(+)-Zaragozic Acid C: Synthesis and Related Studies

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Abstract: The asymmetric synthesis of the potent squalene synthase inhibitor (+)-zaragozic acid C is described. The synthesis allows for the preparation of multigram quantities of the dioxabicyclooctane core common to all members of this class of fungal metabolites. Supporting studies include (1) the use of $[Cr(OAc)_2{\cdot}H_2O]_2$ for the stereoselective reduction of ynones to *trans* enones, (2) an investigation of the diastereoselective dihydroxylation of γ-alkoxy-α,β-*trans* enones, and (3) nucleophilic addition of $Me_3SiC{\equiv}CLi$ to a dioxabicyclooctanone, wherein the product diastereoselectivity is observed to vary as a function of cosolvents (tertiary amines) and additives (LiBr). In addition, an acylation protocol is reported which permits the regioselective installation of the C(6) *O*-acyl side chain.

Introduction

The zaragozic acids and squalestatins constitute a class of recently isolated fungal metabolites which are important targets for chemical synthesis as a consequence of their complex molecular structure and potent biological activity.[1] These natural products share a common 2,8-dioxabicyclo[3.2.1]octane core and differ exclusively at the C(1) alkyl and C(6) *O*-acyl side chains.[2] All members of this family display picomolar inhibition of mammalian squalene synthase, the enzyme responsible for mediating the first committed step in sterol biosynthesis.[3] Thus, these compounds have potential application as therapeutically useful serum cholesterol-lowering agents. Herein, we provide a detailed account of our synthesis of (+)-zaragozic acid C (**1**, Figure 1).[4]

Background. Zaragozic acids and squalestatins were first isolated in 1991 by research teams working independently at Merck and Glaxo (Figure 2). Zaragozic acid A was extracted from the sterile fungal culture *Sporormiella intermedia*, while zaragozic acids B and C were isolated from a fungal strain identified as *Leptodontium elatius*. The three squalestatins were extracted from the fungus *Phoma* sp. C2932. The structures of these natural products were determined by a combination of chemical degradation and NMR spectroscopy.[1,5] X-ray crystallographic analysis and exciton-coupled circular dichroism studies on various derivatives confirmed the structural assignments and established the absolute stereochemistry. These molecules are characterized by a novel 4,6,7-trihydroxyl-2,8-dioxabicyclo-[3.2.1]octane-3,4,5-tricarboxylic acid core, which has been shown to be biosynthetically derived from succinate and acetate precursors.[6] Syntheses of partially functionalized model systems of the bicyclic core as well as the preparation of both side chains have been described.[7-9] Additionally, the asymmetric synthesis

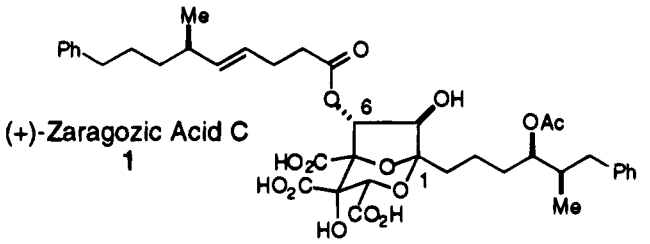

Figure 1. (+)-Zaragozic acid C.

[⊗] Abstract published in *Advance ACS Abstracts,* July 15, 1995.

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(3) (a) Dawson, M. J.; Farthing, J. E.; Marshall, P. S.; Middleton, R. F.; O'Neil, M. J.; Shuttleworth, A.; Stylli, C.; Tait, R. M.; Taylor, P. M.; Wildman, H. G.; Buss, A. D.; Langley, D.; Hayes, M. V. *J. Antibiot.* **1992**, *45*, 639. (b) Baxter, A.; Fitzgerald, B. J.; Hutson, J. L.; McCarthy, A. D.; Motteram, J. M.; Ross, B. C.; Sapra, M.; Snowden, M. A.; Watson, N. S.; Williams, R. J.; Wright, C. *J. Biol. Chem.* **1992**, *267*, 11705. (c) Hasumi, K.; Tachikawa, K.; Sakai, K.; Murakawa, S.; Yoshikawa, N.; Kumazawa, S.; Endo, A. *J. Antibiot.* **1993**, *46*, 689. (d) Bergstrom, J. D.; Kurtz, M. M.; Rew, D. J.; Amend, A. M.; Karkas, J. D.; Bostedor, R. G.; Bansal, V. S.; Dufresne, C.; VanMiddlesworth, F. L.; Hensens, O. D.; Liesch, J. M.; Zink, D. L.; Wilson, K. E.; Onishi, J.; Milligan, J. A.; Bills, G.; Kaplan, L.; Nallin-Omstead, M.; Jenkins, R. G.; Huang, L.; Meinz, M. S.; Quinn, L.; Burg, R. W.; Kong, Y. L.; Mochales, S.; Mojena, M.; Martin, I.; Pelaez, F.; Diez, M. T.; Alberts, A. W. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 80. (e) Lindsey, S.; Harwood, H. J., Jr. *J. Biol. Chem.* **1995**, *270*, 9083.

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(5) Hensens, O. D.; Dufresne, C.; Liesch, J. M.; Zink, D. L.; Reamer, R. A.; VanMiddlesworth, F. *Tetrahedron Lett.* **1993**, *34*, 399.

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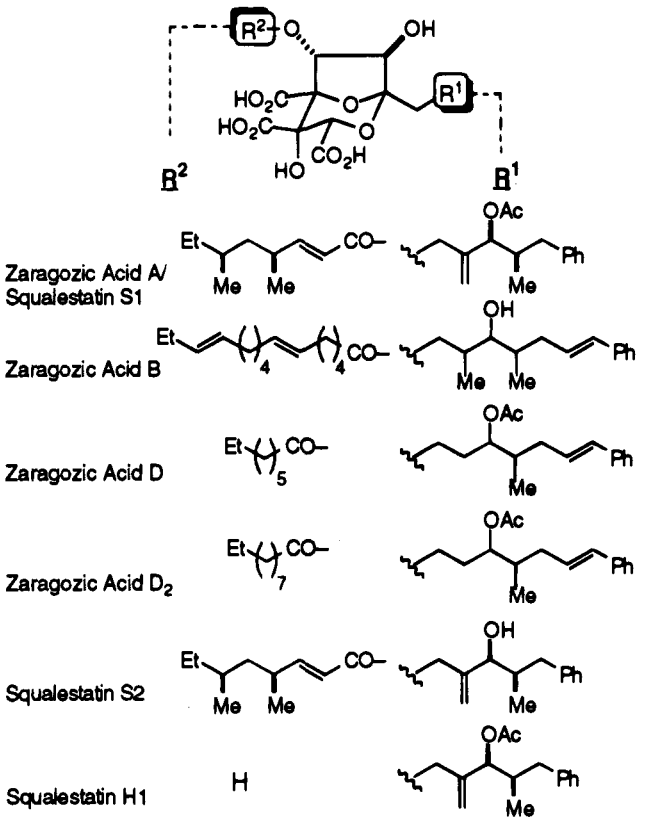

Figure 2. Selection of other known zaragozic acids and squalestatins.

of zaragozic acid A/squalestatin S1 and a second synthesis of (+)-zaragozic acid C have been accomplished by Nicolaou and Evans, respectively.[10,11]

Zaragozic acids A, B, and C exhibit potent inhibitory activity toward rat liver squalene synthase, with apparent K_i values from 29 to 78 pM. In addition, these fungal metabolites have been shown to effect a decrease in cholesterol synthesis in whole cells (Hep G2) and in mice.[1b,12] The squalestatins display similar efficacy toward both mammalian (rat liver) and microsomal (*Candida albicans*) squalene synthase. This enzyme is responsible for catalyzing a two-step reaction sequence in which farnesyl pyrophosphate (FPP) is dimerized in a head-to-head manner to form pre-squalene pyrophosphate (PSPP). This cyclopropylcarbinyl pyrophosphate undergoes a series of enzyme–mediated cationic rearrangements, followed by reduction with NADPH to furnish squalene.[13,14] It has been shown that both biosynthetic steps (dimerization and reductive rearrangement) are inhibited by the zaragozic acids and the squalestatins. The structural homology between these compounds and presqualene pyrophosphate has led to the suggestion that they act by effectively mimicking the binding of PSPP to the enzyme (Figure 3).[3d,15]

Analysis. The retrosynthetic disconnections which formed the basis of our plan for the preparation of zaragozic acid C are illustrated in Scheme 1. Removal of the C(6) *O*-acyl side chain would provide the C(6)/C(7) diol **6**; subsequent unraveling of the dioxabicyclic ketal would give a functionalized acyclic precursor. As a consequence of these disconnections, the stereochemical complexity of the dioxabicyclooctane is redefined as a problem in acyclic asymmetric synthesis. At the outset, however, we were concerned that cyclization of a highly functionalized acyclic intermediate (e.g., **5**) to the appropriate bicyclic ketal might be complicated by side reactions such as δ- and γ-lactonization, as well as formation of undesired ketal products.[16] A synthetic route was developed which we hoped would avoid such competing processes.[17]

With these considerations in mind, a plan was developed in which the quaternary center at C(4) would be established following the formation of the dioxabicyclooctane framework.

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(9) For reports on the synthesis of the zaragozic acid side chains, see: (a) Robichaud, A. J.; Berger, G. D.; Evans, D. A. *Tetrahedron Lett.* **1993**, *34*, 8403. (b) Santini, C.; Ball, R. G.; Berger, G. D. *J. Org. Chem.* **1994**, *59*, 2261. (c) Parsons, J. G.; Rizzacasa, M. A. *Tetrahedron Lett.* **1994**, *35*, 8263.

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(11) Zaragozic acid C, see: Evans, D. A.; Barrow, J. C.; Leighton, J. L.; Robichaud, A. J.; Sefkow, M. J. *J. Am. Chem. Soc.* **1994**, *116*, 12111.

(12) The zaragozic acids have also been investigated as inhibitors of farnesyl-protein transferase: (a) Gibbs, J. B.; Pompliano, D. L.; Mosser, S. D.; Rands, E.; Lingham, R. B.; Singh, S. B.; Scolnick, E. M.; Kohl, N. E.; Oliff, A. *J. Biol. Chem.* **1993**, *268*, 7617. (b) Tamanoi, F. *Trends Biochem. Sci.* **1993**, *18*, 349.

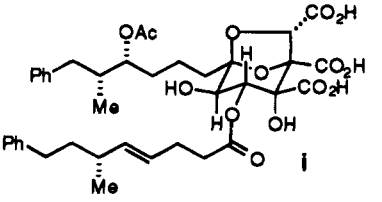
(13) (a) Poulter, C. D. *Acc. Chem. Res.* **1990**, *23*, 70. (b) Poulter, C. D.; Rilling, H. C. In *Biosynthesis of Isoprenoid Compounds*; Porter, J. W., Spurgeon, S. L., Eds.; Wiley: New York, 1981; Vol. 1, Chapter 8.

(14) For a recent investigation of non-head-to-tail isoprenoid biosynthesis by recombinant yeast squalene synthase, see: Zhang, D. L.; Poulter, C. D. *J. Am. Chem. Soc.* **1995**, *117*, 1641.

(15) A number of analogs have been prepared for structure–activity relationship studies: (a) Burk, R. M.; Berger, G. D.; Bugianesi, R. L.; Girotra, N. N.; Parsons, W. H.; Ponpipom, M. M. *Tetrahedron Lett.* **1993**, *34*, 975. (b) Lester, M. G.; Gilbin, G. M. P.; Inglis, G. G. A.; Procopiou, P. A.; Ross, B. C.; Watson, N. S. *Tetrahedron Lett.* **1993**, *34*, 4357. (c) Chiang, Y. P.; Biftu, T.; Doss, G. A.; Plevyak, S. P.; Marquis, R. W.; Bergstrom, J. D.; Kurtz, M. M.; Rew, D. J.; Berger, G. D. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2029. (d) Kuo, C. H.; Plevyak, S. P.; Biftu, T.; Parsons, W. H.; Berger, G. D. *Tetrahedron Lett.* **1993**, *34*, 6863. (e) Lester, M. G.; Evans, G. L.; Henson, R. A.; Procopiou, P. A.; Sareen, M.; Snowden, M. A.; Spooner, S. J.; Srikantha, A. A. P.; Watson, N. S. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2683. (f) Shaw, R. E.; Burgess, C.; Cousins, R. P. C.; Giblin, G. M. P.; Livermore, D. G. H.; Shingler, A. H.; Smith, C.; Youds, P. M. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 2155. (g) Cox, B.; Hudson, J. L.; Keeling, S. E.; Kirk, B. E.; Srikantha, A. R. P.; Watson, N. S. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1931. (h) Kuo, C. H.; Robichaud, A. J.; Rew, D. J.; Bergstrom, J. D.; Berger, G. D. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 1591. (i) Andreotti, D.; Procopiou, P. A.; Watson, N. S. *Tetrahedron Lett.* **1994**, *35*, 1789. (j) Sharratt, P. J.; Hutson, J. L.; Inglis, G. G. A.; Lester, M. G.; Procopiou, P. A.; Watson, N. S. *Bioorg. Med. Chem. Lett.* **1994**, *4*, 661. (k) Biftu, T.; Acton, J. J.; Berger, G. D.; Bergstrom, J. D.; Dufresne, C.; Kurtz, M. M.; Marquis, R. W.; Parsons, W. H.; Rew, D. R.; Wilson, K. E. *J. Med. Chem.* **1994**, *37*, 421. (l) Pompipom, M. M.; Girotra, N. N.; Bugianesi, R. L.; Roberts, C. D.; Berger, G. D.; Burk, R. M.; Marquis, R. W.; Parsons, W. H.; Bartizal, K. F.; Bergstrom, J. D.; Kurtz, M. M.; Onishi, J. C.; Rew, D. J. *J. Med. Chem.* **1994**, *37*, 4031. (m) Additional citations to this literature can be found in the references above.

(16) For alternative strategies in which differently functionalized acyclic precursors are cyclized to the dioxabicyclooctane core intermediates, see refs 10 and 11.

(17) Early structure determination studies by ^{1}H NMR spectroscopy on the zaragozic acids excluded the other possible [3.2.1]bicyclic ketal ring system i. Evans and co-workers have performed molecular mechanics calculations on both [3.2.1]dioxabicyclooctanes and concluded that the unnatural isomer i is more stable (ref 11). No data are available on the kinetics of formation of each of the two bicyclic ketals from acyclic precursors.



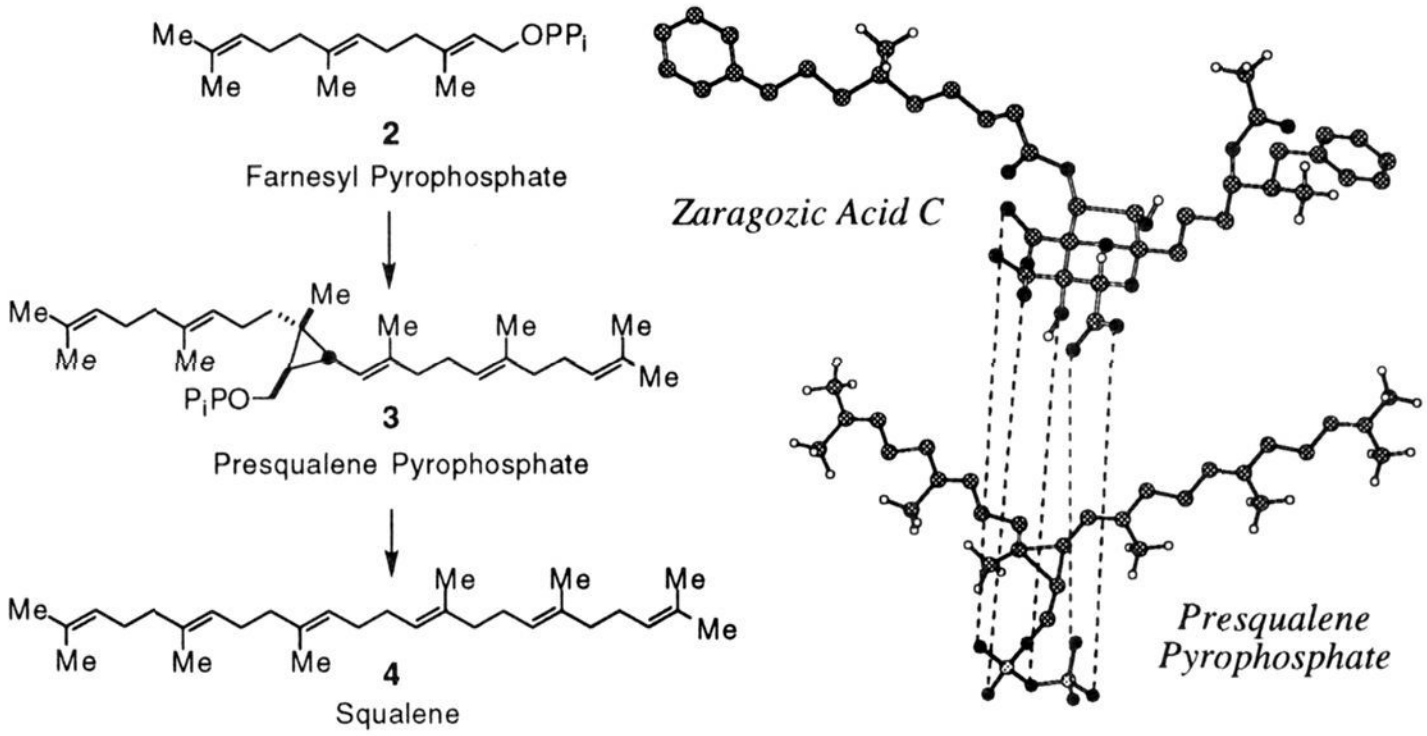


Figure 3. Structural comparison of presqualene pyrophosphate and zaragozic acid C.

Scheme 1

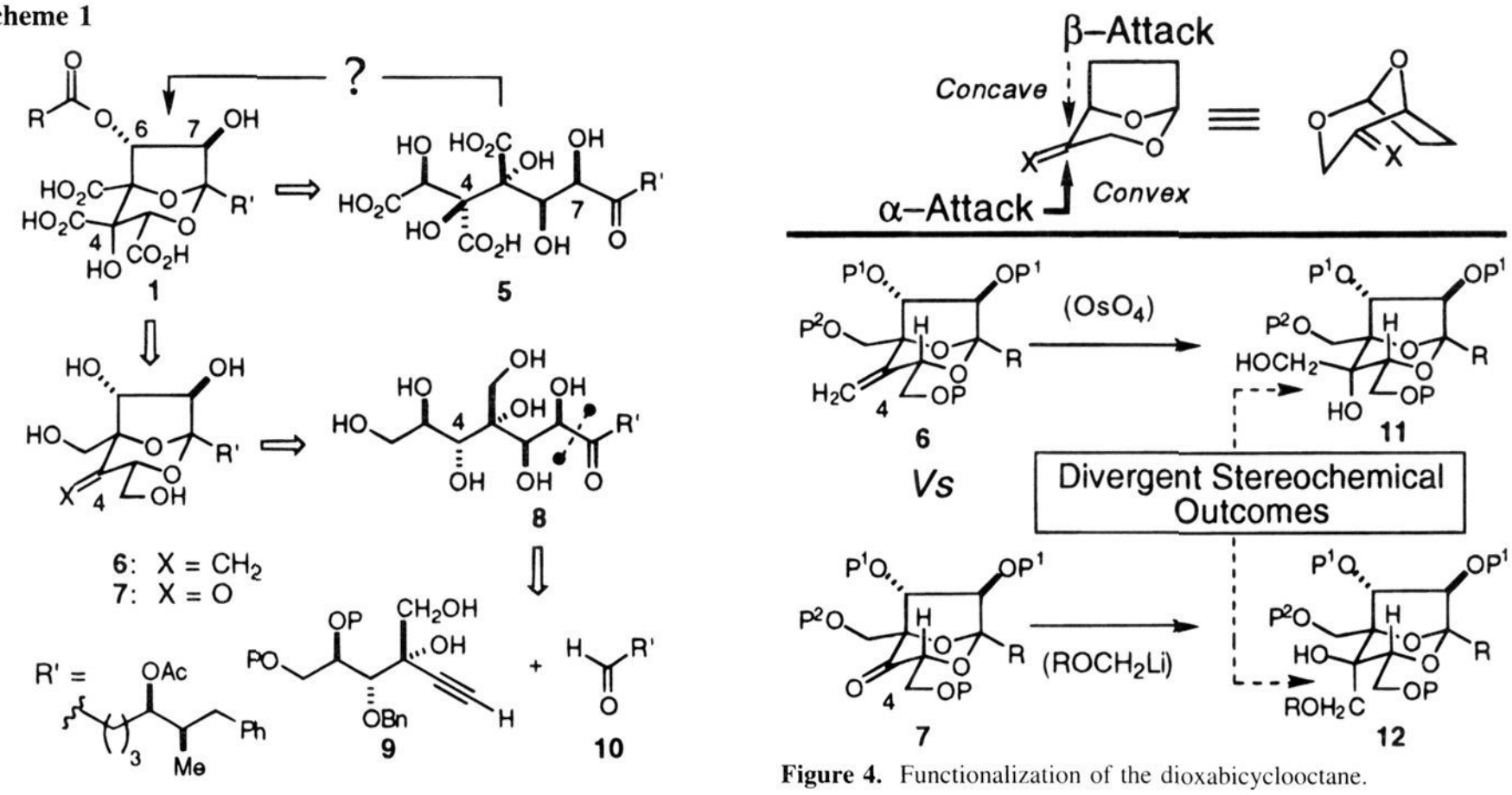


Figure 4. Functionalization of the dioxabicyclooctane.

Installation of the C(4) hydroxy acid would require either oxidative functionalization of olefin **6** or nucleophilic addition to ketone **7**. On the basis of molecular models, we anticipated that dihydroxylation of dioxabicyclooctane **6** would occur preferentially from the convex face to provide the desired C(4) carbinol. Analysis of ketone **7** suggested a similar preference for addition to the convex face to give the undesired stereochemistry at C(4) (Figure 4). Therefore, we initially expected to install the desired C(4) hydroxy acid functionality via the alkene intermediate **6**, which would be prepared from ketone **7**. Disconnection of ketone **7** led to the acyclic fragment **8**, in which a hydroxy group at C(4) would serve as the latent carbonyl. Fragmentation of the C(1)−C(7) bond in **8** afforded two subunits: **9**, which includes most of the stereochemical information present in the dioxabicyclooctane skeleton, and **10**, which encompasses the C(1′) alkyl side chain with its attendant stereogenic centers (Scheme 1).

Results and Discussion

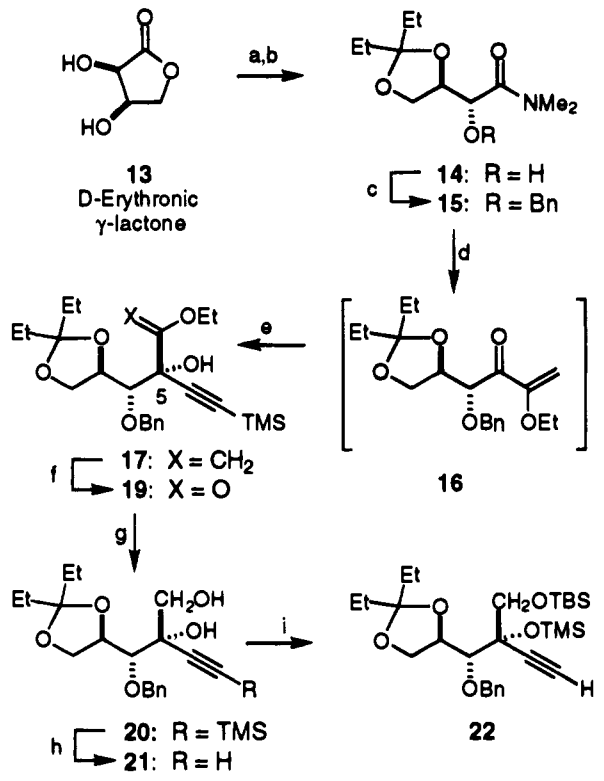
Synthesis of Alkyne 22. The synthesis of zaragozic acid C commenced with the preparation of alkyne **22** (Scheme 2) from D-erythronic γ-lactone **13**, which is readily available from D-araboascorbic acid (H_2O_2/K_2CO_3, then H_3O^+).[18] Condensation of **13** with dimethylamine (MeOH, 0 °C) afforded the derived 2,3,4-trihydroxybutyramide, which was selectively ketalized ($Et_2C(OMe)_2$, catalytic TsOH) to give **14**. Protection of the secondary alcohol as its corresponding benzyl ether (BnBr, NaH) furnished amide **15**.

Installation of the C(5) quaternary center was effected, starting with amide **15**, through two sequential carbanion additions. Treatment of **15** with (ethoxyvinyl)lithium (ethyl vinyl ether, ^{t}BuLi) yielded an intermediate α-ethoxy-α,β-unsaturated ketone **16**. Subsequent addition of TMSC≡CMgBr to **16** afforded a 20:1 mixture of diastereomeric products **17/18**, as determined by ^{1}H NMR spectroscopy.[19]

(18) Cohen, N.; Banner, B. L.; Lopresti, R. J.; Wong, F.; Rosenberger, M.; Liu, Y.-Y.; Thom, E.; Liebmann, A. A. *J. Am. Chem. Soc.* **1983**, *105*, 3661. D-Araboascorbic acid is available from Aldrich Chemical Co.

(19) The stereochemistry of the major product was assumed to be as shown on the basis of a chelation-controlled addition. This was established unambiguously by 1H NMR NOE difference experiments following cyclization to the dioxabicyclooctane core; see Scheme 5 and Figure 9.

Scheme 2[a]



[a] (a) Me_2NH, MeOH, 0 °C, 97%; (b) $(MeO)_2CEt_2$, catalytic TsOH, 90%; (c) NaH, BnBr, THF, 96%; (d) (ethoxyvinyl)lithium, THF, −78 °C; (e) TMSC≡CMgBr, THF, −78 °C, 84%; (f) O_3, CH_2Cl_2/EtOH, −78 °C, 84%; (g) $NaBH_4$, MeOH; (h) K_2CO_3, MeOH, 78% in two steps; (j) ^{t}BuMe$_2$SiCl, Et_3N, 4-DMAP then Me_3SiCl, Et_3N, CH_2Cl_2, 88%.

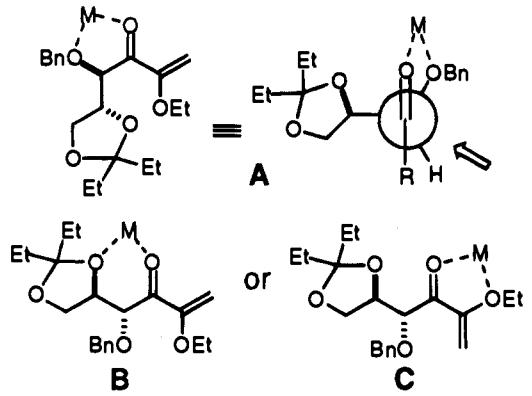
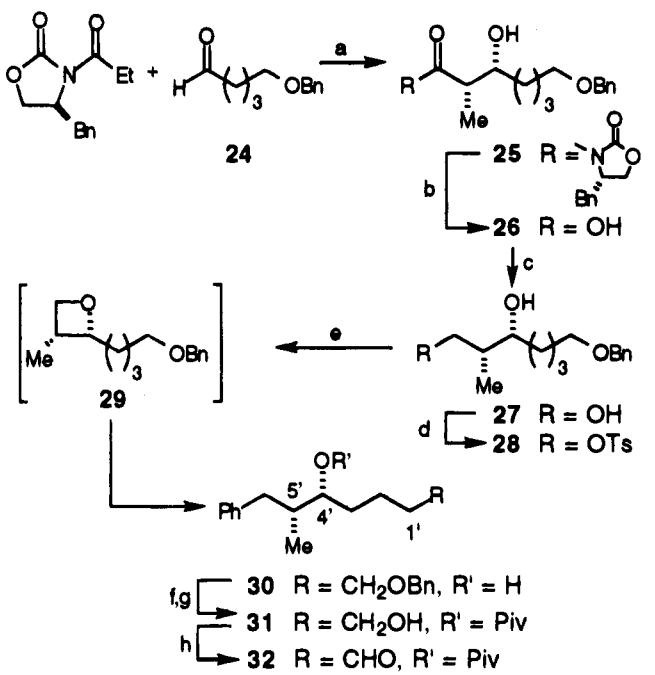


Figure 5. Stereoselective addition of TMSC≡CMgBr to **16**: putative chelate structures.

Nucleophilic addition to the intermediate ketone **16** was conducted under reaction conditions which favored a chelation-controlled process. In principle, this ketone can form three different magnesium chelates, **A**, **B**, and **C** (Figure 5).[20] The observed stereochemical outcome of the reaction is consistent with the addition of TMSC≡CMgBr occurring through the intermediacy of a 5-membered chelate formed by the α-benzyloxy and the ketone carbonyl oxygens (**A**, Figure 5).[21] Ketone addition proceeding through 1,3-chelate **B** was expected to favor formation of the product bearing the undesired stereochemistry at the newly installed quaternary center (**18**). Similarly, addition proceeding through chelate **C** was anticipated to give the unwanted Felkin−Ahn product **18**.[22]

Scheme 3[a]



[a] (a) 9-BBNOTf, ^{i}Pr$_2$NEt then H_2O_2/MeOH, 84%; (b) LiOH, H_2O_2, aqueous THF; (c) $LiAlH_4$, THF, 92%; (d) TsCl, C_5H_5N, 0 °C, 89%; (e) PhLi, BF_3·OEt_2, 91%; (f) ^{t}BuCOCl, 4-DMAP, CH_2Cl_2, 90%; (g) H_2, Pd−C, EtOAc, 99%; (h) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 96%.

Subsequent elaboration to diol **20** was accomplished through ozonolysis of the hydroxy vinyl ether **17** under carefully controlled conditions (Scheme 2).[23] Treatment of **17** with a dilute stream of ozone (~1 equiv, −78 °C) effected oxidation of the vinyl ether in reproducibly high yields (84%). Mild reduction of α-hydroxy ester **19** with $NaBH_4$ in MeOH (23 °C) furnished diol **20**, along with a small amount (5−10%) of **21**, the product of alkyne desilylation. In practice, the unpurified product from this reduction was reacted directly with anhydrous K_2CO_3 in MeOH to effect complete conversion to the desired terminal acetylene **21**. Differential protection of the primary and tertiary carbinols in **21** was accomplished using a one-pot procedure involving silylation with ^{t}BuMe$_2$SiCl (TBSCl) and Me_3SiCl (TMSCl), respectively. A solution of the diol, 4-DMAP, and Et_3N was initially treated with TBSCl, and upon consumption of **21** (as indicated by thin-layer chromatography), the reaction mixture was subsequently treated with TMSCl to furnish **22**. The nine-step sequence of reactions described has been routinely conducted to prepare **22** on a 30−40 g scale.

Synthesis of the Alkyl Side Chain Aldehyde 32. Preparation of the alkyl side chain was achieved via a seven−step reaction sequence employing Evans's asymmetric aldol addition chemistry to install both the C(4′) and C(5′) stereogenic centers (Scheme 3).[24] Treatment of 5-(benzyloxy)pentanal (**24**) with the di-*n*-butylboryl enolate of *N*-propionyl-(*S*)-benzyloxazo-

(20) (a) Still, W. C.; McDonald, J. H. *Tetrahedron Lett.* **1980**, *21*, 1031. (b) For a recent review of chelation-controlled additions to carbonyl compounds, see: Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462. (c) The preference for 1,2-chelates over 1,3-chelates has been noted: Ida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1986**, *51*, 3769. Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778.

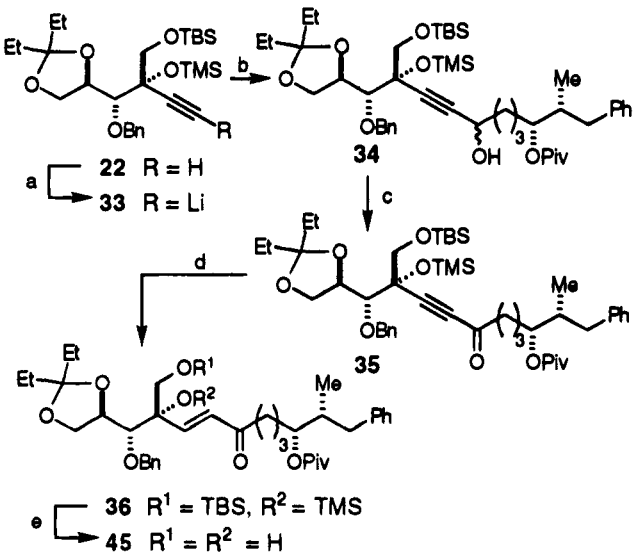
(21) Evans and co-workers have made a related observation in which a 1,2-chelate is assumed to be preferred over a 1,3-chelate; see ref 11.

(22) (a) Anh, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61. (b) Reetz, M. T.; Hullmann, M.; Seitz, T. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 477.

(23) For selective ozonolysis of vinyl ethers over other alkenes or alkynes, see: (a) Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *46*, 1396. (b) Veysoglu, T.; Mitscher, L. A.; Swayze, J. K. *Synthesis* **1980**, 807.

(24) (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (b) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099.

Scheme 4[a]



[a] (a) ^{n}BuLi, THF, −45 °C; (b) **32**, LiBr, THF, 93%; (c) Dess−Martin periodinane, CH_2Cl_2, 93%; (d) $[Cr(OAc)_2{\cdot}H_2O]_2$, THF/H_2O, 60%; (e) ^{n}Bu$_4$NF, THF, 93%.

lidinone gave the aldol adduct **25** in 97% diastereomeric excess (de), as determined by ^{1}H NMR spectroscopy. Hydrolysis of the auxiliary (LiOH, H_2O_2)[25] and reduction of the resulting acid **26** with $LiAlH_4$ furnished diol **27** as a white, crystalline solid (92% in two steps).

Replacement of the primary hydroxyl in **27** with the requisite phenyl substituent was effected following a two-step protocol that involved (1) selective tosylation of the primary carbinol (TsCl, C_5H_5N, 0 °C) to give **28** and (2) *in situ* closure to oxetane **29**, followed by $BF_3{\cdot}OEt_2$-promoted ring opening with phenyllithium.[26] Nucleophilic opening of the intermediate oxetane occurred with complete regioselectivity to provide **30** in 80% yield for the overall sequence. The resulting alcohol **30** was protected as the trimethylacetyl (Piv) ester **31**. Utilization of this hindered protecting group ensured that the C(4′) carbinol would remain masked under the strongly acidic conditions subsequently developed for the cyclization reaction (*vide infra*). Hydrogenolytic removal of the benzyl ether (H_2, Pd−C), followed by Swern oxidation of the resulting alcohol, provided the zaragozic acid C side chain precursor, aldehyde **32**.[27]

Synthesis of the Dioxabicyclooctane Core. We next proceeded to investigate the coupling of acetylene **22** with aldehyde **32** (Scheme 4). Addition of a solution of aldehyde **32** to a solution of acetylide **33** in either THF or Et_2O at −78 °C yielded a mixture of both the desired product **34** and recovered starting materials. We speculated that proton transfer between acetylide **33** and aldehyde **32** was responsible for the reduced yields of **34**. Attempts to attenuate the basicity of the lithium acetylide by transmetalation with either $MgBr_2$ or $CeCl_3$ had little effect in preventing the proton-transfer side reaction.[28] In related model studies, addition of either the lithium, magnesium, or cerium acetylide to hexanoyl chloride (used as a model for the side chain acid chloride) was also unsuccessful.[29] Efficient coupling of the two subunits, **32** and **33**, was accomplished according to a protocol described by Brandsma for the addition of lithium acetylides to readily enolizable ketones.[30] Addition of 0.5 equiv of anhydrous LiBr to a solution of lithium acetylide **33** prior to the addition of a solution of aldehyde **32** provided the desired adduct **34** as a mixture of epimeric alcohols in 93% yield. The mixture of propargylic alcohols **34** was then oxidized with Dess−Martin periodinane to furnish ynone **35**.[31]

Reduction of **35** to the corresponding *trans* enone would provide the intermediate needed for installation of the remaining hydroxyl stereocenters at C(6) and C(7). Thus, we investigated methods for the stereoselective reduction of ynones to *trans* enones. Reagents known to effect this transformation include metal hydride species (e.g., Red-Al), dissolving metal reductions (Li/NH_3), and low-valent chromium salts ($CrSO_4$, $CrCl_2$).[32] Additionally, semireduction with H_2 over Pd−C, followed by photochemical isomerization of the resulting *cis* enone, would afford the desired *trans* product. With the exception of the Cr(II) salts, all other methods screened gave poor isolated yields of ketone **36** and led to extensive decomposition of the starting material. Reactions involving either $CrSO_4$ or $CrCl_2$ were highly capricious, however, and gave variable yields of **36** (10−30%). We suspected that the air sensitivity of the Cr(II) reagents, which necessitated rigorous exclusion of oxygen during their preparation and in the course of the reaction, was the source of the difficulties.[33] A solution to this problem was discovered in our laboratories when the commercially available chromium(II) acetate monohydrate dimer, $[Cr(OAc)_2{\cdot}H_2O]_2$, was used in place of either $CrSO_4$ or $CrCl_2$.[34] The use of $[Cr(OAc)_2{\cdot}H_2O]_2$ gave highly reproducible results and provided **36** in yields more than twice as high (60%) as those obtained with any of the methods previously examined.

Dihydroxylation of enone **36** with OsO_4 under catalytic conditions (NMO, acetone/H_2O) proceeded very slowly (~10% after 48 h at 23 °C).[35] The small amount of product isolated proved to be a 1:1 mixture of *syn* C(6)/C(7) alcohol diastereomers **37**:**38**, as determined by ^{1}H NMR spectroscopy (Figure 6). Selective deprotection of the trimethylsilyl ether at C(5) ($ClCH_2CO_2H$, MeOH) and treatment of the resulting enone **39** with 10 mol % OsO_4 (NMO, acetone/H_2O) afforded the product

(25) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.

(26) Eis, M. J.; Wrobel, J. E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3693.

(27) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.

(28) For a review of organolanthanide chemistry, see: Molander, G. A. *Chem. Rev.* **1992**, *92*, 29.

(29) Attempts to couple an aldehyde or an acid chloride with the alkenylmetal species derived from hydrostannylation, hydrozirconation, or hydrozincanation of acetylene **22** did not provide any of the allylic alcohol or enone product, respectively. For reports of palladium-catalyzed hydrostannylation and alkenylstannane coupling to acid chlorides, see: (a) Zhang, H. X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857. (b) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585. For reports of additions of alkenylzirconocene reagents to aldehydes catalyzed by $AgClO_4$, see: (c) Maeta, H.; Hashimoto, T.; Hasegawa, T.; Suzuki, K. *Tetrahedron Lett.* **1992**, *33*, 5965. Transmetalations of alkenylzirconocenes with either CuBr·SMe_2 or $AlCl_3$ and subsequent coupling to acid chlorides have been documented: (d) Wipf, P.; Xu, W. *Synlett* **1992**, 718. (e) Carr, D. B.; Schwartz, J. *J. Am. Chem. Soc.* **1977**, *99*, 638. Addition of alkenylzinc reagents (derived by transmetalation of alkenylboranes) to aldehydes has been reported: (f) Oppolzer, W.; Radinov, R. N. *Helv. Chim. Acta* **1992**, *75*, 170. (g) Screbnik, M. *Tetrahedron Lett.* **1991**, *32*, 2449.

(30) van Rijn, P. E.; Mommers, S.; Visser, R. G.; Verkruijsse, H. D.; Brandsma, L. *Synthesis* **1981**, 459.

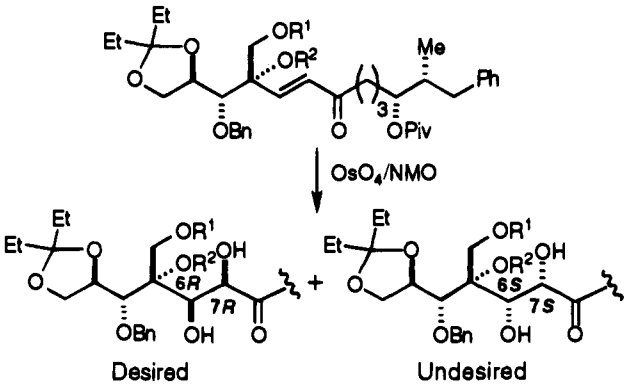
(31) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156. (b) For an excellent procedure for the preparation of multigram quantities of the Dess−Martin reagent, see: Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.

(32) For the reduction of ynones with $CrSO_4$ and $CrCl_2$, see: (a) Smith, A. B., III; Levenberg, P. A.; Suits, J. Z. *Synthesis* **1986**, 184. For reduction of alkynols with Cr(II), see: (b) Castro, C. E.; Stephens, R. D. *J. Am. Chem. Soc.* **1964**, *86*, 4358.

(33) (a) A procedure for *in situ* preparation of $CrSO_4$ is described in ref 32a. (b) For the preparation and isolation of solid $CrSO_4$, see: Lux, H.; Illmann, G. *Chem. Ber.* **1958**, *91*, 2143.

(34) $[Cr(OAc)_2{\cdot}H_2O]_2$ has been used to reduce α-haloketones and α-haloketoximines: (a) Williamson, K. L.; Johnson, W. S. *J. Org. Chem.* **1961**, *26*, 4563. (b) Corey, E. J.; Richman, J. E. *J. Am. Chem. Soc.* **1970**, *92*, 5276. $[Cr(OAc)_2{\cdot}H_2O]_2$ is currently sold by Aldrich Chemical Co.

(35) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973.



Substrate	R^1	R^2	Desired : Undesired
36	TBS	TMS	1 : 1 37:38
39	TBS	H	1 : 9 40:41
42	H	TMS	1 : 9 43:44
45	H	H	1.1 : 1 46:47
45	H	H	1.7 : 1 ★ 46:47

★ conducted with added $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$

Figure 6. Summary of results for enone dihydroxylation reactions.

as a 1:9 mixture of diastereomers **40** and **41**. The major product **41** isolated in the dihydroxylation reaction, however, was shown to possess the incorrect C(6)/C(7) diol stereochemistry.[36] In an analogous experiment, treatment of enone **42** with catalytic OsO_4 provided a 1:9 mixture of products, with the undesired diol diastereomer **44** predominating. Removal of both the TBS and TMS ethers in **36** gave diol **45**. Dihydroxylation of **45** furnished a 1.1:1 mixture of **46** and **47**. Fortunately, **45** could be osmylated in the presence of either Sharpless ligand $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$ with NMO as the reoxidant to give a 1.7:1 mixture of desired/undesired products **46**:**47** in yields greater than 95%.[37,38] It is interesting to note that the use of either of these ligands afforded the diol with the desired C(6)/C(7) stereochemistry preferentially.

Additional enones were examined as a means for potentially improving the dihydroxylation diastereoselectivity (Figure 7). Selective benzoylation of the primary alcohol in **45** with either 4-methoxybenzoyl chloride (4-DMAP, Et_3N, CH_2Cl_2) or 2-nitrobenzoic acid (DCC, DMAP) gave the corresponding esters **48** and **49**, respectively.[39] Subjection of either of these compounds to standard dihydroxylation conditions (OsO_4, NMO, acetone/H_2O/^{t}BuOH) furnished mixtures of carbinol products (1.3−1.8:1 by ^1H NMR spectroscopy), favoring the desired (6*R*,7*R*) diol. Use of either $(DHQ)_2PHAL$ or $(DHQD)_2PHAL$ in the dihydroxylation reaction of substrates **48** and **49** offered no improvement on the reaction diastereoselectivity. Additionally, the derived picolinic ester **50** (prepared in an analogous fashion to **49**), when treated with OsO_4, afforded a similar ratio of products.

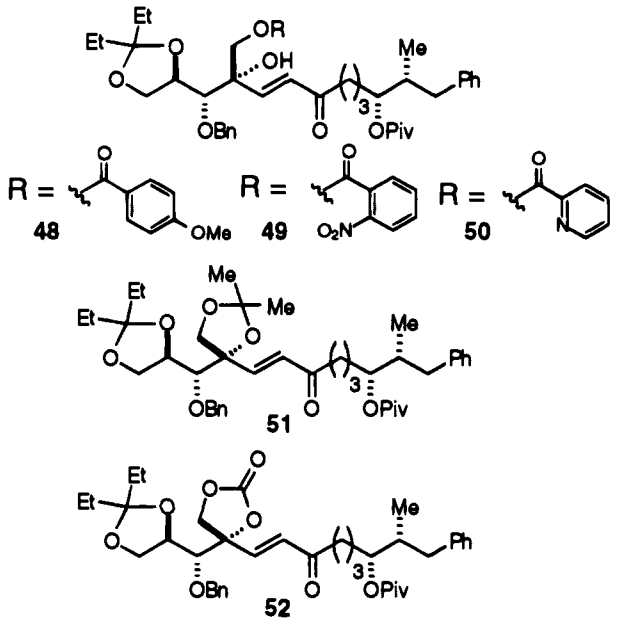


Figure 7. Alternative dihydroxylation substrates.

Treatment of **45** with 2-methoxypropene (PPTS, CH_2Cl_2) cleanly provided the isopropylidene ketal **51**. Reaction of **51** with OsO_4 yielded a 1:2.2 mixture of desired/undesired diol products (6*R*,7*R*)/(6*S*,7*S*). In contrast, dihydroxylation of the cyclic carbonate **52**, derived from treatment of **45** with triphosgene (C_5H_5N, 0−25 °C), gave a 2.2:1 mixture of diols, favoring the desired (6*R*,7*R*) diastereomer.

Formulation of a useful model that accounts for the observed selectivities in the dihydroxylation reactions of the derivatized enones **36**, **45**, and **48**−**52** is difficult. The data do suggest that placement of an electron-withdrawing group at C(10) promotes the formation of the desired (6*R*,7*R*) product. We speculate that changes to the electronic structure of the enone system may be altering the mechanism and, consequently, the stereochemical outcome of the dihydroxylation reaction.

Stereochemical Proof. The two diastereomers **46** and **47** isolated from the dihydroxylation reaction could not be separated by chromatography on silica gel. Cyclization of the mixture of unpurified **46** and **47** with 0.5% HCl in MeOH afforded the corresponding 2,8-dioxabicyclooctanes **53** and **56** (86% combined yield for two steps), which were separated by chromatography on silica gel (Scheme 5). In practice, however, separation of the mixture was most easily effected following selective protection of both primary hydroxyls as TBS ethers (Scheme 5, **53** → **54** and **56** → **57**). This two-step sequence (cyclization−protection) cleanly provided the desired bicyclic ketal **54**. Treatment of either diastereomer with 2 equiv of benzoyl chloride (4-DMAP, CH_2Cl_2) afforded the bis(benzoate) esters **55** and **58**, respectively. ^1H NMR difference NOE experiments on both **55** and **58** unambiguously established the proper stereochemical assignment for each diastereomer.

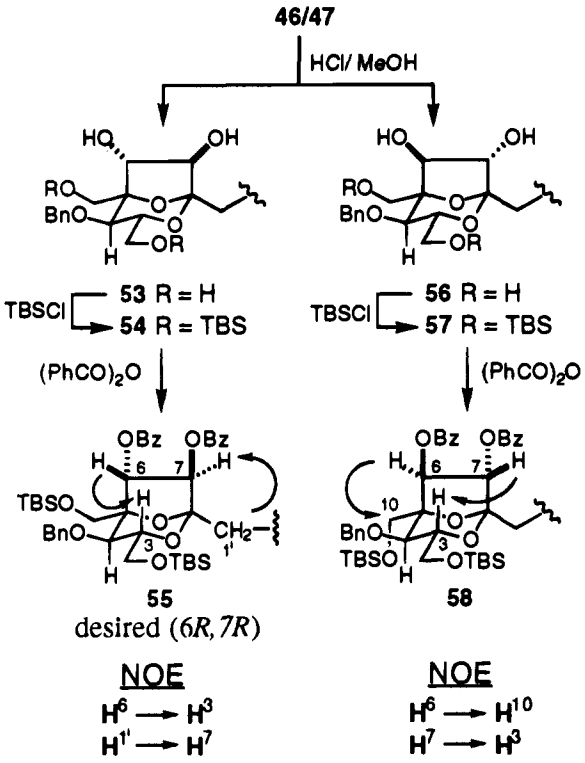
(36) In each of the dihydroxylations examined, the products were cyclized to the dioxabicyclooctane ketal by treatment with 0.5% HCl/MeOH, and the ratio of diastereomers was determined by ^1H NMR spectroscopy of the unpurified ketal products (yield 85−95%).

(37) For a recent discussion of the asymmetric dihydroxylation reaction, see: Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483 and references therein.

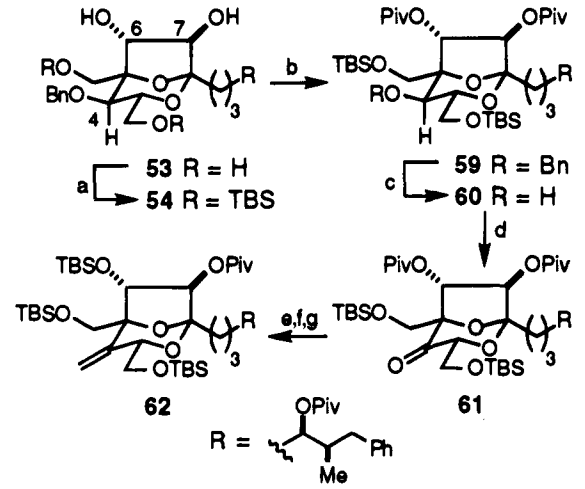
(38) (a) Sharpless has described a protocol for the dihydroxylation of α,β-unsaturated ketones with either $(DHQD)_2PHAL$ or $(DHQ)_2PHAL$ and $K_3Fe(CN)_6$ as the reoxidant: Walsh, P. J.; Sharpless, K. B. *Synlett* **1993**, 605. When **45** was subjected to these conditions, no reaction was observed following 1 month of stirring. (b) We are grateful to Professor K. Barry Sharpless (Scripps Research Institute) for helpful discussions and for providing additional ligands for study.

(39) The dramatic effect of an allylic *p*-methoxybenzoyl ester on the enantioselectivity of olefin dihydroxylation by OsO_4 has been reported: Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 12109.

Scheme 5



Scheme 6[a]



[a] (a) TBSCl, 4-DMAP, Et_3N, CH_2Cl_2, 74%; (b) ^{t}BuCOCl, 4-DMAP, $ClCH_2CH_2Cl$, 97%; (e) H_2 (1 atm), $Pd(OH)_2$–C, Pd–$CaCO_3$, EtOH, 99%; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 96%; (e) $TMSCH_2Li$, LiBr, THF/HMPA, −78 °C; (f) 18-C-6, KHMDS, THF, −78 °C with warming to −20 °C; (g) TBSOTf, 2,6-lutidine, <35% in three steps.

Synthesis and Functionalization of the 2,8-Dioxabicyclo-octan-4-one 61. Selective protection of tetraol **53** (TBSCl, Et_3N, 4-DMAP) furnished diol **54** (Scheme 6). Reaction of **54** with trimethylacetyl chloride (4-DMAP, $ClCH_2CH_2Cl$) gave triester **59**, which was then subjected to hydrogenolysis (H_2, 1 atm, $Pd(OH)_2$–C, Pd–$CaCO_3$) to effect cleavage of the benzylic ether at C(4).[40] Swern oxidation of the resulting secondary alcohol **60** provided ketone **61**, a key advanced intermediate in the synthesis.

Our initial plan for conversion of ketone **61** to the requisite α-hydroxy carboxylic acid involved dihydroxylation of olefin **62** and oxidation of the resulting diol. Methylenation of ketone **61** was accomplished through a two-step Peterson olefination sequence to give **62**.[41] Prior to developing these reaction conditions, a number of other C=O methylenation methods were screened, including (1) Wittig olefination with Ph_3PCH_2,[42] (2) reaction with both Tebbe (Cp_2TiCl_2, Me_3Al)[43] and Nozaki (CH_2Br_2, Zn, $TiCl_4$) reagents,[44] and (3) addition of MeMgBr, followed by dehydration of the resulting tertiary alcohol.[45] Under a variety of conditions, these approaches (e.g., 1 and 2) either returned unreacted ketone **61** or gave the enone product arising from β-elimination of the C(8) OTBS group. The addition of MeMgBr was effected in good yield (>80%); however, successful dehydration conditions could not be found. Preparation of the desired exocyclic olefin was accomplished when (trimethylsilyl)methyllithium ($TMSCH_2Li$) was added to **61** in the presence of 0.5 equiv of LiBr (THF, −78 °C), followed by subsequent elimination of the resulting vicinal hydroxysilane ($KN(TMS)_2$, 18-crown-6, THF/HMPA, −78 → −20 °C).[46] Although alkene **62** was prepared using this protocol, the yields for both reactions were highly variable (5–35%) and were sensitive to the source and age of both the $TMSCH_2Li$ and the $KN(TMS)_2$ base.

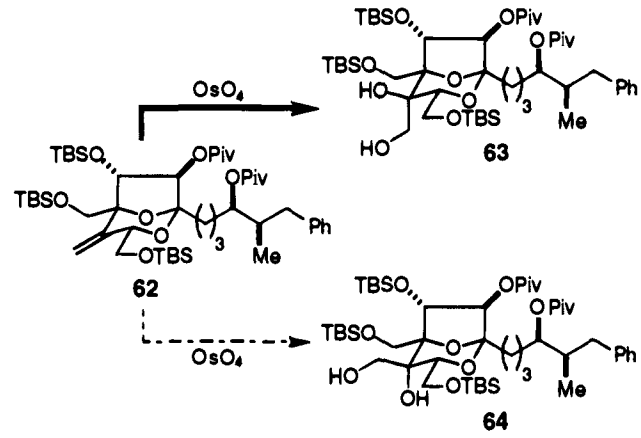


Figure 8. Dihydroxylation of olefin **62**.

Upon treatment of **62** with catalytic OsO_4 (NMO, acetone/^{t}BuOH), a single diol diastereomer **63**, possessing the undesired stereochemistry at C(4), was isolated (Figure 8). ^{1}H NMR NOE difference experiments on **62** indicated that the 1,3-dioxane ring was in the chair conformation illustrated; moreover, analysis of molecular models suggested that distortions leading to a half-chair arrangement would result in further blocking of the concave face of the *exo*-methylene. Additionally, dihydroxylation of exocyclic olefins in related ring systems has been shown to favor attack of OsO_4 from the convex face.[47] In light of these observations, the stereochemical outcome of this transformation was surprising.

(40) Pd–$CaCO_3$ was a necessary additive; in its absence, the TBS protecting groups were cleaved under the reaction conditions.

(41) (a) Hudrlik, P. F.; Peterson, D. *Tetrahedron Lett.* **1974**, *15*, 1133. (b) Burford, C.; Cooke, F.; Roy, G.; Magnus, P. *Tetrahedron* **1983**, *39*, 867.

(42) (a) Greenwald, R.; Chaykovsky, M.; Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128. (b) Pirrung, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 7130. (c) Corey, E. J.; Smith, J. G. *J. Am. Chem. Soc.* **1979**, *101*, 1038. (d) Still, W. C.; Tsai, M.-Y. *J. Am. Chem. Soc.* **1980**, *102*, 3654. (e) Fitjer, L.; Quabeck, U. *Synth. Commun.* **1985**, *15*, 855.

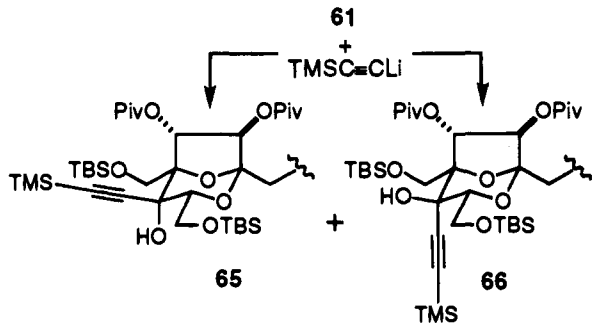
(43) (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611. (b) Pine, S. H.; Pettit, R. J.; Geib, G. D.; Cruz, S. G.; Gallego, C. H.; Tijerina, T.; Pine, R. D. *J. Org. Chem.* **1985**, *50*, 1212.

(44) (a) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, *19*, 2417. (b) Lombardo, L. *Org. Synth.* **1987**, *65*, 81.

(45) (a) Corey, E. J.; Ohno, M.; Mitra, R. B.; Vatakencherry, P. A. *J. Am. Chem. Soc.* **1964**, *86*, 478. (b) Paquette, L. A.; Poupart, M.-A. *J. Org. Chem.* **1993**, *58*, 4245.

(46) Under the conditions of the elimination, cleavage of both the C(10)–OTBS and C(6)–OPiv protecting groups was observed. The reason for the selective cleavage of these protecting groups is unclear at present. Reprotection with TBSOTf afforded **62**.

Table 1. Summary of Results from TMSC≡CLi Addition to Ketone **61**



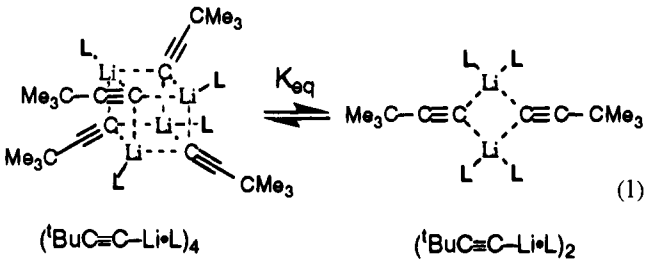
Entry	Conditions[a]	65:66[b,c]
1	THF	1.5 : 1
2	THF/TMEDA	1 : 2
3	Et_2O/150 equiv LiBr	1 : 1.7
4	Et_2O/diglyme	2.2 : 1
5	Et_2O/pyridine	2.1 : 1
6	Et_2O/1equiv LiBr	3.1 : 1
7	Et_2O	3.5 : 1
8	Et_2O/*i*-Pr_2NEt	3.8 : 1
9	Et_2O/Et_3N	4.3 : 1
10	Et_2O/Me_3N	6.1 : 1

[a] Reactions were conducted at −78 °C with slow warming to 0 °C in a 1:1 mixture of cosolvents with the exception of entry 5 (3:1 Et_2O/pyridine). [b] The diastereoselectivity was determined by integration of the ^1H NMR C(6) methine resonances for **65** and **66** at δ 5.51 and 5.72 ppm, respectively. [c] Yields uniformly range from 75 to 90%.

We proceeded to investigate additions to ketone **61** with nucleophiles that could be subsequently converted to the desired C(4) carboxylate.[48] This decision was based on an earlier finding that $TMSCH_2Li$ added to **61** to give an approximately equal mixture of epimeric β-hydroxysilanes (*vide supra*). In further studies, it was demonstrated that lithium (trimethylsilyl)-acetylide (TMSC≡CLi) could be added to ketone **61** in THF to give a 1.5:1 mixture of carbinol adducts **65** and **66** (Table 1, entry 1). This diastereomeric mixture could be readily separated by chromatography on silica gel, following alkyne desilylation ($AgNO_3$), to furnish the corresponding desired acetylenic alcohol **67** (Scheme 7).[49]

The effect of both cosolvents and additives on the diastereochemical outcome of the lithium acetylide reaction was investigated (Table 1).[50] When **61** was added to a THF/TMEDA solution of TMSC≡CLi, the diastereoselectivity reversed, and a 1:2 mixture of propargylic alcohol diastereomers **65** and **66** was isolated (entry 2). The use of Et_2O as solvent had a beneficial effect on the reaction diastereoselection (entry 7, **65**:**66** = 3.5:1). The same reaction, when conducted with added LiBr (1 equiv), led to a slight attenuation in the product diastereoselectivity (entry 6, **65**:**66** = 3.1:1); in the presence of excess LiBr (150 equiv), a reversal in the product distribution resulted as **66** was formed preferentially (entry 3, **65**:**66** = 1:1.7). These results suggested that the reaction diastereoselection might be influenced by changes to the aggregation state of the lithium acetylide.[51] Solution studies on lithium acetylides indicate that their aggregation equilibria can be shifted in the presence of added tertiary amines (*vide infra*). On this basis, we investigated the effect of amine cosolvents on the diastereochemical outcome of this reaction.[52] When an ethereal solution of ketone **61** was added to a suspension of TMSC≡CLi in 1:1 Et_2O/Me_3N at −78 °C, a significant improvement in the product ratio of **65**:**66** (6.1:1) was observed, favoring the desired C(4) tertiary alcohol (entry 10). In the presence of other tertiary amines (Et_3N, $^iPr_2NEt$), similar positive effects on the reaction diastereoselection were noted (**65**:**66** ≥ 3.8:1, see entries 8 and 9).

The structures of lithium acetylides have been studied in the solid state and in solution. X-ray crystallographic analysis of PhC≡CLi shows a dimeric structure in which two phenylethynyl units bridge two cationic lithium centers.[53] Cryoscopic measurements and ^6Li and ^{13}C NMR studies reveal that in solution this dimer is in equilibrium with other tetrameric aggregates.[54] Further work by Fraenkel has established qualitatively the effect of solvent and additives on the $[^tBuC{\equiv}CLi{\cdot}L_x]_2 \rightarrow [^tBuC{\equiv}CLi{\cdot}L_y]_4$ equilibrium (eq 1).[55] These studies demonstrate



(1)

that diamine ligands such as TMEDA and donating solvents like THF promote dimer formation, whereas tetrameric aggregation states prevail when simple ethers (Et_2O) and tertiary amines are employed. Our findings, in conjunction with these previous investigations, suggest that the observed reaction diastereoselection in the addition of TMSC≡CLi to ketone **61** responds in a dramatic fashion to the aggregation state of the acetylide.

Stereochemical Assignment of the C(4) Center. The initial stereochemical assignment of the acetylenic adducts **65** and **66**

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(49) For the use of $AgNO_3$ in the deprotection of silylacetylenes, see: Schmidt, H. M.; Arens, J. F. *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 1138.

(50) Addition of either TMSC≡CMgBr or the alkynylmetal reagents derived by transmetalation of the lithium acetylide with $CeCl_3$, Me_3Al, $BF_3{\cdot}OEt_2$, $YbCl_3$, or $Ti(O\text{-}i\text{-}Pr)_4$ resulted in extensive decomposition of the starting material **61**.

(51) For a discussion of the structure and reactivity of enolates as related to their aggregation phenomena, see: Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624.

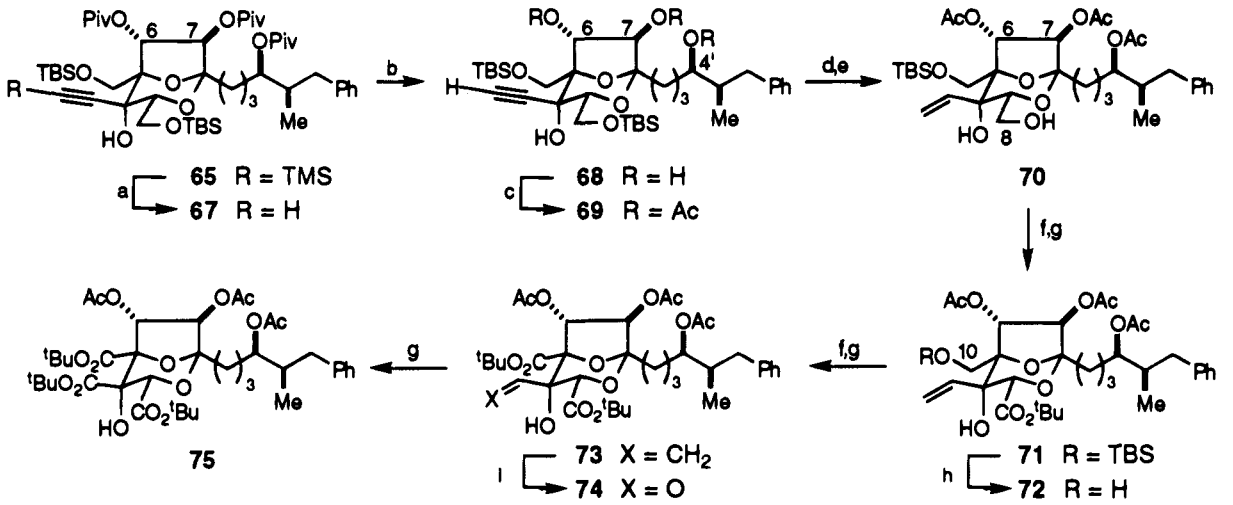
(52) The effect of Et_3N and TMEDA on diastereoselective Grignard additions to chiral keto oxazolines has been documented: Meyers, A. I.; Slade, J. *J. Org. Chem.* **1980**, *45*, 2785.

(53) (a) Schubert, B.; Weiss, E. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 496. (b) Schubert, B.; Weiss, E. *Chem. Ber.* **1983**, *116*, 3212. (c) Seebach, D.; Hässig, R.; Gabriel, J. *Helv. Chim. Acta* **1983**, *66*, 308.

(54) (a) Hässig, R.; Seebach, D. *Helv. Chim. Acta* **1983**, *66*, 2269. (b) Bauer, W.; Seebach, D. *Helv. Chim. Acta* **1984**, *67*, 1972.

(55) (a) Fraenkel, G.; Pramanik, P. *J. Chem. Soc., Chem. Commun.* **1983**, 1527. (b) Fraenkel, G. *Polym. Prepr., Am. Chem. Soc. Div. Polym. Chem.* **1986**, *27*, 132. (c) The crystal structure of $[t\text{-}BuC{\equiv}CLi{\cdot}THF]_4$ has been reported: Geissler, M.; Kopf, J.; Schubert, B.; Weiss, E.; Neugebauer, W.; von Ragué Schleyer, P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 587.

Scheme 7[a]



[a] (a) $AgNO_3$, 2,6-lutidine, 90%; (b) Dibal-H, CH_2Cl_2/toluene, 84%; (c) Ac_2O, 4-DMAP, CH_2Cl_2, 94%; (d) Cl_2CHCO_2H, MeOH, 90%; (e) H_2, Pd–C, C_5H_5N, 99%; (f) Dess–Martin, CH_2Cl_2, 80–95%; (g) $NaClO_2$, NaH_2PO_4, β-isoamylene, THF/H_2O then *N,N'*-diisopropyl-*O-tert*-butylisourea, CH_2Cl_2, 70–85%; (h) HF·pyr, THF/C_5H_5N, 90%; (i) O_3, CH_2Cl_2/MeOH, 97%.

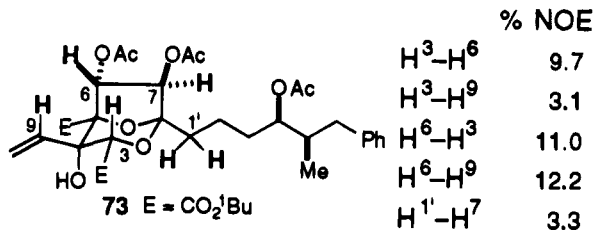


Figure 9. ^1H NMR difference NOE data for **73.**

was based on a small coupling constant (J < 2 Hz) between the C(3)–H methine and the C(4)–OH that was only observed in the ^1H NMR spectrum (500 MHz) of the desired diastereomer **65**. ^1H NMR difference NOE data for the minor diastereomer **66** provided tentative support of this conclusion.[56] Similar experiments performed on intermediate **73** (Scheme 7) allowed for definitive assignment of the stereochemistry at C(3), C(4), C(6), and C(7). Irradiation of the C(6)–H methine resulted in strong enhancement of both the C(3)–H methine (11%) and the C(9)–H vinylic proton (12%). Similarly, NOE enhancement of both C(6)–H (9%) and C(9)–H (3%) was observed upon irradiation of the C(3)–H methine. Irradiation of the signals corresponding to the side chain C(1')–H_2 methylene protons resulted in an enhancement (3%) of the methine signal at C(7)–H (Figure 9). These results secured the configuration of the stereocenter at C(4) and provided additional support for the stereochemical assignment of the dihydroxylation reaction (**45** → **46** + **47**). Moreover, the NOE data accumulated paralleled those reported for the natural product itself.[5]

Synthesis of the Tris-*tert*-butyl Ester 75. Completion of the synthesis of (+)-zaragozic acid C required installation of the C(4') acetate, oxidation at C(8), C(9), and C(10), and coupling of the C(6) *O*-acyl side chain. Treatment of **67** with Dibal-H (CH_2Cl_2/toluene) effected removal of all three trimethylacetyl esters (Scheme 7).[57] Subsequent exposure of the resulting tetraol **68** to excess Ac_2O (4-DMAP, CH_2Cl_2) furnished **69** and installed the requisite acetate at C(4').

In our first synthesis of zaragozic acid C, the oxidations at C(8), C(9), and C(10) were performed in a stepwise manner to give the dioxabicyclooctane tricarboxylate ester **75**. To this end, intermediate **69** was exposed to mildly acidic conditions (Cl_2CHCO_2H, MeOH) to effect selective cleavage of the C(8)–OTBS ether. Semihydrogenation of the terminal acetylene (H_2, Pd–C, pyridine) provided olefin **70**. Oxidation of the primary alcohol in **70** to the corresponding carboxylic acid was accomplished using the Dess–Martin periodinane, followed by treatment of the intermediate aldehyde with buffered $NaClO_2$ solution (NaH_2PO_4, β-isoamylene, THF/H_2O).[58] Esterification of the unpurified acid with *N,N'*-diisopropyl-*O-tert*-butylisourea afforded the *tert*-butyl ester **71**.[59] Following a similar sequence of steps, the TBS ether at C(10) was cleaved (HF·pyridine, THF/pyridine)[60] to give alcohol **72**, which was oxidized and subsequently esterified to give the bis-*tert*-butyl ester **73**.

Deprotection of the C(10)–OTBS ether was best accomplished with HF•pyridine buffered in a THF/pyridine solution and gave the desired product **72** in 90% yield. Attempts to cleave this silyl ether under acidic conditions with either aqueous HF in CH_3CN or Cl_3CCO_2H in MeOH gave some of **72** (60%), along with the product arising from acyl transfer of the C(6)–OAc to the C(10)–OH **76** (Figure 10). Desilylation conditions such as $Et_3N·3HF$ (CH_3CN) and $^nBu_4NF·2H_2O$/HF (aqueous CH_3CN)[61] were examined and yielded similar mixtures of **72** and **76**. Deprotection under basic conditions with $^nBu_4NF$ (THF) or $^nBu_4NF·2H_2O$ (CH_3CN) also resulted in the formation of **76** and, additionally, led to extensive product decomposition.

The remaining carboxylate at C(9) was installed following ozonolysis of **73** and oxidation of the resulting aldehyde **74** with buffered $NaClO_2$ (Scheme 7). Esterification with *N,N'*-diisopropyl-*O-tert*-butylisourea furnished the desired tris-*tert*-butyl ester **75**.

A more expeditious route to **75** from **69** was subsequently developed (Scheme 8). Semihydrogenation of **69** (H_2, Pd–C, pyridine) furnished olefin **77**; exposure of **77** to HF·pyridine (THF/pyridine) provided triol **78**. Longer reaction times (~4

(56) A small NOE was observed (<3%) from the C(6)–H methine to the tertiary OH in the undesired diastereomer **66**.

(57) The use of Dibal-H in CH_2Cl_2/toluene proved to be critical for the successful cleavage of the pivaloate esters. Reactions in either THF or Et_2O failed to remove all three pivaloates.

(58) (a) Lindgren, B. O.; Nilsson, T. *Acta. Chem. Scand.* **1973**, *27*, 888. (b) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175. (c) Kraus, G. A.; Roth, B. *J. Org. Chem.* **1980**, *45*, 4825.

(59) For a review of the synthetic application of isoureas, see: Mathias, L. J. *Synthesis* **1979**, 561.

(60) For the preparation of HF·pyridine buffered with excess pyridine in THF, see: Trost, B. M.; Caldwell, C. G.; Murayama, E.; Heissler, D. *J. Org. Chem.* **1983**, *48*, 3252.

(61) Robinson, R. A.; Clark, J. S.; Holmes, A. B. *J. Am. Chem. Soc.* **1993**, *115*, 10400.

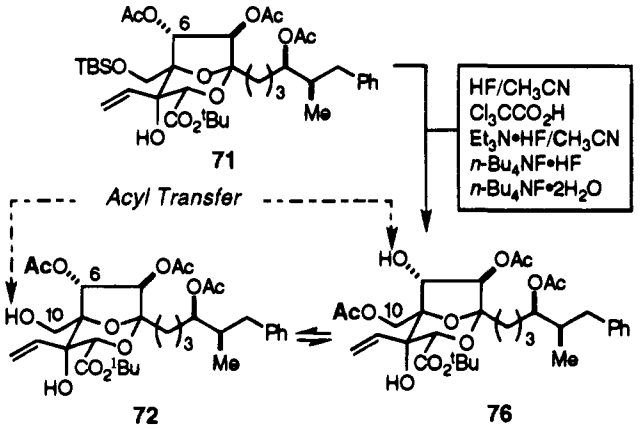
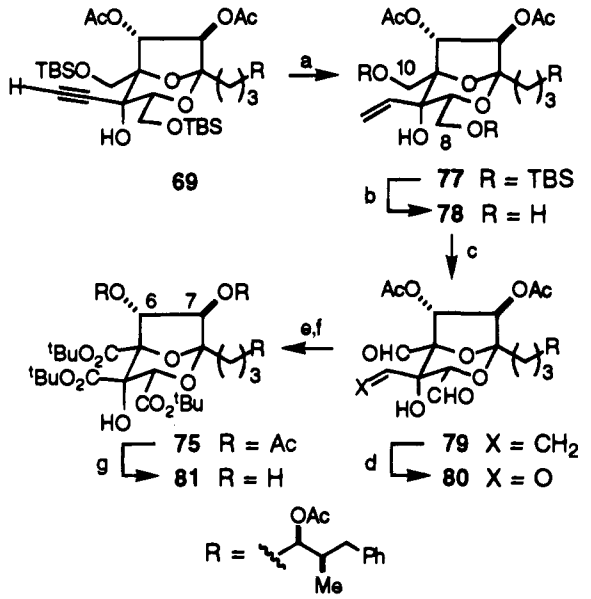


Figure 10. Reagents which cause C(6)—OAc to C(10)—OH acyl transfer.

Scheme 8[a]



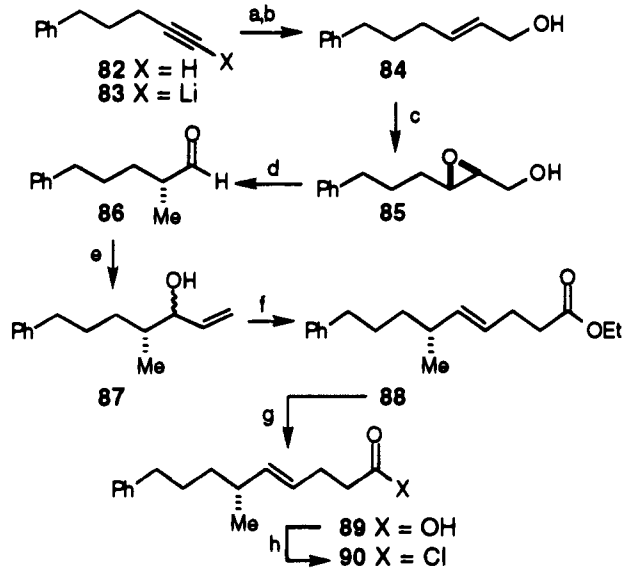
[a] (a) H_2, Pd—C, C_5H_5N; (b) HF•pyr, THF/C_5H_5N, 64% in two steps; (c) Dess—Martin periodinane, CH_2Cl_2/C_5H_5N, 93%; (d) O_3, CH_2Cl_2/MeOH, −78 °C; (e) $NaClO_2$, NaH_2PO_4, β-isoamylene, THF/H_2O; (f) *N,N'*-diisopropyl-*O-tert*-butylisourea, CH_2Cl_2, 72% in three steps; (g) K_2CO_3, MeOH, 90%.

h) were necessary to effect cleavage of both the C(8) and C(10) silyl ethers. As a result, a small percentage (~10—15%) of the product arising from acyl migration of the C(6)—OAc formed (*vide supra*). Fortunately, separation of this material from the desired compound **78** was possible by chromatography on silica gel. Simultaneous oxidation of both primary carbinols at C(8) and C(10) gave dialdehyde **79**. Treatment of a solution of **79** with a dilute stream of ozone (CH_2Cl_2/MeOH, −78 °C), followed by reductive workup with Ph_3P, provided **80**.[62] The unpurified trialdehyde was then treated with a buffered $NaClO_2$ solution and the resulting triacid esterified to give the tris-*tert*-butyl ester **75** (72% in three steps). Selective hydrolysis of the C(6) and C(7) acetates with 0.2% K_2CO_3 in MeOH (0.5 h) yielded **81**.[1a]

Synthesis of the C(6) *O*-Acyl Side Chain. Preparation of the C(6) *O*-acyl side chain was achieved using a Claisen rearrangement-based strategy for the construction of the derived γ,δ-unsaturated carboxylic acid **89** (Scheme 9). Treatment of a suspension of paraformaldehyde in THF with alkynyllithium

(62) The ^1H NMR spectrum of **80** shows a mixture of at least three products, presumed to be hydrated forms of the trialdehyde.

Scheme 9[a]



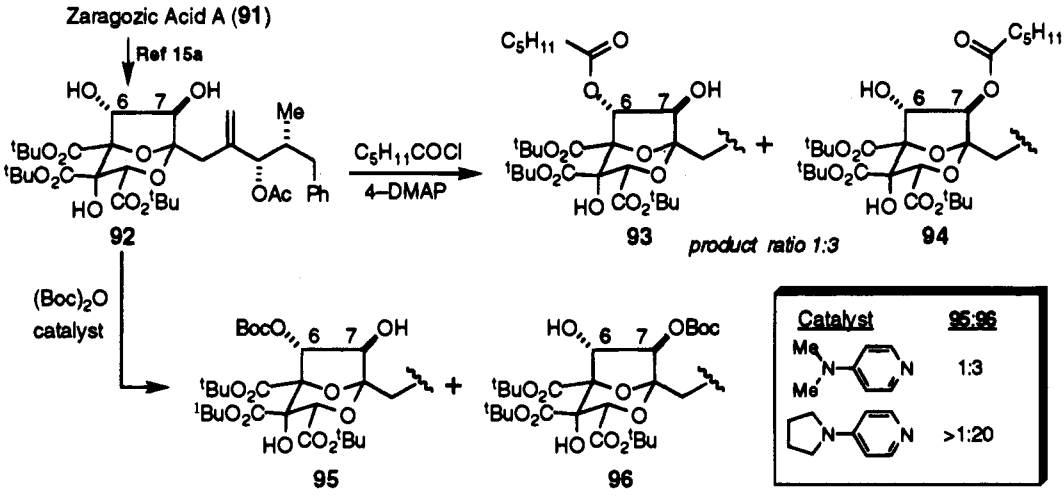
[a] (a) ^{n}BuLi, $(CH_2O)_n$, THF, 92%; (b) $LiAlH_4$, Et_2O, 79%; (c) ^{t}BuOOH, $Ti(O^iPr)_4$, L-(+)-DIPT, 4 Å molecular sieves, CH_2Cl_2, 98%; (d) Me_3Al then $NaIO_4$, aqueous THF; (e) vinyl MgBr, THF, 62% three steps; (f) $(EtO)_3CCH_3$, H^+, 89%; (g) NaOH, H_2O/THF, 100%; (h) $(COCl)_2$, catalytic DMF, CH_2Cl_2.

83 afforded a propargylic alcohol which was reduced with $LiAlH_4$ to give *trans* allylic alcohol **84**.[63] Sharpless asymmetric epoxidation of **84** provided the epoxy alcohol **85** in >95% ee, as determined by analysis of the ^1H NMR spectrum of the corresponding Mosher (*S*)-MTPA ester.[64,65] Regioselective epoxide opening with Me_3Al using conditions described by Roush and Nozaki for related epoxy alcohols, followed by $NaIO_4$ cleavage of the resulting 1,2-diol, yielded **86**.[66] Aldehyde **86** was treated with vinylmagnesium bromide to give a 60:40 mixture of alcohol diastereomers **87**. Upon heating a solution of **87** in triethyl orthoacetate (catalytic diglycolic acid), the *trans* ester **88** was formed exclusively, as determined by ^1H NMR spectroscopy. Saponification of the ethyl ester provided the corresponding carboxylic acid **89**, suitable for coupling to the zaragozic acid core **81**.

Model Studies with Zaragozic Acid A. Previously, it was shown that treatment of **81** (4-DMAP, CH_2Cl_2) with acid chloride **90** prepared from **89** afforded a 1:3 mixture of desired C(6) to undesired C(7) regioisomers.[4] Thus, we initiated an investigation of reaction conditions that would favor formation of desired C(6) *O*-acylated compound. As a model substrate we chose to examine the acylation chemistry of zaragozic acid A (**91**), which was available in multigram quantities.[67] In addition, hexanoyl chloride was employed as a surrogate acyl side chain (Scheme 10). Condensation of **92** with hexanoyl chloride (4-DMAP, CH_3CN) led to the formation of products **93** and **94** in a ratio similar to that observed in our original studies (~1:3). Acylation procedures which utilized either bis-(tributyltin) oxide or dibutyltin oxide and hexanoyl chloride did not provide either **93** or **94**. Hexanoyl chloride was found to

(63) Corey, E. J.; Katzenellenbogen, J. A.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 4245.
(64) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
(65) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.
(66) (a) Suzuki, T.; Saimoto, H.; Tomioka, H.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3597. (b) Roush, W. R.; Adam, M. A.; Peseckis, S. M. *Tetrahedron Lett.* **1983**, *24*, 1377.
(67) We are grateful to Drs. Gregory Berger and Albert Robichaud (Merck Research Laboratories) for generously providing the tris-*tert*-butyl ester of zaragozic acid A.

Scheme 10



couple to **92** in the presence of excess 2-*tert*-butyl-2-(diethylamino)-1,3-dimethylperhydro-1,3,2-diazaphosphorine.[68] In the event, it was discovered that the undesired product **94** had formed predominantly (**93**:**94**, ~1:10 by ^{1}H NMR spectroscopy).

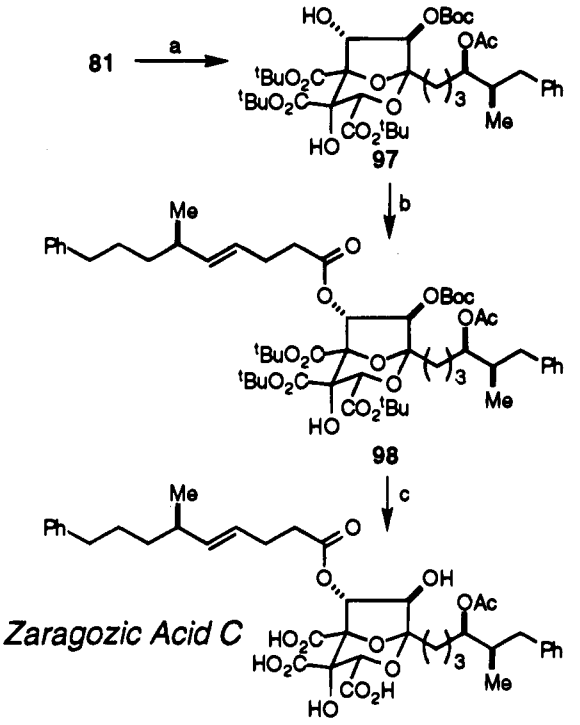
The development of a strategy which involved *in situ* protection of the C(7)−OH and subsequent acylation of the C(6) carbinol was then investigated and ultimately realized. Upon treatment of **92** with di-*tert*-butyl dicarbonate (Et_3N, CH_2Cl_2, 0 °C) and catalytic 4-DMAP, a ~1:3 mixture of C(6)/C(7) carbonates **95** and **96** was isolated (52% combined), along with recovered starting material **92** (~25%) and a small amount (≤15%) of the bis-protected material.[69] Alternatively, when 4-pyrrolidinopyridine was used instead of 4-DMAP, the reaction yielded C(7) *O*-Boc intermediate **96** as the *exclusive* product (80−85%).[70] This highly regioselective transformation made it possible to perform the subsequent coupling of hexanoyl chloride (4-DMAP, Et_3N) to the C(6)−OH in a single operation.[71]

(+)-Zaragozic Acid C. Completion of the zaragozic acid C synthesis was accomplished by following a strategy similar to that developed with the zaragozic acid A model (Scheme 11). Treatment of **81** with di-*tert*-butyl dicarbonate and catalytic 4-pyrrolidinopyridine (Et_3N, CH_2Cl_2) gave **97** in 82% yield. Subsequent addition of a solution of carboxylic acid **89** and 1,3-dicyclohexylcarbodiimide (4-DMAP, CH_2Cl_2) furnished **98** (78%). Complete deprotection of **98** was effected with a 25% solution of trifluoroacetic acid in CH_2Cl_2 (16 h) to afford the target compound, (+)-zaragozic acid C.[1c] Zaragozic acid C, prepared via the synthetic route described, was identical in all respects (^{1}H NMR, ^{13}C NMR, IR, HRMS, TLC, HPLC co-injection, optical rotation) to an authentic sample of the natural product.[72]

Conclusion

We have described an enantioselective synthesis of the potent squalene synthase inhibitor, (+)-zaragozic acid C. This route is highlighted by (1) a highly diastereoselective addition of TMSC≡CMgBr to an α,β-unsaturated ketone to establish the quaternary center at C(5); (2) the use of $[Cr(OAc)_2{\cdot}H_2O]_2$ for the stereoselective reduction of an α,β-ynone to a *trans* enone; (3) an investigation of the effect of amine cosolvents on the nucleophilic addition of TMSC≡CLi to a key dioxabicyclooctanone intermediate; and (4) a solution to the problem of coupling the acyl side chain to the C(6)−OH by regioselective protection of the C(7) carbinol. Additionally, we have outlined a protocol for installing the three carboxylic acids at C(8), C(9), and C(10) by simultaneous oxidation of the corresponding trisaldehyde, which represents a more efficient strategy than that which we have previously reported.[4] This work has resulted in the development of a synthesis which allows for rapid assembly of the dioxabicyclooctane skeleton common to all of the zaragozic acids and squalestatins. Moreover, a number of synthetic transformations on the bicyclic core have been delineated which may be useful for the preparation of synthetic and semisynthetic analogs.

Scheme 11



[a] (a) $(Boc)_2O$, 4-pyrrolidinopyridine, CH_2Cl_2, 82%; (b) **89**, DCC, 4-DMAP CH_2Cl_2 78%; (c) TFA, CH_2Cl_2, 100%.

(68) Schwesinger, R.; Schlemper, H. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1167.

(69) The ratio of **95**:**96** was dependent on the extent of conversion of **92**.

(70) We speculated that the bulkier acylating agent generated with 4-pyrrolidinopyridine would be more selective for the less sterically hindered secondary alcohol at C(7).

(71) In practice, a higher yield of the desired product was isolated when the reaction was performed in a two-step sequence.

(72) We thank Dr. Conrad Santini (Merck Research Laboratories) for generously providing us with an authentic sample of zaragozic acid C.

Experimental Section

General Procedures. All reagents were commercially obtained except where noted. Where appropriate, reagents were purified prior to use. All nonaqueous reactions were performed using flame-dried glassware under an atmosphere of dry nitrogen. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 45 °C at ~25 mmHg (water aspirator). Diethyl ether and tetrahydrofuran were distilled from sodium benzophenone ketyl prior to use. *N,N*-Diisopropylethylamine, dichloromethane, pyridine, triethylamine, and boron trifluoride etherate were distilled from calcium hydride prior to use. Dimethyl sulfoxide and dimethylformamide were distilled under reduced pressure from calcium hydride and stored over 4 Å molecular sieves. Methanol was distilled from magnesium methoxide prior to use. Chromatographic purification of products was accomplished using forced-flow chromatography on Baker 7024-R silica gel according to the method of Still.[73] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60F plates (230–400 mesh). Visualization of the developed chromatogram was performed by either fluorescence quenching, aqueous ceric ammonium molybdate (CAM) stain, or an ethanolic *p*-anisaldehyde spray.

NMR spectra were recorded on a Bruker AM-500 operating at 500 and 125 MHz for ^1H and ^{13}C, respectively, and are referenced internally to residual protio solvent signals. Data for ^1H are reported as follows: chemical shift (δ, ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; qn, quintet; m, multiplet), integration, coupling constant (Hz), and assignment (when indicated, numbered protons refer to zaragozic acid C numbering[1c]). Data for ^{13}C are reported in terms of chemical shift. ^1H NMR NOE difference spectra were recorded on degassed samples and were quantitated by integrating the difference spectra. IR spectra were recorded on a Perkin-Elmer 1600 series spectrometer using NaCl salt plates and are reported in terms of frequency of absorption (ν, cm^{-1}). Melting points were determined on a Mel-Temp apparatus and are uncorrected. Combustion analysis was performed by Galbraith Laboratories, Inc. (Knoxville, TN). High-resolution mass spectra were obtained from the UC Irvine Mass Spectral facility. Optical rotations were determined on a JASCO DIP-181 polarimeter operating at either the sodium D line or Hg_{365} and are reported as follows: $[\alpha]^{23}$, concentration (g/100 mL), and solvent.

***N,N*-Dimethyl-2,3,4-trihydroxybutyramide.** Gaseous Me_2NH (~40 mL, 83 mmol, 1.2 equiv) was condensed directly into a reaction flask containing a suspension of 81.3 g (68.8 mmol) of D-erythronic γ-lactone[18] **13** in 240 mL of reagent-grade methanol at 0 °C. The resulting homogeneous solution was stirred at 0 °C for 15 min and then warmed to 23 °C. Consumption of the starting lactone ($R_f = 0.80$) was monitored by TLC with 1% H_2O–CH_3CN as eluent. After being stirred at 23 °C for 30 min, the solvent was evaporated under reduced pressure to afford a white solid. Recrystallization of the unpurified product from hot/cold methanol yielded 112.3 g (97%) of a white crystalline solid: mp 108–110 °C; $[\alpha]_{Hg}$ −117.4° ($c = 0.15$, CH_3OH); ^1H NMR (CD_3OD, 500 MHz) δ 4.49 (d, 1H, $J = 7.1$ Hz, H_4), 3.74–3.65 (m, 3H, H_3 and H_8), 3.13 (s, 3H, -NCH_3), 2.97 (s, 3H, -NCH_3); ^{13}C NMR (CD_3OD, 125 MHz) δ 174.9, 74.8, 69.5, 64.2, 37.7, 36.2; IR (thin film) ν 3356 (br), 2936, 1629, 1508, 1401, 1257, 1064. Anal. Calcd for $C_6H_{13}NO_4$: C, 44.16; H, 8.03. Found: C, 44.12; H, 8.09.

α-Hydroxy Amide 14. To a solution of 3,3-dimethoxypentane (107 g, 809 mmol, 1.2 equiv) and anhydrous *p*-toluenesulfonic acid (5.5 g, 29 mmol, 0.04 equiv) in 1 L of THF was added *N,N*-dimethyl-2,3,4-trihydroxybutyramide (110 g, 674 mmol) portionwise. The pale yellow solution was heated at reflux for 4 h before being cooled to 23 °C. The reaction was made basic with 20.0 mL of Et_3N and concentrated *in vacuo* to afford a pale yellow oil. The unpurified material was filtered through silica gel (gradient elution, 3:1 → 1:2 hexanes/EtOAc) to give 140 g (90%) of **14** as a clear, colorless oil: TLC $R_f = 0.56$ (1:1 CH_2Cl_2/EtOAc); $[\alpha]_{Hg}$ −27.8° ($c = 0.18$, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 4.38 (d, 1H, $J = 7.4$ Hz, H_4), 4.10 (dd, 1H, $J = 8.2$, 6.2 Hz, H_8), 3.99–3.95 (m, 1H, H_3), 3.90 (dd, 1H, $J = 8.2$, 7.4 Hz, H_8), 3.53 (br s, 1H, secondary -OH), 3.07 (s, 3H, -NCH_3), 2.99 (s, 3H, -NCH_3), 1.69–1.59 (m, 2H, -CH_2CH$_3$), 1.54 (q, 2H, $J = 7.4$ Hz, -CH_2CH$_3$), 0.88 (t, 3H, $J = 7.5$ Hz, -CH$_2$CH_3), 0.81 (t, 3H, $J = 7.4$ Hz, -CH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.2, 113.8, 77.6, 69.0, 67.8, 36.9, 36.0, 29.4, 28.5, 8.1, 8.0; IR (thin film) ν 3417 (br), 2972, 2940, 2883, 1789, 1644, 1504, 1463, 1392, 1172, 1078, 919. Anal. Calcd for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15. Found: C, 56.81; H, 9.17.

α-Benzyloxy Amide 15. A 60% dispersion of NaH in mineral oil (4.4 g, 110 mmol) was washed under a stream of N_2 three times with dry pentane and dried briefly under vacuum. THF was added (125 mL), and the suspension was cooled to 0 °C. A solution of amide **14** (25.0 g, 108 mmol) in 200 mL of THF was added dropwise over a 30 min period. The mixture was stirred until H_2 gas evolution subsided, at which time benzyl bromide (16 mL, 135 mmol) was added via syringe. The reaction was held at 0 °C for 15 min before being warmed to 23 °C. After 3 h at 23 °C, the reaction was quenched with 200 mL of 1.0 M K_2HPO_4, and the product was extracted with Et_2O (3 × 200 mL). The combined organic extracts were washed with saturated aqueous NaCl (1 × 250 mL), dried over Na_2SO_4, and evaporated under reduced pressure. Purification by silica gel chromatography (gradient elution, 5:1 → 1:1 hexanes/EtOAc) gave 33.4 g (96%) of **15** as a colorless oil which solidified *in vacuo*: TLC $R_f = 0.38$ (1:1 hexanes/EtOAc); mp 55–56 °C; $[\alpha]_{Na}$ +136.8° ($c = 0.23$, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.35–7.27 (m, 5H, H_{arom}), 4.62 (d, 1H, $J = 11.8$ Hz, -CH_2Ph), 4.46 (d, 1H, $J = 11.8$ Hz, -CH_2Ph), 4.35 (dd, 1H, $J = 13.1$, 6.5 Hz, H_3), 4.28 (d, 1H, $J = 6.4$ Hz, H_4), 4.15 (dd, 1H, $J = 8.4$, 6.3 Hz, H_8), 3.93 (dd, 1H, $J = 8.4$, 7.0 Hz, H_8), 2.99 (s, 3H, -NCH_3), 2.97 (s, 3H, -NCH_3), 1.66–1.56 (m, 4H, both -CH_2CH$_3$), 0.85 (m, 6H, both -CH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.5, 137.2, 128.4, 127.97, 127.94, 113.4, 76.8, 76.3, 71.8, 67.4, 36.9, 36.05, 36.03, 29.5, 28.4, 8.1; IR (thin film) ν 3030, 2971, 2939, 2881, 1650, 1497, 1455, 1172, 1129, 1083, 1058, 919, 699; HRMS (EI) calcd for $C_{18}H_{27}NO_4$ 321.2120, found 321.1971. Anal. Calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36. Found: C, 67.09; H, 8.47; N, 4.12.

Propargylic Alcohol 17. A 1.7 M solution of ^{t}BuLi in pentane (182 mL, 310 mmol, 3.0 equiv) was added to a solution of ethyl vinyl ether (59 mL, 620 mmol, 6.0 equiv) in 125 mL of THF at −78 °C. After 1 h, the yellow suspension was warmed to 0 °C and stirred for an additional 2 h. The resulting colorless solution was recooled to −78 °C before a cold solution (0 °C) of amide **15** (33.2 g, 103 mmol) in 150 mL of THF was added dropwise. The mixture was stirred at −78 °C for 10 min and then transferred via cannula into 500 mL of a vigorously stirred solution of 1:1 Et_2O/0.2 M aqueous Na_2CO_3 at 0 °C. The organic phase was separated and the aqueous layer extracted with Et_2O (2 × 300 mL). The combined organic extracts were washed with saturated aqueous NaCl (1 × 400 mL), dried over Na_2SO_4, and concentrated to afford 36.0 g of an unpurified yellow oil, **16**: TLC $R_f = 0.57$ (4:1 hexanes/EtOAc).

The unpurified product **16** (36.0 g, 103 mmol) was dissolved in 200 mL of THF, cooled to −78 °C, and added via cannula to a cold suspension (-78 °C) of the Grignard reagent derived from trimethylsilyl acetylene and ethylmagnesium bromide (359 mL of a 0.86 M solution in THF/Et_2O, 3.0 equiv). Following addition, the reaction was warmed to 0 °C and stirred for 15 min before being quenched with 300 mL of saturated aqueous NH_4Cl. The organic phase was collected, and the aqueous layer was extracted with 2 × 300 mL of Et_2O. The organic extracts were combined, washed with saturated aqueous NaCl (1 × 500 mL), dried over Na_2SO_4, and concentrated *in vacuo* to a yellow oil. Purification by chromatography on silica gel (gradient elution, 10:1 → 9:1 hexanes/EtOAc) afforded propargyl alcohol **17** as a single diastereomer (38.7 g, 84%, colorless oil): TLC $R_f = 0.59$ (4:1 hexanes/EtOAc); mp 37–40 °C; $[\alpha]_{Na}$ +71.9° ($c = 0.41$, CH_2Cl_2); ^1H NMR (C_6D_6, 500 MHz) δ 7.44 (d, 2H, $J = 7.2$ Hz, H_{arom}), 7.18 (t, 2H, $J = 7.6$ Hz, H_{arom}), 7.10 (t, 1H, $J = 7.4$ Hz, H_{arom}), 4.98 (d, 1H, $J = 2.3$ Hz, -C=CH_2), 4.93 (d, 1H, $J = 10.8$ Hz, -OCH_2Ph), 4.88 (d, 1H, $J = 10.8$ Hz, -OCH_2Ph), 4.57 (ddd, 1H, $J = 9.0$, 5.7, 2.9 Hz, H_3), 4.47 (d, 1H, $J = 3.3$ Hz, H_4), 4.18 (dd, 1H, $J = 8.1$, 6.2 Hz, H_8), 4.09 (t, 1H, $J = 8.3$ Hz, H_8), 3.98 (d, 1H, $J = 2.3$ Hz, -C=CH_2), 3.39–3.34 (m, 2H, -OCH_2CH$_3$), 3.20 (s, 1H, tertiary -OH), 1.74–1.62 (m, 4H, both -CH_2CH$_3$), 1.00 (t, 3H, $J = 7.0$ Hz, -OCH$_2$CH_3), 0.94 (t, 6H, $J = 7.5$ Hz, both -CH$_2$CH_3), 0.10 (s, 9H, H_{TMS}); ^{13}C NMR (CD_2Cl_2, 125 MHz) δ 160.3, 139.1, 128.8, 128.5, 128.2, 112.7, 106.0, 90.8, 84.6, 82.1, 77.0, 76.1, 74.5, 66.7, 64.4, 30.3, 29.4, 14.8, 8.7, 8.5, 0.01; IR (thin film) ν 3421 (br), 2973, 2940, 2170, 1654, 1628, 1498, 1458, 1376, 1251, 1130,

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1072, 1058, 843, 759, 698. Anal. Calcd for $C_{25}H_{38}SiO_5$: C, 67.23; H, 8.57. Found: C, 67.32; H, 8.15.

Alkynyl Ester 19. A solution of vinyl ether **17** (43.2 g, 96.7 mmol) in 450 mL of CH_2Cl_2 and 50 mL of absolute EtOH was cooled to −78 °C before being treated with a dilute stream of ozone in oxygen (0.8 mmol/min). Careful monitoring by TLC showed the reaction to be complete after 2.5 h (~1 equiv of O_3). Triphenylphosphine (26.2 g, 100 mmol) was then added to the reaction, and the mixture was slowly warmed to 23 °C. Concentration of the reaction mixture yielded an orange oil. Purification by chromatography on silica gel (gradient elution, 12:1 → 6:1 hexanes/EtOAc) gave 36.4 g (84%) of a clear, viscous oil, **19**: TLC $R_f = 0.42$ (4:1 hexanes/EtOAc); $[\alpha]_{Hg}$ +92.3° (c = 0.17, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38−7.27 (m, 5H, H_{arom}), 5.03 (d, 1H, J = 11.1 Hz, -CH_2Ph), 4.77 (d, 1H, J = 11.1 Hz, -CH_2Ph), 4.41−4.36 (m, 1H, -OCH_2CH$_3$), 4.27 (m, 1H, H_3), 4.17 (m, 1H, -OCH_2CH$_3$), 4.09 (d, 1H, J = 5.9 Hz, H_4), 4.03 (dd, 1H, J = 8.2, 6.3 Hz, H_8), 3.73 (t, 1H, J = 8.1 Hz, H_8), 3.69 (s, 1H, tertiary -OH), 1.61−1.54 (m, 4H, both -CH_2CH$_3$), 1.32 (t, 3H, J = 7.1 Hz, -OCH$_2$CH_3), 0.85 (m, 6H, both -CH$_2$CH_3), 0.16 (s, 9H, H_{TMS}); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.7, 137.8, 128.3, 127.84, 127.78, 112.88, 102.1, 91.3, 83.7, 76.0, 74.7, 73.1, 67.0, 62.9, 29.4, 28.7, 13.8, 8.1, −0.49, −0.52; IR (thin film) ν 3482 (br), 2970, 2941, 2883, 1743, 1498, 1464, 1295, 1251, 1127, 1094, 1077, 1060, 1028, 845, 698 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{36}SiO_6$ 448.2550, found 448.2271.

Core Fragment 21. A solution of the alkynyl ester **19** (36.2 g, 80.7 mmol) in 200 mL of CH_3OH was cooled to 0 °C, and $NaBH_4$ (9.1 g, 240 mmol, 3.0 equiv) was cautiously added portionwise. Once gas evolution had subsided, the mixture was warmed to 23 °C. After 2 h, the reaction was recooled to 0 °C, diluted with 100 mL of Et_2O, and acidified to pH 2 with aqueous 1.0 M $NaHSO_4$. The ethereal layer was collected, and the aqueous layer was extracted with 3 × 300 mL of CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and then concentrated to a colorless, viscous oil (32.8 g). The product **20** was used without further purification: TLC $R_f = 0.52$ (2:1 hexanes/EtOAc).

To a solution of **20** (32.8 g, 80.7 mmol) in 200 mL of CH_3OH was added solid K_2CO_3 (11.2 g, 80.7 mmol). The reaction was stirred for 8 h at 23 °C before 300 mL of Et_2O was added. The resulting precipitate was removed via filtration through Celite. Evaporation of the filtrate under reduced pressure afforded a pale brown oil, which was purified by chromatography on silica gel (gradient elution, 9:1 → 1:1 hexanes/EtOAc) to furnish 21.0 g (78%) of diol **21** as a clear, colorless oil: TLC $R_f = 0.27$ (2:1 hexanes/EtOAc); $[\alpha]_{Na}$ +68.5° (c = 0.43, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.38−7.32 (m, 5H, H_{arom}), 4.85 (d, 1H, J = 11.4 Hz, -CH_2Ph), 4.65 (d, 1H, J = 11.4 Hz, -CH_2Ph), 4.52−4.47 (m, 1H, H_3), 4.43 (s, 1H, tertiary -OH), 4.10 (dd, 1H, J = 8.4, 6.2 Hz, H_8), 3.84−3.80 (m, 2H, H_{10}), 3.65 (d, 1H, J = 8.4 Hz, H_4), 3.59 (t, 1H, J = 7.9 Hz, H_8), 2.54 (s, 1H, -C≡CH), 2.35 (dd, 1H, J = 9.9, 4.4 Hz, primary -OH), 1.67−1.60 (m, 4H, both -CH_2CH$_3$), 0.89 (t, 6H, J = 7.4 Hz, both -CH$_2$CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.5, 128.5 (2), 128.2, 114.1, 82.8, 78.5, 76.3, 74.76, 74.72, 73.9, 68.4, 66.1, 29.8, 28.9, 8.1, 8.0; IR (thin film) ν 3446 (br), 3283, 2972, 2939, 1456, 1355, 1200, 1077, 917. Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 67.89; H, 7.91.

Core Fragment 22. To a solution of diol **21** (18.9 g, 56.5 mmol) in 250 mL of CH_2Cl_2 were added Et_3N (23.6 mL, 169.0 mmol, 3.0 equiv), ^{t}BuMe$_2$SiCl (12.8 g, 84.8 mmol, 1.5 equiv), and 4-DMAP (696 mg, 5.7 mmol, 0.1 equiv). The reaction mixture was stirred at 23 °C for 12 h before an additional 3.0 equiv of Et_3N (23.6 mL) was added, along with 700 mg of 4-DMAP and Me_3SiCl (10.7 mL, 84.8 mmol, 1.5 equiv). A precipitate formed immediately following addition of Me_3SiCl. After 30 min, the pale red mixture was poured into 200 mL of a 1.0 M K_2HPO_4 solution. The product was extracted into CH_2Cl_2 (3 × 100 mL), and the combined extracts were dried over Na_2SO_4 and concentrated to a red-brown oil. Purification by chromatography on silica gel (gradient elution, 30:1 → 20:1 hexanes/Et_2O) afforded 26.0 g (88%) of **22** as a colorless oil: TLC $R_f = 0.65$ (8:1 hexanes/EtOAc); $[\alpha]_{Hg}$ +150.0° (c = 0.17, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36 (dd, 2H, J = 7.4, 1.5 Hz, H_{arom}), 7.34−7.31 (m, 2H, H_{arom}), 7.28−7.26 (m, 1H, H_{arom}), 4.87 (d, 1H, J = 11.1 Hz, -CH_2Ph), 4.80 (d, 1H, J = 11.1 Hz, -CH_2Ph), 4.47 (ddd, J = 8.5, 6.6, 1.7 Hz, 1H, H_3), 4.13−4.06 (m, 3H, H_4, H_8), 3.78 (d, 1H, J = 10.3 Hz, H_{10}), 3.60 (d, 1H, J = 10.3 Hz, H_{10}), 2.47 (s, 1H, -C≡CH), 1.69−1.55 (m, 4H, both -CH_2CH$_3$), 0.94−0.87 (m, 6H, both -CH$_2$CH_3), 0.92 (s, 9H, $H_{TBS\text{-}^t Bu}$), 0.19 (s, 9H, H_{TMS}), 0.09 (s, 3H, $H_{TBS\text{-}Me}$), 0.07 (s, 3H, $H_{TBS\text{-}Me}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 139.0, 128.1, 127.5, 127.2, 111.0, 83.8, 80.1, 76.6, 76.0, 75.5, 74.3, 68.4, 65.0, 29.8, 28.7, 25.9, 18.3, 8.4, 8.1, 1.9, −5.2, −5.3; IR (thin film) ν 2930, 2857, 1463, 1359, 1251, 1129, 1102, 984, 924, 840, 778; HRMS (EI) calcd for $C_{28}H_{48}Si_2O_5$ 520.3265, found 520.3045.

Aldol Adduct 25. To a solution of (*S*)−benzyloxazolidinone[24] (20.0 g, 85.7 mmol) in 400 mL of CH_2Cl_2 at −78 °C was added a solution of 25.5 g of 9-BBNOTf (94.3 mmol, 1.1 equiv) in 50.0 mL of CH_2Cl_2, followed by neat ^{i}Pr$_2$NEt (20.9 mL, 120.0 mmol, 1.4 equiv). The mixture was allowed to stir for 30 min at −78°C and was then warmed to 0 °C, where it was held for an additional 3 h. Upon recooling the contents to −78 °C, a cold solution (−78 °C) of aldehyde **24** (18.1 g, 94.3 mmol, 1.1 equiv) in 100 mL of CH_2Cl_2 was transferred via cannula to the reaction flask. The solution was allowed to warm slowly to 23 °C over 12 h. After cooling to 0 °C, the reaction was diluted with 400 mL of MeOH and 90 mL of a 1.0 M aqueous K_2HPO_4−H_3PO_4 solution (pH 7). Careful addition of 180 mL of a 1:1 MeOH/30% H_2O_2 solution resulted in the formation of a milky white suspension, which was stirred vigorously at 0 °C for 2 h. The mixture was partitioned between 400 mL of H_2O and 400 mL of CH_2Cl_2, the organic phase was collected, and the aqueous layer was extracted with 2 × 400 mL of CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and concentrated *in vacuo* to a yellow oil. Purification by chromatography on silica gel (gradient elution, 5:1 → 1:1 hexanes/EtOAc) gave **25** (30.4 g, 84%) as a single diastereomer: TLC $R_f = 0.12$ (2:1 hexanes/EtOAc); $[\alpha]_{Na}$ +101.9° (c = 0.41, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35−7.33 (m, 6H, H_{arom}), 7.30−7.26 (m, 2H, H_{arom}), 7.20 (d, 2H, J = 7.2 Hz, H_{arom}), 4.72−4.68 (m, 1H, -OCH$_2$CH(N)Bn), 4.50 (s, 2H, -OCH_2Ph), 4.24−4.18 (m, 2H, -OCH_2CH(N-)Bn), 3.96−3.95 (m, 1H, $H_{5'}$), 3.76 (ddd, 1H, J = 14.1, 7.0, 2.6 Hz, $H_{4'}$), 3.48 (t, 2H, J = 6.5 Hz, -CH_2OCH$_2$Ph), 3.25 (dd, 1H, J = 13.4, 3.3 Hz, -OCH$_2$CH(N)CH_2Ph), 2.89 (d, 1H, J = 3.0 Hz, secondary -OH), 2.79 (dd, 1H, J = 13.4, 9.5 Hz, -OCH$_2$CH(N)-CH_2Ph), 1.68−1.55 (m, 4H, $H_{1'}$, $H_{3'}$), 1.47−1.41 (m, 2H, $H_{2'}$), 1.25 (d, 3H, J = 7.0 Hz, $H_{13'}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.5, 153.0, 138.6, 135.0, 129.4, 129.0, 128.3, 127.6, 127.45, 127.43, 72.9, 71.4, 70.2, 66.2, 55.1, 42.1, 37.8, 33.6, 29.6, 22.7, 10.4; IR (thin film) ν 3512 (br), 2938, 2861, 1779, 1695, 1496, 1454, 1385, 1210, 1109, 738; HRMS (FAB$^+$) calcd for $C_{25}H_{31}NO_5$ 425.2202, found 426.2287 (MH$^+$).

Diol 27. To a solution of aldol adduct **25** (28.0 g, 65.8 mmol) in 1 L of a 3:1 THF/H_2O mixture at 0 °C was added 30% H_2O_2 (26.4 mL, 264 mmol, 4.0 equiv) dropwise. LiOH·H_2O (5.5 g, 132 mmol, 2.0 equiv) was transferred in five equal portions to the reaction flask. Stirring continued at 0 °C for 3 h before 200 mL of a 1.5 M aqueous Na_2SO_3 solution (4.5 equiv) was carefully added. The mixture was made alkaline by the addition of 250 mL of saturated aqueous $NaHCO_3$, then acidified to pH = 1 with ~500 mL of a 10% v/v HCl solution. The organic phase was collected, and the aqueous layer was extracted with 4 × 750 mL of CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4 and concentrated to a pale orange, viscous oil (17.5 g). The product was used without further purification.

A solution of the unpurified acid (17.5 g, 65.8 mmol) in 500 mL of THF was cooled to 0 °C, and solid $LiAlH_4$ (11.4 g, 300.0 mmol) was cautiously added portionwise. Following addition, the gray suspension was heated to reflux. After 8 h at reflux, the mixture was cooled to 0 °C, diluted with 250 mL of Et_2O, and quenched by the dropwise addition of 500 mL of a 10% v/v HCl solution. The ethereal layer was collected and the aqueous phase extracted with 3 × 400 mL of Et_2O. The combined organic extracts were dried over Na_2SO_4, and the solvent was removed under reduced pressure to afford a pale orange oil. Purification of the residue by chromatography on silica gel (gradient elution, 2:1 → 1:3 CH_2Cl_2/EtOAc) furnished the diol **27** as a white solid (15.2 g, 92%): TLC $R_f = 0.30$ (1:1 CH_2Cl_2/EtOAc); mp 43−44 °C; $[\alpha]_{Na}$ +40.8 (c = 0.42, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.35−7.34 (m, 4H, H_{arom}), 7.33−7.28 (m, 1H, H_{arom}), 4.50 (s, 2H, -OCH_2Ph), 3.82 (m, 1H, $H_{4'}$), 3.69 (m, 2H, $H_{6'}$), 3.49 (dt, 2H, J = 6.3, 1.6 Hz, -CH_2OCH$_2$Ph), 2.47 (br s, 2H, primary -OH and secondary -OH), 1.78−1.74 (m, 1H, $H_{5'}$), 1.68−1.51 (m, 4H, $H_{1'}$, $H_{3'}$), 1.49−1.41 (m, 2H, $H_{2'}$), 0.90 (d, 3H, J = 7.1 Hz, $H_{13'}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 138.5, 128.4, 127.7, 127.6, 74.5, 73.0, 70.3, 67.2, 39.1, 33.7, 29.6, 22.9, 10.1; IR (thin film) ν 3367 (br), 2935, 1361, 1099,

1027, 734, 696. Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.25; H, 9.51.

Tosylate 28. To an ice-cold solution of diol **27** (15.0 g, 59.5 mmol) in 300 mL of pyridine was added solid *p*-TsCl (11.3 g, 59.5 mmol, 1.0 equiv). The solution was stirred at 0 °C for 42 h and then partitioned between 300 mL of a 10% v/v HCl solution and 400 mL of Et_2O. The ethereal layer was collected and washed with 300 mL of 10% v/v HCl. The combined aqueous portions were extracted with 3 × 300 mL of Et_2O. The ethereal extracts were washed successively with 1 × 400 mL of 10% v/v HCl, 1 × 400 mL of 0.2 M aqueous $CuSO_4$, and 1 × 400 mL of saturated aqueous NaCl and then dried over Na_2SO_4. Evaporation of the Et_2O under reduced pressure yielded a pale brown residue which was purified by chromatography on silica gel (gradient elution, 5:1 → 1:1 hexanes/EtOAc) to give the product **28** as a colorless oil (21.5 g, 89%): TLC $R_f = 0.62$ (1:1 hexanes/EtOAc); $[\alpha]_{Na}$ +45.8° (c = 0.38, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.79 (d, 2H, J = 8.2 Hz, H_{arom}), 7.36–7.32 (m, 6H, H_{arom}), 7.31–7.27 (m, 1H, H_{arom}), 4.50 (s, 2H, -OCH_2Ph), 4.06 (dd, 1H, J = 9.7, 7.9 Hz, $H_{6'}$), 3.88 (dd, 1H, J =9.7, 6.0 Hz, $H_{6'}$), 3.70 (m, 1H, $H_{4'}$), 3.49–3.45 (m, 2H, -CH_2OCH$_2$Ph), 2.45 (s, 3H, -SO_2ArCH_3), 1.91–1.86 (m, 1H, $H_{5'}$), 1.67–1.34 (m, 6H, $H_{1'}$, $H_{2'}$, $H_{3'}$), 0.84 (d, 3H, J = 7.0 Hz, $H_{13'}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 144.8, 138.6, 133.1, 129.9, 128.4, 127.9, 127.7, 127.5, 72.9, 72.7, 70.5, 70.2, 37.8, 34.1, 29.6, 22.9, 21.6, 9.5; IR (thin film) ν 3433 (br), 2938, 2861, 1598, 1495, 1454, 1357, 1188, 1176, 1097, 963, 814, 737. Anal. Calcd for $C_{22}H_{30}SO_5$: C, 65.00; H, 7.44. Found: C, 64.94; H, 7.53.

Alcohol 30. A 1.3 M solution of PhLi (64.5 mL, 83.8 mmol, 1.5 equiv) in 70:30 cyclohexane/Et_2O was added dropwise to a solution of **28** (22.7 g, 55.8 mmol) in 500 mL of THF at 0 °C. The mixture was warmed to 23 °C and stirred for 30 min and then transferred via cannula over a 1 h period to a solution of PhLi (1.3 M *c*-hex/Et_2O, 129.0 mL, 167.6 mmol, 3.0 equiv) and BF_3·OEt_2 (21.0 mL, 167.6 mmol, 3.0 equiv) in 250 mL of THF at −78 °C. Following addition, the reaction was warmed to 0 °C over 1 h and then quenched by addition of 600 mL of saturated aqueous $NaHCO_3$. The aqueous phase was collected and extracted with 3 × 300 mL of Et_2O. The combined organic extracts were washed once with saturated aqueous NaCl (500 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification of the isolated brown residue by chromatography on silica gel (gradient elution, 7:1 → 3:1 hexanes/EtOAc) afforded 15.8 g (91%) of **30** as a clear, colorless oil: TLC $R_f = 0.23$ (4:1 hexanes/EtOAc); $[\alpha]_{Na}$ +4.5° (c = 0.43, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36–7.34 (m, 4H, H_{arom}), 7.31–7.27 (m, 3H, H_{arom}), 7.21–7.17 (m, 3H, H_{arom}), 4.50 (s, 2H, -OCH_2Ph), 3.55–3.51 (m, 1H, $H_{4'}$), 3.48 (t, 2H, J = 6.4 Hz, -CH_2OCH$_2$Ph), 2.78 (dd, 1H, J = 13.4, 6.3 Hz, $H_{6'}$), 2.46 (dd, 1H, J = 13.4, 8.6 Hz, $H_{6'}$), 1.85–1.82 (m, 1H, $H_{5'}$), 1.83–1.34 (m, 6H, $H_{1'}$, $H_{2'}$, $H_{3'}$), 0.85 (d, 3H, J = 6.9 Hz, $H_{13'}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.2, 138.6, 129.1, 128.33, 128.25, 127.6, 127.5, 125.8, 74.1, 72.9, 70.3, 40.3, 39.9, 34.5, 29.7, 23.0, 13.1; IR (thin film) ν 3419 (br), 2935, 1494, 1452, 1359, 1099, 735; HRMS (FAB$^+$) calcd for $C_{21}H_{28}O_2$ 312.2089, found 313.2167 (MH$^+$).

C(1) Alkyl Side Chain Alcohol 31. To a solution of alcohol **30** (4.80 g, 15.4 mmol) in 150 mL of CH_2Cl_2 was added 4-DMAP (2.40 g, 20.0 mmol, 1.3 equiv), followed by ^{t}BuCOCl (2.50 mL, 20.0 mmol, 1.3 equiv). The reaction was heated at reflux for 16 h. After cooling to 23 °C, the mixture was poured into 200 mL of saturated aqueous $NaHCO_3$. The aqueous phase was collected and extracted with 2 × 200 mL of CH_2Cl_2. The combined organic extracts were washed with 1 × 250 mL of saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. Purification of the product by chromatography on silica gel (gradient elution, 20:1 → 15:1 hexanes/Et_2O) gave 5.5 g (90%) of the pivaloate ester **30′** as a colorless oil: TLC $R_f = 0.71$ (hexanes/EtOAc); $[\alpha]_{Na}$ +70.8° (c = 0.25, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36–7.33 (m, 5H, H_{arom}), 7.32–7.26 (m, 2H, H_{arom}), 7.18 (t, 1H, J = 7.3 Hz, H_{arom}), 7.11 (d, 2H, J = 7.2 Hz, H_{arom}), 4.89 (dt, 1H, J = 8.4, 4.2 Hz, $H_{4'}$), 4.49 (s, 2H, -OCH_2Ph), 3.46 (t, 2H, J = 6.5 Hz, -CH_2OCH$_2$Ph), 2.75 (dd, 1H, J = 13.4, 5.0 Hz, $H_{6'}$), 2.30 (dd, 1H, J = 13.4, 9.6 Hz, $H_{6'}$), 1.99–1.94 (m, 1H, $H_{5'}$), 1.72–1.54 (m, 4H, $H_{1'}$, $H_{3'}$), 1.40–1.28 (m, 2H, $H_{2'}$), 1.25 (s, 9H, $H_{Piv\text{-}^tBu}$), 0.86 (d, 3H, J = 6.8 Hz, $H_{13'}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.0, 140.7, 138.7, 129.1, 128.33, 128.26, 127.6, 127.5, 125.9, 76.2, 72.9, 70.1, 39.51, 39.49, 38.7, 31.1, 29.6, 27.3, 22.4, 13.9; IR (thin film) ν 2935, 2866, 1724, 1603, 1496, 1479, 1454, 1396, 1362, 1283, 1163, 1102, 1029, 736; HRMS (FAB$^+$) calcd for $C_{26}H_{36}O_3$ 396.2664, found 397.2729 (MH$^+$).

Palladium on carbon (5%, 2.0 g, 25 wt %) was suspended in a 200 mL EtOAc solution of **30′** (8.50 g, 21.4 mmol). The slurry was stirred at 23 °C under 1 atm of H_2 for 12 h. Removal of the palladium catalyst by filtration through Celite, followed by evaporation of the filtrate under reduced pressure, afforded 6.5 g (99%) of a colorless oil. The alcohol **31** was used without further purification: TLC $R_f = 0.17$ (4:1 hexanes/EtOAc); $[\alpha]_{Na}$ +68.5° (c = 0.31, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27 (t, 2H, J = 7.4 Hz, H_{arom}), 7.19 (t, 1H, J = 7.4 Hz, H_{arom}), 7.11 (d, 2H, J = 7.11 Hz, H_{arom}), 4.89 (dt, 1H, J =8.3, 4.2 Hz, $H_{4'}$), 3.62 (t, 2H, J = 6.5 Hz, -CH_2OH), 2.74 (dd, 1H, J = 13.4, 5.2 Hz, $H_{6'}$), 2.31 (dd, 1H, J = 13.4, 9.4 Hz, $H_{6'}$), 1.99–1.94 (m, 1H, $H_{5'}$), 1.70–1.50 (m, 4H, $H_{1'}$, $H_{3'}$), 1.41–1.29 (m, 3H, $H_{2'}$ and -$OH_{1'}$), 1.25 (s, 9H, $H_{Piv\text{-}^tBu}$), 0.87 (d, 3H, J = 6.8 Hz, $H_{13'}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.2, 140.7, 129.1, 128.3, 125.9, 76.0, 62.9, 39.6, 39.1, 38.7, 32.5, 31.1, 27.3, 21.8, 13.9; IR (thin film) ν 3428 (br), 3026, 2935, 2871, 1724, 1602, 1495, 1480, 1457, 1396, 1284, 1164, 1058, 963, 744. Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.46; H, 9.87. Found: C, 74.05; H, 10.16.

C(1) Alkyl Side Chain Aldehyde 32. Dimethyl sulfoxide (6.00 mL, 84.0 mmol, 4.0 equiv) was added dropwise to a solution of oxalyl chloride (3.70 mL, 42.0 mmol, 2.0 equiv) in 100 mL of CH_2Cl_2 at −78 °C. Following gas evolution, the mixture was stirred for 10 min before a solution of alcohol **31** (6.30 g, 20.6 mmol) in 75.0 mL of CH_2Cl_2 was added dropwise over 45 min. The resulting white suspension was stirred at −78 °C for an additional 30 min. Triethylamine (16.7 mL, 120 mmol, ~6.0 equiv) was then added dropwise, causing the solution to clear. The solution was stirred at −78 °C for 15–20 min before warming to 0 °C. The reaction was quenched at 0 °C with 200 mL of a 1.0 M aqueous KH_2PO_4 solution. The organic layer was collected, and the aqueous phase was extracted with 3 × 100 mL of CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the yellow residue by chromatography on silica gel (gradient elution, 8:1 → 6:1 hexanes/EtOAc) gave **32** as a colorless oil (6.0 g, 96%): TLC $R_f = 0.48$ (4:1 hexanes/EtOAc); $[\alpha]_{Na}$ +60.2° (c = 0.34, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.74 (t, 1H, J = 1.4 Hz, -CHO), 7.27 (t, 2H, J = 7.5 Hz, H_{arom}), 7.19 (t, 1H, J = 7.4 Hz, H_{arom}), 7.11 (d, 2H, J = 7.3 Hz, H_{arom}), 4.88 (dt, 1H, J = 8.2, 3.9 Hz, $H_{4'}$), 2.74 (dd, 1H, J = 13.4, 5.3 Hz, $H_{6'}$), 2.46–2.41 (m, 2H, -CH_2-CHO), 2.31 (dd, 1H, J = 13.4, 9.3 Hz, $H_{6'}$), 1.99–1.94 (m, 1H, $H_{5'}$), 1.70–1.52 (m, 4H, $H_{2'}$, $H_{3'}$), 1.26 (s, 9H, $H_{Piv\text{-}^tBu}$), 0.87 (d, 3H, J = 6.8 Hz, $H_{13'}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 201.9, 178.1, 140.5, 129.0, 128.3, 125.9, 75.4, 43.4, 39.4, 39.0, 38.7, 30.7, 27.3, 18.1, 13.9; IR (thin film) ν 3026, 2968, 2873, 2719, 1724, 1495, 1480, 1455, 1396, 1283, 1163, 1031, 961, 743. Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.49; H, 9.56.

Propargylic Alcohol 34. To a solution of alkyne **22** (15.4 g, 29.6 mmol, 1.5 equiv) in 150 mL of THF at −45 °C was slowly added a 1.6 M solution of ^{n}BuLi in hexanes (16.0 mL, 25.6 mmol, 1.3 equiv). The mixture was held at −45 °C for 45 min, and then a 4.0 M solution of LiBr in THF (2.5 mL, 9.9 mmol, 0.5 equiv) was added. After the mixture was stirred for 10 min, a cold solution (−45 °C) of **32** (6.0 g, 19.7 mmol) in 34.0 mL of THF was added via cannula over 40 min. Following addition, the reaction was stirred for 10 min and then quenched with 200 mL of saturated aqueous NH_4Cl. The mixture was partitioned with Et_2O (100 mL), the organic phase was collected, and the aqueous phase was extracted with 3 × 150 mL of Et_2O. The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to a pale yellow oil. Purification by chromatography on silica gel (gradient elution, 10:1 → 2:1 hexanes/Et_2O) afforded 15.2 g (93%) of **34** as a clear, colorless oil. Recovery of excess starting acetylene **22** was essentially quantitative (5.0 g). The product was isolated as a mixture of C(1) alcohol epimers: TLC $R_f = 0.49$ (4:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.36–7.25 (m, 7H, H_{arom}), 7.18 (t, 1H, J = 7.4 Hz, H_{arom}), 7.10 (d, 2H, J = 7.0 Hz, H_{arom}), 4.89 (d, 1H, J = 11.2 Hz, -OCH_2Ph), 4.85 (m, 1H, $H_{4'}$), 4.77 (d, 1H, J = 11.2 Hz, -OCH_2-Ph), 4.46 (ddd, J = 8.5, 6.6, 1.9 Hz, H_3), 4.30–4.26 (m, 1H, H_1), 4.12–4.05 (m, 3H, H_4 and H_8), 3.74 (two d, 1H, J = 10.2 Hz, H_{10} + epimer), 3.56 (d, 1H, J = 10.2 Hz, H_{10}), 2.72 (dd, 1H, J = 13.4, 5.0 Hz, $H_{6'}$), 2.29 (dd, 1H, J = 13.4, 9.4 Hz, $H_{6'}$), 1.99–1.94 (m, 1H, $H_{5'}$), 1.69–1.35 (m, 10H, $H_{1'}$, $H_{2'}$, $H_{3'}$ and both -CH_2CH$_3$), 1.24 (s, 9H, $H_{Piv\text{-}^tBu}$),

0.93−0.85 (m, 9H, $H_{13'}$ and both -CH_2CH_3), 0.91 (s, 9H, $H_{TBS\text{-}^tBu}$), 0.18 (s, 9H, H_{TMS}), 0.08 (s, 3H, $H_{TBS\text{-}Me}$), 0.06 (s, 3H, $H_{TBS\text{-}Me}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.02, 178.00, 140.6, 139.1, 129.1, 128.3, 128.1, 127.3, 127.2, 125.9, 111.1, 110.4, 88.37, 88.35, 84.5, 80.44, 80.35, 76.6, 75.86, 75.82, 75.4, 74.3, 68.3, 65.0, 62.1, 39.5, 39.0, 38.66, 38.62, 37.31, 37.27, 30.82, 30.77, 29.7, 28.6, 27.3, 25.9, 21.41, 21.37, 18.3, 13.9, 8.3, 8.1, 1.98, 1.93, −5.2, −5.3; IR (thin film) ν 3464 (br) 2956, 1726, 1462, 1361, 1284, 1250, 1159, 1131, 1100, 984, 842, 778. Anal. Calcd for $C_{47}H_{76}Si_2O_8$: C, 68.40; H, 9.28. Found: C, 68.40; H, 8.92.

Ynone 35. To a solution of alcohol **34** (15.1 g, 18.3 mmol) in 150 mL of CH_2Cl_2 was added 15.5 g (36.6 mmol, 2.0 equiv) of the Dess−Martin periodinane.[31] The resulting white suspension was stirred at 23 °C for 5 h. To the reaction mixture was then added 300 mL of pentane. The resulting precipitates were removed by filtration through Celite. The filtrate was concentrated *in vacuo* and the isolated pale yellow residue purified by chromatography on silica gel (gradient elution, 15:1 → 10:1 hexanes/Et_2O) to afford 14.0 g (93%) of **35**: TLC R_f = 0.54 (6:1 hexanes/EtOAc); $[\alpha]_{Na}$ +57.8° (c = 0.38, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.36−7.25 (m, 7H, H_{arom}), 7.18 (t, 1H, J = 7.4 Hz, H_{arom}), 7.10 (d, 2H, J = 7.1 Hz, H_{arom}), 4.89 (d, 1H, J = 11.2 Hz, -OCH_2Ph), 4.85−4.83 (m, 1H, $H_{4'}$), 4.76 (d, 1H, J = 11.2 Hz, -OCH_2Ph), 4.42 (ddd, J = 8.4, 6.5, 2.0 Hz, H_3), 4.11 (d, 1H, J = 2.0 Hz, H_4), 4.08−4.01 (m, 2H, H_8), 3.73 (d, 1H, J = 10.2 Hz, H_{10}), 3.65 (d, 1H, J = 10.2 Hz, H_{10}), 2.73 (dd, 1H, J = 13.4, 5.0 Hz, $H_{6'}$), 2.49 (t, 2H, J = 6.8 Hz, $H_{1'}$), 2.27 (dd, 1H, J = 13.4, 9.6 Hz, $H_{6'}$), 1.99−1.94 (m, 1H, $H_{5'}$), 1.67−1.49 (m, 8H, $H_{2'}$, $H_{3'}$ and both -CH_2CH_3), 1.24 (s, 9H, $H_{Piv\text{-}^tBu}$), 0.93−0.88 (m, 6H, both -CH_2CH_3), 0.92 (s, 9H, $H_{TBS\text{-}^tBu}$), 0.84 (d, 3H, J = 6.8 Hz, $H_{13'}$), 0.20 (s, 9H, H_{TMS}), 0.09 (s, 3H, $H_{TBS\text{-}Me}$), 0.07 (s, 3H, $H_{TBS\text{-}Me}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 185.8, 177.9, 140.5, 138.6, 129.1, 128.3, 128.2, 127.46, 127.36, 125.95, 111.4, 91.0, 85.9, 80.4, 76.2, 75.7, 75.1, 67.9, 65.1, 44.8, 39.4, 39.0, 38.6, 30.4, 29.7, 28.6, 27.3, 25.8, 19.5, 18.3, 13.9, 8.3, 8.1, 1.8, −5.32, −5.37; IR (thin film) ν 2957, 2933, 2212, 1726, 1680, 1462, 1360, 1282, 1252, 1159, 1104, 921, 843, 778, 699; HRMS (FAB$^+$) calcd for $C_{47}H_{74}Si_2O_8$ 822.4922, found 823.5022 (MH^+).

***Trans* Enone 36.** To a suspension of $[Cr(OAc)_2{\bullet}H_2O]_2$ (31.7 g, 84.4 mmol, 5.0 equiv) in 50.0 mL of degassed THF was added a solution of ynone **35** (13.9 g, 16.9 mmol) in 310 mL of degassed THF, followed by 36.0 mL of deoxygenated H_2O. The reaction was warmed to 65 °C and stirred for 2 weeks. Filtration of the reaction mixture through Celite removed most of the insoluble salts. The filter cake was rinsed thoroughly with Et_2O (3 × 100 mL), and the combined filtrates were concentrated to a pale blue oil. Purification by chromatography on silica gel (gradient elution, 12:1 → 8:1 hexanes/Et_2O) furnished **36** (8.3 g, 60%) as a colorless oil: TLC R_f = 0.51 (6:1 hexanes/EtOAc); $[\alpha]_{Na}$ +319.5° (c = 0.25, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.36−7.25 (m, 7H, H_{arom}), 7.18 (t, 1H, J = 7.4 Hz, H_{arom}), 7.12 (d, 2H, J = 7.0 Hz, H_{arom}), 6.80 (d, 1H, J = 15.9 Hz, H_6), 6.29 (d, 1H, J = 15.9 Hz, H_7), 4.96 (d, 1H, J = 11.5 Hz, -OCH_2Ph), 4.87−4.85 (m, 1H, $H_{4'}$), 4.61 (d, 1H, J = 11.5 Hz, -OCH_2Ph), 4.38 (ddd, J = 8.5, 6.6, 1.8 Hz, H_3), 4.09 (d, 1H, J = 1.7 Hz, H_4), 3.79 (t, 1H, J = 8.3 Hz, H_8), 3.73 (t, 1H, J = 6.6 Hz, H_8), 3.71 (d, 1H, J = 10.5 Hz, H_{10}), 3.57 (d, 1H, J = 10.5 Hz, H_{10}), 2.75 (dd, 1H, J = 13.4, 5.0 Hz, $H_{6'}$), 2.51 (t, 1H, J = 6.7 Hz, $H_{1'}$), 2.28 (dd, 1H, J = 13.4, 9.6 Hz, $H_{6'}$), 1.99−1.94 (m, 1H, $H_{5'}$), 1.67−1.55 (m, 8H, $H_{2'}$, $H_{3'}$ and both -CH_2CH_3), 1.25 (s, 9H, $H_{Piv\text{-}^tBu}$), 0.91−0.87 (m, 6H, both -CH_2CH_3), 0.89 (s, 9H, $H_{TBS\text{-}^tBu}$), 0.86 (d, 3H, J = 6.9 Hz, $H_{13'}$), 0.18 (s, 9H, H_{TMS}), 0.02 (s, 3H, $H_{TBS\text{-}Me}$), 0.01 (s, 3H, $H_{TBS\text{-}Me}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.3, 178.0, 146.3, 140.6, 138.7, 130.2, 129.1, 128.32, 128.26, 127.5, 127.4, 125.9, 111.3, 80.7, 80.5, 76.4, 75.9, 74.9, 66.5, 64.9, 40.0, 39.5, 38.6, 30.7, 29.6, 28.2, 27.3, 26.0, 19.8, 18.4, 13.8, 8.3, 8.1, 2.4, −5.36, −5.41; IR (thin film) ν 2956, 1725, 1676, 1636, 1459, 1361, 1283, 1251, 1161, 1108, 991, 925, 838, 777, 699. Anal. Calcd for $C_{47}H_{76}Si_2O_8$: C, 68.40; H, 9.28. Found: C, 68.47; H, 8.98.

***Trans* Enone Diol 45.** A solution of enone **36** (2.50 g, 3.03 mmol) in 60.0 mL of THF at 0 °C was treated with 6.7 mL of a 1.0 M THF solution of ^{n}Bu$_4$NF (6.7 mmol, 2.2 equiv). The resulting yellow solution was stirred for 45 min and then partitioned between 75 mL of saturated aqueous NH_4Cl and 50 mL of Et_2O. The organic phase was collected, and the aqueous layer was extracted with 3 × 75 mL Et_2O. The combined organic extracts were washed with 1 × 100 mL of saturated aqueous NaCl, dried over Na_2SO_4, and evaporated under reduced pressure. Purification of the product by chromatography on silica gel (gradient elution, 2:1 → 1:1 hexanes/EtOAc) afforded the product **45** as a colorless oil (1.8 g, 93%): TLC R_f = 0.19 (2:1 hexanes/EtOAc); $[\alpha]_{Na}$ +104.4° (c = 0.27, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.39−7.25 (m, 7H, H_{arom}), 7.18 (t, 1H, J = 7.4 Hz, H_{arom}), 7.11 (d, 2H, J = 7.0 Hz, H_{arom}), 6.95 (d, 1H, J = 15.9 Hz, H_6), 6.53 (d, 1H, J = 15.9 Hz, H_7), 4.88−4.85 (m, 1H, $H_{4'}$), 4.79 (d, 1H, J = 11.3 Hz, -OCH_2Ph), 4.63 (d, 1H, J = 11.3 Hz, -OCH_2Ph), 4.13 (d, 1H, J = 1.7 Hz, tertiary -OH), 4.07−4.02 (m, 2H, H_4 and H_8), 3.80−3.73 (m, 2H, H_{10}), 3.64−3.60 (m, 1H, H_3), 3.43 (dd, 1H, J =11.6, 3.5 Hz, H_8), 2.74 (dd, 1H, J =13.4, 5.0 Hz, $H_{6'}$), 2.58−2.54 (m, 2H, $H_{1'}$), 2.31−2.27 (m, 2H, $H_{6'}$ and primary -OH), 1.98−1.96 (m, 1H, $H_{5'}$), 1.68−1.55 (m, 8H, $H_{2'}$, $H_{3'}$ and both -CH_2CH_3), 1.24 (s, 9H, $H_{Piv\text{-}^tBu}$), 0.91 (t, 3H, J = 7.5 Hz, -CH_2CH_3), 0.85 (d, 3H, J = 6.8 Hz, $H_{13'}$), 0.82 (t, 3H, J = 7.4 Hz, -CH_2CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 199.3, 178.1, 144.9, 140.6, 137.5, 130.4, 129.1, 128.5, 128.3, 128.2, 128.0, 125.9, 114.0, 79.3, 78.8, 76.3, 75.7, 74.9, 68.6, 65.6, 40.4, 39.5, 39.1, 38.6, 30.7, 29.7, 28.8, 27.3, 19.9, 13.8, 8.1, 8.0; IR (thin film) ν 3470 (br), 3028, 2971, 2937, 2880, 1723, 1632, 1480, 1455, 1397, 1379, 1284, 1164, 1078, 1058, 990, 918, 735, 700. Anal. Calcd for $C_{38}H_{54}O_8$: C, 71.44; H, 8.52. Found: C, 71.39; H, 8.63.

Dimethylacetonide Enone 51. A solution of enone **45** (8.0 mg, 12.5 μmol) in 1.5 mL of CH_2Cl_2 was treated with 12 μL of 2-methoxypropene (125 μmol, 10 equiv) and a catalytic amount of anhydrous *p*-toluenesulfonic acid (1 mg, 4 μmol, 0.3 equiv). After 1 h, the mixture was poured into 4 mL of a 1:1 CH_2Cl_2/saturated aqueous $NaHCO_3$ solution. The organic phase was isolated, and the aqueous layer was extracted with 2 × 3 mL of CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and concentrated *in vacuo* to an oily residue. Purification by chromatography on silica gel (9:1 hexanes/EtOAc) afforded 8 mg (94%) of **51** as a colorless oil: TLC R_f = 0.46 (4:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.38−7.31 (m, 5H, H_{arom}), 7.30−7.25 (m, 2H, H_{arom}), 7.18 (t, 1H, J = 7.5 Hz, H_{arom}), 7.11 (d, 2H, J = 7.1 Hz, H_{arom}), 6.87 (d, 1H, J = 15.9 Hz, H_6), 6.39 (d, 1H, J = 15.9 Hz, H_7), 4.98 (d, 1H, J = 11.5 Hz, -OCH_2Ph), 4.87−4.86 (m, 1H, $H_{4'}$), 4.67 (d, 1H, J = 11.4 Hz, -OCH_2Ph), 4.35−4.30 (m, 1H, H_3), 4.05 (d, 1H, J = 9.0 Hz, H_{10}), 3.96 (d, 1H, J = 1.9 Hz, H_4), 3.78 (t, 1H, J = 8.1 Hz, H_8), 3.73 (d, 1H, J = 9.0 Hz, H_{10}), 3.74−3.71 (m, 1H, H_8), 2.75 (dd, 1H, J = 13.3, 5.0 Hz, $H_{6'}$), 2.53 (t, 2H, J = 6.8 Hz, $H_{1'}$), 2.29 (dd, 1H, J = 13.5, 9.7 Hz, $H_{6'}$), 1.99−1.94 (m, 1H, $H_{5'}$), 1.71−1.54 (m, 8H, $H_{2'}$, $H_{3'}$ and both -CH_2CH_3), 1.46 (s, 3H, -CH_3), 1.39 (s, 3H, -CH_3), 1.25 (s, 9H, $H_{Piv\text{-}^tBu}$), 0.92−0.86 (m, 9H, $H_{13'}$ and both -CH_2CH_3); IR (thin film) ν 2970, 1723, 1636, 1458, 1371, 1282, 1162, 1075, 700; HRMS (CI$^+$) calcd for $C_{41}H_{58}O_8$ 678.4131, found 679.4208 (MH^+).

Carbonate Enone 52. To a solution of enone **45** (20.0 mg, 31.3 μmol) in 2.0 mL of pyridine at 0 °C was added solid triphosgene (13.0 mg, 45.0 μmol, 1.5 equiv) in a single portion. A white precipitate formed instantaneously upon addition. The resulting mixture was stirred at 0 °C for 10 min and then allowed to warm over a 2 h period to 23 °C, during which time the solution became homogeneous. The volatiles were removed *in vacuo* to leave a pale yellow residue, which was purified by chromatography on silica gel (5:1 hexanes/EtOAc). The product **52** was isolated as a clear, colorless oil (20 mg, 96%): TLC R_f = 0.34 (4:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.40−7.27 (m, 7H, H_{arom}), 7.19 (t, 1H, J = 7.3 Hz, H_{arom}), 7.11 (d, 2H, J = 7.1 Hz, H_{arom}), 6.91 (d, 1H, J = 15.7 Hz, H_6), 6.48 (d, 1H, J = 15.8 Hz, H_7), 4.88−4.85 (m, 1H, $H_{4'}$), 4.79 (d, 1H, J = 11.1 Hz, -OCH_2Ph), 4.74 (d, 1H, J = 11.1 Hz, -OCH_2Ph), 4.49 (d, 1H, J = 8.6 Hz, H_{10}), 4.17 (d, 1H, J = 8.5 Hz, H_{10}), 4.10 (ddd, 1H, J = 6.8, 5.6 Hz, H_3), 3.94 (dd, 1H, J = 8.2, 6.4 Hz, H_8), 3.84 (d, 1H, J = 5.4 Hz, H_4), 3.71 (t, 1H, J = 7.9 Hz, H_8), 2.74 (dd, 1H, J = 13.3, 5.0 Hz, $H_{6'}$), 2.56−2.54 (m, 2H, $H_{1'}$), 2.30 (dd, 1H, J = 13.3, 9.5 Hz, $H_{6'}$), 1.99−1.94 (m, 1H, $H_{5'}$), 1.67−1.56 (m, 8H, $H_{2'}$, $H_{3'}$ and both -CH_2CH_3), 1.25 (s, 9H, $H_{Piv\text{-}^tBu}$), 0.89−0.85 (m, 9H, $H_{13'}$ and both -CH_2CH_3); IR (thin film) ν 2968, 2936, 1812, 1718, 1458, 1282, 1166, 1067; HRMS (FAB$^+$) calcd for $C_{39}H_{52}O_9$ 664.3611, found 687.3309 (MNa^+).

Carbonate Diols from 52. To a solution of enone **52** (18.0 mg, 27.1 μmol) in 2.5 mL of acetone and 0.1 mL of ^{t}BuOH were added 4-methylmorpholine *N*-oxide (2 mg, 17 μmol) and $CH_3SO_2NH_2$ (2 mg, 21 μmol). A 0.16 M aqueous solution of OsO_4 (10 μL, 1.6 μmol) was added to the mixture via micropipet. The pale yellow solution was

stirred for 18 h, after which time the reaction was quenched by the addition of 5.0 mL 10 wt % aqueous Na_2SO_3. The mixture was stirred vigorously for 20 min and then extracted with 4 × 5 mL of Et_2O. The ethereal extracts were washed once with saturated aqueous NaCl (5 mL), dried over Na_2SO_4, and concentrated under reduced pressure to a milky white oil. Analysis of the ^1H NMR spectrum of the unpurified material showed two major products in a 2.2:1 ratio. Purification by chromatography on silica gel (gradient elution, 7:2 → 3:1 hexanes/EtOAc) afforded both the desired (6*R*,7*R*) (11 mg) and the undesired (6*S*,7*S*) (5 mg) diols as colorless oils (85% combined yield).

Physical data for the (6*R*,7*R*) diol: TLC R_f = 0.41 (2:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.38−7.28 (m, 7H, H_{arom}), 7.20 (t, 1H, J = 7.3 Hz, H_{arom}), 7.11 (d, 2H, J = 7.2 Hz, H_{arom}), 4.93 (d, 1H, J = 8.0 Hz, H_{10}), 4.93 (d, 1H, J = 10.8 Hz, -OCH_2Ph), 4.87−4.83 (m, 1H, $H_{4'}$), 4.60 (d, 1H, J = 10.6 Hz, -OCH_2Ph), 4.55 (d, 1H, J = 4.8 Hz, H_7), 4.43 (dd, 1H, J = 5.6, 1.6 Hz, H_6), 4.36 (d, 1H, J = 8.0 Hz, H_{10}), 4.20 (dd, 1H, J = 8.6, 6.0 Hz, H_8), 4.04−3.96 (m, 2H, H_3, H_4), 3.78−3.72 (m, 3H, H_8 and both secondary -OH), 2.73 (dd, 1H, J = 13.4, 5.1 Hz, $H_{6'}$), 2.59−2.47 (m, 2H, $H_{1'}$), 2.31 (dd, 1H, J = 13.4, 9.4 Hz, $H_{6'}$), 1.96−1.94 (m, 1H, $H_{5'}$), 1.71−1.53 (m, 8H, $H_{2'}$, $H_{3'}$ and both -CH_2CH$_3$), 1.26 (s, 9H, $H_{Piv\text{-}^tBu}$), 0.90 (t, 3H, J = 7.5 Hz, -CH$_2$CH_3), 0.87 (d, 3H, J = 6.8 Hz, $H_{13'}$), 0.83 (t, 3H, J = 7.4 Hz, -CH$_2$CH_3); IR (thin film) ν 3446 (br), 2971, 1804, 1719, 1458, 1362, 1284, 1166, 1078, 911, 741, 700; HRMS (FAB$^+$) calcd for $C_{39}H_{54}O_{11}$ 698.3666, found 699.3756 (MH$^+$).

Physical data for the (6*S*,7*S*) diol: TLC R_f = 0.50 (2:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.35−7.26 (m, 7H, H_{arom}), 7.22 (t, 1H, J = 7.2 Hz, H_{arom}), 7.11 (d, 2H, J = 7.3 Hz, H_{arom}), 4.93 (d, 1H, J = 11.3 Hz, -OCH_2Ph), 4.80−4.76 (m, 2H, H_{10}, $H_{4'}$), 4.58 (d, 1H, J = 11.4 Hz, -OCH_2Ph), 4.45 (d, 1H, J = 8.1 Hz, H_7), 4.39 (d, 1H, J = 9.2 Hz, H_{10}), 4.28 (dd, 1H, J = 12.8, 6.3 Hz, H_3), 4.20 (d, 1H, J = 5.0 Hz, H_4), 4.19−4.16 (m, 2H, H_6, H_8), 4.03 (t, 1H, J = 8.1 Hz, H_8), 3.82 (d, 1H, J = 8.0 Hz, secondary -OH), 3.68 (d, 1H, J = 5.0 Hz, secondary -OH), 2.67 (dd, 1H, J = 13.5, 6.2 Hz, $H_{6'}$), 2.49 (ddd, 1H, J = 13.9, 8.6, 5.6 Hz, $H_{1'}$), 2.37 (dd, 1H, J = 13.4, 8.5 Hz, $H_{6'}$), 1.93−1.88 (m, 1H, $H_{5'}$), 1.83−1.74 (m, 1H, $H_{1'}$), 1.73−1.34 (m, 8H, $H_{2'}$, $H_{3'}$ and both -CH_2CH$_3$), 1.22 (s, 9H, $H_{Piv\text{-}^tBu}$), 0.94 (t, 3H, J = 7.5 Hz, -CH$_2$CH_3), 0.91 (d, 3H, J = 7.0 Hz, $H_{13'}$), 0.89 (t, 3H, J = 7.5 Hz, -CH$_2$CH_3); IR (thin film) ν 3432 (br), 2970, 1802, 1719, 1458, 1363, 1284, 1168, 1063, 700; HRMS (FAB$^+$) calcd for $C_{39}H_{54}O_{11}$ 698.3666, found 699.3745 (MH$^+$).

TBS-Protected Bicyclic Ketal 54. To a solution of **45** (1.40 g, 2.19 mmol) in 85.0 mL of acetone were added $(DHQD)_2PHAL$ (1.0 g, 1.3 mmol), 4-methylmorpholine *N*-oxide (513 mg, 4.38 mmol), and $CH_3SO_2NH_2$ (210 mg, 2.2 mmol). The pale yellow solution was cooled to 0 °C before 4.1 mL of an aqueous solution of OsO_4 (0.66 mmol, 0.16 M) was added dropwise via pipet. Next, 5.0 mL of ^{t}BuOH was added to the slightly turbid mixture. The reaction was warmed to 23 °C and stirred for 12 h, after which time 20 mL of a buffered 1.5 M $NaHSO_3/Na_2SO_4$ solution (pH 7) was poured into the reaction mixture. The resulting slurry was stirred vigorously for 2 h before being partitioned between 20 mL of saturated aqueous NaCl and 50 mL of 20% MeOH/CH_2Cl_2. The organic layer was collected, and the aqueous phase was extracted with 4 × 50 mL of 20% MeOH/CH_2Cl_2. The extracts were combined and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure yielded 1.8 g of a pale brown foam. The desired product was isolated as a 1.7:1 mixture of epimeric diols **46/47** (as shown by ^1H NMR of the unpurified material) and used without further purification.

The unpurified mixture of tetraols **46/47** (1.50 g, 2.19 mmol) was dissolved in 200 mL of MeOH and cooled to 0 °C, and then 1.0 mL of 12 N HCl was added. The solution was warmed to 23 °C and stirred for 2 h. Quenching the reaction at 0 °C with ^{i}Pr$_2$NEt (~2 mL), followed by evaporation of the solvent under reduced pressure, gave a pale yellow viscous oil. Purification by chromatography on silica gel (3:2 CH_2Cl_2/EtOAc) yielded the product as a white foam (1.1 g, 86%). The bicyclic ketal was isolated as a 1.7:1 mixture of C(6)/C(7) *anti* diol diastereomers **53/56**, as shown by ^1H NMR: TLC R_f = 0.49 (1:1 CH_2Cl_2/EtOAc).

To a solution of **53/56** (684 mg, 1.17 mmol) in 10.0 mL of CH_2Cl_2 were added Et_3N (1.6 mL, 11.7 mmol, 10 equiv), ^{t}BuMe$_2$SiCl (369 mg, 2.45 mmol, 2.1 equiv), and 4-DMAP (14.0 mg, 0.12 mmol, 10 mol %) successively. The mixture was stirred at 23 °C for 46 h and then poured onto 20 mL of a 1.0 M aqueous KH_2PO_4 solution. The two phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to a yellow oil. Purification by chromatography on silica gel (gradient elution, 4:1 → 2:1 hexanes/EtOAc) provided both **54** (460 mg, 74%) and **57** (270 mg, 81%) as colorless oils: TLC R_f(**54**) = 0.43, R_f(**57**) = 0.61 (2:1 hexanes/EtOAc).

Physical data for **54**: $[\alpha]_{Na}$ +384.7° (c = 0.27, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.36−7.23 (m, 7H, H_{arom}), 7.18 (t, 1H, J = 7.4 Hz, H_{arom}), 7.11 (d, 2H, J = 7.2 Hz, H_{arom}), 4.86−4.84 (m, 1H, $H_{4'}$), 4.64 (d, 1H, J = 11.3 Hz, -OCH_2Ph), 4.59 (d, 1H, J = 11.3 Hz, -OCH_2Ph), 4.33 (dd, 1H, J = 6.6, 2.6, H_6), 3.95 (d, 1H, J = 11.8 Hz, H_{10}), 3.95−3.93 (m, 1H, H_7), 3.80 (d, 1H, J = 9.5 Hz, H_4), 3.80−3.77 (m, 2H, H_8), 3.71 (d, 1H, J = 11.8 Hz, H_{10}), 3.66−3.63 (m, 1H, H_3), 3.29 (d, 1H, J = 6.6 Hz, secondary -OH), 2.75 (dd, 1H, J = 13.3, 5.0 Hz, $H_{6'}$), 2.29 (dd, 1H, J = 13.4, 9.6 Hz, $H_{6'}$), 2.07 (d, 1H, J = 5.7 Hz, secondary -OH), 2.00−1.94 (m, 1H, $H_{5'}$), 1.78−1.45 (m, 6H, $H_{1'}$, $H_{2'}$, $H_{3'}$), 1.24 (s, 9H, $H_{Piv\text{-}^tBu}$), 0.91 (s, 9H, $H_{TBS\text{-}^tBu}$), 0.89 (s, 9H, $H_{TBS\text{-}^tBu}$), 0.85 (d, 3H, J = 6.8 Hz, $H_{13'}$), 0.08 (s, 3H, $H_{TBS\text{-}Me}$), 0.062 (s, 6H, $H_{TBS\text{-}Me}$), 0.056 (s, 3H, $H_{TBS\text{-}Me}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.0, 140.7, 138.3, 129.1, 128.4, 128.3, 128.0, 127.8, 125.9, 103.6, 86.3, 83.9, 79.3, 76.2, 74.8, 74.1, 71.0, 63.3, 62.7, 39.5, 39.0, 38.3, 35.6, 31.4, 27.3, 25.9, 25.8, 19.3, 18.3, 18.2, 13.7, −4.9, −5.2, −5.32, −5.37; IR (thin film) ν 3447 (br), 2956, 2929, 2856, 1726, 1702, 1496, 1461, 1397, 1360, 1285, 1252, 1162, 1087, 1004, 971, 837, 777, 738, 699. Anal. Calcd for $C_{45}H_{74}Si_2O_9$: C, 66.30; H, 9.15. Found: C, 65.98; H, 8.84.

Pivaloate Ester 59. To a solution of diol **54** (710 mg, 0.87 mmol) in 15.0 mL of 1,2-dichloroethane were added 4-DMAP (635 mg, 5.20 mmol, 6.0 equiv) and ^{t}BuCOCl (320 μL, 2.60 mmol, 3.0 equiv). The contents were warmed to 55 °C and stirred for 8 h. After the solution was allowed to cool to 23 °C, 30 mL of pentane was added. The resulting white precipitate was removed by filtration through Celite. The filter cake was rinsed with pentane (3 × 20 mL), and the combined filtrates were concentrated under reduced pressure to give an oily yellow residue. Purification by chromatography on silica gel (20:1 hexanes/EtOAc) provided 830 mg of **59** (97%) as a clear, colorless oil: TLC R_f = 0.54 (8:1 hexanes/EtOAc); $[\alpha]_{Na}$ +78.1° (c = 0.27, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.35−7.26 (m, 7H, H_{arom}), 7.18 (t, 1H, J = 7.3 Hz), 7.10 (d, 2H, J = 7.1 Hz), 5.38 (d, 1H, J = 2.7 Hz, H_6), 4.98 (d, 1H, J = 2.7 Hz, H_7), 4.85−4.82 (m, 1H, $H_{4'}$), 4.82 (d, 1H, J = 11.7 Hz, -OCH_2Ph), 4.60 (d, 1H, J = 11.7 Hz, -OCH_2Ph), 4.07 (d, 1H, J = 10.0 Hz, H_4), 3.80−3.75 (m, 3H, H_3, H_{10}), 3.71−3.68 (m, 2H, H_8), 2.75 (dd, 1H, J = 13.3, 4.7 Hz, $H_{6'}$), 2.27 (dd, 1H, J = 13.3, 9.8 Hz, $H_{6'}$), 1.99−1.94 (m, 1H, $H_{5'}$), 1.69−1.35 (m, 6H, $H_{1'}$, $H_{2'}$, $H_{3'}$), 1.24 (s, 9H, $H_{Piv\text{-}^tBu}$), 1.21 (s, 9H, $H_{Piv\text{-}^tBu}$), 1.20 (s, 9H, $H_{Piv\text{-}^tBu}$), 0.92 (s, 9H, $H_{TBS\text{-}^tBu}$), 0.89 (s, 9H, $H_{TBS\text{-}^tBu}$), 0.84 (d, 3H, J = 6.8 Hz, $H_{13'}$), 0.11 (s, 3H, $H_{TBS\text{-}Me}$), 0.07 (s, 3H, $H_{TBS\text{-}Me}$), 0.05 (s, 3H, $H_{TBS\text{-}Me}$), 0.02 (s, 3H, $H_{TBS\text{-}Me}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.8, 176.9, 176.8, 140.8, 138.7, 129.1, 128.29, 128.23, 127.5, 125.9, 103.9, 84.8, 81.3, 77.5, 76.3, 74.8, 73.9, 69.4, 62.9, 61.5, 39.5, 39.0, 38.8, 38.7, 38.4, 36.1, 31.3, 27.3, 27.0, 25.9, 19.2, 18.36, 18.34, 13.7, −4.9, −5.1, −5.3, −5.5 ppm; IR (thin film) ν 3028, 2957, 2930, 2857, 1740, 1479, 1460, 1396, 1362, 1282, 1252, 1159, 1098, 1006, 837, 699. Anal. Calcd for $C_{55}H_{90}Si_2O_{11}$: C, 67.17; H, 9.22. Found: C, 66.80; H, 8.81.

Ketone 61. $Pd(OH)_2$ on carbon (20%, 400 mg) and palladium on calcium carbonate (5%, 400 mg) were suspended in 15.0 mL of an absolute EtOH solution of **59** (830 mg, 0.84 mmol). The slurry was stirred vigorously at 23 °C under 1 atm of H_2 for 168 h. Removal of the palladium catalysts by filtration through Celite, followed by evaporation of the filtrate under reduced pressure, afforded 730 mg (99%) of **60** as a colorless oil. The product **60** was used without further purification: TLC R_f = 0.38 (8:1 hexanes/EtOAc); $[\alpha]_{Na}$ +81.4° (c = 0.25, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.27−7.24 (m, 2H, H_{arom}), 7.18 (t, 1H, J = 7.3 Hz, H_{arom}), 7.10 (d, 2H, J = 7.1, H_{arom}), 5.48 (d, 1H, J = 2.6 Hz, H_6), 5.00 (d, 1H, J = 2.6 Hz, H_7), 4.86−4.83 (m, 1H, $H_{4'}$), 3.99 (dd, 1H, J = 9.0, 1.5 Hz, H_4), 3.88 (d, 1H, J = 11.2 Hz, H_{10}), 3.87−3.81 (m, 2H, H_3, H_8), 3.78−3.74 (m, 1H, H_8), 3.74 (d, 1H, J = 11.3 Hz, H_{10}), 3.13 (d, 1H, J = 1.5 Hz, -OH), 2.75 (dd, 1H, J = 13.3, 4.7 Hz, $H_{6'}$), 2.55 (dd, 1H, J = 13.3, 9.8 Hz, $H_{6'}$), 1.96−1.93 (m, 1H, $H_{5'}$), 1.69−1.26 (m, 6H, $H_{1'}$, $H_{2'}$, $H_{3'}$), 1.234 (s, 9H, $H_{Piv\text{-}^tBu}$), 1.229 (s, 9H, $H_{Piv\text{-}^tBu}$), 1.21 (s, 9H, $H_{Piv\text{-}^tBu}$), 0.91 (s, 9H, $H_{TBS\text{-}^tBu}$),

0.90 (s, 9H, $H_{TBS\text{-}^tBu}$), 0.83 (d, 3H, J = 6.8 Hz, $H_{13'}$), 0.092 (s, 6H, $H_{TBS\text{-}Me}$), 0.085 (s, 3H, $H_{TBS\text{-}Me}$), 0.07 (s, 3H, $H_{TBS\text{-}Me}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.9, 176.85, 176.81, 140.8, 129.1, 128.2, 125.9, 104.0, 83.4, 81.1, 76.42, 76.40, 76.2, 73.5, 66.5, 65.2, 62.2, 39.4, 39.0, 38.8, 38.7, 35.8, 31.1, 27.3, 27.01, 26.99, 25.89, 25.86, 19.2, 18.3, 13.8, −5.4; IR (thin film) ν 3027 (br), 2958, 2931, 2857, 1740, 1480, 1462, 1397, 1363, 1283, 1255, 1160, 1036, 1006, 939, 837, 778, 700; HRMS (FAB$^+$) calcd for $C_{48}H_{84}Si_2O_{11}$ 892.6046, found 893.5645 (MH^+). Anal. Calcd for $C_{48}H_{84}Si_2O_{11}$: C, 64.53; H, 9.48. Found: C, 64.34; H, 9.32.

Dimethyl sulfoxide (580 μL, 8.19 mmol, 10.0 equiv) was added dropwise to a solution of oxalyl chloride (360 μL, 4.10 mmol, 2.0 equiv) in 10.0 mL of CH_2Cl_2 at −78 °C. Following gas evolution, the mixture was stirred for 10 min before a solution of alcohol **60** (725 mg, 0.81 mmol) in 2.0 mL of CH_2Cl_2 was added dropwise over 10 min. The resulting white suspension was stirred at -78 °C for an additional 1 h; Et_3N (2.90 mL, 20.5 mmol, 25 equiv) was then added dropwise, which caused the solution to clear. The solution was stirred at −78 °C for 15−20 min and then warmed to 0 °C. The reaction was quenched at 0 °C with 30 mL of a 1.0 M aqueous KH_2PO_4 solution. The organic layer was collected, and the aqueous phase was extracted with 4 × 25 mL of CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and concentrated *in vacuo*. Purification of the yellow residue by chromatography on silica gel (20:1 hexanes/EtOAc) gave the desired product **61** as a colorless oil (6.0 g, 96%): TLC $R_f \approx 0.50$ (8:1 hexanes/EtOAc); $[\alpha]_{Na}$ +42.9° (c = 0.42, CH_2Cl_2); ^{1}H NMR (C_6D_6, 500 MHz) δ 7.23−7.11 (m, 3H, H_{arom}), 7.08−7.04 (m, 2H, H_{arom}), 5.40 (d, 2H, J = 1.8 Hz, H_6, H_7), 5.08−5.04 (m, 1H, $H_{4'}$), 4.61 (dd, 1H, J = 6.4, 4.1 Hz, H_3), 4.32 (d, 1H, J = 10.8 Hz, H_{10}), 4.15 (dd, 1H, J = 10.9, 6.4 Hz, H_8), 4.12 (dd, 1H, J = 11.0, 4.2 Hz, H_8), 4.05 (d, 1H, J = 10.8 Hz, H_{10}), 2.74 (dd, 1H, J = 13.4, 4.8 Hz, $H_{6'}$), 2.22−2.16 (m, 2H, $H_{1'}$, $H_{6'}$), 2.08−2.02 (m, 1H, $H_{1'}$), 1.89−1.83 (m, 1H, $H_{5'}$), 1.81−1.77 (m, 1H, $H_{3'}$), 1.68−1.64 (m, 1H, $H_{3'}$), 1.62−1.56 (m, 1H, $H_{2'}$), 1.39−1.29 (m, 1H, $H_{2'}$), 1.27 (s, 9H, $H_{Piv\text{-}^tBu}$), 1.16 (s, 9H, $H_{Piv\text{-}^tBu}$), 1.10 (s, 9H, $H_{Piv\text{-}^tBu}$), 1.00 (s, 9H, $H_{TBS\text{-}^tBu}$), 0.97 (s, 9H, $H_{TBS\text{-}^tBu}$), 0.78 (d, 3H, J = 6.8 Hz, $H_{13'}$), 0.154 (s, 3H, $H_{TBS\text{-}Me}$), 0.150 (s, 3H, $H_{TBS\text{-}Me}$), 0.14 (s, 3H, $H_{TBS\text{-}Me}$), 0.11 (s, 3H, $H_{TBS\text{-}Me}$); ^{13}C NMR (C_6D_6, 125 MHz) δ 202.8, 177.6, 177.0, 176.8, 141.5, 129.8, 129.0, 126.6, 106.6, 92.0, 82.6, 81.8, 79.5, 76.2, 65.8, 61.3, 40.3, 39.9, 39.5, 39.4, 39.0, 37.9, 32.3, 27.9, 27.42, 27.35, 26.5 (2 lines), 20.2, 19.01, 18.94, 14.4, −4.6, −4.7, −4.9, −5.0; IR (thin film) ν 2958, 2931, 2857, 1743, 1480, 1462, 1396, 1363, 1282, 1256, 1159, 1128, 1037, 838, 779. Anal. Calcd for $C_{48}H_{82}Si_2O_{11}$: C, 64.68; H, 9.27. Found: C, 64.57; H, 9.03.

Alkyne 67. *tert*-Butyllithium (1.7 M, 1.5 mL, 2.5 mmol) was added dropwise to a solution of (trimethylsilyl)acetylene (360 μL, 2.55 mmol) in 1.0 mL of hexanes at −78 °C. The reaction was stirred at −78 °C for 10 min and then warmed to 0 °C. After reaching 0 °C, the white suspension was stirred for an additional 45 min. The suspension of lithium (trimethylsilyl)acetylide (1.7 mL, 1.7 mmol) was added to 5.0 mL of a 1:1 Et_2O/Me_3N mixture at −78 °C. The resulting homogeneous solution was stirred for 5 min before a cold solution (−78 °C) of ketone **61** (155 mg, 0.17 mmol) in 1.5 mL of Et_2O was added dropwise via cannula over a 3 min period. The transfer of **61** was made quantitative with an additional 500 μL of Et_2O. The mixture was stirred at −78 °C for 10 min and then allowed to slowly warm to −20 °C over 2 h. Upon reaching this temperature, the reaction was quenched by the addition of 5.0 mL of saturated aqueous NH_4Cl. The resulting frozen mixture was warmed to 23 °C. The solution was extracted with 3 × 5 mL of Et_2O; the organic extracts were combined, washed once with saturated aqueous NaCl (10 mL), and dried over Na_2SO_4. Evaporation of the ethereal solvent *in vacuo* afforded the product as a 6.1:1 mixture of C(4) carbinol epimers **65/66**, as determined by ^{1}H NMR of the unpurified material. The product was used without prior purification: TLC R_f = 0.52 (8:1 hexanes/EtOAc).

To a solution of (trimethylsilyl)acetylenes **65/66** (172 mg, 0.17 mmol) in 8.0 mL of a 1:1:1:0.1 mixture of THF/H_2O/EtOH/2,6-lutidine was added solid $AgNO_3$ (295 mg, 1.70 mmol, 10 equiv). The white suspension was stirred vigorously for 3.5 h, and then 5 mL of a 1.0 M aqueous KH_2PO_4 solution was added. The resulting yellow slurry was stirred for an additional 30 min. Filtration of the reaction mixture through Celite removed most of the yellow precipitate. The filtrate was extracted with Et_2O (3 × 10 mL), and the combined organic extracts were washed once with saturated aqueous NaCl (20 mL) and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded a pale yellow oil. Purification by chromatography on silica gel (20:1 hexanes/EtOAc) furnished 97 mg of **67** (61%) as a clear, colorless oil. The product **67** was shown to be a single C(4) carbinol epimer by ^{1}H NMR: TLC R_f = 0.36 (10:1 hexanes/EtOAc); $[\alpha]_{Na}$ +10.8° (c = 0.45, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27−7.24 (m, 2H, H_{arom}), 7.17 (t, 1H, J = 7.4 Hz, H_{arom}), 7.11 (d, 2H, J = 7.1 Hz, H_{arom}), 5.52 (d, 1H, J = 1.9 Hz, tertiary -OH), 5.43 (d, 1H, J = 2.8 Hz, H_6), 4.99 (d, 1H, J = 2.8 Hz, H_7), 4.88−4.84 (m, 1H, $H_{4'}$), 4.18 (d, 1H, J = 11.5 Hz, H_{10}), 4.11 (dd, 1H, J = 11.5, 1.7 Hz, H_8), 4.03 (ddd, 1H, J = 7.1, 1.7, 1.6 Hz, H_3) 3.92 (d, 1H, J = 11.5 Hz, H_{10}), 3.89 (dd, 1H, J = 11.5, 7.1 Hz, H_8), 2.76 (dd, 1H, J = 13.3, 4.7 Hz, $H_{6'}$), 2.61 (s, 1H, -C≡C*H*), 2.26 (dd, 1H, J = 13.3, 9.9 Hz, $H_{6'}$), 2.00−1.96 (m, 1H, $H_{5'}$), 1.80−1.25 (m, 6H, $H_{1'}$, $H_{2'}$, $H_{3'}$), 1.23 (s, 9H, $H_{Piv\text{-}^tBu}$), 1.228 (s, 9H, $H_{Piv\text{-}^tBu}$), 1.226 (s, 9H, $H_{Piv\text{-}^tBu}$), 0.91 (s, 9H, $H_{TBS\text{-}^tBu}$), 0.90 (s, 9H, $H_{TBS\text{-}^tBu}$), 0.83 (d, 3H, J = 6.8 Hz, $H_{13'}$), 0.120 (s, 3H, $H_{TBS\text{-}Me}$), 0.116 (s, 3H, $H_{TBS\text{-}Me}$), 0.07 (s, 3H, $H_{TBS\text{-}Me}$), 0.06 (s, 3H, $H_{TBS\text{-}Me}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 177.9, 177.0, 176.6, 140.8, 129.1, 128.2, 125.9, 105.0, 83.7, 81.7, 80.0, 78.8, 78.3, 76.2, 76.0, 69.3, 65.1, 63.5, 39.4, 39.0, 38.8, 38.7, 38.5, 35.8, 31.1, 27.3, 27.02, 26.95, 26.1, 25.8, 19.1, 18.5, 18.3, 13.8, −5.0, −5.2, −5.5, −5.8; IR (thin film) ν 3434, 3258, 2958, 2932, 2858, 1742, 1480, 1462, 1397, 1363, 1282, 1255, 1159, 1033, 973, 837, 780; HRMS (FAB$^+$) calcd for $C_{50}H_{84}Si_2O_{11}$ 916.5552, found 917.5637 (MH^+).

Polyol 68. A 1.5 M solution of Dibal-H in toluene (3.2 mL, 4.7 mmol, 15 equiv) was added to a solution of **67** (290 mg, 0.316 mmol) in 30.0 mL of a 1:1 CH_2Cl_2/toluene mixture at −78 °C. The reaction was stirred at −78 °C for 30 min and then warmed over a 5 h period to ca. −5 °C before being quenched by the addition of 10 mL of EtOAc. A 5.0 M aqueous solution of Na/K tartrate was added (30 mL), and the biphasic mixture was stirred for 12 h. The organic phase was collected, and the aqueous layer was extracted with 3 × 25 mL of EtOAc. The combined extracts were washed once with saturated aqueous NaCl (30 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification by chromatography on silica gel (gradient elution, 2:1 → 3:2 hexanes/EtOAc) provided 176 mg of **68** (84%) as a colorless oil: TLC R_f = 0.20 (2:1 hexanes/EtOAc); $[\alpha]_{Na}$ +18.1° (c = 0.24, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.29−7.26 (m, 2H, H_{arom}), 7.20−7.16 (m, 3H, H_{arom}), 4.70 (d, 1H, J = 1.1 Hz, tertiary -OH), 4.68 (dd, 1H, J = 5.8, 2.7 Hz, H_6), 4.39 (dd, 1H, J = 5.6, 2.6 Hz, H_7), 4.29 (d, 1H, J = 11.3 Hz, H_{10}), 4.09−4.05 (m, 3H, H_8 and H_{10}), 3.95 (dd, 1H, J = 3.4, 3.2 Hz, H_3), 3.51 (br s, 1H, $H_{4'}$), 2.78 (dd, 1H, J = 13.4, 6.3 Hz, $H_{6'}$), 2.74 (br s, 1H, secondary -OH), 2.54 (d, 1H, J = 0.7 Hz, -C≡C*H*), 2.45 (dd, 1H, J =13.3, 8.6 Hz, $H_{6'}$), 1.83−1.46 (m, 7H, $H_{1'}$, $H_{2'}$, $H_{3'}$, $H_{5'}$), 0.90 (s, 9H, $H_{TBS\text{-}^tBu}$), 0.89 (s, 9H, $H_{TBS\text{-}^tBu}$), 0.84 (d, 1H, J = 6.8 Hz, $H_{13'}$), 0.11 (s, 6H, $H_{TBS\text{-}Me}$), 0.09 (s, 6H, $H_{TBS\text{-}Me}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.1, 129.1, 128.3, 125.8, 105.1, 85.8, 84.8, 81.06, 80.93, 75.98, 75.72, 74.1, 68.5, 63.7, 62.5, 40.4, 39.9, 35.5, 34.5, 25.9, 25.7, 19.9, 18.3, 18.1, 13.2, -5.2, −5.3, −5.5, −5.6; IR (thin film) ν 3415 (br), 2954, 2930, 2857, 1463, 1362, 1255, 1086, 971, 837, 781, 700; HRMS (FAB$^+$) calcd for $C_{35}H_{60}Si_2O_8$ 664.4186, found 665.3903 (MH^+).

Tris-acetate 69. To a solution of polyol **68** (130 mg, 0.195 mmol) in 5.0 mL of CH_2Cl_2 was added 4-DMAP (490 mg, 4.0 mmol, 20 equiv), followed by Ac_2O (190 μL, 2.0 mmol, 10 equiv). The solution was stirred for 12 h and then poured into 5 mL of a 1.0 M aqueous KH_2PO_4 solution. The organic phase was collected, and the aqueous layer was extracted with 3 × 5 mL of CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and evaporated under reduced pressure. Purification of the pale yellow residue by chromatography on silica gel (6:1 hexanes/EtOAc) gave the product **69** (145 mg, 94%) as a clear, colorless oil: TLC R_f = 0.16 (6:1 hexanes/EtOAc); $[\alpha]_{Na}$ + 37.0° (c = 0.56, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28−7.25 (m, 2H, H_{arom}), 7.18 (t, 1H, J = 7.4 Hz, H_{arom}), 7.12 (d, 2H, J = 7.3 Hz, H_{arom}), 5.50 (d, 1H, J = 2.9 Hz, H_6), 5.42 (d, 1H, J = 1.6 Hz, tertiary -OH), 5.06 (d, 1H, J = 2.9 Hz, H_7), 4.88−4.84 (m, 1H, $H_{4'}$), 4.17 (d, 1H, J = 11.5 Hz, H_{10}), 4.13 (dd, 1H, J = 11.6, 1.7 Hz, H_8), 4.03 (ddd, 1H, J = 6.9, 1.7, 1.6 Hz, H_3) 3.93 (d, 1H, J = 11.4 Hz, H_{10}), 3.90 (dd, 1H, J = 11.7, 6.9 Hz, H_8), 2.76 (dd, 1H, J = 13.5, 5.0 Hz, $H_{6'}$), 2.60 (s, 1H, -C≡C*H*), 2.28 (dd, 1H, J = 13.4, 9.7 Hz, $H_{6'}$), 2.11 (s, 6H, two -COC*H*$_3$), 2.06 (s, 3H, -COC*H*$_3$), 2.00−1.96 (m, 1H, $H_{5'}$), 1.85−1.25 (m, 6H, $H_{1'}$, $H_{2'}$, $H_{3'}$), 0.91 (s, 9H, $H_{TBS\text{-}^tBu}$), 0.89 (s, 9H, $H_{TBS\text{-}^tBu}$), 0.83 (d, 3H, J = 6.8 Hz, $H_{13'}$), 0.13 (s, 3H, $H_{TBS\text{-}Me}$), 0.12 (s, 3H, $H_{TBS\text{-}Me}$),

0.08 (s, 6H, $H_{TBS\text{-}Me}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.7, 169.7, 169.3, 140.6, 129.0, 128.1, 125.8, 104.8, 83.5, 81.5, 80.29, 80.27, 78.4, 78.2, 76.8, 76.1, 69.0, 64.3, 63.2, 39.3, 38.3, 35.5, 31.1, 25.8, 25.7, 21.1, 20.65, 20.61, 19.0, 18.2, 14.0, −5.0, −5.2, −5.5, −5.8; IR (thin film) ν 3426, 3259, 2955, 2931, 2885, 1753, 1472, 1463, 1372, 1239, 1138, 1088, 1041, 1021, 837, 780; HRMS (FAB^+) calcd for $C_{41}H_{66}Si_2O_{11}$ 790.4143, found 791.4204 (MH^+).

C(8) Alcohol 70. A solution of **69** (104 mg, 0.131 mmol) in 20.0 mL of MeOH was treated with 95 μL (1.2 mmol, 9 equiv) of Cl_2CHCO_2H and stirred for 7 h. The mixture was then diluted with 20 mL of Et_2O and poured into 20 mL of saturated aqueous NH_4Cl. The organic phase was isolated and the aqueous layer extracted with 3 × 20 mL of Et_2O. The combined ethereal extracts were washed with 1 × 40 mL of saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. Purification by chromatography on silica gel (2:1 hexanes/EtOAc) furnished 80 mg (90%) of the alcohol product as a clear, colorless oil: TLC $R_f = 0.19$ (2:1 hexanes/EtOAc).

To a solution of the alcohol (79.0 mg, 0.18 mmol) in 15.0 mL of pyridine was suspended 80 mg of 5% Pd−C. The contents were placed under 1 atm H_2 and stirred vigorously for 2 h. The mixture was filtered through Celite, the filter cake was rinsed with Et_2O (10 mL), and the filtrate was concentrated *in vacuo* to a pale yellow oil. The product **70** was used without further purification: TLC $R_f = 0.17$ (2:1 hexanes/EtOAc); $[\alpha]_{Na}$ −165.2° (c = 0.26, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.28−7.25 (m, 2H, H_{arom}), 7.18 (dt, 1H, J = 7.3, 1.2 Hz, H_{arom}), 7.13 (dd, 2H, J = 6.9, 1.2 Hz, H_{arom}), 5.98 (dd, 1H, J = 16.8, 10.7 Hz, -C*H*=CH_2), 5.69 (dd, 1H, J = 16.8, 1.7 Hz, -CH=C*H*$_2$), 5.44 (d, 1H, J = 3.0 Hz, H_6), 5.42 (dd, 1H, J =10.7, 1.7 Hz, -CH=C*H*$_2$), 5.10 (d, 1H, J = 3.0 Hz, H_7), 4.90−4.86 (m, 1H, $H_{4'}$), 4.71 (br s, 1H, tertiary -OH), 3.88 (dd, 1H, J = 5.3, 3.4 Hz, H_3), 3.80 (dd, 1H, J = 12.0, 5.4 Hz, H_8), 3.79 (d, 1H, J = 11.2 Hz, H_{10}), 3.71 (d, 1H, J = 11.0 Hz, H_{10}), 3.70 (dd, 1H, J = 12.0, 3.3 Hz, H_8), 2.75 (dd, 1H, J = 13.4, 5.0 Hz, $H_{6'}$), 2.29 (dd, 1H, J = 13.4, 9.5 Hz, $H_{6'}$), 2.12 (s, 3H, -COC*H*$_3$), 2.10 (s, 3H, -COC*H*$_3$), 2.07 (s, 3H, -COC*H*$_3$), 2.00−1.95 (m, 1H, $H_{5'}$), 1.87−1.47 (m, 6H, $H_{1'}$, $H_{2'}$, $H_{3'}$), 0.87 (s, 9H, $H_{TBS\text{-}^tBu}$), 0.84 (d, 3H, J = 6.8 Hz, $H_{13'}$), 0.06 (s, 3H, $H_{TBS\text{-}Me}$), 0.04 (s, 3H, $H_{TBS\text{-}Me}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.9, 169.9 (2 lines), 140.7, 134.8, 129.1, 128.2, 125.9, 118.9, 104.5, 84.2, 80.5, 77.4, 77.0 (masked by $CDCl_3$), 75.2, 75.0, 62.9, 61.3, 39.4, 38.4, 35.4, 31.1, 25.7, 21.1, 20.7, 20.6, 19.0, 18.1, 14.0, −5.7, −5.8; IR (thin film) ν 3450 (br), 3026, 2955, 2931, 1749, 1463, 1432, 1372, 1240, 1179, 1093, 1039, 967, 838, 781, 701; HRMS (FAB^+) calcd for $C_{35}H_{54}SiO_{11}$ 678.3929, found 679.3501 (MH^+).

C(8) *tert*-Butyl Ester 71. To a solution of alcohol **70** (15.0 mg, 22.1 μmol) in 3.0 mL of CH_2Cl_2 was added 21 mg (50 mmol) of freshly prepared Dess−Martin periodinane.[31] The white suspension was stirred at 23 °C for 2 h. Et_2O (5 mL) was then added to the reaction mixture, and the resulting precipitates were removed by filtration through Celite. The filtrate was concentrated *in vacuo* to give a white solid residue. Purification by chromatography on silica gel (2:1 hexanes/EtOAc) afforded the product aldehyde (14 mg, 94%) as a colorless oil: TLC $R_f \approx 0.37$ (2:1 hexanes/EtOAc).

The intermediate aldehyde (11.0 mg, 16.3 μmol) was dissolved in 6.0 mL of a 5:1.2 ^{t}BuOH/2-methyl-2-butene solution and cooled to ~10 °C. An ice-cold buffered 1.1 M aqueous solution of $NaClO_2$ (150 μL, 165 μmol, 10 equiv) was added dropwise.[58] The resulting pale yellow solution was stirred for 3 h and then quenched with 5.0 mL of a pH 2 KH_2PO_4−HCl buffer. The solution was extracted with 6 × 3 mL of EtOAc. The combined extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The unpurified product was redissolved in 3.0 mL of CH_2Cl_2, and *N,N'*-diisopropyl-*O-tert*-butylisourea[59] (10 mg, 50 μmol, 3 equiv) was added. The solution was stirred for 22 h, during which time formation of a white precipitate was observed. The mixture was concentrated under reduced pressure to a pale yellow residue. Purification by chromatography on silica gel (5:1 hexanes/EtOAc) gave 9 mg (76%) of **71** as a colorless oil: TLC R_f = 0.24 (4:1 hexanes/EtOAc); $[\alpha]_{Na}$ +11.4° (c = 0.25, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.27−7.24 (m, 2H, H_{arom}), 7.16 (t, 1H, J = 7.3 Hz, H_{arom}), 7.12 (d, 2H, J = 7.4 Hz, H_{arom}), 6.03 (dd, 1H, J = 16.7, 10.8 Hz, -C*H*=CH_2), 5.62 (dd, 1H, J = 16.7, 1.5 Hz, -CH=C*H*$_2$), 5.47 (d, 1H, J = 2.9 Hz, H_6), 5.35 (dd, 1H, J = 10.7, 1.5 Hz, -CH=C*H*$_2$), 5.11 (d, 1H, J = 2.9 Hz, H_7), 4.87−4.85 (m, 1H, $H_{4'}$), 4.38 (s, 1H, H_3), 4.34 (s, 1H, tertiary -OH), 3.77 (d, 1H, J = 11.2 Hz, H_{10}), 3.72 (d, 1H, J = 11.2 Hz, H_{10}), 2.75 (dd, 1H, J = 13.4, 4.9 Hz, $H_{6'}$), 2.29 (dd, 1H, J = 13.4, 9.6 Hz, $H_{6'}$), 2.12 (s, 3H, -COC*H*$_3$), 2.10 (s, 3H, -COC*H*$_3$), 2.06 (s, 3H, -COC*H*$_3$), 2.03−1.93 (m, 1H, $H_{5'}$), 1.91−1.74 (m, 2H, $H_{1'}$), 1.68−1.48 (m, 4H, $H_{2'}$, $H_{3'}$), 1.43 (s, 9H, $H_{^tBu}$), 0.86 (s, 9H, $H_{TBS\text{-}^tBu}$), 0.83 (d, 3H, J = 6.8 Hz, $H_{13'}$), 0.032 (s, 3H, $H_{TBS\text{-}Me}$), 0.027 (s, 3H, $H_{TBS\text{-}Me}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.8, 169.88, 169.73, 165.7, 140.7, 134.3, 129.1, 128.2, 125.8, 117.8, 104.1, 85.1, 82.5, 80.4, 77.1, 76.9, 75.5, 73.9, 62.2, 39.3, 38.2, 35.2, 31.1, 28.2, 25.7, 21.1, 20.8, 20.7, 19.0, 18.1, 13.9, −5.6, −5.7; IR (thin film) ν 3452, 2956, 2931, 1753, 1643, 1603, 1495, 1462, 1416, 1370, 1240, 1153, 1099, 1041, 930, 838, 701; HRMS (FAB^+) calcd for $C_{39}H_{60}SiO_{12}$ 748.4392, found 749.3943 (MH^+).

3,5-Bis-*tert*-butyl Ester 73. To a solution of alcohol **72** (38.0 mg, 60.0 μmol) in 5.0 mL of CH_2Cl_2 were added 25 μL (310 μmol, 5 equiv) of pyridine and 51 mg (120 μmol, 2 equiv) of Dess−Martin periodinane sequentially.[31] The white suspension was stirred for 35 min at 23 °C. The reaction mixture was then diluted with Et_2O (10 mL), and the resulting precipitates were removed by filtration through Celite. Evaporation of the filtrate under reduced pressure gave the product as a pale yellow oil. Purification by chromatography on silica gel (gradient elution, 7:2 → 2:1 hexanes/EtOAc) yielded the desired aldehyde as a colorless oil (32 mg, 84%): TLC R_f = 0.43 (2:1 hexanes/EtOAc).

Oxidation and *tert*-butyl esterification was accomplished according to a procedure outlined for the preparation of compound **71**. The 3,5-bis-*tert*-butyl ester **73** was isolated as a colorless oil (27 mg, 76%): TLC R_f = 0.45 (2:1 hexanes/EtOAc); $[\alpha]_{Na}$ +56.5° (c = 0.26, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.27−7.24 (m, 2H, H_{arom}), 7.16 (t, 1H, J = 7.3 Hz, H_{arom}), 7.12 (d, 2H, J = 7.2 Hz, H_{arom}), 5.96 (dd, 1H, J = 16.7, 10.9 Hz, -C*H*=CH_2), 5.60 (d, 1H, J = 2.6 Hz, H_6), 5.55 (dd, 1H, J = 16.7, 1.5 Hz, -CH=C*H*$_2$), 5.36 (dd, 1H, J = 10.9, 1.5 Hz, -CH=C*H*$_2$), 5.12 (d, 1H, J = 2.6 Hz, H_7), 4.88−4.87 (m, 1H, $H_{4'}$), 4.42 (s, 1H, H_3), 3.61 (br s, 1H, tertiary -OH), 3.77 (d, 1H, J = 11.2 Hz, H_{10}), 3.72 (d, 1H, J = 11.2 Hz, H_{10}), 2.75 (dd, 1H, J = 13.3, 4.9 Hz, $H_{6'}$), 2.29 (dd, 1H, J = 13.3, 9.6 Hz, $H_{6'}$), 2.14 (s, 3H, -COC*H*$_3$), 2.09 (s, 3H, -COC*H*$_3$), 2.06 (s, 3H, -COC*H*$_3$), 2.03−1.94 (m, 1H, $H_{5'}$), 1.94−1.80 (m, 2H, $H_{1'}$), 1.73−1.47 (m, 4H, $H_{2'}$, $H_{3'}$), 1.43 (s, 9H, $H_{^tBu}$), 1.40 (s, 9H, $H_{^tBu}$), 0.83 (d, 3H, J = 6.8 Hz, $H_{13'}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.8, 169.4, 169.0, 165.0, 162.9, 140.7, 132.7, 129.1, 128.2, 125.8, 117.8, 104.1, 89.8, 83.5, 83.0, 80.3, 76.0, 75.4, 73.0 (2 lines), 39.3, 38.4, 35.4, 31.0, 28.1, 28.0, 21.1, 20.7 (2 lines), 19.0, 14.0; IR (thin film) ν 3567, 2978, 2933, 1752, 1603, 1495, 1455, 1415, 1369, 1298, 1240, 1155, 1035, 937, 846, 702; HRMS (FAB^+) calcd for $C_{37}H_{52}O_{13}$ 704.3991, found 705.3482 (MH^+).

Olefin 78. Palladium on carbon (5%, 112 mg, 100 wt %) was suspended in 5.0 mL of a pyridine solution of **69** (112 mg, 0.142 mmol). The slurry was stirred at 23 °C under 1 atm of H_2 for 4.5 h. Removal of the palladium catalyst by filtration through Celite, followed by evaporation of the filtrate under reduced pressure, afforded 115 mg of a colorless oil. The product **77** was used without purification: TLC R_f = 0.26 (6:1 hexanes/EtOAc).

Compound **77** (0.142 mmol) was transferred to a Teflon vial and dissolved in a solution of HF·pyridine in THF/pyridine prepared according to the method of Trost.[60] The solution was stirred at 23 °C for 7.5 h before the reaction was quenched by the addition of 5.0 mL of an 1.0 M aqueous KH_2PO_4 solution. The mixture was extracted with 4 × 5 mL of Et_2O, and the combined organic extracts were washed once with saturated aqueous NaCl (5 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the product as a yellow oil. Purification by chromatography on silica gel (2:3 hexanes/EtOAc) furnished 51 mg of olefin **78** (64%) as a white foam. TLC R_f = 0.13 (1:1 hexanes/EtOAc); $[\alpha]_{Na}$ +33.3° (c = 0.86, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 7.29−7.26 (m, 2H, H_{arom}), 7.19 (t, 1H, J = 7.3 Hz, H_{arom}), 7.12 (d, 2H, J = 7.5 Hz, H_{arom}), 5.97 (dd, 1H, J = 16.7, 10.9 Hz, H_9), 5.79 (dd, 1H, J = 16.9, 0.9 Hz, -CH=C*H*$_2$), 5.51−5.48 (m, 2H, H_6 and -CH=C*H*$_2$), 5.17 (d, 1H, J = 3.0 Hz, H_7), 4.91−4.88 (m, 1H, $H_{4'}$), 3.98 (dd, 1H, J = 4.4, 4.1 Hz, H_3), 3.91 (s, 1H, tertiary -OH), 3.80−3.71 (m, 4H, H_8, H_{10}), 2.74 (dd, 1H, J = 13.5, 5.0 Hz, $H_{6'}$), 2.33 (dd, 1H, J = 13.5, 9.4 Hz, $H_{6'}$), 2.30−2.26 (m, 1H, primary -OH), 2.23 (dd, 1H, J = 6.4, 2.8 Hz, primary -OH), 2.14 (s, 3H, -COC*H*$_3$), 2.13 (s, 3H, -COC*H*$_3$), 2.09 (s, 3H, -COC*H*$_3$), 2.01−1.97 (m, 1H, $H_{5'}$), 1.90−1.43 (m, 6H, $H_{1'}$, $H_{2'}$, $H_{3'}$), 0.86 (d, 3H, J = 6.9 Hz, $H_{13'}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.1, 170.0, 169.7, 140.5, 133.3, 129.0, 128.2,

125.9, 119.6, 104.7, 85.3, 80.1, 76.9, 76.6, 75.2, 74.5, 61.3, 60.9, 39.4, 38.4, 35.1, 31.0, 21.1, 20.7, 20.6, 18.9, 13.9; IR (thin film) ν 3400 (br), 2936, 1748, 1454, 1373, 1240, 1021, 962, 746, 702; HRMS (FAB^+) calcd for $C_{29}H_{40}O_{11}$ 564.2570, found 565.2634 (MH^+).

Dialdehyde 79. To a solution of **78** (40.0 mg, 70.8 μmol) in 4.0 mL of CH_2Cl_2 was added 72 μL of pyridine (0.9 mmol, 12.5 equiv), followed by 150 mg (0.35 mmol, 5 equiv) of the Dess–Martin periodinane.[31] The resulting white suspension was stirred at 23 °C for 2.5 h. To the reaction mixture was then added 5.0 mL of Et_2O, and the resulting precipitates were removed by filtration through Celite. The filtrate was concentrated *in vacuo*, and the isolated pale yellow residue was purified by chromatography on silica gel (3:2 hexanes/EtOAc) to afford 37 mg of **79** (93%) as a white foam: TLC $R_f = 0.16$ (2:1 hexanes/EtOAc); $[\alpha]_{Na}$ +33.1° (c = 0.39, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.47 (s, 1H, -C*H*O), 9.36 (s, 1H, -C*H*O), 7.30–7.26 (m, 2H, H_{arom}), 7.19 (t, 1H, J = 7.3 Hz, H_{arom}), 7.14 (d, 2H, J = 7.1 Hz, H_{arom}), 6.20 (ddd, 1H, J = 16.7, 11.5, 1.6 Hz, H_9), 5.73 (d, 1H, J = 16.7 Hz, -CH=CH_2), 5.65 (d, 1H, J = 11.5 Hz, -CH=CH_2), 5.56 (d, 1H, J = 2.6 Hz, H_6), 5.24 (d, 1H, J = 2.6 Hz, H_7), 4.91–4.89 (m, 1H, $H_{4'}$), 4.40 (s, 1H, H_3), 3.62 (d, 1H, J = 1.6 Hz, tertiary -OH), 2.75 (dd, 1H, J = 13.5, 5.2 Hz, $H_{6'}$), 2.33 (dd, 1H, J = 13.4, 9.3 Hz, $H_{6'}$), 2.15 (s, 3H, -COCH_3), 2.09 (s, 3H, -COCH_3), 2.07 (s, 3H, -COCH_3), 2.01–1.97 (m, 1H, $H_{5'}$), 1.90–1.52 (m, 6H, $H_{1'}$, $H_{2'}$, $H_{3'}$), 0.86 (d, 3H, J = 6.8 Hz, $H_{13'}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 195.3, 192.7, 170.9, 169.7, 169.2, 140.5, 129.3, 129.0, 128.3, 125.9, 122.0, 105.1, 90.1, 79.5, 79.2, 76.4, 76.1, 73.2, 39.4, 38.5, 35.1, 31.0, 21.1, 20.6, 20.4, 18.9, 14.0; IR (thin film) ν 3459, 2966, 1743, 1420, 1373, 1237, 1036, 959, 740, 702; HRMS (FAB^+) calcd for $C_{29}H_{36}O_{11}$ 560.2257, found 561.2356 (MH^+).

Tris-*tert*-butyl Ester 75. A solution of dialdehyde **79** (23.0 mg, 41.0 μmol) in 6.0 mL of a 10% v/v MeOH–CH_2Cl_2 solution was cooled to −78 °C and treated with a dilute stream of ozone in oxygen (0.8 mmol/min). After 30 min, PPh_3 (13 mg, 49 μmol, 1.2 equiv) was added to the reaction mixture, and the resulting suspension was slowly warmed to 23 °C. Concentration of the reaction mixture under reduced pressure yielded a white foam **80**. The product was dissolved in 6.0 mL of a 5:1.2 ^{t}BuOH/2–methyl–2–butene solution and cooled to ~10 °C. An ice-cold buffered 1.1 M aqueous solution of $NaClO_2$ (370 μL, ~410 μmol, 10 equiv) was added dropwise.[58] The resulting pale yellow solution was stirred for 3 h before being quenched with 5.0 mL of a pH 2 KH_2PO_4–HCl buffer. The solution was extracted with 6 × 5 mL of EtOAc. The combined extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The unpurified product was redissolved in 3.0 mL of CH_2Cl_2, and *N,N'*-diisopropyl-*O-tert*-butylisourea[59] (82 mg, 410 μmol) was added dropwise. The solution was stirred for 24 h, during which time formation of a white precipitate was observed. The mixture was filtered through Celite to remove the solid material and concentrated under reduced pressure to a pale yellow oil. Purification by chromatography on silica gel (7:2 hexanes/EtOAc) afforded **75** (23 mg, 72%) as a colorless oil: TLC $R_f = 0.44$ (2:1 hexanes/EtOAc); $[\alpha]_{Na}$ +69.9° (c = 0.29, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27–7.25 (m, 2H, H_{arom}), 7.16 (t, 1H, J = 7.3 Hz, H_{arom}), 7.11 (d, 2H, J = 7.4 Hz, H_{arom}), 6.33 (d, 1H, J = 1.9 Hz, H_6), 5.08 (d, 1H, J = 1.9 Hz, H_7), 4.88 (s, 1H, H_3), 4.88–4.86 (m, 1H, $H_{4'}$), 4.06 (s, 1H, tertiary -OH), 2.75 (dd, 1H, J = 13.4, 4.9 Hz, $H_{6'}$), 2.29 (dd, 1H, J = 13.4, 9.6 Hz, $H_{6'}$), 2.14 (s, 3H, -COCH_3), 2.06 (s, 3H, -COCH_3), 2.05 (s, 3H, -COCH_3), 2.05–1.91 (m, 3H, $H_{1'}$, $H_{5'}$), 1.67–1.50 (m, 4H, $H_{2'}$, $H_{3'}$), 1.61 (s, 9H, $H_{^t Bu}$), 1.46 (s, 9H, $H_{^t Bu}$), 1.45 (s, 9H, $H_{^t Bu}$), 0.83 (d, 3H, J = 6.8 Hz, $H_{13'}$); ^{13}C NMR (CD_3OD, 125 MHz) δ 173.0, 171.2, 170.3, 168.9, 167.5, 165.7, 142.1, 130.3, 129.4, 127.1, 105.7, 91.3, 86.6, 85.5, 85.1, 81.8 (2 lines), 78.1, 77.0, 75.7, 40.7, 39.8, 36.7, 32.5, 28.6 (2 lines), 28.5, 21.2, 20.8, 20.6, 20.3, 14.4; IR (thin film) ν 3447, 2979, 2935, 1760, 1732, 1477, 1457, 1394, 1370, 1236, 1152, 1118, 1039, 995, 702; HRMS (FAB^+) calcd for $C_{40}H_{58}O_{15}$ 778.3775, found 801.3673 (MNa^+).

Alcohol 81. Tris-*tert*-butyl ester **75** (15.0 mg, 19.3 μmol) was treated with 3.0 mL of a 0.2% K_2CO_3 in methanol solution. The solution was stirred for 30 min before the reaction was quenched by the addition of 3.0 mL of a 0.3 M aqueous KH_2PO_4 solution. The mixture was extracted with 5 × 3 mL of Et_2O; the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give the product as a colorless oil. Purification by chromatography on silica gel (3:2 hexanes/EtOAc) furnished 12 mg (90%) of **81** as a colorless film: TLC $R_f = 0.28$ (1:1 hexanes/EtOAc); ^{1}H NMR (CD_3OD, 500 MHz) δ 7.26–7.22 (m, 2H, H_{arom}), 7.16–7.13 (m, 3H, H_{arom}), 4.97 (s, 1H, H_3), 4.95 (d, 1H, J = 2.0 Hz, H_6), 4.90–4.86 (m, 1H, $H_{4'}$), 3.99 (d, 1H, J = 1.9 Hz, H_7), 2.74 (dd, 1H, J = 13.4, 5.6 Hz, $H_{6'}$), 2.35 (dd, 1H, J = 13.4, 9.1 Hz, $H_{6'}$), 2.05 (s, 3H, -COCH_3), 2.05–2.01 (m, 1H, $H_{5'}$), 1.90–1.79 (m, 2H, $H_{1'}$), 1.73–1.62 (m, 2H, $H_{3'}$), 1.60–1.28 (m, 2H, $H_{2'}$), 1.60 (s, 9H, $H_{^t Bu}$), 1.46 (s, 9H, $H_{^t Bu}$), 1.45 (s, 9H, $H_{^t Bu}$), 0.87 (d, 3H, J = 6.8 Hz, $H_{13'}$); ^{13}C NMR (CD_3OD, 125 MHz) δ 173.0, 169.8, 168.2, 167.4, 142.0, 130.2, 129.3, 126.9, 106.4, 93.2, 85.5, 84.3 (2 lines), 84.2, 79.9, 78.3, 76.8, 76.0, 40.6, 39.5, 36.6, 32.5, 28.7, 28.5 (2 lines), 21.1, 20.2, 14.3; IR (thin film) ν 3500 (br), 2978, 2933, 1732, 1455, 1394, 1370, 1255, 1153, 1050, 963, 844, 701; HRMS (FAB^+) calcd for $C_{36}H_{54}O_{13}$ 694.3564, found 717.3462 (MNa^+).

Allylic Alcohol 84. To a suspension of $LiAlH_4$ (3.6 g, 95 mmol, 2.5 equiv) in 200 mL of Et_2O at 0 °C was added, via addition funnel, 150 mL of an ethereal solution of 5-phenylhex-2-yn-1-ol (6.6 g, 38 mmol). The gray suspension was stirred at 0 °C for 10 min. The mixture was warmed to 23 °C and then heated to reflux. After 12 h at reflux, the reaction was recooled to 0 °C and cautiously quenched with 3.6 mL of H_2O, 3.6 mL of 15% aqueous NaOH, and 10.8 mL of H_2O, added sequentially. The resulting viscous suspension was warmed to 23 °C and stirred vigorously for 30 min. The white precipitates were removed by filtration through Celite, and the filter cake was rinsed with 3 × 150 mL of Et_2O. The colorless filtrate was dried over Na_2SO_4 and concentrated under reduced pressure to give a pale yellow oil. Purification by chromatography on silica gel (11:2 hexanes/EtOAc) yielded 5.3 g (79%) of **84** as a clear, colorless oil: TLC $R_f = 0.19$ (4:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30–7.26 (m, 2H, H_{arom}), 7.20–7.18 (m, 3H, H_{arom}), 5.75–5.63 (m, 2H, -C*H*=C*H*CH_2-OH), 4.09 (d, 2H, J = 5.6 Hz, -CH_2OH), 2.64 (t, 2H, J = 7.7 Hz, PhC$H_2$$CH_2$-), 2.10 (dt, 2H, J = 7.1, 6.8 Hz, -CH_2CH=CHCH_2OH), 1.74 (tt, 2H, J = 7.6 Hz, PhCH_2C$H_2$$CH_2$-), 1.38 (br s, 1H, primary -OH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 142.3, 132.8, 129.4, 128.4, 128.3, 125.7, 63.7, 35.3, 31.7, 30.7; IR (thin film) ν 3318 (br), 3025, 2928, 1603, 1496, 1452, 1085, 968, 697. Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.50; H, 9.18.

Epoxy Alcohol 85. A flask containing 1.0 g of freshly activated 4 Å molecular sieves was charged with 140 mL of CH_2Cl_2 and 268 μL of L-(+)-diisopropyl tartrate (1.28 mmol, 0.075 equiv). The mixture was cooled to −30 °C (2:3 ethylene glycol/H_2O–dry ice) before $Ti(O^iPr)_4$ (250 μL, 0.85 mmol, 0.05 equiv) and a 4.0 M CH_2Cl_2 solution of ^{t}BuOOH (8.5 mL, 34 mmol, 2 equiv) were added sequentially. The contents were stirred at −30 °C for 1 h before a solution of alcohol **84** (3.00 g, 17.0 mmol) in 4.0 mL of CH_2Cl_2 was added dropwise via cannula. Transfer of **84** was made quantitative with an additional 2.0 mL of CH_2Cl_2. The reaction was stirred at −30 °C for 20 h, after which time 1.0 mL of a 30% aqueous NaOH solution saturated with NaCl was added, along with 30.0 mL of Et_2O. The mixture was warmed to −10 °C and stirred for 1 h. Following the addition of 2.5 g of Celite and 1.0 g of $MgSO_4$, the slurry was warmed to 23 °C, and the mixture was filtered through Celite. The solids collected were rinsed with Et_2O (~50 mL), and the combined filtrates were concentrated under reduced pressure to give a yellow oil. Purification by chromatography on silica gel (gradient elution, 3:1 → 2:1 hexanes/EtOAc) furnished **85** as a colorless oil (3.2 g, 98%): TLC $R_f = 0.20$ (2:1 hexanes/EtOAc); $[\alpha]_{Na}$ +18.9° (c = 0.42, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.30–7.26 (m, 2H, H_{arom}), 7.21–7.18 (m, 3H, H_{arom}), 3.89 (ddd, 1H, J = 12.5, 5.1, 2.5 Hz, -OC*H*CH_2OH), 3.61 (ddd, 1H, J = 12.5, 7.1, 4.8 Hz, PhC$H_2$$CH_2$$CH_2$*H*CO-), 3.00–2.96 (m, 1H, -CH_2OH), 2.92–2.90 (m, 1H, -CH_2OH), 2.68 (t, 2H, J = 7.7 Hz, PhC$H_2$$CH_2$-), 1.90 (br s, 1H, primary -OH), 1.85–1.73 (m, 2H, PhC$H_2$$CH_2CH_2$-CH-), 1.68–1.57 (m, 2H, PhCH_2C$H_2$$CH_2$-); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 141.8, 128.35, 128.33, 125.9, 61.6, 58.3, 55.7, 35.5, 31.0, 27.6; IR (thin film) ν 3408 (br), 2933, 1602, 1496, 1452, 1092, 1030, 886, 747, 699. Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.61; H, 8.40. The epoxy alcohol **85** was shown to be in >95% ee as determined by analysis of the ^{1}H NMR spectrum of the corresponding Mosher (*S*)-MTPA ester (prepared as described in ref 65).

C(7)–OBoc Compound 97. To a cold solution (0 °C) of **81** (8.5 mg, 12 μmol) and 4-pyrrolidinopyridine (1.5 mg, 10.1 μmol, 0.8 equiv) in 1.0 mL of CH_2Cl_2 was added Et_3N (7 μL, 49 μmol, 4.0

equiv), followed by 140 μL of a 0.10 M CH_2Cl_2 solution of di-*tert*-butyl dicarbonate (14.0 μmol, 1.15 equiv). The resulting mixture was stirred at 0 °C for 6 h. The reaction was then poured into 2.0 mL of 1.0 M aqueous K_2HPO_4 and extracted with 5 × 2 mL of Et_2O. The combined ethereal extracts were washed once with saturated aqueous NaCl (5 mL), dried over Na_2SO_4, and concentrated *in vacuo*. Purification of the white residue by chromatography on silica gel (3:1 hexanes/EtOAc) afforded **97** (8 mg, 82%) as a white foam: TLC R_f = 0.19 (3:1 hexanes/EtOAc); $[\alpha]_{Na}$ +43.3° (c = 0.25, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27−7.24 (m, 2H, H_{arom}), 7.17 (t, 1H, J = 7.3 Hz, H_{arom}), 7.12 (d, 2H, J = 7.1 Hz, H_{arom}), 5.11 (br s, 1H, H_6), 4.88−4.86 (m, 1H, $H_{4'}$), 4.72 (s, 1H, H_3), 4.64 (d, 1H, J = 2.1 Hz, H_7), 3.93 (br s, 1H, tertiary -OH), 2.80 (br s, 1H, secondary -OH), 2.75 (dd, 1H, J = 13.5, 5.1 Hz, $H_{6'}$), 2.30 (dd, 1H, J = 13.5, 9.7 Hz, $H_{6'}$), 2.05 (s, 3H, -COCH_3), 2.05−1.91 (m, 3H, $H_{1'}$, $H_{5'}$), 1.68−1.26 (m, 4H, $H_{2'}$, $H_{3'}$), 1.58 (s, 9H, $H_{Boc\text{-}tBu}$), 1.50 (s, 9H, H_{tBu}), 1.49 (s, 9H, H_{tBu}), 1.45 (s, 9H, H_{tBu}), 0.84 (d, 3H, J = 6.8 Hz, $H_{13'}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.8, 168.5, 165.8, 165.2, 153.7, 140.8, 129.1, 128.2, 125.8, 103.9, 90.7, 85.6, 85.0, 83.9, 83.7, 83.2, 76.92, 76.85, 75.3, 74.1, 39.4, 38.0, 35.6, 30.9, 28.2, 28.1, 28.0, 27.7, 21.2, 18.9, 13.8; IR (thin film) ν 3462 (br), 2980, 2934, 1732, 1456, 1395, 1370, 1278, 1256, 1157, 1119, 1060, 964, 843, 733; HRMS (FAB$^+$) calcd for $C_{41}H_{62}O_{15}$ 794.4088, found 817.3986 (MNa^+).

C(7)-OBoc Zaragozic Acid C, 3,4,5-Tris-*tert*-butyl Ester (98). To a solution of acyl side chain acid **89** (9.0 mg, 36 μmol) in 365 μL of CH_2Cl_2 was added 7.5 mg of 1,3-dicyclohexylcarbodiimide (36 μmol). The resulting suspension was stirred for 15 min before use. A solution of **97** (4.0 mg, 5.0 μmol) and 4-DMAP (2 mg, 16 μmol) in 1.0 mL of CH_2Cl_2 was treated with 60 μL of the **89**−DCC mixture (6 μmol). The mixture was stirred for 40 h and then quenched with 2.0 mL of 50% saturated aqueous $NaHCO_3$. The mixture was extracted with 4 × 2 mL of Et_2O; the organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give a pale yellow oil. Purification by chromatography on silica gel (5:1 hexanes/EtOAc) gave the product **98** (4 mg, 78%) as a colorless film. TLC R_f = 0.37 (3:1 hexanes/EtOAc); $[\alpha]_{Na}$ +8.5° (c = 0.27, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28−7.22 (m, 4H, H_{arom}), 7.18−7.12 (m, 6H, H_{arom}), 6.40 (d, 1H, J = 1.9 Hz, H_6), 5.38−5.29 (m, 2H, $H_{4''}$, $H_{5''}$), 4.91 (s, 1H, H_3), 4.89−4.86 (m, 2H, H_7, $H_{4'}$), 4.05 (br s, 1H, tertiary -OH), 2.76 (dd, 1H, J = 13.4, 4.7 Hz, $H_{6'}$), 2. 57 (t, 2H, J = 7.7 Hz, $H_{9''}$), 2.39−2.27 (m, 3H, $H_{6'}$, $H_{2''}$), 2.12−1.84 (m, 6H, $H_{1'}$, $H_{5'}$, $H_{3''}$, $H_{6''}$), 2.05 (s, 3H, -COCH_3), 1.68−1.26 (m, 8H, $H_{2'}$, $H_{3'}$, $H_{7''}$, $H_{8''}$), 1.62 (s, 9H, $H_{Boc\text{-}tBu}$), 1.47 (s, 9H, H_{tBu}), 1.452 (s, 9H, H_{tBu}), 1.446 (s, 9H, H_{tBu}), 0.93 (d, 3H, J = 6.7 Hz, $H_{16''}$), 0.83 (d, 3H, J = 6.8 Hz, $H_{13'}$); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.8, 170.7, 168.6, 165.6, 164.0, 152.4, 142.8, 140.8, 137.6, 129.1, 128.4, 128.23, 128.21, 126.1, 125.8, 125.6, 103.8, 89.8, 86.0, 83.9, 83.4, 83.3, 83.1, 77.0 (masked by $CDCl_3$), 76.2, 75.3, 74.0, 39.4, 38.0, 36.6, 36.5, 36.1, 35.8, 34.2, 30.9, 29.2, 28.1 (2 lines), 28.0, 27.9, 27.7, 21.2, 20.6, 18.9, 13.9; IR (thin film) ν 3480, 2933, 1746, 1458, 1370, 1279, 1254, 1158, 1118, 700; HRMS (FAB$^+$) calcd for $C_{57}H_{82}O_{16}$ 1022.5602, found 1045.5501 (MNa^+).

Zaragozic Acid C (1). To a solution of **98** (3.0 mg, 2.9 μmol) in 1.5 mL of CH_2Cl_2 was added 500 μL of trifluoroacetic acid. The reaction was stirred for 16 h, after which time the volatiles were removed *in vacuo*. The resulting pale brown residue was dissolved in toluene (5 mL), concentrated *in vacuo*, and lyophilized from 2 mL of benzene to afford 2.2 mg (100%) of **1** as a white flocculent solid: TLC R_f = 0.34 (6:1 CH_3CN/H_2O); HPLC t_R = 12.03 ± 0.5 min (reverse phase, 20% CH_3CN in 0.1% aqueous H_3PO_4 initially, graded to 95% CH_3CN over 20 min); $[\alpha]_{Na}$ +9.0° (c = 0.23, EtOH); ^{1}H NMR (CD_3OD, 500 MHz) δ 7.25−7.21 (m, 4H, H_{arom}), 7.15−7.10 (m, 6H, H_{arom}), 6.23 (d, 1H, J = 1.8 Hz, H_6), 5.37 (dt, 1H, J = 15.3, 6.1 Hz, $H_{4''}$), 5.30 (dd, 1H, J = 15.4, 7.5 Hz, $H_{5''}$), 5.23 (s, 1H, H_3), 4.90−4.86 (m, 1H, $H_{4'}$ masked by CD_3OH signal), 4.01 (d, 1H, J = 1.8 Hz, H_7), 2.73 (dd, 1H, J = 13.3, 5.6 Hz, $H_{6'}$), 2.58−2.54 (m, 2H, $H_{9''}$), 2.37−2.32 (m, 3H, $H_{6'}$, $H_{2''}$), 2.28−2.25 (m, 2H, $H_{3''}$), 2.09−2.01 (m, 2H, $H_{5'}$, $H_{6''}$), 2.05 (s, 3H, -COCH_3), 1.91−1.86 (m, 2H, $H_{1'}$), 1.69−1.66 (m, 2H, $H_{3'}$), 1.61−1.53 (m, 4H, $H_{2'}$, $H_{8''}$), 1.31−1.24 (m, 2H, $H_{7''}$), 0.93 (d, 3H, J = 6.9 Hz, $H_{16''}$), 0.86 (d, 3H, J = 6.8 Hz, $H_{13'}$); ^{13}C NMR (CD_3OD, 125 MHz) δ 173.1, 173.0, 172.6, 170.2, 168.6, 143.9, 142.0, 138.8, 130.2, 129.4, 129.28, 129.26, 127.6, 126.9, 126.6, 107.1, 91.0, 82.3, 81.2, 78.2, 76.7, 75.6, 40.5, 39.7, 37.8, 37.6, 36.9, 36.3, 35.4, 32.5, 30.5, 28.8, 21.2, 21.1, 20.1, 14.3; IR (thin film) ν 3456 (br), 2928, 1732, 1495, 1454, 1372, 1249, 1148, 1028, 969, 746, 700; HRMS (FAB$^+$) calcd for $C_{40}H_{50}O_{14}$ 754.3198, found 777.3098 (MNa^+).

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