JOC Note

Total Synthesis of (−)-5,6-Dihydrocineromycin B

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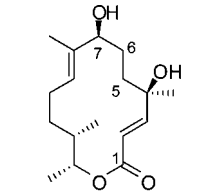
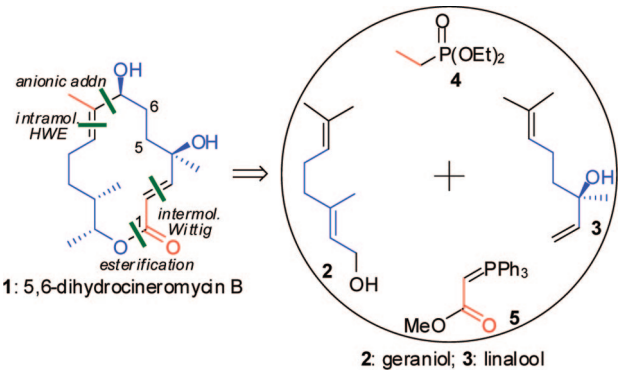


5,6-dihydrocineromycin B

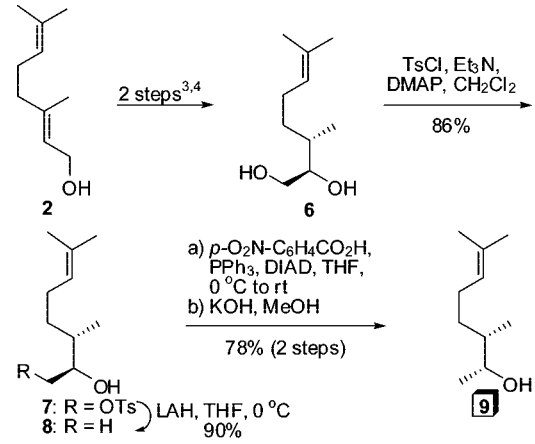
An asymmetric total synthesis of (−)-5,6-dihydrocineromycin B has been accomplished in 13 steps from (−)-linalool *O*-triethylsilyl ether or 12 steps from geraniol. The present synthesis features (i) an intermolecular Wittig reaction involving an aldehyde possessing a ketophosphonate functionality and (ii) an intramolecular Horner−Wadsworth−Emmons olefination.

5,6-Dihydrocineromycin B (**1**),[1a] together with cineromycin B and some other secondary metabolites, was isolated by Zeeck et al. in 1999 from *Streptomyces* sp. (strain Gö 40/10).[1b] The structural features of the macrolide antibiotic include four stereogenic centers, two carbon−carbon double bonds, two hydroxyls, and an ester functionality embedded on a 14-membered macrocycle. Owing to their antibiotic activity against staphylococci, cineromycins and albocyclins have become alluring targets for total synthesis.[2] However, only one total synthesis of 5,6-dihydrocineromycin B has been published so far.[2a] Herein we report a novel asymmetric synthesis of 5,6-dihydrocineromycin B (**1**). As outlined in Scheme 1, our synthetic strategy for assembling **1** would rely on the combination of four components: geraniol (**2**), (−)-linalool (**3**), phosphonate **4**, and ylide **5**. The addition of α-deprotonated phosphonate to aldehyde, Wittig reaction, esterification, and intramolecular Horner−Wadsworth−Emmons (HWE) olefination can serve as key reactions to connect the above four substances.

SCHEME 1. Synthetic Strategy for 5,6-Dihydrocineromycin B



SCHEME 2. Synthesis of Alcohol 9



Our synthesis commenced from elaboration of geraniol (**2**), which was transformed into the known chiral vicinal diol **6** via Sharpless asymmetric epoxidation[3] (TBHP, L-(+)-DIPT, Ti(O-^{i}Pr)$_4$, molecular sieves, CH_2Cl_2) followed by regio- and stereoselective reductive ring opening[4] ($NaBH_3CN$, $BF_3\cdot Et_2O$, THF) according to the documented procedures (Scheme 2). Selective tosylation of the primary hydroxyl (TsCl, Et_3N, DMAP, CH_2Cl_2, 86%) followed by reductive cleavage[5] ($LiAlH_4$, THF, 90%) of the sulfonate led to the formation of alcohol **8** in high overall yield. Configuration inversion of the hydroxyl-bearing stereocenter in **8** was realized via sequential Mitsunobu esterification[6] (p-O_2N−$C_6H_4CO_2H$, PPh_3, DIAD, THF) and methanolysis in the presence of KOH; the key intermediate, **9**, was thus obtained in 78% yield over two steps from **8**.

In the meantime, (−)-linalool (**3**) was converted to triethylsilyl (TES) ether **10**[7] (Scheme 3). A two-step sequence, comprising

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(1) (a) Schiewe, H. J.; Zeeck, A. *J. Antibiot.* **1999**, *52*, 635. (b) As reported by Zeeck et al.,[1a] the isolated sample of dihydrocineromycin B had an optical rotation ($[\alpha]^{20}_D$) of +10 (*c* 0.1, MeOH) corresponding to the proposed structure of **1** (Scheme 1). In contrast, we found that the optical rotation data for the structure **1** had a negative sign after its total synthesis was completed (see text).

(2) (a) For synthesis of 5,6-dihydrocineromycin B, see: Tietze, L. F.; Völkel, L. *Angew. Chem., Int. Ed.* **2001**, *40*, 901. (b) For synthesis of ingramycin, see: Tanner, D.; Somfai, P. *Tetrahedron* **1987**, *43*, 4395. (c) For synthesis of cineromycin B, see: Takahashi, T.; Watanabe, H.; Kitahara, T. *Tetrahedron Lett.* **2003**, *44*, 9219.

(3) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.
(4) Taber, D. F.; Home1, J. B. *J. Org. Chem.* **1994**, *59*, 4004.

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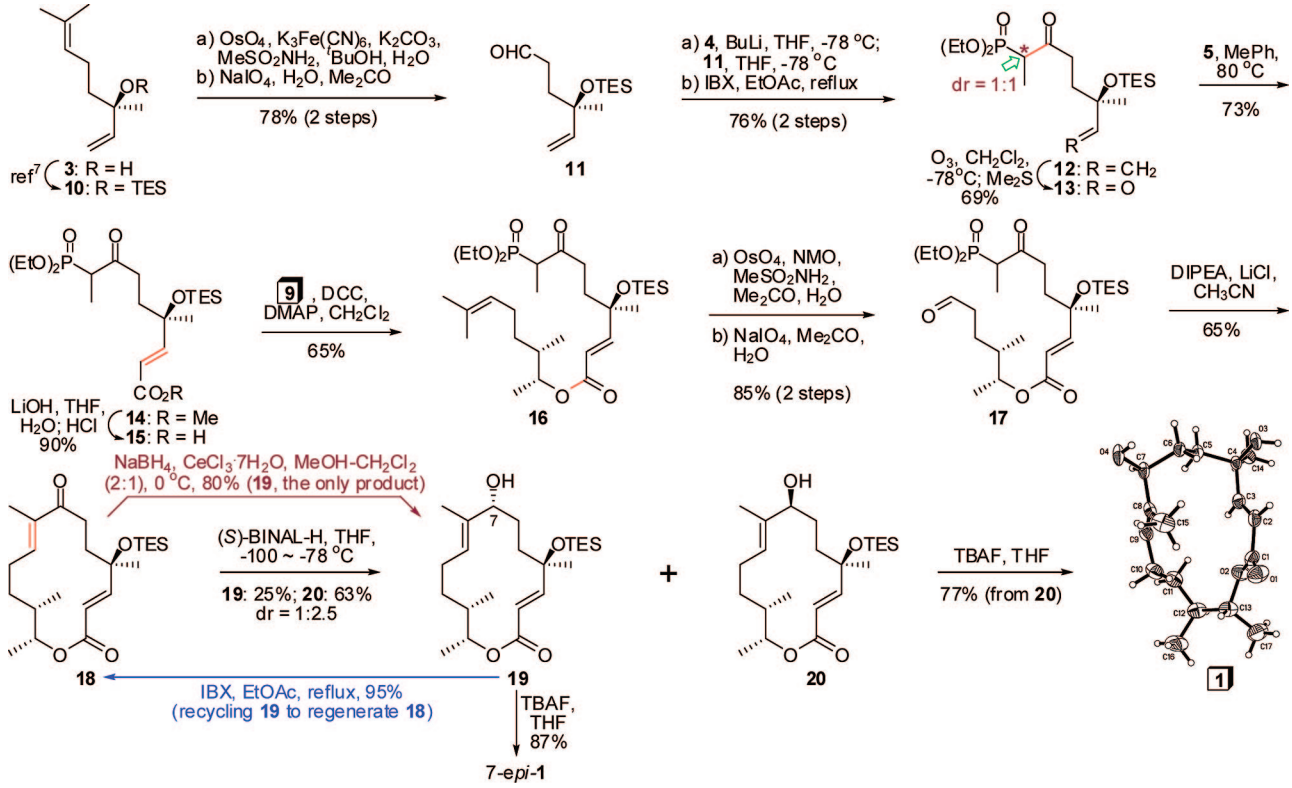
SCHEME 3. Synthesis of (−)-Dihydrocineromycin B (1) and Its Epimer 7-*epi*-1



(i) chemoselective dihydroxylation[8] of the more electron-rich carbon−carbon double bond (OsO_4, $K_3Fe(CN)_6$, K_2CO_3, $MeSO_2NH_2$, ^tBuOH, H_2O) and (ii) vicinal diol cleavage ($NaIO_4$, H_2O, Me_2CO), furnished aldehyde **11** in good yield (78%). Ketophosphonates **12** (dr = 1:1) were prepared in 78% yield over two steps through addition[9] of α-deprotonated phosphonate **4** to aldehyde **11** followed by oxidation[10] of the resultant alcohol with IBX in refluxing EtOAc. Ozonolysis of **12** provided aldehyde **13** (69%), which, after being subjected to Wittig reaction with ylide **5** in toluene at 80 °C overnight, was transformed into **14**, an unsaturated methyl ester (73%). Apparently, the potential tandem intermolecular proton transfer/intramolecular HWE olefination process was not favored since only a little cyclohexenone derivative was formed.[11] Furthermore, oligomerization or polymerization did not seem to take place to an appreciable extent under the reaction conditions. Next, saponification of **14** with LiOH in THF−H_2O (1:1) afforded, after an acidic workup, carboxylic acid **15** in 90% yield; the latter was subsequently coupled with alcohol **9** (DCC, DMAP, CH_2Cl_2)[12] to furnish ester **16** in 65% yield. The trialkyl-substituted olefin moiety was then chemoselectively cleaved to give **17** in good yield (85%) over two steps {(i) OsO_4, NMO, $MeSO_2NH_2$, Me_2CO, H_2O;[8] (ii) $NaIO_4$, Me_2CO, H_2O}. The next step was to perform an intramolecular HWE olefination. Indeed, exposure of **17** to DIPEA and LiCl[13] in acetonitrile effected the desired HWE reaction, which formed macrocycle **18** in moderate yield (65%).

With **18** in hand, the remaining tasks were to stereoselectively reduce[14] the carbonyl functionality of the enone moiety and remove the silyl protecting group. Several reduction methods were examined without success. For instance, Luche reduction[15] gave exclusively **19** (in 80% yield), in which the stereochemical configuration at C-7 was opposite to that of the target molecule. The stereocontrol observed in this reaction might arise from the macrocyclic conformation of **18**. Mitsunobu reaction (p-O_2N−$C_6H_4CO_2H$, PPh_3, DIAD, THF, 0 °C then rt) of allylic alcohol **19** followed by methanolysis (K_2CO_3, MeOH, rt) failed to give **20** because the first step involved an S_N2' rather than S_N2 reaction. In addition, the Corey−Bakshi−Shibata (CBS) reduction protocol[16] proved to be unfruitful on this particular substrate. However, treatment[17] of **18** with (*S*)-BINAL-H[18] (prepared from $LiAlH_4$, (*S*)-BINOL and EtOH, in a 1:1:1 ratio) in THF at −100 to −78 °C provided the anticipated alcohol **20** (63%) together with **19** (25%), which could either be oxidized[10] to regenerate enone **18** (IBX, EtOAc, reflux, 95%) for the recycling purpose or be converted to 7-*epi*-**1** (87%) after desilylation[2c] with TBAF in THF. Finally, desilylation[2c] of **20**

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(6) Mitsunobu, O. *Synthesis* **1981**, 1–28.
(7) Ikawa, T.; Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron* **2004**, *60*, 6901.
(8) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.-Q.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768.
(9) Richardson, T. I.; Rychnovsky, S. D. *Tetrahedron* **1999**, *55*, 8977.
(10) More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001.
(11) To the best of our knowledge, this represents the first example of a successful intermolecular Wittig reaction involving an aldehyde possessing a ketophosphonate functionality. For an example of intermolecular HWE reaction involving an aldehyde possessing a ketophosphonate functionality, see: Hosokawa, S.; Seki, M.; Fukuda, H.; Tatsuta, K. *Tetrahedron Lett.* **2006**, *47*, 2439.
(12) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.
(13) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.
(14) For reduction of macrocyclic ketones, see: (a) Keller, T. H.; Neeland, E. G.; Rettig, S.; Trotter, J.; Weiler, L. *J. Am. Chem. Soc.* **1988**, *110*, 7858. (b) Keller, T. H.; Weiler, L. *J. Am. Chem. Soc.* **1990**, *112*, 450.
(15) Luche, J. L.; Gemal, A. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
(16) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925.
(17) The reaction was performed by following Tietze's protocol.[2a]
(18) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717.

under the same conditions used for **19** produced in 77% yield 5,6-dihydrocineromycin B (**1**) as a colorless solid {mp 143−146 °C; lit.[1a] 145−155 °C}. The structure of **1** was unambiguously confirmed by X-ray crystallographic analysis, while the ^{1}H and ^{13}C NMR spectroscopic data essentially match those disclosed in the literature[1a] (see the Supporting Information). However, the optical rotation data of **1** determined in two different solvents {$[\alpha]^{23}_D$ −72.5 (*c* 0.1, MeOH); $[\alpha]^{25}_D$ −95.5 (*c* 0.15, $CHCl_3$)} were opposite in sign to and prominently different in magnitude from that reported by Zeeck[1a] {$[\alpha]^{20}_D$ +10 (*c* 0.1, MeOH)}.

In summary, a concise asymmetric total synthesis of (−)-dihydrocineromycin B (**1**) has been accomplished in 13 steps (in 3.6% overall yield, without considering recycling of **19**) from (−)-linalool *O*-TES ether. The present synthesis features (i) an intermolecular Wittig reaction involving an aldehyde possessing a ketophosphonate functionality and (ii) an intramolecular HWE olefination. The strategy opens a practically viable way to construct a series of medicinally attractive cineromycin analogues.

Experimental Section

The synthesis, purification, and analytical data of the intermediates **7**−**9** and **11**−**15** are described in the Supporting Information.

Compound 16. To a solution of alcohol **9** (688 mg, 4.40 mmol) and acid **15** (2.38 g, 5.28 mmol) in CH_2Cl_2 (20 mL) at 0 °C were added DCC (1.80 g, 8.72 mmol) and DMAP (54 mg, 0.44 mmol). The mixture was stirred for 5 h. After filtration and evaporation of the solvent, the residue was purified by flash chromatography to give **16** (1.68 g, 65%) as a colorless oil: IR (film) ν 2960, 2936, 2877, 1717, 1456, 1378, 1256, 1162, 1108, 1050, 1023, 964, 744; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.60 (q, J = 7.5 Hz, 3H), 0.61 (q, J = 7.5 Hz, 3H), 0.92 (t, J = 7.5 Hz, 9H), 0.96 (d, J = 10.8 Hz, 1.5H), 0.97 (d, J = 10.5 Hz, 1.5H), 1.10−1.20 (m, 1H), 1.18 (d, J = 6.3 Hz, 3H), 1.31 (t, J = 6.6 Hz, 6H), 1.38 (s, 3H), 1.35−1.39 (m, 3H), 1.63−1.66 (m, 2H), 1.60 (s, 3H), 1.68 (s, 3H), 1.82−2.07 (m, 4H), 2.44−2.94 (m, 2H), 3.11−3.27 (m, 1H), 4.06−4.16 (m, 4H), 4.84−4.93 (m, 1H), 5.09 (t, J = 6.9 Hz, 1H), 5.92 (d, J = 15.3 Hz, 1H), 6.80 (d, J = 15.6 Hz, 0.5H), 6.81 (d, J = 15.6 Hz, 0.5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 6.6 (3C), 7.0 (3C), 10.9 (0.5C), 11.0 (0.5C), 14.4 (1C), 15.8 (0.5C), 15.8 (0.5C), 16.3 (1C), 16.3 (1C), 17.6 (1C), 25.4 (1C), 25.6 (1C), 27.7 (0.5C), 27.8 (0.5C), 32.6 (1C), 36.3 (0.5C), 36.4 (0.5C), 36.9 (1C), 37.8 (0.5C), 37.9 (0.5C), 46.7 (d, J = 126.4 Hz, 1C), 62.4−62.5 (m, 2C), 74.2 (1C), 74.3 (0.5C), 74.3 (0.5C), 119.7 (0.5C), 119.8 (0.5C), 124.3 (1C), 131.5 (1C), 153.5 (0.5C), 153.6 (0.5C), 166.1 (0.5C), 166.2 (0.5C), 205.6 (0.5C), 205.6 (0.5C); ESI-MS *m*/*z* 611 (M + Na); ESI-HRMS calcd for $C_{30}H_{57}O_7SiPNa$ 611.3509, found 611.3503.

Compound 17. To a mixture of **16** (943 mg, 1.60 mmol), acetone (16 mL), and water (2 mL) were added OsO_4 (4% in water, 1 mL, 0.16 mmol), NMO (50% in water, 0.50 mL, 2.4 mmol), and $MeSO_2NH_2$ (152 mg, 1.60 mmol). The mixture was stirred until the color turned light yellow. Then saturated aqueous Na_2SO_3 solution was added, and the stirring was continued for 30 min. After the acetone was removed, the mixture was extracted with EtOAc. The combined organic layers were dried (Na_2SO_4), filtered, and concentrated to give a crude diol, which was used directly in the next step without further purification.

The above crude diol was dissolved in acetone (10 mL), and $NaIO_4$ (680 mg, 3.18 mmol) was added. Then water was added dropwise until $NaIO_4$ was dissolved completely. The resultant mixture was stirred for 1 h and quenched with saturated aqueous $Na_2S_2O_3$ solution. After removing acetone under reduced pressure, the aqueous layer was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography to give **17** (770 mg, 85%) as a colorless oil: IR (film) ν 2958, 2877, 1718, 1458, 1378, 1255, 1162, 1021, 965, 744; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.60 (q, J = 7.5 Hz, 3H), 0.61 (q, J = 7.5 Hz, 3H), 0.93 (t, J = 7.5 Hz, 4.5H), 0.94 (t, J = 7.5 Hz, 4.5H), 0.96 (d, J = 8.1 Hz, 1.5H), 0.97 (d, J = 7.8 Hz, 1.5H) 1.21 (d, J = 6.3 Hz, 3H), 1.32−1.37 (m, 3H), 1.31 (t, J = 6.9 Hz, 6H), 1.38 (d, J = 0.9 Hz, 3H), 1.60−1.64 (m, 2H), 1.78−1.87 (m, 3H), 2.41−2.94 (m, 4H), 3.12−3.27 (m, 1H), 4.06−4.16 (m, 4H), 4.83−4.91 (m, 1H), 5.93 (d, J = 15.6 Hz, 1H), 6.80 (d, J = 15.6 Hz, 0.5H), 6.82 (d, J = 15.6 Hz, 0.5H) 9.78 (t, J = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 6.4 (3C), 6.9 (3C), 10.8 (0.5C), 10.9 (0.5C), 14.5 (1C), 16.1 (1C), 16.2 (1C), 16.2 (1C), 24.3 (1C), 27.7 (0.5C), 27.8 (0.5C), 36.1 (1C), 36.2 (1C), 36.8 (1C), 37.7 (0.5C), 37.8 (0.5C), 41.4 (1C), 46.5 (d, J = 126.5 Hz, 1C), 62.3−62.5 (m, 2C), 73.7 (1C), 74.3 (1C), 119.2 (0.5C), 119.3 (0.5C), 153.9 (0.5C), 154.0 (0.5C), 166.0 (1C), 202.1 (1C), 205.5 (1C); ESI-MS *m*/*z* 617 (M + MeOH + Na), 585 (M + Na); ESI-HRMS calcd for $C_{27}H_{51}O_8SiPNa$ 585.2989, found 585.2983.

Compound 18. (a) Prepared by HWE of 17. To a solution of **17** (60 mg, 0.11 mmol) in CH_3CN (117 mL) were added LiCl (75 mg, 1.8 mmol) and DIPEA (0.30 mL, 1.7 mmol). The mixture was stirred overnight and diluted with water. After CH_3CN was removed under reduced pressure, the residue was extracted with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by flash chromatography to give **18** (28.5 mg, 65%) as a colorless oil: $[\alpha]^{24.3}_D$ −53.48 (*c* 0.746, $CHCl_3$); IR (film) ν 2956, 2876, 1716, 1664, 1456, 1283, 1256, 1159, 1107, 1005, 744; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.63 (q, J = 7.5 Hz, 6H), 0.95 (d, J = 6.9 Hz, 3H), 0.97 (t, J = 7.5 Hz, 9H), 1.22 (d, J = 6.0 Hz, 3H), 1.36 (s, 3H), 1.41−1.52 (m, 3H), 1.75 (s, 3H), 1.97−2.30 (m, 5H), 2.85−2.95 (m, 1H), 4.65−4.75 (m, 1H), 6.05 (d, J = 15.3 Hz, 1H), 6.62 (t, J = 7.2 Hz, 1H), 6.66 (d, J = 15.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 6.6, 7.0, 11.9, 17.5, 18.7, 26.7, 27.9, 31.6, 33.5, 38.8, 39.0, 75.2, 75.6, 120.5, 136.4, 143.7, 153.6, 165.8, 203.5; ESI-MS *m*/*z* 431 (M + Na); ESI-HRMS calcd for $C_{23}H_{40}O_4SiNa$ 431.2594, found 431.2588.

(b) Prepared by Oxidation of 19. To a solution of **19** (35 mg, 0.085 mmol) in EtOAc (5 mL) was added IBX (104 mg, 0.371 mmol), and the reaction was refluxed for 4 h. After filtration through Celite, the filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography to give **18** (33 mg, 95%) as a colorless oil.

Compounds 19 and 20 (Prepared by Reduction with (*S*)-BINAL-H). A solution of compound **18** (26.0 mg, 0.0636 mmol) in THF (1 mL) was treated at −100 °C for 1 h and at −78 °C for 2 h with (*S*)-BINAL-H, which was prepared from $LiAlH_4$ (95%, 15.2 mg, 0.380 mmol), ethanol (22.2 μL, 0.380 mmol), and (*S*)-BINOL (108 mg, 0.377 mmol) in THF (1 mL) at rt. The mixture was quenched with methanol, warmed to rt, and diluted with EtOAc. After evaporation of the solvents, the residue was purified by column chromatography to give **19** (6.6 mg, 25%) and **20** (16.4 mg, 63%) as colorless oils.

Compound 19: $[\alpha]^{22.4}_D$ −49.91 (*c* 0.985, $CHCl_3$); IR (film) ν 3456, 2955, 2876, 1714, 1459, 1376, 1259, 1156, 1107, 1047, 1008, 725; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.61 (q, J = 8.1 Hz, 6H), 0.93 (d, J = 6.6 Hz, 3H), 0.96 (t, J = 8.1 Hz, 9H), 1.29 (d, J = 6.0 Hz, 3H), 1.33 (s, 3H), 1.41−1.52 (m, 2H), 1.56 (s, 3H), 1.64−2.11 (m, 7H), 3.96 (m, 1H), 4.53−4.62 (m, 1H), 5.43 (t, J = 6.9 Hz, 1H), 5.87 (d, J = 15.0 Hz, 1H), 6.92 (d, J = 15.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 6.7, 7.0, 14.9, 16.6, 19.1, 22.9, 27.2, 29.7, 33.1, 37.9, 39.0, 74.7, 75.0, 75.1, 118.2, 126.7, 136.1, 155.5, 166.5; ESI-MS *m*/*z* 433 (M + Na), 393 (M − OH); ESI-HRMS calcd for $C_{23}H_{42}O_4SiNa$ 433.2750, found 433.2753.

Compound 20: $[\alpha]^{22.2}_D$ −71.57 (*c* 0.810, $CHCl_3$), IR (film) ν 3456, 2956, 2876, 1713, 1648, 1458, 1376, 1296, 1258, 1163, 1107,1043, 1010, 743, 725; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.59 (q, J = 7.8 Hz, 6H), 0.92 (d, J = 6.9 Hz, 3H), 0.94 (t, J = 7.8 Hz, 9H), 1.28 (d, J = 6.3 Hz, 3H), 1.33 (s, 3H), 1.36−1.44 (m, 2H), 1.49 (s, 3H), 1.54−1.60 (m, 1H), 1.66−2.06 (m, 6H), 3.86 (dd, J = 5.7, 4.2 Hz, 1H), 4.53−4.63 (m, 1H), 5.41 (dd, J = 9.6, 1.2 Hz, 1H), 5.90 (d, J = 15.0 Hz, 1H), 6.66 (d, J = 15.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 6.6, 7.0, 11.1, 17.0, 19.1, 23.0, 28.5,

29.0, 32.9, 38.1, 39.8, 74.8, 75.3, 80.3, 119.0, 128.4, 135.4, 154.6, 166.4; ESI-MS *m/z* 433 (M + Na), 393 (M − OH); ESI-HRMS calcd for $C_{23}H_{42}O_4SiNa$ 433.2750, found 433.2746.

Compound 19 (Prepared by Luche Reduction). To a solution of **18** (50 mg, 0.12 mmol) in MeOH (2 mL) and CH_2Cl_2 (1 mL) at 0 °C were added $CeCl_3 \cdot 7H_2O$ (68 mg, 0.18 mmol) and $NaBH_4$ (6.4 mg, 0.17 mmol). The mixture was stirred at this temperature for 15 min and diluted with EtOAc and water. The two layers were separated, and the organic layer was washed successfully with water and brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography to give **19** (40 mg, 80%) as a colorless oil.

Compound 1. To a solution of **20** (34 mg, 0.083 mmol) in THF (1 mL) was added TBAF (1 M in THF, 110 μL, 0.110 mmol) at 25 °C. The mixture was stirred for 30 min and diluted with water. The two layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography to give **1** (19 mg, 77%) as a colorless solid: mp 143−146 °C (hexanes−CH_2Cl_2) (lit: 145−155 °C); $[\alpha]^{23}_D$ −72.5 (*c* 0.1, MeOH), $[\alpha]^{25}_D$ −95.5 (*c* 0.15, $CHCl_3$) {lit: $[\alpha]^{20}_D$ +10 (*c* 0.1, MeOH), $[\alpha]^{20}_D$ +53 ± 1 (*c* 0.178, $CHCl_3$)}; IR (film) ν 3421, 2929, 1698, 1645, 1456, 1377, 1268, 1153, 1104, 1042, 984; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.94 (d, J = 6.9 Hz, 3H), 1.25−1.32 (m, 1H), 1.30 (d, J = 6.3 Hz, 3H), 1.35 (s, 3H), 1.37−1.45 (m, 1H), 1.54 (s, 3H), 1.57−1.61 (m, 1H), 1.67−1.73 (m, 2H), 1.75−1.89 (m, 3H), 2.02−2.16 (m, 1H), 3.98 (t, J = 6.0 Hz, 1H), 4.51−4.60 (m, 1H), 5.51 (dd, J = 9.9, 2.7 Hz, 1H), 5.95 (d, J = 15.9 Hz, 1H), 6.84 (d, J = 15.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.1, 17.2, 19.0, 23.8, 28.2, 29.3, 33.2, 38.1, 39.0, 73.1, 75.5, 79.6, 118.9, 128.8, 135.2, 153.8, 166.1; ESI-MS *m/z* 319 (M + Na), 279 (M − OH); ESI-HRMS calcd for $C_{17}H_{28}O_4Na$ 319.1885, found 319.1879.

Compound 7-*epi*-1. To a solution of **19** (27 mg, 0.066 mmol) in THF (1 mL) was added TBAF (1 M in THF, 80 μL, 0.080 mmol) at 25 °C. The mixture was stirred for 30 min and diluted with water. The two layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography to give 7-*epi*-**1** (17 mg, 87%) as a colorless oil: $[\alpha]^{24.6}_D$ −47.2 (*c* 0.186, $CHCl_3$) {lit: $[\alpha]^{20}_D$ −46 ± 1 (*c* 0.195, $CHCl_3$)}; IR (film) ν 3411, 2933, 2876, 1699, 1651, 1644, 1456, 1379, 1269, 1150, 1105, 1044, 983, 732; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.94 (d, J = 6.9 Hz, 3H), 1.29 (d, J = 6.0 Hz, 3H), 1.33 (s, 3H), 1.38−1.52 (m, 2H), 1.60 (s, 3H), 1.68−1.78 (m, 3H), 1.82−1.96 (m, 3H), 2.01−2.18 (m, 1H), 3.92−3.99 (m, 1H), 4.53−4.64 (m, 1H), 5.43−5.52 (m, 1H), 5.91 (d, J = 15.6 Hz, 1H), 7.07 (d, J = 15.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.2, 16.6, 19.1, 23.4, 27.0, 30.1, 33.3, 37.6, 39.1, 72.9, 75.2, 75.3, 118.2, 127.1, 136.2, 154.4, 166.3; ESI-MS *m/z* 319 (M + Na); ESI-HRMS calcd for $C_{17}H_{28}O_4Na$ 319.1885, found 319.1882.

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Supporting Information Available: Experimental procedures, analytical data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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