Synthesis of Tuckolide, a New Cholesterol Biosynthesis Inhibitor

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Tuckolide (decarestrictine D), a 10-membered lactone isolated from *P. corylophilum* and *polyporus tuberaster* fungi that potently inhibits cholesterol biosynthesis, was synthesized. The key steps include a Sharpless catalytic asymmetric dihydroxylation reaction (AD) of the methoxymethyl (MOM) ether protected diene **2** and a direct Corey−Nicolaou lactonization reaction of seco-acid **1** with added silver perchlorate. The selectivity of the dihydroxylation step was found to be highly dependent on the nature of the protecting group adjacent to the diene in **2**. The selectivity of the asymmetric dihydroxylation reaction of **2** indicates that both steric and electronic effects can lead to significant amounts of the undesired isomers. This synthesis establishes the absolute stereochemistry of tuckolide showing the C3 hydroxyl bearing carbon with an *S*-configuration comparable in an absolute sense to that in the lactone portion of the HMG-CoA reductase inhibitor compactin.

Tuckolide (decarestrictine D), recently isolated from *Penicillium corylophilum, simplicissimum*[1] and independently from the Canadian Tuckahoe fungi *polyporus tuberaster*,[2] is an important new member of a growing class of 10-membered lactone natural products (Figure 1).[3] A general panel of whole cell screens demonstrated that tuckolide potently inhibits liver cell cholesterol biosynthesis (HEP cells, IC_{50} of 100 nm).[1] This level of activity is somewhat surprising since the structure of tuckolide is far more simple than the well-known HMG-CoA inhibitors mevinolin and compactin and other synthetic cholesterol-lowering agents.[4a] In addition, it appears that tuckolide is highly selective in that it exhibits no significant antibacterial, antifungal, antiprotozoal, or antiviral activity.[1] Toxicity studies further revealed that tuckolide exhibits good tolerability, showing a lack of change in a standard set of defined safety parameters. A synthesis of tuckolide may then provide for a new, more direct starting point for the design of new HMG-CoA inhibitors.

While the relative stereochemistry was provided by X-ray analysis,[2] the absolute stereochemistry at the C3 hydroxyl-bearing carbon was assumed for the purposes of the synthesis to be in an (*S*)-configuration by analogy to the lactone portion of lovastatin (IC_{50} 24 nm, HEP assay).[4] Other members of the 10-ring lactone class of compounds include the decarestrictines A−C,[1] pheromone phoracantholide I,[5] diplodialides A−D,[6] pyrenolide A,[7] and achaetolide.[8] Synthetic attention has focused primarily on the simplest compound of the class, phoracantholide,[9] where both fragmentation/ring expansion and direct lactonization routes have been developed. An approach to pyrenolide has also recently appeared.[10]

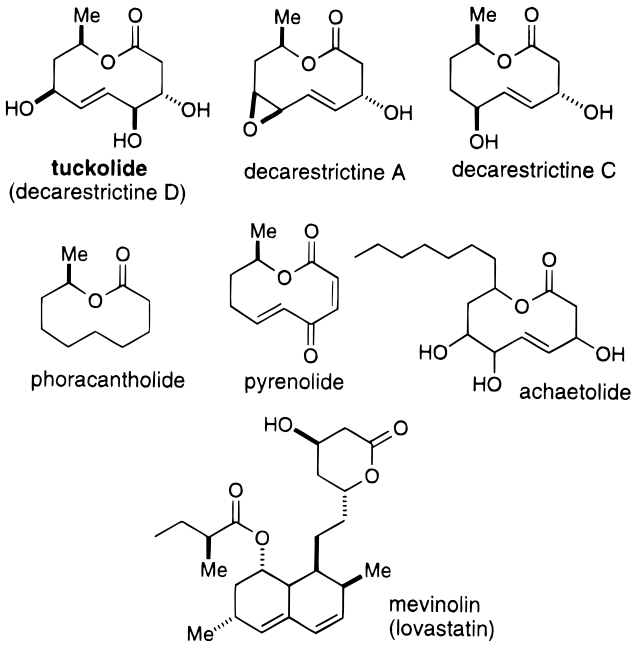

Figure 1. Ten-membered lactone class of natural products and the cholesterol biosynthesis inhibitor mevinolin.

The synthesis of medium-sized lactones is a difficult challenge where destabilizing nonbonded, transannular interactions and unfavorable entropic factors must be overcome.[3] Recent success with the eight-membered lactone octalactin prompted the decision to employ a

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(1) (a) Grabley, S.; Granzer, E.; Hutter, K.; Ludwig, D.; Mayer, M.; Thiericke, R.; Till, G.; Wink, J. Phillips, S.; Zeeck, A. *J. Antibiot.* **1992**, *45*, 56. (b) Gohrt, A.; Zeeck, A.; Hutter, K.; Kirsch, R.; Kluge, H.; Thiericke, R. *J. Antibiot.* **1992**, *45*, 66. (HEP-G2 cell assay, cholesterol sodium [^{14}C]acetate uptake.)

(2) Ayer, W. A.; Sun, M.; Browne, L. M.; Brinen, L. S. Clardy, J. *J. Nat. Prod.* **1992**, *55*, 649.

(3) Rousseau, G. *Tetrahedron* **1995**, *51*, 2777.

(4) (a) Endo, A.; Hasumi, K. *Nat. Prod. Rep.* **1993**, 541. (b) Abe, I.; Tomesch, J. C.; Wattanasin, S.; Prestwich, G. D. *J. Nat. Prod.* **1994**, *56*, 279.

(5) Moore, B. P.; Brown, W. V. *Aust. J. Chem.* **1976**, *29*, 1365.

(6) Wada, K.; Ishida, T. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1154.

(7) Nukina, M.; Sassa, T.; Ikeda, M. *Tetrahedron Lett.* **1980**, *21*, 301.

(8) Bodo, B.; Molho, L.; Davoust, D.; Molho, D. *Phytochemistry* **1983**, *22*, 447.

(9) Synthesis of racemic material: Wakamatsu, T.; Akasaka, K.; Ban, Y. *Tetrahedron Lett.* **1977**, *18*, 2755. Gerlach, H.; Kunzler, P.; Oertle, K. *Helv. Chim. Acta* **1978**, *61*, 1226. Malherbe, R.; Bellus, D. *Helv. Chim. Acta* **1978**, *61*, 3096. Takahashi, T.; Hasiguchi, S.; Kasuga, K.; Tsuji, J. *J. Am. Chem. Soc.* **1978**, *100*, 7424. Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 1595. Wakamatsu, T.; Akasaka, K.; Ban, Y. *J. Org. Chem.* **1979**, *44*, 2008. Mahajan, J. R.; de Araujo, H. C. *Synthesis* **1981**, 49. Vedejs, E.; Powell, D. W. *J. Am. Chem. Soc.* **1982**, *104*, 2046. Ono, N.; Miyaki, H.; Kaji, A. *J. Org. Chem.* **1984**, *49*, 4997. Suginome, H.; Yamada, S. *Tetrahedron Lett.* **1985**, 3715. Wada, M.; Shige,hisa, T.; Akiba, K. *Tetrahedron Lett.* **1985**, 5191. Ohnuma, T.; Hata, N.; Miyachi, N.; Wakamatsu, T.; Ban, Y. *Tetrahedron Lett.* **1986**, *27*, 219. enantioselective routes: Kitahara, T.; Koseki, K.; Mori, K. *Agric. Biol. Chem.* **1983**, *47*, 389. Nagumo, S.; Suemune, H.; Sakai, K. *Tetrahedron* **1992**, *48*, 8667. Jones, G. B.; Chapman, B. J.; Huber, R. S.; Beaty, R. *Tetrahedron: Asymmetry* **1994**, *5*, 1199. Enders, D.; Plant, A.; Drechel, K.; Prokopenko, O. F. *Liebigs Ann.* **1995**, 1127.

(10) Synthesis of racemic material: Moricz, A.; Gassmann, E.; Bienz, S. Hesse, M. *Helv. Chim. Acta* **1995**, *78*, 663.

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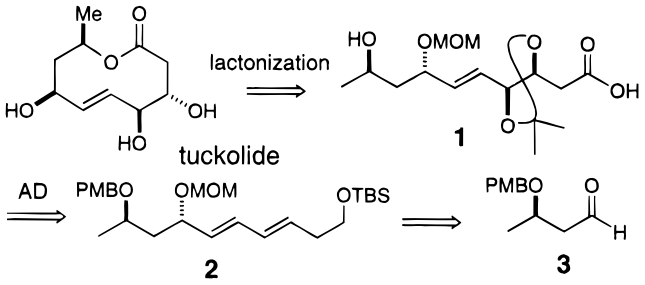
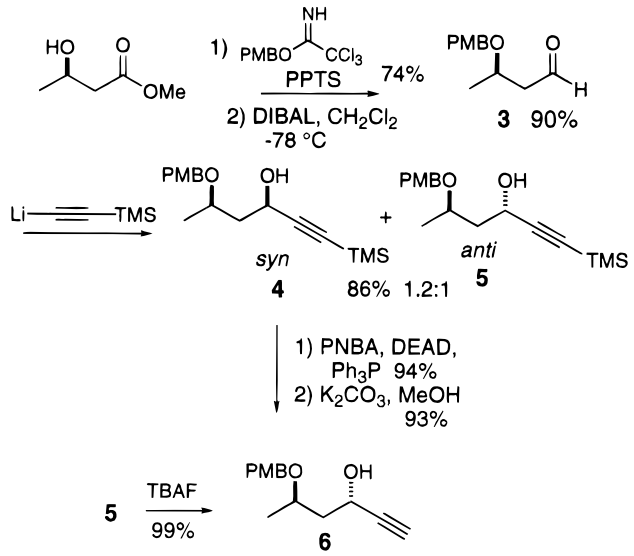


Figure 2. Retrosynthesis of tuckolide involving lactonization of **1** and asymmetric dihydroxylation of diene **2**.

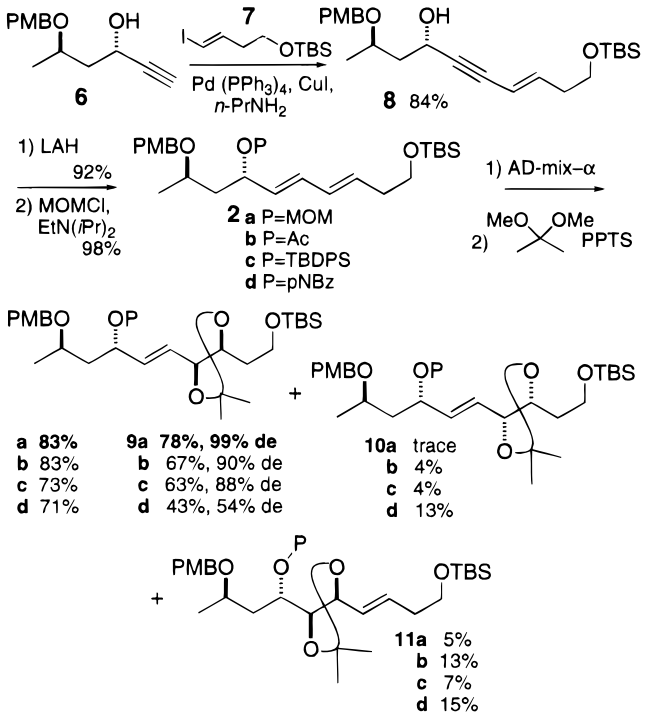
Scheme 1



direct lactonization of the protected seco-acid **1**.[11] The precursor seco-acid **1** was planned to be prepared using a regioselective Sharpless asymmetric dihydroxylation of the diene intermediate **2** (Figure 2). It was anticipated that the nature of the protecting group adjacent to the internal position of diene **2** may prove to be a critical factor for achieving high regio- and diastereoselectivity. Methoxymethyl (MOM) ether, acetate, *p*-nitrobenzoate, and *tert*-butyldiphenylsilyl (TBDPS) ether were screened to optimize the dihydroxylation step.

Our synthesis begins with protection of (*R*)-(−)-methyl 3-hydroxybutanoate[12] as the *p*-methoxybenzyl (PMB) ether,[13] followed by reduction with 1 equiv of diisobutylaluminum hydride (DIBAL) at −78 °C to give aldehyde **3** in 90% yield (Scheme 1).[14] Acetylenic and vinyl reagents were then investigated in an effort to find a substrate-directed route to the desired *anti*-hydroxy diastereomeric product **5**. Lithium, magnesium, and trimethylsilylalkynyl reagents both without and with added Lewis acid failed to give more than essentially a 1:1 ratio of products.[15] This lack of selectivity was circumvented by separating the *syn*-isomer **4** by simple

Scheme 2



flash chromatography from the desired *anti*-isomer **5** after addition of lithio(trimethylsilyl)acetylene.[16] Isomer **4** was subjected to Mitsunobu conditions using *p*-nitrobenzoic acid (PNBA), triphenylphosphine, and diethyl azodicarboxylate (DEAD) to give **5**.[17] The benzoate ester and trimethylsilyl groups in **5** were removed in the same step using potassium carbonate in methanol in 93% yield. The resultant propargyl alcohol **6** was then combined with identical material obtained from the trimethylsilyl removal of the separated *anti*-isomer **5**.

Coupling of **6** with vinyl iodide **7**[18] using a catalytic amount of palladium(0) and cuprous iodide produced the (*E*)-enyne alcohol **8** in 84% yield (Scheme 2).[19] Reduction using LAH gave the corresponding (*E,E*)-diene[20] which was protected as its MOM ether **2a**. Asymmetric catalytic osmium tetroxide dihydroxylation of **2a** using commercial AD-mix-α reagent in the presence of methanesulfonamide according to the Sharpless conditions generated the desired diol **9a** in 78% yield.[21] After workup, the crude diol products were treated with 2,2-dimethoxypropane under acid catalysis (PPTS, 5 mol %)

(11) (a) Buszek, K. R.; Sato, N.; Jeong,Y. *J. Am. Chem. Soc.* **1994**, *116*, 5510. (b) Andrus, M. B.; Argade, A. B. *Tetrahedron Lett.* **1996**, *37*, 5049.

(12) Seebach, D.; Zuger, M. F. *Tetrahedron Lett.* **1985**, *25*, 2747. Seebach, D.; Beck, A. K.; Breitschuh, R. *Org. Synth.* **1991**, *71*, 39.

(13) (a) Nakajima, N.; Horita, K.; Abe, R.; Yonemitsu, O. *Tetrahedron Lett.* **1988**, *29*, 4139. (b) Iversen, T.; Bundle, D. R. *J. Chem. Soc., Chem. Commun.* **1981**, 1240.

(14) Keck, G. E.; Palani, A.; McHardy, S. F. *J. Org. Chem.* **1994**, *59*, 3121.

(15) Mead, K. T. *Tetrahedron Lett.* **1987**, *28*, 1019. Mauvais, A.; Hetru, C.; Luu, B. *Tetrahedron Lett.* **1993**, *34*, 4337.

(16) Compounds **4** and **5** were treated separately with dicyanodichloroquinone giving the isomeric *p*-methoxybenzylidine acetals. The ^{1}H NMR *J*-couplings for the oxygen-bearing methine protons (12 Hz axial, 5 Hz equatorial) were then used to make the *syn*/*anti* assignments.

(17) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.

(18) Obtained from the reaction of DIBAL with 1-hydroxy-3-butyne followed by trapping with iodine and protection as the TBS ether (30% overall yield, unoptimized). Zweifel, G.; Whitney, C. C. *J. Am. Chem. Soc.* **1967**, *89*, 2753. On, H. P.; Lewis, W.; Zweifel, G. *Synthesis* **1981**, 999. Reich, H. J.; Eisenhart, E. K.; Olson, R. E.; Kelly, M. J. *J. Am. Chem. Soc.* **1986**, *108*, 7791.

(19) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.

(20) Rossi, R.; Carpita, A. *Synthesis* **1977**, 561. Holmes, A. B.; Tabor, A. B.; Baker, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3307.

(21) (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) Crispino, G. A.; Jeong, K.; Kolb, H. C.; Wang Z. M.; Xu, D.; Sharpless, K. B. *J. Org. Chem.* **1993**, *58*, 3785. (c) Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570. (d) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.; Kwong, H.; Morikawa, K.; Wang Z. Xu, D.; Zhang, X. *J. Org. Chem.* **1992**, *57*, 2768.

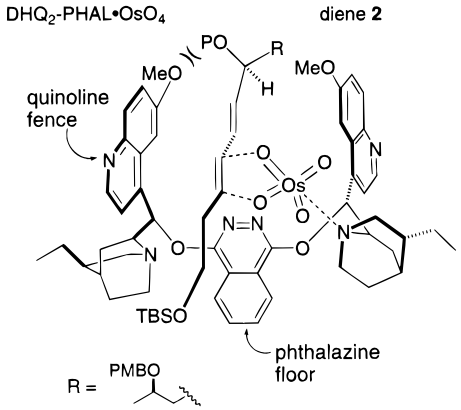
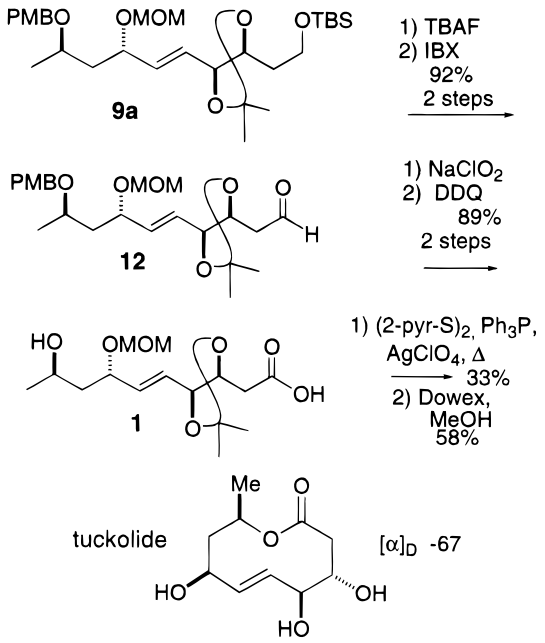


Figure 3. A transition state depiction of the bis-dihydroquinine phthalazine (DHQ_2-PHAL)·OsO_4·diene (**2**) complex that leads to dihydroxylation of the less hindered olefin.

in methylene chloride to form the acetonides **9**−**11**. It was reasoned that the less hindered and more electron rich olefin of the diene would be preferentially dihydroxylated to give the desired (*S,S)*-diol according to the mnemonic of Sharpless.[21b,c] While the reaction proceeded as predicted, a small amount of the minor regioisomer **11a**, which was easily separated by chromatography, was also obtained in 5% yield. Other protecting groups, in place of the MOM ether, were also investigated. Acetate **2b** gave the expected product **9b** in 90% de along with a small amount of the isomeric diol **10b** and a significant amount (13%) of the regioisomeric product **11b**. Dihydroxylation of the TBDPS ether **2c** and the *p*-nitrobenzoate ester **2d** gave diols in lower yield and selectivity.

A model for the selectivity of the asymmetric dihydroxylation reaction with diene **9** is shown in Figure 3. The selectivity is consistent with the transition state arrangement model proposed by Corey where the phthalazine linker acts as a floor for the substrate, the remote quinoline group functions as a perpendicular fence, the proximal quinoline points up forming a U-shaped binding pocket, and the osmium tetroxide is coordinated to the opposite quinuclidine.[22] The diene **9** is situated with the ethylene−TBS ether portion extending out away from the interior and the less hindered less reactive olefin end of the diene is positioned inside the binding cavity where a π-stacking interaction with the fence quinoline can occur. The selectivity of the reaction is a function of both electronic and steric nature of the protecting group (OP). As the size of the protecting group on **2** (OP) increases from MOM (**2a**) to the TBS ether (**2c**), the selectivity drops. More of the diol isomers (**10** and **11**) are formed due to destabilizing steric interactions with the methoxyquinoline. The change to the more electron-withdrawing ester protecting groups, acetate (**2b**) and *p*-nitrobenzoate (**2d**), also leads to formation of more diol isomers, especially the regioisomer **11**. This may be due to an increased tendency to form a favorable π-stacking interaction with the protecting group and the methoxyquinoline. This interaction pulls the diene down into the binding cavity, leading to increased dihydroxylation of the more hindered olefin. Studies by Corey and Sharpless have demonstrated that the nature of protecting groups can have a pronounced effect on AD selectivity with monosubstituted alkenes, in particular benzoate esters and silyl ethers of allyl alcohols.[23] Now with the more extended diene system, simple changes in the allylic protecting group have been shown to greatly affect the selectivity of the AD reaction. The size of this portion of the diene appears to be critical in that the simpler diene substrate where R is replaced with hydrogen gave very poor selectivity when reacted with AD-mix-α.[24]

Scheme 3



To complete the synthesis of tuckolide, the TBS ether of **9b** was removed in high yield using TBAF followed by oxidation using *o*-iodoxybenzoic acid (IBX)[25] to generate aldehyde **12** in 92% overall yield (Scheme 3). Sodium chlorite oxidation of **12** to the corresponding carboxylic acid[26] followed by DDQ (dicyanodichloroquinone) removal of the PMB ether were carried out in high yield to produce hydroxy acid **1**.[13a] Reagents that have proven successful for large-ring lactonizations, carbodiimide and mixed anhydride reagents,[27] were screened without success. In addition a promising new reagent *p*-nitrobenzoic anhydride with catalytic $Sc(OTf)_3$ also failed.[28] Finally it was found that the optimal conditions for cyclization were those of Corey and Nicolaou, using 2,2′-dipyridyl disulfide and triphenylphosphine with added silver perchlorate.[29] The desired 10-membered protected lactone was obtained in 33% isolated yield after chromatography. The low yield is partially the result of MOM ether and acetonide removal (∼15%) that occurred during the reflux

(22) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 319.

(23) Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1995**, *117*, 10805. Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 12109. Wang, Z. -M.; Zhang, X.-L.; Sharpless, K. B. *Tetrahedron Lett.* **1993**, *34*, 2267.

(24) P = MOM, R = H. Four isomers where formed with the approximate ratio: (2:1:1:trace). The stereochemistry was not assigned.

(25) Frigerio, M.; Santagostino, M.; Sputore, S.; Palmisano, G. *J. Org. Chem.* **1995**, *60*, 7272.

(26) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.

(27) For DCC, DMAP·HCl, and DMAP, see: Boden, P. B.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394; no lactone was obtained. Mixed anhydride method: Inanaga, J.; Katsuki, T.; Takimoto, S.; Ouchida, S.; Inone, K.; Nakano, A.; Okunkuda, N.; Yamaguchi, M. *Chem. Lett.* **1979**, 1021.

(28) Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4560.

(29) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614. Corey, E. J.; Nicolaou, K. C.; Melvin, L. S., Jr. *J. Am. Chem. Soc.* **1975**, *97*, 653. Gerlach, von H.; Kunzler, P.; Oertle, K. *Helv. Chim. Acta* **1978**, *61*, 1226.

step. This lactonization, while low in yield, is remarkable in that the parent unsubstituted hydroxy acid, 9-hydroxynonanoic acid, does not lactonize under these conditions. Substrates with suitably placed substituents within the hydroxy acid tether can form medium-sized lactones in high yields with the proper reagents, while the simple parent unsubstituted hydroxy acids fail.[11] Substrates bearing substituents that can occupy pseudoequatorial positions appear to enforce the proper transition state leading to lactone formation. With the eight-membered lactone octalactin, the effect was found to be additive and reinforcing depending on the nature of the substituents.[11b] Finally, one-step removal of the MOM ether and the acetonide was then performed using Dowex resin in methanol at rt to give (−)-tuckolide in 58% yield after chromatography. The synthetic material was found to be identical in all respects to the natural material (^{1}H, ^{13}C NMR, mp 118 °C, TLC, $[\alpha]_D$ −67, nat. $[\alpha]_D$ −62).[1a] The absolute configuration, confirmed as shown by the optical rotation of −62 with an (*S*)-C3 hydroxyl-bearing carbon, suggests a compactin-like mode of action for tuckolide.

Experimental Section

General. Unless otherwise stated, all reactions were run under a nitrogen atmosphere. Anhydrous solvents were freshly distilled before use: diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Methylene chloride was distilled from CaH_2. Triethylamine was distilled from CaH_2 and stored over NaOH. Dimethyl sulfoxide, *n*-propylamine, diisopropylethylamine, and methoxymethyl chloride were purchased and used without purification. ^{1}H (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a QE-300 instrument. ^{1}H NMR spectra were referenced to residual $CHCl_3$ at 7.26 ppm. ^{13}C NMR spectra were referenced to $CDCl_3$ at 77.0 ppm. Multiplicities were reported as the following: s (singlet), d (doublet), t (triplet), dd (doublet of doublets), dt (doublet of triplets), ddd (doublet, doublet of doublets), m (multiplet), br (broad), br s (broad singlet). Combustion analyses and mass spectroscopy were conducted at the Microanalysis Laboratory and Mass Spectrometry Service Laboratory in the Chemistry Department at Purdue University. Optical rotations were measured at 589.3 nm. Column chromatography was gravity-driven using silica gel 60 (70−230 mesh) except where otherwise stated.

(3*R*)-(−)-Methyl 3-((4-Methoxybenzyl)oxy)butanoate. To a stirring solution of (3*R*)-(−)-methyl-3-hydroxybutanoate (2.38 g, 20.2 mmol) in CH_2Cl_2 (5 mL) and cyclohexane (20 mL) was added a solution of *p*-methoxybenzyl trichloroacetimidate in CH_2Cl_2 (10 mL + 5 mL rinse) via cannula. To this mixture was added a catalytic amount of PPTS (0.51 g, 5−10 mol %), and stirring continued at rt for 24 h. The reaction was quenched by the addition of pyridine (1 mL), and the mixture was diluted with H_2O, extracted (CH_2Cl_2)), dried ($MgSO_4$), and concentrated. Column chromatography (hex/EtOAc = 12/1) afforded the PMB-protected ester (3.45 g, 74%) as a clear oil: $[\alpha]_D$ = −22.0 (*c* 10.7, $CHCl_3$); ^{1}H NMR δ 7.24 (2 H, d, J = 8.4 Hz), 6.86 (2 H, d, J = 8.4 Hz), 4.50 (1 H, d, J = 11.2 Hz), 4.42 (1 H, d, J = 11.2 Hz), 3.98 (2 H, m), 3.78 (3 H, d, J = 1.5 Hz), 3.67 (3 H, s), 2.64 (1 H, dd, J = 15.1, 7.3 Hz), 2.42 (1 H, dd, J = 15.1, 5.8 Hz), 1.24 (3 H, d, J = 6.1 Hz); ^{13}C NMR δ 171.8, 159.0, 130.5, 129.1, 113.6, 71.4, 70.4, 55.1, 51.4, 41.7, 19.7; LRMS (EI) *m*/*z* (relative intensity) M^+ 238, 137 (100), 121 (62.4). Anal. Calcd for $C_{13}H_{18}O_4$: C, 65.55; H, 7.56. Found: C, 65.22; H, 7.50.

(3*R*)-3-((4-Methoxybenzyl)oxy)butanal. To a stirring solution of ester (3.17 g, 13.3 mmol) in CH_2Cl_2 (50 mL) at −78 °C was added DIBAL (1.0 M solution in hexane, 16 mmol) via syringe pump over 50 min. After addition was complete, this mixture was stirred for 20 min. The reaction was quenched by the addition of MeOH (3 mL), and the mixture was extracted with CH_2Cl_2 and was filtered through Celite. The organic layer was dried ($MgSO_4$) and concentrated. Column chromatography (CH_2Cl_2) furnished **3** (2.49 g, 90%) as a pale yellow oil: ^{1}H NMR δ 9.76 (1 H, t, J = 2.2 Hz), 7.24 (2 H, d, J = 8.7 Hz), 6.86 (2 H, d, J = 8.7 Hz), 4.53 (1 H, d, J = 11.2 Hz), 4.40 (1 H, d, J = 11.2 Hz), 4.06 (1 H, m), 3.79 (3 H, s), 2.67 (1 H, ddd, J = 16.4, 7.5, 2.2 Hz), 2.49 (1 H, ddd, J = 16.4, 5.0, 2.2 Hz), 1.28 (3 H, d, J = 6.2 Hz); ^{13}C NMR δ 201.5, 159.1, 130.2, 129.2, 113.7, 70.2, 69.8, 55.2, 50.4, 19.7. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.23; H, 7.69. Found: C, 68.85; H, 7.91.

4: (3*R*,5*R*)-3-Hydroxy-5-((4-methoxybenzyl)oxy)-1-(trimethylsilyl)-1-hexyne. 5: (3*S*,5*R*)-3-Hydroxy-5-((4-methoxybenzyl)oxy)-1-(trimethylsilyl)-1-hexyne. A solution of lithio(trimethylsilyl)acetylene was first generated in THF by slowly adding *n*-butyllithium (2.43 M in hexanes, 10.3 mL, 25.1 mmol, 1.05 equiv) to (trimethylsilyl)acetylene (23.9 mmol, 1 equiv) at 0 °C. After the addition was complete, this mixture was allowed to stir at that temperature for 30 min before being cannulated into aldehyde **3**. To a stirring solution of **3** (4.97 g, 23.9 mmol) in THF (45 mL) at −78 °C was added the lithium trimethylacetylide solution in THF solution via cannula. After the mixture was stirred for 40 min, the cooling bath was removed, and this mixture was stirred at ambient temperature for 30 min before being diluted with aqueous 30% NH_4Cl (20 mL). The mixture was extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated. Column chromatography (hex/CH_2Cl_2 = 1/1) afforded **4** (4.39 g, 60%) and **5** (1.933 g, 26.4%) as yellow oils. Thin layer chromatography (hex/EtOAc = 2/1) indicated that the less polar spot corresponded to **5**. The more polar one was **4**. Spectroscopic data for **4**: ^{1}H NMR δ 7.25 (2 H, d, J = 8.7 Hz), 6.87 (2 H, d, J = 8.7 Hz), 4.49−4.71 (2 H, d + m (merge)), 3.79 (4 H, br s), 3.24 (1 H, s), 2.02 (1 H, dt, J = 14.1, 9.3, 8.3 Hz), 1.80 (1 H, ddd, J = 14.1, 5.3, 3.8 Hz), 1.24 (3 H, d, J = 6.1 Hz), 0.16 (9 H, s); ^{13}C NMR δ 159.1, 130.1, 129.3, 113.8, 106.3, 88.8, 73.8, 70.1, 61.8, 55.2, 44.5, 19.5, −0.19. Spectroscopic data for **5**: ^{1}H NMR δ 7.30 (2 H, d, J = 8.5 Hz), 6.88 (2 H, d, J = 8.5 Hz), 4.49−4.65 (2 H, m), 4.40 (2 H, d, J = 10.7 Hz), 3.80 (3 H, s), 3.58 (1 H, d, J = 7.8 Hz), 1.94 (1 H, ddd, J = 14.4, 6.4, 3.3 Hz), 1.83 (1 H, ddd, J = 14.4, 6.4, 3.3 Hz), 1.26 (3 H, d, J = 6.2 Hz), 0.19 (9 H, s); ^{13}C NMR δ 159.2, 130.2, 129.5, 113.9, 106.7, 89.1, 73.3, 70.6, 61.1, 55.2, 43.0, 19.3, −0.07. Anal. Calcd for $C_{17}H_{26}O_3Si$: C, 66.67; H, 8.50. Found: C, 66.49; H, 8.72.

(3*S*,5*R*)-3-Hydroxy-5-((4-methoxybenzyl)oxy)-1-hexyne. To a stirring solution of **5** (0.696 g, 2.27 mmol) in THF (10 mL) was added dropwise TBAF (1.0 M solution in THF, 3 mmol) at 0 °C. After addition was complete, the ice bath was removed and the mixture was stirred at ambient temperature for 15 min. The solution was poured into NH_4Cl (saturated), extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated. Column chromatography (CH_2Cl_2) afforded **6** (0.525 g, 99%) as a pale yellow oil: ^{1}H NMR δ 7.28 (2 H, d, J = 8.5 Hz), 6.88 (2 H, d, J = 8.5 Hz), 4.57 (2 H, br d), 4.41 (1 H, d, J = 10.8 Hz), 4.08−4.15 (1 H, m), 3.79 (3 H, s), 3.71−3.86 (4 H, s + m), 2.46 (1 H, d, J = 2.1 Hz), 1.97 (1 H, septet, J = 14.6, 9.6, 3.3 Hz), 1.82 (1 H, ddd, J = 14.6, 6.4, 3.2 Hz), 1.26 (3 H, d, J = 6.1 Hz); ^{13}C NMR δ 159.2, 130.2, 129.5, 113.8, 84.7, 72.8, 72.6, 70.3, 60.4, 55.2, 42.8, 19.2. Anal. Calcd for $C_{14}H_{1}38O_3$: C, 71.79; H, 7.67. Found: C, 71.51; H, 7.68.

(3*E*,7*S*,9*R*)-1-*O*-(*tert*-Butyldimethylsilyl)-7-hydroxy-9-((4-methoxybenzyl)oxy)-3-decanen-5-yn-1-ol. To a degassed benzene solution of **6** (0.873 g, 3.73 mmol) and vinyl iodide **7** (1.3 g, 4.16 mmol) were added *n*-propylamine (0.46 mL, 5.59 mmol) and $Pd(PPh_3)_4$ (0.108 g, 2.5 mmol %). The solution was stirred at ambient temperature for 45 min. The reaction flask was protected from light by aluminum foil. Copper(I) iodide (0.106 g, 0.556 mmol, 15 mol %) was added to the mixture and stirring continued for 4 h. The mixture was diluted with Et_2O, washed with aqueous 10% NH_4Cl, dried ($MgSO_4$), and concentrated. Column chromatography (hex/EtOAc = 9/1) furnished **8** (2.14 g, 84%) as a yellow oil: ^{1}H NMR δ 7.28 (2 H, d, J = 8.4 Hz), 6.87 (2 H, d, J = 8.4 Hz), 6.13 (1 H, ddd, J = 16.0, 8.0, 7.0 Hz), 5.55 (1 H, d, J = 16 Hz), 4.66 (1 H, br s), 4.52 (1 H, d, J = 10.8 Hz), 4.40 (1 H, d, J = 10.8 Hz), 4.04−4.10 (1 H, m), 3.78 (3 H, s), 3.65 (2 H, t, J = 6.4 Hz), 2.31 (2 H, dd, J = 13.3, 6.4 Hz), 1.97 (1 H, ddd, J = 14.4, 9.8, 3.2 Hz), 1.82 (1 H, ddd, J = 14.4, 6.0, 3.2 Hz), 1.25

(3 H, d, J = 6.0 Hz), 0.89 (10 H (3 × CH_3 + OH), s), 0.05 (6 H, s); ^{13}C NMR δ 159.1, 141.0, 130.1, 129.4, 113.7, 110.9, 88.8, 83.2, 72.9, 70.3, 62.1, 60.9, 55.1, 43.2, 36.5, 25.8, 19.2, 18.2, −5.4. Anal. Calcd for $C_{24}H_{38}O_4Si$: C, 68.90; H, 9.09. Found: C, 68.84; H, 9.38.

(3*E*,5*E*,7*S*,9*R*)-1-*O*-(*tert*-Butyldimethylsilyl)-7-hydroxy-9-((4-methoxybenzyl)oxy)-3,5-decadien-1-ol. To a stirring solution of **8** (1.685 g, 4.03 mmol) in THF (2 mL) was added lithium aluminum hydride (1.0 M solution in Et_2O, 7.5 mmol) at 0 °C. After addition was complete, the ice bath was removed and the reaction mixture was stirred at ambient temperature for 2 h. The reaction mixture was cooled to 0 °C. To this mixture was slowly added Na_2SO_4·$10H_2O$ until the release of hydrogen gas ceased. The solid was filtered washing with methylene chloride, and the organic layer was concentrated. Column chromatography (hex/EtOAc = 9/1) afforded (*E*,*E*)-diene (1.56 g, 92%) as a pale yellow oil: ^{1}H NMR δ 7.26 (2 H, d, J = 8.7 Hz), 6.87 (2 H, d, J = 8.7 Hz), 6.12 (1 H, ddd, J = 15.0, 10.5, 0.9 Hz), 6.07 (1 H, dd, J = 15.0, 5.8 Hz), 4.54 (1 H, d, J = 11.1 Hz), 4.42 (1 H, br s), 4.35 (1 H, d, J = 11.1 Hz), 3.74−3.94 (4 H, s + m (merge)), 3.65 (2 H, t, J = 6.8 Hz), 2.98 (1 H, s), 2.30 (2 H, td, J = 13.1, 6.6 Hz), 1.54−1.87 (2 H, m), 1.24 (3 H, d, J = 6.2 Hz), 0.89 (9 H, s), 0.48 (6 H, s); ^{13}C NMR δ 159.2, 134.1, 131.3, 130.7, 130.3, 129.8, 129.4, 113.8, 72.3, 70.2, 69.4, 62.8, 55.2, 43.0, 36.3, 25.9, 19.3, 18.3, −5.3; LRMS (EI) m/z (relative intensity) M^+ 420, 363 (31), 121 (100). Anal. Calcd for $C_{24}H_{40}O_5Si$: C, 68.57; H, 9.52. Found: C, 68.35; H, 9.74.

(3*E*,5*E*,7*S*,9*R*)-1-*O*-(*tert*-Butyldimethylsilyl)-7-(methoxymethoxy)-9-((4-methoxybenzyl)oxy)-3,5-decadien-1-ol. To a stirring solution of (*E*,*E*)-diene (0.632 g, 1.5 mmol) in CH_2Cl_2 (8 mL) were added diisopropylethylamine (1.37 mL, 7.86 mmol) and methoxymethyl chloride (0.57 mL, 7.5 mmol) at 0 °C. After 1 h, the mixture was warmed to ambient temperature, and stirring continued for 8 h. The mixture was poured into NH_4Cl (saturated) and was extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and purified by column chromatography (hex/EtOAc = 20/1 to 18/1) to afford **2a** (0.681 g, 98%) as a pale yellow oil: ^{1}H NMR δ 7.29 (2 H, d, J = 8.7 Hz), 6.88 (2 H, d, J = 8.7 Hz), 6.18 (1 H, dd, J = 14.8, 10.5 Hz), 6.06 (1 H, dd, J = 14.8, 10.5 Hz), 5.67 (1 H, dd, J = 14.8, 7.1 Hz), 5.42 (1 H, dd, J = 14.8, 8.0 Hz), 4.70 (1 H, d, J = 6.7 Hz), 4.53 (1 H, d, J = 10.9 Hz), 4.49 (1 H, d, J = 6.7 Hz), 4.36 (1 H, d, J = 10.9 Hz), 4.26−4.33 (1 H, m), 3.73−3.87 (4 H, s + br), 3.65 (2 H, t, J = 6.7 Hz), 3.54 (3 H, s), 2.30 (2 H, dd, J = 13.4, 6.7 Hz), 1.67−1.76 (2 H, m), 1.22 (3 H, d, J = 6.1 Hz), 0.89 (9 H, s), 0.05 (6 H, s); ^{13}C NMR δ 159.0, 132.5, 131.4, 131.3, 131.2, 130.9, 129.1, 113.6, 93.8, 73.5, 71.4, 70.1, 62.6, 55.5, 55.1, 43.7, 36.2, 25.8, 19.9, 18.2, −5.3. Anal. Calcd for $C_{26}H_{44}O_5Si$: C, 67.24; H, 9.48. Found: C, 66.83; H, 9.74.

(5*E*,3*S*,4*S*,7*S*,9*R*)-1-*O*-(*tert*-Butyldimethylsilyl)-3,4-(isopropylidenedioxy)-7-(methoxymethoxy)-9-((4-methoxybenzyl)oxy)-5-decen-1-ol. To a stirring solution of **2a** (3.01 g, 6.49 mmol) in *t*-BuOH/H_2O (1:1 (v/v), 64 mL) was added AD-mix-α (Aldrich, 1.4 g/mmol **2a**, 9.08 g) and methanesulfonamide (1.23 g, 12.9 mmol) at 0 °C. This mixture was gradually warmed to ambient temperature and was stirred vigorously for 12 h. An additional amount of AD-mix-α (2.0 g) was added, and stirring continued for an additional 9 h until the starting material was consumed. To the yellow mixture was added Na_2SO_3 (3.27 g, 25.9 mmol), and vigorous stirring continued for 30 min. The mixture was poured into H_2O (20 mL) and was extracted with CH_2Cl_2. The aqueous layer was extracted with EtOAc. The combined organic extracts were dried ($MgSO_4$) and concentrated. The resulting oil was dissolved in CH_2Cl_2 (35 mL). To this solution were added 2,2-dimethoxypropane (24 mL, 0.195 mol) and PPTS (0.166 g, 10 mol %), and the mixture was stirred at rt overnight. After completion, the mixture was poured into $NaHCO_3$ (saturated), extracted (CH_2Cl_2), dried ($MgSO_4$), and concentrated. Column chromatography (hex/EtOAc = 20/1 to 12.5/1) provided **9a** (2.701 g, 77.4%) as a pale yellow oil: ^{1}H NMR δ 7.29 (2 H, d, J = 8.6 Hz), 6.88 (2 H, d, J = 8.6 Hz), 5.67 (2 H, m), 4.65 (1 H, d, J = 6.7 Hz), 4.53 (1 H, d, J = 10.7 Hz), 4.51 (1 H, d, J = 6.7 Hz), 4.23−4.45 (2 H, d + m, J = 10.7 Hz), 4.05 (1 H, dd, J = 8.6, 6.0 Hz), 3.69−3.91 (7 H, s + m), 3.35 (3 H, s), 1.54−1.87 (4 H, m), 1.40 (3 H, s), 1.38 (3 H, s), 1.22 (3 H, d, J = 6.1 Hz), 0.89 (9 H, s), 0.05 (6 H, s); ^{13}C NMR δ 159.0, 134.8, 131.0, 129.4, 129.2, 113.7, 108.5, 94.3, 81.5, 77.5, 73.1, 71.2, 70.1, 59.7, 55.6, 43.7, 34.8, 27.2, 26.8, 25.9, 19.9, 18.2, −5.4. Anal. Calcd for $C_{29}H_{50}O_7Si$: C, 64.68; H, 9.29. Found: C, 64.41; H, 9.48.

(5*E*,3*S*,4*S*,7*S*,9*R*)-3,4-(Isopropylidenedioxy)-7-(methoxymethoxy)-9-((4-methoxybenzyl)oxy)-5-decenal. To a stirring solution of **9a** (0.441 g, 0.82 mmol) was added TBAF (0.9 mmol, 1 M solution in THF) at rt. After being stirred for 3 h, the mixture was poured into H_2O, extracted (CH_2Cl_2), and dried ($MgSO_4$). Without further purification, this colorless oil was dissolved in DMSO (4 mL) and IBX (0.395 g, 1.49 mmol) was added. After being stirred at ambient temperature for 14−20 h, this turbid solution was poured into H_2O, extracted (Et_2O), and dried ($MgSO_4$). Column chromatography (hex/EtOAc = 10/1 to 5/1) afforded the aldehyde **12** (0.319 g, 92%, two steps) as a pale yellow to near-clear oil: ^{1}H NMR δ 9.78 (1 H, t, J = 2.0 Hz), 7.28 (2 H, d, J = 8.6 Hz), 6.87 (2 H, d, J = 8.6 Hz), 5.73 (1 H, dd, J = 6.5 Hz), 5.63 (1 H, dd, J = 15.5, 6.5 Hz), 4.62 (1 H, d, J = 6.7 Hz), 4.53 (1 H, d, J = 10.9 Hz), 4.50 (1 H, d, J = 6.7 Hz), 4.28−4.35 (2 H, d + m, J = 10.9 Hz), 3.99−4.20 (2 H, m), 3.67−3.89 (4 H, s + m), 3.41 (3 H, s), 2.50−2.70 (2 H, m), 1.55−1.82 (2 H, m), 1.41 (3 H, s), 1.40 (3 H, s), 1.21 (3 H, d, J = 6.1 Hz); ^{13}C NMR δ 199.5, 159.0, 136.5, 130.9, 129.2, 127.5, 113.7, 109.4, 94.6, 81.3, 75.4, 73.4, 71.1, 70.1, 55.6, 55.2, 45.1, 43.6, 27.0, 26.9, 19.9. Anal. Calcd for $C_{23}H_{34}O_7$: C, 65.40; H, 8.06. Found: C, 65.13; H, 8.34.

(5*E*,3*S*,4*S*,7*S*,9*R*)-9-Hydroxy-3,4-(isopropylidenedioxy)-7-(methoxymethoxy)-5-decenoic Acid. To a stirring solution of aldehyde **12** (0.277 g, 0.656 mmol) in *tert*-butyl alcohol (3.3 mL) and 2-methyl-2-butene (1.7 mL, 16.0 mmol) was added a solution of $NaClO_2$ (0.6 g, 6.63 mmol) and NaH_2PO_4·H_2O (0.725 g, 5.25 mmol) in H_2O (5 mL) dropwise at rt. This mixture was stirred at that temperature for 5 h. At the end of which time, the turbid solution was diluted with CH_2Cl_2. The organic layer was washed with H_2O and NaCl (saturated) and dried ($MgSO_4$) to give a clear oil. Without further purification, this oil was dissolved in CH_2Cl_2 (6 mL). To this mixture were added $NaHCO_3$ (0.138 g, 1.64 mmol) and DDQ (0.378 g, 1.67 mmol), sequentially, and the mixture was stirred at rt for 5 h. At the end of which time, this brown solution was directly applied on the top of the column for chromatography (hex/EtOAc = 1/1, 15% wet silica gel) furnishing a red oil. This oil was repurified by column chromatography using the same solvent system to supply hydroxy acid **1** (0.186 g, 89%, two steps) as a pale yellow to yellow oil: ^{1}H NMR δ 5.81 (1 H, dd, J = 15.5, 6.7 Hz), 5.68 (1 H, dd, J = 15.5, 6.7 Hz), 4.67 (1 H, d, J = 6.8 Hz), 4.60 (1 H, d, J = 6.8 Hz), 4.36 (1 H, dd, J = 11.9, 6.1 Hz), 3.96−4.2 (3 H, m), 2.69 (1 H, dd, J = 15.2, 6.7 Hz), 2.55 (1 H, dd, J = 15.2, 4.7 Hz), 1.69 (2 H, t, J = 5.8 Hz), 1.43 (3 H, s), 1.42 (3 H, s), 1.20 (3 H, d, J = 6.2 Hz); ^{13}C NMR δ 174.1, 135.1, 128.3, 109.3, 94.5, 81.0, 76.6, 74.2, 64.4, 55.6, 43.7, 36.7, 26.9, 26.8, 23.2; HRMS m/z for $C_{15}H_{26}O_7$ $(M + H)^+$ calcd 319.1757, found 319.1766.

(5*E*,3*S*,4*S*,7*S*,9*R*)-3,4-(Isopropylidenedioxy)-7-(methoxymethoxy)-9-methyl-5-nonene Lactone. To hydroxy acid **1** (50 mg, 0.157 mmol) was added 2,2′-dipyridyl disulfide (Aldrithol-2, 47 mg, 0.213 mmol) and Ph_3P (58 mg, 0.221 mmol). The mixture was dissolved in 10 mL of degassed benzene. The solution was stirred at rt for 3 h. At the end of time, the mixture was added to refluxing benzene (105 mL) containing $AgClO_4$ (0.168 g, 0.81 mmol) over 12 h via a syringe pump. After the first addition was complete, the residual was washed with another 8 mL of benzene that was then added to the refluxing reaction mixture over 4 h. The solution was refluxed for an additional 2 h after the second addition was completed. This mixture was cooled to room temperature and filtered through Celite. The solvent was concentrated, and the mixture was purified by flash column chromatography (hex/EtOAc = 10/1, 230−400 mesh silica gel) to afford an inseparable mixture of conformational isomers with *ca.* 7.25:5:1 ratio (15.4 mg, 33%) as a pale yellow semi-oil: ^{1}H NMR δ 5.69−5.94 (m), 5.53 (dd, J = 15.6, 9.3 Hz), 4.90−5.10 (septet + m), 4.69 (1 H, d, J = 6.7 Hz), 4.50 (1 H, d, J = 6.7 Hz), 3.40−4.30 (3 H, m), 3.33 and 3.35 (s, 3 H), 3.07 (dd, J = 14.8, 5.4 Hz), 2.99 (dd, J = 13.2, 5.4 Hz), 2.79 (dd, J = 11.5, 2.5 Hz), 2.42

(dd, J = 14.8, 10.7 Hz), 2.29 (dd, J = 13.2, 11.5 Hz), 2.09 (dd, J = 14.3, 5.7 Hz), 1.61−1.91 (2 H, m), 1.44 (3 H, s), 1.41 (3 H, s), 1.25 (3 H, d, J = 6.6 Hz).

Tuckolide. To a stirring solution of acetonide MOM-protected lactone (10 mg, 0.033 mmol) in MeOH (2 mL) was added Dowex-50 at rt. The mixture was stirred at that temperature for 4 days. At the end of this time, the resin was removed by filtration and washed with MeOH. The solvent was evaporated, and the residual material was chromatographed (hex/EtOAc = 1/1, 15% wet silica gel) to give tuckolide (4.2 mg, 58%) as a pale yellow to transparent solid: ^{1}H NMR δ 5.91 (1 H, dd, J = 15.8, 8.3 Hz), 5.85 (1 H, dd, J = 15.8, 2.4 Hz), 5.25 (1 H, ddq, J = 14.0, 6.4, 1.9 Hz), 4.54−4.78 (1 H, br s), 4.43 (1 H, dd, J = 3.7, 1.6 Hz), 4.20 (1 H, ddd, J = 11.0, 8.3, 4.0 Hz), 3.94−4.13 (1 H, brs), 2.61 (1 H, d, J = 14.4, 1.9 Hz), 2.40 (1 H, d, J = 14.4, 6.2 Hz), 1.92 (1 H, ddd, J = 14.0, 4.0, 1.9 Hz), 1.81 (1 H, d, J = 14.0, 11.0 Hz), 1.52−1.72 (2 × OH, br s), 1.25 (3 H, d, J = 6.4 Hz); ^{13}C NMR δ 174.9, 133.7, 129.9, 73.9, 72.5, 72.2, 68.2, 43.0, 33.2, 21.3 (lit. (CD_3OD) 174.7, 135.9, 129.4, 75.4, 73.6, 73.1, 69.4, 44.2, 35.6, 21.6); $[\alpha]_D$ = −67 (c 0.26, $CHCl_3$) [lit. $[\alpha]_D$ = −62 (c 0.4, $CHCl_3$)]; mp = 118−120 °C (lit. mp = 114−115 °C).

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Supporting Information Available: Proton and ^{13}C NMR spectra for hydroxy acid **1**, MOM acetonide tuckolide, and (−)-tuckolide (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.

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