Supporting Information

for

Synthetic Studies Toward the C5-C20 Domain of the Azaspiracids

Amy B. Dounay and Craig J. Forsyth*

University of Minnesota, Department of Chemistry, Minneapolis, Minnesota 55455 USA

*Tel: (612)-624-0218
Fax: (612)-626-7541
Email: forsyth@chem.umn.edu

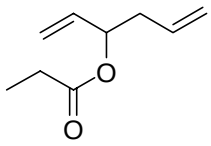
Contents:

Experimental procedures and spectral data for compounds:
5, 6, 7, 7a, 7b, 10, 10a, 10b, 11, 14, 15, 15a, 16, 17, 18, 19.

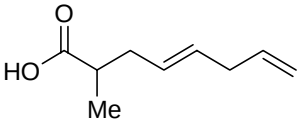
Experimental Section

General

Unless otherwise noted, all reactions were carried out under an Ar or N_2 atmosphere using oven dried glassware and standard syringe, cannula, and septa techniques. Diethyl ether, THF, and benzene were distilled from Na/benzophenone under N_2. Toluene was distilled from Na under N_2. CH_2Cl_2, CH_3CN, Et_3N, and $BF_3{\cdot}OEt_2$ were distilled from CaH_2 under N_2. AD-mix α and ethyl magnesium bromide (3.0 M solution in ether) were purchased from Aldrich Chemical Co. Flash chromatography was performed using ICN silica gel 32-63 and the solvent systems indicated. Analytical TLC was performed with 0.25 mm or 0.50 mm EM silica gel 60 F_{254} plates that were analyzed by fluorescence upon 254 nm irradiation or by staining upon heating with anisaldehyde reagent (450 mL 95% EtOH, 25 mL conc. H_2SO_4, 15 mL acetic acid, and 25 mL anisaldehyde). High resolution mass spectrometric data were obtained by the University of Minnesota Mass Spectrometry Laboratory using CI, FAB, and MALDI techniques. Elemental analyses were performed by M-H-W Laboratories (Phoenix, AZ).

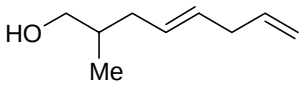


Allylic ester 10. To a stirred 0 °C solution of 1,5-hexadien-3-ol (10.0 g, 102 mmol) in CH_2Cl_2 (500 mL) under Ar was added pyridine (10.7 mL, 133 mmol), followed by freshly distilled propionyl chloride (11.7 mL, 133 mmol). After 1.5 h, saturated aqueous $NaHCO_3$ (150 mL) was added. The organic layer was separated and washed again with saturated aqueous $NaHCO_3$ (150 mL). The separated organic layer was washed with 5% aqueous HCl (2 × 100 mL) and saturated aqueous NaCl (100 mL) and dried over Na_2SO_4. The solution was filtered, concentrated, and purified by silica gel column chromatography (hexanes/ethyl acetate, 12:1 to 8:1, v/v) to provide **10** (15.0 g, 97.4 mmol, 95%) as a clear, colorless oil: R_f 0.60 (hexanes/ethyl acetate, 5:1, v/v); IR (neat): 2978, 1706, 1464, 1417, 1241, 971, 914 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.84-5.66 (m, 2H), 5.33-5.04 (m, 5H), 2.37 (m, 2H), 2.32 (q, *J* = 7.5 Hz, 2H), 1.12 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.6, 136.0, 133.2, 117.9, 116.6, 73.4, 38.8, 27.8, 9.1; Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15; Found: C, 70.28; H, 8.96. HRCIMS calcd for $C_9H_{15}O_2$ $[M + H]^+$ 155.1072, found 155.1088.



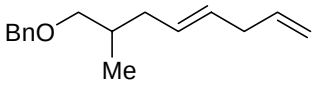
Carboxylic Acid 10a. To a stirred -78 °C solution of **10** (4.0 g, 26 mmol) in THF (200 mL) under Ar, KHMDS (53 mL of a 0.78 M solution in toluene, 42 mmol) was added via syringe over a 15 min period. After an additional 20 min, a solution of TBSCl (6.3 g, 42 mmol) in THF (60 mL) was added via cannula. After an additional 30 min, the cooling bath was removed, allowing the reaction to gradually warm to rt. The reaction mixture

was maintained at this temperature for 1.5 h. The mixture was then cooled to 0 °C, and H_2O (25 mL) and 10% aqueous HCl (100 mL) were added. The mixture was stirred vigorously at rt for 1 h to ensure complete hydrolysis of the silyl ester intermediate, as indicated by TLC analysis. Aqueous NaOH (15%) was added to adjust the aqueous phase to pH 10. The aqueous layer was separated and acidified to pH 2 with aqueous HCl (10%), then washed with CH_2Cl_2 (8×75 mL). The combined organic fractions were washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated to provide **10a** (3.8 g, 25 mmol, 95%) as a pale yellow oil: R_f 0.11 (hexanes/ethyl acetate, 5:1, v/v); IR (neat): 2978, 1708, 1638, 1463, 1417, 1241, 970, 914 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 11.2 (br. s, 1H), 5.81 (dddd, *J* = 16.5, 10.0, 6.0, 6.0 Hz, 1H), 5.52 (ddd, *J* = 15.5, 6.5, 6.5 Hz, 1H), 5.42 (ddd, *J* = 15.0, 7.5, 7.5 Hz, 1H), 5.04-4.98 (m, 2H), 2.76 (dd, *J* = 6.0, 6.0 Hz, 2H), 2.52 (dddd, *J* = 14.0, 7.0, 7.0, 7.0 Hz, 1H), 2.41 (ddd, *J* = 13.5, 6.5, 5.5 Hz, 1H), 2.18 (ddd, *J* = 14.5, 8.0, 6.5 Hz, 1H), 1.18 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 182.8, 136.9, 130.7, 127.7, 115.1, 39.5, 36.6, 36.3, 16.3; Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15; Found: C, 70.19; H, 9.09. HRCIMS calcd for $C_9H_{18}NO_2$ $[M + NH_4]^+$ 172.1336, found 172.1338.



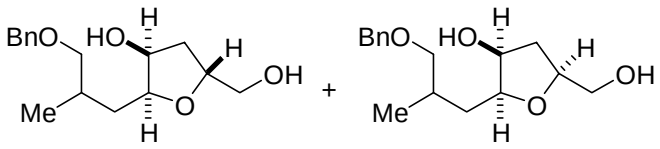
Alcohol 10b. To a stirred 0 °C suspension of lithium aluminum hydride (1.6 g, 42 mmol) in ether (175 mL) under Ar was added a solution of **10a** (3.85 g, 25 mmol) in ether (75 mL) via cannula. After 30 min, H_2O (1.6 mL) was added, followed by 15% aqueous NaOH (1.6 mL), and an additional portion of H_2O (3.2 mL). The mixture was stirred for 15 minutes, and then the white solid was removed by vacuum filtration and washed with

diethyl ether (2 × 20 mL). The combined organic fractions were washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated to provide **10b** (3.2 g, 23 mmol, 90%) as a clear, colorless oil: R_f 0.28 (hexanes/ethyl acetate, 5:1, v/v); IR (neat): 3338, 3079, 2957, 2913, 1638, 1456, 1037, 970, 912 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 5.82 (dddd, *J* = 16.5, 10.0, 6.5, 6.5 Hz, 1H), 5.46 (m, 2H), 5.05-4.97 (m, 2H), 3.52 (dd, *J* = 10.5, 6.0 Hz, 1H), 3.44 (dd, *J* = 10.5, 6.0 Hz, 1H), 2.76 (m, 2H), 2.12 (m, 1H), 1.92 (m, 1H), 1.70 (dddd, *J* = 13.5, 6.5, 6.5, 6.5 Hz, 1H), 1.41 (s, 1H), 0.91 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 137.2, 129.5, 129.4, 114.9, 68.0, 36.7, 36.5, 35.9, 16.4; HRCIMS calcd for $C_9H_{20}NO$ $[M + NH_4]^+$ 158.1544, found 158.1549.



Benzyl ether 11. To a stirred 0 °C solution of **10b** (10.7 g, 76 mmol) in THF (500 mL) under Ar was added NaH (6.1 g of a 60% dispersion in mineral oil, 0.15 mol). The reaction mixture was allowed to warm to rt over a 1 h period. The mixture was recooled to 0 °C and benzyl bromide (13.1 mL, 107 mmol) and tetra-*n*-butylammonium iodide (8.4 g, 24 mmol) were added. After stirring at rt for 15 h, the mixture was cooled to 0 °C and anhydrous methanol (13 mL) was added. The solution was allowed to warm to rt, and after 1 h, saturated NH_4Cl (150 mL) was added. The mixture was diluted with ethyl acetate (200 mL), and the aqueous phase was extracted with ethyl acetate (3 × 150 mL). The combined organic extracts were washed with saturated NaCl (200 mL), dried over Na_2SO_4, filtered, and concentrated. Silica gel chromatography (pentane:ether, 1:0 to 50:1 to 40:1, v/v) provided **11** (15.7 g, 68 mmol, 90%) as a clear, colorless oil: R_f 0.80 (hexanes/ethyl acetate, 5:1, v/v); IR (neat): 3063, 3029, 2956, 2903, 1637, 1453, 1363,

1098 cm^{-1}**;** ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36-7.25 (m, 5H), 5.83 (dddd, *J* = 16.5, 10.2, 6.3, 6.3 Hz, 1H), 5.44 (m, 2H), 5.07-4.97 (m, 2H), 4.51 (s, 2H), 3.34 (dd, *J* = 9.0, 6.0 Hz, 1H), 3.27 (dd, *J* = 9.0, 6.3 Hz, 1H), 2.76 (m, 1H), 2.19 (m, 1H), 1.95-1.79 (m, 2H), 0.94 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.8, 137.4, 129.5, 129.3, 128.3, 127.6, 127.5, 114.8, 75.3, 73.0, 36.8, 36.7, 33.7, 16.9; Anal. Calcd for $C_{16}H_{22}O$: C, 83.42; H, 9.63; Found: C, 83.58; H, 9.80; HRCIMS calcd for $C_{16}H_{23}O$ $[M + H]^+$ 231.1749, found 231.1743.

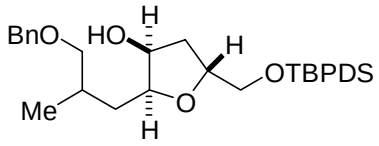


7 **7a**

Tetrahydrofurans 7 and 7a. A rt mixture of AD-mix-α (50 g) in *tert*-butyl alcohol (240 mL) and H_2O (240 mL) was stirred until both phases became clear. Methanesulfonamide (2.27 g, 23.9 mmol) was added, and the mixture was cooled to 0 °C. A solution of **11** (5.5 g, 23.9 mmol) in *tert*-butyl alcohol (10 mL) was added, and the reaction mixture was stirred vigorously at 0 °C for 13 h. Sodium sulfite (~50 g) was added, and the mixture was warmed to rt and stirred for 30 min. The mixture was diluted with ethyl acetate (200 mL) and H_2O (100 mL), and the separated aqueous phase was washed with ethyl acetate (8 ω 50 mL). The combined organic fractions were washed with 20% aqueous KOH and saturated aqueous NaCl (150 mL ea), dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel column chromatography (ethyl acetate/methanol, 1:0 to 20:1, v/v) to provide a mixture of tetraols **8** and **12** (6.5 g, 23 mmol, 96%), which was used directly in the subsequent reaction. To a 0 °C solution of a mixture of **8** and **12** (1.6 g, 5.4 mmol) in THF (90 mL) under Ar was added KHMDS (11.8 mL of a 0.50 M

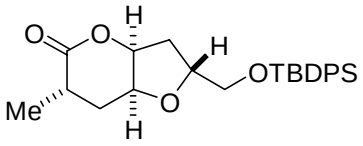
solution in toluene, 5.9 mmol). After 15 min, the cooling bath was removed, and the reaction mixture was maintained at rt for 20 min. The reaction was cooled to 0 °C, and *N*-(2,4,6-triisopropylbenzenesulfonyl)imidazole (2.16 g, 6.44 mmol) in THF (10 mL) was added slowly via syringe over 1 h. The cooling bath was removed, and the mixture was stirred at rt for an additional 1.3 h. The mixture was cooled to 0 °C, and KHMDS (5.0 mL of a 0.50 M solution in toluene, 2.5 mmol) was added. The reaction mixture was gradually warmed to rt, and after an additional 1.6 h, it was again cooled to 0 °C and another portion of KHMDS (5.0 mL of a 0.5 M solution in toluene, 2.5 mmol) was added. The reaction mixture was gradually warmed to rt, and after an additional 1.6 h, the it cooled to 0 °C and another portion of KHMDS (12 mL of a 0.5 M solution in toluene, 5.9 mmol) was added. The cooling bath was removed, and the mixture was stirred at rt for an additional 14 h. Saturated aqueous NH_4Cl (15 mL) and ethyl acetate (50 mL) were added, and the separated aqueous phase was washed with ethyl acetate (3 ω 50 mL). The combined organic fractions were washed with H_2O and saturated aqueous NaCl (75 mL ea), dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by silica gel column chromatography (hexanes/ethyl acetate/methanol, 1:1:0 to 0:1:0 to 0:20:1, v/v) to provide **7** (455 mg, 1.6 mmol, 30%) and **7a** (300 mg, 1.1 mmol, 20%). **7**: R_f 0.45 (ethyl acetate/methanol, 5:1, v/v); IR (neat): 3425, 2925, 2850, 1500, 1435, 1180, 745 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.36-7.26 (m, 5H), 4.52 (s, 1H), 4.50 (s, 1H), 4.33 (m, 0.5H), 4.29 (m, 0.5H), 4.25 (s, 0.5H), 4.21 (s, 0.5H), 3.89 (m, 1H), 3.65 (m, 1H), 3.44 (m, 1H), 3.35 (m, 1H), 3.26 (t, *J* = 7.5 Hz, 0.5H), 3.12 (s, 0.5H), 2.54 (d, *J* = 5.0 Hz, 0.5H), 2.41 (br s, 0.5H), 2.06-1.95 (m, 1.5H), 1.91-1.84 (m, 1.5H), 1.77 (m, 1H), 1.52 (m, 1H), 0.98 (d, *J* = 6.0 Hz, 1.5 H), 0.97 (d, *J* = 6.0 Hz, 1.5 H); ^{13}C NMR ($CDCl_3$, 75 MHz):

δ 138.4, 137.8, 128.5, 128.4, 127.8, 127.6, 127.5, 81.8, 80.2, 77.7, 77.2, 75.8, 75.7, 73.6, 73.4, 73.0, 72.6, 64.5, 36.9, 36.2, 32.9, 32.6, 30.8, 30.6, 18.4, 17.2; HRCIMS calcd for $C_{16}H_{25}O_4$ $[M + H]^+$ 281.1753, found 281.1741. **7a**: R_f 0.55 (ethyl acetate/methanol, 5:1, v/v); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.30 (m, 5H), 4.51 (s, 1H), 4.50 (s, 1H), 4.14-3.71 (m, 4H), 3.31-3.31(m, 3H), 2.30 (m, 1H), 2.03-1.80 (m, 3H), 1.55 (m, 1H), 1.00 (d, *J* = 6.6 Hz, 1.5H), 0.98 (d, *J* = 6.6 Hz, 1.5H).



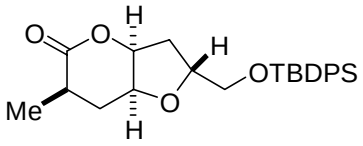
TBDPS ether 7b. To a stirred rt solution of **7** (520 mg, 1.86 mmol) in CH_2Cl_2 (25 mL) was added imidazole (316 mg, 4.65 mmol), *tert*-butylchlorodiphenylsilane (490 μL, 1.95 mmol), and 4-*N*,*N*-dimethylaminopyridine (45 mg, 0.37 mmol). After 8 h, saturated aqueous NH_4Cl (10 mL) was added, and the mixture was diluted with ethyl acetate (75 mL). The separated organic phase was washed with H_2O and saturated aqueous NaCl (30 mL ea), dried over Na_2SO_4, filtered, and concentrated. Silica gel chromatography (hexanes/ethyl acetate, 5:1, v/v) of the crude residue provided **7b** (770 mg, 1.48 mmol, 80%) as a clear, colorless oil: R_f 0.65 (hexanes:ethyl acetate, 2:1, v/v); IR (neat): 3420, 2910, 2840, 1425, 1110 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.73 (m, 4H), 7.45-7.28 (m, 11H), 4.54 (s, 2H), 4.38 (m, 1H), 4.30 (s, 0.5H), 4.25 (s, 0.5H), 4.02 (ddd, *J* = 8.0, 5.5, 2.5 Hz, 0.5H), 3.95 (ddd, *J* = 8.5, 6.0, 2.5 Hz, 0.5H), 3.80 (dd, *J* = 4.5, 4.5 Hz, 0.5H), 3.78 (dd, *J* = 4.5, 4.5 Hz, 0.5H), 3.67 (dd, *J* = 10.5, 4.0 Hz, 0.5H), 3.65 (dd, *J* = 10.0, 4.0 Hz, 0.5 H), 3.39 (m, 1.5 H), 3.31 (m, 0.5 H), 2.74 (s, 0.5 H), 2.24-2.02 (m, 2H), 1.93-1.78 (m, 1.5H), 1.55 (m, 1H), 1.09 (s, 9H), 1.03 (d, *J* = 6.5 Hz, 1.5H), 1.02 (*J* = 6.5 Hz, 1.5H);

^{13}C NMR ($CDCl_3$, 75 MHz): δ 138.6, 138.1, 135.7, 133.6, 129.6, 128.5, 128.4, 127.8, 127.7, 127.6, 127.5, 81.9, 80.4, 77.6, 77.0, 75.9, 75.6, 74.2, 73.3, 73.1, 73.0, 66.4, 66.3, 37.2, 36.7, 32.9, 32.8, 31.1, 30.8, 26.9, 26.8, 19.3, 18.4, 17.2; HRCIMS calcd for $C_{16}H_{25}O_4$ $[M + H]^+$ 519.2931, found 519.2923.



6

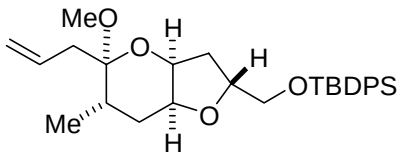
+



14

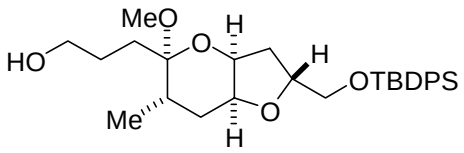
Lactones 6 and 14. To a stirred rt solution of **7b** (364 mg, 0.847 mmol) in CH_2Cl_2 (12 mL) was added crushed 4 molecular sieves (~200 mg), tetra-*n*-propylammonium perruthenate (30 mg, 85 μmol), and 4-methylmorpholine-*N*-oxide (250 mg, 2.1 mmol). After 40 min, the reaction solvent was removed under a stream of N_2, and the resulting crude residue was filtered through a plug of silica gel (hexanes/ethyl acetate, 2:1, v/v) to provide the crude mixture of diastereomeric lactones **6** and **14** (228 mg, 0.533 mmol, 63%). Careful purification using silica gel MPLC (hexanes/ethyl acetate, 10:1 to 8:1 to 5:1, v/v) provided analytically pure **6** (90 mg, 0.21 mmol, 25%) and **14** (107 mg, 0.250 mmol, 29%) as clear, colorless oils: **6**: R_f 0.66 (hexanes/ethyl acetate, 2:1, v/v); $[\alpha]^{24}_D$ = +11.6 (*c* 4.7, $CHCl_3$); IR (neat): 2931, 3047, 1741, 1472, 1428, 1380, 1112, 822, 702 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.68 (m, 4H), 7.46-7.38 (m, 6H), 5.04 (ddd, *J* = 5.0, 5.0, 1.5 Hz, 1H), 4.33 (m, 1H), 4.30 (m, 1H), 3.82 (dd, *J* = 11.0, 3.5 Hz, 1H), 3.64 (dd, *J* = 11.0, 3.5 Hz, 1H), 2.78 (dddd, *J* = 14.0, 7.0, 7.0, 7.0 Hz, 1H), 2.37 (ddd, *J* = 13.5, 7.5, 5.5 Hz, 1H), 2.30-2.22 (m, 2H), 1.80 (ddd, *J* = 13.5, 13.5, 2.5 Hz, 1H), 1.28 (d, *J* = 7.0 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.9, 135.6, 133.2, 129.8, 127.8, 83.4, 78.9, 74.5, 66.0, 36.6, 32.2, 29.5, 26.9, 19.3, 16.0; HRCIMS calcd for $C_{25}H_{36}NSiO_4$

$[M + NH_4]^+$ 442.2414, found 442.2411. **14**: R_f 0.64 (hexanes/ethyl acetate, 2:1, v/v); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.67(m, 4H), 7.45-7.37 (m, 6H), 4.83 (t, *J* = 4.0 Hz, 1H), 4.48 (m, 1H), 4.36 (dddd, *J* = 10.5, 7.5, 3.5, 3.5 Hz, 1H), 3.81 (dd, *J* = 11.0, 3.5 Hz, 1H), 3.64 (dd, *J* = 11.0, 3.5 Hz, 1H), 2.42-2.24 (m, 4H), 1.65 (m, 1H), 1.24 (d, *J* = 6.0 Hz, 3H), 1.06 (s, 9H).



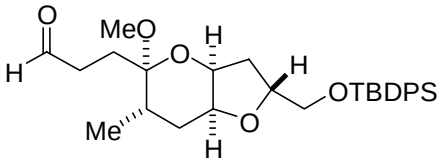
Methyl Ketal 15. To a stirred -78 °C solution of **6** (82 mg, 0.19 mmol) in diethyl ether (8 mL) was added allylmagnesium bromide (0.20 mL of a 1.0 M solution in ether, 0.19 mmol). After 30 min, saturated aqueous NH_4Cl (2 mL) was added, and the mixture was allowed to warm to rt and diluted with ethyl acetate (5 mL). The separated aqueous phase was washed with ethyl acetate (2 ω 5 mL), and the combined organic extracts were washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated. The resulting crude residue was dissolved in CH_2Cl_2 (6 mL), and the solution was cooled to 0 °C. Methanol (2 mL) and camphorsulfonic acid (4 mg, 19 μmol) were added with stirring. After 30 min, the cooling bath was removed, and the reaction was maintained at rt for 1.5 h. Triethylamine (~0.1 mL) was added, and the reaction solvent was removed under a stream of N_2. The resulting crude residue was purified by silica gel column chromatography (hexanes/ethyl acetate, 8:1, v/v) to provide **15** (80 mg, 0.17 mmol, 88% over 2 steps) as a clear, colorless oil: R_f 0.81 (hexanes/ethyl acetate, 2:1, v/v); $[\alpha]^{24}_D$ = -57.5 (*c* 2.25, $CHCl_3$); IR (neat): 3050, 2920, 2870, 1420, 1100, 1020 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.70 (dddd, *J* = 13.0, 6.5, 1.5, 1.5 Hz, 4H), 7.44-7.36 (m, 6H), 5.79 (dddd, *J* = 17.0, 9.5, 9.5, 5.0 Hz, 2H), 5.10-5.03 (m, 2H), 4.33 (dddd, *J* = 9.5, 6.5, 4.0, 4.0

Hz, 1H), 4.07 (t, *J* = 2.0 Hz, 1H), 3.94 (m, 1H), 3.79 (dd, *J* = 11.0, 4.5 Hz, 1H), 3.70 (dd, *J* = 10.5, 3.5 Hz, 1H), 3.27 (s, 3H), 2.57 (dddd, *J* = 13.5, 4.0, 2.5, 2.5 Hz, 1H), 2.25 (dd, *J* = 14.5, 9.5 Hz, 1H), 2.11 (ddd, *J* = 13.0, 9.5, 4.5 Hz, 1H), 2.04 (m, 2H), 1.85-1.70 (m, 2H), 1.06 (s, 9H), 0.85 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 135.8, 134.3, 133.9, 129.8, 127.8, 117.2, 100.9, 78.9, 77.0, 72.5, 66.4, 48.2, 39.1, 36.2, 30.0, 29.2, 27.1, 19.5, 15.3; HRFABMS calcd for $C_{29}H_{40}SiNaO_4$ $[M + Na]^+$ 503.2594, found 503.2610.



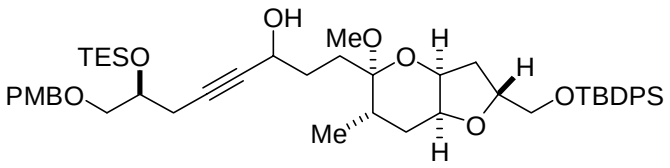
Alcohol 15a. To a stirred 0 °C solution of **15** (44 mg, 91 μmol) in THF (4 mL) was added a freshly prepared solution of 9-BBN (2.8 mL of a 0.20 M solution of 9-BBN dimer in THF, 0.55 mmol). After 1 h, the ice bath was removed, and the reaction was allowed to warm to rt. After 1 h, the reaction mixture was recooled to 0 °C, and 3 N aqueous NaOH and 30% H_2O_2 (1.5 mL ea) were added. The reaction mixture was allowed to gradually warm to rt. After stirring vigorously for an additional 2 h, saturated aqueous $NaHCO_3$ (1 mL) was added, and the mixture was diluted with ethyl acetate (2 mL). The separated aqueous phase was extracted with ethyl acetate (3 ω 2 mL), and the combined organic extracts were washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (hexanes/ethyl acetate, 5:1 to 2:1, v/v) of the crude residue provided **15a** (37 mg, 74 μmol, 81%) as a clear, colorless oil: R_f 0.30 (hexanes/ethyl acetate, 2:1, v/v); $[\alpha]^{25}_D$ = -37.8 (*c* 2.7, $CHCl_3$); IR (neat): 3416, 3071, 2928, 1459, 1427, 1064 cm^{-1}; ^{1}H NMR (C_6D_6, 500 MHz): δ 7.85 (m, 4H), 7.25 (m, 6H), 4.48 (m, 1H), 3.85 (m, 2H), 3.79 (dd, *J* = 11.0, 4.0 Hz, 1H), 3.58 (dd, *J* = 10.5, 4.0 Hz,

1H), 3.46 (m, 2H), 3.06 (s, 3H), 2.20 (dddd, *J* = 12.0, 12.0, 6.5, 6.5 Hz, 1H), 1.94 (dd, *J* = 13.5, 6.5 Hz, 1H), 1.88-1.78 (m, 4H), 1.63-1.44 (m, 4H), 1.18 (s, 9H), 0.87 (d, *J* = 6.5 Hz, 3H) ; ^{13}C NMR (C_6D_6, 125 MHz): δ 135.8, 133.8, 129.6, 128.0, 101.1, 78.5, 76.4, 72.4, 66.5, 62.4, 47.1, 35.6, 31.6, 30.0, 29.8, 28.3, 27.3, 26.7, 22.7, 15.4, 14.0; HRFABMS calcd for $NaC_{29}H_{42}SiO_5$ $[M + Na]^+$ 521.2699, found 521.2697.



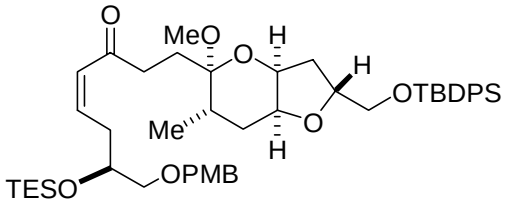
Aldehyde 16. To a stirred rt solution of **15a** (37 mg, 74 μmol) in CH_2Cl_2 (5 mL) were added crushed 4 molecular sieves (~30 mg), tetra-*n*-propylammonium perruthenate (3 mg, 9 μmol), and 4-methylmorpholine-*N*-oxide (22 mg, 0.18 mmol). After 25 minutes, the CH_2Cl_2 was removed under a stream of N_2. The resulting crude residue was purified by silica gel column chromatography (hexanes/ethyl acetate, 8:1 to 5:1, v/v) to provide **16** (25 mg, 50 μmol, 68%) as a clear, colorless oil: R_f 0.39 (hexanes/ethyl acetate, 5:1, v/v); $[\alpha]^{24}_D$ = -38.7 (*c* 1.3, $CHCl_3$); IR (neat): 3048, 2930, 2722, 1725, 1472, 1428, 1109 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.76 (s, 1H), 7.69 (dd, *J* = 13.5, 6.5 Hz, 4H), 7.40 (m, 6H), 4.28 (m, 1H), 4.05 (s, 1H), 3.94 (d, *J* = 2.0 Hz, 1H), 3.80 (dd, *J* = 11.0, 4.0 Hz, 1H), 3.66 (dd, *J* = 11.0, 4.0 Hz, 1H), 3.28 (s, 3H), 2.52 (m, 1H), 2.45 (m, 1H), 2.21 (ddd, *J* = 14.5, 9.0, 7.0 Hz, 1H), 2.12 (ddd, *J* = 13.0, 9.5, 4.5 Hz, 1H), 1.99 (dddd, *J* = 13.0, 6.5, 6.5, 6.5 Hz, 1H), 1.80 (m, 2H), 1.06 (s, 9H), 0.86 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 202.1, 135.6, 133.6, 129.6, 127.6, 100.5, 78.7, 76.6, 72.5, 66.1, 47.9, 39.1,

35.6, 29.6, 28.5, 26.9, 25.9, 19.3, 15.4; HRFABMS calcd for $NaC_{29}H_{40}SiO_5$ $[M + Na]^+$ 519.2543, found 519.2565.



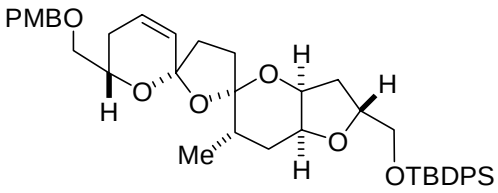
Propargylic Alcohol 18. To a stirred 0 °C solution of **17** (72 mg, 0.22 mmol) in THF (1 mL) under Ar was added EtMgBr (67 μL of a 3.0 M solution in diethyl ether, 0.20 mmol). After 30 min, the mixture was warmed to rt and allowed to stir for an additional 1.2 h. The reaction mixture was then cooled to -60 °C, and a solution of **16** (36 mg, 72 μmol) in THF (1 mL) was added dropwise via syringe. The reaction mixture was gradually warmed to -40 °C, and after 1.5 h saturated aqueous $NaHCO_3$ (2 mL) was added, and the mixture was allowed to warm to rt. The mixture was diluted with ethyl acetate (2 mL), and the separated aqueous phase was washed with ethyl acetate (5 ω 2 mL). The combined organic fractions were washed with saturated aqueous NaCl, dried over Na_2SO_4, filtered, and concentrated. Silica gel column chromatography (hexanes/ethyl acetate, 8:1 to 5:1 to 2:1, v/v) of the crude residue provided **18** (43 mg, 52 μmol, 72%) as a clear, colorless oil: R_f 0.19 (hexanes/ethyl acetate, 5:1, v/v); IR (neat): 3427, 3048, 2930, 1612, 1587, 1512, 1460, 1422, 1248, 1112, 824 cm^{-1}; ^1H NMR (C_6D_6, 500 MHz): δ 7.82 (m, 4H), 7.22 (m, 8H), 6.78 (d, *J* = 8.5 Hz, 2H), 4.42 (m, 2H), 4.35 (s, 2H), 4.04 (dddd, *J* = 12.0, 6.0, 6.0, 6.0 Hz, 1H), 3.82 (m, 2H), 3.76 (m, 1H), 3.54 (m, 1H), 3.48 (m, 1H), 3.27 (s, 3H), 3.09 (s, 1H), 3.08 (s, 2H), 2.56-2.44 (m, 2H), 2.17 (m, 1H), 2.08 (m, 1H), 2.02-1.68 (m, 7H), 1.14 (s, 9H), 1.00 (t, *J* = 7.5 Hz, 9H), 0.89 (d, *J* = 7.0 Hz, 1H), 0.86 (d, *J* = 6.5 Hz, 2H), 0.62 (q, *J* = 7.5 Hz, 6H); ^{13}C NMR (C_6D_6, 125

MHz): δ 159.4, 135.8, 133.8, 130.6, 129.6, 129.1, 128.0, 127.7, 113.7, 101.1, 100.9, 83.6, 81.5, 78.6, 78.5, 76.4, 73.5, 73.4, 72.9, 72.6, 72.5, 70.6, 66.3, 62.8, 62.1, 54.4, 47.3, 35.4, 32.7, 29.8, 29.7, 29.1, 28.6, 28.5, 26.8, 25.2, 19.2, 15.4, 6.8, 5.0; HRFABMS calcd for $NaC_{48}H_{70}Si_2O_8$ $[M + Na]^+$ 853.4507, found 853.4570.



Enone 5. To a stirred solution of **18** (24 mg, 29 μmol) in benzene (2 mL) was added Lindlar's catalyst (5 mg of Pd on $CaCO_3$ poisoned with Pb, 5% Pd by wt, 2 μmol). The reaction flask was repeatedly evacuated and flushed with H_2. After an atmosphere of H_2 was established in the reaction flask, the suspension was vigorously stirred for 1 h, then filtered through Celite with CH_2Cl_2 (8 mL) and concentrated to provide the crude allylic alcohol as a clear, colorless oil. ^{1}H NMR analysis of the crude product verified that the reaction had gone to completion. The crude allylic alcohol was dissolved in CH_2Cl_2 (3 mL). To the stirred rt solution was added crushed 4 molecular sieves (~15 mg), tetra-*n*-propylammonium perruthenate (1 mg, 3 μmol), and 4-methylmorpholine-*N*-oxide (8 mg, 0.07 mmol). After 40 min, the CH_2Cl_2 was removed under a stream of N_2. The resulting crude residue was purified by silica gel column chromatography (hexanes/ethyl acetate, 8:1, v/v) to provide **5** (22 mg, 26 μmol, 90% over two steps) as a clear, colorless oil: R_f 0.73 (hexanes/ethyl acetate, 2:1, v/v); $[\alpha]^{26}_D$ = -20.0 (*c* 0.5, $CHCl_3$); IR (neat): 2454, 1693, 1613, 1514, 1462, 1428, 1250, 1112, 1021, 822, 741, 703 cm^{-1}; ^{1}H NMR (C_6D_6, 500 MHz): δ 7.84 (m, 4H), 7.25-7.18 (m, 8H), 6.77 (d, *J* = 8.5 Hz, 2H), 6.16 (ddd, *J* = 11.5, 7.0, 7.0 Hz, 1H), 5.94 (d, *J* = 12.0 Hz, 1H), 4.42 (m, 1H), 4.28 (s, 2H), 4.03 (dddd,

J = 5.5, 5.5, 5.5, 5.5 Hz, 1H), 3.78 (m, 3H), 3.62 (dd, *J* = 11.0, 4.5 Hz, 1H), 3.38 (dd, *J* = 9.5, 6.0 Hz, 1H), 3.32 (dd, *J* = 9.5, 4.5 Hz, 1H), 3.27 (s, 3H), 3.14 (m, 1H), 3.05 (m, 1H), 3.03 (s, 3H), 2.52 (m, 1H), 2.30 (m, 2H), 2.03 (dddd, *J* = 12.0, 12.0, 6.0, 6.0 Hz, 1H), 1.86-1.74 (m, 4H), 1.16 (s, 9H), 1.00 (dd, *J* = 7.5, 7.5 Hz, 9H), 0.80 (d, *J* = 7.0 Hz, 3H), 0.64 (dddd, *J* = 7.0, 7.0, 7.0, 3.0 Hz, 6H); ^{13}C NMR (C_6D_6, 125 MHz): δ 199.4, 159.4, 143.2, 135.8, 133.8, 130.6, 129.6, 129.1, 128.0, 127.6, 113.7, 100.6, 78.7, 76.4, 74.4, 72.8, 72.3, 71.2, 66.6, 54.4, 47.3, 39.2, 35.7, 35.0, 29.9, 28.6, 27.4, 26.7, 19.2, 15.4, 6.9, 5.1; HRFABMS calcd for $NaC_{48}H_{70}Si_2O_8$ $[M + Na]^+$ 853.4507, found 853.4518.



Trioxadispiroketal 19. To a stirred -40 °C solution of **5** (10 mg, 12 μmol) in CH_3CN (1 mL) under Ar was added TMSOTf (2 μL, 0.01 mmol). After 2 h saturated aqueous $NaHCO_3$ (1 mL) was added, and the CH_3CN was removed under a stream of N_2. The crude residue was dissolved in ethyl acetate (2 mL), and the organic phase was washed with H_2O and saturated aqueous NaCl (1 mL ea). The aqueous extracts were washed with ethyl acetate (2 ω 2 mL), and the combined organic extracts were dried over Na2SO4, filtered, and concentrated to give 19 (7 mg, 10 μmol, 85%) as a clear, colorless oil: R_f 0.65 (hexanes/ethyl acetate, 2:1, v/v); $[\alpha]^{26}_D$ = -44.9 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.68 (m, 4H), 7.40 (m, 6H), 7.29 (d, *J* = 8.0 Hz, 2H), 6.86 (d, *J* = 8.0 Hz, 2H), 5.97 (ddd, *J* = 9.5, 6.0, 2.0 Hz, 1H), 5.61 (dddd, *J* = 9.5 Hz, 1.5, 1.5, 1.5 Hz,

1H), 4.57 (s, 2H), 4.39 (d, *J* = 2.0 Hz, 1H), 4.34 (dddd, *J* = 8.0, 8.0, 4.5, 4.5 Hz, 1H), 4.21 (m, 1H), 3.90 (d, *J* = 2.5 Hz, 1H), 3.72 (m, 1H), 3.75 (s, 3H), 3.64 (dd, *J* = 11.0, 4.0 Hz, 1H), 3.56 (dd, *J* = 10.5, 6.0 Hz, 1H), 3.50 (dd, *J* = 10.5, 4.5 Hz, 1H), 2.24 (ddd, *J* = 13.5, 6.5, 6.5 Hz, 1H), 2.12 (dd, *J* = 7.5, 7.5 Hz, 2H), 2.08 - 1.75 (m, 8H), 1.04 (s, 9H), 0.87 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.1, 135.6, 133.7, 130.6, 129.5, 129.2, 128.5, 127.6, 127.5, 113.7, 109.3, 104.9, 78.6, 77.3, 76.7, 73.3, 72.9, 72.2, 69.1, 66.4, 55.2, 37.4, 35.8, 35.0, 31.1, 26.9, 26.8, 19.3, 15.8; HRFABMS calcd for $NaC_{41}H_{52}SiO_7$ $[M + Na]^+$ 707.3380, found 707.3425.