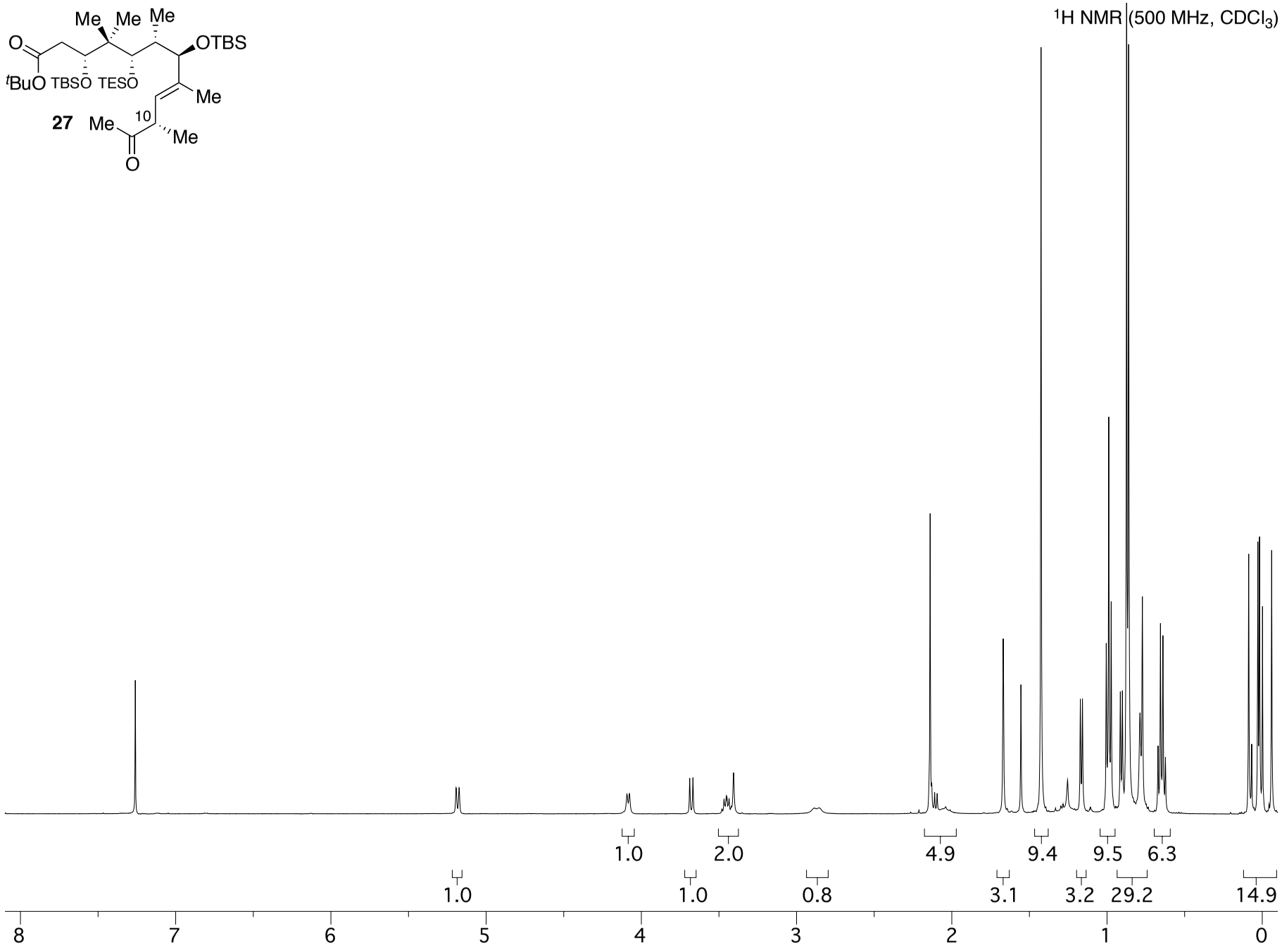

Me Me Me
O
OTBS
tBuO TBSO TESO
Me
24 Me
10
Me
O
13C NMR (125 MHz, CDCl3)
ppm 200
180
160
140
120
100
80
60
40
20
0

(*S*)-Methyl Ketone 27



Substrate diene **21** (20.6 mg, 0.0301 mmol, 1 equiv) was subjected to the general hydroformylation conditions using (*S,R*)-BINAPHOS (23.8 mg, 0.0309 mmol) and $Rh(acac)(CO)_2$ (4.0 mg, 0.0155 mmol) in degassed toluene (1.0 mL) with 300 psi syngas at 30–35 °C for 208 hours. After release of the pressure, the vial was capped with a septum and flushed with nitrogen. This reaction mixture was cannulated through an Ar-flushed Pasteur pipette filled with alumina (neutral, Brockman Activity I, 80–200 mesh) into an Ar-blanketed 25 mL round bottom flask containing a stir bar using 2.5 mL degassed toluene. After this process was complete, the flask was capped and cooled to 0 °C. A yellow solution of $MeTi(O^iPr)_3$ (117 μL , 0.098 mmol, 3.3 equiv) prepared according to the general procedure, was added by syringe. After 100 min, a second addition of $MeTi(O^iPr)_3$ (100 μL, 0.084 mmol, 2.8 equiv) was made. After 35 more min, a third addition of $MeTi(O^iPr)_3$ (100 μL, 0.084 mmol, 2.8 equiv) was made. After another 40 min, the reaction was quenched by pouring into a stirring mixture of 1 *N* HCl and Et_2O (about 5 mL each). The aqueous layer was extracted with Et_2O (5 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to yield a clear oil. The product was purified *via* automated silica column chromatography (0→7% EtOAc/hexanes, 10 g column; TLC R_f = 0.38 in 10% EtOAc/hexanes, anisaldehyde stain) to provide the methyl carbinol intermediate (14.9 mg, 68%) as a mixture of C11 epimers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.22 (d, 1H, *J* = 8.5 Hz), 4.11 (d, 1H, *J* = 7.4 Hz), 3.72-3.60 (m, 2H), 3.41 (s, 1H), 2.98 (d, 1H, *J* = 17.8 Hz), 2.54-2.38 (m, 1H), 2.13 (dd, 1H, *J* = 17.6, 8.4 Hz), 2.05 (s, 1H), 1.58 (s, 3H), 1.44 (s, 9H), 1.02 (d, 3H, 7.3 Hz), 1.00 (t, 9H, *J* = 7.3 Hz), 0.92 (d, 3H, *J* = 6.7 Hz), 0.89 (s, 9H), 0.87 (s, 9H), 0.80 (s, 3H), 0.79 (s, 3H), 0.67 (q, 6H, *J* = 7.8 Hz), 0.09 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H), –0.02 (s, 3H) ppm.

To this methyl carbinol intermediate (14.9 mg, 0.0204 mmol, 1 equiv) in CH_2Cl_2 (4.0 mL) was added sodium bicarbonate (59.9 mg, 0.713 mmol, 35 equiv) in one portion. The solution was cooled to 0 °C, Dess-Martin periodinane (28.5 mg, 0.0672 mmol, 3.3 equiv) was added in one portion, and the reaction was allowed to stir for 160 min. The reaction was quenched by the sequential addition of saturated aqueous $NaHCO_3$ (2.0 mL) and saturated aqueous $Na_2S_2O_3$ (0.5 mL). The mixture was diluted with water (10 mL) and Et_2O (25 mL). The aqueous layer was extracted with Et_2O (4 x 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The product was purified *via* automated silica column chromatography (0→8% Et_2O/hexanes, 4 g column; TLC R_f = 0.78 in 10% EtOAc/hexanes, anisaldehyde stain) to provide methyl ketone **27** (8.7 mg, 58%) as a yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.20 (d, *J* = 9.4 Hz, 1H), 4.11 (d, *J* = 8.3 Hz, 1H), 3.68 (d, *J* = 10.4 Hz, 1H), 3.44 (qd, *J* = 8.1, 6.8 Hz, 1H), 3.35 (s, 1H), 2.96 (br. d, *J* = 17.2 Hz, 1H), 2.15 (s, 3H), 2.11 (dd, *J* = 17.6, 8.6 Hz, 1H), 2.06-1.96 (m, 1H), 1.64 (d, *J* = 1.3 Hz, 3H), 1.43 (s, 9H), 1.16 (d, *J* = 6.8 Hz, 3H), 0.98 (t, *J* = 7.9 Hz, 9H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.88 (s, 9H), 0.86 (s, 9H), 0.78 (s, 6H), 0.63 (q, *J* = 7.9 Hz, 6H), 0.08 (s, 3H), 0.03 (s, 3H), 0.01 (s, 3H), –0.04 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.4, 172.0, 140.3, 127.9, 82.3, 80.0, 77.7, 72.8, 46.7, 44.3, 40.8, 37.5, 28.4, 28.3, 26.3, 25.9, 24.7, 19.9, 18.5, 18.3, 16.1, 12.1, 11.7, 7.2, 6.1, –3.7, –4.3, –4.6, –4.9 ppm; IR (film) 2957, 2931, 2881, 2858, 1733, 1721, 1472, 1463, 1383, 1367, 1300, 1251, 1159, 1081, 1049, 1006, 955, 900, 872, 836, 813, 775, 740, 668 cm^{-1}; $[\alpha]_D^{24}$ = +53.6° (*c* = 1.00, CH_2Cl_2); HRMS (ESI): Exact mass calcd for $C_{39}H_{80}O_6Si_3$ [M +Na]$^+$: 751.5160; Found: 751.5152.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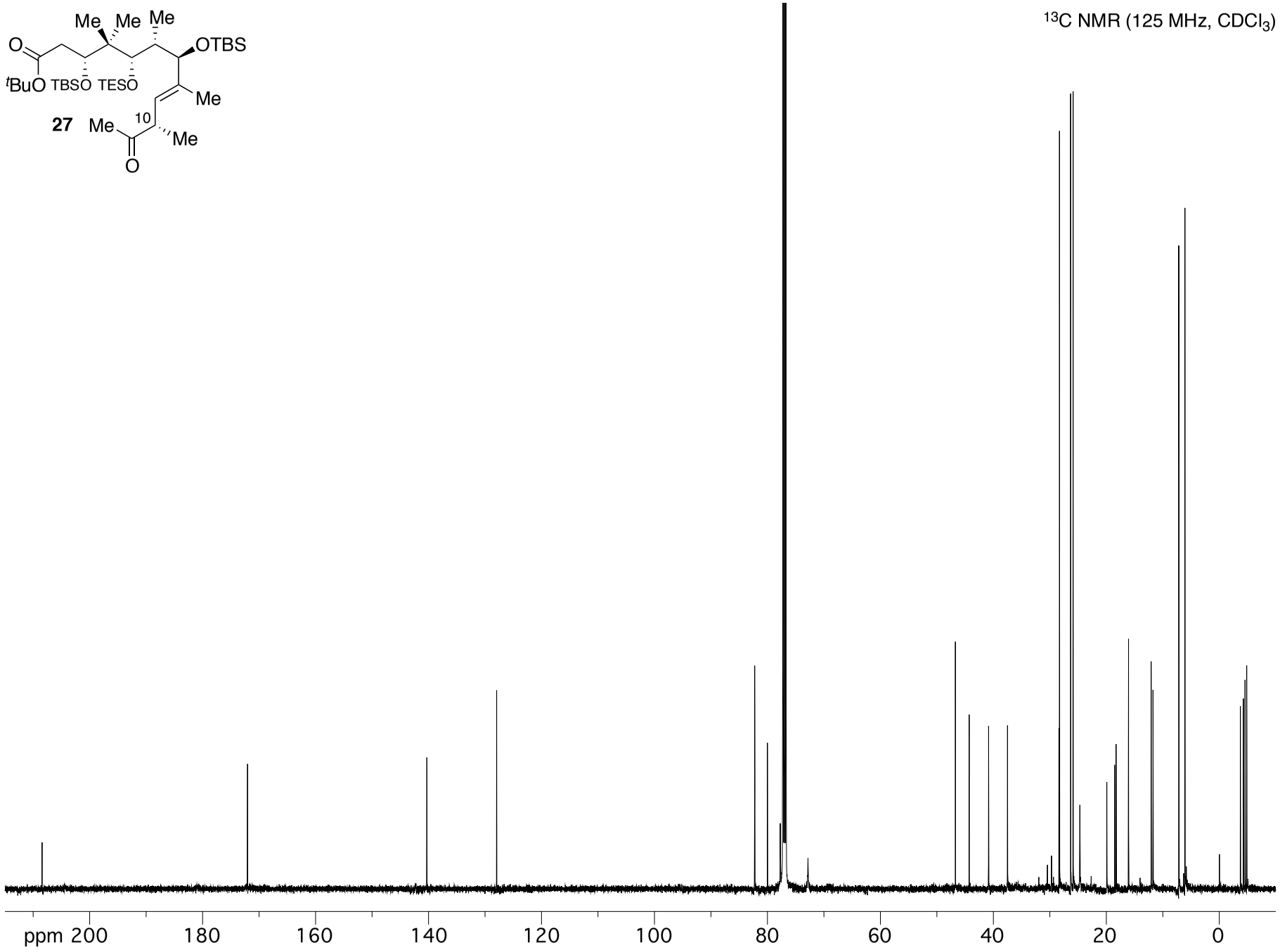
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100
80
60
40
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