Total Syntheses of (+)-Acutiphycin and (+)-*trans*-20,21-Didehydroacutiphycin

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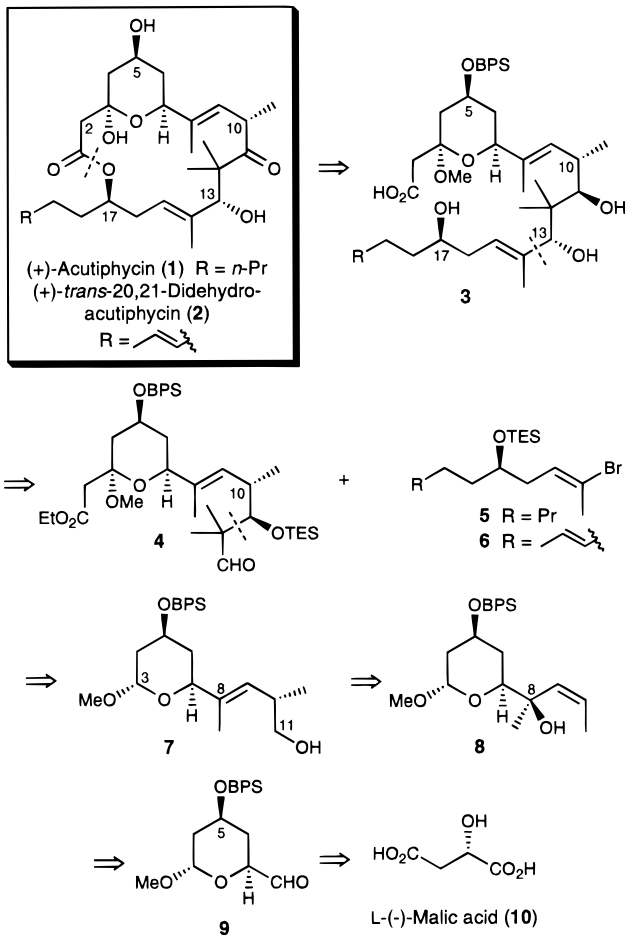
Abstract: The first total syntheses of the cytotoxic macrolides (+)-acutiphycin (**1**) and (+)-*trans*-20,21-didehydroacutiphycin (**2**) have been achieved. An acyclic stereocontrol strategy was employed to establish the configurations at C(5), C(10), and C(13) as well as the *E* geometry of the C(8,9)-trisubstituted olefin. Importantly, the natural source of **1** and **2**, the blue-green alga *Osillatoria acutissima*, no longer produces these metabolites.

In 1984, Moore and co-workers reported the isolation and characterization of the architecturally novel macrolides (+)-acutiphycin (**1**) and (+)-*trans*-20,21-didehydroacutiphycin (**2**).[1] The structures and absolute stereochemistries of **1** and **2** were determined via spectroscopic studies and chemical degradation. Both compounds exhibited significant in vivo antineoplastic activity against murine Lewis lung carcinoma and in vitro cytotoxicity against the KB and NIH/3T3 cell lines.[1] Interestingly, the original source, the blue-green alga *Osillatoria acutissima*, no longer produces these metabolites;[2] further biological evaluation and confirmation of the assigned structures therefore mandated synthesis. Our longstanding interest in the construction of biologically active hemi- and spiroketals led us to undertake the first total syntheses of **1** and **2**.[3] Challenging features of the targets included the anticipated lability of the β-carboalkoxy hemiketal moiety and the C(10) stereocenter as well as the considerable steric congestion of the 16-membered ring.

Retrosynthetic Analysis. Initial cleavage of targets **1** and **2** at the lactone linkage followed by disconnection between C(13) and C(14) led to common advanced aldehyde **4** and vinyl anion precursors **5** and **6** (Scheme 1). Stereocontrolled union of these fragments was expected to yield seco acids **3**, embodying the complete carbon skeleton of (+)-acutiphycin (**1**) and (+)-*trans*-20,21-didehydroacutiphycin (**2**) with all requisite stereochemistry. Alternatively, the C(13) stereocenter could be introduced by 1,3-anti reduction of the derived ketones, directed by the C(11) hydroxyl. Common aldehyde **4** in turn was envisioned to derive from the C(3−11) fragment **7** via oxidation, Cram addition[4] of the enolate derived from ethyl isobutanethiolate, and chemoselective thioester reduction.[5] The trans-trisubstituted olefin **7** in turn would arise from tertiary allylic alcohol **8** in stereocontrolled fashion via a Still [2,3]-sigmatropic rearrangement.[6] To secure the correct configuration of the tertiary alcohol and the cis olefin geometry in **8**, we envisioned a four-step sequence involving addition of propynyllithium to aldehyde **9**, oxidation of the resultant alcohol, chelation-controlled incorporation of the methyl group,[7] and semireduction of the acetylene. For the elaboration of aldehyde **9** from L-malic

Scheme 1



[⊗] Abstract published in *Advance ACS Abstracts*, November 1, 1997.

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(4) Cram, D. J.; Abd Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828. See also: Morrison, J. D.; Mosher, H. S. *Asymmetric Organic Reactions*; Prentice-Hall: Englewood Cliffs, NJ, 1971.

(5) Fukuyama, T.; Lin, S.-C.; Li, L. *J. Am. Chem. Soc.* **1990**, *112*, 7050.

(6) (a) Still, W. C.; Mitra, A. *J. Am. Chem. Soc.* **1978**, *100*, 1927. (b) Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885.

(7) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.

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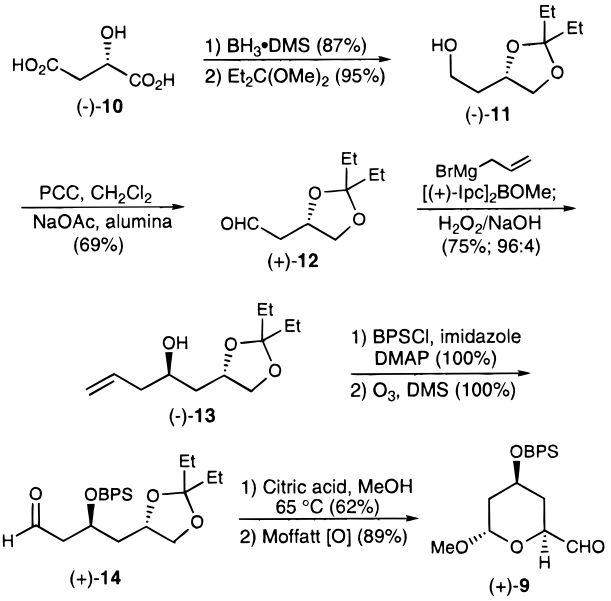
acid (**10**), a Brown enantioselective allylboration[8] would be utilized to set the C(5) stereocenter.

Construction of the C(3−11) Segment 7. The acutiphycin synthetic venture began with borane reduction[9] of L-malic acid (**10**) to furnish the corresponding triol; ketal formation[10] afforded predominantly the more stable[11] dioxolane (−)-**11**[12a] (>10:1, 83% yield from **10**; Scheme 2). Oxidation to (+)-**12**[12a] with

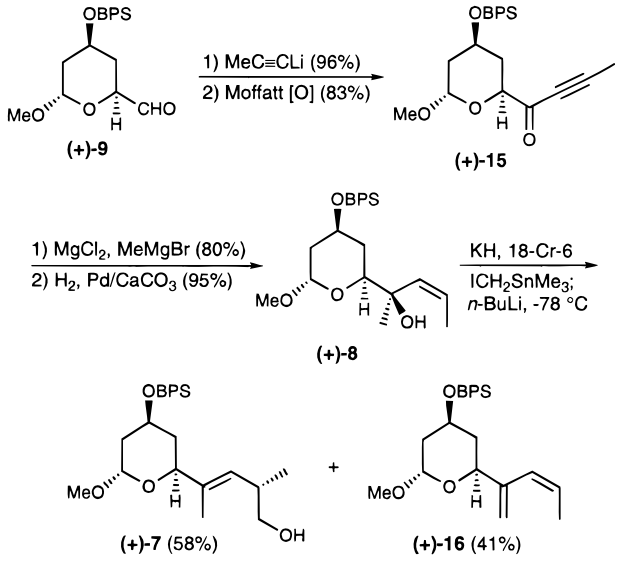
Scheme 2



buffered pyridinium chlorochromate (PCC)[13] (69%) and Brown asymmetric allylation[8] with allyl(diisopinocampheyl)borane selectively produced homoallylic alcohol (−)-**13**[12] after oxidative workup [H_2O_2/NaOH; 75% yield, 92% diastereomeric excess (de)]; the borane was prepared in situ by addition of allylmagnesium bromide to commercially available (+)-*B*-methoxy-(diisopinocampheyl)borane.[8] Protection with *tert*-butyldiphenylsilyl chloride (BPSCl) and reductive ozonolysis provided aldehyde (+)-**14**[12] (ca. 100% yield, two steps). Exposure to citric acid in MeOH at reflux then induced ketal methanolysis and cyclization, furnishing the requisite methyl α-pyranoside and its β-epimer in 62 and 21% yields after chromatography; the axial disposition of the methoxy group is favored by the anomeric effect.[14] Resubmission of the β-isomer to the citric acid/methanol protocol afforded the same epimeric mixture. Moffatt oxidation[15] of the α-isomer then produced aldehyde (+)-**9**[12a] (89%).

To set the stage for the Still [2,3]-sigmatropic rearrangement,[6] we next undertook stereocontrolled installation of the allylic alcohol moiety in **8**. To this end, addition of 1-lithio-1-propyne to aldehyde **9** and subsequent Moffatt oxidation[15] afforded ketone (+)-**15**[12] (80% yield, two steps; Scheme 3). Chelation-

Scheme 3



controlled addition of methylmagnesium bromide[7] (80% yield) and semihydrogenation with Lindlar catalyst (95%) then produced tertiary allylic alcohol (+)-**8**;[12] the relative stereochemistry was confirmed by X-ray analysis of a derivative.[16] The stannyl ether substrate for the [2,3]-sigmatropic rearrangement was prepared by deprotonation of **8** with KH and 18-crown-6 in THF, followed by alkylation with Me_3SnCH_2I at room temperature.[17] The reaction mixture was immediately cooled to −78 °C and treated with *n*-BuLi, affording the rearranged alcohol (+)-**7**[12] (58% yield) and a significant byproduct, diene (+)-**16**[12] (41%); only the *E* isomer of **7** was observed. Kallmerten has attributed similar *E* stereoselectivity to chelation of the lithium cation by an α-alkoxy substituent.[18] The formation of diene **16** may involve E_2 elimination of the hindered stannyl ether or fragmentation of the lithiated intermediate.

Construction of Common Advanced Aldehyde 4. Acidic hydrolysis of **7**, selective protection of the primary alcohol with triethylsilyl chloride (TESCl), and oxidation of the resultant lactol furnished lactone (+)-**17** in 64% yield for the three steps (Scheme 4).[12,19] Following addition of the lithium enolate of ethyl acetate to the lactone carbonyl,[20] treatment with acidic methanol removed the TES ether and installed a mixed methyl ketal to give (+)-**18**[12a] (94%). Dess−Martin oxidation[21] and coupling with the lithium enolate of ethyl isobutanethioate then provided the epimeric alcohols (+)-**19**[12] and (+)-**20**[12] in 62 and 17% yields (3.6:1 ratio); the requisite C(11) erythro stereo-

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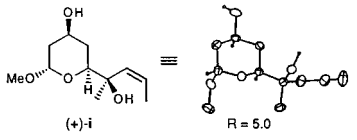
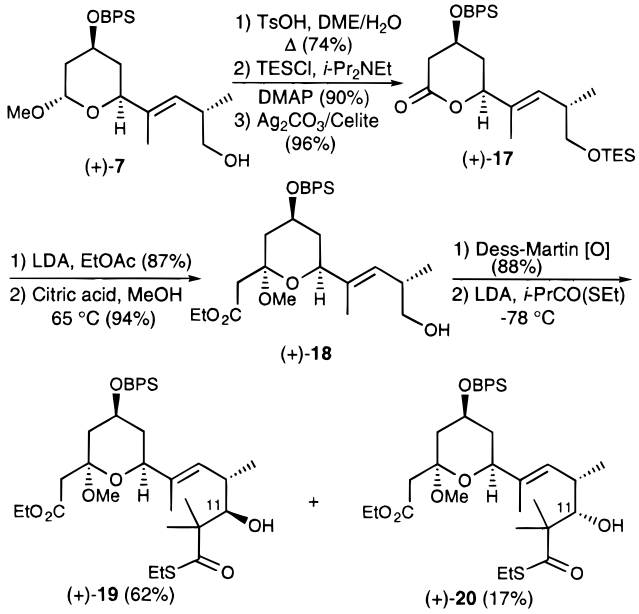
(11) (a) Masamune, S.; Ma, P.; Okumoto, H.; Ellingboe, J. W.; Ito, Y. *J. Org. Chem.* **1984**, *49*, 2834. (b) Meyers, A. I.; Lawson, J. P. *Tetrahedron Lett.* **1982**, *23*, 4883.
(12) (a) The structure assigned to each new compound was in accord with its infrared, 500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR spectra, as well as appropriate parent ion identification by high-resolution mass spectrometry. (b) In addition, an analytical sample of this compound, obtained by recrystallization or liquid chromatography, gave satisfactory combustion analysis (within 0.4%).
(13) Cheng, Y.-S.; Liu, W.-L.; Chen, S.-H. *Synthesis* **1980**, 223.
(14) Delongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Baldwin, J. E., Ed.; Pergamon: New York, 1983; pp 4−21.
(15) Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1965**, *87*, 5670.
(16) Treatment of (+)-**8** with TBAF provided the crystalline diol (+)-**i**[12a] (mp 80−82 °C).



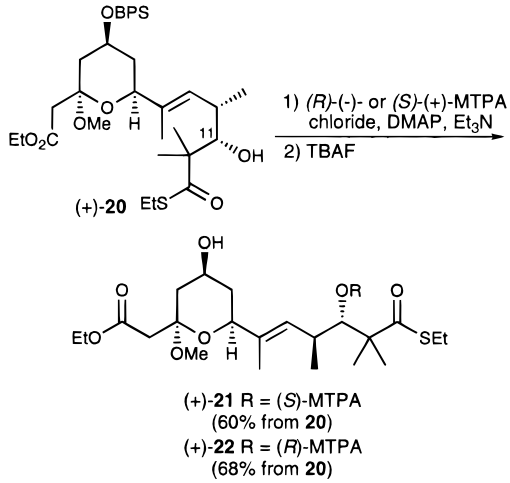
(17) Seyferth, D.; Andrews, S. B. *J. Organomet. Chem.* **1971**, *30*, 151.
(18) (a) Kallmerten, J.; Balestra, M. *Tetrahedron Lett.* **1988**, *29*, 6901. (b) Wittman, M. D.; Kallmerten, J. *J. Org. Chem.* **1988**, *53*, 4631.
(19) McKillop, A.; Young, D. W. *Synthesis* **1979**, 401.
(20) Duggan, A. J.; Adams, M. A.; Brynes, P. J.; Meinwald, J. *Tetrahedron Lett.* **1978**, *45*, 4323.
(21) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

Scheme 4



chemistry in **19** was predicted by the Cram model[4] and verified via the modified Mosher method.[22] The latter exercise entailed treatment of minor alcohol (+)-**20** with both (*R*)-(−)- and (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl (MTPA) chloride; removal of the BPS group with tetrabutylammonium fluoride (TBAF) gave Mosher ester derivatives (+)-**21**[12a] and (+)-**22**[12a] (Scheme 5). Kakisawa analysis[22b−d] of the ^{1}H

Scheme 5



chemical shifts (Figure 1) revealed the *S* absolute configuration at C(11) of **20**.

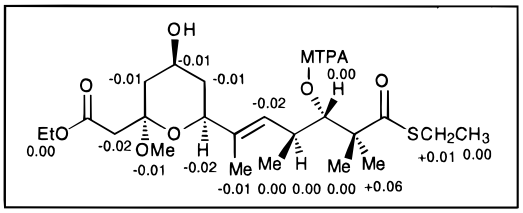
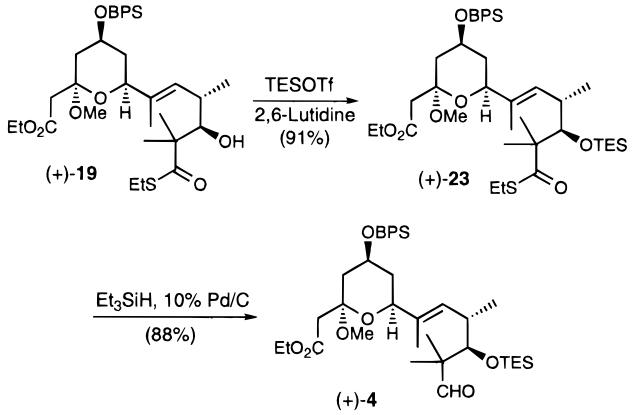


Figure 1. Absolute stereochemistry determination: $\Delta\delta$ values for the Mosher ester derivatives **21** and **22** ($\Delta\delta = \delta_{21} - \delta_{22}$ ppm, 500 MHz).

Secondary alcohol **19** was next masked as TES ether (+)-**23**[12a] in 91% yield (Scheme 6), allowing for selective desily-

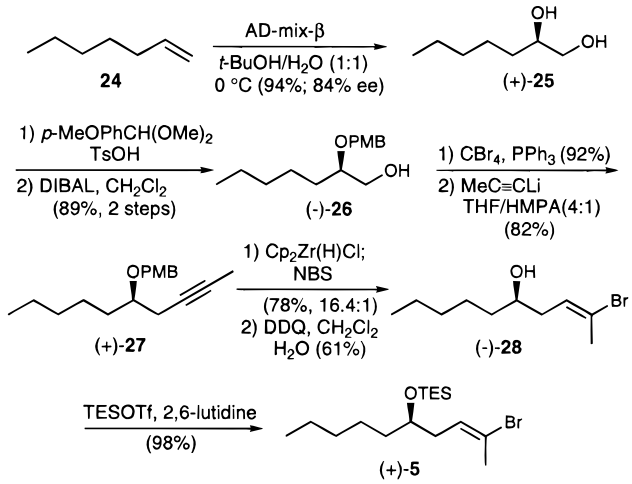
Scheme 6



lation in the presence of the BPS ether. Finally, chemoselective reduction of thiol ester **23** via the Fukuyama method[5] furnished the desired common aldehyde (+)-**4**[12a] (88%).

Synthesis of Vinyl Bromides 5 and 6. Construction of vinyl bromide **5** began with Sharpless asymmetric dihydroxylation[23] of 1-heptene (**24**) (Scheme 7), which furnished (2*R*)-1,2-

Scheme 7



heptanediol [(+)-**25**][12a] in excellent yield with adequate enantioselectivity [94% yield, 84% enantiomeric excess (ee)]. The enantiomeric purity of the diol was determined via ^{1}H NMR analysis of the bis Mosher ester prepared from (*R*)-(−)-MTPA chloride.[24] DIBAL reduction[25] of the derived *p*-methoxybenzylidene (PMB) acetal then gave primary alcohol (−)-**26**[12a] (89%, two steps). Bromination with CBr_4/Ph_3P[26] (92% yield) followed by coupling with 1-lithio-1-propyne provided alkyne

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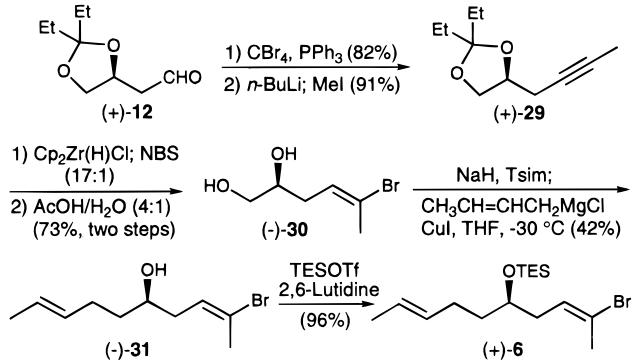
(26) Kocienski, P. J.; Cernigliaro, G.; Feldstein, G. *J. Org. Chem.* **1977**, *42*, 353.

(+)-**27**[12a] (82%). Hydrozirconation[27] of **27** proceeded with high regio- and stereoselectivities, affording a 16.4:1 mixture of regioisomeric bromides after treatment of the vinylzirconium intermediates with *N*-bromosuccinimide. Oxidative removal of the PMB group produced the pure secondary alcohol (−)-**28**[12a] in 61% yield after flash chromatography and HPLC. Protection of alcohol **28** as the TES ether (98% yield) completed the synthesis of vinyl bromide (+)-**5**.[12a]

Vinyl bromide **6**, required for the unsaturated acutiphycin congener **2**, was prepared from aldehyde (+)-**12**, employed earlier en route to common aldehyde **4**. Following Corey−Fuchs dibromomethylenation,[28] treatment with *n*-BuLi and quenching with iodomethane furnished acetylene (+)-**29**[12a] in 75% overall yield (Scheme 8). Selective hydrozirconation/

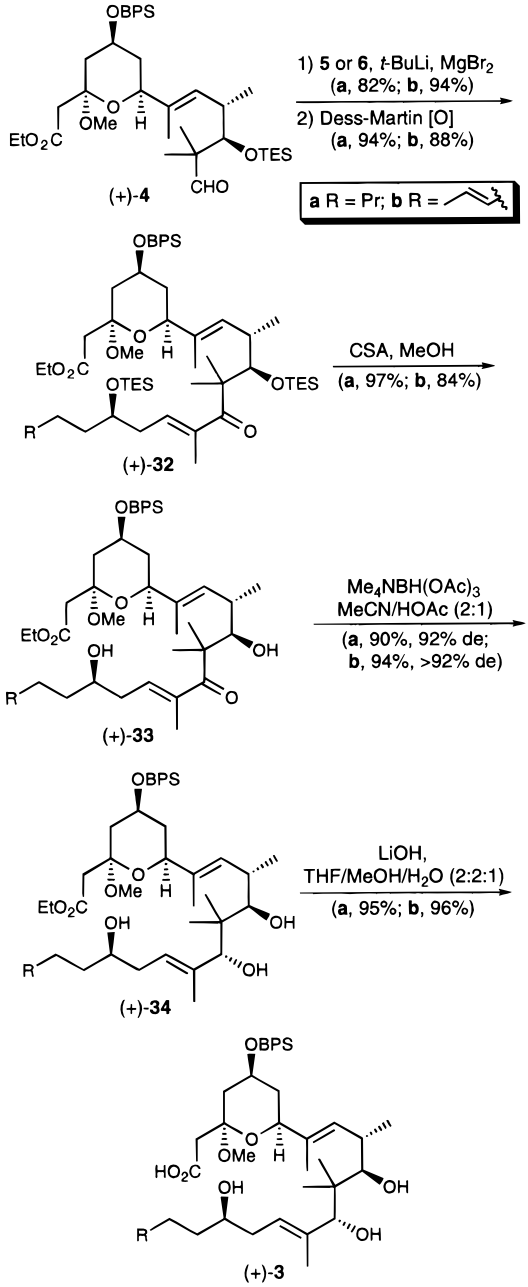
Scheme 8



bromination[27] of **29** and ketal hydrolysis with HOAc/H_2O (4:1) then gave the desired diol (−)-**30**.[12a] The Kishi one-step epoxidation protocol[29] generated a volatile oxirane which was immediately added to the lower-order cuprate prepared from crotylmagnesium chloride; the resultant 2.2:1 *E/Z* mixture of alkenes could be separated by chromatography on silica gel impregnated with silver nitrate,[30] affording pure (−)-**31**[12a] (42%). Silylation with triethylsilyl trifluoromethanesulfonate (TESOTf) then provided the vinyl bromide subunit (+)-**6**[12a] in 96% yield.

Assembly of Seco Acids 3a and 3b. With common aldehyde **4** and vinyl bromides **5** and **6** in hand, we turned to the coupling of the building blocks. Addition of the vinyl Grignard reagent derived from (+)-**5** or (+)-**6** (10 equiv) to aldehyde (+)-**4** (THF, −78 °C) gave a 1:1 mixture of epimeric alcohols; excess in the Grignard reagent was required to drive the reaction to completion. Dess−Martin oxidation then furnished enones (+)-**32a**[12a] and (+)-**32b**[12a] in 77 and 83% yields, respectively, for the two steps (Scheme 9).[21] Selective cleavage of the TES groups with camphorsulfonic acid (CSA) in methanol unmasked β-hydroxy ketones (+)-**33a**[12a] (97% yield) and (+)-**33b**[12a] (84%). Evans anti reduction[31a,b] with the Gribble reagent $Me_4NBH(OAc)_3$,[31c] afforded triols (+)-**34a**[12a] (90% yield, 96:4) and **34b**[12a] (94% yield, >96:4). The C(13) configuration was established in each case via ^{13}C NMR analysis of the derived 1,3-acetonide.[32] Ester

Scheme 9



saponification in turn produced seco acids (+)-**3a**[12a] and (+)-**3b**,[12a] the macrolactonization substrates, in high yield.

Macrolactonization: A Significant Synthetic Challenge. Of the many known methods for macrolactone generation,[33] three appeared best suited to the sensitive acutiphycin structure: the Mukaiyama *N*-methyl-2-chloropyridinium iodide procedure;[33a] the Keck cyclization with 1,3-dicyclohexylcarbodiimide (DCC), 4-(dimethylamino)pyridine (DMAP), and DMAP·HCl,[33b] and the Yamaguchi mixed anhydride protocol.[33c] The Mukaiyama method[33a] was investigated first. A dilute solution of seco acid (+)-**3** and triethylamine (1.5 equiv) in methylene chloride was added over 5 h to a dilute solution of *N*-methyl-2-chloropyridinium iodide in methylene chloride at reflux, and the resultant mixture was stirred overnight at room temperature. No desired macrolactone was isolated. The Keck method,[33b] involving slow addition of (+)-**3** in THF to a solution

(27) (a) Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 679. (b) Carr, D. B.; Schwartz, J. *J. Am. Chem. Soc.* **1979**, *101*, 3521.

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(30) Henrick, C. A. *Tetrahedron* **1977**, *33*, 1845.

(31) (a) Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986**, *27*, 5939. (b) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560. (c) Nutaitis, C. F.; Gribble, G. W. *Tetrahedron Lett.* **1983**, *24*, 4287.

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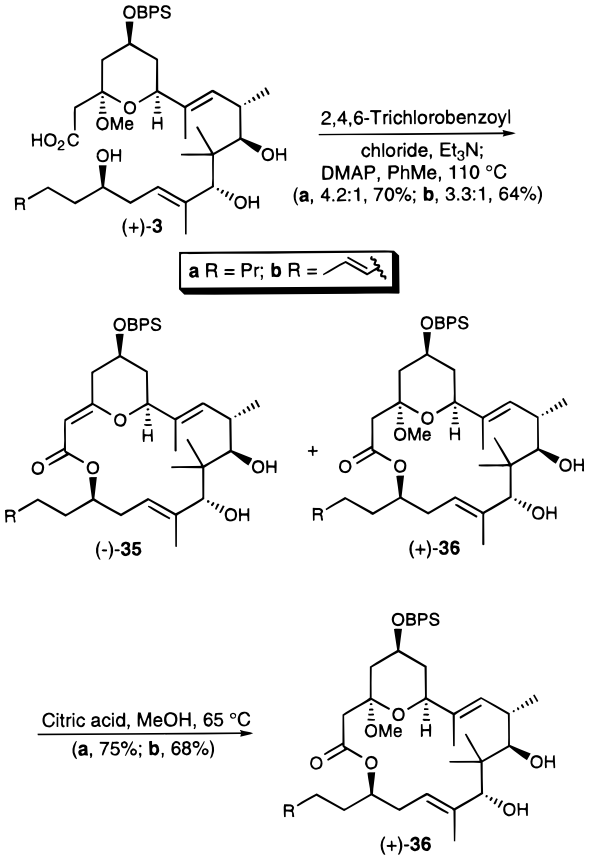
of 1,3-dicyclohexylcarbodiimide, 4-(dimethylamino)pyridine, and DMAP·HCl in ethanol-free chloroform at reflux, resulted only in decomposition of the starting material.

Success was finally realized by exploiting the Yamaguchi protocol[33c] (Scheme 10). Treatment of seco acid (+)-**3a** with

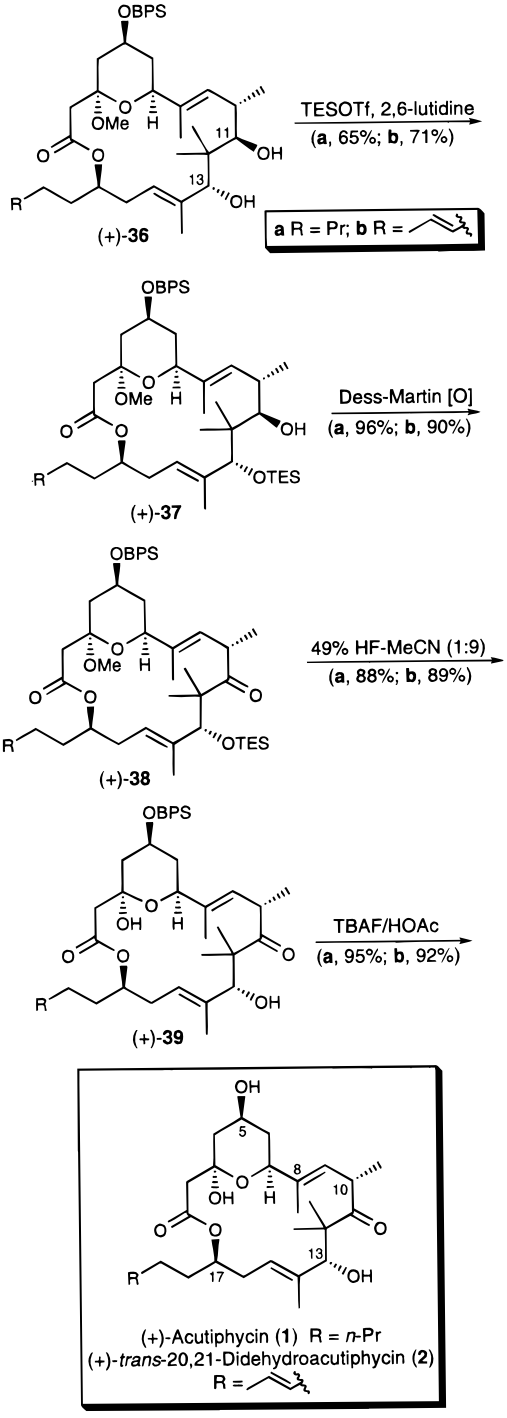
Scheme 10



2,4,6-trichlorobenzoyl chloride and triethylamine (THF, room temperature) gave the requisite mixed anhydride. After the triethylamine hydrochloride was removed, the anhydride was slowly added under high-dilution conditions to a solution of DMAP in toluene at reflux, providing a (ca. 4.2:1) mixture of the macrolide triene (−)-**35**[12a] and the desired macrolactone (+)-**36**[12a] in 70% yield. Detailed spectroscopic analysis, including ^{1}H decoupling and a 2D COSY experiment, established that the major product arose via β-elimination of methanol. When the macrolide mixture was heated in methanolic citric acid for 3 days, reinstallation of the C(3) methoxy group afforded pure (+)-**36a** in 75% yield. In similar fashion seco acid (+)-**3b** was transformed to (+)-**36b** (44% yield, two steps).

The Acutiphycin Endgame. Completion of the syntheses of **1** and **2** required selective protection of the C(13) hydroxyl, oxidation of the C(11) alcohol, and deprotection (Scheme 11). Silylation of the less-hindered C(13) secondary hydroxyl in macrolactones **36a** and **36b** (TESOTf, −78 °C) generated ethers (+)-**37a**[12a] and (+)-**37b**[12a] in 65 and 71% yields. Oxidation with the Dess−Martin periodinane and pyridine[21b] then produced the corresponding ketones (+)-**38a**[12a] (96% yield) and (+)-**38b**[12a] (90%) without observable epimerization at C(10) or migration of the C(8,9) double bond. Exposure to 49% HF/CH_3CN (1:9) for 3−5 min effected removal of the TES group and hydrolysis of the methyl pyranoside, affording hydroxy ketones (+)-**39a**[12a] and (+)-**39b**[12a] (88 and 89%, respectively); longer reaction times resulted in decomposition. Attempted removal of the BPS group in **39a** and **39b** with tetrabutylam-

Scheme 11



monium fluoride (TBAF) likewise led to the demise of these base-sensitive intermediates. However, we were delighted to find that TBAF buffered with HOAc[34] (1:1) smoothly removed the BPS moiety. Synthetic (+)-acutiphycin (**1**)[12a] (95% yield) and (+)-*trans*-20,21-didehydroacutiphycin (**2**)[12a] (92%) were identical with the natural materials in all respects (500 MHz ^{1}H and 125 MHz ^{13}C NMR, IR, HRMS, mp, mmp, optical rotation, and TLC in four solvent systems).[35]

Summary. The first total syntheses of (+)-acutiphycin (**1**) and (+)-*trans*-20,21-didehydroacutiphycin (**2**) have verified the

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(35) We thank Professor Richard E. Moore, University of Hawaii, Mànoa, for samples of natural (+)-acutiphycin and (+)-*trans*-20,21-didehydroacutiphycin.

structures and absolute stereochemistries elucidated by Moore et al. We anticipate that the successful strategy will provide material required for further biological evaluation of **1** and **2**, which no longer are available from the original marine source, and also will prove amenable to the construction of a series of novel analogs.

Experimental Section[36]

Hydroxy Ketal (−)-11. A mechanically stirred solution of borane·dimethyl sulfide complex (10 M; 130 mL, 1.3 mol) and trimethyl borate (136 mL, 1.77 mol) in THF (500 mL) was cooled to 0 °C, and a solution of L-malic acid [(−)-**10**, 54 g, 0.40 mol] in THF (200 mL) was added slowly. The resultant suspension was warmed to room temperature, stirred for two days, cooled to 0 °C, and treated slowly (2 h) with anhydrous methanol (300 mL). The solution was then warmed to room temperature, stirred overnight, and concentrated. Flash chromatography (dichloromethane/methanol, 90:10) afforded the corresponding triol (36.5 g, 87% yield) as a colorless oil. A solution of the triol (30 g, 0.29 mol), 3,3-dimethoxypentane (76.6 mL, 0.58 mol), and *p*-toluenesulfonic acid (7.0 g, 0.037 mol) in DMF (100 mL) was stirred at room temperature overnight. The reaction mixture was then diluted with ethyl acetate (500 mL) and washed with 10% NaOH (300 mL) and water (300 mL). The combined aqueous layers were extracted with ethyl acetate (500 mL), and the combined organic solutions were then washed with brine (400 mL), dried over $MgSO_4$, filtered, and concentrated. Distillation through a 25 cm Vigreux column furnished (−)-**11** (48.1 g, 95% yield) as a colorless liquid: bp 60−65 °C, 0.1 mmHg.

Aldehyde (+)-12. A mechanically-stirred mixture of pyridinium chlorochromate (58 g, 0.27 mol), sodium acetate (4.4 g, 0.054 mol), alumina (70 g), and dichloromethane (400 mL) was cooled to 0 °C, and a solution of alcohol (−)-**11** (11.6 g, 0.066 mol) in dichloromethane (40 mL) was added over 30 min. The black suspension was then warmed to room temperature, stirred 2 h further, diluted with ether (1 L), and filtered through a pad of silica gel, and the pad was washed with CH_2Cl_2 (400 mL). Concentration furnished a clear, green liquid which was distilled through a 15 cm Vigreux column to give (+)-**12** (7.8 g, 69% yield) as a colorless oil: bp 55−60 °C, 0.2 mmHg.

Homoallylic Alcohol (−)-13. At −78 °C a solution of (+)-*B*-methoxy(diisopinocampheyl)borane (16.0 g, 50.6 mmol) in toluene (130 mL) was treated with allylmagnesium bromide (1.0 M in ether; 50.5 mL, 50.5 mmol). After an additional 15 min, the resultant suspension was warmed to room temperature and stirred for 3 h. The clear upper layer was then transferred via cannula over 30 min to a flask containing a solution of aldehyde (+)-**12** (6.7 g, 38.8 mmol) in toluene (35 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 1 h, warmed to room temperature, stirred 1 h further, and treated with aqueous sodium hydroxide (2 M, 40 mL) and hydrogen peroxide (50%, 50 mL). The mixture was stirred overnight at room temperature, diluted with ether (500 mL), washed with water (300 mL) and brine (300 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 24:1) provided (−)-**13** (6.2 g, 75% yield, 96:4 by ^{1}H NMR analysis) as a colorless oil: $[\alpha]_D^{20}$ −6.8° (*c* 1.48, $CHCl_3$); IR ($CHCl_3$) 3500 (m, br), 3100 (m), 3025 (s), 3000 (s), 2960 (s), 1090 (s), 930 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84−5.75 (m, 1 H), 5.10 (m, 2 H), 4.28 (m, 1 H), 4.06 (dd, J = 7.8, 6.0 Hz, 1 H), 3.90 (m, 1 H), 3.50 (t, J = 8.0 Hz, 1 H), 2.41 (br s, 1 H), 2.30−2.18 (m, 2 H), 1.75 (m, 1 H), 1.67−1.54 (m, 5 H), 0.87 (t, J = 7.5 Hz, 3 H), 0.86 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 134.5, 118.1, 112.6, 73.8, 70.1, 68.0, 42.2, 39.2, 29.9, 29.6, 8.2, 7.9; high-resolution mass spectrum (Cl, NH_3) *m/z* 215.1627 [(M + H)$^+$; calcd for $C_{12}H_{23}O_3$ 215.1647].

Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.34; H, 10.25.

Silyloxy Aldehyde (+)-14. A solution of alcohol (−)-**13** (9.2 g, 43 mmol), imidazole (7.3 g, 100 mmol), *tert*-butyldiphenylsilyl chloride (16 mL, 61 mmol), and 4-(dimethylamino)pyridine (150 mg) in DMF (50 mL) was stirred overnight at room temperature. The mixture was then diluted with water (250 mL) and extracted with ether (300 mL), and the organic phase was washed with brine (250 mL) , dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexane/ethyl acetate, 95:5) gave the silyl ether (19.5 g, 100% yield) as a colorless liquid.

Ozone was bubbled through a solution of the silyl ether (19.5 g, 43 mmol) in dichloromethane (300 mL) at −78 °C. When a pale blue color persisted, dimethyl sulfide (80 mL) was added, and the mixture was warmed to room temperature and stirred overnight. Concentration and flash chromatography (hexanes/ethyl acetate, 80:20) provided (+)-**14** (19.5 g, 100% yield) as a colorless liquid.

Acetal Aldehyde (+)-9. A solution of aldehyde (+)-**14** (24.0 g, 53 mmol) and citric acid (20.3 g, 0.106 mol) in methanol (200 mL) was heated at reflux overnight, cooled to room temperature, and concentrated. The resultant liquid was dissolved in dichloromethane (400 mL), the solution was washed with saturated aqueous $NaHCO_3$ (300 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 80:20) furnished the hydroxy acetal (13.3 g, 62% yield) as a colorless liquid.

Pyridine (2.5 mL, 31 mmol) was added to a solution of dicyclohexylcarbodiimide (19.1 g, 93 mmol), dimethyl sulfoxide (50 mL), and the above alcohol (12.4 g, 31 mmol) in benzene (100 mL). Trifluoroacetic acid (1.2 mL, 15.5 mmol) was then introduced, and the resultant suspension was stirred for 5 h at room temperature, diluted with ether (300 mL), and filtered. The filtrate was washed with water (200 mL) and brine (200 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexane/ethyl acetate, 80:20) gave (+)-**9** (11.0 g, 89% yield) as a colorless liquid: $[\alpha]_D^{20}$ +70.4° (*c* 4.77, $CHCl_3$); IR ($CHCl_3$) 3000 (m), 2940 (s), 2860 (s), 1745 (s), 1430 (s), 1110 (s), 1050 (s), 910 (s), 710 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.57 (s, 1 H), 7.66 (m, 4 H), 7.45−7.37 (m, 6 H), 4.89 (s, 1 H), 4.20 (m, 1 H), 4.00 (dd, J = 12.0, 2.8 Hz, 1 H), 3.25 (s, 3 H), 1.97 (m, 2 H), 1.67 (m, 1 H), 1.48 (dd, J = 22.8, 12.2 Hz, 1 H), 1.06 (s, 9 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 200.3, 135.7, 133.9, 129.7, 127.6, 99.4, 73.0, 64.8, 55.0, 39.1, 34.9, 26.8, 19.0; high-resolution mass spectrum (CI, NH_3) *m/z* 416.2271 [(M + NH_4)$^+$; calcd for $C_{23}H_{34}NO_4Si$ 416.2257].

Alkynyl Ketone (+)-15. Propyne (30 mL) was condensed in THF (300 mL) at −78 °C. *n*-Butyllithium (2.4 M in hexanes; 140 mL, 0.34 mol) was added dropwise over 1 h, and the resultant suspension was mechanically stirred for an additional 15 min at −78 °C. A solution of aldehyde (+)-**9** (8.4 g, 21 mmol) in THF (25 mL) was then added dropwise, and the suspension was stirred for 15 min at −78 °C and warmed to room temperature. After 1 h the mixture was poured into cold (0 °C) saturated aqueous NH_4Cl (200 mL), the combined layers were separated, and the aqueous phase was extracted thoroughly with ether (2 × 300 mL). The combined organic layers were washed with brine (400 mL), dried over $MgSO_4$, filtered, and concentrated. Flash

(36) Reactions were carried out in oven- or flame-dried glassware under argon, unless otherwise noted. All solvents were reagent grade. Diethyl ether and tetrahydrofuran (THF) were freshly distilled from sodium/benzophenone under argon. Dichloromethane, benzene, and diisopropylamine were freshly distilled from calcium hydride under argon. Triethylamine, diisopropylethylamine, and tetramethylethylenediamine were distilled from calcium hydride under argon and stored over potassium hydroxide. Hexamethylphosphoramide was distilled from calcium hydride at reduced pressure and stored over 4 Å molecular sieves. Anhydrous pyridine, dimethylformamide, and dimethyl sulfoxide were purchased from Aldrich and used without purification. *n*-Butyllithium was purchased from Aldrich and standardized by titration with menthol/triphenylmethane. Except as otherwise stated, reactions were magnetically stirred and monitored by thin-layer chromatography with 0.25 mm E. Merck precoated silica gel plates. Flash chromatography was performed with silica gel-60 (particle size 0.040−0.062 mm) supplied by E. Merck. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise indicated. Melting points were determined on a Bristoline heated-stage microscope and are corrected. Infrared spectra were recorded on a Perkin-Elmer Model 283B spectrometer with polystyrene as external standard. NMR spectra were recorded on a Bruker AMX-500 spectrometer. Chemical shifts are reported relative to internal tetramethylsilane (δ 0.00) for ^{1}H and chloroform (δ 77.0) for ^{13}C. Optical rotations were obtained with a Perkin-Elmer model 241 polarimeter. High-resolution mass spectra were measured at the University of Pennsylvania Mass Spectrometry Service Center with a VG Micromass 70/70H or VG ZAB-E spectrometer. Microanalyses were performed by Robertson Laboratories, Madison, NJ. High-performance liquid chromatography (HPLC) was performed with a Ranin component analytical/semipreparative system.

chromatography (hexanes/ethyl acetate, 80:20) provided an inseparable mixture of epimeric alcohols (9.0 g, 96% yield) as a colorless liquid.

A solution of dicyclohexylcarbodiimide (30 g, 149 mmol), dimethyl sulfoxide (75 mL), and the above alcohols (21.7 g, 49.5 mmol) in benzene (150 mL) was treated with pyridine (3.9 mL, 49.5 mmol) followed by dropwise addition of trifluoroacetic acid (1.9 mL, 24.8 mmol). The resultant suspension was stirred for 2 h at room temperature and then diluted with ether (400 mL) and filtered. The filtrate was washed with water (300 mL) and brine (300 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 90:10) afforded (+)-**15** (18.0 g, 83% yield) as a colorless liquid.

Allylic Alcohol (+)-8. A suspension of dry magnesium chloride (18.0 g, 0.19 mol) in THF (200 mL) was treated with ketone (+)-**15** (14.0 g, 32 mmol) in THF (70 mL). Upon heating at reflux for 20 min, most of the solid dissolved. The mixture was cooled to room temperature and then to −78 °C, and methylmagnesium bromide (3.0 M in ether; 21.0 mL, 64 mmol) was then added dropwise over 10 min. After 1.5 h at −78 °C, the solution was poured into saturated aqueous NH_4Cl (150 mL). The aqueous layer was extracted with ether (300 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 80:20) gave the desired alcohol (11.7 g, 80% yield) as a colorless liquid.

The above alcohol (14.5 g, 32 mmol) was dissolved in hexane (175 mL), and 5% palladium on calcium carbonate (2.6 g) and quinoline (2.6 mL) were added. The flask was flushed three times with hydrogen, and the mixture was stirred under H_2 for 1.5 h. The suspension was then filtered through a pad of silica gel, and the pad was washed with EtOAc (150 mL). Concentration and flash chromatography (hexanes/ethyl acetate, 90:10) furnished (+)-**8** (13.8 g, 95% yield) as a colorless liquid.

Diol (+)-i. Tetra-*n*-butylammonium fluoride (1.0 M in THF; 0.6 mL, 0.6 mmol) was added to a solution of alcohol (+)-**8** (0.15 g, 0.33 mmol) in THF (5 mL). The reaction mixture was stirred overnight at room temperature, diluted with ether (20 mL), washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 50:50) afforded (+)-**i** as a colorless crystalline solid: mp 80−82 °C.

Rearranged Alcohol (+)-7 and Diene (+)-16. Potassium hydride (35% dispersion in mineral oil; 2.8 g, 24 mmol) was washed with dry hexane (3 × 5 mL), dried under vacuum, and suspended in THF (175 mL). Following the addition of 18-crown-6 (2.0 g, 7.8 mmol), the mixture was cooled to 0 °C, treated dropwise with a solution of alcohol (+)-**8** (7.10 g, 15.6 mmol) in THF (25 mL), warmed to room temperature, and stirred for 45 min. (Trimethylstannyl)methyl iodide (5.70 g, 18.7 mmol) was then added, and the suspension was stirred for an additional 45 min and cooled to −78 °C. *n*-Butyllithium (2.3 M in hexanes; 7.5 mL, 17.2 mmol) was introduced dropwise over 15 min, the reaction mixture was stirred at −78 °C for 1.5 h, and the reaction was quenched with saturated aqueous NH_4Cl (2 mL). The organic layer was washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 80:20) gave alcohol (+)-**7** (4.20 g, 58% yield) as a colorless oil and diene (+)-**16** (3.0 g, 41% yield) as a colorless liquid.

For **7**: $[\alpha]_D^{20}$ +53.4° (*c* 2.47, $CHCl_3$); IR ($CHCl_3$) 3440 (w, br), 3065 (w), 3000 (m), 2960 (s), 2940 (s), 2860 (m), 1260 (s), 1110 (s), 1045 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67 (m, 4 H), 7.43−7.36 (m, 6 H), 5.10 (d, J = 9.4 Hz, 1 H), 4.77 (d, J = 3.3 Hz, 1 H), 4.19 (m, 1 H), 3.84 (d, J = 11.6 Hz, 1 H), 3.46 (dd, J = 10.2, 7.7 Hz, 1 H), 3.36 (dd, J = 10.2, 7.8 Hz, 1 H), 3.19 (s, 3 H), 2.65−2.59 (m, 1 H), 1.95 (dd, J = 12.9, 4.9 Hz, 1 H), 1.73 (m, 1 H), 1.64 (s, 3 H), 1.60 (m, 2 H), 1.48 (dd, J = 23.3, 11.7 Hz, 1 H), 1.05 (s, 9 H), 0.93 (d, J = 6.6 Hz, 3 H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 136.8, 135.7, 134.4, 134.3, 129.5, 128.9, 127.5, 99.4, 72.3, 67.5, 65.7, 54.5, 39.9, 39.3, 35.0, 26.9, 19.0, 16.8, 13.0.

Anal. Calcd for $C_{28}H_{40}O_4Si$: C, 71.75; H, 8.60. Found: C, 72.06; H, 8.55.

For **16**: $[\alpha]_D^{20}$ +87.0° (*c* 2.27, $CHCl_3$); IR ($CHCl_3$) 1600 (w), 1110 (s), 970 (m), 900 (m), 700 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.67 (m, 4 H), 7.44−7.36 (m, 6 H), 5.79 (d, J = 11.8 Hz, 1 H), 5.72−5.66 (m, 1 H), 5.24 (s, 1 H), 4.97 (s, 1 H), 4.81 (d, J = 3.2 Hz, 1 H), 4.22−4.16 (m, 1 H), 3.95 (d, J = 11.7 Hz, 1 H), 3.21 (s, 3 H), 1.99−1.96 (m, 1 H), 1.83−1.77 (m, 1 H), 1.76 (dd, J = 6.9, 1.7 Hz, 3 H), 1.66−1.61 (m, 1 H), 1.46 (dd, J = 23.3, 11.8 Hz, 1 H), 1.05 (s, 9 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 144.5, 135.7, 134.5, 134.4, 129.5, 128.1, 127.53, 127.51, 127.3, 113.5, 99.5, 70.4, 65.7, 54.5, 40.3, 39.4, 26.9, 19.1, 14.8.

Anal. Calcd for $C_{27}H_{36}O_3Si$: C, 74.27; H, 8.31. Found: C, 74.00; H, 8.20.

Lactone (+)-17. A solution of alcohol (+)-**7** (0.63 g, 1.34 mmol) and *p*-toluenesulfonic acid (0.045 g) in DME (54 mL) and water (20 mL) was heated at reflux for 24 h, cooled to room temperature, and concentrated. The resultant liquid was saturated with NaCl and extracted with ethyl acetate (3 × 40 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 50:50) gave the corresponding diol (0.45 g, 74% yield) as a colorless oil.

A solution of the above diol (0.65 g, 1.43 mmol), diisopropylethylamine (0.5 mL, 3.0 mmol), and 4-(dimethylamino)pyridine (50 mg) in dichloromethane (14 mL) was cooled to 0 °C, and triethylsilyl chloride (0.24 mL, 1.43 mmol) was added over 10 min. The reaction mixture was stirred 40 min further, and the reaction was then quenched with water (2 mL). The mixture was diluted with ether (30 mL), washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 90:10) afforded the hydroxy silyl ether (0.73 g, 90% yield) as a colorless oil.

A mixture of the above alcohol (0.73 g, 1.28 mmol), silver carbonate on Celite (50% w/w; 3.5 g, 6.4 mmol), and benzene (43 mL) was heated at reflux for 19 h with azeotropic removal of water via a Dean−Stark trap. The suspension was then cooled to room temperature and filtered through a pad of Celite. The solids were washed thoroughly with ether, and the combined filtrates were concentrated. Flash chromatography (hexanes/ethyl acetate, 80:20) furnished lactone (+)-**17** (0.70 g, 96% yield) as a colorless oil.

Hydroxy Ester (+)-18. *n*-Butyllithium (2.4 M in hexanes; 88 μL, 0.21 mmol) was added dropwise to a cold (0 °C) solution of diisopropylamine (33 μL, 0.24 mmol) in THF (4 mL). The solution was stirred for 20 min and then cooled to −78 °C. Ethyl acetate (21 μL, 0.22 mmol) was added. After 40 min at −78 °C, a solution of lactone **17** (0.11 g, 0.19 mmol) in THF (1 mL) was added. The solution was stirred at −78 °C for 1 h, and then ethanol (1 mL) was added. The solution was concentrated, and flash column chromatography, using hexane/ethyl acetate (90:10) as eluant, afforded the intermediate hemiketal (0.11 g, 87%) as a colorless liquid.

A solution of the hemiketal (0.28 g, 0.43 mmol) and citric acid (0.19 g, 1.0 mmol) in methanol (10 mL) was heated at reflux for 1.5 h; the solution was then cooled to room temperature and concentrated. The resulting liquid was diluted with ethyl acetate, washed with saturated $NaHCO_3$ and brine, dried over magnesium sulfate, and filtered. The solvent was removed, and the product was purified by flash column chromatography, using hexane/ethyl acetate (70:30) as eluant, to afford ketal (+)-**18** (0.22 g, 94%) as a colorless liquid.

Thioesters (+)-19 and (+)-20. The Dess−Martin periodinane (0.74 g, 1.74 mmol) was dissolved in CH_2Cl_2 (7.0 mL) and treated with pyridine (0.31 mL, 3.83 mmol) to produce a clear solution. At room temperature alcohol (+)-**18** (0.48 g, 0.87 mmol) in CH_2Cl_2 (1.5 mL) was then added over 5 min. After 160 min, the reaction mixture was diluted with diethyl ether (25 mL), and the reaction was quenched with saturated aqueous $NaHCO_3/NaHSO_3$ (1:1, 20 mL). The resultant mixture was stirred for 5 min, diluted with additional diethyl ether (40 mL), and separated. The organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 25 mL) and brine (25 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexane/ethyl acetate, 6:1) furnished the corresponding aldehyde (0.42 g, 88% yield) as a colorless oil.

A solution of diisopropylamine (0.24 mL, 1.72 mmol) in THF (6.7 mL) was cooled to 0 °C, and *n*-BuLi (2.47 M in hexanes; 0.67 mL, 1.64 mmol) was added dropwise. After 25 min, the reaction was cooled to −78 °C, a solution of *S*-ethyl isobutanethioate (0.23 g, 1.72 mmol) in THF (2.1 mL) was added via a cannula, and the mixture was stirred for an additional 1.25 h. A solution of the above aldehyde (0.79 g, 1.43 mmol) in THF (4 mL) was then introduced via a cannula, and the reaction was stirred at −78 °C for 1 h, quenched with saturated aqueous

NH_4Cl (10 mL), and diluted with ethyl acetate (30 mL). The aqueous phase was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ether/methylene chloride, 3:1:1) provided the desired β-alcohol (+)-**19** (0.605 g, 62% yield) and undesired α-epimer (+)-**20** (0.174 g, 17% yield) as colorless oils.

For (+)-**19**: $[\alpha]_D^{25}$ +33° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3495 (w, br), 2955 (s), 2930 (s), 2890 (m), 2855 (m), 1730 (s), 1650 (m), 1460 (m), 1425 (m), 1375 (m), 1365 (m), 1305 (m), 1230 (m), 1145 (m), 1110 (s), 1035 (s), 995 (m), 940 (m), 815 (w), 695 (s), 600 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67−7.64 (m, 4 H), 7.42−7.34 (m, 6 H), 5.26 (d, *J* = 9.7 Hz, 1 H), 4.17−4.09 (m, 1 H), 4.11 (qd, *J* = 7.2, 1.2 Hz, 2 H), 3.63 (dd, *J* = 11.7, 1.1 Hz, 1 H), 3.51 (dd, *J* = 7.6, 6.0 Hz, 1 H), 3.06 (s, 3 H), 2.86−2.78 (m, 2 H), 2.68 (d, *J* = 7.7 Hz, 1 H), 2.60 (ABq, J_{AB} = 13.5 Hz, $\Delta\upsilon_{AB}$ = 49.9 Hz, 2 H), 2.60−2.53 (m, 1 H), 2.17 (ddd, *J* = 12.9, 4.8, 1.6 Hz, 1 H), 1.68 (dd, *J* = 12.8, 10.8 Hz, 1 H), 1.62−1.59 (m, 1 H), 1.54 (d, *J* = 1.0 Hz, 3 H), 1.39 (apparent q, *J* = 12.0 Hz, 1 H), 1.244 (s, 6 H), 1.237 (t, *J* = 7.0 Hz, 3 H), 1.22 (t, *J* = 7.4 Hz, 3 H), 1.04 (s, 9 H), 0.91 (d, *J* = 6.7 Hz, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 208.2, 169.3, 135.7, 134.6, 134.4, 132.6, 130.6, 129.5, 127.51, 127.49, 99.5, 80.9, 73.9, 66.6, 60.4, 54.0, 47.8, 42.6, 42.2, 38.8, 34.9, 27.0, 24.5, 23.1, 21.8, 19.1, 16.6, 14.3, 14.2, 12.3; high-resolution mass spectrum (FAB, NBA matrix) *m/z* 707.3438 [(M + Na)$^+$; calcd for $C_{38}H_{56}O_7SSiNa$ 707.3414].

For (+)-**20**: $[\alpha]_D^{25}$ +28.2° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3500 (w, br), 2960 (s), 2925 (s), 2890 (m), 2850 (m), 1730 (s), 1660 (m), 1460 (m), 1425 (m), 1365 (m), 1305 (m), 1225 (m), 1145 (m), 1110 (s), 1035 (s), 990 (m), 940 (m), 810 (m), 690 (s), 600 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67−7.64 (m, 4 H), 7.42−7.34 (m, 6 H), 5.33 (d, *J* = 10.0 Hz, 1 H), 4.17−4.10 (m, 1 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 3.64 (apparent d, *J* = 12.6 Hz, 1 H), 3.62 (dd, *J* = 5.8, 3.3 Hz, 1 H), 3.07 (s, 3 H), 2.87−2.71 (m, 2 H), 2.63 (d, *J* = 5.9 Hz, 1 H), 2.61−2.57 (m, 1 H), 2.59 (ABq, J_{AB} = 13.5 Hz, $\Delta\upsilon_{AB}$ = 49.0 Hz, 2 H), 2.17 (ddd, *J* = 12.8, 4.8, 1.7 Hz, 1 H), 1.69 (dd, *J* = 12.9, 10.8 Hz, 1 H), 1.61 (ddt, *J* = 12.2, 4.1, 1.8 Hz, 1 H), 1.55 (d, *J* = 1.3 Hz, 3 H), 1.38 (apparent q, *J* = 12.0 Hz, 1 H), 1.24 (t, *J* = 7.1 Hz, 3 H), 1.23 (s, 3 H), 1.22 (s, 3 H), 1.20 (t, *J* = 7.5 Hz, 3 H), 1.04 (s, 9 H), 0.97 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 208.0, 169.2, 135.7, 134.6, 134.4, 134.3, 129.5, 127.5, 127.4, 99.5, 80.7, 74.0, 66.6, 60.4, 53.7, 47.7, 42.6, 42.2, 38.8, 34.3, 27.0, 23.0, 22.7, 22.1, 19.7, 19.1, 14.22, 14.17, 12.5; high-resolution mass spectrum (FAB, NBA matrix) *m/z* 707.3432 [(M + Na)$^+$; calcd for $C_{38}H_{56}O_7SSiNa$ 707.3414].

Hydroxy Mosher Ester (+)-21. A stock solution was prepared by dissolving Et_3N (0.17 mL, 1.2 mmol) and 4-(dimethylamino)pyridine (6.4 mg, 52 μmol) in dry CH_2Cl_2 (2.2 mL). A portion of this solution (0.24 mL) was transferred to a vial containing alcohol (+)-**20** (11.8 mg, 17.2 μmol). (*R*)-(−)-α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride (16 μL, 86 μmol) was then added. The reaction mixture was stirred at room temperature overnight, diluted with ether (10 mL), washed with saturated aqueous $NaHCO_3$ (2 × 10 mL) and brine (15 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 9:1) furnished the corresponding Mosher ester (13 mg, 84% yield) as a colorless oil: $[\alpha]_D^{25}$ +33.8° (*c* 0.65, $CHCl_3$); IR ($CHCl_3$) 1740 (s), 1665 (m), 1460 (m), 1225 (s), 1165 (s), 1105 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68−7.65 (m, 4 H), 7.53 (d, *J* = 7.6 Hz, 2 H), 7.42−7.26 (m, 9 H), 5.55 (d, *J* = 2.3 Hz, 1 H), 5.15 (d, *J* = 9.8 Hz, 1 H), 4.16−4.10 (m, 1 H), 4.11 (q, *J* = 7.1 Hz, 2 H), 3.50 (s, 3 H), 3.49 (apparent d, *J* = 12.9 Hz, 1 H), 3.03 (s, 3 H), 2.88−2.77 (m, 2 H), 2.74−2.68 (m, 1 H), 2.58 (ABq, J_{AB} = 13.6 Hz, $\Delta\upsilon_{AB}$ = 75.1 Hz, 2 H), 2.21 (ddd, *J* = 12.9, 4.8, 1.5 Hz, 1 H), 1.66 (dd, *J* = 12.9, 10.8 Hz, 1 H), 1.56−1.52 (m, 1 H), 1.48 (d, *J* = 1.2 Hz, 3 H), 1.36 (apparent q, *J* = 12.0 Hz, 1 H), 1.24 (t, *J* = 7.1 Hz, 3 H), 1.21 (t, *J* = 7.4 Hz, 3 H), 1.13 (s, 3 H), 1.11 (s, 3 H), 1.05 (s, 9 H), 0.87 (d, *J* = 7.1 Hz, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 204.6, 169.2, 165.7, 135.8, 134.6, 134.4, 134.0, 131.9, 129.6, 128.3, 127.7, 127.5, 127.0, 99.5, 82.8, 73.8, 66.5, 60.4, 55.4, 54.1, 47.6, 42.7, 42.2, 38.5, 33.9, 27.0, 23.4, 23.2, 20.6, 19.8, 19.1, 14.3, 14.2, 12.2; high-resolution mass spectrum (FAB, 1-thioglycerol matrix) *m/z* 923.3836 [(M + Na)$^+$; calcd for $C_{48}F_3H_{63}O_9SiSNa$ 923.3812].

A solution of the silyloxy Mosher ester (8.6 mg, 9.5 μmol) in THF (1.9 mL) was treated with TBAF (1.0 M in THF; 95 μL, 95 μmol). The mixture was stirred overnight at room temperature, diluted with ether (10 mL), washed with H_2O (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 2:1) gave (+)-**21** (4.5 mg, 71% yield) as a colorless oil: $[\alpha]_D^{25}$ +24° (*c* 0.41, $CHCl_3$); IR ($CHCl_3$) 3480 (w, br), 3010 (m), 2920 (s), 2850 (m), 1740 (s), 1670 (m), 1015 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.58−7.56 (m, 2 H), 7.42−7.39 (m, 3 H), 5.59 (dd, *J* = 2.3, 0.5 Hz, 1 H), 5.35 (d, *J* = 9.9 Hz, 1 H), 4.15 (m, 2 H), 4.10 (m, 1 H), 3.78 (apparent d, *J* = 11.5 Hz, 1 H), 3.52 (s, 3 H), 3.17 (d, *J* = 0.7 Hz, 3 H), 2.84 (m, 2 H), 2.77 (m, 1 H), 2.65 (ABq, J_{AB} = 13.8 Hz, $\Delta\upsilon_{AB}$ = 102.6 Hz, 2 H), 2.32 (apparent dd, *J* = 12.7, 4.3 Hz, 1 H), 1.82 (ddt, *J* = 12.1, 4.0, 2.0 Hz, 1 H), 1.58 (s, 3 H), 1.52 (m, 1 H), 1.30 (m, 1H), 1.27 (td, *J* = 7.2, 0.9 Hz, 3 H), 1.23 (td, *J* = 7.4, 0.9 Hz, 3 H), 1.18 (s, 3 H), 1.14 (s, 3 H), 0.92 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 204.6, 169.2, 165.8, 133.8, 131.9, 129.6, 128.4, 127.8, 127.4, 99.4, 82.9, 74.2, 65.0, 60.5, 55.3, 54.2, 47.8, 42.7, 42.1, 38.3, 34.0, 23.5, 23.2, 20.5, 19.8, 14.4, 14.2, 12.2; high-resolution mass spectrum (FAB, NBA matrix) *m/z* 685.2620 [(M + Na)$^+$; calcd for $C_{32}F_3H_{45}O_9SNa$ 685.2634].

Hydroxy Mosher Ester Derivative (+)-22. Via the procedure described for the preparation of (+)-**21**, alcohol (+)-**20** (11.2 mg, 16.4 μmol) was acylated with (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (15.3 μL, 82.0 μmol). Workup and flash chromatography as before furnished the Mosher ester (12 mg, 81% yield) as a colorless oil: $[\alpha]_D^{25}$ +48.0° (*c* 0.60, $CHCl_3$); IR ($CHCl_3$) 1740 (s), 1665 (m), 1225 (s), 1180 (s), 1165 (s), 1105 (s), 1030 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68−7.65 (m, 4 H), 7.54 (d, *J* = 7.8 Hz, 2 H), 7.42−7.27 (m, 9 H), 5.54 (d, *J* = 2.7 Hz, 1 H), 5.16 (d, *J* = 9.6 Hz, 1 H), 4.17−4.10 (m, 1 H), 4.11 (q, *J* = 7.1 Hz, 2 H), 3.52 (apparent d, *J* = 12.5 Hz, 1 H), 3.49 (s, 3 H), 3.04 (s, 3 H), 2.85−2.78 (m, 2 H), 2.73−2.66 (m, 1 H), 2.58 (ABq, J_{AB} = 13.6 Hz, $\Delta\upsilon_{AB}$ = 68.9 Hz, 2 H), 2.21 (ddd, *J* = 12.9, 4.8, 1.4 Hz, 1 H), 1.67 (dd, *J* = 12.9, 10.8 Hz, 1 H), 1.57−1.53 (m, 1 H), 1.49 (d, *J* = 0.9 Hz, 3 H), 1.36 (apparent q, *J* = 11.7 Hz, 1 H), 1.24 (t, *J* = 7.1 Hz, 3 H), 1.21 (t, *J* = 7.4 Hz, 3 H), 1.12 (s, 3 H), 1.05 (s, 12 H), 0.86 (d, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 204.5, 169.2, 165.8, 135.8, 134.6, 134.4, 134.3, 131.9, 129.6, 128.4, 127.7, 127.53, 127.52, 127.1, 99.5, 82.9, 73.9, 66.5, 60.4, 55.3, 54.1, 47.6, 42.7, 42.2, 38.6, 34.1, 27.0, 24.0, 23.1, 19.9, 19.7, 19.1, 14.4, 14.2, 12.2; high-resolution mass spectrum (FAB, NBA matrix) *m/z* 923.3810 [(M + Na)$^+$; calcd for $C_{48}F_3H_{63}O_9SiSNa$ 923.3812].

Desilylation, workup, and flash chromatography as described above then gave (+)-**22** (7.4 mg, 84% yield) as a colorless oil: $[\alpha]_D^{25}$ +49° (*c* 0.80, $CHCl_3$); IR ($CHCl_3$) 3500 (w, br), 3005 (s), 2970 (s), 2930 (s), 1735 (s), 1670 (m), 1230 (s), 1185 (s), 1165 (s), 1010 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.59−7.56 (m, 2 H), 7.42−7.39 (m, 3 H), 5.59 (d, *J* = 3.0 Hz, 1 H), 5.37 (d, *J* = 9.7 Hz, 1 H), 4.15 (m, 2 H), 4.11 (m, 1 H), 3.80 (dd, *J* = 11.7, 1.4 Hz, 1 H), 3.52 (s, 3 H), 3.19 (s, 3 H), 2.83 (m, 2 H), 2.76 (m, 1 H), 2.66 (ABq, J_{AB} = 13.9 Hz, $\Delta\upsilon_{AB}$ = 96.8 Hz, 2 H), 2.32 (ddd, *J* = 12.7, 4.7, 1.8 Hz, 1 H), 1.82 (ddt, *J* = 12.1, 4.5, 1.9 Hz, 1 H), 1.59 (d, *J* = 1.1 Hz, 3 H), 1.53 (dd, *J* = 12.6, 11.2 Hz, 1 H), 1.31 (m, 1 H), 1.27 (t, *J* = 7.1 Hz, 3 H), 1.22 (t, *J* = 7.4 Hz, 3 H), 1.18 (s, 3 H), 1.08 (s, 3 H), 0.92 (d, *J* = 7.1 Hz, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 204.5, 169.1, 165.8, 134.2, 131.9, 129.6, 128.4, 127.7, 127.6, 99.4, 83.0, 74.2, 64.9, 60.5, 55.4, 54.1, 47.8, 42.7, 42.0, 38.3, 34.2, 24.2, 23.2, 19.9, 19.7, 14.4, 14.2, 12.2; high-resolution mass spectrum (FAB, NBA matrix) *m/z* 685.2631 [(M + Na)$^+$; calcd for $C_{32}F_3H_{45}O_9SNa$ 685.2634].

TES Ether (+)-23. A solution of alcohol (+)-**19** (0.42 g, 0.61 mmol) in CH_2Cl_2 (12.1 mL) was cooled to 0 °C and treated dropwise with 2,6-lutidine (0.42 mL, 3.6 mmol) and triethylsilyl trifluoromethanesulfonate (0.55 mL, 2.4 mmol). After 20 min, the reaction mixture was quenched with MeOH (0.5 mL), diluted with ethyl acetate (40 mL), washed with 0.1 M aqueous $NaHSO_4$ (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 97:3) provided (+)-**23** (0.44 g, 91% yield) as a colorless oil.

Aldehyde (+)-4. TES ether (+)-**23** (95 mg, 0.12 mmol) was dissolved in CH_2Cl_2 (0.6 mL) and triethylsilane (0.12 mL, 0.77 mmol) and 10% Pd on carbon (16.5 mg, 16.0 μmol) were then added. The mixture was stirred for 2 h at room temperature, diluted with ethyl acetate (3 mL), filtered through Celite, and concentrated. Flash

chromatography (hexanes/ethyl acetate, 95:5) furnished (+)-**4** (77 mg, 88% yield) as a colorless oil: $[\alpha]_D^{25}$ +36° (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3030 (m), 3010 (m), 2970 (s), 2940 (s), 2920 (m), 2880 (m), 2860 (m), 1730 (s), 1465 (m), 1115 (s), 1040 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.59 (s, 1 H), 7.67−7.65 (m, 4 H), 7.42−7.34 (m, 6 H), 5.14 (d, J = 9.7 Hz, 1 H), 4.19−4.13 (m, 1 H), 4.12 (q, J = 7.1 Hz, 2 H), 3.68 (d, J = 4.1 Hz, 1 H), 3.63 (apparent d, J = 11.7 Hz, 1 H), 3.09 (s, 3 H), 2.64−2.53 (m, 1 H), 2.61 (ABq, J_{AB} = 13.6 Hz, $\Delta\upsilon_{AB}$ = 73.8 Hz, 2 H), 2.20 (ddd, J = 11.3, 3.2, 1.6 Hz, 1 H), 1.67 (dd, J = 12.8, 10.9 Hz, 1 H), 1.61 (ddt, J = 12.4, 4.5, 2.2 Hz, 1 H), 1.52 (d, J = 0.8 Hz, 3 H), 1.40 (apparent q, J = 11.9 Hz, 1 H), 1.24 (t, J = 7.1 Hz, 3 H), 1.05 (s, 15 H), 0.97 (t, J = 7.9 Hz, 9 H), 0.87 (d, J = 6.7 Hz, 3 H), 0.64 (q, J = 7.9 Hz, 6 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 206.0, 169.2, 135.8, 135.7, 134.6, 134.4, 134.0, 130.3, 129.5, 127.51, 127.48, 99.5, 81.4, 73.9, 66.5, 60.4, 51.5, 47.7, 42.7, 42.2, 38.8, 34.7, 27.0, 20.0, 19.8, 19.1, 15.9, 14.2, 12.5, 7.1, 5.6; high-resolution mass spectrum (FAB, NBA matrix) *m/z* 761.4253 [$(M + Na)^+$; calcd for $C_{42}H_{66}O_7Si_2Na$ 761.4245].

(+)-(2*R*)-Heptane-1,2-diol (25). To a solution of AD-mix-β (59.9 g) in *t*-BuOH and H_2O (1:1, 428 mL) at 0 °C was added 1-heptene (6.0 mL, 42.8 mmol). The heterogeneous slurry was stirred vigorously at 0 °C, and after 40 h, solid sodium sulfite (54 g) was slowly introduced at 0 °C. The resultant suspension was allowed to warm to room temperature, stirred for an additional 1 h, and diluted with CH_2Cl_2 (400 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 200 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Removal of *t*-BuOH by distillation at atmospheric pressure then gave (+)-**25** (5.3 g, 94% yield) as a colorless oil.

PMB Ether (−)-(26). A solution of diol (+)-**25** (5.73 g, 43.3 mmol) in benzene (140 mL) was treated with *p*-methoxybenzaldehyde dimethyl acetal (15.8 g, 86.6 mmol) and *p*-toluenesulfonic acid monohydrate (0.75 g, 4.3 mmol). The reaction mixture was stirred at ambient temperature for 18 h and then concentrated. The residue was used without purification in the next step.

The crude acetonide (maximum 43.3 mmol) dissolved in CH_2Cl_2 (217 mL) was cooled to −78 °C and treated with diisobutylaluminum hydride (1.0 M in hexane; 147.2 mL, 147.2 mmol). After 30 min, the reaction mixture was gradually warmed to room temperature, quenched with MeOH (4 mL), diluted with ether (300 mL), and treated with a saturated solution of Rochelle's salt (200 mL). The resultant biphasic mixture was stirred vigorously at room temperature until the organic phase turned clear. The organic phase was then dried with $MgSO_4$, filtered through Na_2SO_4, and concentrated. Flash chromatography (hexanes/ethyl acetate, 3:1) afforded (−)-**26** (9.7 g, 89% yield for two steps) as a colorless liquid.

Alkyne (+)-(27). A solution of alcohol (−)-**26** (1.3 g, 5.3 mmol) in CH_2Cl_2 (22 mL) was treated with triphenylphosphine (2.8 g, 10.5 mmol) and cooled to 0 °C. After 15 min, carbon tetrabromide (3.5 g, 10.5 mmol) was added, and the reaction mixture was gradually warmed to room temperature, stirred further for 4 h, and concentrated. Flash chromatography (hexanes/ethyl acetate, 97:3) gave the corresponding bromide (1.5 g, 92% yield) as a colorless oil.

THF (33.8 mL) was cooled to −78 °C, and *n*-BuLi (2.5 M in hexane; 14.2 mL, 35.4 mmol) was slowly added. Propyne was then bubbled into the mixture until the clear solution became milky white. The suspension was slowly warmed to 0 °C, treated with HMPA (8.4 mL) and recooled to −78 °C, and then the above bromide (3.72 g, 11.8 mmol) in THF (4 mL) was introduced via cannula over 15 min. After an additional 15 min, the reaction mixture was warmed to room temperature, stirred for 3 h, and poured into ice-cold saturated aqueous NH_4Cl (50 mL). The organic phase was then washed with brine (40 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 95:5) furnished (+)-**27** (2.66 g, 82% yield) as a colorless liquid.

Bromo Alcohol (−)-(28). A solution of acetylene (+)-**27** (1.51 g, 5.50 mmol) in benzene (36.7 mL) was treated with zirconocene chloride hydride (4.30 g, 16.5 mmol) in one portion, warmed to 40−45 °C for 1 h, and cooled to room temperature. *N*-Bromosuccinimide (1.96 g, 11.0 mmol) was then added, and the reaction was stirred for 15 min and quenched with saturated aqueous $NaHCO_3$ (15 mL). The biphasic mixture was stirred vigorously for 5 min and extracted with hexane/ethyl acetate (9:1, 2 × 30 mL). The combined extracts were washed with brine (50 mL), dried over $MgSO_4$, filtered through a pad of silica gel supported by a pad of Celite, and washed with hexane/ethyl acetate (4:1, 200 mL). Concentration and flash chromatography (hexanes/ethyl acetate, 95:5) provided a 16.4:1 mixture of bromo ethers (1.52 g, 78% yield) as a colorless oil.

Water (1.09 mL) was added to solution of the bromo ethers (1.47 g, 4.15 mmol) in CH_2Cl_2 (19.6 mL). The biphasic mixture was cooled to 7 °C with vigorous stirring, and solid 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 1.23 g, 5.40 mmol) was introduced in one portion. The resultant black slurry containing orange water droplets gave rise to an orange slurry within 10 min. After an additional 20 min, the reaction mixture was diluted with CH_2Cl_2 (200 mL) and then washed with saturated aqueous $NaHCO_3$ (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 9:1) gave a mixture of alcohols. Further purification by normal-phase HPLC (Rainin 60-Å silica column; hexane/ethyl acetate, 85:15) afforded (−)-**28** (0.59 g, 61% yield) as a colorless oil.

TES Ether (+)-(5). At 0 °C, a solution of alcohol (−)-**28** (1.04 g, 4.40 mmol) in CH_2Cl_2 (17.6 mL) was treated with 2,6-lutidine (2.30 mL, 19.8 mmol) and triethylsilyl trifluoromethanesulfonate (2.09 mL, 9.24 mmol). After 30 min, the reaction was quenched with MeOH (0.3 mL), diluted with ethyl acetate (80 mL), washed with 0.1 M aqueous $NaHSO_4$ (40 mL) and brine (40 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes) furnished (+)-**5** (1.50 g, 98% yield) as a colorless oil.

Alkyne (+)-(29). At 0 °C, a solution of triphenylphosphine (18.3 g, 69.6 mmol) in CH_2Cl_2 (75.5 mL) was treated with carbon tetrabromide (11.5 g, 34.8 mmol) dissolved in CH_2Cl_2 (26.0 mL), and the resultant suspension was stirred for 15 min. A solution of aldehyde (+)-**12** (3.0 g, 17.4 mmol) in CH_2Cl_2 (10.2 mL) was then introduced via a cannula over 15 min. After 70 min, the reaction mixture was concentrated *in vacuo* and filtered through a pad of silica gel. Concentration and flash chromatography (hexanes/ethyl acetate, 95:5) provided the dibromomethylene derivative (4.7 g, 82% yield) as a colorless oil.

A solution of the dibromide (4.67 g, 14.2 mmol) in THF (95 mL) was cooled to −78 °C and *n*-BuLi (2.5 M in hexane; 12.5 mL, 31.2 mmol) was added dropwise. The reaction mixture was stirred for 1 h, warmed to room temperature, stirred 1 h further, recooled to −78 °C, and treated with iodomethane (4.42 mL, 71.0 mmol) slowly. After an additional 30 min at −78 °C and 75 min at room temperature, the mixture was concentrated. The resultant liquid was then dissolved in ether (200 mL), and the solution was washed with water (100 mL) and brine (100 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 95:5) afforded (+)-**29** (2.35 g, 91% yield) as a colorless liquid.

Bromo Diol (−)-(30). A solution of alkyne (+)-**29** (1.18 g, 6.47 mmol) in benzene (43 mL) was treated with zirconocene chloride hydride (5.00 g, 19.4 mmol) in one portion, warmed to 40−45 °C for 1 h, and cooled to room temperature. *N*-Bromosuccinimide (2.30 g, 12.9 mmol) was then added, and the reaction was stirred for 30 min and quenched with saturated aqueous $NaHCO_3$ (20 mL). The biphasic mixture was stirred vigorously for 5 min and extracted with hexane/ethyl acetate (9:1, 2 × 40 mL). The combined organic solutions were washed with brine (50 mL), dried over $MgSO_4$, and filtered through a pad of silica gel supported by a pad of Celite, and the pad was washed with hexanes/ethyl acetate (4:1, 200 mL). Concentration gave a mixture of crude bromo acetonides which was used in the next step without purification.

The bromo acetonides were treated with acetic acid/H_2O (4:1, 20 mL). The reaction mixture was stirred at room temperature overnight and then poured into saturated aqueous $NaHCO_3$/ether (1:1, 40 mL). The organic layer was washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 2:1) furnished the desired diol (−)-**30** as a mixture of regioisomers [0.92 g, 73% (2 steps), ca. 17:1 by ^1H NMR] as a colorless oil.

Alkene (−)-(31). A solution of diol (−)-**30** (0.58 g, 2.97 mmol) in THF (9.9 mL) was cooled to 0 °C, and sodium hydride (60% dispersion in mineral oil; 0.36 g, 8.91 mmol) was added all at once. After 15 min, the reaction was warmed to room temperature, diluted with THF

(19.8 mL), stirred for 30 min, and recooled to 0 °C. Solid 1-(*p*-toluenesulfonyl)imidazole (0.99 g, 4.46 mmol) was then introduced in one portion. The reaction mixture was stirred for 15 min, warmed to room temperature, stirred an additional 2 h, and transferred via a cannula to another flask containing copper(I) iodide (0.28 g, 1.49 mmol) and crotylmagnesium chloride (0.3 M in THF; 49.5 mL, 14.9 mol) at −23 °C. After an additional 5 min, the reaction was quenched with 10% aqueous NH_4OH and saturated aqueous NH_4Cl (1:1, 40 mL) and diluted with ether (50 mL). The organic phase was washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 95:5) afforded a mixture of alcohols (0.42 g, 61% yield; ca. 2.2:1 by ^{1}H NMR). Further chromatography on 10% $AgNO_3$/silica gel (hexanes/ethyl acetate, 95:5) then provided (−)-**31** (0.29 g, 42% yield) as a colorless oil.

TES Ether (+)-(6). A solution of alcohol (−)-**31** (67.0 mg, 0.29 mmol) in CH_2Cl_2 (1.15 mL) was cooled to 0 °C and treated with 2,6-lutidine (0.15 mL, 1.29 mmol) and triethylsilyl trifluoromethanesulfonate (0.14 mL, 0.60 mmol). After 30 min, the reaction mixture was quenched with MeOH (0.2 mL), diluted with ethyl acetate (15 mL), washed with 0.1 M aqueous $NaHSO_4$ (8 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes) furnished (+)-**6** (98.3 mg, 98% yield) as a colorless oil.

Enone (+)-32a. To a slurry of powdered magnesium (0.26 g, 10.7 mmol), in ether (7.5 mL) was added a solution of 1,2-dibromoethane (0.86 mL, 10.0 mmol) in benzene (2.5 mL) dropwise over 30 min so as to maintain a gentle reflux. The resulting solution was stirred for an additional 45 min and then allowed to stand for 1−2 h before use in the coupling reaction. The concentration of magnesium bromide was assumed to be 1.0 M.

At −78 °C a solution of vinyl bromide (+)-**5** (0.96 g, 2.76 mmol) in THF (10.1 mL) was treated dropwise with *t*-BuLi (1.7 M in pentane; 3.72 mL, 6.32 mmol), and the resultant yellow solution was stirred for an additional 35 min. A freshly prepared (*vide supra*) solution of magnesium bromide [1 M in Et_2O/benzene (3:1); 3.16 mL, 3.16 mmol] was added, affording a heterogeneous mixture which was stirred for an additional 1 h and then transferred via a cannula into a solution of (+)-**4** (0.19 g, 0.26 mmol) in THF (2.0 mL) at −78 °C. The reaction was stirred for 1 h at −78 °C and quenched with saturated aqueous NH_4Cl (20 mL). After dilution with ethyl acetate (20 mL), the aqueous phase was extracted with ethyl acetate (3 × 20 mL) and the organic solutions were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 9:1) provided a mixture of alcohols (0.21 g, 82% yield; ca. 1:1 by ^{1}H NMR) as a colorless oil.

The Dess−Martin periodinane (0.68 g, 1.6 mmol) and pyridine (0.28 mL, 3.5 mmol) were dissolved in CH_2Cl_2 (5.7 mL); the resultant clear stock solution which was used within 5 min. At room temperature a solution of the above alcohols (0.21 g, 0.21 mmol) in CH_2Cl_2 (1.2 mL) was treated with a portion of the periodinane solution (3.2 mL). After 1 h, the reaction mixture was diluted with ether (15 mL) and quenched with saturated aqueous $NaHCO_3$ and $NaHSO_3$ solutions (1:1, 10 mL). The resultant mixture was stirred for 5 min, diluted with additional ether (10 mL), washed with saturated aqueous $NaHCO_3$ (2 × 10 mL) and brine (15 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 95:5) furnished (+)-**32a** (0.20 g, 94% yield) as a colorless oil.

Enone (+)-32b. Via the procedure described above for the preparation of (+)-**32a**, vinyl bromide (+)-**6** (1.06 g, 3.05 mmol) was coupled with aldehyde (+)-**4** (0.23 g, 0.30 mmol). Workup and flash chromatography as before afforded a mixture of alcohols (0.29 g, 94% yield) as a colorless oil. Dess−Martin oxidation of the alcohols (0.25 g, 0.24 mmol), workup, and flash chromatography as described for **32a** then furnished (+)-**32b** (0.22 g, 88% yield) as a colorless oil.

Diol (+)-33a. A solution of bis TES ether (+)-**32a** (0.20 g, 0.20 mmol) in MeOH (39.3 mL) was cooled to 0 °C and treated with solid 10-camphorsulfonic acid (0.011 g, 0.049 mmol) in one portion. The reaction mixture was stirred for 2 h and allowed to stand at 4°C in a refrigerator overnight, and the reaction was then quenched with solid $NaHCO_3$ (0.02 g) and concentrated *in vacuo*. Flash chromatography (hexanes/ethyl acetate, 3:1) gave (+)-**33a** (0.15 g, 97% yield) as a colorless oil.

Diol (+)-33b. Bis TES ether (+)-**32b** (0.21 g, 0.21 mmol) was desilylated via the procedure described above for the preparation of (+)-**33a**. Workup and flash chromatography as before furnished (+)-**33b** (0.14 g, 84% yield) as a colorless oil.

Triol (+)-34a. A stock solution was prepared by dissolving tetramethylammonium triacetoxyborohydride (310 mg, 1.18 mmol) in anhydrous acetic acid (3.9 mL), and a portion (0.52 mL) was stirred at room temperature for 1 h to effect complete mixing and cooled to 0 °C. Following the addition of dihydroxy ketone (+)-**33a** (12 mg, 15.4 μmol) in acetonitrile (0.8 mL), the reaction was stirred at −25 °C for 17 h and at 0 °C for 2 h and then quenched with methanol (0.5 mL). The mixture was allowed to warm slowly to room temperature and concentrated. The residue was diluted with ethyl acetate (10 mL) and washed with saturated aqueous $NaHCO_3$ (2 × 5 mL). The combined aqueous layers were extracted with ethyl acetate (2 x 10 mL), and the combined organic solutions were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 2:1) gave (+)-**34a** (10.8 mg, 90% yield; 96:4 by ^{1}H NMR analysis) as a colorless oil.

Triol (+)-34b. Dihydroxy ketone (+)-**33b** (34 mg, 43.8 μmol) was reduced as described above for the preparation of (+)-**34a**. Workup and flash chromatography as before afforded (+)-**34b** (32 mg, 94% yield; >92% ee by ^{1}H NMR analysis) as a colorless oil.

Seco Acid (+)-3a. A solution of ester (+)-**34a** (25.2 mg, 0.032 mmol) in THF/MeOH/H_2O (2:2:1, 4.60 mL) was treated with LiOH (33.9 mg, 0.81 mmol), and the mixture was stirred at room temperature overnight and then extracted with ethyl acetate (15 mL). The aqueous layer was acidified to pH 1−2 with 0.1 M aqueous $NaHSO_4$ and extracted with ethyl acetate (2 × 10 mL). The combined organic phases were washed with brine (20 mL), dried over $MgSO_4$, and concentrated, providing (+)-**3a** (23.0 mg, 95% yield; pure by ^{1}H NMR) as a colorless oil.

Seco Acid (+)-3b. Ester (+)-**34b** (25.0 mg, 0.032 mmol) was saponified via the procedure described above for the preparation of (+)-**39**. Workup as before furnished (+)-**3b** (23.0 mg, 96% yield; pure by ^{1}H NMR) as a colorless oil.

Macrolides (−)-35a and (+)-36a. A stock solution was prepared by dissolving Et_3N (91.5 μL, 0.66 mmol) and 2,4,6-trichlorobenzoyl chloride (93.0 μL, 0.60 mmol) in THF (16.6 mL), and a portion (3.13 mL) was added to a flask containing seco acid (+)-**3a** (28.0 mg, 37.2 μmol). The resultant cloudy solution was stirred at room temperature for 15 h and then filtered through a plug of cotton. The filtrate was concentrated, and the resultant yellow oil was dissolved in toluene (9.3 mL). The solution was added over 7 h via a syringe pump to a solution of 4-(dimethylamino)pyridine (27.2 mg, 0.22 mmol) in toluene (37 mL) at reflux. The suspension was stirred for an additional 0.5 h and then cooled to room temperature, diluted with ethyl acetate (50 mL), washed with 0.1 M aqueous $NaHSO_4$ (30 mL) and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 5:1) gave a mixture of (−)-**35a** and(+)-**36a** (18.4 mg, 69.7% yield; ca. 4.2:1 by ^{1}H NMR).

A solution of the macrolides (18.4 mg) in MeOH (63 mL) was treated with anhydrous citric acid (6.0 mg, 31.2 μmol). The reaction mixture was then heated at reflux for 72 h and cooled to room temperature, and the reaction was quenched with solid $NaHCO_3$ (10 mg). Concentration and flash chromatography (hexanes/ethyl acetate, 5:1) afforded (+)-**36a** (14.4 mg, 75% yield) and **35a** (minor component) as a colorless oil: (−)-**35a**: $[\alpha]_D^{25}$ −16° (*c* 0.30, $CHCl_3$); IR ($CHCl_3$) 3495 (w, br), 2995 (m), 2955 (s), 1730 (s), 1675 (m), 1250 (s), 1205 (s), 1105 (s), 1005 (s) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68−7.65 (m, 4 H), 7.46−7.36 (m, 6 H), 5.22 (d, J = 10.8 Hz, 1 H), 5.18 (apparent d, J = 9.8 Hz, 1 H), 4.76−4.71 (m, 1 H), 4.62−4.58 (m, 1 H), 4.61 (s, 1 H), 4.16 (s, 1 H), 4.12 (dd, J = 12.4, 1.3 Hz, 1 H), 3.19 (apparent d, J = 14.8 Hz, 1 H), 2.95 (apparent t, J = 8.9 Hz, 1 H), 2.87 (d, J = 14.8 Hz, 1 H), 2.80 (d, J = 8.4 Hz, 1 H), 2.66−2.59 (m, 1 H), 2.38−2.30 (m, 2 H), 2.07 (apparent t, J = 13.0 Hz, 1 H), 1.96 (td, J = 12.7, 9.5 Hz, 1 H), 1.80−1.77 (m, 1 H), 1.68 (d, J = 1.1 Hz, 3 H), 1.62 (s, 3 H), 1.55−1.45 (m, 2 H), 1.32−1.20 (m, 6 H), 1.07 (s, 3 H), 1.06 (s, 12 H), 0.86 (t, J = 7.0 Hz, 3 H), 0.69 (s, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 170.0, 149.3, 135.8, 135.7, 135.5, 134.1, 134.04, 134.00, 130.6, 129.69, 129.66, 127.6, 125.5, 104.3, 86.8, 82.7, 81.7, 74.2, 65.8, 42.1, 40.6, 38.7, 35.5, 35.4, 32.3, 31.7, 27.0, 26.8, 24.7, 22.7, 22.5, 19.7, 19.1, 14.0, 12.7, 10.6; high-resolution mass spectrum (FAB, 1-thioglycerol matrix) *m/z* 725.4200 [(M + Na)$^+$; calcd for $C_{43}H_{62}O_6SiNa$ 725.4213].

For (+)-**36a**: $[\alpha]_D^{25}$ +19° (*c* 0.91, $CHCl_3$); IR ($CHCl_3$) 3470 (w, br), 2990 (m), 2950 (s), 2920 (s), 1720 (s), 1460 (m), 1105 (s), 1005 (s), 690 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68−7.65 (m, 4 H), 7.44−7.35 (m, 6 H), 5.38 (apparent t, J = 7.0 Hz, 1 H), 5.20 (apparent dd, J = 11.1, 0.9 Hz, 1 H), 4.70−4.65 (m, 1 H), 4.27 (s, 1 H), 4.10−4.03 (m, 1 H), 3.90 (dd, J = 11.9, 2.5 Hz, 1 H), 2.98 (apparent t, J = 8.6 Hz, 1 H), 2.95 (s, 3 H), 2.79 (d, J = 7.9 Hz, 1 H), 2.67−2.59 (m, 1 H), 2.52 (ABq, J_{AB} = 13.1 Hz, $\Delta\upsilon_{AB}$ = 29.1 Hz, 2 H), 2.42−2.37 (m, 2 H), 2.13−2.07 (m, 1 H), 1.99 (ddd, J = 11.2, 4.5, 1.5 Hz, 1 H), 1.72 (d, J = 1.1 Hz, 3 H), 1.72−1.68 (m, 1 H), 1.62 (apparent q, J = 12.1 Hz, 1 H), 1.62 (s, 3 H), 1.47−1.40 (m, 1 H), 1.34 (dd, J = 12.7, 10.9 Hz, 1 H), 1.31−1.22 (m, 7 H), 1.08 (d, J = 6.3 Hz, 3 H), 1.08 (s, 3 H), 1.05 (s, 9 H), 0.87 (t, J = 7.0 Hz, 3 H), 0.72 (s, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 169.2, 135.9, 135.8, 134.3, 133.6, 130.7, 129.65, 129.63, 127.60, 127.59, 125.4, 100.2, 87.0, 81.5, 76.8, 74.7, 66.1, 49.9, 44.5, 43.1, 42.0, 38.7, 38.4, 34.3, 31.7, 30.9, 27.0, 26.3, 25.0, 22.52, 22.48, 19.9, 19.1, 14.0, 12.3, 11.5; high-resolution mass spectrum (FAB, NBA matrix) *m/z* 757.4491 [(M + Na)$^+$; calcd for $C_{44}H_{66}O_7SiNa$ 757.4476].

Macrolides (−)-35b and (+)-36b. Seco acid (+)-**3b** (25.0 mg, 33.3 μmol) was cyclized via the basic procedure described above for the preparation of (+)-**36a**; in this case, the mixed anhydride was added to the solution of 4-(dimethylamino)pyridine over 6 h. Workup and flash chromatography as before afforded a mixture of (−)-**35b** and (+)-**36b** (18.4 mg, 69.7% yield; ca. 3.3:1 by ^1H NMR). Treatment of the macrolides (15.5 mg) with methanolic citric acid, workup, and flash chromatography as before furnished the desired macrolide (+)-**36b** (10.9 mg, 68% yield) and **35b** (minor component) as a colorless oil: (−)-**35b**: $[\alpha]_D^{25}$ −13° (*c* 0.44, $CHCl_3$); IR ($CHCl_3$) 3490 (w, br), 3000 (m), 2955 (s), 2925 (s), 1730 (s), 1675 (m), 1215 (s), 1105 (s), 1005 (s), 695 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68−7.65 (m, 4 H), 7.44−7.36 (m, 6 H), 5.45−5.34 (m, 2 H), 5.22 (d, J = 10.8 Hz, 1 H), 5.17 (apparent d, J = 10.2 Hz, 1 H), 4.77−4.72 (m, 1 H), 4.61−4.58 (m, 1 H), 4.60 (s, 1 H), 4.15 (s, 1 H), 4.12 (d, J = 12.3 Hz, 1 H), 3.19 (apparent d, J = 14.9 Hz, 1 H), 2.97−2.93 (m, 1 H), 2.86 (d, J = 14.8 Hz, 1 H), 2.80 (d, J = 8.4 Hz, 1 H), 2.66−2.58 (m, 1 H), 2.37−2.27 (m, 2 H), 2.07 (apparent t, J = 13.4 Hz, 1 H), 2.01−1.93 (m, 3 H), 1.81−1.77 (m, 1 H), 1.67 (s, 3 H), 1.62 (s, 6 H), 1.26 (s, 2 H), 1.06 (d, J = 11.7 Hz, 3 H), 1.06 (s, 12 H), 0.69 (s, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 170.0, 149.3, 135.78, 135.74, 135.6, 134.2, 134.1, 134.0, 130.6, 130.1, 129.70, 129.67, 127.6, 125.5, 125.3, 104.4, 86.9, 82.8, 81.7, 73.8, 65.8, 42.1, 40.5, 38.7, 35.5, 35.2, 32.2, 28.2, 27.0, 26.8, 22.7, 19.7, 19.1, 17.9, 12.7, 10.6; high-resolution mass spectrum (FAB, NBA matrix) *m/z* 723.4068 [(M + Na)$^+$; calcd for $C_{43}H_{60}O_6SiNa$ 723.4057].

For (+)-**36b**: $[\alpha]_D^{25}$ +19° (*c* 0.3, $CHCl_3$); IR ($CHCl_3$) 3500 (w, br), 3000 (m), 2950 (m), 2920 (s), 1715 (m), 1455 (m), 1195 (s), 1105 (s), 1005 (s), 695 (s), 655 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67−7.65 (m, 4 H), 7.44−7.36 (m, 6 H), 5.45−5.34 (m, 3 H), 5.19 (d, J = 11.1 Hz, 1 H), 4.72−4.67 (m, 1 H), 4.27 (s, 1 H), 4.09−4.03 (m, 1 H), 3.90 (dd, J = 11.7, 2.4 Hz, 1 H), 2.98 (apparent t, J = 8.4 Hz, 1 H), 2.95 (s, 3 H), 2.75 (d, J = 7.9 Hz, 1 H), 2.66−2.60 (m, 1 H), 2.51 (ABq, J_{AB} = 13.1 Hz, $\Delta\upsilon_{AB}$ = 26.1 Hz, 2 H), 2.40 (ddd, J = 15.1, 8.1, 3.2 Hz, 1 H), 2.36 (s, 1 H), 2.13−2.07 (m, 1 H), 2.01−1.94 (m, 3 H), 1.72 (d, J = 0.9 Hz, 3 H), 1.68−1.65 (m, 1 H), 1.62 (d, J = 6.0 Hz, 3 H), 1.62 (s, 3 H), 1.52−1.45 (m, 1 H), 1.34 (dd, J = 12.7, 10.9 Hz, 1 H), 1.30−1.20 (m, 2 H), 1.26 (s, 3 H), 1.08 (d, J = 5.0 Hz, 3 H), 1.05 (s, 9 H), 0.71 (s, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 169.1, 136.0, 135.8, 134.3, 133.5, 130.8, 130.2, 130.0, 129.7, 129.6, 127.6, 125.5, 125.2, 100.2, 87.0, 81.5, 76.8, 74.2, 66.1, 49.9, 44.5, 43.1, 42.0, 38.7, 38.5, 34.0, 30.8, 28.5, 27.0, 26.3, 22.5, 19.9, 19.1, 17.9, 12.3, 11.4; high-resolution mass spectrum (FAB, NBA matrix) *m/z* 755.4336 [(M + Na)$^+$; calcd for $C_{44}H_{64}O_7SiNa$ 755.4319].

TES Ether (+)-37a. A stock solution was prepared at 0 °C by dissolving 2,6-lutidine (57 μL, 0.49 mmol) and triethylsilyl trifluoromethanesulfonate (50 μL, 0.22 mmol) in CH_2Cl_2 (14.7 mL), and a portion (2.2 mL) was then added to a flask containing diol (+)-**36a** (8.0 mg, 10.9 μmol) at −78 °C. The reaction mixture was stirred for an additional 20 min, and the reaction was quenched with MeOH (15 μL) and diluted with Et_2O (10 mL). The organic phase was washed with 0.1 M aqueous $NaHSO_4$ (4 mL) and brine (4 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 9:1) furnished (+)-**37a** (6.0 mg, 65% yield) as a colorless oil: $[\alpha]_D^{25}$ +25° (*c* 0.54, $CHCl_3$); IR ($CHCl_3$) 2975 (s), 2940 (s), 2880 (s), 2870 (s), 1720 (s), 1460 (m), 1230 (s), 1215 (s), 1200 (s), 1115 (s), 1060 (s), 1040 (s), 1005 (s), 700 (s) cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.72−7.65 (m, 4 H), 7.45−7.36 (m, 6 H), 5.59 (apparent t, J = 6.4 Hz, 1 H), 5.40 (d, J = 10.8 Hz, 1 H), 4.81 (m, 1 H), 4.18 (s, 1 H), 4.13 (m, 1 H), 3.71 (d, J = 11.6 Hz, 1 H), 3.06 (d, J = 8.8 Hz, 1 H), 2.95 (s, 3 H), 2.64−2.57 (m, 1 H), 2.62 (ABq, J_{AB} = 14.1 Hz, $\Delta\upsilon_{AB}$ = 190.3 Hz, 2 H), 2.49−2.43 (m, 1 H), 2.31−2.25 (m, 1 H), 1.96 (ddd, J = 12.6, 4.6, 1.6 Hz, 1 H), 1.92−1.86 (m, 1 H), 1.82 (dd, J = 12.5, 10.9 Hz, 1 H), 1.71−1.63 (m, 1 H), 1.63 (s, 3 H), 1.58 (d, J = 0.8 Hz, 3 H), 1.52−1.45 (m, 1 H), 1.41−1.27 (m, 8 H), 1.05 (s, 9 H), 0.96 (t, J = 7.9 Hz, 9 H), 0.948 (s, 3 H), 0.947 (d, J = 7.8 Hz, 3 H), 0.89 (t, J = 6.9 Hz, 3 H), 0.89 (s, 3 H), 0.61 (q, J = 7.9 Hz, 6 H); ^{13}C NMR (125.8 MHz, CD_3OD) δ 171.1, 139.0, 136.92, 136.88, 135.4, 131.7, 131.1, 130.9, 128.73, 128.72, 126.8, 101.0, 83.4, 76.3, 74.9, 68.0, 46.0, 44.3, 43.8, 40.3, 37.9, 35.1, 33.0, 31.9, 27.6, 26.6, 23.6, 22.6, 20.2, 19.9, 14.4, 14.1, 13.8, 7.5, 6.2; high-resolution mass spectrum (FAB, NBA matrix) *m/z* 871.5334 [(M + Na)$^+$; calcd for $C_{50}H_{80}O_7Si_2Na$ 871.5341].

TES Ether (+)-37b. Diol (+)-**36b** (7.5 mg, 10.2 μmol) was selectively monosilylated as described above for the preparation of (+)-**37a**. Workup as before gave (+)-**37b** (6.1 mg, 71% yield) as a colorless oil: $[\alpha]_D^{25}$ +22° (*c* 0.41, $CHCl_3$); IR ($CHCl_3$) 3470 (w, br), 2990 (m), 2950 (s), 2920 (s), 2870 (s), 2850 (s), 1715 (s), 1455 (m), 1210 (s), 1105 (s), 1035 (s), 1000 (s), 690 (s) cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 7.68−7.65 (m, 4 H), 7.45−7.36 (m, 6 H), 5.58 (apparent t, J = 6.6 Hz, 1 H), 5.49−5.39 (m, 2 H), 5.39 (d, J = 10.8 Hz, 1 H), 4.84−4.77 (m, 1 H), 4.19 (s, 1 H), 4.13 (m, 1 H), 3.72 (d, J = 10.8 Hz, 1 H), 3.06 (d, J = 8.7 Hz, 1 H), 2.95 (s, 3 H), 2.62 (ABq, J_{AB} = 14.1 Hz, $\Delta\upsilon_{AB}$ = 185.0 Hz, 2 H), 2.60 (ddd, J = 15.3, 8.7, 6.6 Hz, 1 H), 2.50−2.43 (m, 2 H), 2.31−2.24 (m, 1 H), 2.06−1.99 (m, 1 H), 1.96 (ddd, J = 11.2, 4.9, 1.8 Hz, 1 H), 1.92−1.70 (m, 3 H), 1.63 (s, 3 H), 1.62 (d, J = 4.7 Hz, 3 H), 1.59 (d, J = 0.8 Hz, 3 H), 1.57−1.50 (m, 1 H), 1.39 (apparent q, J = 11.9 Hz, 1 H), 1.05 (s, 9 H), 0.954 (t, J = 8.0 Hz, 9 H), 0.949 (s, 3 H), 0.948 (d, J = 5.6 Hz, 3 H), 0.89 (s, 3 H), 0.60 (q, J = 7.9 Hz, 6 H); ^{13}C NMR (125.8 MHz, CD_3OD) δ 171.0, 139.0, 136.92, 136.89, 135.41, 135.35, 131.7, 131.4, 131.1, 130.9, 128.8, 128.7, 126.7, 126.5, 101.0, 83.4, 75.9, 75.0, 68.9, 68.0, 46.0, 44.3, 43.8, 40.3, 38.0, 34.9, 31.8, 29.9, 27.6, 26.5, 22.6, 20.2, 19.9, 18.1, 14.1, 13.7, 7.5, 6.2; high-resolution mass spectrum (FAB, 1-thioglycerol matrix) *m/z* 869.5170 [(M + Na)$^+$; calcd for $C_{50}H_{78}O_7Si_2Na$ 869.5184].

Ketone (+)-38a. The Dess−Martin periodinane (0.15 g, 0.34 mmol) was dissolved in CH_2Cl_2 (10.7 mL), and pyridine (0.14 mL, 1.71 mmol) was added, producing a clear stock solution which was used within 5 min. At room temperature alcohol (+)-**37a** (8.4 mg, 9.9 μmol) was treated with a portion of the periodinane solution (5.01 mL). After an additional 20 min, the reaction mixture was diluted with ether (5 mL), and the reaction was quenched with saturated aqueous $NaHCO_3$ and $NaHSO_3$ (1:1, 5 mL). The resultant mixture was stirred for 5 min, diluted with ether (20 mL), washed with saturated aqueous $NaHCO_3$ (2 × 10 mL) and brine (15 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 9:1) furnished (+)-**38a** (8.0 mg, 96% yield) as a colorless oil: $[\alpha]_D^{25}$ +112° (*c* 0.73, $CHCl_3$); IR ($CHCl_3$) 1705 (s), 1455 (m), 1205 (s), 1110 (s), 1070 (s), 1040 (s), 695 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68−7.63 (m, 4 H), 7.44−7.35 (m, 6 H), 5.40 (d, J = 10.3 Hz, 1 H), 5.25 (apparent t, J = 6.8 Hz, 1 H), 4.90−4.86 (m, 1 H), 4.18 (s, 1 H), 4.14−4.08 (m, 1 H), 3.99−3.93 (m, 1 H), 3.67 (d, J = 11.8 Hz, 1 H), 2.94 (s, 3 H), 2.62 (ABq, J_{AB} = 14.3 Hz, $\Delta\upsilon_{AB}$ = 244.0 Hz, 2 H), 2.27−2.25 (m, 2 H), 1.97 (ddd, J = 12.8, 4.8, 1.6 Hz, 1 H), 1.96 (ddt, J = 12.3, 4.4, 2.2 Hz, 1 H), 1.78 (dd, J = 12.8, 10.7 Hz, 1 H), 1.68−1.57 (m, 1 H), 1.59 (s, 3 H), 1.56 (d, J = 1.0 Hz, 3 H), 1.41−1.35 (m, 1 H), 1.31−1.23 (m, 6 H), 1.29 (s, 3 H), 1.18 (apparent q, J = 12.0 Hz, 1 H), 1.04 (s, 9 H), 1.00 (d, J = 6.7 Hz, 3 H), 0.99 (s, 3 H), 0.96 (t, J = 8.0 Hz, 9 H), 0.87 (t, J = 7.0 Hz, 3 H), 0.60 (q, J = 7.9 Hz, 6 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 214.5, 169.3, 137.6, 135.8, 135.7, 134.5, 134.2, 133.7, 129.7, 127.58, 127.57, 125.2, 123.2, 99.3, 80.1, 74.4, 72.4, 66.4, 56.2, 48.1, 43.5, 42.0, 40.4, 38.7, 33.1, 31.8, 30.7, 26.9, 25.5, 24.2, 22.6, 19.3, 19.0, 18.6, 14.0, 13.5, 13.1, 7.0, 4.9; high-resolution mass spectrum (FAB, NBA matrix) *m/z* 869.5168 [(M + Na)$^+$; calcd for $C_{50}H_{78}O_7Si_2Na$ 869.5184].

Ketone (+)-38b. Alcohol (+)-**37b** (10.0 mg, 11.8 μmol) was oxidized via the same procedure described above for the preparation of (+)-**38a**; in this case, the reaction mixture was stirred for 15 min after the addition of the periodinane. Workup and flash chromatography as before afforded (+)-**38b** (9.0 mg, 90% yield) as a colorless oil: $[\alpha]_D^{25}$ +119° (*c* 0.20, $CHCl_3$); IR ($CHCl_3$) 1705 (s), 1455 (m), 1200 (s), 1105 (s), 1065 (s), 1040 (s), 695 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68−7.63 (m, 4 H), 7.44−7.35 (m, 6 H), 5.46−5.34 (m, 3 H), 5.23 (apparent t, J = 6.8 Hz, 1 H), 4.92−4.87 (m, 1 H), 4.19 (s, 1 H), 4.14−4.07 (m, 1 H), 3.99−3.93 (m, 1 H), 3.68 (d, J = 11.8 Hz, 1 H), 2.94 (s, 3 H), 2.61 (ABq, J_{AB} = 14.2 Hz, $\Delta\upsilon_{AB}$ = 240.4 Hz, 2 H), 2.27−2.22 (m, 2 H), 2.02−1.89 (m, 3 H), 1.86 (ddt, J = 12.4, 4.4, 2.2 Hz, 1 H), 1.78 (dd, J = 12.7, 10.7 Hz, 1 H), 1.73−1.65 (m, 1 H), 1.61 (apparent d, J = 5.7 Hz, 3 H), 1.59 (s, 3 H), 1.57 (d, J = 1.0 Hz, 3 H), 1.48−1.41 (m, 1 H), 1.28 (s, 3 H), 1.19 (apparent q, J = 12.0 Hz, 1 H), 1.04 (s, 9 H), 1.00 (d, J = 6.6 Hz, 3 H), 0.99 (s, 3 H), 0.96 (t, J = 8.0 Hz, 9 H), 0.60 (q, J = 8.0 Hz, 6 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 214.5, 169.2, 137.7, 135.8, 135.7, 134.4, 134.2, 133.7, 130.1, 129.7, 127.6, 125.4, 125.3, 123.0, 99.3, 80.0, 73.9, 72.5, 66.4, 56.2, 48.2, 43.4, 41.9, 40.4, 38.7, 32.9, 30.7, 28.8, 26.9, 24.2, 19.2, 19.0, 18.6, 17.9, 13.5, 13.1, 7.0, 4.9; high-resolution mass spectrum (FAB, 1-thioglycerol matrix) *m/z* 867.5039 [$(M + Na)^+$; calcd for $C_{50}H_{76}O_7Si_2Na$ 867.5027].

Alcohol (+)-39a. At ambient temperature, TES ether (+)-**38a** (8.0 mg, 9.4 μmol) was treated with 49% aqueous HF in CH_3CN (1:9, 0.71 mL) in one portion. After 3 min, the reaction mixture was diluted with ether (5 mL), and the reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL). Additional ether (10 mL) was then added, and the organic phase was washed with saturated aqueous $NaHCO_3$ (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexanes/ethyl acetate, 5:1) gave (+)-**39a** (6.0 mg, 88% yield) as a colorless amorphous solid: mp 138−139 °C; $[\alpha]_D^{25}$ +131° (*c* 0.55, $CHCl_3$); IR ($CHCl_3$) 3440 (w, br), 3005 (m), 2955 (s), 2930 (s), 1700 (s), 1455 (m), 1105 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.67−7.65 (m, 4 H), 7.43−7.35 (m, 6 H), 5.25 (d, J = 9.5 Hz, 1 H), 5.17 (dd, J = 11.0, 1.2 Hz, 1 H), 5.13 (d, J = 2.5 Hz, 1 H), 4.96−4.90 (m, 1 H), 4.60 (s, 1 H), 4.33−4.26 (m, 1 H), 4.12 (dd, J = 11.8, 2.2 Hz, 1 H), 3.92−3.86 (m, 1 H), 2.53 (ABq, J_{AB} = 14.6 Hz, $\Delta\upsilon_{AB}$ = 47.5 Hz, 2 H), 2.39 (ddd, J = 15.2, 10.6, 2.0 Hz, 1 H), 2.08 (apparent t, J = 12.8 Hz, 1 H), 1.98 (ddt, J = 12.1, 4.6, 1.4 Hz, 1 H), 1.74 (d, J = 1.2 Hz, 3 H), 1.72−1.65 (m, 1 H), 1.64 (s, 3 H), 1.64−1.51 (m, 5 H), 1.35 (td, J = 12.7, 2.5 Hz, 1 H), 1.30−1.18 (m, 5 H), 1.09 (s, 3 H), 1.06 (s, 9 H), 1.01 (d, J = 6.6 Hz, 3 H), 0.87 (t, J = 7.0 Hz, 3 H), 0.83 (s, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 215.4, 172.4, 135.7, 135.1, 134.7, 134.3, 130.6, 129.7, 127.6, 126.4, 96.6, 79.7, 75.8, 74.1, 66.1, 52.6, 44.6, 44.1, 43.1, 38.3, 35.3, 32.6, 31.5, 27.0, 25.5, 24.9, 22.5, 19.2, 19.1, 16.0, 13.9, 12.9, 11.1; high-resolution mass spectrum (FAB, NBA matrix) *m/z* 741.4175 [$(M + Na)^+$; calcd for $C_{46}H_{62}O_7SiNa$ 741.4163].

Alcohol (+)-39b. TES ether (+)-**38b** (8.5 mg, 10.0 μmol) was desilylated via the same procedure described above for the preparation of (+)-**39a**; in this case, the reaction time was 2 min. Workup and flash chromatography as before afforded (+)-**39b** (6.4 mg, 89% yield) as a colorless amorphous solid: mp 136−137 °C; $[\alpha]_D^{25}$ +136.4° (*c* 0.55, $CHCl_3$); IR ($CHCl_3$) 3450 (w, br), 2930 (s), 1700 (s), 1445 (m), 1110 (s), 1000 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.71−7.65 (m, 4 H), 7.44−7.35 (m, 6 H), 5.44−5.32 (m, 2 H), 5.24 (apparent d, J = 9.3 Hz, 1 H), 5.17 (dd, J = 11.0, 1.1 Hz, 1 H), 5.11 (d, J = 2.5 Hz, 1 H), 4.96−4.91 (m, 1 H), 4.59 (d, J = 2.9 Hz, 1 H), 4.32−4.26 (m, 1 H), 4.11 (dd, J = 11.8, 2.2 Hz, 1 H), 3.92−3.86 (m, 1 H), 2.52 (ABq, J_{AB} = 14.6 Hz, $\Delta\upsilon_{AB}$ = 52.9 Hz, 2 H), 2.39 (ddd, J = 13.1, 10.6, 2.1 Hz, 1 H), 2.08 (apparent t, J = 12.7 Hz, 1 H), 2.01−1.93 (m, 3 H), 1.74 (d, J = 1.2 Hz, 3 H), 1.72−1.69 (m, 1 H), 1.67−1.63 (m, 1 H), 1.63 (s, 3 H), 1.62 (d, J = 6.4 Hz, 3 H), 1.62−1.56 (m, 2 H), 1.38−1.33 (m, 2 H), 1.26 (s, 1 H), 1.09 (s, 3 H), 1.06 (s, 9 H), 1.01 (d, J = 6.5 Hz, 3 H), 0.83 (s, 3 H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 215.4, 172.3, 135.7, 135.1, 134.8, 134.3, 130.6, 129.8, 129.7, 127.6, 126.2, 125.8, 96.6, 79.7, 75.7, 73.6, 66.1, 52.6, 44.6, 44.0, 43.1, 38.3, 35.1, 32.6, 28.4, 27.0, 25.5, 19.15, 19.13, 17.9, 16.0, 12.9, 11.1; high-resolution mass spectrum (FAB, 1-thioglycerol matrix) *m/z* 739.4015 [$(M + Na)^+$; calcd for $C_{46}H_{60}O_7SiNa$ 739.4006].

(+)-Acutiphycin (1). A stock solution was prepared by addition of HOAc (0.15 mL) to a solution of tetrabutylammonium fluoride in THF (1.0 M, 2.5 mL). BPS ether (+)-**39a** (6.0 mg, 8.3 μmol) was dissolved in THF (3.3 mL) and treated with a portion of the stock solution (1.5 mL). After 42 h at room temperature, the reaction mixture was diluted with ethyl acetate (25 mL), washed with saturated aqueous $NaHCO_3$ (2 × 15 mL) and brine (15 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (hexane/ethyl acetate, 2:1) afforded (+)-**1** (3.8 mg, 95% yield) as a colorless, amorphorus solid: mp 156−158 °C (lit.[1] 155−156 °C); mmp 155−158 °C; $[\alpha]_D^{25}$ +158° (*c* 0.35, CH_2Cl_2) {lit.[1] $[\alpha]_D^{25}$ +107° (*c* 1.0, CH_2Cl_2)}; IR ($CHCl_3$) 3605 (w), 3460 (w, br), 3015 (m), 2960 (m), 2935 (s), 2855 (m), 1705 (s), 1470 (w), 1450 (m), 1430 (m), 1415 (m), 1370 (m), 1330 (w), 1280 (w), 1220 (s), 1200 (s), 1150 (m), 1060 (m), 1030 (m), 1015 (m), 1000 (m), 900 (m), 700 (m) cm^{-1}; ^1H NMR [500 MHz, $C_6D_6/CDCl_3$ (1:1)] δ 5.35 (d, J = 2.0 Hz, 1 H), 5.21 (apparent d, J = 9.6 Hz, 1 H), 5.16 (apparent dd, J = 11.0, 1.3 Hz, 1 H), 4.90 (dddd, J = 11.4, 8.2, 4.5, 2.1 Hz, 1 H), 4.52 (br s, 1 H), 4.17 (dd, J = 11.9, 2.1 Hz, 1 H), 4.00 (tt, J = 11.1, 4.6 Hz, 1 H), 3.86 (dq, J = 11.1, 6.6 Hz, 1 H), 2.40 (d, J = 14.5 Hz, 1 H), 2.27 (d, J = 14.5 Hz, 1 H), 2.20 (ddd, J = 15.2, 10.6, 2.1 Hz, 1 H), 1.96 (apparent d, J = 13.1 Hz, 1 H), 1.90 (ddd, J = 11.9, 4.6, 1.6 Hz, 1 H), 1.62 (d, J = 1.4 Hz, 3 H), 1.54 (ddt, J = 14.3, 4.5, 1.8 Hz, 1 H), 1.44 (t, J = 1.2 Hz, 3 H), 1.30 (m, 1 H), 1.17 (m, 8 H), 1.10 (s, 3 H), 1.03 (d, J = 6.5 Hz, 3 H), 0.99 (td, J = 12.9, 2.0 Hz, 1 H), 0.85 (s, 3 H), 0.80 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 214.4, 170.8, 136.1, 134.9, 128.1, 123.6, 96.1, 77.3, 74.1, 73.7, 62.6, 53.0, 45.9, 43.5, 41.2, 38.2, 34.3, 31.7, 30.9, 24.3, 23.3, 21.8, 20.5, 16.6, 13.8, 12.8, 11.8; high-resolution mass spectrum (FAB, NBA matrix) *m/z* 503.2972 [$(M + Na)^+$; calcd for $C_{27}H_{44}O_7Na$ 503.2985].

(+)-*trans*-20,21-Didehydroacutiphycin (2). BPS ether (+)-**39b** (6.0 mg, 8.4 μmol) was desilylated via the general procedure described above for the preparation of (+)-**1**; in this case, the reaction time was 50 h. Workup and flash chromatography as before furnished (+)-**2** (3.7 mg, 92% yield) as a colorless, amorphorus solid: mp 155−156 °C (lit.[1] 153−154 °C); mmp 154−156 °C; $[\alpha]_D^{25}$ +130.9° (*c* 0.23, $CHCl_3$) {lit.[1] $[\alpha]_D^{25}$ +110° (*c* 1.0, MeOH)}; IR ($CHCl_3$) 3600 (w), 3440 (w, br), 3010 (m), 2930 (s), 2850 (m), 1735 (m), 1700 (s), 1510 (w), 1445 (m), 1425 (m), 1370 (m), 1325 (w), 1205 (s), 1145 (m), 1100 (m), 1055 (m), 1025 (m), 1015 (m), 995 (m), 900 (s), 710 (s, br), 655 (m) cm^{-1}; ^1H NMR [500 MHz, $C_6D_6/CDCl_3$ (1:1)] δ 5.35−5.23 (m, 2 H), 5.31 (d, J = 2.5 Hz, 1 H), 5.18 (apparent d, J = 9.5 Hz, 1 H), 5.14 (apparent dd, J = 11.1, 1.2 Hz, 1 H), 4.89 (dddd, J = 11.0, 8.4, 4.3, 2.1 Hz, 1 H), 4.49 (d, J = 2.7 Hz, 1 H), 4.15 (dd, J = 12.0, 2.2 Hz, 1 H), 3.99 (tt, J = 11.1, 4.9 Hz, 1 H), 3.84 (dq, J = 11.1, 6.6 Hz, 1 H), 2.39 (d, J = 14.6 Hz, 1 H), 2.26 (d, J = 14.6 Hz, 1 H), 2.19 (ddd, J = 13.1, 10.6, 2.1 Hz, 1 H), 1.94 (apparent d, J = 13.3 Hz, 1 H), 1.90 (ddd, J = 11.9, 4.6, 1.7 Hz, 1 H), 1.85 (apparent q, J = 7.0 Hz, 2 H), 1.60 (d, J = 1.3 Hz, 3 H), 1.54 (ddt, J = 12.2, 4.2, 1.9 Hz, 1 H), 1.52 (dd, J = 5.8, 0.8 Hz, 3 H), 1.42 (s, 3 H), 1.40−1.33 (m, 1 H), 1.13 (m, 2 H), 1.07 (s, 3 H), 1.01 (d, J = 6.5 Hz, 3 H), 0.99 (td, J = 11.7, 2.5 Hz, 1 H), 0.82 (s, 3 H); ^{13}C NMR (125.8 MHz, DMSO-d_6) δ 214.4, 170.7, 136.2, 134.9, 130.2, 128.0, 124.9, 123.4, 96.1, 77.3, 74.1, 73.3, 62.6, 53.0, 45.9, 43.5, 41.2, 38.2, 34.1, 31.5, 27.9, 23.2, 20.6, 17.6, 16.7, 12.9, 11.8; high-resolution mass spectrum (FAB, 1-thioglycerol matrix) *m/z* 501.2806 [$(M + Na)^+$; calcd for $C_{27}H_{42}O_7Na$ 501.2828].

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Supporting Information Available: Characterization data for **i**, **3a**, **3b**, **5**, **6**, **8**, **11**, **12**, **14**, **15**, **17**, **18**, **23**, **25**−**31**, **32a**−**34a**, and **32b**−**34b** (12 pages). See any current masthead page for ordering and Internet access instructions.

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