Free Radical Studies and Solutions to the Synthesis of (+)-Cyclophellitol‡

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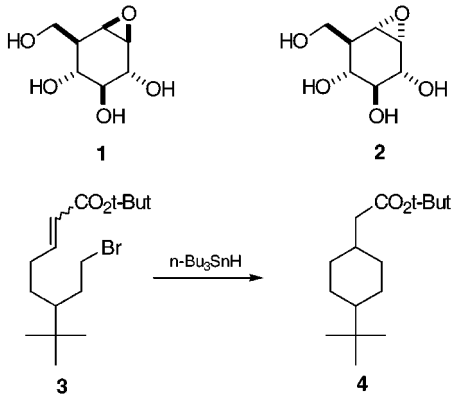
D-Xylose serves as a starting material for approaches to the synthesis of the glucosidase inhibitors, (+)-cyclophellitol (**1**) and (+)-epi-cyclophellitol (**2**). An investigation of the cyclization of diastereomeric oxiranyl radicals to achieve this goal was moderately successful with the diastereomer that would have led to epi-cyclophellitol undergoing cyclization. An alternative route to cyclophellitol from D-xylose employed Grubbs' ring closure metathesis and radical transformations to complete the synthesis.

(+)-Cyclophellitol (**1**) (Chart 1) was isolated from the culture broth of the mushroom *Phellinus sp.* in 1990 by Umezawa et al.[1] and was shown to be a sub-microgram inhibitor of β-glucosidase.[2] These researchers established the structure and absolute stereochemistry of cyclophellitol by X-ray crystallographic analysis. In the same year, Tatsuta reported[3] the first synthesis of (+)-cyclophellitol from L-glucose.[3] Subsequently, syntheses of this substance have been reported as its racemate[4,5] and as the dextrorotatory enantiomer using nature's chiral pool[3,6−11] and through asymmetric induction.[12] Likewise, epi-cyclophellitol (**2**), an inhibitor of α-glucosidase, has been a target of total synthesis.[5,8−10]

Our interest in these substances was stimulated by the opportunity to explore the viability of intramolecular reactions of oxiranyl radicals in systems wherein an attendant six-membered ring is formed. We had previously demonstrated that these cyclizations are effective when the attendant ring is five-membered.[13,14] Because 5-hexenyl radical cyclizes ~40 times faster than 6-heptenyl radical,[15] the success of the larger ring cyclization was not ensured. Moreover, 6-heptenyl radicals are also susceptible to allylic abstraction of a hydrogen atom from C_5. On the positive side, Hanessian has demonstrated that unsaturated esters **3** cyclize in good yield and with a preference for the formation of the trans stereoisomer **4**, a process that proceeds through a chairlike transition state.[16] Herein we describe our efforts to this end using oxiranyl radicals and we expand upon our communication on the synthesis of cyclophellitol.[11]

Chart 1



Isomer	Yield	trans:cis
E	85%	3:1
Z	75%	9:1

The strategy for the synthesis of (+)-cyclophellitol (Scheme 1) was to generate oxiranyl radical **5** of either oxirane configuration by radical decarboxylation of glycidic acids **6**, which would be derived from D-xylose (**7**). The three protected oxygens of radical **5** would serve to anchor the chairlike transition state for cyclization with three equatorial protected oxygen groups and thereby lead to the desired stereochemistry of the acetic acid chain. A related study involving a glucose-derived ω-bromo-2-octenoate led to a mixture of stereoisomers.[17] Starting from the known,[18] readily prepared diethyl thioacetal of D-xylose (Scheme 2), either protected template **10** or **11** could be prepared efficiently. These two substances permitted elaboration on either end of the termini of the carbon chain of the protected pentose. Dithioacetal **11**, which was prepared in 55% overall yield from dithioacetal **8a**, was employed first in our studies.

Oxidation of primary alcohol **11** to an aldehyde proved troublesome in the presence of the thioacetal group

‡ In memory of Professor George Büchi. Deceased August 28, 1998.

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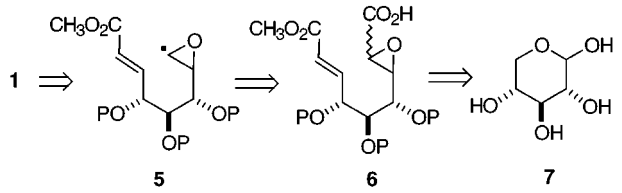
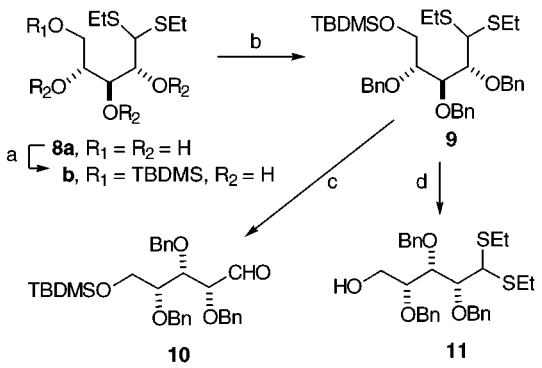
Scheme 1

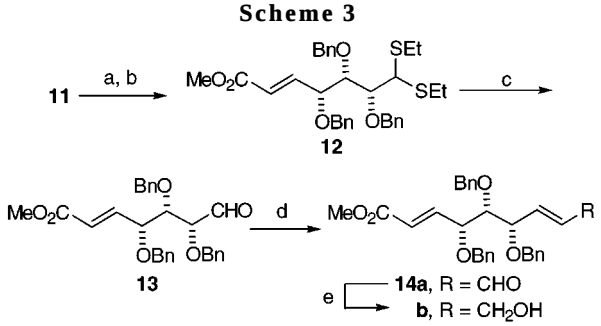


Scheme 2



a) TBDMSCl. b) BnBr, NaH. c) HgO/$HgCl_2$. d) n-Bu_4NF.

Scheme 3

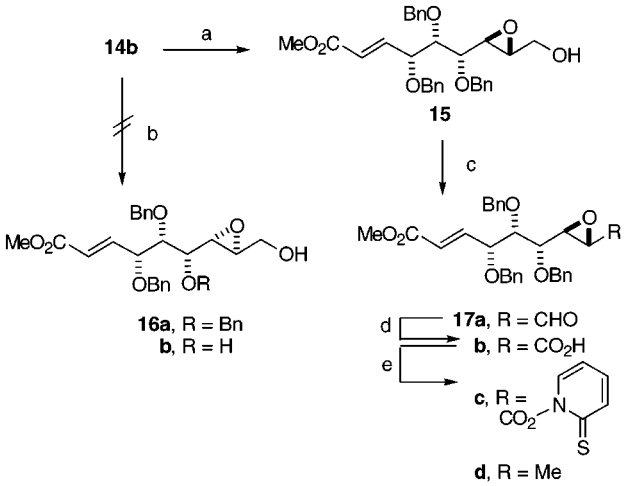


a) nPr_4NRuO_4, NMO. b) Ph_3PCHCO_2Me, CH_2Cl_2.
c) HgO/$HgCl_2$; aq. acetone. d) $Ph_3PCHCHO$, benzene, reflux.
e) $NaBH_4$, MeOH

(Scheme 3). Neither Moffatt–Pfitzner[19] nor Doering–Parikh[20] oxidation, both nonmetal-based protocols, proved effective. However, oxidation with catalytic tetra-*n*-propylammonium perruthenate in the presence of *N*-methylmorpholine *N*-oxide led to the desired aldehyde in 40% yield.[21] Subsequent Wittig reactions and formation of the allylic alcohol **14b** proceeded without incident.

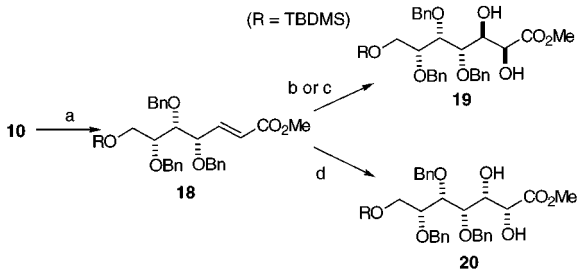
In their studies on the synthesis of carbohydrates using the Sharpless asymmetric epoxidation (SAE), Sharpless and Masamune[22] addressed the epoxidation of benzyloxy allylic alcohols akin to **14b**. Forcing noncatalytic conditions were required to obtain yields in excess of 70%. Unfortunately, epoxy alcohol **15** was obtained in <50% crude yield (contaminated with D-(−)-DET). The contaminant was removed after Dess–Martin oxidation of epoxy alcohol **15** to the epoxy aldehyde **17a** (Scheme 4). The diastereoselectivity of the SAE reaction was readily assessed by comparing the ^{1}H NMR spectrum of epoxy

Scheme 4



a) SAE, D-(-) DET. b) SAE, L-(+) DET. c) Dess-Martin periodinane.
d) $NaClO_2$, NaH_2PO_4, H_2O_2. e) i-BuOCOCl, N-methylmorpholine; Na thiopyridone N-oxide.

Scheme 5



a) $Ph_3P{=}CHCO_2Me$. b) 6% OsO_4, 3 eq. $K_3Fe(CN)_6$, 3 eq. K_2CO_3, 3 eq. $MeSO_2NH_2$.
c) 6% OsO_4, 10% $(DHQD)_2PHAL$, 3 eq. $K_3Fe(CN)_6$, 3 eq. K_2CO_3, 3 eq. $MeSO_2NH_2$.
d) 6% OsO_4, 10% $(DHQ)_2PHAL$, 3 eq. $K_3Fe(CN)_6$, 3 eq. K_2CO_3, 3 eq. $MeSO_2NH_2$.

alcohol **15** with the spectrum of the mixture of epoxy alcohols **15** and **16** obtained when allylic alcohol **14b** was oxidized with *m*-CPBA. Glycidic acid **17b**, formed by Lindgren[23,24] oxidation of aldehyde **17a** and characterized as its methyl ester **17d**, has the correct epoxide stereochemistry to lead ultimately to epi-cyclophellitol **2**. Unfortunately, asymmetric epoxidation of allylic alcohol **14b** with L-(+)-DET failed to afford epoxy alcohol **16a**. Rather, an epoxy diol (presumably **16b**), as evidenced by ^{1}H NMR and HRMS, was formed consistently in low yield. This unexpected turn of events precluded access to cyclophellitol precursors, and an alterative route was required to obtain the glycidic acid.

The Sharpless asymmetric dihydroxylation (AD) offered itself as a means to gain access to both stereoisomers of radical **5** through the *cis*-glycidic acids (Scheme 5).[22] When unsaturated ester **18** was oxidized with OsO_4 (6 mol %) and $K_3Fe(CN)_6$ (3 equiv), a 15/1 ratio of β-diol **19**/α-diol **20** was obtained without the aid of a chiral ligand. This high selective reflects inherent substrate selectivity in the oxidation. This ratio was improved to 20/1 (92% yield) with the inclusion of the β-directing $(DHQD)_2PHAL$ ligand (10 mol %). Initial attempts at reagent-controlled α-dihydroxylation proved difficult owing to the inherent substrate selectivity. AD-mixα, in

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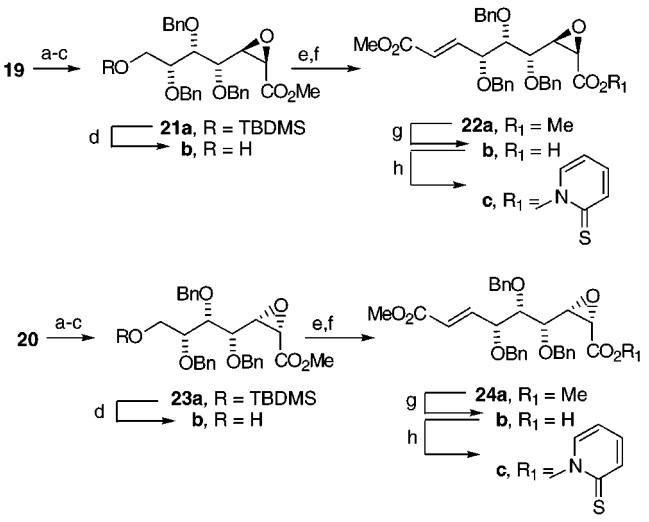
Scheme 6



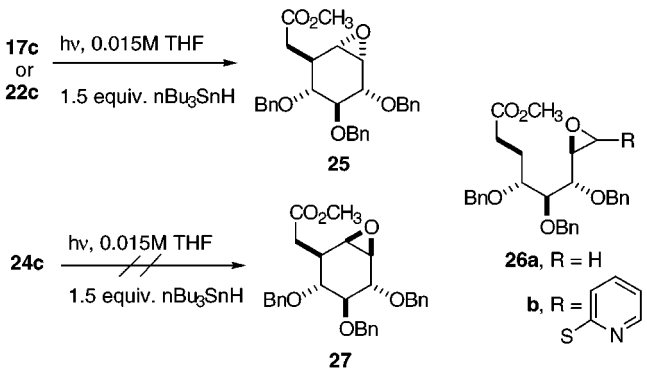
a) NaHMDS, THF. b) NsCl. c) K_2CO_3, MeOH. d) HF, MeCN. e) DMSO, $(COCl)_2$, Et_3N. f) Ph_3PCHCO_2Me. g) LiOH. h) i-BuOCOCl, N-methylmorpholine; Na thiopyridone N-oxide.

addition to being exceptionally slow as a reagent, afforded a 1.5:1 ratio of β: α (**19**:**20**). AD-mixα in conjunction with 6 mol % of OsO_4 and 10 mol % of $(DHQ)_2PYR$ led to a ratio of 3:1 (80%). Substitution of $(DHQ)_2PYR(OMe)_3$, a more effective α-director than $(DHQ)_2PYR$,[25] in the preceding experiment failed to improve the β/α ratio (2.5:1; 81%) in favor of the α-diol **20**. Rewardingly, OsO_4 (6%), $(DHQ)_2PHAL$ (10%), and $K_3Fe(CN)_6$ (3 equiv) gave rise to a predominance of the α-diol **20** (β:α = 1:15) in 88% yield.

Owing to the wide variation in facial selectivity using α-selective protocols, diol **20** was degraded to confirm independently its absolute stereochemistry. Diol **20** was converted into its acetonide (2,2-dimethoxypropane, PPTS) and debenzylated (Pd/C, H_2) to a crude triol. Exhaustive oxidation of the triol ($RuCl_3$, $NaIO_4$)[26] afforded a crude carboxylic acid, which, upon esterification with diazomethane, gave the levorotatory acetonide of dimethyl tartrate derived from natural L-(+)-tartaric acid.

Conversion of the diols **19** and **20** to their respective *cis*-glycidates **21** and **23** was dependent upon the known[27−29] selective C_2 aryl sulfonation of threo α,β-dihydroxy esters followed by base treatment (Scheme 6). This process retains the C_3 stereochemistry, which is necessary in the current study, and effects stereochemical inversion at C_2. Neither diol ester **19** nor **20** could be sulfonated with *p*-nitrobenzenesulfonyl chloride (nosyl chloride, NsCl) in the presence of an amine base as had been prescribed.[29] The diol esters were selectively deprotonated (THF, −40 °C) with 1 equiv of NaHMDS prior to sulfonation with nosyl chloride. Exposure of the nosylates to K_2CO_3 in methanol gave rise to their respective *cis*-glycidic esters.

Scheme 7



N-Hydroxypyridine-2-thione esters **17c**[30] and **22c**, prepared in situ from their respective *trans*- (**17b**) and *cis*- (**22b**) glycidic acids, were independently photolyzed (500 W tungsten lamp) in dilute solution in the presence of *n*-Bu_3SnH to afford consistently a single product of cyclization in ~30% yield after chromatography (Scheme 7). A chromatographic fraction contained a mixture of two additional compounds, which, on the basis of ^1H NMR and past experience, were tentatively assigned as the product of direct reduction **26a** and thiopyridine derivative **26b**. The stereochemistry of the acetic acid residue in epoxide **25** was tentatively assigned the β-configuration (equatorial) in accord with the results of Hanessian (**3** → **4**). Although the yield of product was modest, the reaction was relatively clean. The similar distribution of products in both reactions attests to the rapid inversion of the oxiranyl radical.

With only the *cis*-glycidate **24a** available to test the diastereomeric oxiranyl radical cyclization, its thiohydroxamate ester **24c** was photolyzed under identical conditions. Unfortunately, the reaction mixture was complex, and although no products of the reaction could be isolated in pure form, the ^1H NMR spectrum of some chromatographic fractions indicated the possible presence of the product of cyclization **27**. These results were reproducible, and the difference in the cyclization behavior of the two diastereomeric oxiranyl radicals is unclear.

To ascertain the complete stereochemistry of cyclized epoxide **25** and epoxide **27**, if it indeed did exist in the reaction mixture, an independent route to these substances through cyclohexene **29** was undertaken. Aldehyde **10** was converted into the (*Z*)-vinyl bromide **28** by adaptation of the method of Stork (Scheme 8).[31] When the vinyl bromide was reduced with *n*-Bu_3SnH in dilute solution, the desired cyclohexene **29** was not obtained but rather a product was isolated in ~30% yield whose ^1H NMR spectrum displayed a vinyl group and the absence of enoate vinyl protons. These data coupled with a HRMS molecular ion consistent with $C_{30}H_{32}O_5$ suggested structure **31** in which only three stereocenters could be defined with certainty. The initially generated vinyl radical apparently abstracts a hydrogen atom from the proximate benzyl group followed by benzyl radical cyclization into the α,β-unsaturated ester.

A successful route to the desired cyclohexene **29** employed the ring closure metathesis reaction (RCM).

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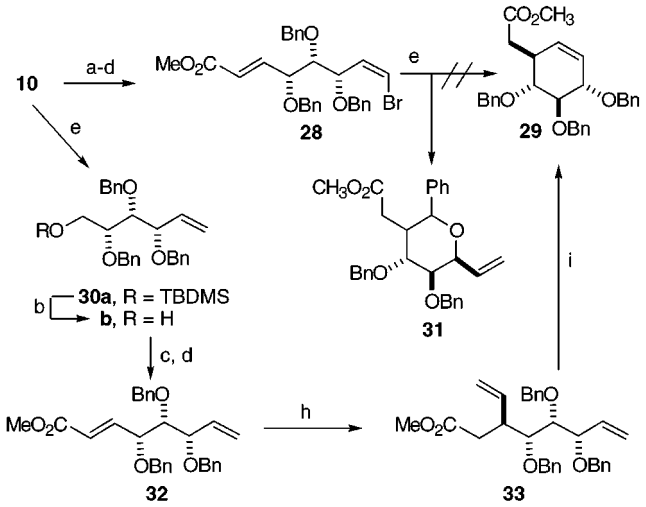
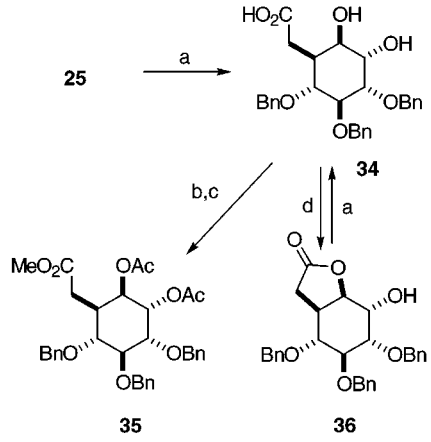
(30) The *N*-hydroxypyridine-2-thione ester **17c** of acid **17b** was prepared in situ as described in the Experimental Section for the esterification of acid **22b** (preparation of **25**).
(31) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173.

Scheme 8



a) Ph_3PCHBr. b) TBAF. c) DMSO, $(COCl)_2$, Et_3N. d) Ph_3PCHCO_2Me. d) n-Bu_3SnH. e) $Cp_2TiCH_2ClAlMe_2$. h) $(CH_2{=}CH)_2CuMgBr$, TMSCl. i) $(Cy_3P)_2Ru(CHPh)Cl_2$.

Scheme 9



a) K_2CO_3, aq. MeOH. b) CH_2N_2. c) Ac_2O. d) EDCI/$(iPr)_2NEt$.

Methylenation of aldehyde **10** under standard Wittig conditions proved too basic as products of elimination of the aldehyde were prevalent. Tebbe's reagent[32] proved to be an effective alternative for the formation of olefin **30a**. At the outset, the formation of divinyl ester **33** by conjugate addition proved to be troublesome. The addition of lithium cuprates to γ-alkoxy-α,β-unsaturated esters had been shown to be stereoselective,[33,34] proceeding through a nonchelation, vinylogous Felkin−Anh transition state.[35,36] A number of instances of the addition lithium vinyl cuprates have been reported[35,36] and on occasion were found to perform inconsistently, an observation that is in accord with our own experience. Different protocols for employing magnesium-based vinyl cuprates in 1,4-additions to γ-alkoxy-α,β-unsaturated esters have been advanced by Augé[37] and Hanessian.[38] The latter procedure was more amenable and reproducible (90% yield) when applied to unsaturated ester **32**. Cyclohexene **29** was formed readily from dienic ester **33** using Grubbs' RCM protocol.[39] At this juncture the stereochemical relationship of the acetic acid residue and the proximate benzyloxy group had been established as a result of the stereoselective vinyl cuprate addition.

Epoxidation of cyclohexene **29** with urea−hydrogen peroxide complex/trifluoroacetic anhydride[40] led to a 3:1 mixture of epoxides **27** and **25**, respectively. The major epoxide **27** was detected in the reaction mixture from the ill-fated cyclization of thiohydroxamate **24c**; the minor epoxide was identical with the epoxide formed from the radical cyclization of thiohydroxamates **17c** and **22c**.

Realizing that the oxiranyl radical cyclization to form six-membered rings was inefficient in this instance, we nonetheless sought to exploit the α-epoxide **25**, which had been formed in modest yield, as a substrate for the synthesis of epi-cyclophellitol (**2**). Whereas β-epoxide **27** underwent saponification to form cleanly the epoxy acid, saponification of α-epoxy ester **25** with K_2CO_3/aqueous MeOH led to the dihydroxy acid **34** (Scheme 9). The stereochemistry of the latter compound was confirmed through the ^1H NMR spectrum of the diacetoxy methyl ester **35**. The dihedral coupling constant, $J = \sim 3.2$ Hz, between the two acetoxy methine hydrogens (triplets) indicated that the two acetoxy groups were diaxial assuming that the four other substituents occupy equatorial positions in a chair cyclohexane. Two mechanisms present themselves for the formation of the dihydroxy acid: direct opening of the epoxide by hydroxide or carboxylate participation. Although no definitive distinction between the two mechanisms could be established, the possibility that carboxylate participation was operable was confirmed by first conversion of dihydroxy acid **34** to hydroxy lactone **36**. The lactone was readily converted into the dihydroxy acid under mild conditions in the presence of K_2CO_3/aqueous MeOH, demonstrating that lactone **36** could have been generated during the saponification and rapidly consumed.

Not only did cyclohexene **29** serve as a means of establishing the stereochemistry of the oxiranyl radical cyclization, but it also presented itself as an attractive entry toward the synthesis of cyclophellitol.[11] Saponification and iodolactonization of ester **29** lead to iodolactone **37** (92%), which, upon exposure to methanolic K_2CO_3, afforded the β-epoxide **27** (Scheme 10). Given the mechanism of iodolactonization, the formation of the β-epoxide confirmed the stereochemical relationship between the epoxide and the acetic acid residue.

Epoxy ester **27**, available stereoselectively through iodolactonization and less so by direct epoxidation of cyclohexene **29**, required oxidative decarboxylation to realize cyclophellitol. As noted earlier, this ester could be saponified without difficulty to acid **41a** (Scheme 11). Its Barton ester **41b**,[41] upon photolysis in the presence

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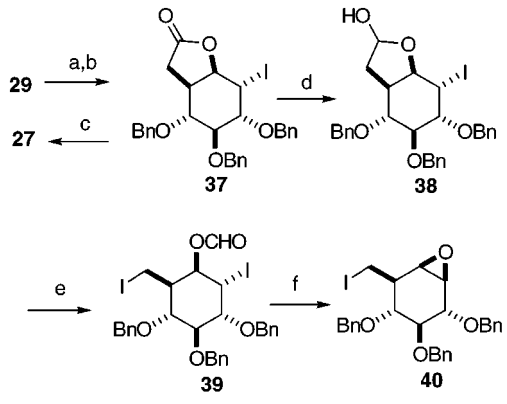
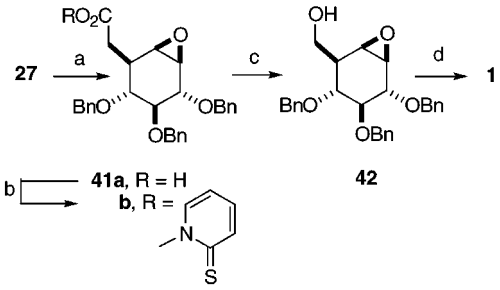
Scheme 10



a) LiOH. b) $KHCO_3$, KI, I_2. c) K_2CO_3, MeOH.
d) DIBALH. e) $PhI(OAc)_2$, I_2, hv. f) KOH.

Scheme 11

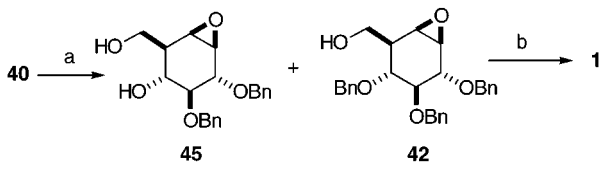


a) LiOH. b) 2,2'-dithiobis(pyridine N-oxide), Bu_3P.
c) $Sb(SPh)_3$, O_2. d) $Pd(OH)_2/C$, H_2.

of O_2,[42] afforded alcohol **42** in modest yield 30% with an equal amount of acid **41a** being recovered. However, oxidative degradation in the presence of $Sb(SPh)_3$ raised the yield of **42** to 60%.[43] Hydrogenolysis of the benzyl ethers in **42** in the presence $Pd(OH)_2/C$ gave rise to (+)-cyclophellitol (**1**), whose 500 MHz ^1H NMR spectrum was identical with that of an enantiomerically pure synthetic sample provided by Professor Tatsuta.

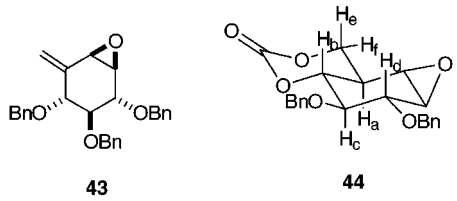
Iodolactone **37** provided an additional route to cyclophellitol in which degradation preceded epoxide formation (Scheme 10). Efforts to degrade the lactone via oxidative cleavage of enol lactone derivatives were unsuccessful as was alkoxy hydroperoxide rearrangement.[44,45] However, Sáurez radical fragmentation[46,47] of lactol **38** with $PhI(OAc)_2/I_2$ readily provided the diodoformate **39**.[48] Attempts to substitute the primary iodide of **39** with hydroxide (KOH, aqueous DMF) at room temperature led to exclusive formation of olefin **43**, which had previously been converted to benzylated cyclophellitol **42**.[49] An improvement in selectivity was seen when KO_2 gave a 1:1 mixture of olefin **43** and epoxy alcohol

Scheme 12

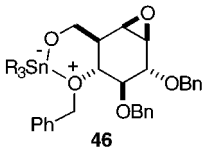


a) n-Bu_3SnH, O_2. b) $Pd(OH)_2/C$, H_2.

42.[50] Although both of these compounds were useful for our ultimate goal, we chose to maximize the formation of alcohol **42**.



The nucleophilic approach was abandoned in favor of a radical solution. Exposure of diiodoformate **39** to KOH in aqueous THF led to iodo epoxide **40** without elimination. Alkyl bromides and iodides have been converted to alcohols with *n*-Bu_3SnH in the presence of O_2.[51−53] Accordingly, iodo epoxide **40** was converted into epoxy alcohol **42** (70%) along with the formation of epoxy diol **45a** (10%) (Scheme 12). The position of the secondary hydroxyl group in the diol was ascertained through the formation of cyclic carbonate **44**. The coupling pattern $J_{ab} = J_{bc}$ =10.2 Hz and J_{ae} = 10.3 Hz in the ^1H NMR spectrum reaffirmed the trans relationship of the acetic acid moiety to the proximate benzyloxy groups. The formation of epoxy diol **45** probably arises through an ionic process in which iodide ion cleaves the proximate benzyl group, which is activated as a stannyl complex (**46**). Finally, the mixture of epoxy alcohol **42** and epoxy diol **45** was hydrogenated to afford (+)-cyclophellitol identical with the sample prepared earlier.



Experimental Section

Unless otherwise stated, all reactions were carried out in flame-dried glassware, under N_2. Ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl under N_2. Methylene chloride (CH_2Cl_2), benzene, toluene, diisopropylamine (*i*-Pr_2NH), and hexanes were distilled from CaH_2. Other solvents (ACS photometric grade) were used without further purification. Commercially available reagents were used as received. Alkyllithiums were titrated by the method of Lipton.[54] Flash chromatography employed J. T. Baker 40 μm silica gel. Workup means drying over $MgSO_4$, filtration, and concentration in *vacuo*.

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Melting points are uncorrected. Optical rotations were recorded in $CHCl_3$ containing 1% EtOH at 20 °C. FT-IR were recorded in $CDCl_3$ or $CHCl_3$. NMR spectra were recorded as follows unless stated otherwise: ^{1}H NMR (300 MHz; $CDCl_3$, $\delta = 7.26$ ppm) and ^{13}C NMR (75 MHz, $\delta = 77.0$ ppm). Low-resolution mass spectra were recorded in either chemical ionization (CI, 2-methylpropane as a reagent gas) or electron ionization (EI) mode. High-resolution mass spectra (HRMS; CI or FAB; ±1 ppm) were recorded at the Mass Spectrometry Laboratory, University of Illinois, Urbana-Champaign, IL. Combustion analyses were determined by Atlantic Microlab, Inc., Norcross, GA.

Compound names were generated by ACD/Name (Advanced Chemistry Development, Inc.) according to IUPAC guidelines.

(2*R*,3*S*,4*R*)-5-{[1-(*tert*-Butyl)-1,1-dimethylsilyl]oxy}-1,1-bis(ethylthio)pentane-2,3,4-triol (8b). A solution of dithioacetal **8a** (15 g, 58.6 mmol) in CH_2Cl_2 (60 mL) was treated with imidazole (5.2 g, 76.2 mmol). After 5 min, (TBDMS)Cl (10.6 g, 70.3 mmol) was added and the resulting white slurry was stirred for 3 h. Saturated NH_4Cl was added, and the mixture was partitioned between H_2O and CH_2Cl_2. The combined organic extracts were washed with brine and worked up. Flash chromatography with 20−50% EtOAc/hexanes afforded silyl ether **8b** (16.9 g, 78%) as a white solid: mp 62 °C; $[\alpha]_D$ +32.9 (*c* 1.0, $CHCl_3$); IR 3552 cm^{-1}; ^{1}H NMR δ 4.15 (bd, $J = 6.6$ Hz, 1H), 4.11 (d, $J = 8.9$ Hz, 1H), 3.83 (m, 1H), 3.75 (d, $J = 5.5$ Hz, 2H), 3.65 (d, $J = 8.0$ Hz, 1H), 3.50 (bs, 1H), 3.10 (bs, 1H), 2.82 (m, 1H), 2.78−2.67 (m, 4H), 1.30 (t, $J = 7.4$ Hz, 6H), 0.93 (s, 9H), 0.11 (s, 6H); ^{13}C NMR δ −5.36, 14.53, 14.66, 18.32, 23.90, 25.79, 25.92, 55.26, 64.11, 69.10, 73.69, 74.60. Anal. Calcd for $C_{15}H_{34}O_4SiS_2$: C, 48.61; H, 9.25. Found: C, 48.67; H, 9.21.

***tert*-Butyl(dimethyl){[(2*R*,3*S*,4*R*)-2,3,4-tris(benzyloxy)-5,5-bis(ethylthio)pentyl]oxy}silane (9).** To a THF (1 mL) suspension of NaH (95%, 27 mg, 1.08 mmol) at 0 °C was added a solution of triol **8b** (100 mg, 0.27 mmol) in THF (0.5 mL), and the mixture was stirred at room temperature for 1.5 h. After cooling of the mixture to 0 °C, benzyl bromide (0.15 mL, 1.26 mmol) and *n*-$Bu_4N^+I^-$ (10 mg, 0.03 mmol) were added. The white slurry was stirred for 8 h at room temperature. A solution of saturated NH_4Cl (2 mL) was slowly added at 4 °C, and the mixture was partitioned between H_2O and Et_2O. The combined organic extracts were washed with brine and worked up. Flash chromatography with 0−10% EtOAc/hexanes afforded tribenzyl ether **9** (0.14 g, 80%) as a light yellow oil: $[\alpha]_D$ −7.5 (*c* 4.0, $CDCl_3$); ^{1}H NMR δ 7.24−7.39 (m, 15H), 4.57−4.92 (m, 6H), 4.07−4.15 (m, 2H), 3.77−3.82 (m, 3H), 3.62 (m, 1H), 2.70 (q, $J = 7.4$ Hz, 2H), 2.55 (qd, $J = 7.3$, 1.6 Hz, 2H), 1.20 (t, $J = 7.0$ Hz, 3H), 1.18 (t, $J = 7.0$ Hz, 3H), 0.90 (s, 9H), 0.04 (d, $J = 4.5$ Hz, 6H); ^{13}C NMR δ −5.26, 14.53, 18.28, 25.11, 25.37, 26.01, 53.80, 63.02, 72.59, 75.25, 75.30, 79.32, 80.16, 83.07, 127.38, 127.62, 127.74, 128.25, 128.32, 128.44, 138.51, 138.74. Anal. Calcd for $C_{36}H_{52}O_4SiS_2$: C, 67.45; H, 8.18. Found: C, 67.55; H, 8.19.

(2*R*,3*S*,4*R*)-2,3,4-Tris(benzyloxy)-5-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}pentanal (10). A mixture of dithioacetal **9** (1 g, 2.19 mmol) and mercuric oxide (0.85 g, 3.92 mmol) in 95% aqueous acetone (18 mL) was heated to reflux at which time a suspension of mercuric chloride (1.06 g, 3.90 mmol) in acetone (4 mL) was added dropwise over a period of 40 min. After 5 h the hot solution was filtered and the filtrate was treated with $NaHCO_3$ (0.33 g in 1 mL of H_2O). The mixture was evaporated, and the residue was taken up in $CHCl_3$. The mixture was washed with H_2O, aqueous KI (10% w/v; 70 mL), and brine. After workup, the crude residue was chromatographed (25% EtOAc/hexanes) to afford aldehyde **10** (0.63 g, 77%) as a light yellow oil: $[\alpha]_D$ +13.6 (*c* 1.0, $CHCl_3$); IR 1727 cm^{-1}; ^{1}H NMR δ 9.73 (s, 1H), 7.24−7.34 (m, 15H), 4.48−4.80 (m, 6H), 3.97 (m, 1H), 3.89 (d, $J = 5.3$ Hz, 1H), 3.67 (m, 2H), 3.55 (m, 1H), 0.87 (s, 9H), 0.00 (d, $J = 1.8$ Hz, 6H); ^{13}C NMR δ −5.33, 18.24, 25.98, 61.67, 73.01, 73.28, 74.23, 78.26, 78.80, 81.30, 127.79, 128.09, 128.27, 128.37, 128.50, 137.44, 137.76, 138.12, 200.83; HRMS (FAB) calcd for $C_{32}H_{43}O_5Si$ $(M + H)^+$ *m/e* 535.2880, found *m/e* 535.2882.

(2*R*,3*S*,4*R*)-2,3,4-Tris(benzyloxy)-5,5-bis(ethylthio)pentan-1-ol (11). To a solution of silyl ether **9** (2.0 g, 3.1 mmol) in THF (12 mL), was added *n*-$Bu_4N^+F^-$ (1.0 M in THF, 4.3 mL, 4.3 mmol) at 0 °C, and the resulting solution was warmed to room temperature and stirred for 2 h. The mixture was then treated with saturated NH_4Cl, diluted with H_2O, and extracted with EtOAc. The combined organic layers were washed with brine and worked up. The residue was chromatographed with 20−45% EtOAc/hexanes to afford alcohol **11** (1.45 g, 88%) as a light yellow oil: $[\alpha]_D$ −4.2 (*c* 1.55, $CHCl_3$); IR 3581 cm^{-1}; ^{1}H NMR δ 7.29−7.41 (m, 15H), 4.59−4.95 (m, 6H), 4.19 (t, $J = 5.1$ Hz, 1H), 4.07 (dd, $J = 5.6$, 4.1 Hz, 1H), 3.99 (d, $J = 4.0$ Hz, 1H), 3.84 (m, 1H), 3.66−3.72 (m, 2H), 2.70 (q, $J = 7.4$ Hz, 2H), 2.57−2.64 (m, 2H), 2.10 (m, 1H), 1.21 (t, $J = 7.4$ Hz, 6H); ^{13}C NMR δ 14.57, 25.30, 25.44, 53.41, 61.63, 72.17, 74.91, 75.13, 78.46, 80.24, 82.31, 127.63, 127.94, 127.99, 128.19, 128.37, 128.53, 128.59, 138.04, 138.27, 138.53. Anal. Calcd for $C_{30}H_{38}O_4S_2$: C, 68.41; H, 7.27. Found: C, 68.48; H, 7.28.

Methyl (*E*,4*R*,5*S*,6*R*)-4,5,6-Tris(benzyloxy)-7,7-bis(ethylthio)-2-heptenoate (12). To a solution of alcohol **11** (0.5 g, 0.95 mmol) in CH_2Cl_2/CH_3CN (4:1, 12 mL) at room temperature was added 4-methylmorpholine *N*-oxide (0.23 g, 1.9 mmol) and powdered 4 Å molecular sieves (0.47 g). After the mixture was stirred for 15 min, *n*-$Pr_4N^+RuO_4^-$ (TPAP) (17 mg, 0.05 mmol) was added in one portion. The dark green mixture turned black after 5 min, and the reaction mixture was stirred for another 45 min until the reaction was complete (TLC). The solvent was removed in *vacuo*. The residue was taken up in CH_2Cl_2 (1 mL), filtered through a short silica gel column, and further eluted with pure EtOAc. The combined filtrate was concentrated to afford a crude aldehyde which was used directly in the next step.

A solution of the crude, intermediate aldehyde and methyl (triphenylphosphoranylidene)acetate (0.6 g, 1.80 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature for 6 h. The reaction was quenched with saturated NH_4Cl and diluted with H_2O, and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with brine and worked up. Chromatography with 5−20% EtOAc/hexanes afforded unsaturated ester **12** (0.24 g, 40%) as a light yellow oil: $[\alpha]_D$ −12.9 (*c* 1.7, $CHCl_3$); IR 1720 cm^{-1}; ^{1}H NMR δ 7.27−7.29 (m, 15H), 7.08 (dd, $J = 15.9$, 5.4 Hz, 1H), 6.12 (dd, $J = 16.1$, 1.1 Hz, 1H), 4.61−4.89 (m, 5H), 4.41 (d, $J = 11.9$ Hz, 1H), 4.15 (m, 1H), 4.09 (dd, $J = 6.4$, 4.1 Hz, 1H), 3.96 (dd, $J = 6.4$, 4.0 Hz, 1H), 3.83 (d, $J = 4.0$ Hz, 1H), 3.76 (s, 3H), 2.62 (q, $J = 7.4$ Hz, 2H), 2.55 (m, 2H), 1.20 (t, $J = 7.5$ Hz, 3H), 1.17 (t, $J = 7.6$ Hz, 3H); ^{13}C NMR δ 14.44, 14.58, 25.19, 25.47, 51.71, 53.39, 71.55, 75.20, 75.25, 77.63, 81.30, 82.52, 122.60, 127.42, 127.64, 127.74, 127.80, 128.09, 128.24, 128.38, 128.53, 128.59, 137.37, 138.10, 138.65, 145.61, 166.37. Anal. Calcd for $C_{33}H_{40}O_5S_2$: C, 68.24; H, 6.94. Found: C, 68.25; H, 6.90.

Methyl (*E*,4*R*,5*S*,6*R*)-4,5,6-Tris(benzyloxy)-7-oxo-2-heptenoate (13). A mixture of dithioacetal **12** (1.85 g, 3.18 mmol) and HgO (1.73 g, 7.99 mmol) in 95% aqueous acetone (34 mL) was heated at reflux. A suspension of mercuric chloride (2.16 g, 6.37 mmol) in acetone (6 mL) was added dropwise over 30 min. After 5 h the hot solution was filtered and the filtrate was treated with $NaHCO_3$ (0.66 g in 2 mL of H_2O). The mixture was evaporated, and the residue was taken up in $CHCl_3$. The mixture was washed successively with H_2O, aqueous KI (10% w/v; 150 mL), and brine. After workup, the crude residue was chromatographed (25% EtOAc/hexanes) to afford aldehyde **13** (1.29 g, 85%) as a light yellow oil: $[\alpha]_D$ +5.6 (*c* 0.71, $CHCl_3$); IR 2871, 1726 cm^{-1}; ^{1}H NMR δ 9.56 (s, 1H), 7.11−7.27 (m, 15H), 6.79 (dd, $J = 15.8$, 6.0 Hz, 1H), 5.93 (dd, $J = 15.6$, 0.9 Hz, 1H), 4.64 (d, $J = 11.8$ Hz, 1H), 4.50 (m, 2H), 4.40 (d, $J = 12.0$ Hz, 2H), 4.29 (d, $J = 11.4$ Hz, 1H), 4.18 (td, $J = 4.6$, 1.0 Hz, 1H), 3.79 (d, $J = 4.4$ Hz, 1H), 3.72 (t, $J = 4.4$ Hz, 1H), 3.65 (s, 3H); ^{13}C NMR δ 51.76, 72.09, 73.40, 74.37, 80.78, 81.78, 123.21, 128.00, 128.20, 128.30, 128.39, 128.55, 128.64, 136.96, 137.10, 137.15, 144.62, 166.29; HRMS (CI) calcd for $C_{29}H_{31}O_6$ $(M + H)^+$ *m/e* 475.2121, found *m/e* 475.2120.

Methyl (2*E*,4*R*,5*R*,6*S*,7*E*)-4,5,6-Tris(benzyloxy)-9-oxo-2,7-nonadienoate (14a). A solution of aldehyde **13** (0.86 g, 1.81 mmol) and triphenylphosphoranylideneacetaldehyde (0.78 g, 2.56 mmol) in benzene (30 mL) was heated at reflux for 12 h. The reaction mixture was cooled to room temperature, quenched with saturated NH_4Cl, and diluted with H_2O. The layers were separated, and the aqueous layer was further extracted with EtOAc. The combined organic layers were washed with brine and worked up. The crude residue was chromatographed with 10−25% EtOAc/hexanes to afford unsaturated aldehyde **14a** (0.53 g, 58%) as an orange oil: $[\alpha]_D$ −13.3 (*c* 0.75, $CHCl_3$); IR 2871, 1720, 1690 cm^{-1}; ^1H NMR δ 9.31 (d, J = 7.9 Hz, 1H), 7.25−7.39 (m, 15H), 6.90 (dd, J = 15.9, 6.0 Hz, 1H), 6.60 (d, J = 15.8, 5.3 Hz, 1H), 6.23 (dd, J = 15.4, 7.7 Hz, 1H), 6.05 (dd, J = 15.3, 0.8 Hz, 1H), 4.54−4.74 (m, 4H), 4.38 (t, J = 11.9 Hz, 2H), 4.22 (q, J = 4.6 Hz, 2H), 3.77 (s, 3H), 3.55 (t, J = 4.9 Hz, 1H); ^{13}C NMR δ 51.79, 71.81, 72.34, 75.05, 77.96, 78.29, 81.87, 123.21, 128.04, 128.16, 128.32, 128.37, 128.49, 128.61, 128.84, 132.82, 137.18, 137.26, 144.82, 153.84, 166.29, 193.37. Anal. Calcd for $C_{31}H_{32}O_6$: C, 74.38; H, 6.44. Found: C, 74.30; H, 6.48.

Methyl (2*E*,4*R*,5*R*,6*S*,7*E*)-4,5,6-Tris(benzyloxy)-9-hydroxy-2,7-nonadienoate (14b). To a solution of unsaturated aldehyde **14a** (0.53 g, 1.06 mmol) in MeOH (16 mL) at 0 °C was added $NaBH_4$ (40 mg, 1.05 mmol) in two portions, and the resulting mixture was stirred for 40 min. Saturated NH_4Cl was slowly added to the reaction mixture. The mixture was diluted with H_2O (16 mL) and extracted with Et_2O, and the combined organic layers were washed with brine and worked up. The crude residue was chromatographed with 30−60% EtOAc/hexane to afford allylic alcohol **14b** (0.42 g, 80%) as a white solid: mp 93.5 °C; $[\alpha]_D$ +10.3 (*c* 1.32, $CHCl_3$); IR 3611, 1719 cm^{-1}; ^1H NMR δ 7.27−7.33 (m, 15H), 6.88 (dd, J = 15.8, 6.2 Hz, 1H), 6.03 (dd, J = 15.6, 1.0 Hz, 1H), 5.74 (td, J = 15.7, 5.0 Hz, 1H), 5.58 (dd, J = 15.8, 7.5 Hz, 1H), 4.75 (dd, J = 16.3, 11.6 Hz, 2H), 4.59 (dd, J = 11.6, 9.1 Hz, 2H), 4.36 (dd, J = 13.5, 11.7 Hz, 2H), 4.26 (td, J = 5.8, 0.9 Hz, 1H), 3.97−4.02 (m, 3H), 3.76 (s, 3H), 3.47 (t, J = 5.1 Hz, 1H); ^{13}C NMR δ 51.70, 62.83, 70.85, 71.79, 75.22, 79.01, 79.62, 83.22, 122.83, 127.64, 127.78, 127.87, 128.15, 128.22, 128.27, 128.37, 128.47, 128.89, 133.59, 137.81, 138.16, 138.24, 145.52, 166.52; HRMS calcd for $C_{31}H_{35}O_6$ (M + H)$^+$ *m/e* 503.2434, found *m/e* 503.2427.

Methyl (*E*,4*R*,5*S*,6*R*)-4,5,6-Tris(benzyloxy)-6-[(2*S*,3*R*)-3-formyloxiran-2-yl]-2-hexenoate (17a). To a mixture of D-(−)-diethyl tartrate (74 mg, 0.36 mmol) and 4 Å molecular sieves (30 mg) in CH_2Cl_2 (4 mL) at −23 °C was added titanium tetraisopropoxide (92 μL, 0.31 mmol) followed by anhydrous *tert*-butyl hydroperoxide (0.12 mL of 3 M solution in isooctane, 0.36 mmol). After 30 min of stirring at −23 °C, allylic alcohol **14b** (52 mg, 0.10 mmol) in 0.6 mL of CH_2Cl_2 was added dropwise to the mixture. After 30 h at −20 °C (freezer), the cold mixture was quickly filtered through a pad of Celite to remove the sieves and the filtrate was recooled to −23 °C. A mixture of saturated $Na_2S_2O_3$ and $NaHCO_3$ solution (5 mL) was then added to the reaction flask, and the mixture was allowed to warm gradually to room temperature. After dilution with H_2O, the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine and worked up. The residue was chromatographed with 30−55% EtOAc/hexanes to afford epoxy alcohol **15** (∼27 mg, 50%) as an oil which was contaminated with D-(−)-diethyl tartrate.

To a CH_2Cl_2 (1.0 mL) solution of Dess−Martin periodinane[55−57] (33 mg, 0.08 mmol) at room temperature was added crude alcohol **15** (27 mg, 0.05 mmol) in CH_2Cl_2 (0.2 mL), and the resulting white slurry was stirred for another 40 min. The reaction mixture was diluted with Et_2O and poured into saturated $NaHCO_3$ containing a 7-fold excess of $Na_2S_2O_3$. The mixture was stirred until two clear layers appeared. After separation, the aqueous layer was extracted with Et_2O. The combined organic layers were washed successively with saturated $NaHCO_3$, H_2O, and brine. After workup, the crude residue was chromatographed with 10−30% EtOAc/hexanes to afford epoxy aldehyde **17a** (16 mg, 30% from allylic alcohol **14b**) as a colorless oil: $[\alpha]_D$ −10.0 (*c* 0.7, $CHCl_3$); IR 1728 cm^{-1}; ^1H NMR δ 8.84 (d, J = 6.0 Hz, 1H), 7.25−7.39 (m, 15H), 6.94 (dd, J = 15.9, 6.0 Hz, 1H), 6.06 (dd, J = 16.1, 1.0 Hz, 1H), 4.39−4.76 (m, 6H), 4.27 (m, 1H), 3.76 (s, 3H), 3.63 (m, 2H), 3.34 (m, 2H); ^{13}C NMR δ 51.79, 55.91, 57.46, 71.98, 73.94, 74.92, 76.12, 78.03, 80.62, 122.95, 128.12, 128.57, 128.64, 137.35, 137.47, 144.72, 166.32, 197.60; HRMS (CI) Calcd for $C_{31}H_{33}O_7$ (M + H)$^+$ *m/e* 517.2226, found *m/e* 517.2228.

(2*S*,3*R*)-3-[(1*R*,2*S*,3*R*,4*E*)-1,2,3-Tris(benzyloxy)-6-methoxy-6-oxo-4-hexenyl]oxirane-2-carboxylic acid (17b). To a CH_3CN (1.3 mL) solution of aldehyde **17a** (65 mg, 0.126 mmol), at 0 °C was added NaH_2PO_4 (9.3 mg, 0.08 mmol) in H_2O (0.6 mL) and H_2O_2 (73 μL of 30% solution, 1.21 mmol). After 5 min a solution of sodium chlorite (45 mg, 0.50 mmol) in H_2O (1.2 mL) was slowly added over 40 min, and the resulting mixture was stirred for 1 h at 0 °C and 3 h at room temperature.[58] The solvent was removed in *vacuo* without heating, and the residue was diluted with H_2O. The mixture was carefully acidified to pH 4 with 1 N HCl, and the mixture was extracted with Et_2O. The combined ether layers were concentrated in *vacuo*, and the residue was redissolved in CH_2Cl_2. The organic layer was washed with brine and worked up to afford acid **17b** (51 mg, 76%) as a colorless oil, which was used directly in the oxiranyl radical cyclization experiment. A sample of this sensitive acid was characterized as its methyl ester.

To a solution of acid **17b** in Et_2O at 0 °C was slowly added diazomethane in Et_2O until the solution became yellow. A small amount of AcOH was added to destroyed the residual diazomethane. The organic layer was washed successively with saturated $NaHCO_3$, H_2O and brine. Workup and chromatography afforded methyl glycidate **17d** as a colorless oil: $[\alpha]_D$ +20.0 (*c* 0.35, $CHCl_3$); IR 1744, 1722 cm^{-1}; ^1H NMR δ 7.25−7.36 (m, 15H), 6.92 (dd, J = 15.8, 6.0 Hz, 1H), 6.04 (dd, J = 15.6, 1.1 Hz, 1H), 4.40−4.75 (m, 6H), 4.36 (td, J = 5.9, 1.1 Hz, 1H), 3.73 (s, 3H), 3.66 (s, 3H), 3.62 (m, 1H), 3.56 (t, J = 4.2 Hz, 1H), 3.48 (t, J = 1.8 Hz, 1H), 3.39 (dd, J = 4.3, 2.0 Hz, 1H); ^{13}C NMR δ 51.63, 51.73, 52.48, 57.32, 71.88, 73.78, 74.96, 76.24, 78.28, 80.73, 122.82, 127.80, 127.86, 127.97, 128.09, 128.47, 137.57, 137.66, 144.82, 166.36, 169.07; HRMS (CI) calcd for $C_{32}H_{35}O_8$ (M + H)$^+$ *m/e* 547.2332, found *m/e* 547.2323.

Methyl (*E*,4*S*,5*R*,6*R*)-4,5,6-Tris(benzyloxy)-7-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}-2-heptenoate (18). To a CH_2Cl_2 (200 mL) solution of aldehyde **10** (9.6 g, 18.0 mmol) was added methyl (triphenylphosphoranylidene)acetate (12 g, 39.4 mmol), and the resulting mixture, was stirred for 10 h. Water was added to the reaction mixture and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with brine and worked up. The residue was chromatographed with 5−20% EtOAc/hexanes to afford unsaturated ester **18** (9.2 g, 86%) as a colorless oil: $[\alpha]_D$ +5.4 (*c* 1.3, $CHCl_3$); IR 1718, 1096 cm^{-1}; ^1H NMR δ 7.27−7.37 (m, 15H), 6.93 (dd, J = 15.8, 6.0 Hz, 1H), 6.01 (d, J = 15.7 Hz, 1H), 4.51−4.57 (m, 5H), 4.41 (d, J = 11.7 Hz, 1H), 4.25 (td, J = 5.8, 1.1 Hz, 1H), 3.74 (s, 3H), 3.59−3.77 (m, 4H), 0.87 (s, 9H), 0.00 (d, J = 1.9 Hz, 6H); ^{13}C NMR δ −5.36, 18.25, 25.95, 51.63, 62.43, 71.85, 73.08, 74.99, 78.79, 79.53, 80.06, 122.21, 127.61, 127.71, 127.78, 127.83, 128.04, 128.09, 128.33, 128.47, 128.58, 137.81, 138.30, 138.61, 145.85, 166.58. Anal. Calcd for $C_{35}H_{46}O_6Si$: C, 71.15; H, 7.85. Found: C, 71.23; H, 7.82.

Methyl (2*S*,3*S*,4*S*,5*S*,6*R*)-4,5,6-Tris(benzyloxy)-7-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy-2,3-dihydroxyheptanoate (19). To a well-stirred mixture of $(DHQD)_2$−PHAL (0.5 g, 0.64 mmol), $K_3Fe(CN)_6$ (6.4 g, 19.43 mmol), K_2CO_3 (2.6 g, 19.3 mmol), and $CH_3SO_2NH_2$ (0.61 g, 6.42 mmol) in 1:1 *t*-BuOH−H_2O (76 mL) at 0 °C was added OsO_4 (2.5 mL of 4% aqueous solution, 0.4 mmol). After 15 min, α,β-unsaturated ester **18** (3.8 g, 6.44 mmol) in *t*-BuOH was added over 20 min and the mixture was stirred for another 36 h at 0 °C. Solid

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sodium sulfite (20 g) was added, and the mixture was stirred for 30 min at 0 °C and allowed to warm to room temperature. EtOAc was added, and the layers were separated. The aqueous layer was further extracted with EtOAc. The combined organic phases were worked up and chromatographed with 20−35% EtOAc/hexanes to afford diol **19** (3.8 g, 92%; **19**:**20**, 20:1) as a colorless oil: $[\alpha]_D$ −13.5 (*c* 2.0, $CHCl_3$); IR 3543, 1743 cm^{-1}; ^1H NMR δ 7.30−7.37 (m, 15H), 4.58−4.77 (m, 6H), 4.46 (d, J = 8.4 Hz, 1H), 4.21 (m, 1H), 3.87−3.95 (m, 2H), 3.76−3.78 (m, 2H), 3.75 (s, 3H), 3.52 (d, J = 2.9 Hz, O*H*, 1H), 3.02 (d, J = 2.9 Hz, O*H*, 1H), 0.91 (s, 9H), 0.06 (s, 6H); ^{13}C NMR δ −5.32, 18.29, 25.79, 25.98, 52.54, 61.98, 70.99, 73.11, 73.45, 73.75, 74.70, 78.79, 127.78, 127.97, 128.06, 128.23, 128.28, 128.39, 128.51, 137.64, 137.86, 137.99, 174.22. Anal. Calcd for $C_{35}H_{48}O_8Si$: C, 67.28; H, 7.74. Found: C, 67.18; H, 7.77.

Methyl (2*R*,3*R*,4*S*,5*S*,6*R*)-4,5,6-Tris(benzyloxy)-7-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}-2,3-dihydroxyheptanoate (20). Diol **20** was prepared from α,β-unsaturated ester **18** (4 g, 6.8 mmol) by the same procedure used for the preparation of diol **19**. After chromatography with 20−35% EtOAc/hexanes, diol **20** (3.75 g, 88%; **20**:**19**, 15:1) was obtained as a colorless oil: $[\alpha]_D$ −16.8 (*c* 1.35, $CHCl_3$); IR 3550, 1741, 1096 cm^{-1}; ^1H NMR δ 7.31−7.37 (m, 15H), 4.53−4.83 (m, 6H), 4.28 (dd, J = 5.5, 2.7 Hz, 1H), 4.09 (bm, 1H), 3.76−3.93 (m, 2H), 3.73 (bs, 3H), 3.61 (s, 3H), 3.06 (d, J = 5.6 Hz, O*H*, 1H), 2.92 (d, J = 7.3 Hz, O*H*, 1H), 0.89 (m, 9H), 0.02 (bs, 6H); ^{13}C NMR δ −5.31, 18.25, 25.99, 52.57, 62.54, 71.61, 73.14, 74.23, 74.53, 77.65, 78.34, 78.80, 78.97, 127.72, 127.88, 127.96, 128.10, 128.22, 128.41, 128.49, 128.54, 138.06, 138.14, 138.46, 173.66. Anal. Calcd for $C_{35}H_{48}O_8Si$: C, 67.28; H, 7.74. Found: C, 67.03; H, 7.81.

Methyl (2*R*,3*S*)-3-((1*R*,2*S*,3*R*)-1,2,3-Tris(benzyloxy)-4-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}butyl)oxirane-2-carboxylate (21a). Glycidate **21a** was prepared from diol ester **19** (3 g, 4.8 mmol) as described for the preparation of glycidate **23a** (vide infra). After flash chromatography with 10−20% EtOAc/hexanes, *cis*-glycidate **21a** (1.96 g, 67%) was obtained as a colorless oil: $[\alpha]_D$ −8.0 (*c* 0.65, $CHCl_3$); IR 1751, 1090 cm^{-1}; ^1H NMR δ 7.28−7.40 (m, 15H), 4.73 (bs, 4H), 4.51 (d, J = 11.3 Hz, 1H), 4.42 (d, J = 11.3 Hz, 1H), 3.76−3.79 (m, 4H), 3.68 (m, 1H), 3.65 (s, 3H), 3.59 (d, J = 4.6 Hz, 1H), 3.48 (dd, J = 6.8, 4.2 Hz, 1H), 0.88 (bs, 9H), 0.01 (bs, 6H); ^{13}C NMR δ −5.30, 18.28, 26.00, 52.33, 52.93, 56.87, 62.89, 72.92, 73.18, 74.86, 74.99, 79.19, 79.80, 127.46, 127.73, 127.82, 128.02, 128.26, 128.32, 128.40, 137.89, 138.34, 138.99, 168.56. Anal. Calcd for $C_{35}H_{46}O_7Si$: C, 69.28; H, 7.64. Found: C, 69.02; H, 7.58.

Methyl (2*R*,3*S*)-3-[(1*R*,2*S*,3*R*)-1,2,3-Tris(benzyloxy)-4-hydroxybutyl]oxirane-2-carboxylate (21b). To a solution of silyl ether **21a** (2.5 g, 4.1 mmol) in CH_3CN (55 mL) at −20 °C was added dropwise a solution of HF (6.1 mL of 48% solution, 146.4 mmol) in CH_3CN (37 mL) via a polyethylene syringe. After 2.5 h of stirring at −20 → −10 °C, $NaHCO_3$ (13 g, 155 mmol) in H_2O (200 mL) was carefully added and the resulting mixture was vigorously stirred at room temperature for 40 min. (Note: It is critical that the mixture is basic.) The mixture was extracted with Et_2O, and the combined organic phases were washed with brine and worked up. The residue was purified 20−50% EtOAc/hexanes to afford alcohol **21b** (1.8 g, 88%) as a colorless oil: $[\alpha]_D$ −5.0 (*c* 1.6, $CHCl_3$); IR 3587, 1750 cm^{-1}; ^1H NMR δ 7.26−7.35 (m, 15H), 4.77 (s, 2H), 4.75 (d, J = 10.4 Hz, 1H), 4.61 (d, J = 11.6 Hz, 1H), 4.57 (d, J = 11.5 Hz, 1H), 4.37 (d, J = 11.6 Hz, 1H), 3.94 (dd, J = 6.3, 3.1 Hz, 1H), 3.83 (m, 1H), 3.68−3.79 (m, 2H), 3.70 (s, 3H), 3.57 (t, J = 5.7 Hz, 1H), 3.51 (dd, J = 7.4, 4.0 Hz, 1H), 2.00 (t, J = 6.4 Hz, 1H); ^{13}C NMR δ 52.50, 53.26, 56.60, 61.78, 72.49, 73.08, 73.92, 74.92, 79.42, 79.51, 127.82, 127.94, 128.00, 128.05, 128.49, 137.44, 138.05, 138.35, 168.53. Anal. Calcd for $C_{29}H_{32}O_7$: C, 70.71; H, 6.55. Found: C, 70.61; H, 6.57.

Methyl (2*R*,3*S*)-3-[(1*R*,2*S*,3*R*,4*E*)-1,2,3-Tris(benzyloxy)-6-methoxy-6-oxo-4-hexenyl]oxirane-2-carboxylate (22a). To a solution of oxalyl chloride (0.12 mL, 1.38 mmol) in dry CH_2Cl_2 (5 mL) at −78 °C was added DMSO (0.22 mL, 3.10 mmol) in CH_2Cl_2 (0.5 mL) over 10 min, and the mixture was stirred for 20 min. A solution of alcohol **21b** (0.4 g, 0.81 mmol) in CH_2Cl_2 (2 mL) was added dropwise over 10 min. After 40 min of stirring at −78 °C, Et_3N (0.56 mL, 4.01 mmol) was added, and the resulting white slurry was stirred for another 15 min and allowed to warm slowly to −30 °C. To the reaction mixture at −30 °C was added methyl (triphenylphosphoranylidene)acetate (0.57 g, 1.79 mmol) in one portion, and the resulting mixture was stirred for 6 h while it was allowed to warm gradually to room temperature. Water was added, and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2, and the combined organic phases were washed with brine and worked up. The residue was chromatographed with 10−30% EtOAc/hexanes to afford unsaturated ester **22a** (0.39 g, 88%) as a colorless oil: $[\alpha]_D$ −4.3 (*c* 3.1, $CHCl_3$); IR 1721, 1280, 1070 cm^{-1}; ^1H NMR δ 7.23−7.33 (m, 15H), 6.91 (dd, J = 15.7, 6.0 Hz, 1H), 5.99 (dd, J = 15.7, 1.1 Hz, 1H), 4.81 (d, J = 11.4 Hz, 1H), 4.74 (d, J = 11.4 Hz, 1H), 4.46−4.58 (m, 3H), 4.27−4.32 (m, 2H), 3.83 (dd, J = 6.4, 3.0 Hz, 1H), 3.72 (s, 3H), 3.67 (s, 3H), 3.64 (t, J = 3.7 Hz, 1H), 3.59 (d, J = 4.0 Hz, 1H), 3.48 (dd, J = 7.3, 4.1 Hz, 1H); ^{13}C NMR δ 51.62, 52.39, 53.30, 56.51, 71.94, 72.59, 74.14, 75.23, 78.67, 81.23, 122.56, 127.78, 127.90, 127.95, 128.03, 128.42, 128.54, 137.51, 137.86, 138.00, 145.06, 166.42, 168.49. Anal. Calcd for $C_{32}H_{34}O_8$: C, 70.31; H, 6.27. Found: C, 70.37; H, 6.29.

Methyl (2*S*,3*R*)-3-((1*R*,2*S*,3*R*)-1,2,3-Tris(benzyloxy)-4-{[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy}butyl)oxirane-2-carboxylate (23a). To a THF (6.5 mL) solution of diol ester **20** (0.4 g, 0.64 mmol) at −78 °C was added sodium bis(trimethylsilyl)amide (0.71 mL of 1.0 M THF solution, 0.71 mmol) over 10 min. After another 10 min, *p*-nitrosulfonyl chloride (0.16 g, 0.71 mmol) was added and the resulting yellow-brown mixture was stirred for 50 min while gradually warming to −40 °C. Saturated NH_4Cl solution was added slowly to the reaction mixture. The layers were separated, and the aqueous layer was extracted with Et_2O. The combined organic phases were washed with brine and worked up to afford crude nosylate as a syrup that was used directly in the next step.

The nosylate in CH_3OH (7 mL) at 0 °C was treated with K_2CO_3 (0.35 g, 2.57 mmol), and the mixture was stirred for 1.5 h at 0 → 25 °C. Saturated NH_4Cl solution was added, and the mixture was carefully acidified to pH 4 with 1 N HCl. The mixture was extracted with Et_2O, and the combined organic phases were washed with brine and worked up. The crude residue was chromatographed with 10−20% EtOAc/hexanes to afford *cis*-glycidate **23a** (0.27 g, 70%) as a colorless oil: $[\alpha]_D$ +26.1 (*c* 0.65, $CHCl_3$); IR 1747, 1093 cm^{-1}; ^1H NMR δ 7.32−7.45 (m, 15H), 4.54−4.95 (m, 6H), 3.88 (m, 1H), 3.83 (dd, J = 7.6, 3.1 Hz, 1H), 3.72 (dd, J = 11.2, 3.8 Hz, 2H), 3.59 (s, 3H), 3.50−3.65 (m, 2H), 3.27 (d, J = 4.7 Hz, 1H), 0.89 (bs, 9H), 0.02 (m, 6H); ^{13}C NMR δ −5.31, 18.34, 26.01, 50.31, 52.29, 58.94, 63.24, 72.33, 73.22, 74.07, 75.13, 78.30, 79.65, 94.10, 127.53, 127.73, 127.81, 127.90, 128.04, 128.32, 128.39, 128.43, 128.51, 128.57, 137.92, 137.98, 138.78, 168.28. Anal. Calcd for $C_{35}H_{46}O_7Si$: C, 69.28; H, 7.64. Found: C, 69.36; H, 7.68.

Methyl (2*S*,3*R*)-3-[(1*R*,2*S*,3*R*)-1,2,3-Tris(benzyloxy)-4-hydroxybutyl]oxirane-2-carboxylate (23b). Alcohol **23b** was prepared from silyl ether **23a** (2.4 g, 3.96 mmol) as described for the preparation of alcohol **21b**. After flash chromatography with 20−50% EtOAc/hexanes alcohol **23b** (1.6 g, 82%) was obtained as a colorless oil: $[\alpha]_D$ +49.7 (*c* 2.35, $CHCl_3$); IR 3587, 1749, 1710 cm^{-1}; ^1H NMR δ 7.34−7.37 (m, 15H), 4.55−4.91 (m, 6H), 3.78 (m, 1H), 3.65 (m, 1H), 3.62 (s, 3H), 3.52−3.59 (m, 2H), 3.43 (dd, J = 7.6, 4.7 Hz, 1H), 3.16−3.23 (m, 2H), 1.86 (t, J = 4.9 Hz, 1H); ^{13}C NMR δ 49.92, 52.54, 58.58, 61.01, 72.11, 73.17, 74.73, 78.83, 79.77, 127.91, 127.98, 128.06, 128.43, 128.56, 128.79, 137.41, 137.83, 168.26. Anal. Calcd for $C_{29}H_{32}O_7$: C, 70.71; H, 6.55. Found: C, 70.58; H, 6.52.

Methyl (2*S*,3*R*)-3-[(1*R*,2*S*,3*R*,4*E*)-1,2,3-Tris(benzyloxy)-6-methoxy-6-oxo-4-hexenyl]oxirane-2-carboxylate (24a). Unsaturated ester **24a** was prepared from alcohol **23b** (0.5 g, 1.01 mmol) as described above for unsaturated ester **22a**. After chromatography with 10−30% EtOAc/hexanes, methyl

ester **24a** (0.42 g, 76%) was isolated as a colorless oil: $[\alpha]_D$ +57.2 (*c* 0.75, $CHCl_3$); IR 1723 cm^{-1}; ^1H NMR δ 7.31−7.36 (m, 15H), 6.64 (dd, *J* = 15.8, 6.4 Hz, 1H), 5.91 (d, *J* = 5.7 Hz, 1H), 4.85 (d, *J* = 11.7 Hz, 1H), 4.78 (d, *J* = 11.8 Hz, 1H), 4.58 (m, 3H), 4.42 (d, *J* = 11.5 Hz, 1H), 4.33 (d, *J* = 6.3 Hz, 1H), 3.72 (s, 3H), 3.60 (s, 3H), 3.58 (d, *J* = 2.2 Hz, 1H), 3.42 (dd, *J* = 7.5, 4.9 Hz, 1H), 3.36 (dd, *J* = 6.5, 2.3 Hz, 1H), 3.17 (d, *J* = 4.7 Hz, 1H); ^{13}C NMR δ 50.04, 51.67, 52.38, 58.56, 71.92, 72.15, 74.75, 75.12, 78.87, 80.69, 123.28, 127.87, 128.06, 128.39, 128.52, 128.65, 128.85, 137.52, 137.61, 137.70, 144.37, 166.16, 168.16; HRMS (CI) Calcd for $C_{32}H_{35}O_8$ $(M + H)^+$ *m/e* 547.2332, found *m/e* 547.2318.

Methyl 2-[(1a*S*,2*R*,3*R*,4*S*,5*R*,5a*S*)-3,4,5-Tris(benzyloxy)-perhydro-1-benzoxiren-2-yl]acetate (25). To a THF (3 mL) solution of diester **22a** (0.18 g, 0.33 mmol) at 10 °C was added a 0.2 M LiOH solution (2.5 mL, 0.49 mmol), and the resulting mixture was stirred for 2 h while gradually warming to room temperature. Another two portions of LiOH (2 × 0.6 mL, 0.24 mmol) were added over 2 h to complete the reaction. The mixture was diluted with H_2O (8 mL), carefully acidified to pH 4 with 1 N HCl, and extracted with Et_2O. The combined organic layers were washed with brine and worked up as usual to afford a crude acid **22b** (0.15 g, 85%) as a thick oil which was used directly in the next step.

To a solution of isobutyl chloroformate (38 μL, 0.29 mmol) in THF (3 mL) at −23 °C was added dropwise a precooled THF (1.5 mL) solution of acid **22b** (0.15 g, 0.28 mmol) and *N*-methylmorpholine (34 μL, 0.31 mmol) via a cannulating needle. After 5 min, sodium thiopyridone *N*-oxide (46 mg, 0.31 mmol) was added and the resulting mixture was stirred for 3 h at −23 °C in the dark. The cold mixture was filtered rapidly through a pad of Celite, diluted to 0.015 M with THF (18 mL in total), and degassed in the dark. Tri-*n*-butyltin hydride (23 μL, 0.08 mmol) was added to the resulting bright yellow solution and irradiated with a 500 W tungsten lamp at 5 °C while the remaining portion of the n-Bu_3SnH (91 μL, 0.33 mmol) was added over 15 min. The entire irradiation took about 30 min. Solvent was removed in *vacuo* without heating, and the residue was purified on silica gel packed with 1% Et_3N/hexane. The column was first eluted with pentane and then with 10−20% EtOAc/hexanes (gradient) to afford epoxide **25** (38 mg, 30%) as a light yellow solid: $[\alpha]_D$ +35.9 (*c* 0.5, $CHCl_3$); IR 1731 cm^{-1}; ^1H NMR δ 7.27−7.44 (m, 15H), 4.81−4.94 (m, 5H), 4.52 (d, *J* = 11.1 Hz, 1H), 3.94 (dd, *J* = 8.5, 1.6 Hz, 1H), 3.72−3.78 (m, 1H), 3.61 (s, 3H), 3.29−3.38 (m, 2H), 3.05 (d, *J* = 3.9 Hz, 1H), 2.61 (dd, *J* = 16.5, 4.7 Hz, 1H), 2.51 (dd, *J* = 16.6, 6.2 Hz, 1H), 2.38−2.43 (m, 1H); ^{13}C NMR δ 34.23, 38.69, 51.76, 55.28, 72.95, 75.20, 75.82, 77.28, 77.34, 79.93, 82.33, 127.67, 127.80, 127.94, 128.02, 128.13, 128.30, 128.42, 128.48, 138.28, 138.66, 172.31. HRMS (CI) for $C_{30}H_{33}O_6$ $(M + H)^+$ *m/e* 489.2277, found *m/e* 489.2259.

Methyl 2-[(1a*R*,2*R*,3*R*,4*S*,5*R*,5a*R*)-3,4,5-Tris(benzyloxy)perhydro-1-benzoxiren-2-yl]acetate (27). A solution of iodolactone **37** (0.2 g, 0.34 mmol) and Na_2CO_3 (0.22 g, 2.07 mmol) in methanol (4 mL) at room temperature was stirred for 8 h. The mixture was filtered through a pad of Celite, and the solid was further rinsed with EtOAc. The combined filtrate was concentrated, and the residue was chromatographed with 30% EtOAc/hexanes to afford epoxy ester **27** (0.16 g, 98%) as a colorless solid: mp 65 °C; $[\alpha]_D$ +77.0 (*c* 1.4, $CHCl_3$); IR 1732 cm^{-1}; ^1H NMR δ 7.25−7.37 (m, 15H), 4.95 (d, *J* = 11.1 Hz, 1H), 4.81 (m, 4H), 4.50 (d, *J* = 11.1 Hz, 1H), 3.87 (d, *J* = 8.1 Hz, 1H), 3.64 (s, 3H), 3.58 (app t, *J* = 9.2 Hz, 1H), 3.37 (d, *J* = 3.2 Hz, 1H), 3.22 (d, *J* = 8.1 Hz, 2H), 3.19 (d, *J* = 8.2 Hz, 1H), 2.77 (dd, *J* = 11.9, 2.1 Hz, 1H), 1.56−2.55 (m, 2H); ^{13}C NMR δ 33.97, 38.95, 51.80, 54.65, 56.62, 73.16, 75.48, 79.87, 84.88, 127.68, 127.74, 127.90, 128.01, 128.42, 128.62, 137.69, 138.28, 138.57, 172.73. Anal. Calcd for $C_{30}H_{32}O_6$: C, 73.75; H, 6.60. Found: C, 73.72; H, 6.57.

Methyl 2-[(1*S*,4*S*,5*R*,6*R*)-4,5,6-Tris(benzyloxy)-2-cyclohexenyl]acetate (29). To a CH_2Cl_2 solution of divinyl ester **33** (1.0 g, 2 mmol) under N_2 was added 0.1 equiv of bis(tricyclohexylphosphine)benzylideneruthenium dichloride (0.17 g, 0.2 mmol; Strem Inc.) at room temperature. The dark red solution was stirred for 24 h. Another 0.04 equiv of catalyst (0.06 g, 0.08 mmol) was added in two portions over the next 36 h. The reaction mixture was quenched by exposure to air (turns greenish black after 3 h), concentrated, and chromatographed with 5−20% EtOAc/hexanes to afford cyclohexene **29** (0.89 g, 94%) as an oil: $[\alpha]_D$ +109.8 (*c* 1.5, $CHCl_3$); IR 1733 cm^{-1}; ^1H NMR δ 7.33−7.40 (m, 15H), 5.73 (dt, *J* = 10.2, 2.3 Hz, 1H), 5.61 (dt, *J* = 10.1, 1.5 Hz, 1H), 5.06 (d, *J* = 11.1 Hz, 1H), 4.96 (d, *J* = 1.7 Hz, 2H), 4.75 (s, 2H), 4.64 (d, *J* = 11.1 Hz, 1H), 4.3 (m, 1H), 3.88 (dd, *J* = 9.9, 7.8 Hz, 1H), 3.65 (s, 3H), 3.51 (t, *J* = 9.7 Hz, 1H), 2.88 (m, 1H), 2.66 (dd, *J* = 15.3, 5.1 Hz, 1H), 2.34 (dd, *J* = 15.3, 5.0 Hz, 1H); ^{13}C NMR δ 36.35, 40.34, 51.66, 72.07, 75.20, 75.33, 76.68, 80.97, 81.29, 85.17, 126.70, 127.64, 127.71, 127.90, 127.99, 128.45, 129.43, 138.48, 138.77, 172.62; LRMS (CI) $(M + H)^+$ *m/e* 473. Anal. Calcd for $C_{30}H_{32}O_5$: C, 76.25; H, 6.83. Found: C, 74.29; H, 6.72.

***tert*-Butyl(dimethyl){[(2*R*,3*S*,4*R*)-2,3,4-tri(benzyloxy)-5-hexenyl]oxy}silane (30a).** To a solution of aldehyde **10** (0.020 g, 0.04 mmol) and pyridine (2 μL) in 3:1 toluene/THF (0.8 mL) was added Tebbe's reagent ((*μ*-chloro)(*μ*-methylene)-[bis(cyclopentadienyl)titanium]dimethylaluminum, 0.51 M in toluene, 0.11 mL, 0.06 mmol) at −78 °C over 5 min. The mixture was vigorously stirred and allowed to warm to −15 °C over 2 h. The reaction mixture was quenched with 15% NaOH (0.1 mL), diluted with H_2O, and extracted with EtOAc. The combined organic layers were washed with brine and worked up. The residue was chromatographed with 0−5% EtOAc/hexanes to afford olefin **30a** (0.017 g, 80%) as a light yellow oil: $[\alpha]_D$ +7.6 (*c* 1.05, $CHCl_3$); ^1H NMR δ 7.25−7.35 (m, 15H), 5.81 (ddd, *J* = 17.4, 10.2, 7.4 Hz, 1H), 5.22−5.29 (m, 2H), 4.83 (d, *J* = 11.4 Hz, 1H), 4.70 (d, *J* = 11.8 Hz, 2H), 4.62 (d, *J* = 11.7 Hz, 1H), 4.56 (d, *J* = 11.7 Hz, 1H), 4.41 (d, *J* = 11.6 Hz, 1H), 4.15 (t, *J* = 6.8 Hz, 1H), 3.62−3.71 (m, 4H), 0.88 (s, 9H), 0.00 (s, 6H); ^{13}C NMR δ −5.35, 18.22, 25.95, 62.76, 70.76, 73.11, 75.23, 80.13, 81.15, 81.66, 118.75, 127.96, 128.07, 128.20, 128.25, 128.36, 128.46, 135.79, 138.55, 138.93, 139.00; LRMS (CI) $(M + H)^+$ *m/e* 533. Anal. Calcd for $C_{33}H_{44}O_4Si$: C, 74.39; H, 8.32. Found: C, 74.19; H, 8.35.

(2*R*,3*R*,4*S*)-2,3,4-Tris(benzyloxy)-5-hexen-1-ol (30b). To a solution of silyl ether **30a** (1.65 g, 3.1 mmol) in THF (12 mL) at 0 °C was added *n*-$Bu_4N^+F^-$ (1.0 M in THF, 4.2 mL, 4.2 mmol), and the resulting solution was allowed to warm to room temperature and stir for 2 h. The mixture was treated with saturated NH_4Cl (10 mL), diluted with H_2O, and extracted with EtOAc. The combined organic layers were washed with brine and worked up. The residue was chromatographed with 20−45% EtOAc/hexanes to afford unsaturated alcohol **30b** (1.1 g, 88%) as a light yellow oil: $[\alpha]_D$ +5.7 (*c* 1.4, $CHCl_3$); IR 3581 cm^{-1}; ^1H NMR δ 7.29−7.33 (m, 15H), 5.90 (ddd, *J* = 17.7, 10.0, 7.52 Hz, 1H), 5.35−5.30 (m, 2H), 4.37−4.75 (m, 6H), 4.1 (dd, *J* = 7.2, 3.55 Hz, 1H), 3.65−3.75 (m, 3H), 3.57 (m, 1H), 2.16 (t, *J* = 6.2, 5.7 Hz, 1H); ^{13}C NMR δ 61.53, 70.78, 72.88, 74.88, 79.58, 80.48, 81.74, 118.98, 127.77, 127.87, 127.97, 128.10, 128.44, 128.50, 135.15, 138.02, 138.32, 138.47. LRMS (CI) $(M + H)^+$ *m/e* 419. Anal. Calcd for $C_{27}H_{30}O_4$: C, 77.48; H, 7.22. Found: C, 77.38; H, 7.29.

Methyl (2*E*,4*R*,5*R*,6*S*)-4,5,6-Tris(benzyloxy)-2,7-octadienoate (32). To a solution of oxalyl chloride (0.23 mL, 2.64 mmol) in dry CH_2Cl_2 (7 mL) at −78 °C was added DMSO (0.39 mL, 5.50 mmol) in CH_2Cl_2 (2 mL) over 10 min, and the mixture was stirred for 20 min. A solution of alcohol **30b** (0.5 g, 1.20 mmol) in CH_2Cl_2 (2 mL) was added dropwise over 10 min. After 40 min of stirring at −78 °C, Et_3N (0.91 mL, 6.65 mmol) was added, and the resulting white slurry was stirred for another 15 min and allowed to warm slowly to −30 °C.

To the above mixture at −30 °C was added methyl (triphenylphosphoranylidene) acetate (0.84 g, 2.64 mmol) in one portion, and the resulting mixture was stirred for 6 h while it was allowed to warm gradually to room temperature. Water was added, and the layers were separated. The aqueous layer was further extracted with CH_2Cl_2, and the combined organic phases were washed with brine and worked up. The residue was chromatographed with 10−30% EtOAc/hexanes to afford unsaturated ester **32** (0.50 g, 88%) as a colorless oil: $[\alpha]_D$ +3.0 (*c* 1.0, $CHCl_3$); IR 1719 cm^{-1}; ^1H NMR δ 7.27−7.31 (m, 15H), 6.87 (dd, *J* = 15.8, 6.2 Hz, 1H), 6.02 (dd, *J* = 15.8, 1.1 Hz,

1H), 5.83 (m, 1H), 5.27 (s, 1H), 5.22 (d, J = 2.9 Hz, 1H), 4.73 (s, 2H), 4.58 (dd, J = 11.6, 7.2 Hz, 2H), 4.35 (dd, J = 11.5, 8.7 Hz, 2H), 4.22 (dt, J = 5.8, 1.1 Hz, 1H), 3.99 (dd,J = 7.5, 4.9 Hz, 1H), 3.74 (s, 3H), 3.48 (t, J = 5.0 Hz, 1H); ^{13}C NMR δ 51.66, 70.72, 71.86, 75.37, 79.13, 80.78, 83.51, 119.04, 122.79, 127.62, 127.71, 127.81, 128.07, 128.17, 128.26, 128.41, 128.58, 135.34, 137.83, 138.15, 138.25, 145.57, 166.49; HRMS (CI) calcd for $C_{30}H_{33}O_5$ (M + H)$^+$ *m/e* 473.2328, found *m/e* 473.2294.

Methyl (3*S*,4*R*,5*R*,6*S*)-4,5,6-Tris(benzyloxy)-3-vinyl-7-octenoate (33). To a slurry of CuI (3.2 g, 16.3 mmol), which was weighed in a glovebox, in THF (100 mL) at −78 °C was added vinylmagnesium bromide (1.0 M in THF, 33 mL, 32.6 mmol) via an addition funnel. The resulting mixture was stirred for 40 min and treated with chlorotrimethylsilane (4.4 mL, 35 mmol) followed by the addition of unsaturated ester **32** (1.1 g, 2.3 mmol) in THF (4 mL) at −78 °C. Stirring was continued for 2 h, and then the reaction mixture was treated with concentrated NH_4OH and saturated NH_4Cl (200 mL) at −78 °C. After being warmed to room temperature, the reaction mixture was diluted with ether and the layers were separated. The aqueous layer was extracted with ether, and the combined organic layers were washed with brine and worked up. The residue was chromatographed with 5−15% EtOAc/hexanes to afford divinyl ester **33** (1.06 g, 90%) as an oil: $[\alpha]_D$ +32.3 (*c* 2.1, $CHCl_3$); IR 1729 cm^{-1}; ^{1}H NMR δ 7.26−7.40 (m, 15H), 5.90 (m, 1H), 5.74 (m, 1H), 5.35 (s, 1H), 5.30 (d, J = 4.2 Hz, 1H), 5.01 (m, 2H), 4.35−4.82 (m, 6H), 4.07 (t, J = 6.5 Hz, 1H), 3.70 (t, J = 5.5 Hz, 1H), 3.57−3.61 (m, 1H), 3.58 (s, 3H), 2.98 (m, 1H), 2.63 (dd, J = 15.2, 4.1 Hz, 1H), 2.41 (dd, J = 15.3, 9.8 Hz, 1H); ^{13}C NMR δ 35.27, 42.05, 51.50, 70.68, 73.46, 74.99, 81.16, 82.55, 116.71, 119.08, 127.46, 127.51, 127.66, 128.09, 128.17, 128.31, 128.38, 135.46, 138.26, 138.68, 138.78, 138.82, 173.17. Anal. Calcd for $C_{32}H_{36}O_5$: C, 76.77; H, 7.25. Found: C, 76.72; H, 7.29.

Methyl 2-[(1*R*,2*R*,3*R*,4*R*,5*S*,6*R*)-2,3-Di(acetyloxy)-4,5,6-tri(benzyloxy)cyclohexyl]acetate (35). A mixture of ester **25** (8.1 mg, 0.017 mmol) and K_2CO_3 (40 mg, 0.28 mmol) in 25% aqueous MeOH (1.0 mL) at room temperature was stirred for 20 h. The mixture was diluted with H_2O, acidified to pH 4 with 1 N HCl, and extracted with EtOAc. The combined organic layers were washed with brine and worked up as usual to afford crude dihydroxy acid **34** (6.4 mg, 78%) as a semisolid. The crude acid was esterified with ethereal diazomethane and used without purification.

To a solution of the dihydroxy ester in CH_2Cl_2 (0.4 mL) at room temperature was added pyridine (10 μL, 0.12 mmol) and acetic anhydride (10 mL, 0.11 mmol) followed by a catalytic amount of DMAP ("one crystal"). After being stirred for 1 h, the mixture was treated with H_2O and extracted with CH_2Cl_2 (3 × 3 mL). Workup afforded diacetate **35** (4.0 mg, 40% from **25**) as a colorless oil: ^{1}H NMR δ 7.29−7.34 (m, 15H), 5.43 (t, J = 3.5 Hz, C*H*OAc, 1H), 5.12 (t, J = 3.0 Hz, C*H*OAc, 1H), 5.03 (d, J = 11.0 Hz, 1H), 4.96 (d, J = 10.6 Hz, 1H), 4.78 (d, J = 10.6 Hz, 1H), 4.73 (d, J = 11.1 Hz, 1H), 4.57 (d, J = 8.6 Hz, 1H), 4.54 (d, J = 8.9 Hz, 1H), 3.90 (t, J = 9.3 Hz, 1H), 3.76 (dd, J = 9.3, 3.1 Hz, 1H), 3.54 (s, CH_3O, 3H), 3.48 (m, 1H), 2.56−2.69 (m, 2H), 2.16−2.23 (m, 1H), 2.17 (s, OC(O)-CH_3, 3H), 2.05 (s, OC(O)CH_3, 3H); HRMS (CI) calcd for $C_{34}H_{39}O_9$ (M + H)$^+$ *m/e* 591.2594, found *m/e* 591.2594.

(3a*R*,4*R*,5*S*,6*S*,7*R*,7a*R*)-4,5,6-Tris(benzyloxy)-7-hydroxyperhydrobenzo[*b*]furan-2-one (36). A solution of acid **34** (3 mg, 0.006 mmol), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (3 mg, 0.014 mmol), and *i*-Pr$_2$NEt (1 drop) in CH_2Cl_2 (0.4 mL) was stirred for 1 h. The reaction mixture was diluted with CH_2Cl_2 and washed with H_2O and brine. Workup and chromatography with 10−30% EtOAc/hexanes afforded lactone **36** (1.5 mg, 52%) as an oil: IR 3690, 1786 cm^{-1}; ^{1}H NMR δ 7.32−7.43 (m, 15H), 4.97 (d, J = 11.4 Hz, 1H), 4.88 (d, J = 11.0 Hz, 1H), 4.82 (d, J = 11.5 Hz, 1H), 4.78 (d, J = 11.2 Hz, 1H), 4.73 (d, J = 11.5 Hz, 1H), 4.63 (d, J = 10.9 Hz, 1H), 4.61 (d, J = 5.1 Hz, C*H*OC(O), 1H), 4.32 (dd, J = 6.4, 3.0 Hz, C*H*OH, 1H), 3.95 (t, J = 7.9 Hz, 1H), 3.77 (dd, J = 7.3, 3.0 Hz, 1H), 3.38 (d, J = 9.9, 8.7 Hz, 1H), 2.71−2.81 (m, C*H*CH$_2$, 1H), 2.65 (dd, J = 17.7, 7.4 Hz, C*H*(O)-CO, 1H), 2.47 (d, J = 7.3 Hz, C*H*(O)CO, 1H); LRMS (CI) (M + H)$^+$ *m/e* 475.

(3a*R*,4*R*,5*S*,6*R*,7*R*,7a*R*)-4,5,6-Tris(benzyloxy)-7-iodoperhydrobenzo[*b*]furan-2-one (37). To a THF (40 mL) solution of ester **29** (0.89 g, 1.9 mmol) was added LiOH (0.46 g, 19.2 mmol) in H_2O (30 mL), and the resulting mixture was stirred for 4 h. The reaction mixture was carefully neutralized with concentrated HCl and then treated with $KHCO_3$ (1.13 g, 11.3 mmol) and KI (0.78 g, 4.7 mmol). After 5 min, I_2 (2.1 g, 8.3 mmol) was added, and the mixture was stirred for another 6 h. Saturated $Na_2S_2O_3$ (30 mL) was added, and the mixture was extracted with Et_2O. The combined organic layers were washed with brine and worked up. The crude residue was chromatographed with 5−20% EtOAc/hexanes to afford iodo lactone **37** (1.01 g, 92%) as a white solid: mp 138 °C; $[\alpha]_D$ +29.9 (*c* 1.4, $CHCl_3$); IR 1785 cm^{-1}; ^{1}H NMR δ 7.30−7.48 (m, 15H), 4.96 (m, 2H), 4.88 (d, J = 11.0 Hz, 1H), 4.76 (m, 2H), 4.69 (m, 2H), 4.62 (d, J = 11.1 Hz, 1H), 3.99 (t, J = 7.2 Hz, 1H), 3.43 (dd, J = 10.1, 8.4 Hz, 1H), 3.34 (m, 1H), 2.98 (m, 1H), 2.70 (dd, J = 17.1, 7.3 Hz, 1H), 2.53 (d, J = 17.6 Hz, 1H); ^{13}C NMR δ 28.14, 35.03, 39.13, 72.77, 74.24, 75.28, 78.78, 79.67, 83.36, 83.85, 128.10, 128.18, 128.58, 128.67, 137.31, 137.79, 174.90. LRMS (CI) (M + H)$^+$ *m/e* 585. Anal. Calcd for $C_{29}H_{29}O_5I$: C, 59.60; H, 5.00. Found: C, 59.53; H, 5.06.

(3a*R*,4*R*,5*S*,6*R*,7*R*,7*aR*)-4,5,6-Tris(benzyloxy)-7-iodoperhydrobenzo[*b*]furan-2-ol (38). To a solution of lactone **37** (0.35 g, 0.60 mmol) in ether (5 mL) and CH_2Cl_2 (2 mL) at −78 °C was added dropwise DIBAL-H (0.12 mL, 0.67 mmol) in hexane (0.6 mL) over a period of 20 min. After 40 min, precooled methanol (0.3 mL) was added slowly, and the reaction mixture was allowed to warm to room temperature. Rochelle's salt solution (15 mL of 30% aqueous sodium potassium tartrate) was added, and the mixture was stirred until two clear layers appeared. The organic layer was separated and washed with another 10 mL of Rochelle's salt solution. The combined aqueous portions were extracted with Et_2O, and the organic phases were combined, washed with brine, and worked up. The crude residue was chromatographed with 20−40% EtOAc/hexanes to afford lactols **38** (0.30 g, 85%) as an oil: $[\alpha]_D$ +34.5 (*c* 1.3, $CHCl_3$); IR 3597 cm^{-1}; ^{1}H NMR: major δ 7.41−7.27 (m, 15H), 5.53 (m, 1H), 4.54−4.95 (m, 8H), 3.96 (m, 1H), 3.33 (t, J = 9.4 Hz, 1H), 3.25 (dd, J = 7.0, 3.3 Hz, 1H), 2.74 (bm, 1H), 2.62 (bm, 1H), 2.16 (m, 1H), minor (partial) δ 4.07 (dd, J = 11.1, 8.2 Hz, 1H); 3.52 (m, 1H); 1.91−2.00 (m, 2H); ^{13}C NMR: mixture δ 31.12, 32.69, 37.11, 38.60, 40.66, 42.04, 72.26, 72.41, 73.86, 74.64, 75.17, 79.00, 80.24, 81.00, 81.56, 81.61, 84.32, 84.50, 84.62, 98.44, 98.96, 127.77, 127.93, 128.02, 128.13, 128.18, 128.53, 137.80, 137.86, 138.28, 138.41. Anal. Calcd for $C_{29}H_{31}O_5I$: C, 59.39; H, 5.33. Found: C, 59.51; H, 5.33.

(1*R*,2*R*,3*R*,4*S*,5*R*,6*R*)-3,4,5-Tris(benzyloxy)-2-iodo-6-(iodomethyl)cyclohexyl formate (39). A solution of iodolactol **38** (0.30 g, 0.51 mmol) in dry cyclohexane (34 mL) containing iodobenzene diacetate (0.20 g, 0.62 mmol) and I_2 (0.15 g, 0.59 mmol) was irradiated with a 500 W tungsten lamp at 4−20 °C for 2 h. To the reaction mixture was added saturated aqueous $Na_2S_2O_3$ (20 mL) and H_2O (30 mL). The two layers were separated, and the aqueous layer was extracted with EtOAc/hexanes (1:4) and worked up. The residue was chromatographed with 0−20% EtOAc/hexanes to afford diiodo formate **39** (0.2 g, 78%) as a colorless oil: $[\alpha]_D$ +31.3 (*c* 0.77, $CHCl_3$); IR 1733 cm^{-1}; ^{1}H NMR δ 7.98 (s, 1H), 7.29−7.40 (m, 15H), 5.60 (bs, 1H), 4.96 (dd, J = 10.7, 2.8 Hz, 2H), 4.80 (d, J = 11.1 Hz, 1H), 4.70 (d, J = 11.1 Hz, 1H), 4.61−4.56 (m, 2H), 3.94 (t, J = 9.2 Hz, 1H), 3.51−3.60 (m, 1H), 2.97 (dd, J = 9.2, 4.2 Hz, 1H), 2.91 (m, 2H); ^{13}C NMR δ 2.90, 30.28, 42.93, 71.99, 75.19, 75.79, 76.81, 80.27, 84.55, 127.78, 128.02, 128.05, 128.11, 128.16, 128.54, 128.59, 159.18; HRMS (FAB) calcd for $C_{29}H_{29}O_5I_2$ (M − H)$^+$ *m/e* 711.0105, found *m/e* 711.0104.

(1a*R*,2*R*,3*R*,4*S*,5*R*,5a*R*)-2,3,4-Tris(benzyloxy)-5-(iodomethyl)perhydro-1-benzoxirene (40). To a solution of diiodoformate **39** (0.32 g, 0.45 mmol) in THF (4.4 mL) and H_2O (1.2 mL) was added KOH (76 mg, 1.36 mmol). After being stirred for 3 h, the reaction mixture was diluted with H_2O and neutralized with 1 N HCl. The mixture was diluted with H_2O

and Et_2O. The combined extracts were washed with brine and worked up. The residue was chromatographed with 0−15% EtOAc/hexanes to yield iodo epoxide **40** (0.19 g, 76%) as a white solid: mp 83 °C; $[\alpha]_D$ +60.9 (*c* 0.95, $CHCl_3$); ^{1}H NMR δ 7.26−7.36 (m, 15H), 4.94 (d, J = 11.0 Hz, 1H), 4.71−4.89 (m, 4H), 4.55 (d, J = 10.9 Hz, 1H), 3.92 (d, J = 8.2 Hz, 1H), 3.49−3.60 (m, 3H), 3.19−3.28 (m, 3H), 2.29 (m, 1H); ^{13}C NMR δ 4.79, 44.29, 53.80, 56.94, 73.22, 75.47, 75.85, 79.69, 84.88, 127.74, 127.89, 128.04, 128.10, 128.46, 128.61, 137.60, 138.02, 138.48; HRMS (FAB) calcd for $C_{28}H_{30}O_4I$ M^+ *m/e* 557.1189, found *m/e* 557.1188.

2-[(1a*R*,2*R*,3*R*,4*S*,5*R*,5a*R*)-3,4,5-Tris(benzyloxy)perhydro-1-benzoxiren-2-yl]acetic Acid (41a). To a solution of ester **27** (0.10 g, 0.20 mmol) in THF (6 mL) was added a 0.2 M LiOH solution (4.2 mL, 0.84 mmol) in 3 portions over 5 h, and the resulting mixture was stirred overnight. The mixture was concentrated in *vacuo*, diluted with H_2O, acidified to pH 4 with 1 N HCl, and extracted with EtOAc. The combined organic layers were washed with brine and worked up to afford crude acid **41b** (95 mg, 94%) as a colorless semisolid: $[\alpha]_D$ +74.1 (*c* 1.05, $CHCl_3$); IR 3511−3069 (b), 1712 cm^{-1}; ^{1}H NMR δ 7.27−7.37 (m, 15H), 4.95 (d, J = 11.0 Hz, 1H), 4.87 (d, J = 11.0 Hz, 1H), 4.84 (d, J = 11.4 Hz, 1H), 4.82 (d, J = 11.6 Hz, 1H), 4.73 (d, J = 11.4 Hz, 1H), 4.51 (d, J = 11.1 Hz, 1H), 3.88 (d, J = 8.2 Hz, 1H), 3.58 (dd, J = 9.1, 8.7 Hz, 1H), 3.35 (d, J = 3.3 Hz, 1H), 3.22 (d, J = 7.0 Hz, 1H), 3.19 (d, J = 8.8 Hz, 1H), 2.73−2.80 (m, 1H), 2.46−2.56 (m, 2H); ^{13}C NMR δ 34.15, 38.81, 54.71, 56.55, 73.17, 75.52, 76.75, 79.83, 84.87, 127.74, 127.84, 127.91, 127.96, 128.07, 128.46, 128.51, 128.64, 137.70, 138.18, 138.54, 178.49; HRMS (CI) calcd for $C_{29}H_{29}O_6$ $(M - H)^+$ *m/e* 473.1964, found *m/e* 473.1955.

[(1a*R*,2*R*,3*R*,4*S*,5*R*,5a*R*)-3,4,5-Tris(benzyloxy)perhydro-1-benzoxirene-2-yl]methanol (42) from 41a. A round-bottomed flask containing a solution of acid **41a** (16 mg, 0.034 mmol) in CH_2Cl_2 (1 mL) was wrapped with Al foil. To the solution at 0 °C was added dithiobis(pyridine *N*-dioxide) (12 mg, 0.048 mmol) followed by the addition of tri-*n*-butylphosphine (10.2 μL, 0.041 mmol). The reaction mixture was stirred for 15 min at 0 °C and 2 h at room temperature. The Al foil was removed, and the reaction mixture was treated with tris(phenylthio)antimony (20 mg, 0.043 mmol). After the flask was purged with oxygen for about 2 min, the mixture was stirred and exposed to air for 2 h. The mixture was diluted with CH_2Cl_2 and washed with 5% $NaHCO_3$ and brine. After workup, the crude residue was chromatographed with 20−40% EtOAc/hexanes to afford alcohol **42** (9 mg, 60%) as a colorless solid. See below for analytical data.

[(1a*R*,2*R*,3*R*,4*S*,5*R*,5a*R*)-3,4,5-Tris(benzyloxy)perhydro-1-benzoxirene-2-yl]methanol (42) and (1a*R*,2*R*,3*R*,4*S*,5*R*,5a*R*)-4,5-Bis(benzyloxy)-2-(hydroxymethyl)perhydro-1-benzoxiren-3-ol (45) from 41a. Oxygen was bubbled through a solution of iodo epoxide **40** (110 mg, 0.20 mmol), *n*-Bu_3SnH (0.2 mL, 0.74 mmol), and AIBN (36 mg, 0.22 mmol) in toluene (3 mL) at 60 °C for 1 h. Another portion of *n*-Bu_3SnH (0.05 mL, 0.19 mmol) and AIBN (10 mg, 0.06 mmol) was added as oxygen was passed through the solution for another 2 h at 60 °C. The reaction mixture was cooled, transferred onto a column of SiO_2, and eluted with hexanes to remove tin residues. Further elution with 10−45% EtOAc/hexanes (gradient) afforded epoxy alcohol **42** (62 mg, 70%) as a white solid: mp 92−93 °C; $[\alpha]_D$ +71.0 (*c* 0.9, $CHCl_3$); IR 3690, 3628 cm^{-1}; ^{1}H NMR δ 7.28−7.37 (m, 15H), 4.94 (d, J = 10.9 Hz, 1H), 4.88 (d, J = 2.0 Hz, 2H), 4.79 (q, J = 11.5 Hz, 2H), 4.56 (d, J = 10.9 Hz, 1H), 3.97 (m, 1H), 3.89 (m, 2H), 3.61(t, J = 9.1 Hz, 1H), 3.48 (t, J = 9.9 Hz, 1H), 3.36 (d, J = 2.3 Hz, 1H), 3.18 (d, J = 3.6 Hz, 1H), 2.20 (m, 1H), 1.95 (dd, J = 8.0, 3.1 Hz, 1H); ^{13}C NMR δ 44.00, 53.02, 55.96, 62.86, 73.24, 75.44, 75.62, 79.87, 85.00, 127.68, 127.87, 128.03, 128.25, 128.44, 128.61, 137.64, 138.60; HRMS (FAB) calcd for $C_{28}H_{31}O_5$ M^+ *m/e* 447.2171, found *m/e* 447.2172.

Further elution with 50% EtOAc/hexanes afforded diol **45** (5 mg, 7%) as a white semisolid: ^{1}H NMR δ 7.31−7.40 (m, 10H), 4.97 (d, J = 11.3 Hz, 1H), 4.83 (d, J = 10.5 Hz, 1H), 4.68 (t, J = 10.7 Hz, 2H), 4.04 (dd, J = 10.8, 6.9 Hz, 1H), 3.93 (dd, J = 10.8, 4.8 Hz, 1H), 3.84 (d, J = 7.9 Hz, 1H), 3.51 (t, J = 9.9 Hz, 1H), 3.41 (t, J = 9.9 Hz, 1H), 3.29 (bs, 1H), 3.18 (d, J = 3.6 Hz, 1H), 2.19 (m, 1H); LRMS (EI) $(M - C_7H_7)^+$ *m/e* 265.

(1a*R*,2*R*,3*R*,3a*R*,7a*S*,7b*R*)-2,3-Bis(benzyloxy)perhydrooxireno[2′,3′:3,4]benzo[*d*][1,3]dioxin-5-one (44). To a solution of diol **45** (4 mg, 0.01 mmol) and pyridine (9.1 μL, 0.11 mmol) in CH_2Cl_2 (0.7 mL) at room temperature was added triphosgene (3.3 mg, 0.01 mmol), and the mixture was stirred for 2 h. Buffer (pH7) was added, and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with brine and worked up. The crude residue was chromatographed with 30% EtOAc/hexanes to afford carbonate **44**: IR 1760, 1601 cm^{-1}; ^{1}H NMR δ 7.30−7.40 (m, 10H), 4.97 (d, J = 11.1 Hz, 1H), 4.76 (s, 1H), 4.74 (d, J = 9.9 Hz, 1H), 4.63 (dd, J = 10.3, 5.2 Hz, 1H), 4.47 (t, J = 11.3 Hz, 1H), 4.26 (t, J = 10.1 Hz, 1H), 3.97 (d, J = 6.5 Hz, 1H), 3.68 (dd, J = 10.1, 6.9 Hz, 1H), 3.27 (m, 2H), 2.58 (m, 1H); MS (EI) $(M - C_7H_7)^+$ *m/e* 291.

(1a*S*,2*R*,3*S*,4*R*,5*R*,5a*R*)-5-(Hydroxymethyl)perhydro-1-benzoxirene-2,3,4-triol [(+)-Cyclophellitol] (1). A solution of tribenzyl ether **42** (23 mg, 0.05 mmol) in CH_3OH (1.5 mL) containing $Pd(OH)_2$/C (12 mg, 50% w/w) was purged with H_2 for 2 min, and the mixture was stirred under atmospheric hydrogen for 10 h. The suspension was filtered through a pad of Celite and rinsed with CH_3OH (5 mL). The filtrate was concentrated in *vacuo*, and the residue was chromatographed with 10−30% $CH_3OH/CHCl_3$ to afford (+)-cyclophellitol **(1)** (7.8 mg, 85%) as a white solid: $[\alpha]_D$ +97.0 (*c* 0.35, H_2O), lit.[1] $[\alpha]^{27}_D$ +103 (c 0.5, H_2O); ^{1}H NMR (500 MHz, D_2O, DOH at δ 4.80) δ 4.02 (dd, J = 11.2, 3.8 Hz, 1H), 3.84 (dd, J = 11.2, 7.5 Hz, 1H), 3.80 (d, J = 8.5 Hz, 1H), 3.54 (br m, 1H) 3.37−3.41 (m, 1H), 3.25−3.28 (m, 2H), 2.08−2.18 (br m,1H).

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Supporting Information Available: Copies of the ^{1}H NMR spectra of compounds **10**, **13**, **14b**, **17a**,**d**, **24a**, **25**, **28** and precursor, **31**, **32**, **35**, **36**, **39**, **40**, **41a**, **42**, **44** and **45**, which are lacking combustion analyses, and comparison ^{1}H NMR spectra of **1** and text describing complete experiments for the formation of **28** and **31** from aldehyde **10** (21 pages). This material is contained in libraries on microfiche, immediately following this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead for ordering information.

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