Total Synthesis of (+)-Zaragozic Acid C

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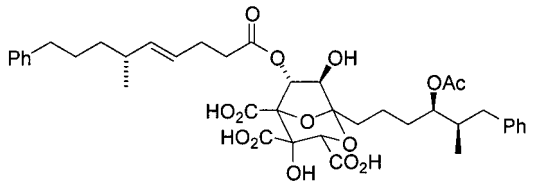
A total synthesis of (+)-zaragozic acid C is described. Key features of the synthesis are the use of a double Sharpless asymmetric dihydroxylation reaction of diene **6** to control stereochemistry at four contiguous stereocenters from C3 to C6; the introduction of the C1-side chain by reaction between the anion derived from the dithiane monosulfoxide **27** and the core aldehyde **12**; a high yielding, acid-mediated simultaneous acetonide deprotection−dithiane removal−ketalization procedure leading exclusively to the 2,8-dioxabicyclo[3.2.1]octane core **34**; and a novel triple oxidation procedure allowing installation of the tricarboxylic acid.

Introduction

The development of drugs that inhibit cholesterol biosynthesis has proved to be an effective strategy for reducing the risk of hypercholesterolemia, and hence coronary heart disease.[1] The successful compounds currently on the market are inhibitors of HMGCoA reductase, and thus act early in the biosynthetic pathway. Intervention at this point can interfere with the production of other important steroids, leading to possible side effects. In the pursuit of therapeutic agents that act at a later point of the biosynthetic pathway, attention has recently focused on inhibition of the enzyme squalene synthase. Random screening procedures led to the independent discovery by three groups[2] of a family of natural products possessing exceptionally potent squalene synthase inhibitory properties. These compounds were named by the Merck workers as the zaragozic acids, while the Glaxo group termed them the squalestatins. An example of these compounds, zaragozic acid C **1**, illustrates the key features common to most of the natural product family: an intriguing and highly oxygenated 2,8-dioxabicyclo[3.2.1]octane core, displaying a tricarboxylic acid unit; an alkyl side chain at C1; and a C6-acyl unit. Several members of the series have been reported, commonly differing at the C1-alkyl and C6-acyl side chains, although some of the natural products show lower oxidation levels at C6 and C7.



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In view of the potent biological activity of these compounds and their intriguing structures, it is not surprising that interest in their synthesis has been intense.[3] As well as numerous approaches to the bicyclic core,[3,4] several total syntheses have been achieved: the groups of Nicolaou[5] and Heathcock[6] have accomplished

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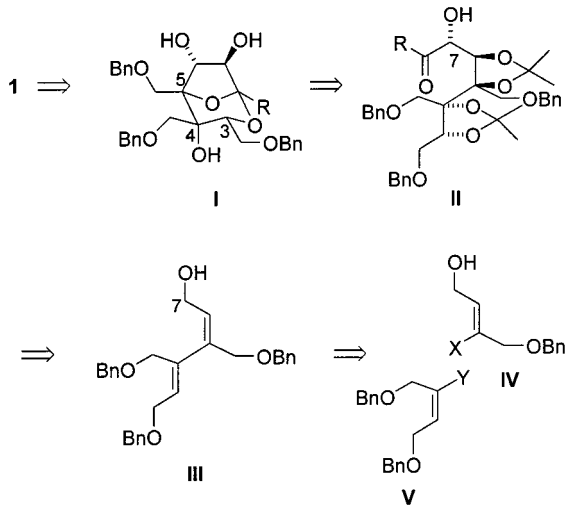


Figure 1. Retrosynthetic analysis.

the synthesis of zaragozic acid A (squalestatin 1) while the groups of Carreira,[7] Evans[8] and Hashimoto[9] have prepared zaragozic acid C. Martin has also described a synthesis of 6,7-dideoxysqualestatin H5.[10]

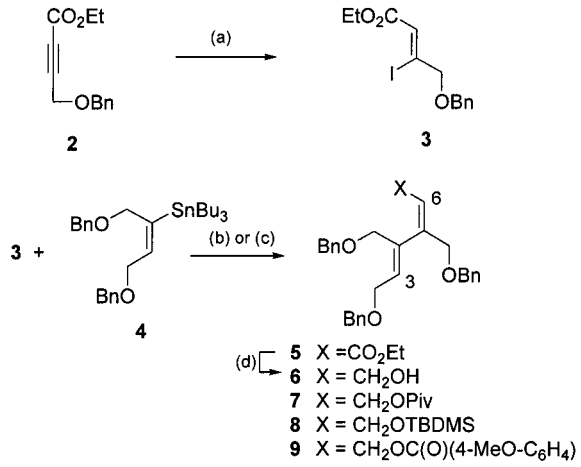
In this paper, we describe in full[11] our own work in this area, which has also led to a total synthesis of **1**.

Results and Discussion

Our retrosynthetic analysis is shown in Figure 1. We envisaged late introduction of the C1-alkyl and C6-acyl side chains in order to allow a flexible route to several members of the natural product family. Our first key disconnection was to imagine the introduction of the tricarboxylic acid moiety in **1** by oxidation of protected hydroxymethyl groups at C3, C4, and C5 in **I**. This would expand the range of anion chemistry that could be performed at a late stage in the synthesis, as well as greatly facilitating the alkene oxidation chemistry that was to be a major feature of our strategy (vide infra). We hoped that **I** would be formed as the thermodynamically most stable of the possible ketal isomers upon treatment of acyclic precursor **II** with acid. Protected polyol **II** could itself be obtained by double Sharpless asymmetric dihydroxylation of 1,3-diene **III**, with the C7-stereocenter subsequently being introduced by addition of an acyl anion equivalent to a C7-aldehyde. Diene **III** would in turn arise from an sp^2-sp^2 coupling between appropriately functionalized alkene precursors **IV** and **V**.

At the outset of our work, there was no precedent for several of the key aspects of this strategy. While our work was underway, however, Nicolaou's total synthesis of zaragozic acid A was published which employs a conceptually similar route.[5] However, our approach as described in this paper effects several of the key oxidation steps simultaneously at several sites in the molecule, allowing a significant shortening of the overall synthesis.

Scheme 1[a]



[a] Reagents and conditions: (a) LiI, AcOH, 70 °C, 1.5 h, 95%; (b) 2 mol % $Pd_2(dba)_3$, 4 mol % P(2-furyl)$_3$, DMF, 65 °C, 4.5 d, 86%; (c) Cu(2-thiophenecarboxylate), NMP, 2 h, rt, 87%; (d) DIBAL-H, CH_2Cl_2, −30 °C, 94%.

To accomplish our initial goal of 1,3-diene assembly, we opted to employ the Stille coupling between a vinyl stannane and vinyl iodide, in view of the high functional group tolerance this process is known to display.[12] An appropriate vinyl stannane **4** (Scheme 1) was readily obtained by a literature procedure involving palladium-catalyzed cis-addition of Bu_3SnH to an alkyne.[13] We spent some time investigating various methods of preparing a suitable vinyl iodide, but best results were obtained by addition of lithium iodide[14] to acetylenic ester **2** in acetic acid, which proceeded cleanly to give **3** as a single stereoisomer according to ^{1}H NMR analysis. After screening several alternative sets of reaction conditions, palladium-catalyzed cross coupling of **3** and **4** was found to proceed reproducibly in 86% yield in the presence of trifuryl phosphine. In our preliminary communication, we stated that the addition of $ZnCl_2$ was necessary in this coupling step, but we have since found that this is not required. More recently, we have found this coupling can be effected in good yield at room temperature using stoichiometric copper(I) thiophenecarboxylate as described by Liebeskind.[15] With this efficient preparation of **5** established, DIBAL-H reduction then provided the alcohol **6** which could be converted to several ether or ester derivatives **7**−**9** under standard conditions.

The Sharpless asymmetric dihydroxylation (AD) is now well established as one of the most reliable and selective methods for asymmetric synthesis.[16] Application of Sharpless's simple mnemonic device[16] to the diene **5**, with the overriding factor considered to be the need to place the olefinic hydrogens in the unhindered "south east" quadrant, led to the prediction that both alkenes required the β-series of ligand, derived from dihydroquinidine, to provide the stereochemistry of the natural product. Thus,

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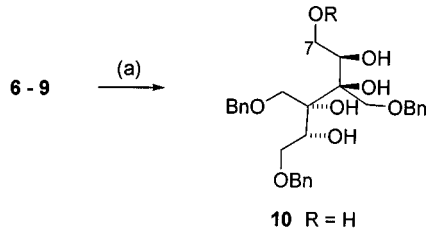
we hoped to effect a double asymmetric dihydroxylation to introduce simultaneously the four stereocenters at C3 to C6. Our initial attempts to effect dihydroxylation of diene **5** under standard AD conditions were not promising. Exposure of **5** to the commercial AD-Mix β-reagent (stoichiometric co-oxidant $K_3Fe(CN)_6$) in the presence of 1 equiv $MeSO_2NH_2$ resulted in very low conversion. Bitmann had reported that the use of $K_2S_2O_8$ as additional co-oxidant allowed the use of reduced volumes of solvent and enhanced rates.[17] We therefore exposed **5** again to standard AD-mix conditions at higher concentration (0.34 M in alkene), and with 1 eq $K_2S_2O_8$ added. Pleasingly, almost all of the starting material had disappeared by TLC after 2 h, affording what was assigned by ^{1}H NMR analysis of the crude product as a mixture of regioisomeric diols. However, even after several days under forcing conditions, with several equivalents of reagents, very little further reaction was observed. The small amounts of fully dihydroxylated products that were formed underwent partial cyclization to give a mixture of lactones, which complicated product analysis. To avoid this problem, and to render the diene more electron rich, we turned our attention to the alcohol **6** and its derivatives. We were pleased to find that **6** did indeed appear qualitatively to be more reactive than **5**, being converted to an inseparable mixture of regioisomeric triol products in relatively short times. However, even after several days at higher concentration and with larger quantities of osmium and ligand, only small amounts (ca. 10%) of pentaols were observed.

At this point, we became aware of some important background work by Sharpless, who had examined the dihydroxylation of *E,E*-1,4-diphenyl-1,3-butadiene.[18] Sharpless found that dihydroxylation of this diene using AD-mix in the two-phase ^{t}BuOH/H_2O solvent system stopped cleanly at the diol, resulting from reaction at only one of the two alkenes. However, under monophasic conditions using NMO in acetone/water as the co-oxidant, the same diene was converted directly into the tetraol. Sharpless explained this difference in reactivity in the two co-oxidant systems in terms of a "two-cycle" mechanism. In either solvent system, interaction of the alkene with the osmium gives rise to an osmate ester. In the biphasic system, this osmate ester undergoes hydrolysis to give the product diol. In the monophasic system, however, further contact with the co-oxidant effects oxidation of the osmate ester to a trisoxo osmium (VIII) glycolate species which is capable of effecting alkene dihydroxylation, albeit without enantioselectivity since the chiral ligand is not involved. Sharpless suggested that hydrogen bonding to this intemediate trisoxo osmium (VIII) glycolate was responsible for the rate enhancement of the second dihydroxylation event involving the ene diol intermediate. We were therefore attracted to this monophasic system as a possible means of effecting exhaustive dihydroxylation of our 1,3-dienes. Initial results with alcohol **6** were highly encouraging: a good yield of the desired pentaol **10** was obtained with high diastereoselectivity (ca. 8:1) (Scheme 2 and Table 1, entry 1). To minimize future protecting group manipulations, we also performed dihydroxylation on the protected derivatives **7** and **8**. However, these substrates afforded lower

Scheme 2[a]



10 R = H

[a] Reagents and conditions: see Table 1.

Table 1. Double Asymmetric Dihydroxylation of Dienes 6−9

entry	diene	conditions[a]	ratio of diastereomers[b]	ee[c] (%)	yield (%)
1	**6**	A	8:1	24	74
2	**7**	A	2:1	*d*	37
3	**8**	A	3:1	*d*	59
4	**9**	A	*d*	29	76
5	**6**	B	>9:1	76	45

[a] Conditions: (A) 1 mol % OsO_4, 5 mol % $(DHQD)_2$−PHAL, 3 equiv of NMO, 5:1 acetone/H_2O, rt; (B) (i) AD-Mix β, 1 mol % OsO_4, 5 mol % $(DHQD)_2$−PHAL, 2 equiv of $CH_3SO_2NH_2$, 2 equiv of $K_2S_2O_8$, 1:1 ^{t}BuOH/H_2O, 0 °C to rt, 4 days; (ii) 1 mol % OsO_4, 5 mol % $(DHQD)_2$−PHAL, 2 equiv of NMO, 5:1 acetone/H_2O, rt. [b] Estimated by integration of crude ^{13}C NMR spectrum with pulse delay 10 s. [c] Measured by NMR analysis of the Mosher's ester derivative of compound **11**. [d] Not determined.

diastereoselectivity (entries 2 and 3). This was surprising, since the C7-hydroxyl group was expected to lie in the "north eastern" quadrant of the Sharpless mnemonic, generally regarded as a "sterically neutral" region.[16]

While these results with the monophasic system were highly encouraging in terms of yield and diastereoselectivity, the eventual determination of the enantioselectivity (vide infra) afforded disappointing results: dihydroxylation of **6** had proceeded in only 24% ee (Table 1, entry 1). In work with the conventional AD-mix BuOH/H_2O system, Corey had reported that enhanced enantioselectivity could be obtained in the AD of allylic alcohols by converting them first to their *para*-methoxybenzoate esters.[19] However, no such improvement was observed using **9** with the NMO acetone/H_2O procedure (entry 4).

It seemed likely that the low enantioselectivities in the monophasic NMO system were due to the intervention of the trisoxo osmium (VIII) glycolate in Sharpless' "second catalytic cycle". We therefore decided to adopt a new procedure in which the exhaustive dihydroxylation of **6** was performed in two steps. In the first, **6** was subjected to dihydroxylation with Super AD-Mix (commercial AD-Mix supplemented with ligand (5 mol %) and osmium tetroxide (1 mol %)). The resulting mixture of regioisomeric triols (78% yield) was then converted to the pentaols **10** (58% yield) on exposure to 1 mol % OsO_4, 5 mol % $(DHQD)_2$−PHAL and 2 equiv. NMO in acetone/water. The product was obtained with good diastereoselectivity (>9:1) and with much improved enantioselectivity (76% ee) (Table 1, entry 5). This procedure allowed us access to multigram quantities of the key intermediate **10**, possessing the correct natural product stereochemistry at C3−C6. However, the overall procedure required a total reaction time of several days. In attempting to speed up the first dihydroxylation step, we found that

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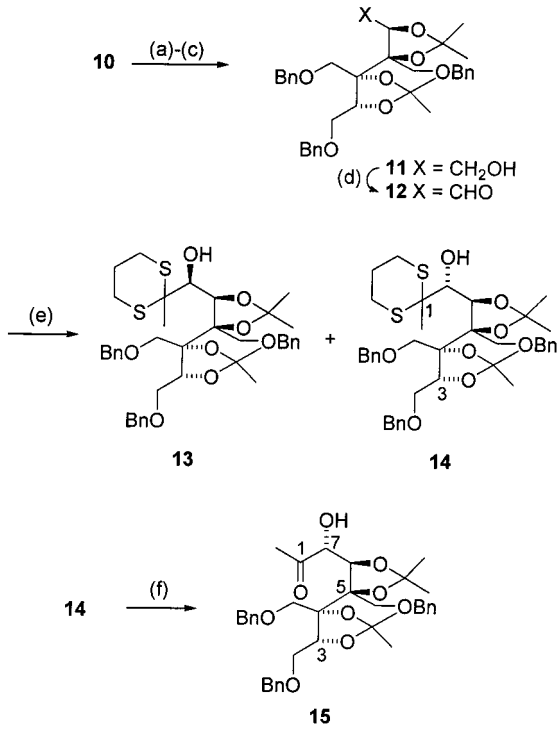
replacing the $K_2S_2O_8$ with the more soluble sodium salt, in conjunction with higher loadings of osmium and ligand, resulted in greatly improved rates (complete consumption of starting material in 18 h rather than 4 days), although at the expense of a slight decrease in enantioselectivity (68% ee).

Since the first dihydroxylation step introduces asymmetry, the question arises as to why we needed chiral ligand in the second one. In practical terms, this is because we found that reaction rates were greater using the $(DHQD)_2$−PHAL ligands than with achiral quinuclidine. An additional intriguing possibility was that if the second dihydroxylation were performed using a chiral reagent, the enantioselectivity of the final product might be improved relative to that of the intermediate triols, since the minor enantiomer from the first dihydroxylation could be converted to the minor diastereomer of **10**. We tested this possibility by dividing a sample of the intermediate triols from the first dihydroxylation step into two portions, submitting one to the second, monophasic dihydroxylation in the presence of $(DHQD)_2$−PHAL ligand, and one in the presence of quinuclidine. The pentaols from the two reactions had equal enantiomeric excesses, suggesting that the species responsible for the second dihydroxylation was likely to be achiral, such as the trisoxo osmium (VIII) glycolate suggested by Sharpless.

While our work was underway, the Nicolaou group reported their results on the dihydroxylation of a range of similar 1,3-dienes en route to the first total synthesis of zaragozic acid A.[5] Our overall process compares well to the Nicolaou work, which provided material of 78% ee but in low yield (20%; 40% based on recovered starting material). Nicolaou went on to perform a second achiral dihydroxylation later in the synthesis. As will be seen, a major advantage of carrying out the two dihydroxylations consecutively, as we have done, is the resulting reduction in the number of synthetic steps due to the possibility of carrying out subsequent manipulations of protection group and oxidation state at several sites simultaneously.

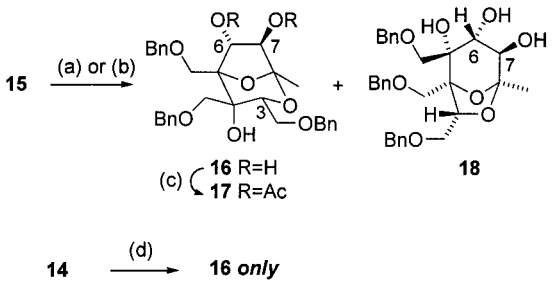
With pentaol **10** in hand, differential protection of the hydroxyl groups was accomplished by a sequence of selective primary pivalate esterification, bis-acetonide formation and reductive removal of the pivalate ester (Scheme 3). The minor diastereomer from the dihydroxylation could be removed from the resulting alcohol **11** by column chromatography, and the enantiomeric excess determined at this stage by formation of the Mosher's ester derivative. Clearly, for an eventual total synthesis, we desired enantiomerically pure **11**. We discovered that two successive recrystallizations of **11** from cold methanol provided racemic crystals but an enantiomerically enriched mother liquor with 96% ee (61% recovery of the desired enantiomer). At this point, however, the stereochemical assignment to our dihydroxylation products rested solely on the Sharpless mnemonic device. Using material of ca. 76% ee, we decided to proceed to bicyclic ketal derivatives in order to facilitate stereochemical assignments. Oxidation to the aldehyde **12** was accomplished under Swern conditions, although care was required in order to avoid α-epimerization: it was necessary, 1 h after addition of triethylamine at −78 °C, to quench the reaction with saturated aqueous NH_4Cl at that temperature before allowing the reaction to warm to room temperature. We now needed to add an acyl anion equivalent to the C7-aldehyde **12**. To give the correct stereochemistry at C7, we required this reaction to proceed with chelation control by the α-oxygen of the acetonide ring. However, we were aware of the possibility of alternative modes of attack which may lead to the wrong C7-epimer. We selected 2-lithio-2-methyl-1,3-dithiane as a simple acyl anion model for the C1-side chain, and in the event this reacted with **12** to afford the diastereomeric alcohols **13** and **14** in essentially quantitative yield, but as a readily separable 1:1.2 mixture. Attempts to improve this ratio by adding chelating metal salts ($MgBr_2$ or $ZnCl_2$) were not successful, however. Removal of the 1,3-dithiane protecting group from the correct diastereomer **14** provided the ketone **15**, setting the scene for the key acid ketalization event. We were aware that, depending on which two of the three hydroxyls at C3, C4 and C5 underwent cyclization, there were three possible isomeric ketals, two of which are shown in Scheme 4. The third possibility, a dioxabicyclo-[2.2.0]heptane system, was considered to be the least thermodynamically favorable alternative due to inherent ring strain. At this time, there was no precedent to suggest which of the isomer(s) would be formed, but we hoped that the natural system would be thermodynamically preferred. We found that heating **15** with 2% HCl in methanol did indeed effect cyclization, providing a mixture of two isomeric ketals **16** (45%) and **18** (47%). Subsequently, we discovered that the same two compounds were obtained using TFA/CH_2Cl_2/H_2O (38% **16**, 38% **18**). The structure and stereochemistry of ketal **16** was assigned by extensive ^{1}H NMR studies on **16** itself and on the derived bisacetate **17**. The observed *J* H6−H7 value of 2.8 Hz is characteristic of the desired ring

Scheme 3[a]



[a] Reagents and conditions: (a) PivCl, pyridine, CH_2Cl_2, 5 mol % DMAP, 22 h, 77%; (b) 2-methoxypropene, cat. *p*-TsOH, DMF, rt, 17 h, 77%; (c) DIBAL-H, CH_2Cl_2, −78 °C, 91%; (d) (i) $(COCl)_2$/DMSO, CH_2Cl_2, −78 °C; (ii) Et_3N, −78 °C, 1 h, 75%; (e) 2-lithio-2-methyl-1,3-dithiane, THF, −78 °C, 20 min, 97%; 53% of **14** after flash chromatography; (f) $Hg(ClO_4)_2$, $CaCO_3$, 5:1 THF/H_2O, 30 min, 92%.

Scheme 4[a]



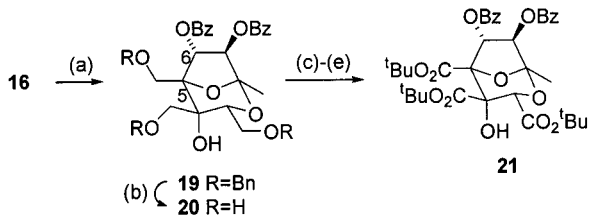
[a] Reagents and conditions: (a) 2% HCl, MeOH, rt, 10.5 h, then 50 °C, 5 h, 45% of **16** and 47% of **18**; (b) 20:10:1 CH_2Cl_2/TFA/H_2O, rt, 16 h, 38% of **16** and 38% of **18**; (c) Ac_2O, pyridine, CH_2Cl_2, 1.5 d (73%); (d) 20:10:1 CH_2Cl_2/TFA/H_2O, rt, 16 h, 78%.

system and of the correct 6*R*, 7*R* relative stereochemistry. Important cross-peaks in the NOESY spectrum of **17** were observed between the C1-methyl group and H7, and between H6 and H3. This last interaction was confirmed in a nOe difference spectrum (14% enhancement of H3 upon irradiation of H6), providing strong evidence for the stereochemistry assigned and thus for the sense of diastereoselectivity of the dihydroxylation process.

While we were encouraged that our dihydroxylations appeared to have provided the correct relative stereochemistry, and that the correct ketal isomer could be secured, we were intrigued by the formation of two ketal isomers, and speculated on how the reaction might be coerced into providing exclusively the desired ketal. Over the past few years, this question of the formation of these isomeric ketals has been the subject of much study, and several factors have been implicated.[20] Depending on the substrate, the ketalization can proceed under kinetic or thermodynamic control. In our own case, we believed that we were observing the kinetic product ratio, since we found that re-submitting the separate ketal isomers to the reaction conditions did not result in their interconversion over a 16 h time period (the length of time taken for the ketalization reaction to reach completion). We speculated that the relative rates of hydrolysis of the two acetonides present in **15** might have an effect on the ketal ratio. Conceivably, if the C3−C4 acetonide was removed first, then formation of a six-membered ring through closure of the C4 hydroxyl onto the C1 carbonyl might lead eventually to **18**. Conversely, initial hydrolysis of the C5−C6 acetonide might be followed by rapid cyclization of the C5 hydroxyl group onto the C1 carbonyl, leading to a five-membered ring which may then remain closed until hydrolysis of the second acetonide and subsequent closure of the second ring occurred. To test our hypothesis, we sought to remove this additional complication. We would therefore require deprotection of both acetonides before unmasking the C1 carbonyl carbon. This was attempted by treatment of the dithiane **14** with TFA/H_2O. To our delight, this reaction effected not only acetonide hydrolysis, but also dithiane removal and cyclization, giving the desired ketal **16** as the only observed isomer in 78% yield. Although dithianes are generally resistant to acid hydrolysis, in this system intramolecular attack of the C5 hydroxyl group onto the presumed thionium ion intermediate would facilitate its removal.

(20) Dominey, A. P.; Goodman, J. M. *Organic Lett.* **1999**, *1*, 473, and references therein.

Scheme 5[a]



[a] Reagents and conditions: (a) BzCl, DMAP, pyridine, 50 °C, 100%; (b) H_2, 10% Pd−C (cat.), 68%; (c) 3.5 equiv of $(COCl)_2$, 7.0 equiv of DMSO, CH_2Cl_2, −78 °C, then 10.5 equiv of NEt_3; (d) $NaClO_2$, 5:1.2 ^{t}BuOH/β-isoamylene, KH_2PO_4, 10 °C; (e) *N*,*N*′-diisopropyl-O-*tert*-butylisourea, CH_2Cl_2, rt, 24 h, 45% from **20**.

After these model ketalization studies, Hashimoto also suggested that formation of a mixture of ketal isomers could be attributed to differential rates of protecting group hydrolysis.[9] Whatever the true mechanistic explanation, this modification represents a substantial improvement on the original synthesis of the model core because formation of the undesired ketal isomer **18** has been eliminated. Additionally, since mercury(II)-mediated deprotection of the dithiane moiety is no longer required, the synthesis of the core is shortened by one step.

The remaining major challenge in our synthetic approach to the zaragozic acids was the oxidation to the tricarboxylic acid level. We hoped from the outset that this transformation could be performed simultaneously at all three sites. Encouraging observations by Carreira[7] had previously shown that a trialdehyde, obtained by simultaneous oxidations at the C3 and C5 methanols and ozonolysis of an exocyclic alkene at C4, could be converted to the triacid using sodium chlorite. We therefore proceeded to perform initial investigations on our model bicyclic ring system **16** (Scheme 5). Benzoate protection was selected for the C6 and C7 hydroxyl groups since preliminary studies showed that C6-acetates were prone to migration onto the C5-hydroxymethyl. Benzyl ether deprotection provided cleanly the tetraol **20** (Scheme 5). Oxidation of tetraol **20** suffered the risk that initial oxidation at one of the three primary alcohols would lead to lactol/lactone formation and hence incomplete oxidation. Indeed, attempted oxidation of **20** to the triacid using Jones reagent or potassium perruthenate,[21] followed by treatment of the crude reaction product with N,N′-diisopropyl-O-*tert*-butylisourea, gave a complex mixture of products, none of which was the desired triester. We reasoned that success was more likely if we employed an activated DMSO oxidation system,[22] where the product aldehyde is not liberated until the addition of base at the end of the reaction. Indeed, Ley and co-workers had previously reported use of this strategy to overcome problems of lactol/lactone formation during oxidation of a 1,4-diol intermediate in their synthesis of the antifeedant polygodial.[23] Although treatment of the tetraol **20** with 3.5 equiv of the Swern reagent provided a mixture of compounds by TLC analysis, presumably due to facile hydrate formation, we were pleased to find that the crude

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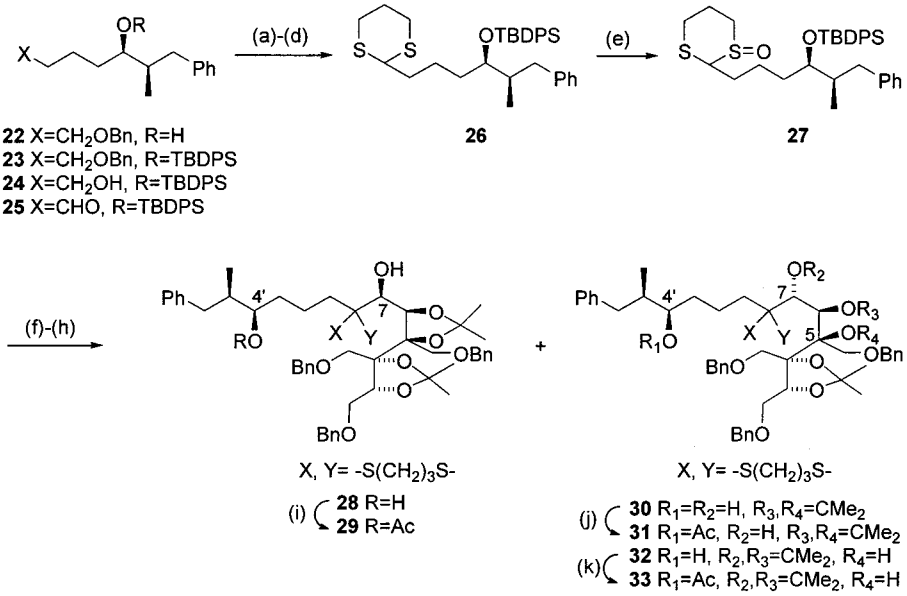
(22) Tidwell, T. T. *Org. React.* **1990**, *39*, 297.
(23) Hollinshead, D. M.; Howell, S. C.; Ley, S. V.; Mahon, M.; Ratcliffe, N. M.; Worthington, P. A. *J. Chem. Soc.; Perkin Trans. 1* **1983**, 1579.

Scheme 6[a]



[a] Reagents and conditions: (a) TBDPSCl, imidazole, DMF, 100 °C, 24 h, 93%; (b) BCl_3·SMe_2, CH_2Cl_2, rt, 1 h, 94%; (c) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C then NEt_3, 0 °C, 97%; (d) $HS(CH_2)_3SH$, BF_3·OEt_2, CH_2Cl_2, rt, 1 h, 92%; (e) mCPBA, CH_2Cl_2, 0 °C, 78%, trans/cis 5:1; (f) 3 equiv of **27**, 3.1 equiv of ^{n}BuLi, THF, −78 °C, 15 min then 1 equiv of **12**, −78 °C, 15 min.; (g) 0.55 equiv of P_2I_4, 1 equiv of NEt_3, CH_2Cl_2, rt, dark, 15 min, 59% from **12**; (h) TBAF, THF, 80 °C, 36% **28** and 32% **30**; (i) Ac_2O, DMAP (cat.), pyridine, 80 °C, 12 h, 85%; (j) Ac_2O, DMAP (cat.), pyridine, 60 °C, 3 h, 85%; (k) Ac_2O, DMAP (cat.), pyridine, 80 °C, 26 h, 86%.

^{1}H NMR spectrum showed three aldehydic protons. Pinnick (sodium chlorite) oxidation[24] of the crude trialdehyde followed by *tert*-butyl esterification provided the triester **21** in pleasing overall yield (45% over three steps, Scheme 5). Interestingly, use of larger excesses of the Swern reagent (9 eq.) led to facile formation of a methylthiomethyl (MTM) ether on the C4 tertiary hydroxyl, which could not be removed following treatment with mercury(II) chloride. However, demonstration of the successful triple oxidation allowed a highly concise synthesis of the fully functionalized natural product core and is likely to be of interest to other workers in the field as it could be utilized in the progression of other reported model syntheses.

Having optimized the acid-catalyzed ketalization reaction and shown that the triple oxidation to the triacid was a viable approach, we were now ready to focus on the total synthesis of zaragozic acid C. This aim required synthesis of the 1,3-dithiane **26** corresponding to the full C1-side chain. Synthesis of **26** began with the alcohol **22**, prepared according to the route described by Carreira,[7] employing Evans aldol methodology to control relative and absolute stereochemistry. Silyl ether protection of **22** provided **23** in 93% yield (Scheme 6). Debenzylation using BCl_3·SMe_2 in CH_2Cl_2[25] followed by Swern oxidation of the resulting alcohol **24** provided aldehyde **25**. Protection with 1,3-propanedithiol in the presence of catalytic BF_3·OEt_2 furnished the fully functionalized C1 side chain dithiane **26**.

With the dithiane **26** now in hand, we proceeded to investigate its coupling with the core aldehyde **12**. However, despite examining a range of bases, reaction times, temperatures and additives, we were unable to effect clean metalation of **26**. Difficulties in metalating 1,3-dithianes which have oxygenation in the δ-position have been noted previously,[26] but have been circumvented by use of, for example, sodium bases.[26b] In our case, these modifications did not prove successful. These difficulties are surprising since Nicolaou had already reported the successful metalation of a structurally similar dithiane using ^{n}BuLi.[5] We briefly explored the use of alternative acyl anion equivalents derived from aldehyde **25** (e.g., the triethylsilyl cyanohydrin[27]), to no avail. We considered that the problems in deprotonating **26** could be solved by conversion to the more acidic monosulfoxide, a strategy that had previously proved successful for Soll and Seitz.[28] Treatment of dithiane **26** with mCPBA at 0 °C provided the monosulfoxide **27** as a mixture of four possible diastereomers that appeared as two major separable spots by TLC (more polar, 63%; less polar, 15%). Based on literature precedent by Carey,[29] we assigned the major fraction as being a mixture of two diastereomers having the trans-relationship between the alkyl chain and the sulfoxide oxygen, with the minor fraction being the cis-isomers. Carey has shown that peracid oxidation of simpler monosubstituted 1,3-dithianes indeed gives predominantly the trans-isomer. Additionally, Carey observed that the trans-compounds all exhibited a one-proton multiplet centered between 3.2 and

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3.5 ppm in the ^{1}H NMR, assigned to the C6 equatorial proton in the ring (dithiane numbering), and that the corresponding signal appeared at higher field in the cis-series. For the two compounds in the major fraction of **27**, we observed a one-proton multiplet at 3.40−3.35 ppm in the ^{1}H NMR spectrum, which is therefore indicative of the trans-isomers. The corresponding multiplet is shifted upfield (masked by other dithiane ring protons) in the minor fraction of **27**, which is accordingly assigned the cis-stereochemistry.

With **27** in hand, we were pleased to find that it indeed underwent clean metalation and subsequent reaction with simple electrophiles. Continuing with the total synthesis, the major, trans-monosulfoxide **27** was treated with ^{n}BuLi at −78 °C for 15 min, followed by addition of the core aldehyde **12** to the resulting anion. TLC analysis of the addition reaction mixture showed complete consumption of the starting aldehyde **12** after 15 min, and column chromatography allowed separation of unreacted side chain. Deoxygenation of the mixture of adducts to regenerate the 1,3-dithiane moiety was accomplished[28,30] using P_2I_4, crucially in the presence of NEt_3, providing an inseparable mixture of C7-epimers in a ratio of 1:1 by NMR, and in 59% overall yield from the aldehyde **12** (Scheme 6). It was decided at this stage to remove the C4′ TBDPS ether, since it was likely that the TBDPS group would not withstand the subsequent acidic ketalization conditions.[5] The resulting diols **28** (less polar isomer) and **30** were readily separable by column chromatography and were isolated in 36% and 32% yield, respectively. At this stage, the assignment of C7-stereochemistry was based on similarities in the ^{1}H NMR spectra of each isomer with the corresponding model compounds previously synthesized (**13** and **14**). In particular, the shift, multiplicity and coupling constants associated with H7 for the pairs of C7 epimers seemed to concur. These stereochemical assignments were confirmed by eventual conversion of **30** to the natural product.

To improve the stereoselectivity of the coupling reaction we wondered if the use of a single monosulfoxide diastereomer might make a difference. In speculative studies, we endeavored to synthesize the monosulfoxide side chain in diastereomerically enriched form by asymmetric oxidation of **26** under Kagan conditions.[31] Thus, dithiane **26** was treated with $Ti(O^iPr)_4$ and ^{t}BuOOH in the presence of (+)-diethyl tartrate ((+)-DET) and 1 molar equivalent of water at −30 °C. These conditions provided only the trans-monosulfoxide **27** in 41% yield after 3 days. Although we did not determine the diastereomeric purity of the sulfoxide at this stage, we found that coupling with the core aldehyde **12** again led through to a ca. 1:1 mixture of the C7 epimers **28** and **30**. The process was repeated with (−)-DET as the chiral ligand in the oxidation step, but the sequence again led to a 1:1 mixture of adducts.

Since we were not able to effect a diastereoselective addition of the side chain to the core aldehyde using this method, we hoped that it may be possible to recycle the undesired C7-epimer. Thus, selective acetylation of the C4′-hydroxyl group of **28** provided **29** and similarly, the desired epimer **30** afforded **31**. However, hindered alcohol **29** proved to be unreactive to Mitsunobu inversion (DIAD, PPh_3, nitrobenzoic acid, THF). In an alternative approach, **29** could be oxidized to the corresponding ketone (Dess−Martin periodinane, 62%), but reduction using $NaBH_4$/EtOH or $Zn(BH_4)_2$ both returned the undesired C7-epimer **29**. Attempted reduction using L-Selectride (lithium tri-*sec*-butylborohydride) resulted in no reaction.

When the process of C1-side chain addition to the core aldehyde **12** was repeated on a smaller scale (0.22 mmol aldehyde) we obtained a rather surprising result. Addition of the metalated monosulfoxide **27** to **12** proceeded smoothly as before, to give a mixture of inseparable diastereomers. Reduction of the sulfoxide moiety to the 1,3-dithiane gave, by TLC, two compounds that corresponded to the expected adducts. However, when the mixture was treated with TBAF to deprotect the C4′-hydroxyl, the less polar 'incorrect" C7 epimer **28** was obtained, but none of the desired diastereomer **30** could be detected. Instead, a new compound, more polar than **30**, was isolated. Spectroscopic analysis suggested that this new material was isomeric with **30**, but further elucidation of the structure proved difficult owing to the complexity of the ^{1}H NMR spectrum. Following acetylation of the C4′ hydroxyl, we were able to tentatively assign this new material the structure **33** resulting from acetonide migration from the C5−C6 to the C6−C7 position. The ^{1}H NMR spectra of **33** and **31** were very similar, except for an apparent shift in H7 from 4.78 ppm for **31** to 5.09 ppm for **33**. This observation could be a result of H7 being part of a five-membered isopropylidene ring in **33** and therefore experiencing a downfield shift. We were unable to ascertain at what stage in the smaller scale synthesis the acetonide migration had occurred, or indeed why it had transpired. We can only speculate that an acid-catalyzed rearrangement may have taken place (possibly during the deoxygenation step due to the incomplete quenching of phosphorus oxyacids) to form the more thermodynamically stable trans-C6−C7 acetonide **32**.[32] Since our successful model synthesis relied upon deprotection of both acetonides before ketalization, we hoped that conversion of either **31** or **33** to the bicyclic core should be possible. We were pleased to find that treatment of either **31** or **33** with TFA/H_2O indeed furnished the same ketal **34** in excellent yield (Scheme 7), thus supporting our original postulate that only acetonide migration had taken place. Therefore, from a synthetic viewpoint, this was not considered to be a problem.

The scene was now set for the final major challenge in the synthesis: oxidation to the tricarboxylic acid level. Following the protocol already established with the model system, benzoate protection and subsequent removal of the benzyl ethers provided **36** (Scheme 7). We were pleased to find that treatment of **36** with 3.5 equiv of the Swern reagent followed by Pinnick oxidation and *tert*-butyl esterification provided the triester **37** in good yield over three steps (33%). Pleasingly, selective deprotection of the C6- and C7-benzoates proceeded remarkably smoothly using 0.2% K_2CO_3 in MeOH. Synthesis of **38** completes a formal synthesis of (+)-zaragozic acid C by intersecting a late intermediate in the Carreira synthesis.[7] All that was required now was to follow the Carreira precedent in order to complete the total synthesis of

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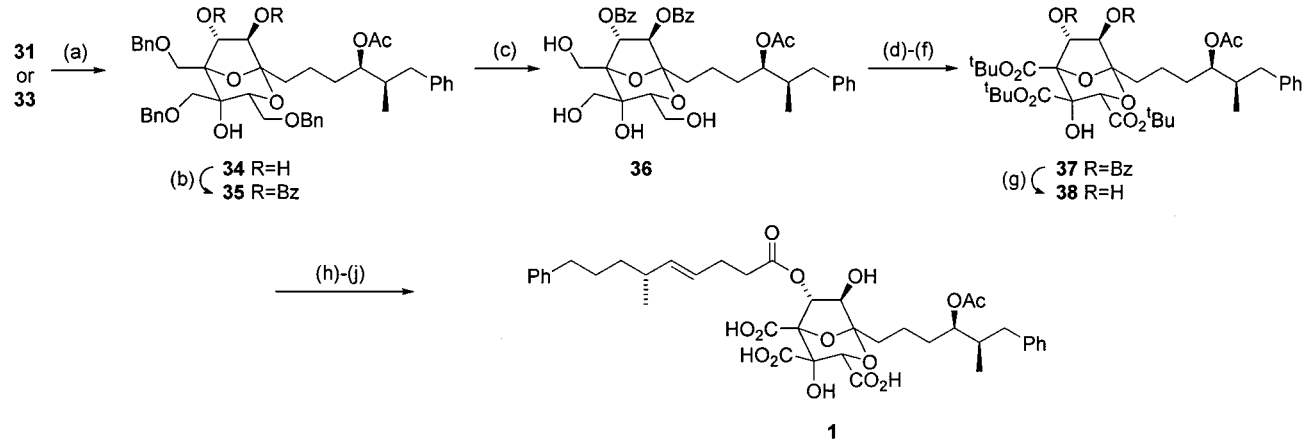
Scheme 7[a]



[a] Reagents and conditions: (a) 20:10:1 CH_2Cl_2/TFA/H_2O, 30 min, 90%; (b) BzCl, DMAP (cat.), pyridine, rt, 24 h, 97%; (c) H_2, 10% Pd/C (cat.), 89%; (d) 3.5 equiv of $(COCl)_2$, 7 equiv of DMSO, CH_2Cl_2, −78 °C then 10.5 equiv of NEt_3; (e) $NaClO_2$, pH 3.5 aqueous phosphate buffer, 5:1.2 ^{t}BuOH/β-isoamylene; (f) *N,N′*-diisopropyl-*O*-*tert*-butylisourea, CH_2Cl_2, 23 h, 33% (three steps); (g) 0.2% K_2CO_3 in MeOH, 30 min, 75%; (h) $(Boc)_2O$, Et_3N, CH_2Cl_2, 4-pyrrolidinopyridine (cat.), 70%; (i) DCC, DMAP (cat.), CH_2Cl_2, 87%; (j) 25% TFA, CH_2Cl_2, 100%.

zaragozic acid C. Thus, selective Boc-protection of the C7 hydroxyl group, introduction of the C6-acyl side chain,[33] and final simultaneous hydrolysis of the Boc-group and the *tert*-butyl esters afforded (+)-zaragozic acid C (**1**), $[\alpha]^{24}_D$ +9.6 (*c* 1.0, EtOH) (lit.[34] +9.6 (*c* 0.3, EtOH)), HRMS (FAB) M+Na 777.3166 ($C_{40}H_{50}O_{14}Na$ requires 777.3098), identical to an authentic sample of the natural product by ^{1}H NMR, ^{13}C NMR, IR and TLC. The successful completion of this total synthesis served to confirm the stereochemical assignment of the double Sharpless AD process and the dithiane addition steps.

Conclusions

We have achieved a relatively concise, stereoselective synthesis of the natural product (+)-zaragozic acid C (**1**). A key feature of the synthesis was the use of a double Sharpless asymmetric dihydroxylation reaction to control stereochemistry at four contiguous stereocenters from C3 to C6, further exemplifying the power of the Sharpless AD reaction in synthesis. Other notable features include the introduction of the C1-side chain using a dithiane monosulfoxide anion mediated coupling reaction between **27** and the core aldehyde **12**; a high yielding, acid-mediated simultaneous acetonide deprotection−dithiane removal−ketalization procedure leading exclusively to the 2,8-dioxabicyclo[3.2.1]octane core **34**; and a novel triple oxidation procedure allowing installation of the tricarboxylic acid. This strategy is likely to be of value in the advancement of several of the model syntheses reported by other groups. Our approach should be sufficiently flexible to allow extension to other members of the natural product family, investigation of which is currently underway.

Experimental Section

General Procedures. Diethyl ether and tetrahydrofuran solvents were distilled from sodium-benzophenone ketyl; toluene from sodium; dichloromethane and *N*-methylpyrrolidinone from calcium hydride; and dimethylformamide from calcium hydride or from anhydrous magnesium sulfate. Petrol refers to petroleum ether bp 40−60 °C which was distilled prior to use. Other solvents and reagents were purified by standard procedures as necessary.[35] Flash chromatography was performed on Merck Kieselgel 60 (230−400 mesh) unless otherwise stated. Analytical thin-layer chromatography was performed using precoated glass-backed plates (Merck Kieselgel 60 F_{254}). Chemical shifts for ^{1}H and ^{13}C NMR are expressed in ppm relative to internal C*H*Cl_3, (7.26 ppm) or *C*DCl_3 (77.0 ppm, t). *J* values are measured in Hertz. Multiplicities in ^{13}C spectra were determined by DEPT experiments and are expressed as q (CH_3), t (CH_2), d (CH), and s (C). IR spectra were recorded as thin films on NaCl plates unless otherwise stated.

(*Z*)-Ethyl 4-(benzyloxy)-3-iodo-2-butenoate (3). To a stirred solution of **2**[36] (9.22 g, 42.30 mmol) in glacial acetic acid (40 mL) was added LiI (6.23 g, 46.53 mmol). The reaction was heated at 70 °C for 1.5h and then allowed to cool to room temperature. The mixture was evaporated in vacuo (azeotroping with toluene) and the residue was taken up in Et_2O and filtered to remove the inorganics. Additional Et_2O was added and washed with saturated aqueous $NaHCO_3$ (×5). The aqueous layers were combined and back extracted with Et_2O (×3), and the ethereal layers combined and washed with saturated aqueous sodium thiosulfate (×3), then water (×2) and saturated aqueous brine (×3). The organics were dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (10% Et_2O/petrol) to give iodide **3** (14.67 g, 95%) as a pale yellow liquid: IR (film) 1726, 1632, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 7.30−7.16 (m, 5H), 6.73 (t, 1H, *J* 1.8), 4.48 (s, 2H), 4.16 (d, 2H, *J* 2.1), 4.15 (q, 2H, *J* 7.0), 1.22 (t, 3H, *J* 7.0); ^{13}C NMR (100 MHz, $CDCl_3$) 164.3, 137.0, 128.4, 127.9, 127.6, 123.7, 115.8, 78.9, 72.4, 60.6, 14.1; *m*/*z* (EI) 346 (M^+). Found: C, 45.5; H, 4.6. $C_{13}H_{15}IO_3$ requires C, 45.1; H, 4.4.

(2*Z*,4*E*)-Ethyl 6-benzyloxy-(3,4-*bis*-(benzyloxymethyl))-2,4-hexadienoate (5). (a) Pd Catalysis. Vinyl iodide **3** (16.50 g, 47.69 mmol) was dissolved in dry DMF (170 mL). The solution was degassed by ultrasonication under argon flow before the addition of P(2-furyl)$_3$ (332 mg, 1.91 mmol) and Pd_2(dba)$_3$ (665 mg, 0.95 mmol). The solution was stirred under argon for 25 min before the addition of the vinyl stannane **4** (31.93 g, 57.22 mmol) neat via cannula, rinsing in with DMF (10 mL). The mixture was heated at 65 °C for 20h and then allowed to cool to room temperature. The mixture was then

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poured into a separating funnel containing saturated aqueous NH_4Cl (150 mL) and Et_2O (200 mL). The ethereal layer was separated and the aqueous layer extracted with Et_2O (4 × 150 mL). The organics were combined and washed with saturated aqueous sodium thiosulfate (2 × 100 mL), H_2O (1 × 100 mL) and saturated brine (3 × 100 mL), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (15% EtOAc/petrol) to give the dienoate **5** (19.93 g, 86%) as a pale yellow oil: IR 1716, 1636 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 7.25−7.17 (m, 15H), 6.00 (d, 1H, *J* 1.8), 5.56 (t, 1H, *J* 6.4), 4.48 (s, 2H), 4.43 (s, 2H), 4.37 (s, 2H), 4.15 (s, 2H), 4.10−3.99 (m, 6H, m), 1.16 (t, 3H, *J* 7.0); ^{13}C NMR (100 MHz, $CDCl_3$) 165.8 (s), 156.6 (s), 138.1 (s), 137.8 (s), 128.9 (d), 128.4 (d), 128.3 (d), 127.9 (d), 127.7 (d), 127.64 (d), 127.59 (d), 115.4 (d), 73.2 (t), 72.6 (t), 72.2 (t), 68.0 (t), 65.9 (t), 59.9 (t), 14.2 (q); *m*/*z* (CI, isobutane) 487 (M^+). Found: C, 76.4; H, 7.2. $C_{31}H_{34}O_5$ requires C, 76.5; H, 7.0.

(b) Cu-Mediated Coupling.[15] To a solution of vinyl iodide **3** (29.8 g, 0.086 mol) and stannane **4** (40 g, 0.072 mol) in NMP (280 mL) at 0 °C under N_2 was added Cu(I) thiophencarboxylate (20.28 g, 0.108 mol). The mixture was allowed to warm to room temperature and stirred for 2 h, then diluted with ether and filtered though an alumina pad, washing through with ether. The combined ether washings were washed successively with water and brine, dried (K_2CO_3) and evaporated. Column chromatoraphy on silica gel (5−20% ether-petrol) gave the product (30.39 g, 87%) as an oil; data as above.

(2*Z*,4*E*)-6-Benzyloxy-(3,4-*bis*-(benzyloxymethyl))-2,4-hexadienol (6). To a cooled (−40 °C), stirred solution of dienic ester **5** (32.44 g, 66.75 mmol) in dry CH_2Cl_2 (150 mL) was added DIBAL-H (140 mL, 1.0 M solution in CH_2Cl_2, 140 mmol) dropwise under argon over 30 min. The temperature was raised to −20 °C and maintained for 1h, then quenched at −10 °C by careful addition of dry MeOH (10 mL). The mixture was then stirred at 0 °C and then a solution of Rochelle's salt (33 mL of saturated solution in 200 mL H_2O) was cautiously added in 4 portions. The mixture was then allowed to warm to room temperature and stirred for 30 min. The organic phase was separated and the aqueous phase was acidified with 2M HCl until all the aluminum salts had dissolved, then extracted with CH_2Cl_2 (4 × 150 mL). The organics were combined, then washed with 2M HCl (2 × 100 mL), H_2O (1 × 100 mL), saturated aqueous brine (2 × 100 mL), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow oil was purified by flash chromatography (50−70% Et_2O/petrol) to give alcohol **6** (27.86 g, 94%) as a clear oil: IR 3421 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 7.35−7.24 (m, 15H), 5.90 (t, 1H, *J* 7.1), 5.64 (t, 1H, *J* 6.4), 4.48 (s, 2H), 4.45 (s, 2H), 4.43 (s, 2H,), 4.20−4.09 (m, 4H), 4.05 (s, 4H), 2.04 (t, 1H, *J* 6.4); ^{13}C NMR (100 MHz, $CDCl_3$) 140.9, 138.1, 138.0, 137.5, 136.6, 130.7, 129.1, 128.5, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 73.0, 72.8, 72.2, 71.8, 66.1, 65.6, 59.1; *m*/*z* (+FAB) 467 (M + Na), 445 (M + H). Found: C, 78.7; H, 7.4. $C_{29}H_{32}O_4$ requires C, 78.4; H, 7.3.

(2*R*,3*R*,4*R*,5*S*)-2,3,4,5-Tetrahydroxy-6-benzyloxy-(3,4-bis(benzyloxymethyl))hexan-1-ol (10). Double dihydroxylation procedure (entry 5, Table 1). A 1 L three-necked flask was charged with ^{t}BuOH (130 mL) and H_2O (160 mL). To this was added AD-mix-β (44 g) followed by $(DHQD)_2PHAL$ (1.23 g, 1.58 mmol), OsO_4 (80 mg, 0.32 mmol), $K_2S_2O_8$ (17.05 g, 63.06 mmol), and $CH_3SO_2NH_2$ (5.99 g, 63.06 mmol). This mixture was stirred well for 20 min, then cooled to 0 °C before dropwise addition of dienic alcohol **6** (14.00 g, 31.53 mmol) in ^{t}BuOH (30 mL). The reaction came to room temperature after a few hours, and stirring was continued for an additional 4 d at room temperature, after which time solid Na_2SO_3 (45 g) and EtOAc (300 mL) were added and the mixture stirred for 1 h. The organic layer was separated and the aqueous layer extracted with EtOAc (3 × 150 mL). The combined organics were washed sequentially with 2 M KOH (3 × 100 mL), H_2O (2 × 100 mL) and brine (3 × 100 mL), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (80% Et_2O/petrol) to give a mixture of the intermediate triols (11.75 g, 78%). To a stirred solution of the triols (11.75 g, 24.58 mmol) in acetone (47 mL) and H_2O (9 mL) was added $(DHQD)_2PHAL$ (957 mg, 1.23 mmol) and OsO_4 (63 mg, 0.25 mmol) followed by NMO (5.76 g, 49.16 mmol). After 3.5d solid $Na_2S_2O_5$ was added, followed by CH_2Cl_2 (100 mL). After a further 1 h, the mixture was filtered, evaporated under reduced pressure, and azeotroped with benzene. The residual black oil was purified by flash chromatography (75−100% EtOAc/petrol) to give the pentaol **10** as a >9:1 diastereomeric mixture (7.30 g, 58%) as a clear oil: $[\alpha]^{19}_D$ +4.5 (*c* 1.0 in $CHCl_3$) at ca. 76% ee; IR (film) 3423 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 7.38−7.21 (m, 15 H), 4.57−3.40 (m, 18H), 2.67 (br s, 1H), 1.27−1.07 (m, 2H); δ_C (100 MHz, $CDCl_3$) 137.6, 136.9, 136.2, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.13, 128.05, 128.0, 127.9, 78.7, 77.7, 74.1, 73.9, 73.5, 73.2, 71.5, 71.4, 70.5, 70.4, 63.2; *m*/*z* (CI, isobutane) 513 (M + H). Found: C, 67.6; H, 7.1. $C_{29}H_{36}O_8$ requires C, 68.0; H, 7.1.

(2*R*,3*R*,4*R*,5*S*)-6-Benzyloxy-(3,4-bis(benzyloxymethyl))-1-pivaloyloxymethyl-hexan-2,3,4,5-tetraol. To a cooled (0 °C) stirred solution of pentaol **10** (14.58 g, 28.48 mmol) in CH_2Cl_2 (100 mL) was added pivaloyl chloride (4.14 mL, 34.17 mmol) followed by DMAP (173 mg, 1.42 mmol) and pyridine (3.46 mL, 42.7 mmol). The reaction was then allowed to come to room temperature and stirred for 16 h, then quenched by addition of saturated aqueous NH_4Cl (50 mL). The organic layer was separated and the aqueous extracted with CH_2Cl_2 (4 × 50 mL). The organics were combined then washed with 2M HCl (3 × 50 mL), H_2O (2 × 50 mL), saturated aqueous $NaHCO_3$ (2 × 50 mL), H_2O (1 × 50 mL), saturated aqueous brine (2 × 50 mL), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (60% Et_2O/petrol) to give the pivalate ester (13.07 g, 77%) as a pale yellow oil: $[\alpha]^{19}_D$ +7.4 (*c* 1.0 in $CHCl_3$) at ca. 76% ee, IR (film) 3442, 1724 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 7.37−7.17 (m, 15H), 4.53−4.18 (m, 10H, includes 4.52 (d, 1H, *J* 11.2)), 4.50 (s, 4H), 4.40 (dd, 2H, *J* 19.3 and 6.5), 4.35 (d, 1H, *J* 8.8), 4.32 (d, 1H, *J* 11.7), 4.24 (d, 1H, *J* 11.2), 4.17 (s, 1H), 4.07 (s, 1H), 3.78 (dd, 2H, *J* 16.6 and 10.3), 3.66−3.63 (m, 3H, includes 3.64 (d, 1H, *J* 8.8)), 3.54 (br s, 1H), 3.45 (d, 1H, *J* 10.3), 1.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) 178.9 (s), 137.6 (s), 136.9 (s), 136.3 (s), 128.6 (d), 128.5 (d), 128.5 (d), 128.3 (d), 128.2 (d), 128.0 (d), 127.9 (d), 127.7 (d), 78.2 (s), 77.1 (s), 74.0 (t), 73.8 (t), 73.5 (t), 72.7 (d), 71.6 (d), 71.2 (t), 70.7 (t), 70.4 (t), 66.2 (t), 38.7 (s), 27.2 (q), 27.2 (q), 27.2 (q). Found: C, 68.5; H, 7.6. $C_{34}H_{44}O_9$ requires C, 68.4; H, 7.4.

(2*R*,3*R*,4*S*,5*S*)-2,3,4,5-Bis(di-*O*-isopropylidene)-6-benzyloxy-(3,4-bis(benzyloxymethyl))-1-(pivaloyloxymethyl-)hexane. To a stirred solution of the above tetraol (13.00 g, 21.81 mmol) in DMF (125 mL) containing *p*-TsOH (400 mg, catalytic amount) was added dropwise 2-methoxypropene (7.84 mL, 87.25 mmol). After 13h the reaction was quenched by addition of saturated aqueous $NaHCO_3$ (100 mL), then extracted with Et_2O (4 × 100 mL). The organics were combined and washed with saturated aqueous $NaHCO_3$ (1 × 100 mL), H_2O (1 × 100 mL), saturated aqueous brine (2 × 100 mL), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residue was purified by flash chromatography (30% Et_2O/petrol) to give the bis-acetonide (13.07 g, 77%) as a pale orange oil: $[\alpha]^{18}_D$ −5.1 (*c* 1.0 in $CHCl_3$) at ca. 76% ee; IR (film) 1730 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 7.40−7.20 (m, 15H), 4.72−4.34 (m, 10H), 3.86−3.68 (m, 4H), 3.62 (d, 1H, *J* 10.8), 3.54 (d, 1H, *J* 10.8), 1.42 (s, 3H), 1.35 (s, 6H), 1.32 (s, 3H), 1.21 (s, 9H); *m*/*z* (+FAB) 677 (M + H). Found: C, 71.0; H, 7.8.$C_{40}H_{52}O_9$ requires C, 71.0; H, 7.7.

(2*R*,3*R*,4*S*,5*S*)-2,3,4,5-Bis(di-*O*-isopropylidene)-6-benzyloxy-(3,4-bis(benzyloxymethyl))hexan-1-ol (11). To a cooled (−78 °C), stirred solution of pivaloate ester (10.68 g, 15.79 mmol) in dry CH_2Cl_2 (85 mL) was added DIBAL-H (39.5 mL, 1.0 M solution in CH_2Cl_2, 39.5 mmol) dropwise under argon over 20 min. After 45 min the reaction was quenched by careful addition of dry MeOH (5 mL). The mixture was allowed to warm to 0 °C and stirred at this temperature for 10 min before careful addition of a solution of Rochelle's salt (33 mL of a saturated solution in 200 mL H_2O) in 3 portions. The mixture was then allowed to warm to room temperature

and stirred for 30 min. The organic phase was separated and the aqueous phase was acidified with 2 M HCl until all the aluminum salts had dissolved, then extracted with CH_2Cl_2 (4 × 100 mL). The organics were combined, then washed with 2M HCl (1 × 100 mL), H_2O (1 × 100 mL), brine (2 × 100 mL), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow oil was purified by flash chromatography (50% Et_2O/petrol) to give the title compound **11** (8.51 g, 91%) as a clear oil: $[\alpha]^{18}_D$ −9.1 (*c* 1.0 in $CHCl_3$) at ca. 76% ee; IR (film) 3491 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 7.37−7.20 (m, 15H), 4.68 (dd, 1H, *J* 8.0 and 2.6), 4.61 (d, 1H, *J* 12.3), 4.58−4.47 (m, 5H, includes 4.50 (d, 1H, *J* 12.6)), 4.39 (d, 1H, *J* 11.9), 4.03−3.96 (m, 1H), 3.92−3.84 (m, 1H), 3.83−3.72 (m. 5H, includes 3.81 (d, 1H, *J* 19.6) and 3.75 (d, 1H, *J* 19.6)), 3.50 (d, 1H, *J* 11.0), 2.55 (dd, 1H, *J* 7.7 and 6.0), 1.46 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 138.2 (s), 137.8 (s), 137.6 (s), 128.4 (d), 128.3 (d), 128.3 (d), 127.8 (d), 127.6 (d), 127.5 (d), 110.5 (s), 108.7 (s), 86.2 (s), 85.0 (s), 81.0 (d), 79.9 (d), 73.9 (t), 73.6 (t), 73.2 (t), 71.6 (t), 70.6 (t), 69.4 (t), 60.7 (t), 27.9 (q), 27.1 (q), 26.1 (q), 25.9 (q); HRMS (FAB) M + Na, 615.2936. $C_{35}H_{44}NaO_8$ requires M + Na, 615.2934.

(2*R*,3*R*,4*S*,5*S*)-2,3,4,5-Bis(di-*O*-isopropylidene)-6-benzyloxy-(3,4-bis(benzyloxymethyl))hexan-1-al (12). To a cooled (−78 °C), stirred solution of oxalyl chloride (67 μL, 0.76 mmol in dry CH_2Cl_2 (1.7 mL) was added a solution of anhydrous DMSO (107 μL, 1.52 mmol) in CH_2Cl_2 (1.5 mL) dropwise via cannula over 4 min. After 14 min a solution of alcohol **11** (300 mg, 0.51 mmol) in CH_2Cl_2 (1.4 mL) was added dropwise over 5 min and stirred at −78 °C for 25 min. Then Et_3N (354 μL, 2.53 mmol) was added over 4 min. After 1h, the reaction was quenched at −78 °C by addition of saturated aqueous NH_4Cl (0.8 mL) and the mixture was then allowed to warm to room temperature. The organics were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 5 mL). The organics were combined and washed with saturated aqueous NH_4Cl (2 × 5 mL), H_2O (1 × 5 mL), saturated aqueous brine (1 × 5 mL), then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow oil was purified by flash chromatography (30% Et_2O/petrol) to give the aldehyde **12** (248 mg, 83%) as a clear oil: $[\alpha]^{27}_D$ −15.1 (*c* 0.94 in $CHCl_3$) at 68% ee, IR (film) 1729 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 9.70 (s, 1H), 7.36−7.23 (m, 15H), 4.86 (s, 1H), 4.61 (d, 1H, *J* 12.3), 4.55 (d, 1H, *J* 11.9), 4.51 (d, 1H, *J* 11.9), 4.46−4.41 (m, 3H), 4.31 (d, 1H, *J* 12.1), 3.90 (d, 1H, *J* 10.5), 3.85 (d, 1H, *J* 10.5), 3.71 (dd, 1H, *J* 10.5 and 1.8), 3.60 (dd, 1H, *J* 10.5 and 8.3), 3.52 (d, 1H, *J* 9.9), 3.48 (d, 1H, *J* 9.9), 1.41 (s, 3H), 1.39 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 195.5, 138.0, 137.5, 128.4, 128.3, 127.9, 127.8, 127.8, 127.7, 127.6, 110.1, 109.9, 86.9, 85.2, 83.5, 79.5, 73.8, 73.3, 73.1, 70.6, 69.4, 68.9, 28.6, 27.0, 26.4, 26.0. Found C, 71.3; H, 7.2. $C_{35}H_{42}O_8$ requires C, 71.2; H, 7.2.

(5*R*,6*R*)-*O*-Benzyl-5-(*tert*-butyldiphenylsilyloxy)-6-methyl-7-phenylheptan-1-ol (23). To a stirred solution of alcohol **22**[7] (3.19 g, 12.5 mmol) in DMF (30 mL) under N_2 was added imidazole (3.74 g, 55 mmol) followed by TBDPSCl (7.8 mL, 30.0 mmol). The mixture was stirred at 100 °C for 24 h before dilution with Et_2O. The organics were separated and washed with aqueous 1.0 M HCl then water, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual orange oil was purified by flash chromatography (8% EtOAc/petrol) to give the silyl ether **23** (6.40 g, 93%) as a yellow oil: R_f 0.69 (20% EtOAc/petrol); $[\alpha]^{23}_D$ +8.0 (*c* 0.50, $CHCl_3$); IR ($CHCl_3$ solution) 1589 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) 7.72−7.67 (m, 4H), 7.41−7.11 (m, 14H), 7.04−7.00 (m, 2H), 4.39 (s, 2H), 3.72−3.66 (m, 1H), 3.23 (t, 2H, *J* 7.5), 2.86 (dd, 1H, *J* 13.5, 5.0), 2.41 (dd, 1H, *J* 13.5, 9.9), 1.87 (1H, m, C*H*(CH_3)), 1.52−1.27 (m, 6H), 1.09 (s, 9H), 0.78 (d, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) 141.7 (s), 136.0 (s), 136.0 (d), 134.9 (s), 134.3 (s), 129.5 (d), 129.4 (d), 129.1 (d), 128.3 (d), 128.1 (d), 127.5 (d), 127.5 (d), 127.3 (d), 125.5 (d), 76.7 (d), 72.7 (t), 70.1 (t), 39.5 (d), 39.2 (t), 33.5 (t), 29.5 (t), 27.2 (q), 22.5 (t), 19.6 (s), 13.4 (q); *m*/*z* (EI+) 551 (M + H). Found: C, 80.4; H, 8.5. $C_{37}H_{46}SiO_2$ requires C, 80.7; H, 8.4.

(5*R*,6*R*)-5-(*tert*-Butyldiphenylsilyloxy)-6-methyl-7-phenylheptan-1-ol (24). To a stirred solution of benzyl ether **23** (6.4 g, 11.6 mmol) in CH_2Cl_2 (100 mL) under N_2 was added BCl_3·SMe_2 (40 mL, 2.0 M solution in CH_2Cl_2, 81.3 mmol). The resulting brown mixture was stirred at room temperature for 1 h before the cautious addition of saturated aqueous $NaHCO_3$. The mixture was then extracted with Et_2O (×4) and the ethereal layers were combined then dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow/brown oil was purified by flash chromatography (20−50% EtOAc-petrol) to give the title compound **24** (5.0 g, 94%) as a colorless oil: R_f 0.23 (20% EtOAc/petrol); $[\alpha]^{23}_D$ +8.9 (*c* 0.5, $CHCl_3$); IR ($CHCl_3$ solution) 3625 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 7.72−7.68 (m, 4H), 7.43−7.33 (m, 6H), 7.25−7.12 (m, 3H), 7.05−7.02 (m, 2H), 3.72−3.65 (m, 1H), 3.37 (t, 2H, *J* 6.3), 2.88 (dd, 1H, *J* 13.5, 5.0), 2.42 (dd, 1H, *J* 13.5, 9.9), 1.89−1.85 (m, 1H), 1.52−1.13 (m, 6H), 1.09 (s, 9H), 0.81 (d, 3H, *J* 6.9); ^{13}C NMR (68 MHz, $CDCl_3$) 141.7 (s), 136.1 (d), 136.0 (d), 134.9 (s), 134.3 (s), 129.6 (d), 129.4 (d), 129.1 (d), 128.1 (d), 127.6 (d), 127.5 (d), 127.4 (d), 125.6 (d), 76.9 (d), 62.7 (t), 39.6 (d), 39.2 (t), 33.4 (t), 32.5 (t), 27.0 (q), 22.1 (t), 19.6 (s), 13.5 (q); *m*/*z* (FAB+) 461 (M + H); HRMS obsd 403.2109. $C_{26}H_{31}SiO_2$ (M − ^{t}Bu) requires 403.2093.

(5*R*,6*R*)-5-(*tert*-Butyldiphenylsilyloxy)-6-methyl-7-phenylheptanal (25). To a cooled (−78 °C), stirred solution of oxalyl chloride (27 μL, 0.30 mmol) in dry CH_2Cl_2 (1.0 mL) was added anhydrous DMSO (43 μL, 0.61 mmol) slowly dropwise. Following gas evolution, the mixture was stirred for a further 10 min at −78 °C before a solution of alcohol **24** (70 mg, 0.15 mmol) in CH_2Cl_2 (1.0 mL) was added dropwise over 45 min. The resulting white mixture was stirred for a further 30 min. at −78 °C. NEt_3 (127 μL, 0.91 mmol) was then added dropwise and the mixture stirred for 20 min. After warming to 0 °C the reaction mixture was quenched with aqueous 1.0 M KH_2PO_4 and extracted with Et_2O (×4). The ethereal layers were combined and dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual orange oil was purified by flash chromatography (12% EtOAc/petrol) to give the aldehyde **25** (68 mg, 97%) as a colorless oil: R_f 0.57 (20% EtOAc/petrol); $[\alpha]^{23}_D$ +12.8 (*c* 0.48, $CHCl_3$); IR (film) 1722 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 9.49 (t, 1H, *J* 1.7), 7.71−7.65 (m, 4H), 7.44−7.40 (m, 2H), 7.38−7.35 (m, 4H), 7.23−7.21 (m, 2H), 7.17−7.14 (m, 1H, m), 7.03 (d, 2H, *J* 7.2), 3.68−3.65 (m, 1H), 2.89 (dd, 1H, *J* 13.3, 4.9), 2.40 (dd, 1H, *J* 13.3, 9.9), 2.04−2.00 (m, 2H), 1.92−1.87 (m, 1H), 1.51−1.30 (m, 4H), 1.10 (s, 9H), 0.80 (d, 3H, *J* 6.8); ^{13}C NMR (125 MHz, $CDCl_3$) 202.3 (d), 141.4 (s), 136.0 (d), 134.6 (s), 134.1 (s), 129.6 (d), 129.5 (d), 129.0 (d), 128.1 (d), 127.5 (d), 127.4 (d), 125.6 (d), 76.1 (d), 43.4 (t), 39.6 (d), 38.9 (t), 33.0 (t), 27.1 (q), 19.6 (s), 18.5 (t), 13.7 (q); *m*/*z* (EI+) 459 (M + H). Found: C, 78.6; H, 8.7. $C_{30}H_{38}SiO_2$ requires C, 78.5; H, 8.4.

(4′*R*,5′*R*)-2-[4′-(*tert*-Butyldiphenylsilyloxy)-5′-methyl-6′-phenylhex-1′-yl][1,3]-dithiane (26). To a stirred solution of aldehyde **25** (4.74 g, 10.3 mmol) in dry CH_2Cl_2 (40 mL) under N_2 was added propane-1,3-dithiol (1.03 mL, 10.3 mmol) and BF_3·OEt_2 (258 μL, 2.1 mmol). The mixture was stirred at room temperature for 1 h before the addition of saturated aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (×4), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The residual yellow oil was purified by flash chromatography (6% EtOAc/petrol) to give the dithiane **26** (5.17 g, 92%) as a viscous colorless oil: R_f 0.35 (6% EtOAc/petrol); $[\alpha]^{23}_D$ +4.4 (*c* 0.48, $CHCl_3$); IR ($CHCl_3$ solution) 1589 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.72−7.69 (m, 4H), 7.45−7.37 (m, 6H), 7.27−7.21 (m, 2H), 7.17−7.15 (m, 1H), 7.05−7.03 (m, 2H), 3.78 (t, 1H, *J* 7.0), 3.71−3.68 (m, 1H), 2.85 (dd, 1H, *J* 13.5, 4.8), 2.81−2.76 (m, 4H), 2.43 (dd, 1H, *J* 13.5, 10.2), 2.11−2.06 (m, 1H), 1.89−1.72 (m, 2H); 1.53−1.25 (m, 6H), 1.11 (s, 9H), 0.81 (d, 3H, *J* 6.8); ^{13}C NMR (68 MHz, $CDCl_3$) 141.5 (s), 136.0 (d), 136.0 (d), 134.8 (s), 134.1 (s), 129.5 (d), 129.4 (d), 129.0 (d), 128.0 (d), 127.6 (d), 127.5 (d), 127.3 (d), 125.5 (d), 76.3 (d), 47.2 (d), 39.3 (d), 35.0 (t), 33.3 (t), 30.2 (t), 27.2 (q), 25.9 (t), 22.9 (t), 19.5 (s), 13.3 (q); *m*/*z* (EI+) 548 (M+); HRMS obsd 491.1892. $C_{29}H_{35}OSiS_2$ (M − ^{t}Bu) requires 491.1899.

1,3-Dithiane monosulfoxides (27). To a cooled (0 °C) stirred solution of dithiane **26** (805 mg, 1.47 mmol) in CH_2Cl_2 (10.0 mL) under N_2 was added *m*CPBA (362 mg of 70% purity, 1.47 mmol). The reaction mixture was stirred for 1 min. before the addition of aqueous sodium sulfite solution. The mixture was extracted with CH_2Cl_2 (×4), dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual white foam was purified by flash chromatography (100% EtOAc) to give a separable mixture of the trans and cis pairs of diastereomers (**27** trans: 538 mg, 65%; **27** cis: 105 mg, 13%) both as white foams, which gave complex NMR spectra indicating the presence of mixtures of diastereomers. Data for trans: R_f 0.54 (10% MeOH/EtOAc); HRMS obsd 564.2542. $C_{33}H_{44}S_2SiO_2$ requires 564.2552. Data for cis isomers: R_f 0.62 (10% MeOH/EtOAc); HRMS obsd 564.2523, $C_{33}H_{44}S_2SiO_2$ requires 564.2552.

(4′*R*,5′*R*,1″*R*,2″*R*,3″*R*,4″*S*,5″*S*)-2-[6″-Benzyloxy-3″,4″-bis(benzyloxymethyl)-2″,3″,4″,5″-bis(di-*O*-isopropylidene)-1″-hydroxyhex-1″-yl]-2-[4′-hydroxy-5′-methyl-6′-phenylhex-1′-yl][1,3]dithiane (30) and (4′*R*,5′*R*,1″*S*,2″*R*,3″*R*,4″*S*,5″*S*)-2-[6″-Benzyloxy-3″,4″-bis(benzyloxymethyl)-2″,3″,4″,5″-bis(di-*O*-isopropylidene)-1″-hydroxyhex-1″-yl]-2-[4′-hydroxy-5′-methyl-6′-phenylhex-1′-yl][1,3]dithiane (28). To a cooled (−78 °C) stirred solution of monosulfoxide **27** (3.29 g, 5.83 mmol) in THF (17.0 mL) under Ar was added ^{n}BuLi (2.33 mL, 2.5 M solution in THF, 5.83 mmol) slowly dropwise. After 15 min., a solution of aldehyde **12** (1.27 g, 2.15 mmol) in THF (8.0 mL) was added dropwise. The reaction mixture was stirred for 15 min. before the addition of water and was then allowed to warm to room temperature. Saturated aqueous NH_4Cl was added and the mixture extracted with Et_2O (×4), dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual pale yellow foam was purified by flash chromatography (40−100% EtOAc-petrol) to separate the adduct as a mixture of diastereomers (2.87 g) from the excess monosulfoxide **27** (1.77 g, 3.14 mmol).

To a stirred solution of P_2I_4 (780 mg, 1.37 mmol) in CH_2Cl_2 (40.0 mL) under Ar in the dark was added NEt_3 (347 μL, 2.49 mmol) followed by a solution of monosulfoxide adducts (2.87 g, 2.49 mmol) in CH_2Cl_2 (40.0 mL) via cannula. The reaction mixture was stirred for 5 min. before the addition of aqueous sodium thiosulfate. The mixture was extracted with CH_2Cl_2 (×4), washed with aqueous sodium thiosulfate (×2), dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual pale yellow foam was purified by flash chromatography (24% EtOAc-petrol) to give the 1,3-dithiane adducts (1.43 g, 59% from aldehyde **12**) as a white foam and an inseparable mixture of C7-epimers in a ∼1:1 ratio.

To a stirred solution of these adducts (720 mg, 0.80 mmol) in THF (20.0 mL) under N_2 was added TBAF (4.04 mL, 1.0 M solution in THF, 4.04 mmol). The reaction mixture was stirred for 16 h at 80 °C before the addition of water. The mixture was extracted with Et_2O (×4), dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow oil was purified by flash chromatography (40−60% Et_2O-petrol) to give a readily separable mixture of C7-epimers (**30**: 230 mg, 32%; **28**: 260 mg, 36%) as colorless oils.

Data for **30**: R_f 0.27 (50% Et_2O/petrol); $[\alpha]^{18}_D$ +17.0 (*c* 0.74, $CHCl_3$); IR (film) 3456 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.37−7.28 (m, 17H), 7.23−7.16 (m, 3H), 4.93 (s, 1H), 4.76 (d, 1H, *J* 8.4), 4.65 (d, 1H, *J* 12.6), 4.57−4.51 (m, 4H), 4.48 (m, 1H), 4.43 (d, 1H, *J* 11.9), 4.17 (d, 1H, *J* 11.0), 3.91−3.76 (m, 4H), 3.56 (d, 1H, *J* 11.0), 3.51 (m, 1H), 2.83−2.81 (m, 1H), 2.78 (dd, 1H, *J* 13.3, 6.3), 2.72−2.70 (m, 1H), 2.57 (m, 1H), 2.45 (dd, 1H, *J* 13.3, 8.6), 2.30 (m, 1H), 1.85−1.73 (m, 5H), 1.68−1.55 (m, 4H), 1.47 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H), 0.85 (d, 3H, *J* 6.9); ^{13}C NMR (68 MHz, $CDCl_3$) 141.1 (s), 138.5 (s), 138.1 (s), 137.8 (s), 129.1 (d), 128.2 (d), 128.2 (d), 128.0 (d), 128.0 (d), 127.8 (d), 127.6 (d), 127.4 (d), 127.3 (d), 125.8 (d), 110.2 (s), 108.8 (s), 86.4 (s), 81.0 (d), 77.2 (s), 75.5 (d), 73.7 (t), 73.6 (d), 73.5 (t), 73.0 (t), 71.3 (t), 69.1 (t), 66.1 (d), 59.4 (s), 40.3 (d), 39.9 (t), 35.2 (t), 34.3 (t), 28.2 (q), 27.2 (q), 26.1 (q), 26.0 (q), 25.6 (t), 24.3 (t), 21.3 (t), 13.1 (q); HRMS (FAB) obsd 923.4227, $C_{52}H_{68}S_2O_9Na$ (M + Na) requires 923.4203.

Data for **28**: R_f 0.42 (50% Et_2O/petrol); $[\alpha]^{23}_D$ −3.8 (*c* 0.71, $CHCl_3$); IR (film) 3456 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.39−7.36 (m, 2H), 7.34−7.22 (m, 15H), 7.18−7.15 (m, 3H), 5.04 (d, 1H, *J* 9.1), 4.74 (dd, 1H, *J* 7.8, 2.2), 4.65−4.59 (m, 3H), 4.56−4.47 (m, 3H), 4.44 (d, 1H, *J* 12.1), 4.27 (d, 1H, *J* 3.6), 3.97 (d, 1H, *J* 11.0), 3.82−3.74 (m, 4H), 3.55 (d, 1H, *J* 11.0), 3.47−3.44 (m, 1H), 3.28 (ddd, 1H, *J* 13.5, 10.0, 3.0), 3.13 (ddd, 1H, *J* 13.5, 10.0, 3.0), 2.77 (dd, 1H, *J* 13.5, 6.2), 2.68 (ddd, 1H, *J* 13.5, 6.5, 3.0), 2.57 (ddd, 1H, *J* 13.5, 6.5, 3.0), 2.42 (dd, 1H, *J* 13.5, 8.7), 2.04−1.97 (m, 1H), 1.95−1.83 (m, 3H), 1.80−1.73 (m, 1H), 1.50 (s, 3H), 1.36−1.31 (m, 10H), 1.21 (s, 3H), 0.83 (d, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) 141.2 (s), 138.1 (s), 138.0 (s), 137.5 (s), 129.1 (d), 128.4 (d), 128.2 (d), 127.9 (d), 127.7 (d), 127.6 (d), 127.5 (d), 125.7 (d), 110.9 (s), 108.2 (s), 86.2 (s), 85.4 (s), 80.7 (d), 78.5 (d), 77.2 (d), 74.0 (t), 73.6 (d), 73.5 (t), 73.2 (t), 70.7 (t), 70.2 (t), 69.0 (t), 57.1 (s), 40.4 (d), 39.9 (t), 37.8 (t), 34.9 (t), 27.7 (t), 27.7 (q), 27.0 (q), 26.1 (q), 25.6 (q), 25.1 (t), 21.2 (t), 13.1 (q); HRMS (FAB+) obsd 901.4382, $C_{52}H_{69}S_2O_9$ (M + H) requires 901.4383.

(4′*R*,5′*R*,1″*R*,2″*R*,3″*R*,4″*S*,5″*S*)-2-[4′-Acetoxy-5′-methyl-6′-phenyl-hex-1′-yl]-2-[6″-benzyloxy-3″,4″-bis(benzyloxymethyl)-2″,3″,4″,5″-bis(di-*O*-isopropylidene)-1″-hydroxyhex-1″-yl][1,3]dithiane (31). To a stirred solution of **30** (210 mg, 0.23 mmol) in pyridine (15.0 mL) under N_2 was added acetic anhydride (133 μL, 1.40 mmol) and DMAP (cat.). The reaction mixture was stirred at 60 °C for 3 h before the addition of water. The mixture was extracted with Et_2O (×4), washed with saturated aqueous $CuSO_4$, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow oil was purified by flash chromatography (40% Et_2O/petrol) to give the acetate **31** (186 mg, 85%) as a white foam: R_f 0.38 (50% Et_2O/petrol); $[\alpha]^{26}_D$ −5.6 (*c* 0.71, $CHCl_3$); IR (film) 3448, 1733 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.37−7.23 (m, 16H), 7.20−7.15 (m, 2H), 7.13−7.12 (m, 2H), 4.93 (s, 1H), 4.92−4.88 (m, 1H), 4.78 (d, 1H, *J* 8.1), 4.67 (d, 1H, *J* 12.6), 4.58−4.47 (m, 4H), 4.44−4.41 (m, 2H, including 4.42 (d, 1H, *J* 11.9)), 4.15 (d, 1H, d, *J* 9.5), 3.91−3.75 (m, 4H), 3.55 (d, 1H, d, *J* 11.0), 3.01 (m, 1H), 2.78−2.73 (m, 1H), 2.75 (dd, 1H, *J* 13.5, 5.0), 2.73−2.57 (m, 1H), 2.57−2.55 (m, 1H), 2.31−2.26 (m, 2H), 2.28 (dd, 1H, *J* 13.5, 9.7), 2.07 (s, 3H), 2.04−1.96 (m, 1H), 1.80−1.51 (m, 7H), 1.48 (s, 3H), 1.37 (s, 6H), 1.34 (s, 3H), 0.84 (d, 3H, *J* 6.8); ^{13}C NMR (68 MHz, $CDCl_3$) 170.8 (s), 140.6 (s), 138.6 (s), 138.1 (s), 137.8 (s), 129.1 (d), 128.2 (d), 128.1 (d), 127.9 (d), 127.8 (d), 127.6 (d), 127.4 (d), 127.3 (d), 125.8 (d), 110.2 (s), 108.8 (s), 86.3 (s), 81.1 (d), 76.5 (d), 75.6 (d), 73.9 (t), 73.5 (t), 73.0 (t), 71.3 (t), 69.1 (t), 66.1 (d), 59.3 (s), 39.3 (t), 38.4 (d), 31.6 (t), 28.3 (q), 27.2 (q), 26.1 (q), 26.0 (q), 25.6 (t), 24.2 (t), 21.2 (q), 20.5 (t), 13.9 (q); *m*/*z* (FAB+) 943 (M+). Found: C, 68.9; H, 7.8. $C_{54}H_{70}S_2O_{10}$ requires C, 68.8; H, 7.5.

(4′*R*,5′*R*,1″*R*,2″*R*,3″*R*,4″*S*,5″*S*)-2-[4′-Acetoxy-5′-methyl-6′-phenylhex-1′-yl]-2-[6″-benzyloxy-3″,4″-bis(benzyloxymethyl)-1″,2″,4″,5″-bis(di-*O*-isopropylidene)-3″-hydroxyhex-1″-yl][1,3]dithiane (33). To a cooled (−78 °C) stirred solution of trans-monosulfoxide **27** (373 mg, 0.66 mmol) in THF (1.7 mL) under Ar was added ^{n}BuLi (297 μL, 2.3 M solution in THF, 0.68 mmol) slowly dropwise. After 15 min., a solution of aldehyde **12** (130 mg, 0.22 mmol) in THF (0.8 mL) was added dropwise. The reaction mixture was stirred for 15 min. before the addition of water and the mixture was then allowed to warm to room temperature. Saturated aqueous NH_4Cl was added and the mixture extracted with Et_2O (×4), dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual pale yellow foam was purified by flash chromatography (40−100% EtOAc/petrol) to separate the adduct as a mixture of diastereomers (194 mg) from the excess monosulfoxide **27** (147 mg, 0.26 mmol).

To a stirred solution of P_2I_4 (36 mg, 0.062 mmol) in CH_2Cl_2 (2.0 mL) under N_2 in the dark was added NEt_3 (9 μL, 0.062 mmol) followed by a solution of the intermediate mixture of monosulfoxide adducts (131 mg, 0.114 mmol) in CH_2Cl_2 (2.0 mL) via syringe. The reaction mixture was stirred for 5 min. before adding aqueous sodium thiosulfate solution. The mixture was extracted with Et_2O, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual viscous yellow oil was purified by flash chromatography (24% EtOAc/petrol) to give an inseparable mixture of 1,3-dithianes (57 mg, 34% from aldehyde **12**) as a colorless oil.

To a stirred solution of the intermediate mixture of TBDPS ethers (57 mg, 0.05 mmol) in THF (1.5 mL) under N_2 was added TBAF (150 μL, 1.0 M solution in THF, 0.15 mmol). The reaction mixture was stirred for 12 h at 80 °C before the addition of water. The mixture was extracted with Et_2O, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual pale yellow oil was purified by flash chromatography (40% Et_2O-petrol) to give a readily separable mixture of **28** and **32** (**28**: 20 mg, 44%; **32**: 15 mg, 33%) as colorless oils.

To a stirred solution of alcohol **32** (110 mg, 0.12 mmol) in pyridine (5.0 mL) under N_2 was added acetic anhydride (69 μL, 0.73 mmol) and DMAP (cat.). The reaction mixture was stirred at 80 °C for 26 h before the addition of water. The mixture was extracted with Et_2O (×4), washed with saturated aqueous $CuSO_4$, dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow oil was purified by flash chromatography (32−40% Et_2O/petrol) to give the acetate **33** (99 mg, 86%) as a white foam: R_f 0.47 (50% Et_2O/petrol); $[\alpha]^{22}_D$ −3.0 (*c* 0.99, $CHCl_3$); IR (film) 3361, 1731 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) 7.30−7.12 (m, 18H), 7.08 (m, 2H), 5.09 (d, 1H, *J* 6.6), 4.85−4.83 (m, 2H), 4.65 (d, 1H, *J* 12.5), 4.54 (d, 1H, *J* 6.6), 4.47−4.38 (m, 5H), 4.16 (s, 1H), 3.87 (d, 1H, *J* 9.9), 3.78−3.75 (m, 2H), 3.70−3.63 (m, 2H), 3.55 (d, 1H, *J* 9.9), 2.89 (m, 1H), 2.71 (dd, 1H, *J* 13.5, 4.8), 2.59−2.47 (m, 3H), 2.25 (dd, 1H, *J* 13.5, 9.6), 2.01 (s, 3H), 1.99−1.53 (m, 9H), 1.45 (br s, 6H), 1.38 (s, 3H), 1.35 (s, 3H), 0.79 (d, 3H, *J* 6.6); *m*/*z* (FAB+) 944 (M + H); HRMS obsd 941.4413. $C_{54}H_{69}S_2O_{10}$ (M − H) requires 941.4332.

(1*S*,3*R*,4*S*,5*R*,6*R*,7*R*,4′*R*,5′*R*)-1-[4′-Acetoxy-5′-methyl-6′-phenylhex-1′-yl]-34,5-tris(benzyloxymethyl)-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane (34). To a stirred solution of **31** (181 mg, 0.19 mmol) in CH_2Cl_2 (4.0 mL) was added water (200 μL) and TFA (2.0 mL). The mixture was stirred for 30 min. before the addition of saturated aqueous sodium bicarbonate. The mixture was extracted with CH_2Cl_2 (×4), dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual pale yellow oil was purified by flash chromatography (30% EtOAc/petrol) to give the ketal **34** (130 mg, 90%) as a colorless oil: R_f 0.61 (50% EtOAc/petrol); $[\alpha]^{21}_D$ +12.6 (*c* 0.92, CH_2Cl_2); IR (film) 3458, 1730 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 7.31−7.23 (m, 15H), 7.17−7.15 (m, 3H), 7.10−7.09 (m, 2H), 4.85−4.83 (m, 1H), 4.76 (br s, 1H), 4.54−4.43 (m, 4H), 4.38 (m, 1H), 4.32−4.27 (m, 2H), 3.98 (br s, 1H), 3.90 (d, 1H, *J* 9.6), 3.77 (dd, 1H, *J* 10.7, 3.0), 3.59−3.56 (m, 3H), 3.46−3.45 (m, 2H), 3.32 (s, 1H), 2.71 (dd, 1H, *J* 13.5, 4.8), 2.30 (br s, 1H), 2.28 (dd, 1H, *J* 13.5, 9.6), 2.02 (s, 3H), 1.95 (m, 1H), 1.82−1.45 (m, 6H), 0.82 (d, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) 170.9 (s), 140.5 (s), 138.0 (s), 137.6 (s), 136.7 (s), 129.0 (d), 128.5 (d), 128.3 (d), 128.2 (d), 128.1 (d), 127.8 (d), 127.6 (d), 127.5 (d), 125.8 (d), 105.1 (s), 86.6 (s), 83.5 (d), 79.4 (d), 76.8 (d), 73.8 (t), 73.4 (t), 73.1 (t), 72.8 (d), 70.9 (s), 69.5 (t), 69.3 (t), 68.4 (t), 39.3 (t), 38.2 (d), 35.2 (t), 31.0 (t), 21.1 (q), 19.1 (t), 13.9 (q); HRMS (FAB+) obsd 755.3850, $C_{45}H_{55}O_{10}$ (M + H) requires 755.3795.

Repeating the above procedure starting from **33** gave identical results.

(1*S*,3*R*,4*S*,5*R*,6*R*,7*R*,4′*R*,5′*R*)-1-[4′-Acetoxy-5′-methyl-6′-phenylhex-1′-yl]-6,7-bis(benzoyloxy)-3, 4, 5-tris(benzyloxymethyl)-4-hydroxy-2,8-dioxabicyclo[3.2.1]octane (35). To a stirred solution of triol **34** (111 mg, 0.15 mmol) in pyridine (3.0 mL) under N_2 was added benzoyl chloride (68 μL, 0.59 mmol) and DMAP (cat.). The reaction mixture was stirred at room temperature for 24 h before the addition of water. The mixture was extracted with Et_2O (×4), washed with saturated aqueous $CuSO_4$ (×4) then water (×1), 2.0 M aqueous HCl (×1) and again with water (×1), dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual yellow oil was purified by flash chromatography (40−50% Et_2O/petrol) to give the benzoate **35** (138 mg, 97%) as a colorless oil: R_f 0.41 (50% Et_2O/petrol); $[\alpha]^{25}_D$ +53.7 (*c* 0.26, $CHCl_3$); IR (film) 3473, 1727, 1602 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 8.09−8.03 (m, 4H), 7.59 (t, 1H, *J* 7.4), 7.52 (t, 1H, *J* 7.4), 7.45 (t, 2H, *J* 7.7), 7.31−7.13 (m, 18H), 7.07−7.06 (m, 4H), 6.42 (d, 1H, *J* 2.3), 5.50 (d, 1H, *J* 2.3), 4.86−4.84 (m, 1H), 4.75 (dd, 1H, *J* 5.8, 2.2), 4.61 (d, 1H, *J* 12.0), 4.53 (d, 1H, *J* 12.0), 4.46 (d, 1H, *J* 12.0), 4.35 (d, 1H, *J* 12.0), 4.32 (d, 1H, *J* 11.5), 4.20 (d, 1H, *J* 11.5), 4.04 (s, 1H), 3.94−3.90 (m, 2H), 3.75−3.70 (m, 3H), 3.60 (d, 1H, *J* 10.3), 2.72 (dd, 1H, *J* 13.5, 4.8), 2.25 (dd, 1H, *J* 13.5, 9.5), 1.96 (s, 3H), 1.94−1.85 (m, 3H), 1.70−1.48 (m, 4H), 0.80 (d, 3H, *J* 6.8); ^{13}C NMR (68 MHz, $CDCl_3$) 170.8 (s), 165.3 (s), 164.9 (s), 140.6 (s), 138.4 (s), 137.6 (s), 136.8 (s), 133.3 (d), 133.2 (d), 130.0 (d), 129.8 (d), 129.6 (s), 129.2 (s), 129.0 (d), 128.4 (d), 128.2 (d), 128.2 (d), 127.9 (d), 127.8 (d), 127.5 (d), 127.4 (d), 125.8 (d), 105.0 (s), 85.7 (s), 80.8 (d), 78.1 (d), 76.8 (d), 74.2 (d), 74.0 (t), 73.4 (t), 73.2 (t), 71.8 (s), 69.8 (t), 69.7 (t), 69.2 (t), 39.2 (t), 38.1 (d), 35.7 (t), 30.9 (t), 21.0 (q), 19.1 (t), 13.9 (q); *m*/*z* (FAB+) 985 (M + Na). Found: C, 73.6; H, 6.6. $C_{59}H_{62}O_{12}$ requires C, 73.6; H, 6.6.

(1*S*,3*R*,4*S*,5*R*,6*R*,7*R*,4′*R*,5′*R*)-1-[4′-Acetoxy-5′-methyl-6′-phenylhex-1′-yl]-6,7-bis(benzoyloxy)-4-hydroxy-3,4,5-trihydroxymethyl-2,8-dioxabicyclo[3.2.1]octane (36). To a stirred solution of tris-benzyl ether **35** (116 mg, 0.12 mmol) in EtOAc (6.0 mL) was added Pd−C 10% (cat.) and 2.0 M aqueous HCl (20 μL). The mixture was stirred at room temperature under 1 atm of H_2 for 5 h before being filtered through Celite and evaporated under reduced pressure. The residual white foam was purified by flash chromatography (100% EtOAc) to give the alcohol **36** (74 mg, 89%) as a white foam: R_f 0.55 (100% EtOAc); $[\alpha]^{27}_D$ +87.2 (*c* 0.26, $CHCl_3$); IR (film) 3425, 1726, 1602 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) 8.10−8.06 (m, 2H), 8.05−8.01 (m, 2H), 7.61−7.57 (m, 2H), 7.48−7.44 (m, 4H), 7.26−7.21 (m, 2H), 7.18−7.10 (m, 1H), 7.08−7.05 (m, 2H), 5.96 (d, 1H, *J* 2.9), 5.58 (d, 1H, *J* 2.9), 4.86 (dt, 1H, *J* 8.2, 4.0), 4.26 (dd, 1H, *J* 5.1, 3.9), 4.01−3.88 (m, 7H), ∼3.80−2.80 (br s, 3H), 2.70 (dd, 1H, *J* 13.4, 5.2), 2.29 (dd, 1H, *J* 13.4, 9.3), 2.03 (s, 3H), 1.97−1.82 (m, 3H), 1.71−1.47 (m, 4H), 0.83 (d, 3H, *J* 6.8); ^{13}C NMR (125 MHz, $CDCl_3$) 171.3 (s), 166.1 (s), 165.2 (s), 140.5 (s), 133.7 (d), 133.6 (d), 133.5 (d), 130.1 (d), 129.9 (d), 129.9 (s), 129.0 (s), 128.8 (d), 128.6 (d), 128.6 (d), 128.4 (d), 128.2 (d), 125.9 (d), 104.8 (s), 86.2 (s), 80.7 (d), 77.8 (d), 76.6 (d), 74.3 (d), 72.5 (s), 61.7 (t), 61.5 (t), 60.2 (t), 39.4 (t), 38.3 (d), 35.1 (t), 30.9 (t), 21.1 (q), 18.9 (t), 13.8 (q); *m*/*z* (FAB+) 715 (M + Na), 693 (M + H); HRMS obsd 693.2911. $C_{38}H_{45}O_{12}$ (M + H) requires 693.2911.

(1*S*,3*R*,4*S*,5*R*,6*R*,7*R*,4′*R*,5′*R*)-1-[4′-Acetoxy-5′-methyl-6′-phenyl-hex-1′-yl]-6,7-bis(benzoyloxy)-3,4,5-tris(2,2-dimethylpropionyl)-4-hydroxy-2,8-dioxabicyclo[3.2.1]-octane (37). To a cooled (−78 °C) stirred solution of oxalyl chloride (31 μL, 0.35 mmol) in CH_2Cl_2 (1.3 mL) under N_2 was added anhydrous DMSO (51 μL, 0.71 mmol). The mixture was stirred for 10 min. at −78 °C before a solution of **36** (70 mg, 0.10 mmol) in CH_2Cl_2 (1.3 mL) was added dropwise. The resulting white mixture was stirred for 45 min before the dropwise addition of NEt_3 (148 μL, 1.06 mmol). The clear solution was stirred for a further 30 min. before the addition of water. The mixture was extracted with CH_2Cl_2 (×5), washed with aqueous 2.0 M HCl (×1), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give 71 mg of a colorless oil. The product trialdehyde was used without further purification.

To a cooled (10 °C) stirred solution of the intermediate trialdehyde (71 mg, assume 0.10 mmol from **36**) in 5:1.2 ^{t}BuOH/2-methyl-2-butene (14.8 mL) was added an ice-cold buffered 1.1 M aqueous solution of $NaClO_2$ (1.71 mL, 1.52 mmol) slowly dropwise. The reaction mixture was stirred for 3 h and then quenched with pH 2 KH_2PO_4−HCl buffer. The mixture was extracted with EtOAc (×6) and then extracted into saturated aqueous $NaHCO_3$. This solution was then reacidified with 2.0 M aqueous HCl, extracted with EtOAc (×6), dried ($MgSO_4$), filtered and evaporated under reduced pressure to give 53 mg of a colorless oil. The product triacid was used without further purification.

To a solution of the intermediate triacid (53 mg) in CH_2Cl_2 (2.5 mL) under N_2 was added *N*,*N*′-diisopropyl-*O*-*tert*-butylisourea (400 μL). The reaction mixture was stirred for 23 h during which time formation of a white precipitate was observed. The mixture was diluted with pentane, filtered and evaporated under reduced pressure. The residual yellow oil was purified by flash chromatography (32% EtOAc/petrol) to give the title compound **37** (30 mg, 33% from tris-1°-alcohol

36) as a white foam: R_f 0.28 (20% EtOAc/petrol); $[\alpha]^{28}_D$ +54.2 (*c* 0.82, $CHCl_3$); IR (film) 1760, 1730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.08−8.03 (m, 2H), 8.04−8.03 (m, 2H, Ph), 7.65−7.57 (m, 2H), 7.51−7.42 (m, 4H), 7.25−7.24 (m, 2H), 7.18−7.15 (m, 1H), 7.11 (d, 2H, *J* 7.0), 6.82 (d, 1H, *J* 2.0), 5.43 (d, 1H, *J* 2.0), 5.14 (s, 1H), 4.90−4.87 (m, 1H), 4.16 (s, 1H), 2.76 (dd, 1H, *J* 13.4, 4.8), 2.28 (dd, 1H, *J* 13.4, 9.9), 2.16−2.06 (m, 2H,), 2.05−2.01 (m, 1H), 2.00 (s, 3H), 1.78−1.65 (m, 4H), 1.63 (s, 9H), 1.48 (s, 9H), 1.28 (s, 9H), 0.83 (d, 3H, *J* 6.8); ^{13}C NMR (125 MHz, $CDCl_3$) 170.8 (s), 168.6 (s), 165.6 (s), 165.1 (s), 164.3 (s), 163.5 (s), 140.8 (s), 133.7 (d), 133.5 (d), 130.1 (d), 129.8 (s), 129.1 (s), 129.0 (d), 128.9 (d), 128.6 (d), 128.4 (d), 128.2 (d), 125.8 (d), 104.4 (s), 90.2 (s), 86.3 (s), 84.4 (s), 83.6 (s), 81.4 (d), 77.0 (d), 76.4 (d), 75.5 (d), 74.0 (s), 39.3 (t), 38.0 (d), 36.0 (t), 30.9 (t), 28.1 (q), 28.0 (q), 27.9 (q), 21.1 (q), 19.1 (t), 13.8 (q); HRMS (FAB) obsd 925.3884, $C_{50}H_{62}O_{15}Na$ (M + Na) requires 925.3986.

(1*S*,3*R*,4*S*,5*R*,6*R*,7*R*,4′*R*,5′*R*)-1-[4′-Acetoxy-5′-methyl-6′-phenylhex-1′-yl]-3,4,5-tris(2,2-dimethylpropionyl)-4,6,7-trihydroxy-2,8-dioxabicyclo[3.2.1]octane (38). Bis-benzoate **37** (7 mg, 7.75 μmol) was treated with 0.2% K_2CO_3 methanolic solution (1.2 mL). The reaction mixture was stirred for 5 h at room temperature before the reaction was quenched with 0.3 M aqueous KH_2PO_4 solution. The mixture was extracted with Et_2O (×5), dried ($MgSO_4$), filtered and evaporated under reduced pressure. The residual colorless oil was purified by flash chromatography (50% EtOAc/hexanes) to give the title compound **38** (4 mg, 75%) as a colorless oil: R_f 0.28 (50% EtOAc/hexanes); $[\alpha]^{23}_D$ +9.6 (*c* 0.27, $CHCl_3$); δ_H (270 MHz, $CDCl_3$) 7.30−7.11 (m, 5H), 5.02 (br s, 1H), 4.91 (br s, 1H), 4.89−4.86 (m, 1H), 3.91 (br s, 1H), 2.75 (dd, 1H, *J* 13.5, 4.6), 2.35 (dd, 1H, *J* 13.5, 9.9), 2.07 (s, 1H), 2.05 (s, 3H), 1.99−1.92 (m, 3H), 1.62−1.31 (m, 4H), 1.59 (s, 9H), 1.49 (s, 9H), 1.44 (s, 9H), 0.85 (d, 3H, *J* 6.6 Hz). These data concur with those reported by Carreira.[7]

Conversion of 38 to 1. This was performed according to the procedure of Carreira.[7] Full details are given in the Supporting Information.

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Supporting Information Available: Preparation of and data for **2**, **4**, and **7**−**9**; typical procedure for monophasic dihydroxylation of **6**−**9**; preparation of and data for Mosher's ester of **11**, **13**−**21**, **29**, and conversion of **38** to **1**; ^{13}C NMR spectrum of **7**; ^1H NMR spectra of **9**, **11**; ^1H and ^{19}F NMR spectra of Mosher's ester of **11**; ^1H NMR spectra of **14**, **16**−**21**, **24**, **26**, **27**, **28**−**31**, **33**, **34**, and **36**−**38**; intermediates in the conversion of **38** to **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

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