Total Synthesis of Zaragozic Acid A (Squalestatin S1). Degradation to a Relay Compound and Reassembly of the Natural Product

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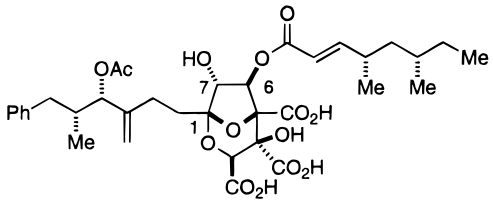
Zaragozic acid A (squalestatin S1) (**1**) was converted into the simpler derivative **2**, which was reconverted into the natural product, thus establishing **2** as a viable relay compound for total synthesis of **1**. The degradation (Scheme 1) consisted of formation of the tri-*tert*-butyl ester (**3**), from which the two side chains were sequentially removed to obtain **8**. Aldehyde **8** was converted into dimethyl acetal **2** in standard fashion. The C6 acyl side chain **14** was prepared from (*S*)-2-methylbutanol ("active amyl alcohol"), and the desired 4*S* configuration was obtained by use of Evans asymmetric enolate methylation (Scheme 2). The C1 alkyl side chain was prepared as stannane **23a** from (*R*)-2-methyl-3-phenylpropanol (**21**) as shown in Scheme 5. For conversion of **2** back into zaragozic acid A, the dimethyl acetal was first converted into the cyclic acetal **17**, thus protecting the C7 hydroxyl group. The remaining hydroxyl group was then acylated with acid **14** to obtain **18**, which was transformed into aldehyde **20** (Scheme 4). The C1 alkyl chain was elaborated by the addition of a chiral α-alkoxyorganocerium reagent, obtained from **23a**, to aldehyde **20**. The resulting mixture of diastereomeric secondary alcohols was converted into zaragozic acid A (**1**) in six steps (Scheme 6).

In 1992 the isolation of several potent (picomolar) inhibitors of squalene synthase was reported independently by chemists at Glaxo[1] and Merck.[2] These compounds were named "squalestatins" by the Glaxo group and "zaragozic acids" by the Merck group. Additional squalestatins[3] and zaragozic acids[4] were subsequently reported.[5] The archetypal representative of this group of natural products is zaragozic acid A (squalestatin S1), **1**. As inhibitors of squalene synthase, the zaragozic acids interfere with cholesterol biosynthesis *downstream* from the step inhibited by mevinolin and its analogs. They are of potential significance because inhibition of HMG CoA reductase early in the biosynthetic pathway interferes with the production of important biomolecules (ubiquinones, dolichols, isopentenylnucleosides) in addition to cholesterol. Through intervention at the step in which the triterpene skeleton is created, possible side effects that accompany hypercholesterolemic therapy might be avoided. In this article, we report the interconversion of zaragozic acid A (squalestatin S1, **1**)[6] with **2**. In the accompanying article, we report the *de novo* synthesis of **2**, thus completing a total synthesis of **1**.[7]



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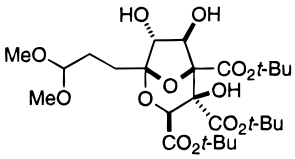

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[⊗] Abstract published in *Advance ACS Abstracts,* December 1, 1996.

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(2) (a) 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. (b) Hensens, O. D.; Dufresne, C.; Liesch, J. M.; Zink, D. L.; Reamer, R. A.; VanMiddlesworth, F. *Tetrahedron Lett.* **1993**, *34*, 399. (c) Dufresne, C.; Wilson, K. E.; Zink, D.; Smith, J.; Bergstrom, J. D.; Kurtz, M.; Rew, D.; Nallin, M.; Jenkins, R.; Bartizal, K.; Trainor, C.; Bills, G.; Meinz, M.; Huang, L.; Onishi, J.; Milligan, J.; Mojena, M.; Pelaez, F. *Tetrahedron* **1992**, *48*, 10221. (d) Wilson, K. E.; Burk, R. M.; Biftu, T.; Ball, R. G.; Hoogsteen, K. *J. Org. Chem.* **1992**, *57*, 7151.

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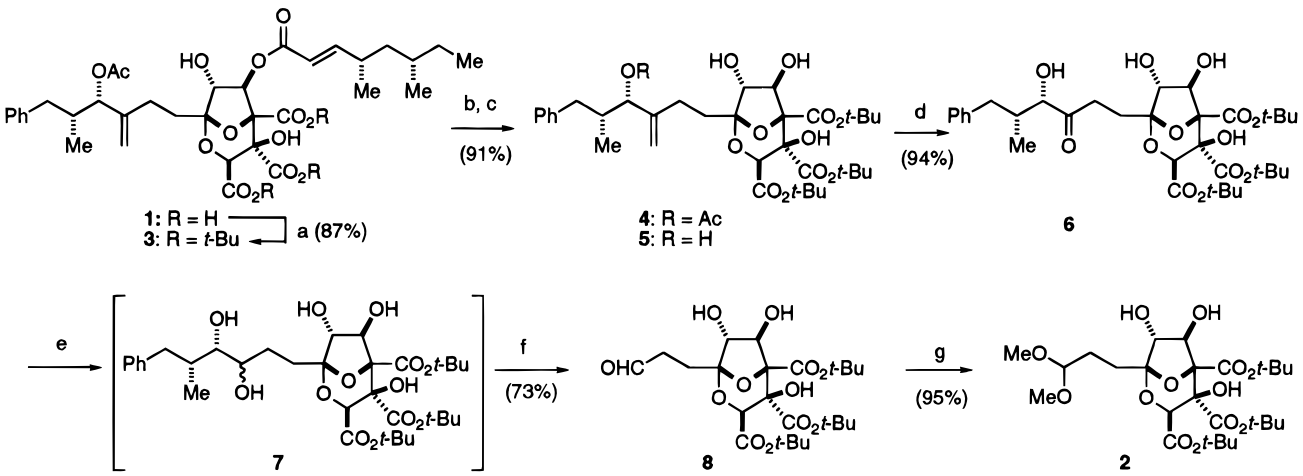
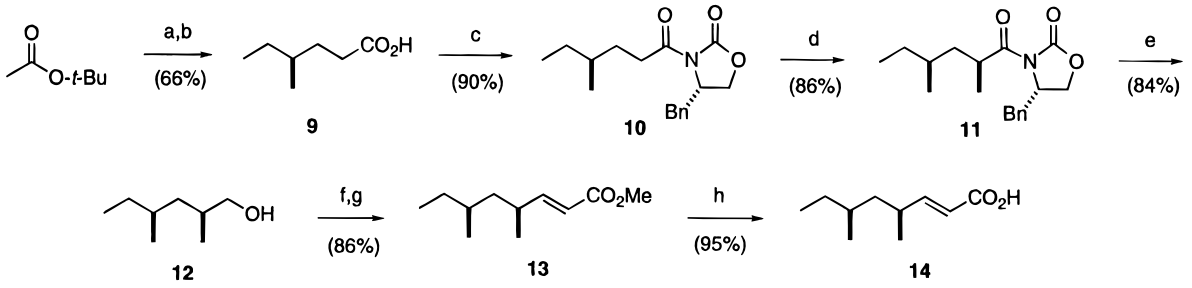
Scheme 1[a]



[a] Reagents and conditions: (a) *i*-PrN=C(O-*t*-Bu)NH-*i*-Pr, CH_2Cl_2, reflux; (b) $HONH_2$·HCl, NaOAc, MeOH; (c) EtMgBr, $CeCl_3$, −78 °C; (d) (i) O_3, CH_2Cl_2, −78 °C; (ii) Me_2S; (e) $NaBH_4$, MeOH, 0 °C; (f) $Pb(OAc)_4$, benzene, 10 °C; (g) MeOH, $(MeO)_3CH$, PPTS rt, 3 h.

Scheme 2[a]



[a] Reagents and conditions: (a) (i) LDA, THF −78 °C; (ii) (*S*)-1-iodo-2-methylbutane, DMPU, −78 °C to −45 °C to rt; (b) CF_3CO_2H; (c) (i) $(COCl)_2$, DMF (cat.), CH_2Cl_2; (ii) (*S*)-3-lithio-4-benzyl-2-oxazolidinone, THF; (d) (i) NaHMDS, THF, −78 °C; (ii) CH_3I, −78 °C to rt; (e) $LiBH_4$, MeOH, Et_2O, 0 °C to rt; (f) $(COCl)_2$, DMSO, Et_2N, CH_2Cl_2; (g) Ph_3P=$CHCO_2Me$, CH_2Cl_2, rt; (h) LiOH, H_2O, THF.

The degradation of zaragozic acid A into the relay compound **2** is summarized in Scheme 1. As reported by Ponpipom and co-workers,[8] tri-*tert*-butyl ester **3** is formed in excellent yield when zaragozic acid A is treated with *O*-*tert*-butyl-*N*,*N*′-diisopropylisourea in methylene chloride at reflux. The selective cleavage of the C6 α,β-unsaturated ester was readily effected by treatment of **3** with hydroxylamine,[8,9] providing **4** as a crystalline solid in virtually quantitative yield. Removal of the acetate from **4** was also accomplished by using the general method of Ponpipom and co-workers.[8] Thus, treatment of **4** with ethylmagnesium bromide and cerium(III) chloride at low temperature afforded the desired tetrol **5** in good yield. This method was superior to transesterification or hydrolysis of the acetate under basic conditions because of the lability of the C3 *tert*-butyl ester under these conditions.[10] Ozonolytic cleavage of the double bond afforded ketone **6**, which was reduced with methanolic sodium borohydride to yield the diol **7** as a 3:2 mixture of diastereomers. Selective cleavage of the side chain glycol over the trans glycol on the core using $Pb(OAc)_4$ next provided aldehyde **8**; the isomeric cyclic hemiacetal of **8** was never observed by NMR spectroscopy. Treatment of **8** with methanol and trimethyl orthoformate in the presence of pyridinium *p*-toluenesulfonate afforded acetal **2**.

For the reconstitution of zaragozic acid A, it was first necessary to prepare α,β-unsaturated acid **14**. This was accomplished as shown in Scheme 2. Alkylation of the lithium enolate of *tert*-butyl acetate with (*S*)-1-iodo-2-methylbutane[11] followed by treatment of the resulting *tert*-butyl ester with trifluoroacetic acid afforded (*S*)-4-methylhexanoic acid (**9**).[12] This acid was converted into the corresponding acyl chloride and used to acylate (*S*)-3-lithio-4-benzyl-2-oxazolidinone. The resulting imide **10** was methylated by the method of Evans[13] to obtain **11** and its C2 diastereomer in a 17:1 ratio. The diastereomers were readily separable by column chromatography, and **11** could be obtained in high yield and diastereomeric purity. An alternative approach, which involved alkylation of the mixed lithium−potassium enolate of (*R*)-1-propanoyl-2-pyrrolidinemethanol[14] with (*S*)-1-iodo-2-methylbutane, gave the two C2 diastereomers in a ratio

(8) Ponpipom, 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.

(9) Panfil, I.; Maciejewski, S.; Belzecki, C.; Chmielewski, M. *Tetrahedron Lett.* **1989**, *30*, 1527.

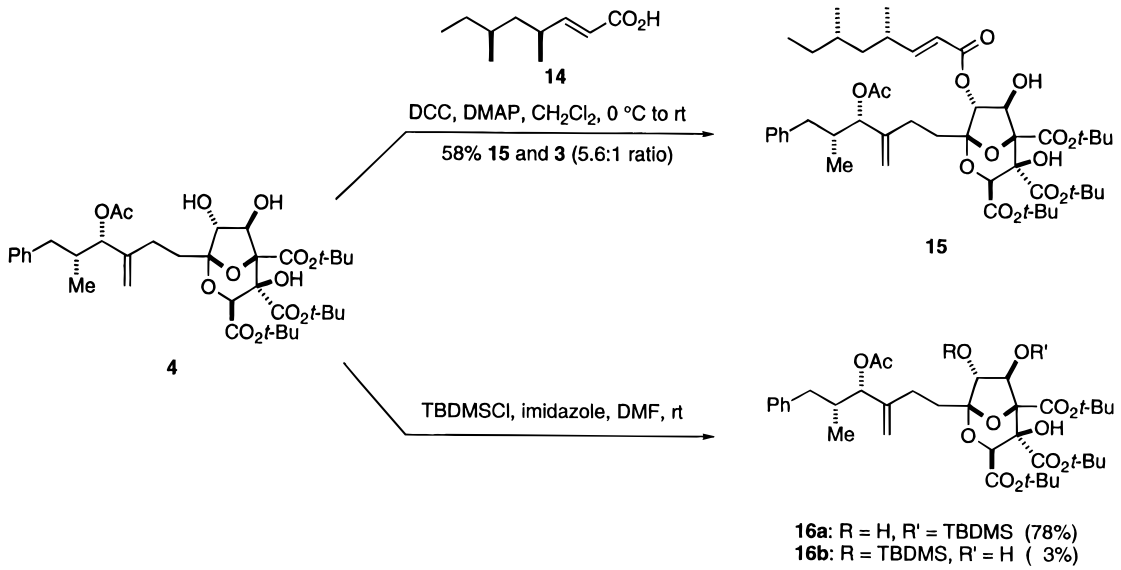
(10) The carboxy group attached to C3 of the zaragozic acid core has been shown to be more reactive than those attached to C4 and C5. See ref 8 and: Kuo, C. H.; Plevyak, S. P.; Biftu, T.; Parsons, W. H.; Berger, G. D. *Tetrahedron Lett.* **1993**, *34*, 6863.

(11) (*S*)-1-Iodo-2-methylbutane (>99% ee) was prepared (I_2, PPh_3, imidazole, Et_2O/CH_3CN, 0 °C) from the corresponding alcohol derived from methyl (*R*)-3-hydroxy-2-methylpropanoate (Aldrich, >99% ee) as described by Mori and Wu: Mori, K.; Wu, J. *Liebigs Ann. Chem.* **1991**, 213.

(12) An alternative three-step preparation of this acid using diethyl malonate and (*S*)-1-bromo-2-methylbutane has been reported by Volger: Volger, K.; Chopard-dit-Jean, L. H. *Helv. Chim. Acta* **1960**, *36*, 279.

(13) Evans, D. A.; Ennis, M. D.; Mathre, J. D. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

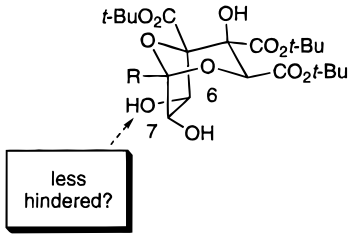
Scheme 3



of 17−19:1. This approach was abandoned because the diastereomers were separable only with difficulty and in rather low yield by column chromatography.[15] Reduction of **11** with lithium borohydride in a mixture of methanol and ether[16] typically afforded alcohol **12** in greater than 80% yield, accompanied by about 65% of recovered oxazolidinone. Oxidation of **12** under standard Swern conditions[17] gave an aldehyde that was immediately condensed with $Ph_3P{=}CHCO_2Me$ to yield exclusively the (*E*)-α,*β*-unsaturated ester **13**. Saponification of **13** with lithium hydroxide in aqueous THF afforded acid **14**. The saponification was initially carried out with lithium hydroxide in aqueous methanol. However, the product obtained using those conditions was contaminated with a small amount of the *β*,*γ*-isomer, which was difficult to separate from **14**. The overall yield for the eight-step sequence leading to **14** was 35%.[18] The synthetic side chain was identical in all respects to that obtained by degradation of zaragozic acid A.[1b]

Having completed the synthesis of **2** and **14**, we were prepared to begin the reconstruction of zaragozic acid A by attaching acid **14** to the C6 hydroxyl group of **2**. We had originally thought that the C6-OH, syn to the one-atom bridge, would be less hindered and therefore more reactive than the C7-OH, syn to the three-atom bridge.

However, preliminary esterifications of diol **4** with various derivatives of acid **14** showed that this was not the case. For example, activation of acid **14** with dicyclohexylcarbodiimide and catalytic 4-(dimethylamino)-pyridine (DMAP) in the presence of diol **4** gave a 6:1 mixture of the C7- and C6-acylated products **15** and **3** (Scheme 3). Treatment of **4** with the acid chloride derived from **14** in the presence of triethylamine and catalytic DMAP also led to preferential acylation of the C7 hydroxyl group. These results prompted us to revise our strategy so that the labile C7-OH would first be



protected, leaving the C6-OH free for acylation with **14**. Compound **4** was again used as a model for **2** and was treated with *tert*-butyldimethylsilyl chloride and imidazole in DMF. To our surprise, the C6 silyl ether **16a** was produced in good yield. Only 3% of the desired product **16b** was isolated, along with 10% of recovered starting material.[19,20]

These seemingly contradictory results may be rationalized by the difference in steric accessibility and acidity of the C6 and C7 hydroxyl groups. It has been shown that the mechanism of silylation of an alcohol involves attack on silicon by the neutral hydroxyl group.[21] Thus, the preferential formation of **16a** presumbably reflects the greater steric accessibility of the C6 hydroxyl group. However, the C7-OH is expected to be more acidic than the C6-OH because of the electron-withdrawing effect of the two acetal oxygens. If acylation involves prior deprotonation of the alcohol and attack on the activated acid by an alkoxide ion, it is reasonable that **15** is the major monoester formed in this reaction. In DMAP-catalyzed acylations, the counterion associated with the activated *N*-acyl-4-(dimethylamino)pyridinium ion participates in general base catalysis.[22]

(14) (a) Evans, D. A.; Takacs, J. M. *Tetrahedron Lett.* **1980**, *21*, 4233. (b) Sonnet, P. E.; Heath, R. R. *J. Org. Chem.* **1980**, *45*, 3137.

(15) This alkylation has also been investigated by White and Johnson, who obtained similar diastereomeric ratios. (a) White, J. D.; Johnson, A. T. *J. Org. Chem.* **1994**, *59*, 3347. (b) White, J. D.; Johnson, A. T. *J. Org. Chem.* **1990**, *55*, 5938.

(16) Penning, T. D.; Djuric, S. W.; Haack, R. A.; Kalish, V. J.; Miyashiro, J. M.; Rowell, B. W.; Yu, S. S. *Synth. Commun.* **1990**, *20*, 307.

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

(18) The C6 acyl side chain has also been synthesized by Nicolaou and co-workers by a different route; see refs 6d and 6f.

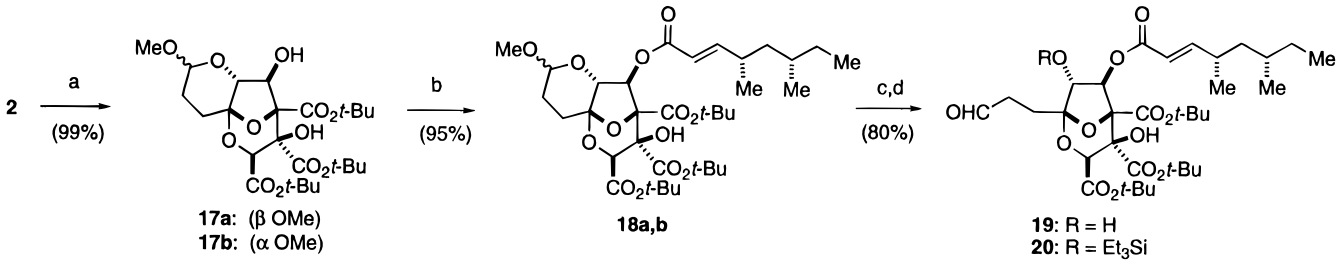
(19) Other researchers have reported studies dealing with the relative reactivity of the C6 and C7 hydroxyl groups of the zaragozic acid core; see refs 6b and 6f.

(20) The structure assignments of **16a** and **16b** were confirmed by an unambiguous synthesis of **16b**. Treatment of **3** with TBDMSCl and imidazole followed by $HONH_2{\cdot}HCl$ and $NaOAc{\cdot}3H_2O$ in methanol afforded **16b**.

(21) Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, 99.

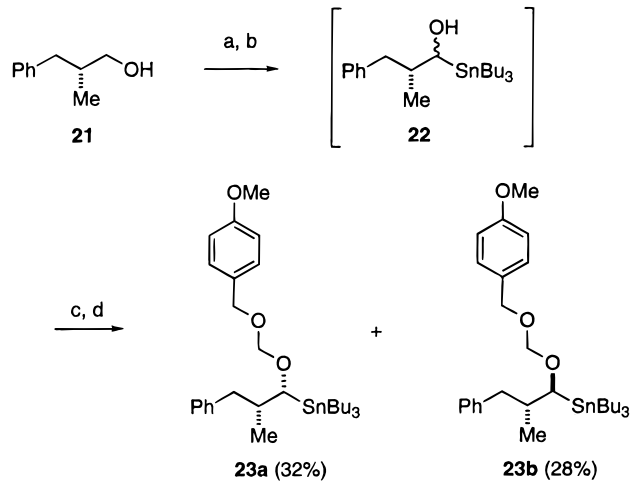
(22) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.

Scheme 4[a]



[a] Reagents and conditions: (a) PPTS, benzene, reflux, 4 Å sieves; (b) **14**, DCC, DMAP, CH_2Cl_2, 0 °C to rt; (c) H_2O acetone, PPTS, 50 °C; (d) Et_3SiCl, pyridine, rt.

Scheme 5[a]



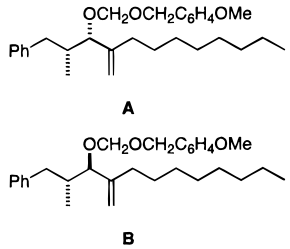
[a] Reagents and conditions: (a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2; (b) Bu_3SnLi, THF, −78 °C; (c) *p*-$MeOC_6H_4CH_2OCH_2Cl$, Hüing's base, CH_2Cl_2; (d) HPLC separation.

The problem of regiocontrol in the acylation was nicely solved when we discovered that treatment of **2** with pyridine *p*-toluenesulfonate in refluxing benzene in the presence of 4 Å molecular sieves resulted in smooth transformation to a 6:1 diastereomeric mixture of cyclic methyl acetals, **17a**,**b** (Scheme 4). Acylation of the free hydroxyl group gave **18a**,**b** and a small amount (2−3%) of side products arising from the acylation of **17a**,**b** with the β,γ-unsaturated isomer of **14**. We speculated that this side product was the result of deprotonation of the activated acid intermediate by DMAP. Reduction of the amount of DMAP from 0.1−0.4 to 0.03−0.05 equiv led to the formation of **18a**,**b** only. The diastereomers were hydrolyzed to hydroxy aldehyde **19**. Treatment of this material with triethylsilyl chloride provided **20**.

To reinstall the full C1 side chain, we elected to use the α-alkoxystannane methodology of Still[23] (Scheme 5). To this end, (*R*)-2-methyl-3-phenylpropanol[13] (**21**) was oxidized using the Swern procedure[17] and the resulting aldehyde immediately treated with (tributylstannyl)-lithium at low temperature. The resulting diastereomeric mixture of hydroxy stannanes (**22**) was alkylated with *p*-methoxybenzyl chloromethyl ether,[24] and the mixture of diastereomeric ethers was separated by preparative HPLC to obtain the pure diastereomers **23a** and **23b** in yields of about 30% each.[25]

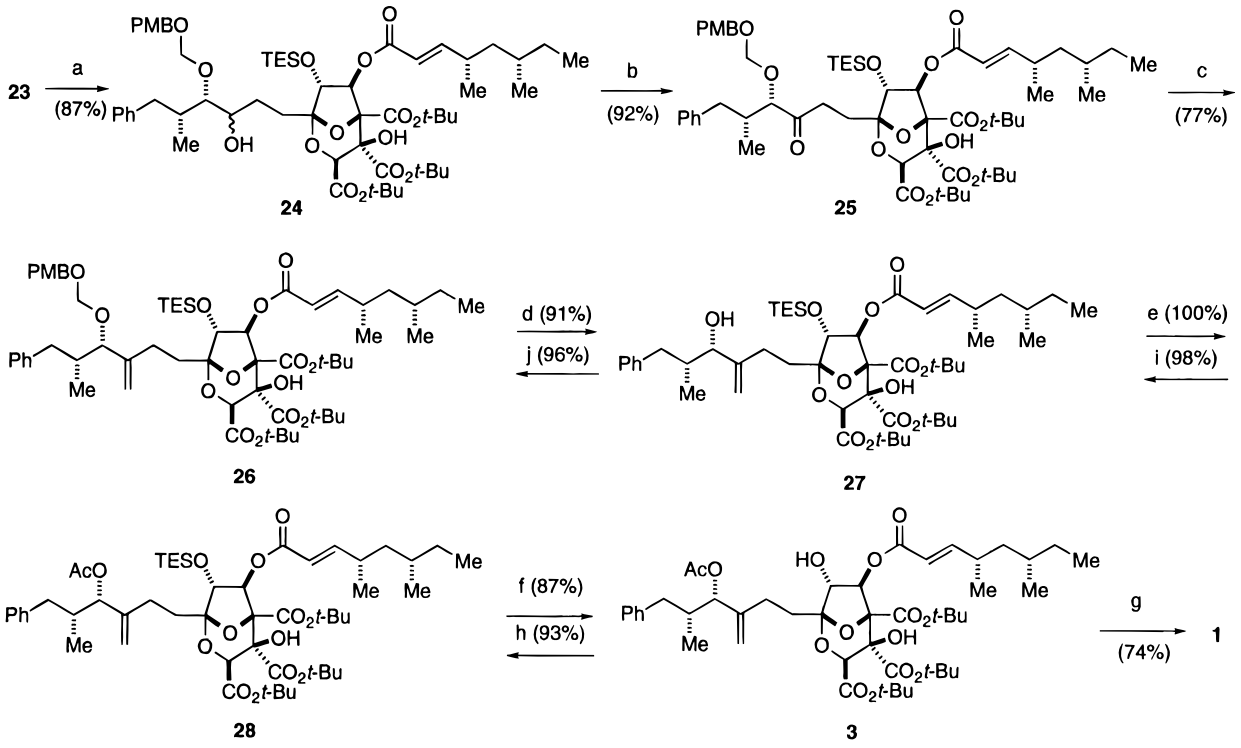
Stannane **23a** was transmetalated with *n*-butyllithium at −78 °C, and the resulting α-alkoxyorganolithium was treated with anhydrous $CeCl_3$[26] to obtain the α-alkoxyorganocerium(III) reagent. Addition of aldehyde **20** to the organocerium reagent afforded alcohols **24a**,**b** as a 15:1 diastereomeric mixture in 87% yield (Scheme 6).[27] Use of the organocerium reagent in this procedure was found to be crucial. If the addition was carried out with the α-alkoxyorganolithium reagent, much enolization occurred and **24a**,**b** was obtained in only 27% yield, with about 70% recovery of aldehyde **20** after aqueous workup. The diastereomeric ratio when using the organolithium reagent was 1:1. We did not determine the relative configuration of the major and minor diastereomers of **24**. However, on the basis of a previous study dealing with additions of chiral α-alkoxyorganometal reagents to aldehydes, we would expect that the major diastereomer has a syn relationship between the alcohol and [(*p*-methoxybenzyl)oxy]methoxy group.[28] Oxidation of the mixture of diastereomeric alcohols with Dess−Martin reagent[29] provided ketone **25** in an overall yield for the two steps of about 80%. For introduction of the final carbon, we first explored the use of the Wittig reaction. However, treatment of **25** with methylenetriphenylphosphorane[30] gave **26** in only low yield, accompanied by recovered starting material. The highly selective, non-basic $Zn/TiCl_4/CH_2Br_2$ methylenation procedure of Lombardo[31] also proved ineffective, giving only recovered starting material. On the other hand, the Tebbe reaction, using the procedure of Pine and co-workers,[32] served admirably, affording **26** in 77% yield along with 15% of recovered starting material. Removal of the [(*p*-meth-

(25) A model study of the C1 side chain was used to tentatively assign the configuration at C1 of the diastereomers **23a**,**b**. Model compounds **A** and **B** were synthesized in three steps from **23a**,**b** and nonanal. The ^1H NMR spectrum of **A** more closely resembled that of the C1 alkyl side chain in **26**, prepared from natural zaragozic acid (Scheme 6).



(23) (a) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.* **1980**, *102*, 1201. (b) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481.
(24) Benneche, T.; Strande, P.; Undheim, K. *Synthesis* **1983**, 762.
(26) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* **1984**, *25*, 4233.
(27) Before purification the ratio of diastereomeric alcohols **24** was 10:1.
(28) McGarvey, G. J.; Kimura, M. *J. Org. Chem.* **1982**, *47*, 5420.
(29) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(30) Fitjer, L.; Quabeck, U. *Synth. Commun.* **1985**, 855.
(31) (a) Lombardo, L. *Tetrahedron Lett.* **1982**, *23*, 4293. (b) Lombardo, L. *Org. Synth.* **1987**, *65*, 81.
(32) Pine, S. H.; Kim, G.; Lee, V. *Org. Synth.* **1990**, *69*, 72.

Scheme 6[a]



[a] Reagents and conditions: (a) (i) *n*-BuLi, THF; (ii) $CeCl_3$; (iii) **20**; (b) Dess−Martin periodinane, pyridine, CH_2Cl_2; (c) Tebbe reagent, THF, 0 °0; (d) DDQ, CH_2Cl_2, H_2O; (e) $(CH_3CO)_2O$, DMAP, Et_3N, CH_2Cl_2, 0 °C; (f) HF, pyridine, THF, 0 °C; (g) CF_3CO_2H, CH_2Cl_2, rt; (h) Et_3SiCl, imidazole, DMF, rt; (i) EtMgBr, $CeCl_3$, THF, −78 °C; (j) *p*-$MeOC_6H_4CH_2OCH_2Cl$, Hüing's base, CH_2Cl_2, rt.

oxybenzyl)oxy]methyl protecting group was smoothly effected by treatment of **26** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in methylene chloride. The resulting alcohol **27** was acetylated in quantitative yield to obtain **28**. The synthesis of zaragozic acid A was completed by removal of the triethylsilyl group (HF and pyridine in THF) followed by cleavage of the three *tert*-butyl esters (trifluoroacetic acid in methylene chloride). The resulting material was identical in all spectral and chromatographic aspects to an authentic sample of zaragozic acid A (**1**). Intermediates **26**, **27**, and **28** were also prepared by degradation of **1**, as shown in the retrograde reaction arrows in Scheme 6.

In summary, we have developed a seven-step degradation of zaragozic acid A (**1**) into dimethyl acetal **2**; the optimized process provides **2** in 52% overall yield. In addition, intermediate **2** has been converted back into **1** by a 10-step route that proceeds in 27% yield.

Experimental Section

General. Unless otherwise indicated, all starting materials were obtained from commercial suppliers and used without further purification. Benzene, toluene, pyridine, Et_3N, *i*-Pr_2NH, *i*-Pr_2NEt, and CH_2Cl_2 were distilled under N_2 from CaH_2, and THF was distilled under N_2 from sodium/benzophenone prior to use. Dimethyl sulfoxide (DMSO) was distilled from CaH_2 and stored over 4 Å molecular sieves. All reactions were conducted under a N_2 atmosphere. Flash chromatography was performed according to the procedure of Still[33] using Merck 60 230−400 mesh silica gel. Reaction mixtures and chromatography fractions were analyzed using Merck silica gel 60 F-254 TLC plates. ^1H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ unless otherwise stated. Chemical shifts are expressed in ppm relative to internal $CHCl_3$ (7.26 ppm). *J* values are in Hertz. For ^{13}C NMR spectra, carbon type is defined as 3 (CH_3), 2 (CH_2), 1 (CH), or 0 (C) on the basis of DEPT experiments. Melting points were determined in Pyrex capillaries open to air. IR spectra were recorded as solutions in the solvent indicated or as thin films on NaCl plates. The $CHCl_3$ used to measure optical rotations was filtered through alumina, basic Brockman activity I, 60−325 mesh.

[1*S*-[1α(4*S*,5*R*),3α,4*β*,5α,6α(2*E*,4*S*,6*S*),7*β*]]-1-[4-Acetyloxy-5-methyl-3-methylene-6-phenylhexyl]-6-(4,6-dimethyl-2-octenoyl)-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid 3,4,5-Tris(1,1-dimethylethyl) Ester (3). A. From Zaragozic Acid (1). This compound was prepared by a procedure similar to one described by Ponpipom.[8] Zaragozic acid A (**1**) (634.2 mg (≤89% pure), 0.821 mmol) was dissolved in CH_2Cl_2 (8 mL), and *O*-*tert*-butyl-*N,N*′-diisopropylisourea (0.58 mL, 2.46 mmol) was added at rt. The resulting solution was heated at reflux for 2 h, and additional isourea was added (0.6 mL). The solution was allowed to cool to rt and stir overnight (14 h). The mixture was again warmed to reflux, and more isourea (two 0.6-mL portions) was added over 6 h. An aqueous acetic acid solution (pH 5) was added, and the mixture was extracted with EtOAc (4 × 40 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 × 80 mL), water (80 mL), and brine (80 mL), dried over $MgSO_4$, filtered, and concentrated. To the crude residue was added 1:5 EtOAc/hexanes. Following filtration and concentration of the filtrate, the crude product was subjected to chromatography on SiO_2 (1:5 EtOAc/hexanes). The product **3** was isolated as a white foam (610.7 mg, 87%). TLC: R_f 0.27 (1:3 EtOAc/hexanes). $[\alpha]_D$: +15.3 (*c* 4.8, $CHCl_3$). IR ($CDCl_3$): 3550, 3450, 1735, 1655 cm^{-1}. ^1H NMR (500 MHz): δ 0.80−0.85 (m, 9), 1.03 (d, 3, J = 6.7), 1.09−1.14 (m, 2), 1.26−1.41 (m, 3), 1.44 (s, 9), 1.48 (s, 9), 1.59 (s, 9), 2.07−2.15 (m, 3), 2.09 (s, 3), 2.29−2.37 (m, 2), 2.41−2.49 (m, 2), 2.69 (dd, 1, J = 13.5, 5.5), 2.98 (br s, 1), 4.02 (dd, 1, J = 3.1, 2.1), 4.07 (s, 1), 4.95 (s, 1), 4.97 (s, 1), 5.05 (s, 1), 5.10 (d, 1, J = 4.8), 5.76 (dd, 1, J = 15.7, 0.9), 6.01 (d, 1, J = 1.9), 6.90 (dd, 1, J = 15.6, 8.4), 7.13−7.26 (m, 5). ^{13}C NMR (100 MHz): δ 10.85 (3), 13.40 (3), 18.63 (3), 20.00 (3), 20.78 (3), 25.32 (2), 27.79 (3), 27.90 (3), 29.46 (2), 31.62 (1), 34.01 (2), 34.23 (1), 36.37

(33) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(1), 39.80 (2), 42.97 (2), 74.03 (0), 75.15 (1), 78.74 (1), 80.36 (1), 82.09 (1), 82.69 (0), 83.45 (0), 85.38 (0), 88.91 (0), 104.18 (0), 110.93 (2), 118.16 (1), 125.64 (1), 128.02 (1), 128.93 (1), 140.12 (0), 145.70 (0), 156.85 (1), 163.88 (0), 165.55 (0), 166.10 (0), 168.47 (0), 169.99 (0). The ^{1}H NMR data agrees with that published by Ponpipom.[8]

B. From 28. To a solution of the triethylsilyl ether **28** (29.2 mg, 30.0 μmol) in THF (0.3 mL) at 0 °C was added two drops of hydrogen fluoride−pyridine complex from a disposable Pasteur pipet (*ca.* 70 μL). The solution was stirred at 0 °C under N_2 for 6 h. During this time the septum was removed three times and additional hydrogen fluoride−pyridine complex (a total of 7 drops) was added. The cold solution was diluted with Et_2O (5 mL) and neutralized with saturated aqueous $NaHCO_3$ (5 mL). The mixture was poured into a separatory funnel, the phases were separated, and the aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic phases were washed with water (5 mL) and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was concentrated twice from toluene (2 × 10 mL) to remove residual pyridine and purified by flash chromatography on SiO_2 (gradient elution, 1:7 to 1:3 EtOAc/hexanes) to provide **3** (22.4 mg, 87%). The ^{1}H NMR spectrum of this material was identical to that obtained by procedure A.

[1*S*-(1α(4*S*,5*R*),3α,4*β*,5α,6α,7*β*)]-1-[4-(Acetyloxy)-5-methyl-3-methylene-6-phenylhexyl)]-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid 3,4,5-Tris(1,1-dimethylethyl) Ester (4). To 5 mL of a methanol solution 0.2 M in $HONH_2$·HCl and 0.2 M in $NaOAc·3H_2O$ was added **3** (75.8 mg, 88.0 μmol). The solution was heated at reflux for 2.5 h, concentrated *in vacuo*, diluted with EtOAc (20 mL), washed with H_2O (15 mL), and dried over $MgSO_4$. Evaporation of the solvent yielded a colorless oil which was purified by flash chromatography on SiO_2 (1:2 EtOAc/hexanes) to afford **4** (60.1 mg, 97%) as an analytically pure white solid. A sample was crystallized (EtOAc/hexanes) to give white crystals, mp 135.0−135.5 °C. TLC: R_f 0.15 (2:3 EtOAc/hexanes). $[\alpha]_D$: +9.2 (*c* 1.06, $CHCl_3$). IR ($CHCl_3$): 3600−3400 (br), 1730 cm^{-1}. ^{1}H NMR (500 MHz): δ 0.84 (d, 3, J = 6.8), 1.45 (s, 9), 1.50 (s, 9), 1.59 (s, 9), 2.04−2.16 (m, 3), 2.11 (s, 3), 2.20−2.28 (m, 1), 2.32 (d, 1, J = 4.7), 2.41 (dd, 1, J = 13.4, 8.9), 2.40−2.48 (m, 1), 2.47 (d, 1, J = 5.1), 2.69 (dd, 1, J = 13.5, 5.7), 3.93 (s, 1), 4.07 (dd, 1, J = 4.7, 2.1), 4.91 (s, 1), 4.97 (s, 1), 5.01 (s, 1), 5.02 (dd, 1, J = 5.1, 2.1), 5.09 (d, 1, J = 4.5), 7.13−7.28 (m, 5). ^{13}C NMR (100 MHz): δ 13.51 (3), 21.06 (3), 25.77 (2), 27.95 (3), 28.01 (3), 28.14 (3), 33.29 (2), 36.60 (1), 40.02 (2), 74.28 (0), 75.14 (1), 78.78 (1), 78.90 (1), 82.39 (1), 83.08 (0), 83.98 (0), 84.97 (0), 91.23 (0), 104.65 (0), 110.97 (2), 125.95 (1), 128.30 (1), 129.07 (1), 140.30 (0), 145.85 (0), 165.98 (0), 166.21 (0), 168.65 (0), 170.64 (0). Anal. Calcd for $C_{37}H_{54}O_{13}$: C, 62.87; H, 7.68. Found: C, 62.55; H, 7.80.

[1*S*-(1α(4*S*,5*R*),3α,4*β*,5α,6α,7*β*)]-1-(4-Hydroxy-5-methyl-3-methylene-6-phenylhexyl)-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid 3,4,5-Tris(1,1-dimethylethyl) Ester (5). Dry $CeCl_3$[26] (626 mg, 2.54 mmol) was stirred in THF (4 mL) for 2 d to yield a thick white paste. THF (2 mL) was added to form a slurry which was cooled to −78 °C. A solution of ethylmagnesium bromide in THF (1.9 mL, 1.9 mmol) was added. After 20 min, **4** (103.6 mg, 146.5 μmol) in THF (2 mL) at −78 °C was added *via* cannula to the slurry, and the mixture was stirred for 20 min at −78 °C. Saturated aqueous NH_4Cl (15 mL) was added, and the mixture was allowed to warm to rt and was extracted with EtOAc (3 × 25 mL). The combined organic extracts were washed with water (30 mL) which was back-extracted with EtOAc (25 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. Extensive purification by flash chromatography on SiO_2 (performed three times, 2:3 EtOAc/hexanes) provided **5** (78.8 mg, 81%) as a white foam and recovered starting material (13.8 mg, 13%). TLC: R_f 0.11 (1:1 EtOAc/hexanes). $[\alpha]_D$: +2.1 (*c* 0.52, $CHCl_3$). IR ($CDCl_3$): 3600−3460 (br), 1735 cm^{-1}. ^{1}H NMR (400 MHz): δ 0.85 (d, 3, J = 6.6), 1.46 (s, 9), 1.49 (s, 9), 1.58 (s, 9), 1.92−1.99 (m, 1), 2.14 (t, 2, J = 7.3), 2.32 (dd, 1, J = 13.5, 9.4), 2.29−2.36 (m, 1), 2.47 (m, 1), 2.73−2.78 (br s, 1), 2.75 (dd, 1, J = 13.4, 5.0), 2.82−2.84 (m, 1), 3.07 (br s, 1), 3.89 (s, 1), 4.02 (d, 1, J = 6.0), 4.10 (d, 1, J = 1.7), 4.96 (s, 1), 5.00 (s, 1), 5.08 (s, 1), 5.13 (s, 1), 7.15−7.28 (m, 5). ^{13}C NMR (100 MHz): δ 13.88, 25.82, 27.99, 28.11, 28.23, 33.94, 38.23, 40.10, 74.39, 75.23, 78.38, 78.72, 82.81, 83.43, 84.43, 84.84, 91.20, 104.95, 112.10, 125.72, 128.20, 129.20, 141.16, 150.81, 165.96, 166.21, 168.06. Anal. Calcd for $C_{35}H_{52}O_{12}$: C, 63.23; H, 7.88. Found: C, 62.88; H, 7.98.

[1*S*-(1α(4*S*,5*R*),3α,4*β*,5α,6α,7*β*)]-1-(4-Hydroxy-5-methyl-3-oxo-6-phenylhexyl)-4,6,7-trihydroxy-2,8-dioxabicyclo-[3.2.1]octane-3,4,5-tricarboxylic Acid 3,4,5-Tris(1,1-dimethylethyl) Ester (6). Ozone was bubbled through a solution of **5** (72.0 mg, 0.108 mmol) in CH_2Cl_2 (2 mL) at −78 °C until the solution turned pale blue. Dimethyl sulfide (1 mL) was added, and the solution was stirred for 10 min at −78 °C, warmed to rt, and concentrated *in vacuo*. Purification by flash chromatography on SiO_2 (1:1 EtOAc/hexanes) provided **6** (68.0 mg, 94%) as a white foam. TLC: R_f 0.12 (3:2 EtOAc/hexanes). $[\alpha]_D$: +25.2 (*c* 0.50, $CHCl_3$). IR (CH_2Cl_2): 3585, 3473, 3258, 1725 cm^{-1}. ^{1}H NMR (400 MHz): δ 0.72 (d, 3, J = 6.8), 1.43 (s, 9), 1.47 (s, 9), 1.58 (s, 9), 2.13−2.21 (m, 1), 2.25−2.34 (m, 2), 2.60−2.71 (m, 2), 2.82−2.87 (m, 2), 2.92−3.00 (m, 1), 3.22 (d, 1, J = 4.3), 3.59 (d, 1, J = 4.5), 3.98 (s, 1), 4.09 (m, 1), 4.18 (m, 1), 4.92 (s, 1), 5.00 (m, 1), 7.18−7.31 (m, 5). ^{13}C NMR (100 MHz): δ 12.80 (3), 27.96 (3), 28.01 (3), 28.17 (3), 30.18 (2), 31.81 (2), 38.17 (1), 40.19 (2), 74.08 (0), 75.10 (1), 78.42 (1), 78.68 (1), 83.35 (0), 83.45 (1), 84.32 (0), 85.38 (0), 91.32 (0), 104.03 (0), 126.03 (1), 128.30 (1), 129.31 (1), 140.30 (0), 165.98 (0), 166.06 (0), 168.75 (0), 214.08 (0). Anal. Calcd for $C_{34}H_{50}O_{13}$: C, 61.24; H, 7.56. Found: C, 60.94; H, 7.55.

[1*S*-(1α,3α,4*β*,5α,6α,7*β*)]-1-(3-Oxopropyl)-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid 3,4,5-Tris(1,1-dimethylethyl) Ester (8). Sodium borohydride (25.7 mg, 0.679 mmol) was added to a solution of **6** (70.0 mg, 0.105 mmol) in methanol (1 mL) at 0 °C. The mixture was stirred for 5 min, and additional $NaBH_4$ (30 mg) was added. The mixture was stirred an additional 1 min, and then water (10 mL) was added. The mixture was extracted with EtOAc (4 × 20 mL). The combined organic extracts were washed once with water (30 mL), dried over $MgSO_4$, filtered, and concentrated to provide 62.2 mg (89%) of a 1.5:1 mixture of diastereomeric alcohols **7**.

This material was dissolved in benzene (0.8 mL) and cooled to ∼10 °C. Lead tetraacetate (85.9 mg, 0.194 mmol) was added, and the mixture was stirred for 17 min. After addition of saturated aqueous $NaHCO_3$ (10 mL), the mixture was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with water, dried over $MgSO_4$, filtered, and concentrated. Purification of the crude product by flash chromatography on SiO_2 (gradient elution, 1:1 to 3:2 EtOAc/hexanes) provided aldehyde **8** (39.7 mg, 73%) as a white solid, mp 160 °C dec. TLC: R_f 0.32 (4:1 EtOAc/hexanes). $[\alpha]_D$: −1.9 (*c* 2.21, CH_2Cl_2). IR ($CHCl_3$): 3450 (br), 1730 cm^{-1}. ^{1}H NMR (500 MHz): δ 1.45 (s, 9), 1.48 (s, 9), 1.58 (s, 9), 2.21 (dt, 1, J = 14.7, 6.9), 2.33 (dt, 1, J = 14.5, 7.2), 2.75 (dtd, 1, J = 18.3, 7.0, 1.2), 2.79 (d, 1, J = 5.1), 2.92 (dtd, 1, J = 18.3, 7.1, 1.3), 3.11 (d, 1, J = 4.3), 3.95 (s, 1), 4.10−4.12 (m, 1), 4.93 (s, 1), 5.02 (dd, 1, J = 5.0, 2.0), 9.83 (t, 1, J = 1.3). ^{13}C NMR (100 MHz): δ 27.89, 27.93, 28.12, 28.53, 37.75, 74.14, 75.19, 78.64, 82.99, 83.30, 84.02, 85.11, 91.23, 104.13, 165.80, 166.13, 168.62, 203.24. Anal. Calcd for $C_{24}H_{38}O_{12}$: C, 55.59; H, 7.39. Found: C, 55.86; H, 7.10.

[1S-(1α,3α,4*β*,5α,6α,7*β*)]-1-(3,3-Dimethoxypropyl)-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid 3,4,5-Tris(1,1-dimethylethyl) Ester (2). Pyridinium *p*-toluenesulfonate (66.0 mg, 0.263 mmol) was added to a solution of aldehyde **8** (193.9 mg, 0.374 mmol) and trimethyl orthoformate (2 mL) in methanol (8 mL) at rt. Saturated aqueous K_2CO_3 (20 mL) was added after 3 h, and the mixture was extracted with EtOAc (4 × 30 mL). The combined organic layers were washed with saturated aqueous NH_4Cl (30 mL) and water (30 mL), dried over $MgSO_4$, filtered, and evaporated. Purification of the crude product by flash chromatography on SiO_2 pretreated with Et_3N (1:1 EtOAc/hexanes) provided **2** (200.1 mg, 95% yield) as a white solid, mp 141 °C dec. TLC: R_f 0.31 (4:1 EtOAc/hexanes). $[\alpha]_D$: +1.8 (*c* 0.50, CH_2Cl_2). IR ($CDCl_3$): 3600−3400 (br), 1760, 1730 cm^{-1}.

^{1}H NMR (400 MHz): δ 1.45 (s, 9), 1.48 (s, 9), 1.58 (s, 9), 1.89−1.92 (m, 1), 1.95−2.01 (m, 2), 2.04−2.09 (m, 1), 2.59 (m, 1), 3.29 (m, 1), 3.343 (s, 3), 3.345 (s, 3), 3.92 (s, 1), 4.10 (s, 1), 4.48 (t, 1, J = 5.0), 4.96 (s, 1), 5.02 (s, 1). ^{13}C NMR (100 MHz): δ 26.46, 27.99, 28.07, 28.18, 31.04, 53.21, 74.35, 75.11, 78.92, 82.57, 83.09, 84.14, 84.93, 91.15, 104.77, 104.87, 165.93, 166.38, 168.57. Anal. Calcd for $C_{26}H_{44}O_{13}$: C, 55.31; H, 7.85. Found: C, 55.65; H, 7.64.

(*S*)-4-Methylhexanoic Acid (9). A solution of diisopropylamine (3.88 mL, 29.6 mmol) in THF (26 mL) was cooled to −78 °C, and *n*-BuLi in hexanes (11.0 mL, 28.3 mmol) was added. The resulting pale yellow solution was stirred in an ice bath for 10 min and cooled to −78 °C. To the solution was added slowly *tert*-butyl acetate (3.63 mL, 26.9 mmol). The solution was stirred for 50 min at −78 °C and cooled to −100 °C. In a separate flask, a solution of (*S*)-1-iodo-2-methylbutane[11] (8.28 g, 41.8 mmol) in THF (46 mL) and *N*,*N*′-dimethylpropyleneurea (23 mL) was stirred and cooled to −78 °C. The *tert*-butyl lithioacetate solution was added *via* Teflon cannula over 2 min to the alkyl iodide. After 5 min, the milky white reaction mixture was warmed to −42 °C, stirred for 3 h, and warmed slowly to rt. The mixture was poured into saturated aqueous NH_4Cl (50 mL) and extracted with ether (150 mL). The organic phase was washed with water (2 × 50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Excess alkyl iodide was separated from the product, (*S*)-*tert*-butyl-4-methylhexanoate, by flash chromatography on SiO_2 (pentane followed by 1:4 ether/pentane). Concentration of the appropriate fractions yielded recovered iodide (1.83 g) and *tert*-butyl ester (4.36 g, 87%). The ester was found to be approximately 90% pure by ^{1}H NMR analysis and was used directly in the following step. Further purification of the ester on SiO_2 (1:100 ether/pentane) provided a clear, colorless liquid for characterization. TLC: R_f 0.45 (1:20 EtOAc/hexanes). $[\alpha]_D$: +8.67 (*c* 2.03, CH_2Cl_2). IR (neat): 1732 cm^{-1}. ^{1}H NMR (400 MHz): δ 0.84−0.88 (m, 6), 1.11−1.22 (m, 1), 1.27−1.40 (m, 3), 1.43 (s, 9), 1.56−1.66 (m, 1), 2.13−2.27 (m, 2). ^{13}C NMR (100 MHz): δ 11.28, 18.83, 28.08, 29.17, 31.59, 33.40, 33.99, 79.84, 173.55. Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90. Found: C, 71.05; H, 12.19.

A solution of 4.36 g of ester, prepared as described above, in CH_2Cl_2 (30 mL) was cooled to 0 °C, and trifluoroacetic acid (10 mL) was added. The solution was stirred at 0 °C for 2.5 h. Additional trifluoroacetic acid (10 mL) was added, and the solution was warmed to rt, stirred for 2.5 h, concentrated *in vacuo*, and distilled (128 °C, 29 mmHg) to yield acid **9** (2.31 g, 66%) as a clear, colorless liquid. $[\alpha]_D$: +12.09 (neat) [lit.[12] $[\alpha]_D$ +11.80 (neat)]. IR (neat): 3470−2600 br, 1711 cm^{-1}. ^{1}H NMR (400 MHz): δ 0.88 (t, 3, J = 7.3), 0.88 (d, 3, J = 6.4), 1.12−1.23 (m, 1), 1.30−1.50 (m, 3), 1.64−1.73 (m, 1), 2.28−2.43 (m, 2). ^{13}C NMR (100 MHz): δ 11.08 (3), 18.59 (3), 29.02 (2), 31.13 (2), 31.85 (2), 33.84 (1), 180.95 (0).

[3(4*S*),4*S*]-3-(4-Methyl-1-oxohexyl)-4-(phenylmethyl)-2-oxazolidinone (10). Oxalyl chloride (0.59 mL, 6.81 mmol) was added to a solution of acid **9** (0.739 g, 5.68 mmol) and *N*,*N*-dimethylformamide (1 μL) in CH_2Cl_2 (5 mL). The solution was stirred for 2 h at rt and concentrated *in vacuo* to provide the acid chloride (0.835 g) in 99% crude yield. In a separate flask, a solution of *n*-BuLi in hexanes (2.24 mL, 5.68 mmol) was added slowly to a −78 °C solution of (*S*)-(−)-4-benzyl-2-oxazolidinone (1.006 g, 5.68 mmol) in THF (20 mL). The solution was stirred for 20 min, and the acid chloride was added *via* cannula followed by two THF (0.5 mL) rinses. The reaction mixture was stirred at −78 °C for 2.5 h and allowed to warm slowly to rt. Saturated aqueous NH_4Cl (10 mL) was added, and the THF was removed *in vacuo*. The mixture was poured into a separatory funnel and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (30 mL), water (30 mL), and brine (30 mL), dried over $MgSO_4$, filtered, and concentrated. Purification of the crude product by flash chromatography on SiO_2 (1:5 EtOAc/hexanes) provided **10** (1.48 g, 90%) as a clear, colorless oil. TLC: R_f 0.34 (1:5 EtOAc/hexanes). $[\alpha]_D$: +74.2 (*c* 4.1, CH_2Cl_2). IR (thin film): 1783, 1700 cm^{-1}. ^{1}H NMR (500 MHz): δ 0.88−0.92 (m, 6), 1.16−1.25 (m, 1), 1.36−1.47 (m, 2), 1.49−1.56 (m, 1), 1.68−1.75 (m, 1), 2.76 (dd, 1, J = 13.4, 9.6), 2.88 (ddd, 1, J = 15.8, 9.8, 5.8), 2.99 (ddd, 1, J = 15.6, 10.0, 5.5), 3.29 (dd, 1, J = 13.4, 3.2), 4.14−4.21 (m, 2), 4.67 (m, 1), 7.20−7.34 (m, 5). ^{13}C NMR (100 MHz): δ 11.12, 18.76, 29.04, 30.70, 33.18, 33.82, 37.69, 54.93, 65.94, 127.10, 128.72, 129.24, 135.21, 153.24, 173.45. Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.39; H, 8.08; N, 4.83.

[3(2*S*,4*S*),4*S*]-3-(2,4-Dimethyl-1-oxohexyl)-4-(phenylmethyl)-2-oxazolidinone (11). To a solution of imide **10** (2.82 g, 9.75 mmol) in THF (10 mL) at −78 °C was added a solution of sodium bis(trimethylsilyl)amide in THF (14.6 mL, 14.6 mmol) over 20 min. The solution was stirred at −78 °C for 1 h, and iodomethane (2.50 mL, 40.2 mmol) was added over 5 min. After being stirred for 1.5 h at −78 °C, the reaction mixture was allowed to warm to rt and the reaction was quenched with saturated aqueous NH_4Cl (30 mL). The THF was evaporated *in vacuo*. The mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over $MgSO_4$, filtered, and evaporated to leave a yellow oil which was purified by flash chromatography on SiO_2 (1:12 EtOAc/hexanes). Imide **11** was isolated as a clear, colorless oil (2.54 g, 86%). TLC: R_f 0.38 (1:5 EtOAc/hexanes). $[\alpha]_D$: +86.9 (*c* 4.4, CH_2Cl_2). IR (thin film): 1781, 1698 cm^{-1}. ^{1}H NMR (400 MHz): δ 0.85 (d, 3, J = 6.5), 0.86 (t, 3, J = 7.1), 1.08−1.19 (m, 2), 1.20 (d, 3, J = 6.9), 1.25−1.43 (m, 2), 1.85 (ddd, 1, J = 13.6, 8.6, 5.4), 2.75 (dd, 1, J = 13.4, 9.4), 3.20 (dd, 1, J = 13.4, 3.2), 3.82−3.90 (m, 1), 4.10−4.16 (m, 2), 4.62−4.67 (m, 1), 7.17−7.31 (m, 5). ^{13}C NMR (100 MHz): δ 11.00, 18.11, 19.10, 29.17, 32.00, 35.08, 37.50, 40.16, 54.97, 65.68, 127.00, 128.59, 129.21, 135.10, 152.72, 177.06. Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.25; H, 8.31; N, 4.62. Found: C, 71.10; H, 8.43; N, 4.51.

(2*S*,4*S*)-2,4-Dimethylhexanol (12). A stirred solution of imide **11** (1.7032 g, 5.614 mmol) in Et_2O (112 mL) was cooled to 0 °C. Methanol (250 μL, 6.18 mmol) was added followed by a solution of $LiBH_4$ in THF (3.09 mL, 6.18 mmol). The reaction was allowed to warm to rt. After 1 h, 1.5 M NaOH (10 mL) was added and stirring was continued until both phases were clear. The mixture was poured into a separatory funnel and washed with water (30 mL) and brine (40 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by flash chromatography on SiO_2 (gradient elution, 1:9 to 1:7 followed by 3:2 EtOAc/hexanes) yielded alcohol **12** (601.4 mg, 84%) as a clear, colorless liquid and recovered oxazolidinone (671.7 mg, 68%). TLC: R_f 0.24 (1:5 EtOAc/hexanes). $[\alpha]_D$: −3.9 (*c* 1.63, $CHCl_3$) [lit.[15a] $[\alpha]_D$ +3.7 (*c* 1.67, $CHCl_3$) for the antipode of **12**]. IR (thin film): 3620−3040 (br) cm^{-1}. ^{1}H NMR (400 MHz): δ 0.85 (t, 3, J = 7.5), 0.86−0.96 (m, 1), 0.87 (d, 3, J = 6.6) , 0.91 (d, 3, J = 6.7), 1.02−1.13 (m, 1), 1.24−1.47 (m, 4), 1.65−1.76 (m, 1), 3.37 (dd, 1, J = 10.5, 6.8), 3.51 (dd, 1, J = 10.5, 5.2). ^{13}C NMR (100 MHz): δ 11.04 (3), 17.24 (3), 19.72 (3), 28.96 (2), 31.54 (1), 33.08 (1), 40.58 (2), 68.24 (2). These data agree with the literature data.[15a,b]

(2*E*,4*S*,6*S*)-4,6-Dimethyl-2-octenoic Acid Methyl Ester (13). To a stirring solution of oxalyl chloride (0.18 mL, 2.06 mmol) in CH_2Cl_2 (6 mL) at −78 °C was added slowly dimethyl sulfoxide (0.262 mL, 3.69 mmol). After 20 min, alcohol **12** (0.200 g, 1.54 mmol) in CH_2Cl_2 (1 mL followed by 2 × 0.5 mL rinses) was added *via* cannula over 5 min. The cloudy white mixture was stirred at −78 °C for 40 min, and triethylamine (1.07 mL, 7.68 mmol) was added. The thick slurry was stirred for 1.5 h at −78 °C, diluted with CH_2Cl_2 (20 mL), and washed with 10% aqueous $NaHSO_4$ (12 mL), saturated aqueous $NaHCO_3$ (10 mL), water (2 × 10 mL), and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered, concentrated to ∼2 mL, and filtered through a plug of cotton into a 25-mL round bottomed flask. The cotton was rinsed with dry CH_2Cl_2 (4 mL) which was also collected in the same flask. To this solution was added methyl (triphenylphosphoranylidene)-acetate (0.6738 g, 2.015 mmol). The reaction mixture was stirred under N_2 for 18 h at rt, during which time additional methyl (triphenylphosphoranylidene)acetate (0.400 g) was added. The solution was concentrated to ∼2.5 mL and filtered through a column of SiO_2 (1:40 Et_2O/hexanes). The eluent was concentrated, and **13** (0.2830 g, 86%) was isolated after

purification by HPLC (1:30 Et_2O/hexanes) as a clear, colorless liquid. TLC: R_f 0.23 (1:20 EtOAc/hexanes). $[\alpha]_D$: +53.2 (*c* 1.48, CH_2Cl_2). IR (CH_2Cl_2): 1716, 1656 cm^{-1}. ^1H NMR (400 MHz): δ 0.83−0.87 (m, 6), 1.03 (d, 3, J = 6.7), 1.09−1.14 (m, 2), 1.26−1.40 (m, 3), 2.41 (m, 1), 3.73 (s, 3), 5.79 (d, 1, J = 15.7), 6.82 (dd, 1, J = 15.7, 8.5). ^{13}C NMR (100 MHz): δ 11.11, 18.79, 20.34, 29.80, 31.86, 34.26, 43.36, 51.33, 119.18, 155.01, 167.30. Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.63; H, 10.88. The NMR data agrees with that published by Nicolaou *et. al.*[6f]

(2*E*,4*S*,6*S*)-4,6-Dimethyl-2-octenoic Acid (14). A mixture of methyl ester **13** (228.0 mg, 1.237 mmol), lithium hydroxide monohydrate (58.0 mg, 1.38 mmol), THF (0.9 mL), and water (0.3 mL) was stirred for 22 h at rt. Additional lithium hydroxide monohydrate (103.8 mg, 2.47 mmol) was added, and stirring was continued for 2 d. The mixture was added to water (10 mL) and washed with Et_2O (20 mL). The organic layer was extracted with saturated aqueous $NaHCO_3$ (5 mL). The aqueous layers were combined and acidified with 6 M HCl and extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with H_2O (20 mL) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude acid was purifed by flash chromatography on silver impregnated SiO_2[34] (gradient elution, 1:20 to 1:7 Et_2O/pentane). The product was isolated as a clear, colorless liquid (200.1 mg, 95%). $[\alpha]_D$: +58.2 (*c* 0.067, $CHCl_3$). IR (neat): 3414−3278 (br), 1697, 1650 cm^{-1}. ^1H NMR (400 MHz): δ 0.85−0.88 (m, 6), 1.05 (d, 3, J = 6.7), 1.11−1.17 (m, 2), 1.22−1.43 (m, 3), 2.42−2.49 (m, 1), 5.80 (dd, 1, J = 15.6, 0.8), 6.94 (dd, 1, J = 15.6, 8.4). ^{13}C NMR (100 MHz): δ 11.14, 18.86, 20.20, 29.79, 31.93, 34.40, 43.29, 119.00, 157.64, 172.26. These data are in excellent agreement with those published for the acid side chain obtained from the natural product.[1b]

[1*S*-[1α(4*S*,5*R*),3α,4*β*,5α,6α,7*β*(2*E*,4*S*,6*S*)]]-1-[4-Acetyloxy-5-methyl-3-methylene-6-phenylhexyl]-7-(4,6-dimethyl-2-octenoyl)-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid 3,4,5-Tris(1,1-dimethylethyl) Ester (15). Triol **4** (18.2 mg, 25.7 μmol) and acid **14** (4.4 mg, 25.7 μmol) were dissolved in CH_2Cl_2 (0.1 mL) containing 4-dimethylaminopyridine (DMAP, 0.094 mg, 0.77 μmol). The solution was cooled to 0 °C, and 1,3-dicyclohexylcarbodiimide (DCC, 7.1 mg, 34 μmol) was added. The reaction mixture was allowed to warm to rt and was stirred for 12 h. The CH_2Cl_2 was evaporated under a flow of N_2. The resulting residue was diluted with 1:5 EtOAc/hexanes and filtered through a plug of Celite. The filtrate was concentrated *in vacuo*. Purification by flash chromatography on SiO_2 (gradient elution, 1:5 to 2:3 EtOAc/hexanes) provided a 5.6:1 mixture of **15** and **3** (12.7 mg, 58%) in addition to the C6-OH and C7-OH diacylated derivative of **4** (1.2 mg, 4%) and recovered **4** (7.0 mg, 38%). The major product **15** was further purified for characterization using HPLC and was isolated as a colorless oil. TLC: R_f 0.14 (1:3 EtOAc/hexanes). $[\alpha]_D$: +23.0 (*c* 0.94, CH_2Cl_2). IR (thin film): 3469 (br), 1761, 1728, 1648 cm^{-1}. ^1H NMR (500 MHz): δ 0.81 (d, 3, J = 6.7), 0.84−0.87 (m, 6), 1.05 (d, 3, J = 6.7), 1.08−1.19 (m, 2), 1.25−1.44 (m, 3), 1.46 (s, 9), 1.50 (s, 9), 1.56 (s, 9), 2.09 (s, 3), 2.05−2.18 (m, 3), 2.31−2.47 (m, 4), 2.71 (dd, 1, J = 13.4, 5.3), 2.90 (d, 1, J = 3.5), 3.97 (s, 1), 4.74 (s, 1), 4.84 (d, 1, J = 2.0), 4.97 (s, 2), 5.09−5.12 (m, 2), 5.89 (d, 1, J = 15.7), 6.94 (dd, 1, J = 15.7, 8.4), 7.13−7.29 (m, 5). ^{13}C NMR (100 MHz): δ 11.14, 13.68, 18.91, 20.13, 21.05, 25.40, 27.99, 28.06, 28.09, 29.71, 31.94, 33.94, 34.43, 36.63, 40.02, 43.25, 74.05, 75.43, 76.84, 79.21, 83.32, 83.68, 83.89, 85.08, 90.90, 104.06, 111.41, 118.07, 125.93, 128.27, 129.14, 140.39, 145.57, 157.65, 165.07, 165.83, 166.93, 168.48, 170.16. Anal. Calcd for $C_{47}H_{70}O_{14}$: C, 65.71; H, 8.21. Found: C, 65.47; H, 8.28.

[1*S*-[1α(4*S*,5*R*),3α,4*β*,5α,6α,7*β*]]-1-[4-(Acetyloxy)-5-methyl-3-methylene-6 phenylhexyl]-6-[dimethyl(1,1-dimethylethyl)silyl]-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]-octane-3,4,5-tricarboxylic Acid 3,4,5-Tris(1,1-dimethylethyl) Ester (16a) and [1*S*-[1α(4*S*,5*R*),3α,4*β*,5α,6α,7*β*]]-1-[4-(Acetyloxy)-5-methyl-3-methylene-6 phenylhexyl]-7-[dimethyl(1,1-dimethylethyl)silyl]-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid 3,4,5-Tris(1,1-dimethylethyl) Ester (16b). To a solution of **4** (23.0 mg, 32.5 mmol) in *N*,*N*-dimethylformamide (0.3 mL) at rt were added imidazole (49 mg, 0.72 mmol) and *tert*-butyldimethylsilyl chloride (54 mg, 0.36 mmol). The solution was stirred for 6 h, diluted with EtOAc (15 mL), and washed with saturated aqueous NH_4Cl (5 mL), saturated aqueous $NaHCO_3$ (5 mL), water (5 mL), and brine (5 mL). The organic phase was dried over $MgSO_4$, filtered, and evaporated *in vacuo*. The crude product was subjected to flash chromatography on SiO_2 (1:5 EtOAc/hexanes) to provide **16a** (20.9 mg, 78%), recovered **4** (2.4 mg, 10%), and **16b** (0.8 mg, 3%).

Major Product 16a. White solid, mp 164−164.5 °C. TLC: R_f 0.29 (1:3 EtOAc/hexanes). $[\alpha]_D$: −0.9 (*c* 0.34, CH_2Cl_2). IR (CH_2Cl_2): 3550, 3450, 1740 cm^{-1}. ^1H NMR (500 MHz): δ 0.12 (s, 3), 0.19 (s, 3), 0.83 (d, 3, J = 6.8), 0.92 (s, 9), 1.44 (s, 9), 1.47 (s, 9), 1.61 (s, 9), 1.97−2.25 (m, 5), 2.10 (s, 3), 2.39 (dd, 1, J = 13.4, 8.9), 2.43−2.51 (m, 1), 2.69 (dd, 1, J = 13.4, 5.7), 3.98−4.00 (m, 2), 4.90 (s, 1), 4.96 (s, 1), 5.00 (s, 1), 5.01 (d, 1, J = 1.3), 5.08 (d, 1, J = 4.8), 7.12−7.28 (m, 5). ^{13}C NMR (100 MHz): δ −4.65, −4.38, 13.71, 17.98, 21.04, 25.82, 28.06, 28.12, 28.19, 33.65, 36.70, 40.03, 74.51, 75.57, 78.77, 79.33, 82.96, 83.00, 84.55, 84.82, 91.98, 104.54, 111.33, 125.96, 128.32, 129.08, 140.33, 145.79, 164.97, 166.10, 168.98, 170.30. Anal. Calcd for $C_{43}H_{68}O_{13}Si$: C, 62.90; H, 8.35. Found: C, 62.94; H, 8.56.

Minor Product 16a. Colorless oil. TLC: R_f 0.19 (1:3 EtOAc/hexanes). $[\alpha]_D$: +9.4 (*c* 1.45, CH_2Cl_2). IR (thin film): 3463 (br), 1737 cm^{-1}. ^1H NMR (500 MHz): δ 0.11 (s, 3), 0.17 (s, 3), 0.80 (d, 3, J = 6.7), 0.91 (s, 9), 1.44 (s, 9), 1.49 (s, 9), 1.58 (s, 9), 1.93−2.17 (m, 3), 2.09 (s, 3), 2.26−2.43 (m, 3), 2.43 (d, 1, J = 5.1), 2.72 (dd, 1, J = 13.3, 5.0), 3.91 (s, 1), 4.00 (d, 1, J = 1.9), 4.90 (s, 1), 4.90 (dd, 1, J = 5.2, 1.9), 4.98 (s, 1), 4.99 (s, 1), 5.13 (d, 1, J = 5.4), 7.12−7.27 (m, 5). ^{13}C NMR (100 MHz): δ −5.23, −4.65, 13.77, 17.81, 21.09, 25.18, 25.65, 27.99, 28.05, 28.20, 33.83, 36.64, 39.93, 74.36, 74.88, 79.18, 79.72, 82.68, 82.82, 84.08, 84.60, 91.12, 104.70, 111.61, 125.91, 128.26, 129.15, 140.36, 145.84, 166.08, 166.62, 168.69, 170.13. Anal. Calcd for $C_{43}H_{68}O_{13}Si$: C, 62.90; H, 8.35. Found: C, 63.21; H, 8.52.

[1*R*,3*R*,8*S*-(1α,2α,5α,10α,11*β*)]-5-Methoxy-2,11-dihydroxy-4,9,12-trioxatricyclo[6.3.1.0^{3,8}]dodecane-1,10,11-tricarboxylic Acid 1,10,11-Tris(1,1-dimethylethyl) Ester (17a) and [1*R*,3*R*,8*S*-(1α,2α,5*β*,10α,11*β*)]-5-Methoxy-2,11-dihydroxy-4,9,12-trioxatricyclo[6.3.1.0^{3,8}]dodecane-1,10,11-tricarboxylic Acid 1,10,11 Tris(1,1-dimethylethyl) Ester (17b). Benzene (8 mL) was heated at reflux for 1 h in a 25-mL flask equipped with a small Soxhlet extractor filled with activated 4 Å molecular sieves. Dimethyl acetal **2** (20.5 mg, 0.036 mmol) was added to the flask, and the solution was heated at reflux for 30 min to remove any trace amount of H_2O. Anhydrous pyridinium *p*-toluenesulfonate (*ca.* 4 mg, 0.016 mmol) was added to the hot solution, which was then heated at reflux for 7 min. After the solution had cooled slightly, triethylamine (1 mL) was added and the reaction was allowed to cool to rt. Ethyl acetate (15 mL) was added, and the solution was washed with saturated aqueous NH_4Cl (3 × 10 mL), water (10 mL), and brine (10 mL). The aqueous layers were back-extracted with EtOAc (20 mL). The organic phases were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. After purification by flash chromatography on SiO_2 (gradient elution, 1:5 to 1:1 EtOAc/hexanes), a 6:1 mixture of diastereomers **17a** and **17b** (19.2 mg, 99%) was isolated as a white foam. Anal. Calcd for $C_{25}H_{40}O_{12}$: C, 56.38; H, 7.57. Found: C, 56.37; H, 7.86. The diastereomers were separated by HPLC for full characterization.

Major Diastereomer 17a. White solid, mp 137−139 °C. TLC: R_f 0.37 (1:1 EtOAc/hexanes). $[\alpha]_D$: +57.7 (*c* 1.19, CH_2Cl_2). IR (CH_2Cl_2): 3570, 3455, 1755, 1726 cm^{-1}. ^1H NMR (500 MHz): δ 1.44 (s, 9), 1.50 (s, 9), 1.59 (s, 9), 1.76−1.79 (m, 1), 2.09−2.22 (m, 3), 2.58 (d, 1, J = 3.4), 3.40 (s, 3), 3.94 (s, 1), 4.06 (d, 1, J = 5.2), 4.66 (s, 1), 4.80 (d, 1, J = 3.0), 5.18 (dd, 1, J = 5.1, 3.5). ^{13}C NMR (100 MHz): δ 27.29, 27.97, 28.09, 28.20, 29.53, 54.83, 72.43, 74.45, 74.76, 78.86, 83.13, 84.56, 85.04, 91.44, 99.82, 100.06, 165.71, 166.53, 168.36.

Minor Diastereomer 17b. White solid, mp 151−152 °C

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dec. TLC: R_f 0.29 (1:1 EtOAc/hexanes). $[\alpha]_D$: −29.7 (*c* 0.64, CH_2Cl_2). IR (CH_2Cl_2): 3582, 3455, 1756, 1725 cm^{-1}. ^1H NMR (500 MHz): δ 1.42 (s, 9), 1.49 (s, 9), 1.57 (s, 9), 1.82−1.91 (m, 2), 1.96−2.04 (m, 1), 2.30−2.33 (m, 1), 2.66 (d, 1, J = 3.1), 3.58 (s, 3), 3.66 (d, 1, J = 5.1), 3.95 (s, 1), 4.62 (dd, 1, J = 9.2, 2.6), 4.75 (s, 1), 5.22 (dd, 1, J = 5.1, 3.1). ^{13}C NMR (100 MHz): δ 27.98, 28.07, 28.19, 28.27, 30.94, 57.29, 72.13, 74.19, 74.77, 83.02, 84.70, 85.04, 85.20, 92.20, 99.44, 105.70, 165.48, 166.55, 168.37.

[1*R*,3*R*,8*S*-(1α,2α(2*E*,4*S*,6*S*),5α,10α,11*β*)]-2-(4,6-Dimethyl-2-octenoyl)-5-methoxy-2,11-dihydroxy-4,9,12-trioxatricyclo[6.3.1.0^{3,8}]dodecane-1,10,11-tricarboxylic Acid 1,10,11-Tris(1,1-dimethylethyl) Ester (18a) and [1*R*,3*R*,8*S*-(1α,2α(2*E*,4*S*,6*S*),5*β*,10α,11*β*)]-2-(4,6-Dimethyl-2-octenoyl)-5-methoxy-2,11-dihydroxy-4,9,12-trioxatricyclo[6.3.1.0^{3,8}]-dodecane-1,10,11-tricarboxylic Acid 1,10,11-Tris(1,1-dimethylethyl) Ester (18b). Acid **14** (28.5 mg, 167 μmol), **17a**,**b** (50.9 mg, 95.6 μmol), and 10 μL of a 0.286 M solution of DMAP in CH_2Cl_2 (2.86 μmol) were combined, concentrated three times from benzene, and diluted with CH_2Cl_2 (0.25 mL). The solution was cooled to 0 °C, and DCC (35.5 mg, 172 μmol) was added. The resulting cloudy white mixture was stirred at 0 °C for 2 h and at rt for 12 h. Additional **14** (16.7 mg, 98.1 μmol) and DCC (20.8 mg, 101 μmol) were added, and stirring was continued for another 12 h. The solvent was evaporated under a flow of N_2, and the residue was diluted with 1:7 EtOAc/hexanes and filtered through a plug of Celite. The filtrate (15 mL) was washed with saturated aqueous $NaHCO_3$ (5 mL), saturated aqueous NH_4Cl (5 mL), water (5 mL), and brine (5 mL), dried over $MgSO_4$, filtered, and concentrated. The product was purified by flash chromatography on SiO_2 (gradient elution, 1:7 to 1:5 EtOAc/hexanes), and the product **18a**,**b** (63.0 mg, 96%) was isolated as a clear, colorless oil. IR (CH_2Cl_2): 3450, 1762, 1737, 1733, 1652 cm^{-1}. Anal. Calcd for $C_{35}H_{56}O_{13}$: C, 61.38; H, 8.24. Found: C, 61.62; H, 8.30. The diastereomers were separated by flash chromatography for further characterization.

Major Diastereomer 18a. White foam. TLC: R_f 0.46 (2:3 EtOAc/hexanes). $[\alpha]_D$: +80.5 (*c* 0.84, CH_2Cl_2). ^1H NMR (500 MHz): δ 0.81−0.84 (m, 6), 1.02 (d, 3, J = 6.7), 1.08−1.13 (m, 2), 1.24−1.39 (m, 3), 1.45 (s, 9), 1.47 (s, 9), 1.60 (s, 9), 1.75−1.78 (m, 1), 2.13−2.25 (m, 3), 2.37−2.42 (m, 1), 3.27 (s, 3), 4.12 (s, 1), 4.15 (d, 1, J = 4.8), 4.76 (s, 1), 4.82 (d, 1, J = 3.1), 5.74 (dd, 1, J = 15.7, 0.9), 6.40 (d, 1, J = 4.8), 6.87 (dd, 1, J = 15.7, 8.3). ^{13}C NMR (100 MHz): δ 11.11, 18.87, 20.16, 27.24, 27.99, 28.06, 28.08, 29.68, 29.78, 31.87, 34.38, 43.23, 54.61, 72.66, 74.43, 74.64, 78.70, 83.26, 83.86, 86.02, 90.22, 99.84, 100.14, 118.52, 156.35, 163.98, 164.76, 165.58, 168.71.

Minor Diastereomer 18b. White foam. TLC: R_f 0.38 (2:3 EtOAc/hexanes). $[\alpha]_D$: +30.6 (*c* 0.51, CH_2Cl_2). ^1H NMR (500 MHz): δ 0.83−0.86 (m, 6), 1.02 (d, 3, J = 6.7), 1.08−1.16 (m, 2), 1.25−1.39 (m, 3), 1.43 (s, 9), 1.44 (s, 9), 1.62 (s, 9), 1.83−1.87 (m, 1), 1.90−1.96 (m, 1), 2.00−2.06 (m, 1), 1.34−2.43 (m, 2), 3.57 (s, 3), 3.77 (d, 1, J = 4.6), 4.14 (s, 1), 4.60 (dd, 1, J = 9.8, 2.7), 4.87 (s, 1), 5.74 (dd, 1, J = 15.7, 1.0), 6.51 (d, 1, J = 4.6), 6.89 (dd, 1, J = 15.7, 8.2). ^{13}C NMR (100 MHz): δ 11.07, 18.86, 20.14, 27.98, 28.00, 28.07, 28.30, 29.65, 31.10, 31.78, 34.32, 43.23, 57.26, 71.71, 74.22, 74.62, 83.14, 84.12, 84.77, 86.33, 91.45, 99.35, 105.78, 118.67, 156.38, 163.78, 164.39, 165.52, 168.78.

[1*S*-(1α,3α,4*β*,5α,6α(2*E*,4*S*,6*S*),7*β*)]-1-(3-Oxopropyl)-6-(4,6-dimethyl-2-octenoyl)-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid 3,4,5-Tris(1,1-dimethylethyl) Ester (19). The combined diastereomers **18a**,**b** (36.3 mg, 53.0 μmol) were dissolved in acetone (1 mL). To the solution were added 1 drop of water from a Pasteur pipet and pyridinium *p*-toluenesulfonate (14 mg, 56 μmol). The solution was heated at 50 °C for 7 h, cooled to rt, poured into saturated aqueous $NaHCO_3$ (5 mL), and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with saturated aqueous NH_4Cl (10 mL), water (10 mL), and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was subjected to flash chromatography on SiO_2 (1:4 EtOAc/hexanes). Aldehyde **19** was isolated as a white foam (33.3 mg, 97%). TLC: R_f 0.19 (2:3 EtOAc/hexanes). $[\alpha]_D$: +15.5 (*c* 1.4, CH_2Cl_2). IR (thin film): 3459 (br), 1755, 1732, 1651 cm^{-1}. ^1H NMR (500 MHz): δ 0.82−0.85 (m, 6), 1.02 (d, 3, J = 6.7), 1.08−1.14 (m, 2), 1.23−1.38 (m, 3), 1.45 (s, 9), 1.46 (s, 9), 1.59 (s, 9), 2.20−2.25 (m, 1), 2.32−2.38 (m, 1), 2.38−2.43 (m, 1), 2.76−2.81 (m, 1), 2.90−2.95 (m, 1), 3.10 (d, 1, J = 3.1), 4.06−4.07 (m, 2), 5.05 (s, 1), 5.74 (dd, 1, J = 15.7, 0.9), 6.01 (d, 1, J = 2.0), 6.88 (dd, 1, J = 15.7, 8.5), 9.83 (t, 1, J = 1.1). ^{13}C NMR (100 MHz): δ 11.09, 18.81, 20.22, 27.99, 28.01, 28.15, 28.87, 29.70, 31.84, 34.50, 37.83, 43.17, 74.09, 75.33, 80.66, 82.62, 83.33, 84.04, 85.89, 88.92, 103.84, 118.17, 157.45, 163.85, 165.57, 166.57, 168.64, 202.16. Anal. Calcd for $C_{34}H_{54}O_{13}$: C, 60.88; H, 8.11. Found: C, 60.83; H, 8.11.

[1*S*-(1α,3α,4*β*,5α,6α(2*E*,4*S*,6*S*),7*β*)]-1-(3-Oxopropyl)-6-(4,6-dimethyl-2-octenoyl)-7-(triethylsilyl)-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid 3,4,5-Tris(1,1-dimethylethyl) Ester (20). Aldehyde **19** (48.2 mg, 71.9 μmol) was dissolved in pyridine (2.50 mL). The solution was cooled to 0 °C, and a solution of triethylsilyl chloride (0.40 mL, 2.4 mmol) in pyridine (2.0 mL) was added over 5 min. The ice bath was removed, and the solution was stirred at rt for 22 h, diluted with Et_2O (30 mL), and washed with 0.5 M HCl (2 × 30 mL), saturated aqueous $NaHCO_3$ (20 mL), water (20 mL), and brine (20 mL). The aqueous layers were back-extracted with Et_2O (30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and evaporated. The crude product was purified by flash chromatography on SiO_2 (gradient elution, 1:7 to 1:5 EtOAc/hexanes) to yield **20** (46.3 mg, 82%). TLC: R_f 0.49 (2:3 EtOAc/hexanes). $[\alpha]_D$: +33.0 (*c* 3.58, CH_2Cl_2). IR (thin film): 3459, 1762, 1730 cm^{-1}. ^1H NMR (400 MHz): δ 0.60 (q, 6, J = 7.9), 0.81−0.84 (m, 6), 0.93 (t, 9, J = 7.9), 1.00 (d, 3, J = 6.7), 1.07−1.13 (m, 2), 1.24−1.35 (m, 3), 1.38 (s, 9), 1.45 (s, 9), 1.64 (s, 9), 2.07 (m, 1), 2.30 (m, 1), 2.39 (m, 1), 2.80 (m, 1), 2.98 (m, 1), 4.06 (s, 1), 4.11 (d, 1, J = 1.4), 5.07 (s, 1), 5.75 (d, 1, J = 15.7), 6.35 (d, 1, J = 1.2), 6.89 (dd, 1, J = 15.7, 8.4), 9.87 (s, 1). ^{13}C NMR (100 MHz): δ 4.59 (2), 6.57 (3), 11.11 (3), 18.74 (3), 20.15 (3), 27.95 (3), 28.05 (3), 28.75 (2), 29.72 (2), 31.87 (1), 34.39 (1), 37.99 (2), 43.23 (2), 73.92 (0), 75.12 (1), 78.50 (1), 83.02 (1), 83.14 (0), 84.07 (0), 86.07 (0), 89.91 (0), 103.71 (0), 118.58 (1), 156.65 (1), 163.93 (0), 164.49 (0), 165.96 (0), 168.98 (0), 202.15 (1). Anal. Calcd for $C_{40}H_{68}O_{13}Si$: C, 61.20; H, 8.73. Found: C, 61.48; H, 8.84.

(1*R*,2*R*)-1-[[(*p*-Methoxybenzyl)oxy]methoxy]-2-methyl-3-phenyl-1-(tri-*n*-butylstannyl)propane (23a) and (1*S*,2*R*)-1-[[(*p*-Methoxybenzyl)oxy]methoxy]-2-methyl-3-phenyl-1-(tri-*n*-butylstannyl)propane (23b). Dimethyl sulfoxide (0.28 mL, 3.95 mmol) was added slowly to a solution of oxalyl chloride (0.19 mL, 2.18 mmol) in CH_2Cl_2 (6 mL) at −78 °C. The solution was stirred for 15 min at −78 °C. Alcohol **21**[13] (250.0 mg, 1.66 mmol) in CH_2Cl_2 (1 mL) was added, followed by two CH_2Cl_2 rinses (1 mL and 0.5 mL) *via* cannula over 10 min. The cloudy white reaction mixture was stirred for 1 h, and triethylamine (1.16 mL, 8.32 mmol) was added. The resulting thick white mixture was stirred for 1.5 h at −78 °C and then poured while still cold into 10% $NaHSO_4$ (7 mL). The mixture was immediately extracted with 20% Et_2O in hexanes (20 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (7 mL), water (7 mL), and brine (7 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford a yellow liquid (0.260 g). The crude aldehyde was concentrated twice from benzene (3 mL) and used directly in the next step.

To a solution of diisopropylamine (262 μL, 2.00 mmol) in THF (5 mL) at 0 °C was added *n*-BuLi in hexanes (0.88 mL, 1.83 mmol) over 3 min. The solution was stirred for 30 min, and tributylstannane (0.54 mL, 2.00 mmol) was added. The solution was stirred for 30 min and then cooled to −78 °C, and the aldehyde was added in THF (1 mL, followed by 2 × 1 mL rinses) *via* cannula over 10 min. After 45 min, the reaction was quenched with 5% NH_4Cl solution (3 mL) and allowed to warm up. The cold mixture was extracted with Et_2O (2 × 8 mL). The combined organic extracts were washed with water (2 × 6 mL), dried over Na_2SO_4, filtered, and concentrated. The crude hydroxy stannane **22** was diluted with CH_2Cl_2, filtered through a plug of cotton to remove the small amount of water still present, and then concentrated again and taken directly onto the next step.

Hydroxy stannane **22** was dissolved in CH_2Cl_2 (2.8 mL) and cooled to 0 °C. Diisopropylethylamine (1.16 mL, 6.66 mmol)

and *p*-methoxybenzyl chloromethyl ether[24] (0.932 g, 4.99 mmol, slightly contaminated with *p*-methoxybenzyl chloride) were added. The reaction mixture was stirred at 0 °C for 2 d, during which time additional diisopropylethylamine and *p*-methoxybenzyl chloromethyl ether were added until the hydroxy stannane was no longer visible by TLC analysis of the reaction. The solution was diluted with 20% Et_2O in hexanes (20 mL), washed with 0.5 M HCl solution (10 mL), water (2 × 10 mL), and brine (10 mL), then dried over $MgSO_4$, filtered, and concentrated. Purification of the product was accomplished by first performing flash chromatography on SiO_2 (1:90 EtOAc/hexanes). The isolated product was contaminated with *p*-methoxybenzyl chloride, which was subsequently removed by heating the product at 50 °C under high vacuum. The two diastereomers were separated by HPLC (1% EtOAc in hexanes) to afford **23a** (321.0 mg, 32%) and **23b** (269.3 mg, 28%) as colorless liquids. Anal. Calcd for $C_{31}H_{50}O_3Sn$: C, 62.20; H, 8.55. Found: C, 62.34; H, 8.70.

23a: TLC: R_f 0.17 (1:20 EtOAc/hexanes). IR (neat): 1613, 1514, 1248, 1031 cm^{-1}. ^1H NMR (500 MHz): δ 0.87 (d, 3, J = 6.6), 0.90 (t, 9, J = 7.3), 0.91−0.95 (m, 6), 1.31 (m, 6, J = 7.2), 1.48−1.54 (m, 6), 2.25 (m, 1), 2.32 (dd, 1, J = 12.8, 9.8), 3.02 (dd, 1, J = 12.8, 4.4), 3.81 (s, 3), 4.16 (m, 1), 4.53 (d, 1, J = 11.5), 4.61 (d, 1, J = 11.5), 4.68 (d, 1, J = 6.6), 4.76 (d, 1, J = 6.6), 6.87 (m, 2), 7.14−7.19 (m, 3), 7.5−7.28 (m, 4). ^{13}C NMR (100 MHz): δ 10.07, 13.67, 16.85, 27.53 ($^3J(^{119}Sn-^{13}C)$ = 28 Hz), 29.22 ($^3J(^{119}Sn-^{13}C)$ = 10 Hz), 40.46, 41.86, 55.25, 69.29, 80.50, 94.79, 113.77, 125.67, 128.18, 129.11, 129.37, 130.08, 141.53, 159.17.

23b: TLC: R_f 0.17 (1:20 EtOAc/hexanes). IR (neat): 1613, 1514, 1248, 1031 cm^{-1}. ^1H NMR (400 MHz): δ 0.89−0.99 (m, 18), 1.34 (m, 6, J = 7.4), 1.50−1.61 (m, 6), 2.30−2.37 (m, 2), 2.79 (d, 1, J = 8.7), 3.81 (s, 3), 4.16 (d, 1, J = 4.6), 4.50 (d, 1, J = 11.4), 4.59 (d, 1, J = 11.4), 4.66 (d, 1, J = 6.7), 4.74 (d, 1, J = 6.7), 6.88 (d, 2, J = 8.7), 7.16−7.31 (m, 7). ^{13}C NMR (100 MHz): δ 10.10, 13.67, 18.22, 27.55 ($^3J(^{119}Sn-^{13}C)$ = 29 Hz), 29.25 ($^3J(^{119}Sn-^{13}C)$ = 10 Hz), 40.06, 40.69, 55.25, 69.27, 81.40, 94.62, 113.76, 125.77, 128.22, 128.99, 129.41, 130.07, 141.14, 159.17.

[1*S*-[1α(4*S*,5*R*),3α,4*β*,5α,6α(2*E*,4*S*,6*S*),7*β*]]-1-[4-[[(*p*-Methoxybenzyl)oxy]methoxy]-5-methyl-3-oxo-6-phenylhexyl]-6-(4,6-dimethyl-2-octenoyl)-7-(triethylsilyl)-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid 3,4,5-Tris(1,1-dimethylethyl) Ester (25). The reaction was carried out in a flask shaped like an inverted "Y" with the volume of each arm approximately 0.8 mL. Dry $CeCl_3$[26] (35.0 mg, 142 μmol) was added to one arm of the flask, and organostannane **23a** (36.3 mg, 61.6 μmol) was added to the other. THF (0.2 mL) was added to the $CeCl_3$, and the white slurry was stirred for 5 h at rt, during which time additional THF was added to keep the volume at 0.2−0.3 mL. THF (0.3 mL) was added to **23a** to yield a clear, colorless solution. The flask was cooled to −78 °C. A solution of *n*-BuLi in hexanes (21 μL, 51 μmol) was added to the solution of **23a**, and after being stirred for 5 min, the resulting yellow solution was added to the $CeCl_3$ slurry by quickly tipping the flask. After 0.5 min, a 0.124 M solution of aldehyde **20** in THF (100 μL, 12.4 μmol) was added to the organocerium reagent. The reaction mixture was stirred for 5 min and then the reaction quenched with saturated aqueous NH_4Cl (3 mL) and the mixture warmed to rt. The mixture was diluted with EtOAc (15 mL) and washed with 0.5 M HCl (7 mL), saturated aqueous $NaHCO_3$ (7 mL), water (7 mL), and brine (7 mL). The aqueous layers were back-extracted with EtOAc (15 mL). The combined organic phases were dried over $MgSO_4$, filtered, evaporated *in vacuo*, and purified by flash chromatography on SiO_2 (gradient elution 1:7 to 1:3 EtOAc/hexanes) to provide a 15:1 mixture of alcohols **24a**,**b** (11.6 mg, 87%). TLC (**24a**,**b**): R_f 0.43 (2:3 EtOAc/hexanes).

Major Diastereomer 24a. ^1H NMR (400 MHz): δ 0.59 (q, 6, J = 8.0), 0.81−0.85 (m, 6), 0.89−0.94 (m, 12), 1.00 (d, 3, J = 6.7), 1.07−1.14 (m, 2), 1.25−1.42 (m, 3), 1.39 (s, 9), 1.42 (s, 9), 1.57−1.71 (m, 1), 1.64 (s, 9), 1.85−1.98 (m, 2), 2.04−2.18 (m, 2), 2.40 (m, 1), 2.56 (dd, 1, J = 13.5, 8.5), 2.80 (dd, 1, J = 13.5, 6.5), 3.27 (dd, 1, J = 6.4, 2.9), 3.46 (d, 1, J = 4.3), 3.80 (s, 3), 3.89 (m, 1), 4.01 (s, 1), 4.08 (d, 1, J = 1.7), 4.62 (d, 1, J = 11.5), 4.68 (d, 1, J = 11.6), 4.75 (d, 1, J = 6.8), 4.95 (d, 1, J = 6.7), 5.08 (s, 1), 5.76 (dd, 1, J = 15.7, 1.0), 6.34 (d, 1, J = 1.8), 6.86−6.92 (m, 3), 7.13−7.31 (m, 7).

To alcohol **24a**,**b** (11.6 mg, 10.7 μmol) was added a heterogeneous mixture of Dess−Martin periodinane[29] (22.6 mg, 53.4 μmol) and pyridine (21.6 μL, 268 μmol) in CH_2Cl_2 (0.9 mL). The mixture was stirred for 40 min at rt. A solution of 1:1 saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ (4 mL) was added, and the mixture was stirred for 5 min, diluted with Et_2O (15 mL), and washed with saturated aqueous $NaHCO_3$ (2 × 5 mL) and brine (5 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated. Ketone **25** was isolated after flash chromatography on SiO_2 (gradient elution, 1:7 to 1:5 EtOAc/hexanes) as a colorless oil (10.7 mg, 92%). TLC: R_f 0.51 (1:2 EtOAc/hexanes). $[\alpha]_D$: +22.0 (*c* 0.75, CH_2Cl_2). IR (thin film): 3481 (br), 1759, 1727 cm^{-1}. ^1H NMR (500 MHz): δ 0.60 (q, 6, J = 7.9), 0.81−0.84 (m, 9), 0.92 (t, 9, J = 7.9), 1.00 (d, 3, J = 6.7), 1.07−1.14 (m, 2), 1.24−1.38 (m, 3), 1.38 (s, 9), 1.42 (s, 9), 1.65 (s, 9), 1.99 (m, 1), 2.25 (m, 1), 2.35−2.44 (m, 2), 2.58 (dd, 1, J = 13.5, 9.1), 2.84 (dd, 1, J = 13.5, 5.7), 2.90 (ddd, 1, J = 18.4, 10.9, 5.2), 3.03 (ddd, 1, J = 18.5, 10.4, 4.5), 3.79 (s, 3), 4.09−4.10 (m, 2), 4.19 (d, 1, J = 3.3), 4.57 (d, 1, J = 11.6), 4.66 (d, 1, J = 11.6), 4.71 (d, 1, J = 7.0), 4.78 (d, 1, J = 7.0), 5.07 (s, 1), 5.76 (dd, 1, J = 15.7, 1.0), 6.36 (d, 1, J = 1.8), 6.86−6.92 (m, 3), 7.17−7.21 (m, 3), 7.25−7.28 (m, 4). ^{13}C NMR (100 MHz): δ 4.59, 6.59, 11.11, 13.62, 18.74, 20.17, 27.97, 28.05, 29.69, 29.73, 31.88, 33.51, 34.39, 37.49, 40.08, 43.25, 55.23, 69.69, 73.99, 75.10, 78.43, 82.87, 83.26, 83.98, 85.23, 85.96, 90.00, 94.54, 103.81, 113.76, 118.66, 126.02, 128.32, 129.25, 129.44, 129.95, 140.23, 156.56, 159.14, 164.02, 164.54, 166.01, 169.01, 210.58. Anal. Calcd for $C_{59}H_{90}O_{16}Si$: C, 65.40; H, 8.37. Found: C, 65.14; H, 8.39.

[1*S*-[1α(4*S*,5*R*),3α,4*β*,5α,6α(2*E*,4*S*,6*S*),7*β*]]-1-[4-[[(*p*-Methoxybenzyl)oxy]methoxy]-5-methyl-3-methylene-6-phenylhexyl]-6-(4,6-dimethyl-2-octenoyl)-7-(triethylsilyl)-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid 3,4,5-Tris(1,1-dimethylethyl) Ester (26). A. From 25. Tebbe reagent was prepared following the procedure of Pine *et al.*[32] and added dropwise to a stirred solution of ketone **25** (7.5 mg, 6.9 μmol) in THF (0.8 mL) at 0 °C over 4.5 h. The reaction was monitored carefully by TLC and stopped when overmethylenated product was observed. Approximately 0.5 mL of 0.1 M NaOH was added slowly, and the mixture was stirred for 10 min and added to H_2O (5 mL). The mixture was extracted with Et_2O (2 × 15 mL). The organic layer was washed with brine and dried over $MgSO_4$. After extensive purification by flash chromatography on SiO_2 (gradient elution, 1:9 to 1:5 EtOAc/hexanes), **26** was isolated as a colorless oil (5.8 mg, 77%). In addition, 1.1 mg (15%) of **25** was recovered. The optical rotation and ^1H NMR spectrum were identical to those obtained for **26** when synthesized from **27**.

B. From 27. *N*,*N*-Diisopropylethylamine (0.15 mL, 0.86 mmol) and *p*-methoxybenzyl chloromethyl ether[24] (6 drops from a disposable Pasteur pipet, *ca.* 75 mg, 0.402 mmol) were added to a solution of alcohol **27** (61.3 mg, 65.8 μmol) in CH_2Cl_2 (0.3 mL) at 0 °C. The reaction mixture was stirred at rt for 36 h. During this time additional *N*,*N*-diisopropylethylamine and *p*-methoxybenzyl chloromethyl ether were added to drive the reaction to completion. The yellow solution was diluted with EtOAc (20 mL) and washed with 10% aqueous $NaHSO_4$ (10 mL), saturated aqueous $NaHCO_3$ (10 mL), H_2O (10 mL), and brine (10 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The product was isolated as a clear, colorless oil (68.6 mg, 96%) after purification by flash chromatography on SiO_2 (1:8 EtOAc/hexanes). TLC: R_f 0.64 (1:2 EtOAc/hexanes). $[\alpha]_D$: −2.4 (*c* 0.67, CH_2Cl_2). IR (thin film): 3476, 1761, 1735 cm^{-1}. ^1H NMR (500 MHz): δ 0.57 (q, 6, J = 7.9), 0.81−0.84 (m, 6), 0.86 (d, 3, J = 6.6), 0.90 (t, 9, J = 7.9), 1.00 (d, 3, J = 6.7), 1.07−1.13 (m, 2), 1.24−1.40 (m, 3), 1.39 (s, 9), 1.43 (s, 9), 1.65 (s, 9), 1.93−1.99 (m, 1), 2.05−2.10 (m, 1), 2.12−2.18 (m, 1), 2.27−2.33 (m, 2), 2.37−2.43 (m, 1), 2.49−2.54 (m, 1), 2.80 (dd, 1, J = 13.5, 4.1), 3.79 (s, 3), 3.96 (d, 1, J = 6.5), 4.03 (s, 1), 4.12 (d, 1, J = 1.8), 4.45 (d, 1, J = 11.3), 4.65 (d, 1, J = 6.9), 4.68 (d, 1, J = 6.9), 4.70 (d, 1, J = 11.4), 5.06−5.07 (m, 2), 5.07 (s, 1), 5.78 (dd, 1, J = 15.7,

0.9), 6.36 (d, 1, J = 1.7), 6.86 (dm, 2, J = 8.7), 6.90 (dd, 1, J = 15.7, 8.4), 7.13−7.28 (m, 7). ^{13}C NMR (100 MHz): δ 4.62, 6.58, 11.09, 14.37, 18.78, 20.15, 24.55, 27.98, 28.06, 29.71, 31.88, 34.26, 34.38, 37.20, 40.25, 43.26, 55.24, 69.39, 74.18, 75.15, 78.62, 82.67, 82.80, 83.75, 83.94, 85.73, 89.97, 91.88, 104.27, 113.11, 113.79, 118.71, 125.61, 128.11, 129.25, 129.47, 130.15, 141.05, 146.51, 156.44, 159.17, 164.15, 164.57, 166.11, 168.96. Anal. Calcd for $C_{60}H_{92}O_{15}Si$: C, 66.63; H, 8.58. Found: C, 66.56; H, 8.75.

[1*S*-[1α(4*S*,5*R*),3α,4*β*,5α,6α(2*E*,4*S*,6*S*),7*β*]]-1-[4-Hydroxy-5-methyl-3-methylene-6-phenylhexyl]-6-(4,6-dimethyl-2-octenoyl)-7-(triethylsilyl)-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid 3,4,5-Tris(1,1-dimethylethyl) Ester (27). A. Preparation from 26. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ, 6.3 mg, 0.028 mmol) was added to ether **26** (25.1 mg, 23.2 μmol) and H_2O (5 μL) in CH_2Cl_2 (0.1 mL) at 0 °C. The ice bath was removed, and the mixture was stirred at rt. After 1 h, additional DDQ (1.8 mg) was added. The mixture was stirred for 1.5 h more and then was diluted with CH_2Cl_2 (20 mL) and washed with saturated aqueous $NaHCO_3$ (10 mL), H_2O (10 mL), and brine (10 mL). The organic phase was dried over $MgSO_4$, filtered, concentrated *in vacuo*, and purified by flash chromatography on SiO_2 (1:7 EtOAc/hexanes). Allylic alcohol **27** was obtained as a clear, colorless oil (19.6 mg, 91%). The ^{1}H and ^{13}C NMR spectra and $[\alpha]_D$ value were identical to that obtained for **27** when synthesized from **28**.

B. Preparation from 28. A slurry of dry $CeCl_3$[26] (650 mg, 2.64 mmol) in THF (2 mL) was stirred at rt for 22 h under N_2. More THF (1.25 mL) was added, and the slurry was cooled to −78 °C. A solution of ethylmagnesium chloride in THF (0.75 mL, 1.51 mmol) was added, and the flask was put in an ice bath for 20 min and then recooled to −78 °C. To the slurry was added **28** (58.8 mg, 60.4 μmol) in THF (1 mL, then 2 × 0.5 mL rinses) at −78 °C *via* cannula over 10 min. The reaction mixture was stirred for 15 min at −78 °C and then the reaction quenched with 1 M HCl (2 mL). The mixture was warmed to rt, diluted with EtOAc (20 mL), and washed with 1 M HCl (8 mL), saturated aqueous $NaHCO_3$ (8 mL), water (8 mL), and brine (8 mL). The aqueous phases were back-extracted with EtOAc (20 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. Purification of the resulting yellow residue by flash chromatography on SiO_2 (1:5 EtOAc/hexanes) provided **27** (55.1 mg, 98%) as a clear, colorless oil. TLC: R_f 0.54 (1:2 EtOAc/hexanes). $[\alpha]_D$: +36.7 (*c* 3.72, CH_2Cl_2). IR (thin film): 3458, 1736 cm^{-1}. ^{1}H NMR (400 MHz): δ 0.58 (q, 6, J = 7.9), 0.82−0.85 (m, 9), 0.93 (t, 9, J = 7.9), 1.01 (d, 3, J = 6.7), 1.04−1.14 (m, 2), 1.26−1.38 (m, 3), 1.40 (s, 9), 1.45 (s, 9), 1.65 (s, 9), 1.91−2.04 (m, 2), 2.13 (ddd, 1, J = 14.5, 9.0, 5.9), 2.32−2.50 (m, 5), 2.81 (dd, 1, J = 13.5, 5.4), 3.96 (s, 1), 4.09 (m, 2), 5.01 (s, 1), 5.07 (s, 1), 5.13 (s, 1), 5.77 (dd, 1, J = 15.7, 0.9), 6.35 (d, 1, J = 1.8), 6.90 (dd, 1, J = 15.7, 8.4), 7.14−7.27 (m, 5). ^{13}C NMR (100 MHz): δ 4.62, 6.58, 11.09, 13.21, 18.76, 20.16, 26.52, 27.98, 28.08, 28.11, 29.72, 31.88, 34.27, 34.39, 38.03, 40.28, 43.25, 74.19, 75.11, 77.31, 78.47, 82.93, 83.08, 83.98, 85.57, 89.85, 104.37, 110.72, 118.67, 125.59, 128.11, 129.22, 141.39, 151.23, 156.48, 164.10, 164.52, 166.10, 168.31. Anal. Calcd for $C_{51}H_{82}O_{13}Si$: C, 65.77; H, 8.88. Found: C, 66.00; H, 8.96.

[1*S*-[1α(4*S*,5*R*),3α,4*β*,5α,6α(2*E*,4*S*,6*S*),7*β*]]-1-[4-(Acetyloxy)-5-methyl-3-methylene-6-phenylhexyl]-6-(4,6-dimethyl-2-octenoyl)-7-(triethylsilyl)-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane-3,4,5-tricarboxylic Acid 3,4,5-Tris(1,1-dimethylethyl) Ester (28). Preparation from 27. To a solution of **27** (61.4 mg, 65.9 μmol), triethylamine (32 μL, 0.23 mmol), and DMAP (1.2 mg, 9.8 μmol) in CH_2Cl_2 (0.33 mL) at 0 °C was added acetic anhydride (16 μL, 0.165 mmol). The solution was stirred for 1 h at 0 °C, and saturated aqueous $NaHCO_3$ (2 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 7 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl (7 mL), water (7 mL), and brine (7 mL), dried over $MgSO_4$, filtered, and concentrated. After purification by flash chromatography on SiO_2 (1:7 EtOAc/hexanes), **28** was isolated as a colorless oil (64.0 mg, 100%). The ^{1}H NMR spectrum and $[\alpha]_D$ value were identical to those obtained for **28** when synthesized from **3**.

Preparation from 3. To a solution of **3** (0.427 g, 0.497 mmol) in DMF (1.65 mL) at rt were added imidazole (88 mg, 1.29 mmol) and triethylsilyl chloride (108 μL, 0.647 mmol). The solution was stirred, and additional imidazole (88 mg) and triethylsilyl chloride (108 mL) were added after 18 h. After another 10 h, saturated aqueous NH_4Cl (8 mL) was added, and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (30 mL) and water (30 mL), dried over $MgSO_4$, filtered, and concentrated. After purification by flash chromatography on SiO_2 (1:7 EtOAc/hexanes), 0.450 g (93%) of **28** was obtained. TLC: R_f 0.70 (1:2 EtOAc/hexanes). $[\alpha]_D$: +35.1 (*c* 1.1, CH_2Cl_2). IR ($CDCl_3$): 3455, 1738, 1650 cm^{-1}. ^{1}H NMR (500 MHz): δ 0.59 (q, 6, J = 7.9), 0.81−0.85 (m, 9), 0.92 (t, 9, J = 7.9), 1.02 (d, 3, J = 6.6), 1.07−1.16 (m, 2), 1.26−1.41 (m, 3), 1.41 (s, 9), 1.45 (s, 9), 1.66 (s, 9), 1.90−1.96 (m, 1), 2.06−2.20 (m, 2), 2.09 (s, 3), 2.32−2.43 (m, 3), 2.50−2.56 (m, 1), 2.73 (dd, 1, J = 13.4, 5.1), 4.05 (s, 1), 4.10 (d, 1, J = 1.7), 4.97 (s, 1), 4.98 (s, 1), 5.08 (s, 1), 5.14 (d, 1, J = 5.1), 5.79 (dd, 1, J = 15.7, 0.9), 6.36 (d, 1, J = 1.8), 6.91 (dd, 1, J = 15.7, 8.4), 7.15−7.17 (m, 3), 7.24−7.27 (m, 2). ^{13}C NMR (100 MHz): δ 4.54, 6.50, 11.02, 13.55, 18.69, 20.11, 20.96, 25.30, 27.90, 27.96, 27.98, 29.65, 31.81, 34.21, 34.33, 36.42, 39.91, 43.18, 74.04, 75.04, 78.54, 79.35, 82.71, 82.77, 83.63, 85.72, 89.91, 104.11, 111.23, 118.64, 125.75, 128.14, 129.11, 140.30, 146.05, 156.36, 164.10, 164.45, 166.02, 168.93, 169.97. Anal. Calcd for $C_{53}H_{84}O_{14}Si$: C, 65.40; H, 8.70. Found: C, 65.44; H, 8.75.

Zaragozic Acid A (1). A solution of **3** (16.6 mg, 19.3 μmol) and trifluoroacetic acid (0.35 mL) in CH_2Cl_2 (1.0 mL) was stirred for 11 h at rt and then concentrated *in vacuo*. The crude product was concentrated from toluene (4 × 4 mL) to remove residual trifluoroacetic acid and purified using reverse phase HPLC (semipreparative C18 column, 7:3 CH_3CN/0.1% aqueous H_3PO_4, flow rate: 3 mL/min, R_t = 13.7 min) to afford zaragozic acid A (**1**) (9.9 mg, 74%) as a white film in ≥95% purity by ^{1}H NMR analysis. IR (thin film): 3458 (br), 1721, 1648 cm^{-1}. ^{1}H NMR (CD_3OD, 500 MHz): δ 0.84−0.89 (m, 9), 1.02 (d, 3, J = 6.6), 1.10−1.16 (m, 2), 1.28−1.41 (m, 3), 1.96−2.07 (m, 2), 2.09 (s, 3), 2.22−2.45 (m, 5), 2.68 (dd, 1, J = 13.4, 6.3), 4.03 (d, 1, J = 1.7), 4.96 (s, 1), 5.01 (s, 1), 5.06 (d, 1, J = 4.7), 5.26 (s, 1), 5.79 (d, 1, J = 15.7), 6.30 (d, 1, J = 1.7), 6.84 (dd, 1, J = 15.6, 8.5), 7.12−7.26 (m, 5). ^{13}C NMR (CD_3OD, 100 MHz): δ 11.52, 14.23, 19.30, 20.59, 20.97, 26.57, 30.86, 33.23, 35.05, 35.65, 37.79, 40.99, 44.46, 75.65, 76.69, 80.23, 81.11, 82.61, 91.18, 106.95, 111.62, 119.92, 126.99, 129.39, 130.27, 141.69, 147.84, 157.63, 166.59, 168.48, 170.16, 172.18, 172.55. The spectra are identical with those obtained with an authentic sample of zaragozic acid A obtained from Glaxo, U.K.

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