Synthesis of 1,3-Diol Synthons from Epoxy Aromatic Precursors: An Approach to the Construction of Polyacetate-Derived Natural Products

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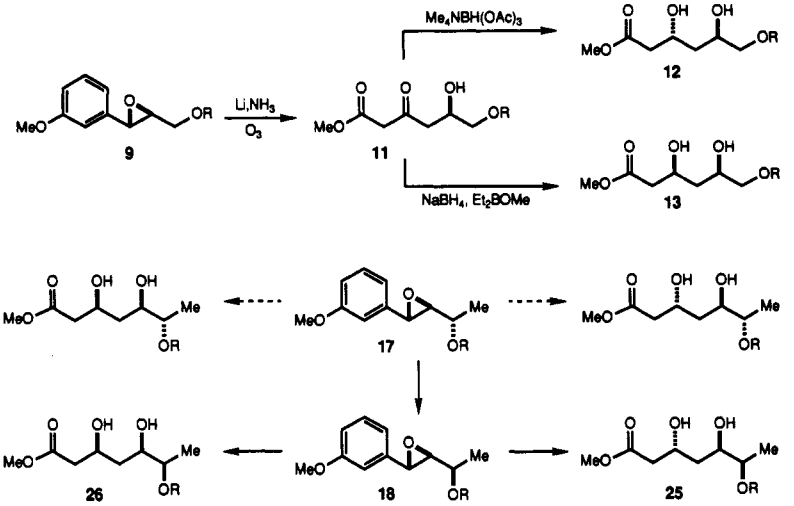
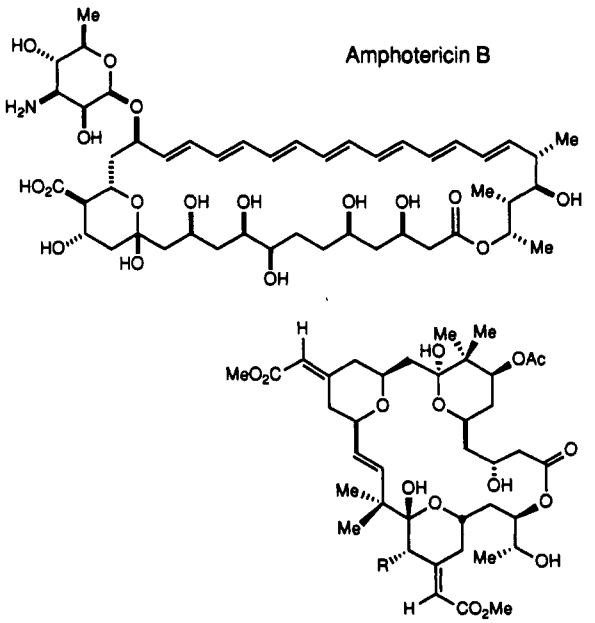
The identification of stereoregular polyol subunits within polyacetate-derived natural products such as bryostatin 1 and amphotericin B has led to the convergent synthesis of six- and seven-carbon 1,3-diol fragments in high yields and stereoselectivities. This plan relies upon the enantioselective asymmetric epoxidation/kinetic resolution of cinnamyl alcohols and the use of meta-substituted anisyl rings as masked β-keto ester synthons. Birch reduction



of **9** (R = Si^iPr_3) followed by ozonolysis afforded the hydroxyl keto ester **11** in 66% overall yield. Anti-selective β-selective β-hydroxy ketone reduction employing $Me_4NBH(OAc)_3$ afforded **12** in 93% yield and 13:1 diastereoselectivity while syn-selective reduction with $Et_2BOMe/NaBH_4$ gave **13** in 82% yield and 15:1 diastereoselectivity. An analogous sequence of reactions provided **25** and **26** from epoxy alcohol **18**. Epoxy aromatic alcohol **17** (R = H) was easily converted to **18** (93% yield, >99:1) by Mitsunobu inversion followed by methanolysis. This reaction sequence provides access to all stereoisomers of 3,5,6-trihydroxyhexanoic acid heptanoic acids which should be useful chiral subunits of polyacetate-derived natural products such as amphotericin and bryostatin.

The head-to-tail polymerization of acetate units is a general pathway in the biosynthesis of polyketides. This basic skeletal type with its subsequent secondary modifications is the source of a host of natural products including fatty acids, polyphenols, prostaglandins, and macrolides.[1,2] Members of this diverse class include the polyene macrolide antibiotics of current interest, amphotericin B[3] and bryostatin 1.[4]

These two representative natural products contain the familiar oxygenation pattern diagnostic of their biogenetic origin from acetate. Having recognized the *similarities* shared by the two structures in oxygenation pattern, we were intrigued by the *difference* in the stereochemical motif found in each family, wherein the polyene macrolides such as amphotericin contain a preponderance of recurring syn 1,3-diol relationships while the bryostatins contain the complementary anti 1,3-diol stereochemical pattern. On the basis of this observation we have attempted to develop a general approach to the asymmetric synthesis of chiral subunits which might be employed to assemble either



Bryostatin 1 R = $O_2C(CH)_4(CH_2)_2Me$ (1)
Bryostatin 11 R = H

family of natural products. The realization of this objective forms the basis of the present study.

Bryostatin. Bryostatin 1 (1) was isolated as a constituent of the sea-mat *Bugula neritina* in 1982, and its

(1) For a general discussion of polyacetate biosynthesis, see: Mann, J. *Secondary Metabolism*, 2nd ed; Clarendon: Oxford, 1980; Chapter 1.
(2) (a) Vederas, J. C. *Nat. Prod. Rep.* **1987**, *4*, 277–327. (b) Simpson, T. J. *Chem. Soc. Rev.* **1987**, *16*, 123–160. (c) Simpson, T. J. *Nat. Prod. Rep.* **1987**, *4*, 339–376. (d) Simpson, T. J. *Nat. Prod. Rep.* **1985**, *2*, 323–347.
(3) Vandeputte, J.; Watchtel, J. L.; Stiller, E. T. *Antibiot. Annu.* **1956**, 587.
(4) Pettit, G. R.; Herald, C. L.; Clardy, J.; Arnold, E.; Doubek, D. L.; Herald, D. L. *J. Am. Chem. Soc.* **1982**, *104*, 6846–6848.

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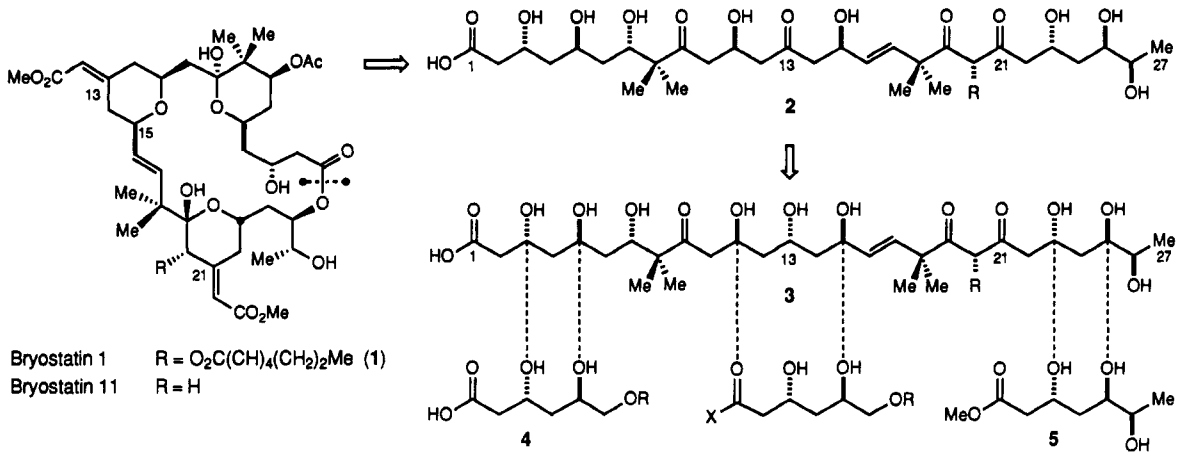
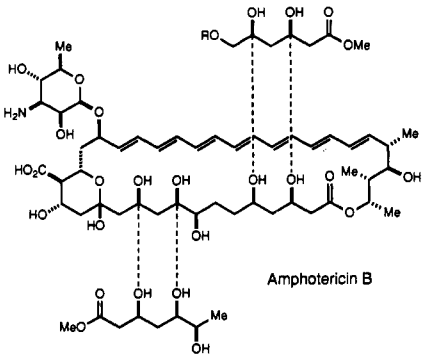
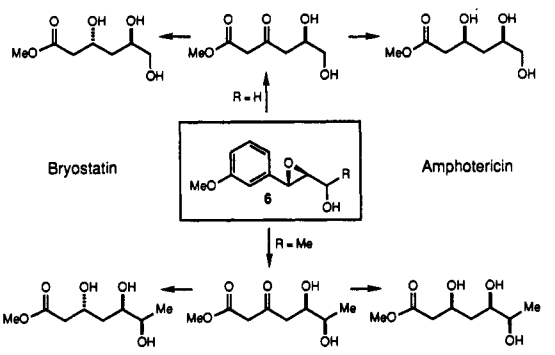
Scheme I



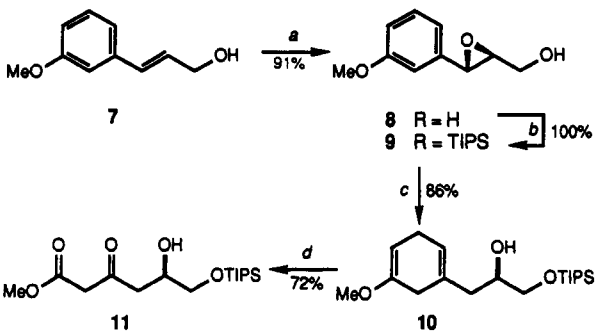
Scheme II



Scheme III



Scheme IV[a]



[a] (a) L-(+)DIPT, Ti(O*i*-Pr)$_4$, *t*-BuO$_2$H, 4-Å sieves; (b) TIPSCl, Im, DMAP, CH_2Cl_2, −20 °C; (c) Li, NH_3, THF, *t*-BuOH, −78 °C; (d) O_3, CH_2Cl_2, MeOH, py, −78 °C; Me_2S.

structure established by NMR spectroscopy and X-ray crystallography. Eleven congeners, bryostatins 2–7 and 9–13, have been isolated from the same species; and one, bryostatin 8, has been obtained from a closely related bryozoan, *Amathia convulata*.[5] These marine metabolites display a diverse range of biological properties including demonstrated activity against lymphocytic leukemia and carcinosarcoma.[6]

Recognition of the acetate-derived oxygenation pattern displayed on the bryostatin backbone is enhanced when plausible precursor fragments such as the seco acid **2** are evaluated (Scheme I). Replacement of the unsaturated esters at C_{13} and C_{21} in the bryostatin skeleton by ketones provides this fragment, in which the anti 1,3-diol stereochemical relationship may be amplified by further substitution of the same two ketone carbonyls with hydroxyl substituents, as illustrated in structure **3**.

Inspection of **3** reveals a recurring structural motif of six- or seven-carbon subunits. Thus, the same triol ester synthon can serve as the precursor to both the C_1–C_6 and C_{11}–C_{16} portions, while the C_{21}–C_{27} segment may be derived from the one-carbon homologue containing an additional stereogenic center.

Amphotericin. A similar analysis may be applied to the polyene macrolide antibiotics.[7] For example, dissection of amphotericin B reveals the related subunits with the complementary syn stereochemical relationship (Scheme II).

Polyol Synthons. An expedient approach to the synthesis of each of the polyol fragments required for amphotericin and bryostatin is illustrated below (Scheme III). This plan relies upon the enantiocelective Sharpless epoxidation of cinnamyl alcohols[8] and the use of meta-substituted anisyl rings as masked β-keto ester synthons.[9]

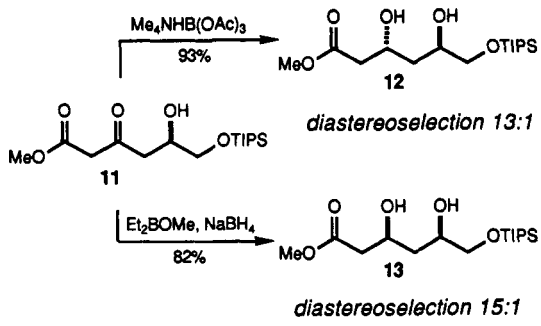
(5) (a) Bryostatin 2: Pettit, G. R.; Herald, C. L.; Kamano, Y.; Gust, D.; Aoyagi, R. *J. Nat. Prod.* **1983**, *46*, 528–531. (b) Bryostatin 3: Pettit, G. R.; Herald, C. L.; Kamano, Y. *J. Org. Chem.* **1983**, *48*, 5354–5356. (c) Bryostatin 4: Pettit, G. R.; Kamano, Y.; Herald, C. L.; Tozawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6768–6771. (d) Bryostatins 5–7: Pettit, G. R.; Kamano, Y.; Herald, C. L.; Tozawa, M. *Can. J. Chem.* **1985**, *63*, 1204–1208. (e) Bryostatin 8: Pettit, G. R.; Aoyagi, R.; Kamano, Y.; Herald, C. L.; Doubek, D. L.; Schmidt, J. M.; Rudloe, J. J. *Tetrahedron* **1985**, *41*, 985–994. (f) Bryostatin 9: Pettit, G. R.; Kamano, Y.; Herald, C. L. *J. Nat. Prod.* **1986**, *49*, 661–664. (g) Bryostatins 10 and 11: Pettit, G. R.; Kamano, Y.; Herald, C. L. *J. Org. Chem.* **1987**, *52*, 2848–2854. (h) Bryostatins 12 and 13: Pettit, G. R.; Leet, J. E.; Herald, C. L.; Kamano, Y.; Boettner, F. E.; Baczynskyj, L.; Nieman, R. A. *J. Org. Chem.* **1987**, *57*, 2854–2860.

(6) For a recent review on the isolation, characterization, and biological activity of the bryostatins, see: Pettit, G. R. *The Chemist* **1989**, 11–21.

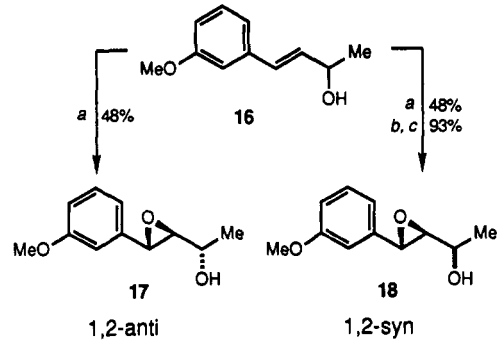
(7) *Macrolide Antibiotics*; Omura, S., Ed.; Academic Press: Orlando, FL, 1984; pp 520–521.

(8) Gao, R.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765–5780.

Scheme V



Scheme VI[a]



[a] (a) L-(+)-DIPT, Ti(O*i*-Pr)$_4$, *t*-BuOOH, 4-Å sieves, CH_2Cl_2, −20 °C, 3 h; (b) DEAD, PPh_3, PhCOOH, THF, 20 °C, 1 h; (c) K_2CO_3, MeOH, 20 °C, 6 h.

The inherent flexibility of this synthesis plan provides access to all stereoisomers of 3,5,6-trihydroxyhexanoic and heptanoic acids from epoxyaromatic alcohols **6** (R = H, R = Me). The absolute stereochemistry of the C_5 hydroxyl stereocenters in each synthon may be established in the epoxidation step, and in turn, the relative stereochemistry of the C_3 hydroxyl stereocenters may be established thereafter by the selection of the appropriate syn-[10] or anti-selective[11] β-hydroxy ketone reducing agent.

Results and Discussion

Synthesis of the Six-Carbon Triol Synthon. Preparation of the epoxyaromatic precursor was initiated with the reduction of methyl 3-methoxy-*trans*-cinnamate (DIBAL-H, toluene, −78 °C) to afford allylic alcohol **7** (Scheme IV).[12,13] Enantioselective epoxidation of **7** with the modified conditions of Sharpless provided epoxide **8** in 91% yield and 94% enantiomeric excess. The enantiomeric purity was assayed by ^{1}H NMR spectral analysis of the diastereomeric AB pair of the ABX doublet-of-doublets (δ 4.23 (major) and 4.08 (minor) ppm in C_6D_6) observed for the terminal methylene protons of the Mosher ester derivative.[14] Treatment of **8** with triisopropylsilyl chloride (Im, DMAP, CH_2Cl_2, −20 °C) afforded **9**, which was then subjected to dissolving metal-ammonia reduction (10 equiv of Li, NH_3, *tert*-butyl alcohol, −78 °C) to give dihydroanisole **10** in 86% yield. The ketoester functionality was then revealed by ozonolysis (CH_2Cl_2, MeOH, pyridine, Sudan Red dye III, −78 °C; Me_2S),[15] to provide hydroxy keto ester **11** (72%). When ozonolytic cleavage was performed on the unpurified Birch product, the overall yield was improved to 66% since the dihydroaromatic intermediate shows some tendency to undergo rearomatization during chromatographic purification. We have successfully executed this route on large scale to obtain 20-g quantities of **11** without difficulty.

Both anti (bryostatin) and syn (amphotericin) diol fragments are readily available from β-keto ester precursor **11**. The directed reduction of β-hydroxy ketones with $Me_4NBH(OAc)_3$ to afford anti 1,3-diols has been investigated in these laboratories and found to afford high levels of diastereoselection.[11a,16] The desired anti diols are typically more polar than their syn counterparts and are readily purified by chromatography on silica gel. Reduction of **11** with tetramethylammonium triacetoxyborohydride (8.0 equiv, $MeCN/MeCO_2H$, −40 °C, 16 h) provided diol **12** in 93% yield (Scheme V). The diastereoselectivity of this reduction (anti/syn, 13:1) was determined by conversion of the unpurified product mixture to the dibenzoate (PhCOCl, Et_3N, DMAP, CH_2Cl_2, 25 °C, 18 h) and integration of the ^{1}H NMR resonances of the corresponding methoxyl group for the diastereomeric anti (δ 4.64 ppm) and syn (δ 4.60) derivatives. Alternatively, reduction of **11** according to the procedure of Prasad and co-workers[10c] (Et_2BOMe, $NaBH_4$, −78 °C, CH_2Cl_2) afforded a 15:1 mixture of syn/anti diastereomers from which the syn diol **13** was isolated in 82% yield.

The stereochemical outcome of the syn- and anti-selective reductions was confirmed by conversion of diol esters **12** and **13** to their corresponding lactones **14** and **15**, respectively. Saponification of the individual methyl esters (1 N NaOH, aqueous MeOH) provided the derived diol–acids which, when heated at reflux in benzene, were dehydrated to lactones **14** and **15**.[17] The magnitude of the observed ^{1}H NMR vicinal coupling constants for both **14** and **15** fully support the structures proposed for the lactones. The large coupling of the C_5 axial methine proton to H_4 (J_{45} = 9.0 Hz) suggests that the siloxymethylene group is disposed equatorially in both heterocycles. As summarized below, the coupling constants J_{32} of lactone **14** (7.5 and 5.5 Hz) and of lactone **15** (4.5 and 4.0 Hz) are fully consistent with the data accumulated for similarly substituted lactones.[11a,16]

Synthesis of the Seven-Carbon Triol Synthon. Aldol condensation of *m*-anisaldehyde and acetone (NaOH,

(9) For other instances where such synthons have been employed, see: (a) Birch, A. J. *J. Chem. Soc.* **1944**, 430–436. (b) Birch, A. J.; Fitton, P.; Smith, C. C.; Steere, D. E.; Stelfox, A. R. *J. Am. Chem. Soc.* **1963**, *85*, 2209–2216. For an extension of this work, see: (c) White, J. D.; Kikermo, C. L. *J. Org. Chem.* **1985**, *50*, 1316–1319. (d) Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1986**, *27*, 3119–3122. (e) Bringmann, G. Künkel, G.; Geuder, T. *Synlett* **1990**, 253–255.

(10) For reductions of β-hydroxy ketones which afford syn diols, see: (a) Nakata, T.; Takao, S.; Fukui, M.; Tanaka, T.; Oishi, T. *Tetrahedron Lett.* **1983**, *24*, 3873–3876. (b) Narasaka, K. *Tetrahedron* **1984**, *40*, 2233–2238. (c) Chen, K.-M.; Hardtmann, G.; Prasad, K.; Repic, O.; Shapiro, M. J. *Tetrahedron Lett.* **1987**, *28*, 155–158. Kathawala, F. G.; Prager, B.; Repec, O.; Repic, O.; Shapiro, M. J.; Stabler, R. S.; Wilder, L. *Helv. Chim. Acta* **1986**, *69*, 803–805. (d) Kiyooka, S.; Kuroda, H.; Shimasaki, Y. *Tetrahedron Lett.* **1986**, *27*, 3009–3012. (e) Mori, Y.; Kuhara, M.; Takeuchi, A.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5419–4322.

(11) For reductions of β-hydroxy ketones which afford anti diols, see: (a) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560–3578. (b) Anwar, S.; Davis, A. P. *J. Chem. Soc., Chem. Commun.* **1986**, 831–832.

(12) The ester methyl 3-methoxy-*trans*-cinnamate was prepared by Fischer esterification of the commercially available 3-methoxycinnamic acid. See: Bhide, G. V. *Steroids* **1979**, 361–378.

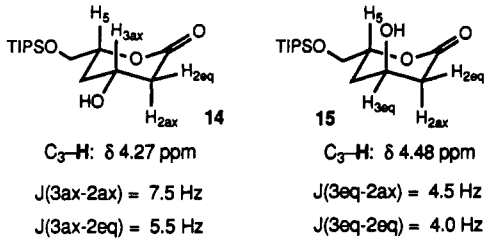
(13) Snyder, E. I. *J. Org. Chem.* **1967**, *32*, 3531–3534.

(14) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.

(15) For the use of dyes in ozonolysis, see: Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis* **1980**, 807–810.

(16) (a) Chapman, K. T., Ph.D. Dissertation, Harvard University, Cambridge, MA, 1987. (b) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. Am. Chem. Soc.* **1990**, *112*, 866–868.

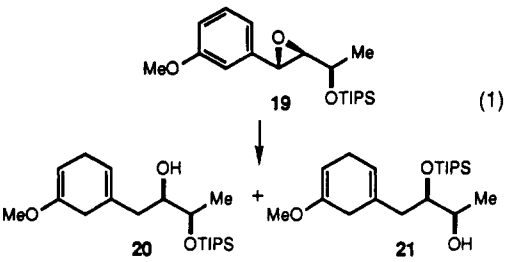
(17) Numerous conditions were screened for lactone formation (HF, MeCN; TsOH, CH_2Cl_2; DBU, CH_2Cl_2); the conditions we eventually selected are those reported previously. See: Lynch, J. E.; Volante, R. P.; Wattley, R. V.; Shinkai, I. *Tetrahedron Lett.* **1987**, *28*, 1385–1388.



water, 23 °C, 1 h), followed by ketone reduction with sodium borohydride/cerium trichloride,[18] afforded allylic alcohol **16** in 67% overall yield. Sharpless kinetic resolution (L-(+)-diisopropyl tartrate, $Ti(Oi\text{-}Pr)_4$, $t\text{-}BuO_2H$, CH_2Cl_2, −20 °C, 3 h) provided epoxy alcohol **17** (Scheme VI). In this transformation, reaction progress was monitored by capillary GLC and allowed to proceed to 49% conversion. The starting material and the epoxy alcohol exhibited similar chromatographic behavior on silica and complete separation of the unreacted allylic alcohol required multiple chromatographic resolutions. However, treatment of the unpurified mixture with ozone (CH_2Cl_2, −78 °C; Me_2S) led to consumption of the undesired olefin contaminant and greatly simplified the subsequent purification of the desired epoxy alcohol **17**, which was isolated as a crystalline solid (mp 69.1–70.1 °C) in 48% yield (theoretical: 50%). The diastereoselectivity in the epoxidation/kinetic resolution was assayed by capillary GLC and the enantioselectivity by ^1H NMR spectroscopy of the derived Mosher[14] esters. Integration of the resonances for the corresponding methyl doublets (major: δ 1.50 ppm; minor: δ 1.38 ppm) showed an enantioselectivity better than 95:5.

The diastereomeric syn epoxy alcohol **18** was prepared by Mitsunobu inversion of the secondary alcohol (DEAD, Ph_3P, $PhCO_2H$, THF, 20 °C) and saponification of the resulting benzoate ester (K_2CO_3, MeOH) in an overall yield of 93% for the two steps.[19] The facility with which this displacement process occurs suggests that the epoxide is exerting an activating effect analogous to that observed with cyclopropylcarbinyl substitution processes. Protection of **18** with triisopropylsilyl triflate (Et_3N, CH_2Cl_2, −60 °C) furnished **19** in 87% yield.

We next turned out attention toward the elaboration of **19** to the desired triol fragment. Birch reduction of **19** according to the procedure described earlier (Li, NH_3, *tert*-butyl alcohol, −78 °C) afforded a 2.5:1 mixture of products consisting of the desired dihydroanisole **20** along with **21**, the product of silyl group migration (eq 1). Some improvement in the product ratio was observed when the proton source was varied through the series MeOH, EtOH, *i*-PrOH (**20**:**21**, 3.4), and H_2O (**20**:**21**, 4.4); however, when water was employed, low conversion (40%) to the product



was observed. This might be attributed to reduction of the aromatic ring at a rate competitive with consumption of lithium by water. Alternate reducing metals such as Ca[20] and Yb[21] had no effect on the product ratio.[22]

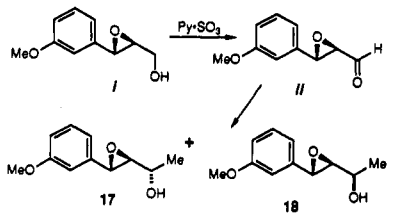
The solution to the problem of executing the Birch reduction/epoxide cleavage without attendant silyl group migration was to carry out the consecutive reductions under more controlled conditions. When the epoxide was reductively cleaved via hydrogenolysis and the Birch reduction was performed on the derived dialkylaluminum alkoxide, complications arising from silyl migration were completely suppressed (Scheme VII). Hydrogenolysis of **19** (5% $Pd/BaSO_4$, EtOH) afforded **22a** (97% yield), which was then converted to **22b** upon treatment with DIBAL-H. The solution of this aluminum alkoxide was transferred by cannula to the reagent mixture of lithium in ammonia (−78 °C) to provide dihydroanisole **23** in 80% overall yield. ^1H NMR spectroscopy revealed that no detectable silyl group migration takes place under these conditions. Thus, by proceeding through the intermediacy of the dialkylaluminate **22b** during the reduction sequence, the nucleophilicity of the alkoxide and its propensity to undergo silyl migration is attenuated. The unpurified dihydroanisole **23** was subsequently ozonolyzed (CH_2Cl_2, MeOH, pyridine, Sudan Red dye III, −78 °C; Me_2S) to give β-keto ester **24** in 70% yield.

The anti 1,3-diol stereochemical relationship in **25** was established by reduction of **24** with $Me_4NBH(OAc)_3$ (8.0 equiv. MeCN, $MeCO_2H$, −40 °C, 16 h) to afford a 9:1 mixture of anti/syn diols from which **25** was isolated in 82% yield (Scheme VIII). Moreover, treatment with $Et_2BOMe/NaBH_4$ (THF, −78 °C) provided the complementary syn diol in 82% yield after separation from the 12:1 mixture of syn/anti diastereomers. The observed diastereoselection for both transformations was determined by conversion of **25** and **26** to their corresponding dibenzoates (PhCOCl, Et_3N, DMAP, CH_2Cl_2, 25 °C, 18 h) followed by analysis by HPLC.[23]

We were gratified to find that it is possible to directly differentiate the two hydroxyl functions in **25** without resorting to an involved lactonization–derivatization sequence. Silylation of **25** with 1 equiv of chlorotriethylsilane afforded **27** in 77% yield (eq 2). Selective manipulation of the hydroxyl groups in **27** is crucial within the context of both bryostatin and amphotericin syntheses.

(18) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226–2227.

(19) We also pursued diastereoselective additions of methyl anion to ii. Under all conditions employed (MeMgBr, Et_2O, −78 °C; MeMgBr, hexane, CH_2Cl_2, −78 °C; MeMgBr, $ZnBr_2$, Et_2O, −78 °C; MeMgBr, Zn(OTf)$_2$, CH_2Cl_2, −78 °C; MeMgBr, MAD, toluene, −78 °C), at best a 3:1 ratio of 17:18 (desired) was obtained. Other reagents (CuI, MeMgBr, THF, DMS, −78 °C; $TiCl_4$, Me_2Zn, CH_2Cl_2, −78 °C) led to extensive decomposition of the starting material (ii).

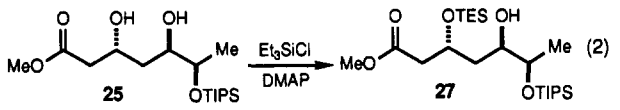


(20) Hwu, J. R.; Chua, V.; Schroeder, J. E.; Barrans, R. E.; Khoudary, K. P.; Wang, N.; Wetzel, J. M. *J. Org. Chem.* **1986**, *51*, 4731–4733.

(21) White, J. D.; Larson, G. L. *J. Org. Chem.* **1978**, *43*, 4555–4556.

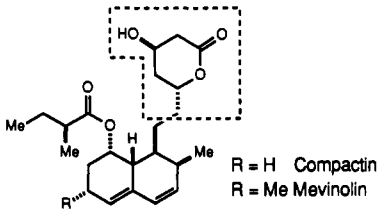
(22) Protecting groups other than triisopropylsilyl were also investigated; for example, the *tert*-butyldimethylsilyl ether gave a 2.7:1 ratio of the desired to rearranged product. In addition, protection as the methoxyethoxymethyl ether gave clean conversion to the desired dihydroanisole, but the protecting group did not survive the subsequent ozonolysis.

(23) Since our objectives include the use of these fragments for the assembly of bryostatin and amphotericin where a 1,2-syn stereorelationship is required, we only report here the synthesis of **25** and **26** from the common precursor **18**; the same sequence of reactions starting from **17** is expected to lead to the diastereomeric 1,2-anti diols in similar yields and selectivities.

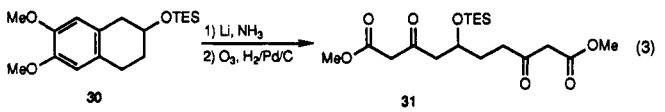


Applications to the Synthesis of Compactin and Its Analogues. The six-carbon synthon may be identified as a subunit in other natural products such as the mevinic acids compactin[24] and mevinolin.[25] These compounds have been found to possess activity against HMG-CoA reductase, the enzyme which regulates the rate-limiting step in cholesterol biosynthesis.[26] Identification of the β-hydroxy δ-lactone moiety as the key structural feature for inhibition has led to the development of analogues wherein the hexahydronaphthyl subunit is replaced with aromatic surrogates.[27]

Lactone **15**, prepared in connection with the structure proof of the diol reduction products (Scheme V) bears the required relative stereochemistry between the hydroxyl and (silyloxy) methylene substitutents; the protected hydroxy methylene may be suitably refunctionalized for preparation of hypocholesterolemic agents.



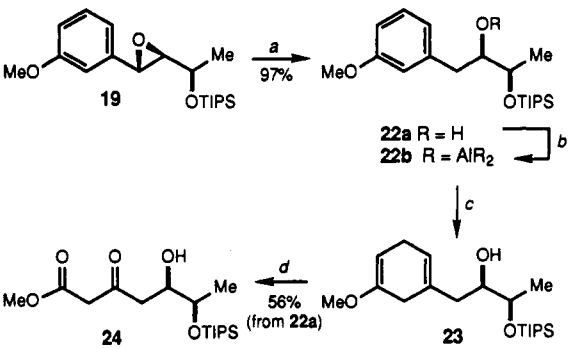
Additional Applications to the Preparation of Polyol Arrays. The methodology presented herein may also be employed in the synthesis of other more highly functionalized polyhydroxylated arrays. For example, two β-keto ester fragments may be concealed within a 6,7-dimethoxytetralone synthon (eq 3). In the reduction of this



transformation to practice, dissolving metal reduction of **30**[28] followed by ozonolysis of the dihydroaromatic intermediate cleanly afforded the acid-sensitive diketo diester **31** in 90% yield. Although **31** could be purified by chromatography (45% recovery), it was best to carry this compound through the subsequent sequence of reactions without purification due to its instability on silica gel.

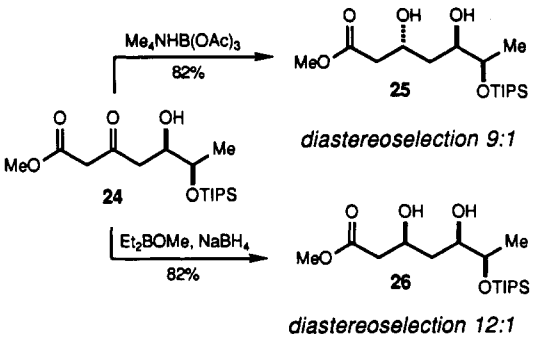
Hydrolysis of the triethylsilyl protecting group (HF·py, THF) provided **32** as an equilibrating mixture of ring–chain tautomers. Reduction of the unpurified hydroxy diketone **32** with $Me_4NBH(OAc)_3$ gave **33** as a tautomeric mixture, which upon exposure to mild acid (PPTS, CH_2Cl_2, 23 °C) afforded bicyclic ketal **34** as a single compound as determined by ^1H NMR spectroscopy. Analysis of the coupling constants of the carbinol proton at the newly generated stereocenter with the ring methylene protons is fully consistent with the structure illustrated.

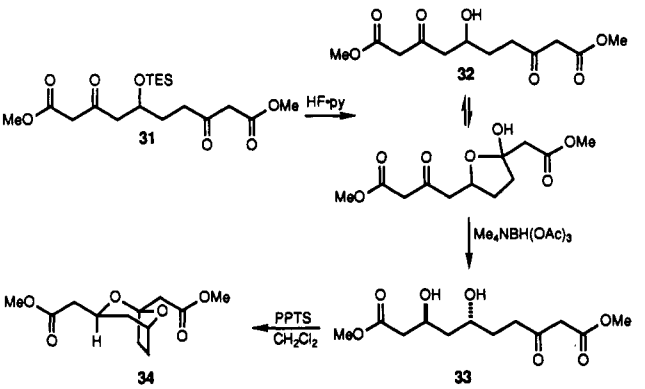
Scheme VII[a]



[a] (a) Pd/$BaSO_4$, H_2, EtOH; (b) DIBAL-H, THF, −78 °C; (c) Li, NH_3, *i*-PrOH, −78 °C, 4 h; (d) O_3, CH_2Cl_2, MeOH, py, −78 °C; Me_2S.

Scheme VIII





Conclusion

The convergent preparation of all the stereoisomers of 3,5,6-trihydroxyhexanoic and heptanoic acids has been described. The approach includes: (1) the epoxidation and kinetic resolution of 3-methoxycinnamyl alcohol and its one-carbon homologue, respectively; (2) the refunctionalization of the aromatic nucleus to a β-keto ester by the Birch reduction/ozonolysis sequence; and (3) the stereoselective reduction of β-hydroxy ketones to syn and anti diols. The resulting synthons are differentially protected at the oxygen functional groups and properly functionalized for use in the synthesis of reduced polyacetate-derived natural products.

Experimental Section

General Methods. All nonaqueous reactions were performed under an oxygen-free atmosphere of nitrogen with rigid exclusion

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(28) The racemic Birch/ozonolysis substrate (**30**) was obtained by reduction ($NaBH_4$, EtOH) of the commercially available 6,7-dimethoxy-2-tetralone (100%) followed by protection with triethylsilyl triflate (95%).

of moisture from reagents and glassware. Liquid chromatography was performed using a forced flow (flash chromatography)[29] of the indicated solvent system on EM Reagents silica gel 60 (230–400 mesh). Data are reported as follows: eluant composition and column diameter (cm) × column length (cm). Infrared spectra were recorded on a Perkin-Elmer 781 spectrophotometer and are reported in reciprocal centimeters (cm^{-1}). ^1H NMR spectra were recorded in deuteriochloroform on a Bruker AM-300, AM-400, or AM-500 spectrometer. Chemical shifts are reported in ppm on the δ scale from an internal standard of residual chloroform (7.26 ppm) or added tetramethylsilane (0.00 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet), integration, coupling constants in hertz, and assignment. ^{13}C NMR spectra were recorded in deuterochloroform on a Bruker AM-300, AM-400, or AM-500 spectrometer. Chemical shifts are reported in ppm from the central peak of deuteriochloroform (77.0 ppm) on the δ scale. In the case of keto–enol tautomerization, only the peaks corresponding to the keto form are reported. Optical rotations were determined with a JASCO DIP-181 digital polarimeter at 546 nm using a Hg lamp. Data are reported as follows: $[\alpha]_{546}$ (concentration g/100 mL, solvent). When necessary, solvents and reagents were dried prior to use. Tetrahydrofuran was distilled from sodium metal/benzophenone ketyl. Dichloromethane and triethylamine were distilled from calcium hydride. Benzene was distilled from sodium metal.

(*E*)-3-(3-Methoxyphenyl)-2-propen-1-ol (7). To a solution of 41.9 g (218 mmol) of methyl *m*-methoxycinnamate in 1 L of toluene at −78 °C was added 490 mL (490 mmol, 2.25 equiv) of a 1.0 M solution of diisobutylaluminum hydride (DIBAL-H) in toluene. The resulting solution was warmed to 0 °C, stirred for 1 h, and transferred to a suspension of 300 g of disodium tartrate in 500 mL of water. The mixture was stirred overnight at room temperature, and the two phases were separated. The aqueous layer was extracted with 3 × 200 mL of ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The oil obtained was distilled in vacuo to afford 34.7 g (97%) of the desired known alcohol:[12] bp 120 °C (1 Torr); R_f 0.16 (2:1 hexane/ethyl acetate); ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (t, 1 H, J = 7.8 Hz, Ar*H*), 6.97 (m, 2 H, Ar*H*), 6.80 (m, 1 H, Ar*H*), 6.59 (d, 1 H, J = 15.9 Hz, ArC*H*), 6.37 (dt, 1 H, J = 15.9, 5.5 Hz, ArCH=C*H*), 4.32 (d, 2 H, J = 5.5 Hz, CH_2OH), 3.81 (s, 3 H, OCH_3), 1.67 (s, 1 H, O*H*).

(2*S*,3*R*)-2,3-Epoxy-3-(3-methoxyphenyl)propan-1-ol (8). To a solution of 0.97 mL (4.6 mmol, 0.075 equiv) of L-(+)-diisopropyl tartarate in 570 mL of dichloromethane was added 3.30 g of 4-Å molecular sieves. The mixture was cooled to −30 °C and treated sequentially with 0.91 mL (3.1 mmol, 0.050 equiv) of titanium tetraisopropoxide and 41 mL (123 mmol, 2.0 equiv) of a 3.0 M solution of *tert*-butyl hydroperoxide in 2,2,4-trimethylpentane according to the procedure reported by Sharpless.[8] The mixture was stirred for 1 h at −30 °C before it was treated with a solution of 10.1 g (61.5 mmol) of *m*-methoxycinnamyl alcohol in 11.5 mL of dichloromethane. The suspension was stirred at −30 °C for 7 h and quenched at −30 °C with 3.5 mL of a 30% sodium hydroxide solution saturated with sodium chloride followed by 100 mL of ether. The mixture was stirred at −10 °C for 20 min, at which time 7.0 g of Celite and 1.0 g of anhydrous magnesium sulfate were added. The mixture was stirred overnight, filtered through a plug of Celite, and concentrated in vacuo to give a colorless oil. Purification by chromatography on silica gel (2:1:1 hexane/ethyl acetate/dichloromethane, 6 × 25 cm) afforded 10.1 g (91%) of the desired epoxide as a colorless oil: R_f 0.26 (2:1:1 hexane/ethyl acetate/dichloromethane); $[\alpha]_{546}$ −66.8° (*c* 0.820, CH_2Cl_2); IR (thin film) 3400, 3000, 2850, 2840, 1608, 1590, 1495, 1470, 1325, 1292, 1278, 1264, 1242, 1155, 1078, 1045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (t, 1 H, J = 7.9 Hz, ArH), 6.86 (m, 3 H, ArH), 4.07 (ddd, 1 H, J = 12.8, 5.2, 2.3 Hz, C*H*OH), 3.92 (d, 1 H, J = 2.1 Hz, C*H*CHCH$_2$OH), 3.81 (s, 3 H, CH_3), 3.80 (ddd, 1 H, J = 12.8, 7.9, 3.8 Hz, C*H*OH), 3.21 (ddd, 1 H, J = 3.8, 2.3, 2.1 Hz, C*H*CH$_2$OH), 1.84 (m, 1 H, O*H*); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 160.0, 138.4, 129.6, 118.2, 114.1, 110.9, 62.3, 61.3, 55.6, 55.3. Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.46; H, 6.84.

A small portion of the above epoxyalcohol was converted to the corresponding Mosher ester[14] ((+)-Mosher acid chloride, Et_3N, CH_2Cl_2, room temperature, 1 h). Integration of the peaks at 4.08 and 4.23 ppm, each of which correspond to one of the protons of the AB system, gave a 97:3 ratio of diastereoisomers.

(2*S*,3*R*)-2,3-Epoxy-3-(3-methoxyphenyl)-1-[(triisopropylsilyl)oxy]propane (9). To a solution of 0.630 g (3.50 mmol) of epoxy alcohol 8 in 50 mL of dichloromethane were added 0.536 g (7.88 mmol, 2.25 equiv) of imidazole, 1.24 mL (7.35 mmol, 2.10 equiv) of chlorotriisopropylsilane, and several crystals of 4-(*N*,*N*-dimethylamino)pyridine. After stirring overnight at room temperature, the reaction was poured into 25 mL of 0.25 M aqueous potassium hydrogen sulfate solution. The aqueous layer was extracted with 3 × 15 mL of dichloromethane. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (10:1 hexane/ethyl acetate, 6 × 25 cm) gave 1.182 g (100%) of a colorless oil: R_f 0.35 (9:1 hexane/ether); $[\alpha]_{546}$ −44.1° (*c* 0.870, CH_2Cl_2); IR (thin film) 2950, 2900, 2875, 1620, 1590, 1495, 1470, 1385, 1370, 1325, 1290, 1275, 1260, 1240, 1155, 1140, 1110, 1075, 1050, 1018, 1000 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (t, 1 H, J = 7.8 Hz, Ar*H*), 6.86 (m, 3 H, Ar*H*), 4.03 (dd, 1 H, J = 11.8, 3.1 Hz, C*H*OTIPS), 3.90 (dd, 1 H, J = 11.8, 4.2 Hz, C*H*OTIPS), 3.83 (d, 1 H, J = 2.0 Hz, C*H*CHCH$_2$OTIPS), 3.80 (s, 3 H, OCH_3), 3.15 (ddd, 1 H, J = 4.2, 3.1, 2.0 Hz, C*H*CH$_2$OTIPS), 1.90 (m, 21 H, Si[C*H*(C*H*$_3$)$_2$]$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.9, 139.1, 129.4, 118.2, 113.9, 110.7, 63.2, 62.8, 55.8, 55.2, 17.9, 12.0. Anal. Calcd for $C_{19}H_{32}O_3Si$: C, 67.81; H, 9.58. Found: C, 67.89; H, 9.70.

(*R*)-Methyl 5-Hydroxy-3-oxo-6-[(triisopropylsilyl)oxy]hexanoate (11). To a solution of 0.694 g (100.0 mmol, 10.0 equiv) of lithium in 50 mL of ammonia at −78 °C was added a solution of 3.39 g (10.0 mmol) of epoxysilyl ether **9** in 5 mL of THF. The mixture was stirred at −33 °C for 45 min, cooled to −78 °C, and treated with 5 mL of *tert*-butyl alcohol. The blue solution was stirred for 1 h and treated sequentially with 15 mL of *tert*-butyl alcohol, 6 mL of benzene, and 8.5 g of solid ammonium acetate. The ammonia was allowed to evaporate through a bubbler, and the residue was partitioned between 150 mL of brine and 300 mL or ethyl acetate. The aqueous layer was extracted with 3 × 200 mL of ethyl acetate, and the combined organic layers were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to afford a colorless oil. The product was carried on to the next step without purification.

To a solution of dihydroanisole **10** in 25 mL of dichloromethane and 5 mL of methanol was added 0.5 mL of pyridine and a small amount of Sudan III red. The pink solution was treated with a dilute stream of ozone in oxygen at −78 °C until it turned light yellow, at which point 15 mL of dimethyl sulfide was added. The mixture was stirred at room temperature for 12 h. The reaction was partitioned between 100 mL of brine and 100 mL of ethyl acetate, and the aqueous layer was extracted with 3 × 100 mL of ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (3:1 hexane/ethyl acetate, 6 × 25 cm) gave 2.2 g (66%) of the keto ester as a colorless oil: R_f 0.50 (1:1 hexane/ethyl acetate); $[\alpha]_{546}$ +17.3° (*c* 0.780, CH_2Cl_2); IR (thin film) 3550, 2945, 2880, 1755, 1722, 1658, 1648, 1468, 1442, 1410, 1388, 1370, 1325, 1250, 1125, 1070, 1018, 1000 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.15 (m, 1 H, C*H*OH), 3.73 (s, 3 H, CH_3O), 3.71 (dd, 1 H, J = 9.7, 4.8 Hz, C*H*OTIPS), 3.62 (dd, 1 H, J = 9.7, 6.3 Hz, C*H*OTIPS), 3.54 (s, 2 H, CH_2COOCH_3), 2.74 (d, 2 H, J = 6.2 Hz, CH_2CHOH), 1.06 (m, 21 H, Si[C*H*(C*H*$_3$)$_2$]$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 201.9, 167.3, 68.3, 66.6, 52.2, 49.7, 46.2, 17.9, 12.0. Anal. Calcd for $C_{16}H_{32}O_5Si$: C, 57.79; H, 9.70. Found: C, 58.02; H, 9.86.

(3*R*,5*R*)-Methyl 3,5-Dihydroxy-6-[(triisopropylsilyl)oxy]hexanoate (12). To a solution of 1.27 g (4.8 mmol, 8.0 equiv) of tetramethylammonium triacetoxyborohydride[11a] in 3 mL of acetonitrile was added 3 mL of anhydrous acetic acid. The mixture was stirred at room temperature for 30 min, cooled to −40 °C, and treated with a solution of 200 mg (0.6 mmol) of hydroxy keto ester 11 in 1 mL of acetonitrile. The reaction was stirred at −40 °C for 16 h before it was quenched with 4 mL of

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1 N aqueous disodium tartrate solution and 4 mL of acetone. The mixture was allowed to warm to room temperature over 10 min, the acetone was removed in vacuo, and the residue was poured into 10 mL of saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with 3 × 10 mL of dichloromethane. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (2:1 hexane/ethyl acetate, 3 × 25 cm) afforded 186 mg (93%) of a colorless oil: R_f 0.40 (1:1 hexane/ethyl acetate); $[\alpha]_{546}$ −4.6° (*c* 0.87, CH_2Cl_2); IR (thin film) 3450, 2950, 2870, 1738, 1460, 1440, 1385, 1368, 1250, 1203, 1165, 1126, 1071, 1018, 1000 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.35 (m, 1 H, C*H*OHCH$_2$COOCH$_3$), 3.97 (m, 1 H, C*H*OHCH$_2$OTIPS), 3.71 (s, 3 H, CH$_3$O), 3.72 (dd, 1 H, *J* = 9.97, 4.0 Hz, C*H*OTIPS), 3.56 (dd, 1 H, *J* = 9.7, 7.5 Hz, C*H*OTIPS), 3.38 (d, 1 H, *J* = 4.2 Hz, O*H*), 2.82 (d, 1 H, *J* = 3.4 Hz, O*H*), 2.54 (m, 2 H, CH$_2$COOCH$_3$), 1.61 (m, 2 H, CHOHCH$_2$CHOH), 1.06 (m, 21 H, Si[CH(CH$_3$)$_2$]$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.9, 69.3, 67.5, 65.5, 51.6, 41.6, 38.8, 17.9, 11.9. Anal. Calcd for $C_{16}H_{34}O_5Si$: C, 57.45; H, 10.24. Found: C, 57.38; H, 10.36.

A small portion of the above diol was converted to the corresponding dibenzoate (PhCOCl, Et_3N, DMAP, CH_2Cl_2, room temperature, 18 h). Integration of the ^1H NMR signals at 4.64 (anti) and 4.60 (syn) ppm gave a 13:1 ratio of diastereomers.

(3*S*,5*R*)-Methyl 3,5-Dihydroxy-6-[(triisopropylsilyl)oxy]hexanoate (13). To a cooled solution (−78 °C) of 100 mg (0.30 mmol) of hydroxy keto ester **11** in 2.5 mL of THF and 0.5 mL of methanol was added 33 mg (0.33 mmol, 1.1 equiv) of diethylmethoxyborane.[30] The reaction mixture was stirred at −78 °C for 15 min, and then 13 mg (0.33 mmol, 1.1 equiv) of sodium borohydride was added in one portion. The mixture was stirred at −78 °C for 5 h before it was quenched at −78 °C by the addition of 0.3 mL of acetic acid. The mixture was poured into 10 mL of saturated aqueous sodium bicarbonate solution and extracted with 3 × 10 mL of ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was taken up in 10 mL of methanol and the solvent removed in vacuo. This procedure was repeated 10 times. The oil obtained was purified by chromatography on silica gel (2:1 hexane/ethyl acetate, 2.5 × 25 cm) to afford 82 mg (82%) of a colorless oil: R_f 0.41 (1:1 hexane/ethyl acetate); $[\alpha]_{546}$ +6.6° (*c* 0.65, CH_2Cl_2); IR (thin film) 3450, 2950, 2875, 1745, 1467, 1463, 1388, 1371, 1255, 1205, 1163, 1125, 1070, 1018, 1000 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.32 (m, 1 H, C*H*OHCH$_2$COOCH$_3$), 3.95 (m, 1 H, C*H*OHCH$_2$OTIPS), 3.71 (s, 3 H, CH$_3$O), 3.66 (dd, 1 H, *J* = 9.8, 4.4 Hz, C*H*OTIPS), 2.56 (dd, 1 H, *J* = 9.8, 7.0 Hz, C*H*OTIPS), 2.57 (dd, 1 H, *J* = 16.0, 7.7 Hz, C*H*COOCH$_3$), 2.49 (dd, 1 H, *J* = 16.0, 5.1 Hz, C*H*COOCH$_3$), 1.67 (dt, 1 H, *J* = 14.3, 3.3 Hz, CHOHC*H*CHOH), 1.57 (dd, 1 H, *J* = 14.3, 9.3 Hz, CHOHC*H*CHOH), 1.06 (m, 21 H, Si[CH(CH$_3$)$_2$]$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.6, 72.0, 68.0, 67.3, 51.6, 41.6, 38.8, 17.9, 11.9. Anal. Calcd for $C_{16}H_{34}O_5Si$: C, 57.45; H, 10.24. Found: C, 57.49; H, 10.30.

A small portion of the above diol was converted to the corresponding dibenzoate (PhCOCl, Et_3N, DMAP, CH_2Cl_2, room temperature, 18 h). Integration of the ^1H NMR signals at 4.60 (syn) and 4.64 (anti) ppm gave a 15:1 ratio of diastereomers.

(4*R*,6*S*)-4-Hydroxy-6-[[(triisopropylsilyl)oxy]methyl]-2*H*-tetrahydropyran-2-one (14). Lactone formation was performed according to the procedure reported.[17] To a solution of 354 mg (1.05 mmol) of diol **12** in 5 mL of methanol was added 1.5 mL of 1 N aqueous sodium hydroxide solution. After being stirred at room temperature for 1 h, the solution was acidified to pH 3 by addition of 1 N hydrochloric acid and then diluted with 10 mL of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford a colorless oil.

The unpurified acid was dissolved in 10 mL of benzene, and the solution heated at 80 °C for 8 h. The reaction was concentrated in vacuo, and the product was purified by chromatography on silica gel (2:1 hexane/ethyl acetate, 20 × 3 cm) to afford 230 mg (72%) of lactone **14** as a colorless oil: R_f 0.20 (1:1 hexane/ethyl acetate); $[\alpha]_{546}$ −13.2° (*c* 0.900, CH_2Cl_2); IR (thin film) 3450, 2950, 2900, 2880, 1740, 1468, 1388, 1360, 1250, 1160, 1140, 1115, 1080, 1018, 1000 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.41 (m, 1 H, C*H*CH$_2$OTIPS), 4.27 (m, 1 H, C*H*OH), 3.93 (dd, 1 H, *J* = 17.5, 10.5 Hz, C*H*OTIPS), 3.88 (dd, 1 H, *J* = 17.5, 10.6 Hz, C*H*OTIPS), 2.89 (ddd, 1 H, *J* = 17.4, 5.5, 1.5 Hz, CH$_{eq}$C=O), 2.53 (dd, 1 H, *J* = 17.4, 7.5 Hz, CH$_{ax}$C=O), 2.37 (dtd, 1 H, *J* = 13.7, 4.6, 1.5 Hz, CH$_{eq}$CHCH$_2$OTIPS), 1.87 (dt, 1 H, *J* = 13.7, 9.0 Hz, CH$_{ax}$CHCH$_2$OTIPS), 1.08 (m, 21 H, Si[CH(CH$_3$)$_2$]$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.9, 77.3, 65.4, 63.6, 39.6, 34.0, 17.9, 11.9. Anal. Calcd for $C_{15}H_{30}O_4Si$: C, 59.55; H, 10.00. Found: C, 59.57; H, 10.10.

(4*S*,6*S*)-4-Hydroxy-6-[[(triisopropylsilyl)oxy]methyl]-2*H*-tetrahydropyran-2-one (15). Lactone formation was performed according to the procedure reported.[17] To a solution of 354 mg (1.05 mmol) of diol **13** in 5 mL of methanol was added 1.5 mL of 1 N aqueous sodium hydroxide solution. After stirring at room temperature for 1 h, the solution was acidified to pH 3 by addition of 1 N hydrochloric acid and then diluted with 10 mL of ethyl acetate. The aqueous layer was extracted with 3 × 10 mL of ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford a colorless oil.

The unpurified acid was dissolved in 10 mL of benzene, and the solution was heated at 80 °C for 8 h. The reaction was concentrated in vacuo, and the product purified by chromatography on silica gel (2:1 hexane/ethyl acetate, 20 × 3 cm) to afford 230 mg (72%) of lactone **15** as a colorless oil: R_f 0.26 (1:1 hexane/ethyl acetate); $[\alpha]_{546}$ +2.0° (*c* 0.53, HC_2Cl_2); IR (thin film) 3450, 2950, 2880, 1750, 1720, 1470, 1395, 1372, 1350, 1258, 1142, 1079, 1061, 1018, 1000 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.74 (m, 1 H, C*H*CH$_2$OTIPS), 4.48 (m, 1 H, C*H*OH), 3.93 (dd, 1 H, *J* = 10.7, 4.8 Hz, C*H*OTIPS), 3.85 (dd, 1 H, *J* = 10.7, 3.5 Hz, C*H*OTIPS), 2.72 (dd, 1 H, *J* = 17.7, 4.5 Hz, CH$_{eq}$C=O), 2.61 (dd, 1 H, *J* = 17.7, 4.0 Hz, CH$_{ax}$C=O), 2.03 (m, 2 H, CH$_2$CHCH$_2$OTIPS), 1.07 (m, 21 H, Si[CH(CH$_3$)$_2$]$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.7, 76.1, 65.3, 62.9, 38.9, 32.3, 17.9, 12.0. Anal. Calcd for $C_{15}H_{30}O_4Si$: C, 59.55; H, 10.00. Found: C, 59.45; H, 10.04.

(*E*)-4-(3-Methoxyphenyl)-3-buten-2-one. To a solution of 102 g (0.749 mol) of *m*-anisaldehyde in 600 mL of acetone was added in one portion a solution of 50 g (1.0 mol, 1.4 equiv) of sodium hydroxide in 600 mL of H_2O, and the resulting mixture was stirred at room temperature for 1 h. The reaction was diluted with 1 L of ether, and the layers were separated. The organic layer was washed with brine, dried over sodium sulfate, and concentrated in vacuo. The oil obtained was distilled in vacuo to afford 90.6 g (70%) of the desired known ketone[31] as a light yellow liquid: bp 110–115 °C (0.030 Torr); R_f 0.42 (3:2 hexane/ethyl acetate); IR (thin film) 3010, 2960, 2840, 1690, 1640, 1610, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.48 (d, 1 H, *J* = 16.2 Hz, C*H*=CHCOCH$_3$), 7.45–7.26 (m, 1 H, Ar*H*), 7.14–7.12 (m, 1 H, Ar*H*), 7.05 (m, 1 H, Ar*H*), 6.97–6.93 (m, 1 H, Ar*H*), 6.70 (d, 1 H, *J* = 16.2 Hz, CH=C*H*COCH$_3$), 3.83 (s, 3 H, OCH$_3$), 2.38 (s, 3 H, COCH$_3$).

(*E*)-1-(3-Methoxyphenyl)-1-buten-3-ol (16). To a solution of 10.0 g (56.8 mmol) of the precursor ketone in 100 mL of methanol at −78 °C was added 23.3 g (62.5 mmol, 1.1 equiv) of cerium(III) chloride heptahydrate.[18] After 5 min, 2.36 g (62.5 mmol, 1.1 equiv) of sodium borohydride was added in one portion. The resulting mixture was stirred at −78 °C for 15 min and then allowed to slowly warm to room temperature, at which temperature it was stirred for 30 min before it was quenched by slow addition of 50 mL of water. The resulting mixture was diluted with 200 mL of ether, and the layers were separated. The organic layer was washed with 50 mL of water followed by 50 mL of brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The resulting oil was purified by chromatography (3:2 hexane/ethyl acetate) to afford 9.55 g (96%) of the desired alcohol as a colorless liquid: R_f 0.39 (1:1 hexane/ethyl acetate); IR (thin film) 3380, 2980, 1600, 1580, 1270, 1155, 1050, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23–6.78 (m, 4 H, Ar*H*), 6,54 (d, 1 H, *J* = 15.9 Hz, ArC*H*), 6.26 (dd, 1 H, *J* = 15.9, 6.3 Hz, ArCH=C*H*), 4.53–4.45

(30) Prepared according to Köster, R.; Fenzl, W.; Siedel, G. *Liebigs Ann. Chem.* **1975**, 352–372.

(31) Hamdi, S. T.; Jones, J. R.; Rumney, T. G. *J. Chem. Soc., Perkin Trans. 2* **1976**, 846–848.

(m, 1 H, CHOH), 3.82 (s, 3 H, OCH_3), 1.37 (d, 3 H, J = 6.4 Hz, $CH(OH)CH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.9, 138.2, 133.9, 129.5, 129.2, 119.1, 113.3, 111.8, 68.8, 55.2, 23.4. Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.12; H, 7.92. Found: C, 74.09; H, 7.99.

(2*R*,3*S*,4*R*)-3,4-Epoxy-4-(3-methoxyphenyl)-2-butanol (17). To a solution of 9.55 g (53.6 mmol) of alcohol **16** and 1.70 mL (8.04 mmol, 0.15 equiv) of D-(+)-diisopropyl tartrate in 214 mL of dichloromethane was added 2.1 mL of tridecane as internal standard for GLC analysis. The solution was cooled to −20 °C, and 1.60 mL (5.36 mmol, 0.10 equiv) of freshly distilled titanium tetraisopropoxide was added. The clear solution was stirred at −20 °C for 30 min, and an aliquot was quenched for capillary GLC analysis. After an additional 5 min of stirring at −20 °C, 12.5 mL (37.5 mmol, 0.70 equiv) of a 3.0 M solution of *tert*-butyl hydroperoxide in 2,2,4-trimethylpentane was added over 10 min. The resulting mixture was stirred at −20 °C for 3 h, after which time GLC analysis (30 m DB-1, 100 °C, 15 psi, t_R(starting material) 13.22 min, t_R(product) 15.40 min) showed 49% consumption of starting material. The reaction mixture was quenched with 50 mL of water and warmed to room temperature. After the mixture was stirred for 45 min, 50 mL of aqueous 2 N sodium hydroxide solution was added. The reaction mixture was then stirred at room temperature for 1 h and filtered through Celite. The layers were separated, and the aqueous layer was washed with 3 × 100 mL of dichloromethane. The combined organic layers were dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was dissolved in 125 mL of dichloromethane and 159 mL of methanol and Sudan III (ca. 5 mg) was added. The clear solution was cooled to −78 °C and treated with a dilute stream of ozone in oxygen. When the pink color turned to yellow, 50 mL of dimethyl sulfide was added in one portion. The reaction was then warmed to room temperature and stirred for 2 h. The mixture was concentrated under reduced pressure, and the residue was purified by chromatography (7:3 hexane/ethyl acetate) to afford 4.95 g (48%) of the desired epoxide as a white solid: mp 69.1–70.1 °C; R_f 0.23 (60:40 hexane/ethyl acetate); $[\alpha]_D$ −40.4° (*c* 1.21, CH_2Cl_2); IR (thin film) 3580, 2980, 1610, 1495, 1275, 1260, 1240, 1160, 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 1 H, ArH), 6.85 (m, 3 H, ArH), 4.08 (m, 1 H, CHOH), 3.94 (d, 1 H, J = 2.0 Hz, ArCH), 3.80 (s, 3 H, OCH_3), 3.06 (dd, 1 H, J = 2.8, 2.3 Hz, $CH_3CH(OH)CHO$), 2.41 (s, 1 H, OH), 1.31 (d, 3 H, J = 6.5 Hz, CH_3CHOH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.8, 138.6, 129.5, 118.1, 113.9, 110.8, 65.5, 65.0, 55.1, 54.7, 18.7. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 68.08; H, 7.32.

(2*S*,3*S*,4*R*)-3,4-Epoxy-4-(3-methoxyphenyl)-2-butanol (18). To a solution of 315 mg (1.60 mmol) of epoxy alcohol **17** and 1.36 g (5.20 mmol, 3.20 equiv) of triphenylphosphine in 15 mL of THF at 0 °C was added a solution of 990 mg (8.1 mmol, 5.0 equiv) of benzoic acid in 15 mL of benzene. After 5 min, 900 μL (5.70 mmol, 3.50 equiv) of diethyl azodicarboxylate was added, and the reaction mixture stirred at room temperature for 1 h. The solvents were evaporated in vacuo, and the residue was purified by chromatography on silica gel (4:1 hexane/ethyl acetate, 3 × 28 cm): IR (thin film) 3000, 1790, 1720, 1600, 1450, 1270, 1210, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.12 (dd, 2 H, J = 8.4, 1.4 Hz, ArH), 7.58 (dq, 1 H, J = 8.4, 1.4 Hz, ArH), 7.49 (dt, 2 H, J = 8.4, 1.4 Hz, ArH), 7.29 (t, 1 H, J = 7.9 Hz, ArH), 6.88 (m, 3 H, ArH), 5.24 (m, 1 H, CHOBz), 3.88 (d, 1 H, J = 2.0 Hz, CHCHCHOBz), 3.83 (s, 3 H, OCH_3), 3.28 (dd, 1 H, J = 5.5, 2.0 Hz, CHCHOBz) 1.52 (d, 3 H, J = 6.6 Hz, CH_3CHOBz).

To a solution of the resulting epoxybenzoate in 40 mL of methanol was added 743 mg (5.40 mmol, 3.40 equiv) of anhydrous potassium carbonate, and the suspension was stirred at room temperature for 6 h. The solvent was evaporated under reduced pressure, and the residue was purified by chromatography on silica gel (2:1 hexane/ether)[32] to afford 293 mg (93%) of the desired epoxy alcohol as a colorless oil: R_f 0.31 (7:3 hexane/ethyl acetate); $[\alpha]_{546}$ −41.9° (*c* 0.84, CH_2Cl_2); IR (thin film) 3420, 2980, 2940, 2840, 1625, 1608, 1592, 1497, 1465, 1440, 1375, 1322, 1195, 1155, 1110, 1050 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (t, 1 H, J = 7.9 Hz, ArH), 6.85 (m, 3 H, ArH), 3.85 (d, 1 H, J = 2.1 Hz, CHCHCHOH), 3.83 (m, 1 H, CHOH), 3.80 (s, 3 H, CH_3), 3.03 (dd, 1 H, J = 4.7, 2.1 Hz, CHCHOH), 1.36 (d, 3 H, J = 6.5 Hz, CH_3CHOH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.9, 138.4, 129.5, 118.1, 114.1, 110.8, 67.2, 66.2, 56.4, 55.2, 19.9. Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 68.28; H, 7.37.

(2*S*,3*S*,4*R*)-3,4-Epoxy-4-(3-methoxyphenyl)-2-[(triisopropylsilyl)oxy]butane (19). To a solution of 13.5 g (69.5 mmol) of epoxy alcohol **18** and 19.4 mL (139 mmol, 2.0 equiv) of triethylamine in 200 mL of methylene chloride at −60 °C was added 22.4 mL (83.4 mmol, 1.2 equiv) of triisopropylsilyl trifluoromethanesulfonate. After being stirred at this temperature for 6 h, the reaction mixture was poured into 100 mL of 0.25 M aqueous potassium hydrogen sulfate solution. The aqueous layer was extracted with 3 × 100 mL of ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (98:2 hexane/ethyl acetate, 12 × 24 cm) gave 21.3 g (87%) of **19** as a colorless oil: R_f 0.46 (9:1 hexane/ethyl acetate); $[\alpha]_{546}$ −17.4° (*c* 1.08, CH_2Cl_2); IR (thin film) 2950, 2900, 2870, 1605, 1590, 1495, 1465, 1385, 1375, 1320, 1290, 1275, 1260, 1240, 1160, 1120, 1095, 1065, 1050, 1000 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (t, 1 H, J = 7.9 Hz, ArH), 6.86 (m, 3 H, ArH), 3.87 (quint, 1 H, J = 6.3 Hz, CHOTIPS), 3.80 (s, 3 H, OCH_3), 3.73 (d, 1 H, J = 2.1 Hz, CHCHCHOTIPS), 3.03 (dd, 1 H, J = 5.7, 2.1 Hz, CHCHOTIPS), 1.31 (d, 3 H, J = 6.3 Hz, $CH_3CHOTIPS$), 1.10 (m, 21 H, $Si[CH(CH_3)_2]_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.9, 139.0, 129.4, 118.0, 113.7, 110.6, 69.4, 67.0, 55.9, 55.1, 20.6, 18.0, 12.3. Anal. Calcd for $C_{20}H_{34}O_3Si$: C, 68.52; H, 9.78. Found: C, 68.50; H, 9.80.

(2*S*,3*R*)-4-(3-Methoxyphenyl)-2-[(triisopropylsilyl)oxy]-3-butanol (22a). To a solution of 18.4 g (52.4 mmol) of epoxide **19** in 150 mL of absolute ethanol was added 0.92 g of 5% palladium on barium sulfate. The reaction mixture was degassed, flushed with hydrogen, and stirred under a hydrogen atmosphere for 9 h. The black suspension was filtered through Celite, and the filtrate was concentrated in vacuo. The residue was purified by chromatography on silica gel (9:1 hexane/ethyl acetate, 12 × 23 cm) to afford 17.94 g (97%) of a colorless oil: R_f 0.31 (9:1 hexane/ethyl acetate); $[\alpha]_{546}$ +12.1° (*c* 0.86, CH_2Cl_2); IR (thin film) 3550, 2950, 2900, 2870, 1605, 1588, 1492, 1465, 1440, 1385, 1255, 1168, 1155, 1140, 1100, 1060, 1000 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22 (t, 1 H, J = 7.9 Hz, ArH), 6.80 (m, 3 H, ArH), 3.93 (quint, 1 H, J = 6.1 Hz, CHOH), 3.80 (s, 3 H, OCH_3), 3.65 (m, 1 H, CHOTIPS), 2.97 (dd, 1 H, J = 13.8, 3.3 Hz, CHCHOH), 2.64 (dd, 1 H, J = 13.8, 8.9 Hz, CHCHOH), 2.43 (d, 1 H, J = 4.7 Hz, OH), 1.25 (d, 3 H, J = 6.2 Hz, $CH_3CHOTIPS$), 1.09 (m, 21 H, $Si[CH(CH_3)_2]_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.6, 140.7, 129.3, 121.6, 114.9, 111.6, 76.8, 71.2, 55.1, 39.2, 19.7, 18.2, 18.1, 12.6. Anal. Calcd for $C_{20}H_{36}O_3Si$: C, 68.13; H, 10.29. Found: C, 68.28; H, 10.39.

(5*R*,6*S*)-Methyl 5-Hydroxy-3-oxo-6-[(triisopropylsilyl)oxy]heptanoate (24). To a solution of 6.01 g (17.0 mmol) of alcohol **22a** in 40 mL of THF at −78 °C was added 20.4 mL (20.4 mmol, 1.20 equiv) of a 1 M solution of diisobutylaluminumhydride in hexane. The resulting clear solution was stirred at 0 °C for 15 min, cooled to −78 °C, and added over 15 min to a dark blue solution of 2.36 g (340 mmol, 20.0 equiv) of lithium in 100 mL of liquid ammonia at −78 °C. After 10 min at −78 °C, 10 mL of 2-propanol was added. The reaction mixture was sirred at −78 °C for 4 h and treated sequentially with 20 mL of benzene and 10 g of solid ammonium acetate. The ammonia was allowed to evaporate through a bubbler, and the residue was partitioned between 100 mL of saturated aqueous ammonium chloride solution and 100 mL of ethyl acetate. The aqueous layer was extracted with 3 × 200 mL of ethyl acetate, and the combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated in vacuo. The residue was diluted with 100 mL of ethyl acetate and stirred with 100 mL of a 1 M sodium potassium tartrate solution for 15 min. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated in vacuo to afford a colorless oil. The product was carried on to the next step without purification.

To a solution of dihydroanisole **20** in 70 mL of dichloromethane and 30 mL of methanol was added 1 mL of pyridine and a small amount of Sudan III red. The pink solution was treated with a dilute stream of ozone in oxygen at −78 °C until it turned light yellow, at which point 50 mL of dimethyl sulfide was added. The

(32) If ethyl acetate is used in place of ether, 30% of the desired alcohol is converted to the corresponding acetate.

mixture was stirred at room temperature for 12 h and concentrated in vacuo. Purification of the residue by chromatography (4:1 hexane/ethyl acetate, 6 × 30 cm) gave 3.31 g (56%) of a colorless oil: R_f 0.48 (7:3 hexane/ethyl acetate); $[\alpha]_{546}$ +22.8° (*c* 0.870, CH_2Cl_2); IR (thin film) 3500, 2950, 2900, 2870, 1755, 1710, 1660, 1635, 1465, 1440, 1410, 1388, 1320, 1250, 1140, 1100, 1070, 1015 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) shows a 7:1 mixture of keto and enol forms δ 5.09 (s, 1 H, C*H*$COOCH_3$, enol), 3.94 (m, 2 H, C*H*OH, C*H*OTIPS), 3.73 (s, 3 H, OCH_3, keto), 3.72 (s, 3 H, OCH_3, enol), 2.77 (m, 3 H, CH_2CHOH, O*H*, keto), 2.46 (dd, 1 H, *J* = 14.2, 3.4 Hz, C*H*CHOH, enol), 2.27 (dd, 1 H, *J* = 14.2, 9.6 Hz, C*H*CHOH, enol), 1.21 (d, 3 H, *J* = 6.2 Hz, CH_3CHOTIPS, enol), 1.18 (d, 3 H, *J* = 6.1 Hz, CH_3CHOTIPS, keto), 1.06 (m, 21 H, Si[C*H*$(CH_3)_2]_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.7, 167.4, 90.5, 73.1, 71.6, 70.9, 70.5, 52.2, 51.0, 49.7, 45.2, 38.6, 19.3, 18.8, 18.1, 18.0, 12.4. Anal. Calcd for $C_{17}H_{34}O_5Si$: C, 58.92; H, 9.89. Found: C, 58.86; H, 9.89.

(3*R*,5*R*,6*S*)-Methyl 3,5-Dihydroxy-6-[(triisopropylsilyl)oxy]heptanoate (25). To a solution of 1.05 g (4.0 mmol, 8.0 equiv) of tetramethylammonium triacetoxyborohydride[11a] in 2 mL of acetonitrile was added 2.4 mL of anhydrous acetic acid. The mixture was stirred at room temperature for 30 min, cooled to −40 °C, and treated with a solution of 173 mg (0.60 mmol) of hydroxy keto ester **24** in 1 mL of acetonitrile. The reaction was stirred at −40 °C for 16 h before it was quenched with 4 mL of 1 N aqueous disodium tartrate solution and 4 mL of acetone. The mixture was allowed to warm slowly to room temperature, the acetone was removed in vacuo, and the residue was poured into 10 mL of saturated aqueous sodium bicarbonate solution. The aqueous layer was extracted with 3 × 10 mL of dichloromethane. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (2:1 hexane/ethyl acetate, 3 × 25 cm) afforded 143 mg (82%) of a colorless oil: R_f 0.15 (7:3 hexane/ethyl acetate); $[\alpha]_D$ −60.9° (*c* 0.790, CH_2Cl_2): IR (thin film) 3450, 2950, 2870, 1740, 1465, 1440, 1385, 1300, 1255, 1200, 1150, 1105, 1075, 1012, 1000 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.31 (m, 1 H, C*H*OHCH_2COOCH_3), 3.82 (quint, 1 H, *J* = 5.9 Hz, C*H*OTIPS), 3.68 (s, 3 H, CH_3O), 3.66 (m, 1 H, C*H*OHCHOTIPS), 2.52 (m, 2 H, CH_2COOCH_3), 1.60 (m, 2 H, CHOHC*H*$_2$CHOH), 1.17 (d, 3 H, *J* = 6.1 Hz, CH_3CHOTIPS), 1.05 (m, 21 H, Si[C*H*$(CH_3)_2]_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.9, 73.1, 72.1, 65.6, 51.6, 41.4, 38.7, 19.7, 18.1, 18.0, 12.6. Anal. Calcd for $C_{17}H_{36}O_5Si$: C, 58.58; H, 10.41. Found: C, 58.64; H, 10.55.

A small portion of the unpurified product was converted to the corresponding dibenzoate (PhCOCl, ET_3N, DMAP, CH_2Cl_2, room temperature, 18 h) an the anti/syn ratio was found to be 9:1 by HPLC (4.6 mm × 25 cm Dupont Zorbax, 5 μm silica gel, 92:8 hexane/ ethyl acetate, 254 nm, 2.0 mL/min).

(3*S*,5*R*,6*S*)-Methyl 3,5-Dihydroxy-6-[(triisopropylsilyl)oxy]heptanoate (26). To a solution of 173 mg (0.500 mmol) of keto ester **24** in 4.8 mL of THF and 1.2 mL of methanol at −78 °C was added 55 mg (0.55 mmol, 1.1 equiv) of diethylmethoxyborane.[30] After 15 min, the solution was treated with 21 mg (0.55 mmol, 1.1 equiv) of sodium borohydride. The resulting suspension was stirred at −78 °C for 7 h, after which the reaction was quenched with 0.5 mL of acetic acid at −78 °C. The mixture was partitioned between 15 mL of brine and 15 mL of ethyl acetate, and the aqueous layer was extracted with 3 × 15 mL of ethyl acetate. The combined organic layers were washed with 10 mL of saturated aqueous sodium bicarbonate solution followed by 10 mL of brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. The residue was taken up in 10 mL of methanol, and the solvent was removed in vacuo. This procedure was repeated 10 times. The final oil obtained was purified by chromatography on silica gel (3:1 hexane/acetate, 3 × 24 cm) to give 144 mg (82%) of a colorless oil: R_f 0.63 (1:1 hexane/ethyl acetate); $[\alpha]_{546}$ +5.6° (*c* 0.90, CH_2Cl_2); IR (thin film) 3450, 2950, 2900, 2870, 1745, 1470, 1440, 1385, 1255, 1205, 1155, 1110, 1090, 1070, 1018, 1002 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.28 (m, 1 H, C*H*OHCH$_2$COOMe), 3.94 (d, 1 H, *J* = 1.4 Hz, O*H*), 3.84 (quint, 1 H, *J* = 6.0 Hz, C*H*OTIPS), 3.69 (s, 3 H, OCH_3), 3.66 (m, 1 H, C*H*OHCHOTIPS), 3.22 (d, 1 H, *J* = 3.0 Hz, O*H*), 2.53 (dd, 1 H, *J* = 16.0, 7.4 Hz, C*H*COOMe), 2.47 (dd, 1 H, *J* = 16.0, 5.3 Hz, C*H*COOMe), 1.68 (dt, 1 H, *J* = 14.1, 2.6 Hz, C*H*CHOHCHOTIPS), 1.54 (td, 1 H, *J* = 14.1, 9.7 Hz, C*H*CHOHCHOTIPS), 1.15 (d, 3 H, *J* = 6.2 Hz, CH_3CHOTIPS), 1.05 (m, 21 H, Si[C*H*$(CH_3)_2]_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 172.6, 76.1, 71.5, 68.5, 51.7, 41.7, 37.7, 19.1, 18.1, 18.0, 12.5. Anal. Calcd for $C_{17}H_{36}O_5Si$: C, 58.58; H, 10.41. Found: C, 58.79; H, 10.61.

A small portion of the unpurified product was converted to the corresponding dibenzoate (PhCOCl, Et_3N, DMAP, CH_2Cl_2, room temperature, 18 h), and the syn/anti ratio was found to be 12:1 by HPLC (4.6 mm × 25 DuPont Zorbax, 5 μm silica gel, 92:8 hexane/ethyl acetate, 254 nm, 2.0 mL/ min).

(3*R*,5*R*,6*R*)-Methyl 3-[(Triethylsilyl)oxy]-5-hydroxy-6-[(triisopropylsilyl)oxy]heptanoate (27). To a solution of 2.15 g (6.17 mmol) of diol **25** in 25 mL of dichloromethane at 0 °C was added 0.830 g (6.79 mmol, 1.10 equiv) of 4-(*N*,*N*-dimethylamino)pyridine followed by 1.09 mL (6.48 mmol, 1.05 equiv) of chlorotriethylsilane. The resulting clear solution was stirred at 0 °C for 15 min, and the reaction was quenched with 5 mL of saturated aqueous sodium bicarbonate solution. The mixture was diluted with 125 mL of ether, and the organic layer was washed with saturated aqueous sodium bicarbonate, brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (1:9 ethyl acetate/hexane, 4 × 20 cm) gave 2.20 g (77%) of a colorless oil: R_f 0.40 (1:4 ethyl acetate/hexane); $[\alpha]_D$ +3.82° (*c* 0.785, CH_2Cl_2); IR (thin film) 2960, 2870, 1750, 1460, 1380, 1240, 1150, 1080, 1005, 870, 750, 675 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.48–4.40 (m, 1 H, C*H*OTES), 3.86–3.78 (m, 1 H, C*H*OTIPS), 3.65 (s, 3 H, OCH_3), 3.60 (m, 1 H, C*H*OH), 2.81 (d, 1 H, *J* = 4.2 Hz, O*H*), 2.57–2.55 (m, 2 H, $H_3COOCCH_2$), 1.65–1.60 (m, 2 H, TESOCHC*H*$_2$CHOH), 1.17 (d, 3 H, *J* = 6.1 Hz, CHC*H*$_3$), 1.05 (m, 21 H, Si[C*H*$(CH_3)_2]_3$), 0.95 (t, 9 H, *J* = 8.0 Hz, OSi$(CH_2CH_3)_3$), 0.61, (q, 6 H, *J* = 7.9 Hz, OSi$(CH_2CH_3)_3$; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 171.8, 72.4, 71.8, 67.6, 51.4, 42.9, 39.7, 19.4, 18.1, 12.6, 6.7, 4.8. Anal. Calcd for $C_{23}H_{50}O_5Si_2$: C, 59.69; H, 10.88. Found: C, 59.80; H, 11.05.

6,7-Dimethoxy-2-tetralol. To a solution of 494 mg (2.40 mmol) of 6,7-dimethoxy-2-tetralone in 25 mL of absolute ethanol was added 181 mg (4.80 mmol, 2.00 equiv) of sodium borohydride. The reaction mixture was stirred at room temperature for 15 min and treated with 6 mL of 1 N aqueous hydrochloric acid solution. The solution was partitioned between 50 mL of water and 50 mL of ether, and the aqueous layer was extracted with 3 × 50 mL of ether. The combined organic layers were washed twice with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (1:1 hexane/ethyl acetate, 3 × 20 cm) gave 499 mg (100%) of white crystals: mp 98–99 °C; R_f 0.58 (3.7 hexane/ethyl acetate); IR ($CHCl_3$) 3610, 3020, 2950, 1615, 1520, 1465, 1445, 1355, 1330, 1250, 1115, 1040, 1020 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.59 (s, 1 H, ArC*H*), 6.56 (s, 1 H, ArC*H*), 4.14 (m, 1 H, C*H*OH), 3.84 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 3.00 (dd, *J* = 15.9, 4.8 Hz, 1 H, ArC*H*$_2$CHOH), 2.88 (dt, *J* = 16.7, 5.9 Hz, 1 H, ArC*H*$_2$CH$_2$), 2.77 (ddd, *J* = 16.7, 8.4, 6.4 Hz, 1 H, ArC*H*$_2$CH$_2$), 2.69 (dd, *J* = 15.9, 7.7 Hz, 1 H, ArC*H*$_2$CHOH), 2.02 (m, 1 H, ArCH$_2$C*H*$_2$), 1.81 (m, 1 H, ArCH$_2$C*H*$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 147.4, 127.4, 125.9, 112.2, 111.5, 67.3, 55.9, 55.9, 38.0, 31.5, 26.6. Anal. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74. Found: C, 69.09; H, 7.68.

6,7-Dimethoxy-2-[(triethylsilyl)oxy]tetralin (30). To a solution of 100 mg (0.48 mmol) of 6,7-dimethoxy-2-tetralol in 5 mL of dichloromethane at −78 °C was added 112 μL (0.96 mmol, 2.0 equiv) of 2,6-lutidine, followed by 130 μL (0.58 mmol, 1.2 equiv) of triethylsilyl trifluoromethanesulfonate. The reaction mixture was stirred at −78 °C for 5 min, warmed to room temperature, and then partitioned between 25 mL of 0.25 M aqueous potassium dihydrogenphosphate solution and 25 mL of ether. The layers were separated, and the aqueous layer was extracted with 3 × 25 mL of ether. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (9:1 hexane/ethyl acetate, 1 × 23 cm) gave 148 mg (95%) of a colorless oil: R_f 0.68 (7:3 hexane/ethyl acetate); IR (thin film) 2960, 2920, 2880, 1615, 1525, 1465, 1415, 1355, 1335, 1265, 1250, 1230, 1210, 1115, 1095, 1070, 1020 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.57 (s, 1 H, ArC*H*), 6.55 (s, 1 H, ArC*H*), 4.04 (m, 1 H, C*H*OTES), 3.84 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 2.87 (dd, *J* = 16.0, 5.2 Hz, 1 H, ArC*H*$_2$CHOTES), 2.79 (m, 2 H, ArC*H*$_2$CH$_2$), 2.70 (dd, *J* = 16.0, 8.8 Hz, 1 H, ArC*H*$_2$CHOTES), 1.97 (m, 1 H, ArCH$_2$C*H*$_2$), 1.76 (m, 1 H, ArCH$_2$C*H*$_2$), 0.97 (m, 9 H, Si(CH(C-

$H_2CH_3)_3$), 0.64 (m, 6 H, $Si(CH_2CH_3)_3$; ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1, 127.6, 126.8, 111.9, 111.2, 68.1, 55.9, 38.8, 32.6, 27.6, 6.9, 4.9. Anal. Calcd for $C_{18}H_{30}O_3Si$: C, 67.03; H, 9.38. Found: C, 67.11; H, 9.45.

Dimethyl 3,8-Dioxo-5-[(triethylsilyl)oxy]decanedioate (31). A solution of 22 mg (3.2 mmol, 10 equiv) of lithium in 10 mL of ammonia at −33 °C was stirred for 15 min, cooled to −78 °C, and treated with a solution of 104 mg (0.32 mmol) of silyl ether **30** in 2 mL of THF and 2 mL of *tert*-butyl alcohol. The reaction mixture was stirred at −78 °C for 15 min and quenched with 2 g of ammonium acetate. The ammonia was evaporated through a bubbler, and the residue was partitioned between 25 mL of distilled water and 25 mL of 3:1 hexane/dichloromethane. The aqueous layer was extracted with 3 × 25 mL of 3:1 hexane/dichloromethane, and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to afford a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 3.84 (m, 1 H, C*H*OTES), 3.50 (s, 3 H, OCH_3), 3.48 (s, 3 H, OCH_3), 2.61 (m, 4 H, $MeOCCH_2$), 2.06–1.55 (m, 6 H, CH_2CHOTES, CH_2CH_2CHOTES, CH_2CH_2CHOTES), 1.03 (t, J = 7.9 Hz, 9 H, $Si(CH_2CH_3)_3$, 0.61 (q, J = 7.9 Hz, 6 H, $Si(CH_2CH_3)_3$). The product was carried on to the next step without purification.

A solution of the dihydroanisole in 20 mL of ethyl acetate at −78 °C was treated with a dilute stream of ozone in oxygen. When the solution turned light blue, it was flushed with oxygen until the blue color disappeared. The reaction mixture was warmed to room temperature and hydrogenated for 3 h over 10 mg (10% in weight) of 10% palladium on carbon. The reaction mixture was then filtered through Celite, and the solvent was removed in vacuo. Purification by chromatography on silica gel (7:3 hexane/ethyl acetate, 2 × 18 cm) gave 56 mg (45%) of a colorless oil: R_f 0.38 (7:3 hexane/ethyl acetate); IR (thin film) 2955, 2915, 2880, 1750, 1720, 1655, 1630, 1440, 1435, 1410, 1375, 1355, 1325, 1240, 1200, 1150, 1080, 1010 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.22 (quint, J = 5.8 Hz, 1 H, C*H*OTES), 3.72 (m, 6 H, 2 OCH_3), 3.46 (m, 4 H, 2 CH_2COOMe), 2.71 (dd, J = 16.2, 6.3 Hz, 1 H, C(O)CH_2CHOTES), 2.60 (m, 3 H, C(O)CH_2OTES, C(O)CH_2CH_2), 1.78 (m, 2 H, CH_2CH_2CHOTES), 0.92 (m, 9 H, $Si(CH_2CH_3)_3$), 0.58 (m, 6 H, $Si(CH_2CH_3)_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.7, 195.8, 167.2, 167.1, 66.9, 52.05, 52.01,49.9, 49.7, 48.7, 38.0, 30.3, 6.5, 4.5. Anal. Calcd for $C_{18}H_{32}O_7Si$: C, 55.64, H, 8.30. Found: C, 55.74; H, 8.24.

To 75 mg (0.19 mmol) of silyl ether **31** was added 5 mL of 0.4 M pyridinium hydrogen fluoride solution in THF and pyridine, and the resulting solution was stirred at room temperature for 1 h. The reaction mixture was then partitioned between 25 mL of saturated aqueous sodium bicarbonate solution and 25 mL of ethyl acetate, and the aqueous layer was extracted with 3 × 25 mL of ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 5.07 (s), 5.02 (s), 4.78 (d), 4.78 (quint), 4.52 (d), 4.46 (m), 4.06 (m), 3.74 (m), 3.74 (m), 3.51 (m), 3.01 (dd), 2.85–2.61 (m), 2.40–2.27 (m), 2.24–2.03 (m), 1.95–1.52 (m). The product was carried on to the next step without purification.

A solution of 500 mg (1.90 mmol, 10.0 equiv) of tetramethylammonium triacetoxyborohydride in 1 mL of acetonitrile was treated with 1 mL of acetic acid, stirred at room temperature for 1 h, and cooled to −40 °C. A solution of unpurified **32** in 1 mL of acetonitrile was then added, and the reaction mixture was stirred at −40 °C for 16 h. The reaction was quenched with 1 mL of acetone and 1 mL of 1 N aqueous disodium tartrate. The mixture was partitioned between 25 mL of saturated aqueous sodium bicarbonate solution and 25 mL of ethyl acetate, and the aqueous layer was extracted with 3 × 25 mL of ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give a colorless oil: R_f 0.46 (ethyl acetate); ^1H NMR (300 MHz, $CDCl_3$) δ 4.73–4.01 (m), 3.73 (m), 3.51 (m), 3.36–3.17 (m), 2.83–2.41 (m), 2.30–1.50 (m). The product was carried on to the next step without purification.

Bicyclic Ketal 34. To a solution of unpurified **33** in 5 mL of dichloromethane was added a few crystals of pyridinium *p*-toluenesulfonate. The reaction mixture was stirred at room temperature for 12 h, and partitioned between 20 mL of saturated aqueous sodium bicarbonate solution and 20 mL of ethyl acetate. The aqueous layer was extracted with 3 × 20 mL of ethyl acetate. The combined organic layers were then washed with brine, filtered, and concentrated in vacuo. Purification by chromatography on silica gel (1:1 hexane/ethyl acetate, 2 × 19 cm) gave 21 mg (42% for three steps) of a colorless oil: R_f 0.45 (3:7 hexane/ethyl acetate); IR (thin film) 2960, 2930, 1745, 1645, 1470, 1440, 1370, 1345, 1295, 1275, 1210, 1165, 1120, 1090, 1055, 1015 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.56 (m, 1 H, C*H*(O)CH_2CH_2CO), 4.32 (m, 1 H, MeO_2CCH_2CHO), 3.68 (s, 3 H, OCH_3), 3.67 (s, 3 H, OCH_3), 2.84 (d, J = 14.3 Hz, 1 H, MeO_2CCH_2CO), 2.74 (d, J = 14.3 Hz, 1 H, MeO_2CCH_2CO), 2.58 (dd, J = 15.4, 6.8 Hz, 1 H, MeO_2CCH_2CHO), 2.39 (dd, J = 15.4, 6.4 Hz, 1 H, MeO_2CCH_2CHO), 2.19 (m, 3 H, CH_2CH_2CO), 1.85 (m, 1 H, CH_2CH_2CO), 1.76 (m, 1 H, $CHOCH_2$), 1.46 (ddd, J = 13.0, 3.5, 2.1 Hz, 1 H, $CHOCH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 169.6, 104.4, 75.0, 65.7, 51.7, 51.6, 42.7, 40.9, 36.2, 32.9, 28.1. Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.80; H, 7.03. Found: C, 55.90; H, 6.94.

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