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A New Synthetic Approach to High-Purity (15*R*)-Latanoprost

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This paper describes a new synthesis of latanoprost (**1**) that afforded high purity latanoprost in 16.9% overall yield in eight synthetic steps from sulfone **4**. The "α chain" in a derivative of the (–)-"Corey lactone" was elongated first, followed by the attachment of a novel, enantiomerically pure "ω chain" synthon. This ensured the absence of the undesired (15*S*)-**1** diastereomer in the synthesized prostaglandin. The crystalline nature of the novel sulfone **4** facilitated its purification. A variation of the new synthesis of latanoprost is described, where the laboratory-scale synthesis was further adapted to a hundred-gram scale. In the course of the present synthesis, a new prostaglandin sulfone intermediate, **21**, which may find application in the synthesis of diverse prostaglandin analogs, was introduced. A practical synthesis of novel, enantiomerically pure "ω chain" synthons **15**, **16**, and **17** has also been carried out, employing diol **12**, which was obtained from derivatives of the D-mannitol chiral pool.

Introduction

Natural prostaglandins are unsaturated fatty acids derived from arachidonic acid. Many classes of prostaglandins are characterized by very high biological activity, their K_D values being within 10^{-8}–10^{-12} M. Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), for example, is known to be a very potent vasoconstrictor and oxytoxic agent. The medicinal chemistry of these natural products has experienced dynamic growth since their discovery in 1934 by von Euler.[1] The synthesis of prostaglandins was the subject of considerable scientific effort, which led to many discoveries and developments that have now become a part of the standard arsenal of organic chemistry methodologies.[1c,2] More recently, solid-phase strategies have been developed for the design and synthesis of combinatorial libraries of antiviral and other bioactive compounds based on prostaglandin templates including PGF analogs.[3] Importantly, research into the pharmacological properties of PGF derivatives has led to the discovery[4] of latanoprost (**1**) and structurally related derivatives (Figure 1), which are very effective as anti-glaucoma agents and are currently broadly marketed against glaucoma.

Latanoprost continues to hold a key position in the anti-glaucoma market, although certain newer prostaglandin analogs [e.g. travoprost and bimatoprost (Figure 1)] show similarly high levels of intraocular pressure reduction[5] in clinical trials. All[4,6] but one[6j] of the reported synthetic approaches toward **1** make use of one of known variations of the Corey method,[2a–2c] in which the side chains are sequentially attached in a specific order to a derivative of the commercially available (–)-"Corey lactone".[4,6h] Thus, the Corey strategy, as applied to the synthesis of latanoprost, comprises a sequence of the following reactions: (a) addition of an "ω chain" precursor to the (–)-"Corey lactone" resulting in a 13-en-15-one, (b) reduction of the enone to a 13-en-15-ol, (c) hydrogenation of the 13,14-alkene, (d) addition of the "α chain", leading to a *cis*-5,6-alkene, and (e) further transformations (the numbering used herein corresponds to the prostaglandin numbering system[2c]).

The very high potency of prostaglandins dictates that contamination with diastereomeric prostaglandins of unknown activity should be avoided in prostaglandins used as pharmaceutical active ingredients.[1] However, the multiple chiral centers present in these molecules continue to create practical challenges, and existing synthetic routes to latanoprost by the Corey strategy, in spite of the considerable progress made in this field,[6] are not completely free of the contaminating diastereomers. Besides the occurrence of the 5,6-*trans* olefin, particular difficulty has been associated with maintaining the purity at the C(15) carbinol asymmetric center, which typically is formed by a stereoselective reduction. Such reductions require expensive reagents[2a,6g,7] and often low-temperature conditions. However, in practice

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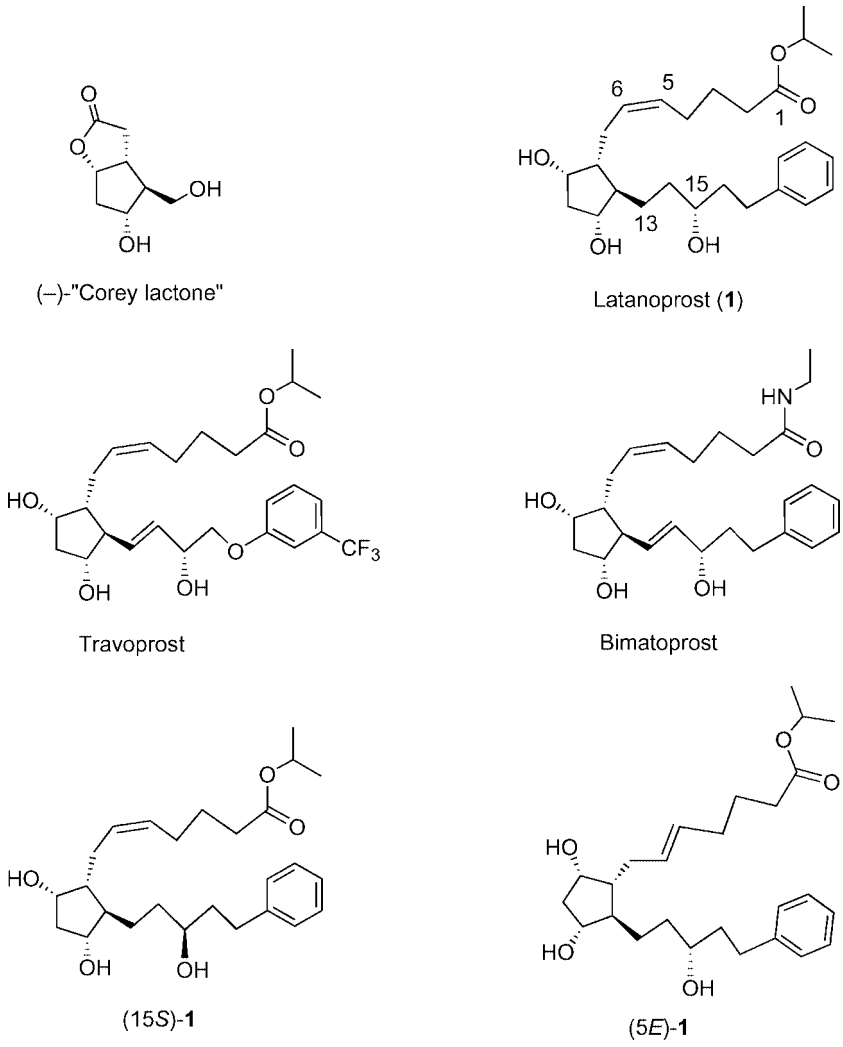


Figure 1. Structures of the (–)-"Corey lactone", synthetic $PGF_{2\alpha}$ analogs, and key impurities (15*S*)-**1** and (5*E*)-**1** of latanoprost (**1**).

these methods do not lead to a completely stereoselective formation of the desired (15*R*) isomer. The (15*S*) diastereomer of latanoprost [(15*S*)-**1** in Figure 1] has been described,[4a] and it has been reported to typically occur[6a] in the product in amounts exceeding 1%. In addition, the physicochemical properties of **1** and (15*S*)-**1** are very similar. Indeed, it is not a straightforward task to discern between these two compounds by 500 MHz ^{1}H NMR, optical rotation, or even by analytical reversed-phase HPLC. Furthermore, the application of preparative scale HPLC to rid **1** of the (15*S*) diastereomer is very costly and far from trivial, while the 5,6-*trans* isomer of **1** [(5*E*)-**1**] is much easier to separate by HPLC.[6a] Other methods for the preparation of prostaglandin F analogs[8] from the (–)-Corey lactone were reported, in which the introduction of the ω chain already in the correct stereochemical arrangement preceded the attachment of the α chain. Thus, the problematic reduction of a 13-en-15-one to the corresponding (15*R*)-13-en-15-ol was avoided. However, the efficiency of these approaches was poor. On the other hand, a "reversed" order of side chain attachment was conducted by Schaaf and Corey[9a] during their synthesis of $PGF_{1\alpha}$ and more recently by the Procter & Gamble research group,[9b] but the reduction of a 13-en-15-one could not be avoided. Moreover, a synthesis of 13,14-dihydro-$PGF_{2\alpha}$ analogs by this route would require a difficult regioselective hydrogenation of the 13,14-alkene in the presence of the 5,6-alkene. Recently, the 1,4-addition approach[2d,e,f] to prostaglandin synthesis has been applied to the synthesis of latanoprost (**1**), which resulted in a series of elegant but laborious transformations[6j] that had to be extensively supported by Simulated Moving Bed (SMB) chiral chromatography in order to provide intermediates of sufficient enantiomeric purity. Another lengthy synthetic route of this type has been reported recently.[6k] Thus, the Corey method[2a,2b] still promises to provide the most facile and practical access to latanoprost (**1**), yet the difficulty with the (15*S*)-**1** stereoisomer needs to be overcome. Therefore, a synthesis of latanoprost (**1**) cap-

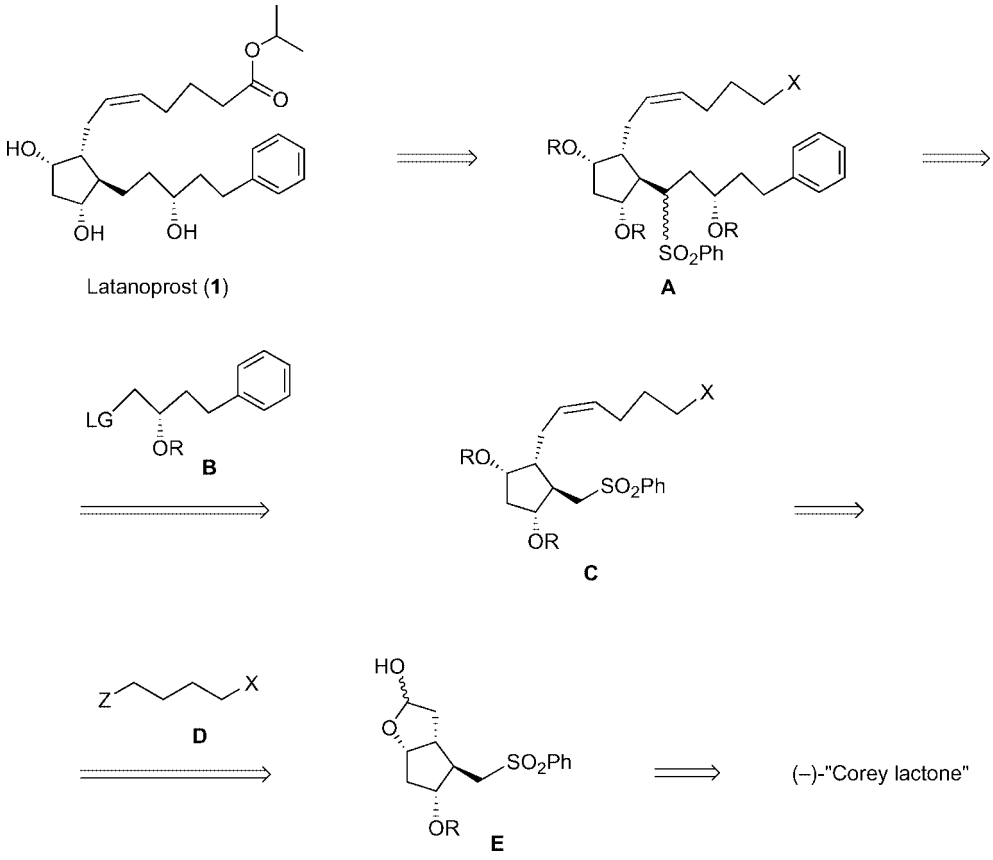
able of delivering the desired product free of its (15*S*) diastereomer is expected to have considerable scientific and practical merit.

Results and Discussion

As shown in Scheme 1, we envisioned that latanoprost (**1**) could be prepared by the reductive desulfonation of phenylsulfone **A**, followed by simple protecting group transformations. Intermediate **A** could be formed from key prostaglandin sulfone **C** through an S_N2 alkylation of the carbanion generated at C(13), α to the phenylsulfonyl group, with an electrophilic alkylating agent **B** possessing the stereochemical arrangement corresponding to the (15*R*) stereochemistry in the product. Critical to this disconnection, the enantiomeric purity of the ω chain synthon **B** should be very high (e.g. above 99.8%), thus a priori establishing very high diastereomeric excess of the (15*R*) product. With a well-chosen protecting group, alkylating agent **B** should not be capable of epimerization under the reaction conditions. We expected that the utility of synthon **C** would not be limited to the synthesis of latanoprost (**1**), as alkylating synthons other than **B** could easily be proposed. Additionally, the utility of the -CH_2SO_2Ar group in the synthesis of substituted alkenes is well documented.[10] Synthon **C** could be synthesized by a Wittig reaction from lactol **E**, which is readily accessible from commercially available derivatives of the (–)-Corey lactone and a suitably protected α chain precursor **D**. The 4-methyl-2,6,7-trioxabicyclo[2.2.2]-octane protective group was selected as the latent carboxyl group X introduced in **D**, due to its ease of formation and stability under the basic conditions[11] required to successfully carry out the alkylation of sulfone **C**.

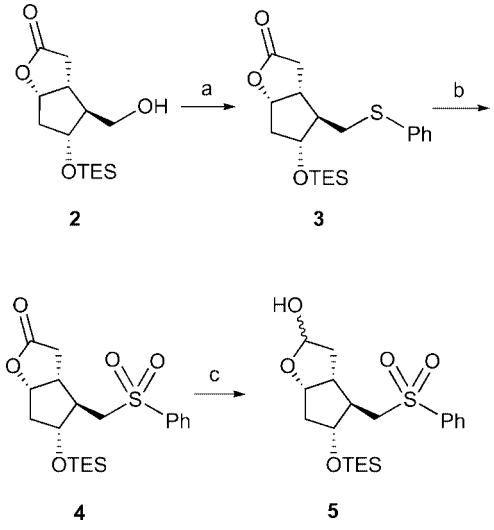
Synthesis of the Central Building Block, Hemiacetal 5

The commercially available (3a*R*,4*S*,5*R*,6a*S*)-4-(hydroxymethyl)-5-(triethylsilyloxy)-hexahydro-cyclopenta[*b*]furan-2-one (**2**) (>98% *de*) was selected as the starting material for the synthesis of latanoprost. The high enantiomeric purity of this material was expected to be further enhanced upon crystallization of one of the subsequent intermediates. The transformation of alcohol **2** to sulfide **3** was carried out over 40 h in the presence of diisopropyl azodicarboxylate (DIAD)[12] and required slightly elevated temperatures. The oxidation of compound **3** to sulfone **4** was conveniently carried out with magnesium monoperoxyphthalate (MMPP) in the biphasic H_2O/CH_2Cl_2 solvent system.[13] Use of an excess of the oxidizing agent ensured a fast and clean conversion to the sulfone. Contrary to the report on microwave-catalyzed MMPP oxidation of sulfides to sulfoxides under



Scheme 1. Projected synthesis of latanoprost (**1**).

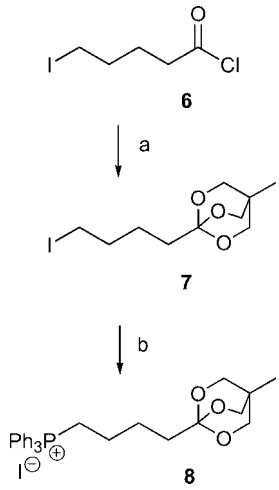
similar conditions,[13b] we have not observed the sulfoxide during the entire course of the reaction. Sulfone **4** crystallized readily from EtOAc/hexanes or from Et_2O/hexanes, and the crystalline product was completely diastereomerically pure, as indicated by chiral HPLC. DIBALH reduction of lactone **4** to hemiacetal **5** (Scheme 2) afforded the product in excellent purity after column chromatography.



Scheme 2. The Synthesis of hemiacetal **5**. Reagents and conditions: a) DIAD, Ph_3P, PhSH, THF/CH_2Cl_2, 15–40 °C, 72%; b) (i) MMPP, H_2O/CH_2Cl_2, 95%; (ii) crystallization, 79%; c) DIBALH, THF, –70 °C, 91.3%.

Synthesis of the α Chain Synthon, 8

Alkyl iodide **7**, possessing the latent C(1)-carboxyl group protected in the form of a bicyclic orthoester, was obtained from commercially available 5-iodopentanoic acid chloride **6**, according to previously described procedures.[11a,14] Compound **7** was then converted into quaternary phosphonium salt **8** with triphenylphosphane (PPh_3) in sulfolane in the presence of pyridine (Scheme 3). Acetonitrile is typically used[15a] as the solvent for Wittig salt formation from alkyl halides and PPh_3, but in our hands iodide **7** did not react with in acetonitrile, even after a prolonged reflux. However, the use of melted sulfolane[15b] as the reaction medium resulted in a clean conversion to the desired salt, **8**. Interestingly, this Wittig salt has not been described in the literature to date, although the corresponding bromide is known.[16] Due to its limited stability in acidic media, the 4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (methyl-OBO) carboxyl masking group has been used only sporadically in the prostaglandin field.[2a,2b,15] However, the methyl-OBO group shows good stability under basic conditions and easily survives hydrolysis or alcoholysis,[11] which are transformations occurring in the final steps of the present synthesis of latanoprost.



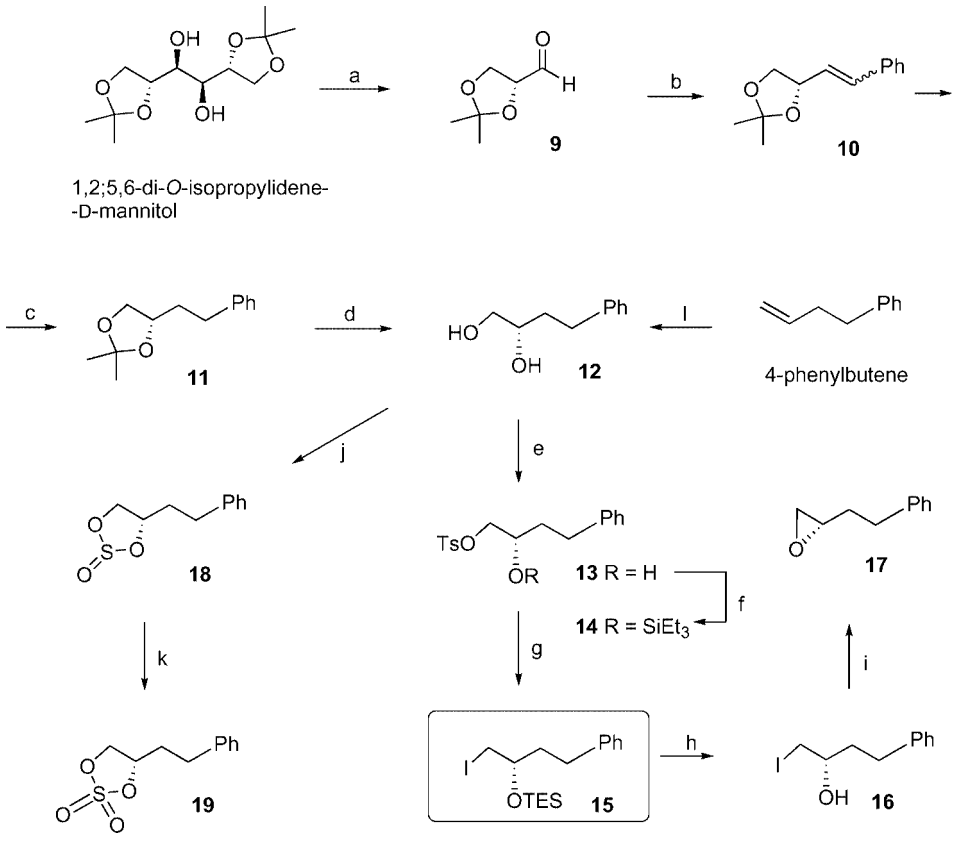
Scheme 3. The Synthesis of triphenylphosphonium iodide **8**. Reagents and conditions: a) ref.[14]; b) (i) PPh_3, sulfolane + trace C_5H_5N, 80 °C, 1 h; (ii) Et_2O/EtOAc/$CHCl_3$ + trace C_5H_5N, crystallization, 48%, or (ii) 2-propanol + trace C_5H_5N, crystallization, 65.6%.

Synthesis of the ω Chain Synthon, 15

The synthon used for the construction of the ω chain of latanoprost (**1**), according to the strategy of our synthesis (Scheme 1), contains a stereogenic center at the carbon corresponding to C(15) in the target molecule, with chirality corresponding to the (*R*) configuration in the product, and with a very high diastereomeric excess, preferably above 99.8%. Individual impurity content below 0.1% facilitates the registration process of active pharmaceutical ingredients.

A number of structural arrangements were possible for synthon **B** (Scheme 1) including ones in which the –OR group and the leaving group (LG) are a part of the same functionality (e.g. an epoxide, cyclic sulfate, or cyclic sulfite).[17] In fact, we synthesized these three ω chain precursors (compounds **17**, **18**, and **19**) in enantiomerically pure form as (*S*) enantiomers, which is illustrated in Scheme 4. However, at the next stage of the synthesis of **1**, the best results for ω chain introduction were obtained with (*S*)-1-iodo-4-phenyl-2-(triethylsiloxy)butane (**15**), which was synthesized from the corresponding tosylate **14** (Scheme 4) in a straightforward manner.

α-Hydroxytosylates (such as **13**) are best accessed from the corresponding nonracemic diols, which are available by asymmetric dihydroxylation of terminal alkenes.[18a–18d] We carried out the synthesis of the key optically active substrate, (*S*)-4-phenylbutane-1,2-diol[18e–18i] **12** in two ways: by asymmetric synthesis and by a natural, chiral-pool starting material. An asymmetric synthesis of (*R*)-4-phenylbutane-1,2-diol[18d] (*ent*-**12**) from 4-phenylbutene, in the presence of $(DHQD)_2PHAL$, was reported to give the product with 84% enantiomeric excess (84% *ee*). To directly obtain the (*S*)-diol **12** in an analogous reaction, we had to use DHQ-based chiral catalysts.[18a] Diol **12** was obtained with $(DHQ)_2PYR$ with a diminished *ee* of 65%. Exactly the same *ee* was realized when we employed the newer genera-



Scheme 4. The Synthesis of alkyl iodide **15** and other potential ω chain synthons. Reagents and conditions: a) ref.[19a], 53%; b) $PhCH_2P(Ph)_3Br$, THF, 0 – >25 °C, 62%; c) H_2, 10% Pd/C, 99%; d) PTSA, MeOH, 40 °C, 99%, 99.3% *ee*; e) (i) nBu_2SnO, TsCl, Et_3N, 0 – >20 °C; (ii) Et_2O, crystallization, 67.4%, 99.92% *ee* for the chiral-pool run; f) Et_3SiCl, imidazole, DMF, 99.5%; g) NaI, DMF, 89%, 99.92% *ee*; h) *p*TsOH, acetone/H_2O, 72%; i) KOH, THF/H_2O, 81%; j) $SOCl_2$, diisopropylethylamine, CH_2Cl_2, 96%, 99.92% *ee*; k) (i) $NaIO_4$, $RuCl_3$, MeCN/H_2O; (ii) Et_2O, crystallization, 42%, >99.99% *ee*; l) $(DHQ)_2AQN$, $K_3Fe(CN)_6$, $K_2OsO_2(OH)_4$, *t*BuOH/H_2O, K_2CO_3, 0 °C, 17 h, 98%, 65.3% *ee*.

tion catalyst, $(DHQ)_2AQN$.[18b] A much higher enantiomeric purity of diol **12** was achieved when we employed (*R*)-2,3-*O*-isopropylideneglyceraldehyde[19] (**9**) as the source of chirality (Scheme 4). Aldehyde **9** was synthesized in high enantiomeric purity from 1,2:5,6-di-*O*-isopropylidene-D-mannitol, which is available commercially or can be prepared from D-mannitol.[19a] A chain elongation protocol by the Wittig reaction of **9** with the ylide obtained in situ from benzyltriphenylphosphonium bromide gave alkenes **10** as a 7:3 *cis*/*trans* mixture, which was then successfully hydrogenated in methanol solution to acetonide **11**. Removal of the acetonide in the next step (**11** to **12**) required high dilution in methanol at 40 °C and quenching with triethylamine prior to workup to circumvent the reversibility of the hydrolysis process. Diol **12** was thus prepared in quantities up to 250 g in 99.3% *ee*. Selective monotosylation of **12** was best conducted with tin-derived catalysts, of which dibutyltin oxide proved to be the most efficient and very easy to use.[20] Importantly, we discovered that known[21] compound **13** crystallized readily from Et_2O with efficient enhancement of enantiomeric purity. This property was critical to the synthesis of enantiomerically pure ω chain synthons. The silylation of hydroxytosylate **13** afforded protected derivative **14** in high yield. The optimized synthesis of iodide **15** required heating of compound **14** with sodium iodide in DMF at about 75 °C for 2.5–3.5 h, which ensured almost complete conversion while still preventing decomposition of the product. At higher temperatures, desilylation became noticeable, while at 60 °C the reaction was not complete after several days. Synthon **15** was very easy to purify on a silica gel column, and quantities up to about 300 g of highly enantiomerically pure **15** were thus prepared (99.93% *ee*).

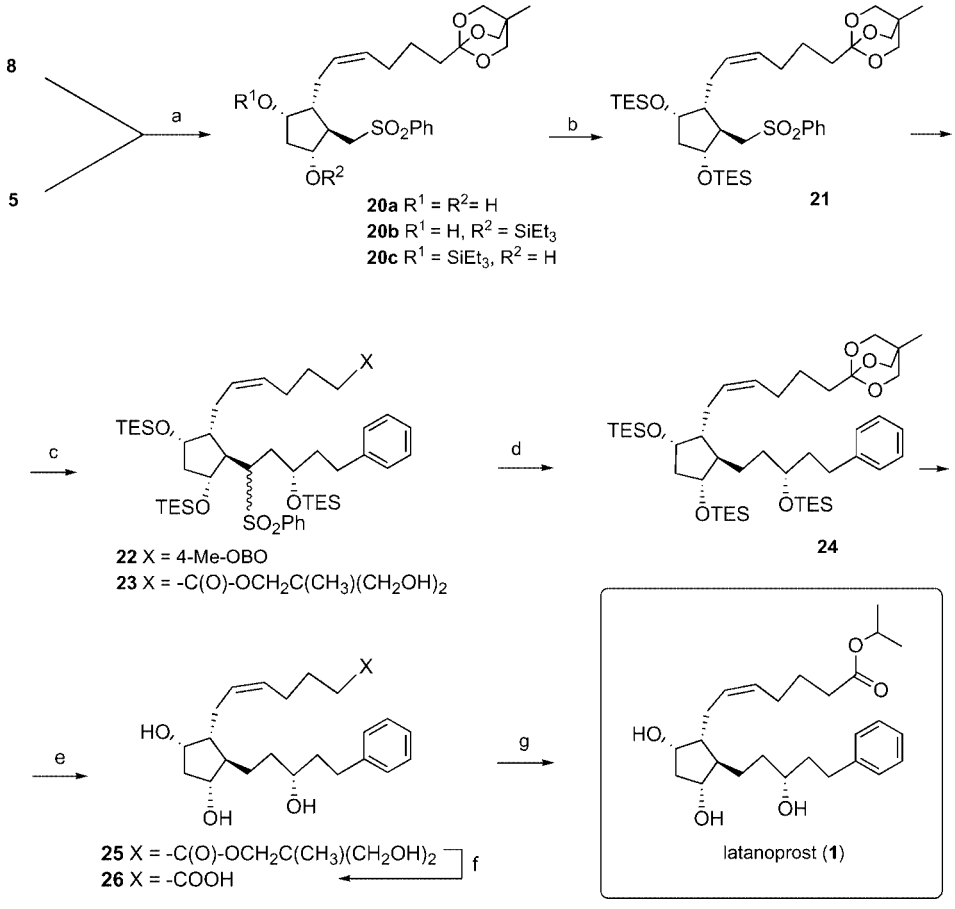
The Synthesis of Latanoprost (1)

With the three necessary components **5**, **8**, and **15** in hand, we continued the synthesis of target compound **1** according to the strategy described in Scheme 1. Initial attempts to obtain **21** were discouraging. The Wittig reaction of pure lactol **5** with the ylide generated from compound **8** was very sluggish. When *t*BuOK alone was used as the base, only 25% of product **20a** was obtained after stirring for 5 h at room temperature, with 10% recovery of **5**. Longer reaction times resulted in decomposition. Fortunately, in the course of the optimization of the reaction conditions, we observed that the yields improved by about 20%

when crude **5** was used as the substrate. The known oxophilic character[22] of many aluminum compounds led us to speculate that aluminum impurities present in **5** prior to chromatography must positively influence the reactivity of this hemiacetal, perhaps by assisting in the lactol ring opening. Indeed, the addition of a catalytic amount of aluminum tri-*tert*-butoxide resulted in a marked improvement in the efficiency for this Wittig reaction (Scheme 5). However, under the optimized conditions, we also observed desilylation, which led to **20a** (65.5% yield), and a partial triethylsilyl group migration, which gave a 35/65 mixture of **20b** and **20c** (15.4% yield). Analogous silyl group migrations have been reported[6] in the prostaglandin field. Alcohols **20a**–**c** were readily resilylated, which afforded the important prostaglandin sulfone intermediate, **21**. Orthoester **21** was stable when stored in pure form at about 0 °C in the presence of a trace of pyridine. After routine chromatography, both HPLC analysis as well as ^{1}H and ^{13}C NMR spectra indicated the absence of the *trans* isomer of **21**. The 5,6-*cis* stereochemistry of the sulfone was in agreement with the NMR spectra.

The ω chain elongation of sulfone **21** to the prostaglandin **22** initially encountered serious difficulties, mainly due to the moderate reactivity of the iodide **15** and the lability of the C(11)-*O*-silyl group in **21**. Based on the known behavior of alkyl or aryl sulfones,[23,24] we chose the lithium hexamethyldisilazane (LHMDS)/THF conditions for the alkylation of the carbanion generated at C(13) of sulfone **21**, which eventually led to the desired substitution product **22**, albeit in a modest isolated yield of 46%. This alkylation reaction required room temperature. However, reaction times longer than about 4 h did not result in a better yield of **22**. In spite of stringently maintained basic conditions throughout the entire process, including chromatography, OBO hydrolysis product **23** (13.5% yield) was isolated after the purification procedure. Clearly, the acidity of the silica gel may have been sufficient to cause partial hydrolysis of **22**, even though we attempted to attenuate it with traces of pyridine.

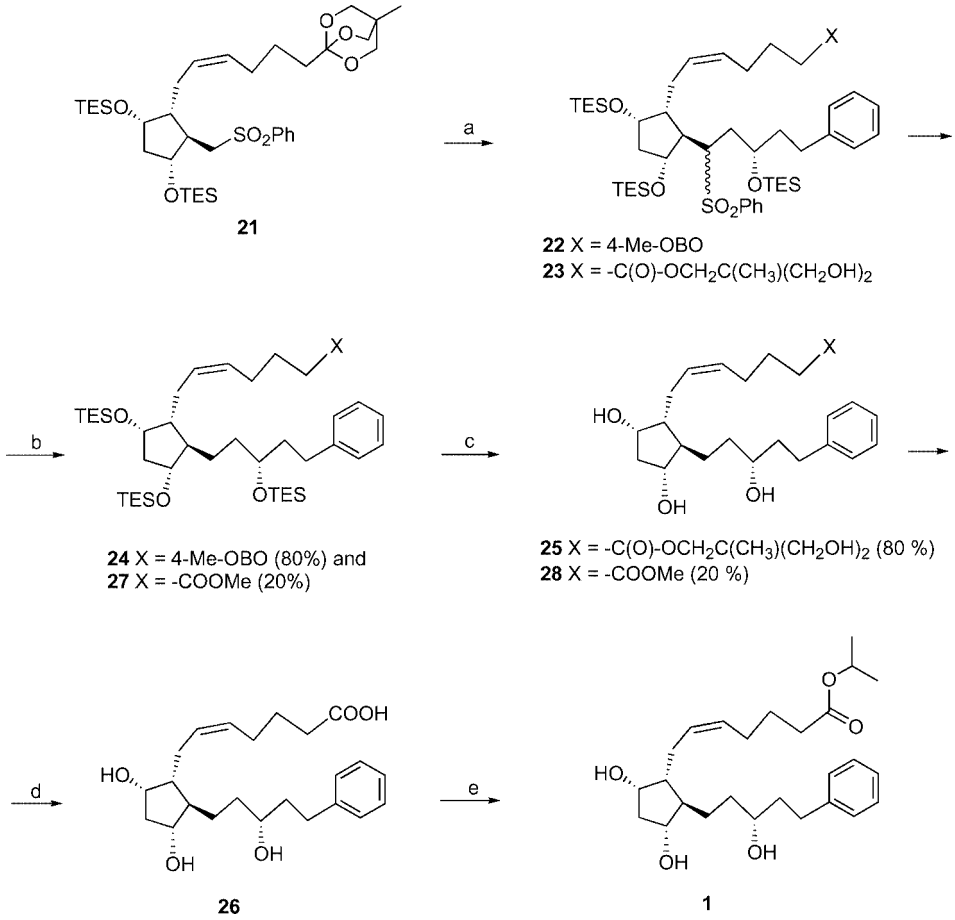
Alternatively, the lithium salts present in the crude reaction product may have facilitated the oxabicyclooctane ring opening. This is additionally corroborated by our observation on thin layer chromatograms (TLC) of the crude reaction product of a spot corresponding to compound **23** (ca. 5–10% estimated yield; the TLC analyses of compounds **20**–**24** were performed in solvent systems containing 0.2%



Scheme 5. Laboratory scale synthesis of latanoprost. Reagents and conditions: a) (i) **8**, *t*BuOK, THF, 0 – >25 °C; (ii) **5**, $(t\text{BuO})_3$Al, 0 – >25 °C, isolate products: 65.5% of **20a** plus 15.4% of **20b**/**20c**; b) Et_3SiCl, Et_3N, imidazole, DMF, 87% from **20a** or 67% from **20b**/**20c**; c) **15**, LHMDS, THF, 46.2% of **22** plus 13.5% of **23**; d) **22**, 10% Na/Hg, Na_2HPO_4, MeOH, 99%; e) PPTS, acetone/H_2O, 95%; f) (i) LiOH, MeOH/H_2O; (ii) $NaHSO_4$, NH_4Cl, H_2O, 99%; g) *i*PrI, DBU, acetone, 63.2% after chromatography; chiral HPLC purity 99.83%.

triethylamine). Compounds **22** and **23** were both obtained as a 5:2 mixture of two diastereomers, epimeric at the C(13) center (the prostaglandin numbering system).[2c] In order to gain a better insight into this alkylation reaction and to determine the structure of these isomers, a small sample of **22** was additionally separated into the components, (13*R*)-**22** and (13*S*)-**22**. 500 MHz NMR spectra including ^{1}H-^{1}H COSY, ROESY, and ^{13}C-^{1}H HETCOR were acquired for these compounds, which revealed very similar coupling constants to C(13)–H in both isomers, and nOe/ROESY data were inconclusive. To examine the substitution geometry, MacroModel/BatchMin conformational searches for compound **21** were carried out with the MMFF force field, Polak–Ribiere conjugate gradient (PRCG) minimization, and the Monte Carlo method.[25] The structures of the lowest energy conformers thus found suggested that the pro-*R* approach of the electrophile should be sterically less encumbered than a pro-*S* approach. Therefore, we propose that the major isomer of **22** had (13*R*) configuration, and the minor had a (13*S*) configuration.

Using the phosphate-buffered conditions of Trost,[26a] the epimeric mixture of compounds **22** was subsequently subjected to reductive desulfonylation to give OBO-prostaglandin **24** in 99% yield. This result was obtained after much less successful yet extensive experimentation, which included reductions with calcium, sodium, or lithium in liquid ammonia or *n*-propylamine and Mg in ethanol/$HgCl_2$ or Mg/MeOH conditions.[25b] Desired compound **24** was formed in all the dissolving metal reductions, but in each case the product was contaminated with 15–25% of a phenylsulfinic acid elimination product, which was not separable from **24**.[25a] In our hands, the most successful application of the sodium amalgam method of desulfonylation specifically required that an excess of newly purchased 10% Na/Hg reagent was used. Compound **24** showed no signs of *cis-trans* isomerisation of the 5,6-olefin by HPLC or NMR spectroscopy. However, during the final steps of the synthesis (**24** → **1**) the formation of a small amount (ca. 5–9%) of the 5,6-*trans* isomer of **1** could not be avoided. Fortunately, this contamination was easily removed from **1** by preparative HPLC on silica gel stationary phases. The triethylsilyl protecting groups in compound **24** were all removed under the action of pyridinium *p*-toluenesulfonate (PPTS) in aqueous acetone, which also led to the intended hydrolytic opening of the OBO group, affording pentol **25** in 95% yield. This 2,2-bis(hydroxymethyl)propyl ester was



Scheme 6. Multigram scale synthesis of **1**. Reagents and conditions: a) **15** (99.93% *ee*), LHMDS, THF, 62.8% of **22** plus 16.4% of **23**; b) **22** (81%) + **23** (19%), 10% Na/Hg, Na_2HPO_4, MeOH, 90%; c) PPTS, acetone/H_2O, 60%; d) (i) LiOH, MeOH/H_2O; (ii) $NaHSO_4$, NH_4Cl, H_2O, 91.5%; e) *i*PrI, DBU, acetone, flash chromatography, then preparative HPLC, 65% from **26**, chiral HPLC purity of **1** > 99.9%.

subsequently cleaved with lithium hydroxide and, after acidification with $NaHSO_4/NH_4Cl$, latanoprost acid[4a] **26** was isolated in an almost quantitative yield. In the final step of the synthesis, acid **26** was successfully converted to latanoprost (**1**), with *i*PrI/DBU/acetone, conditions commonly used in the prostaglandin field.[2,6] The crude isopropyl ester (91% purity) was further purified by preparative HPLC on silica gel, which afforded latanoprost (**1**) in 63.2% yield from **25** and in 99.83% HPLC purity. Latanoprost was obtained from the readily available sulfone **5** in 17.3% overall yield in seven synthetic steps. This result was unoptimized, and further improvements were clearly possible.

With this goal in mind, we undertook a multigram-scale ("proof of concept") synthesis of latanoprost (Scheme 6). Very gratifyingly, the alkylation of synthon **21**, carried out on a 104 g scale, gave a noticeably higher yield of the alkylation products (79.2%) than did the smaller scale experiment discussed above. TLC monitoring indicated that, in the present case, the formation of **22** was still slowly progressing after 8 h of reaction at room temperature, and therefore, the large-scale reaction mixture was stirred overnight. Compound **23** (as a 5:2 mixture of both C(13) epimers) was isolated in 16.4% yield. Due to the quantity of material and high enantiomeric purity of the C(15) fragment incorporated in **23**, we decided that the practical synthesis of **1** should be continued without separating compounds differing in the substitution pattern at C(1). Thus, a mixture of **22** (81%) and **23** (19%) was subjected to the reductive desulfonylation conditions, as discussed above.

Desulfonylation of **22** and **23** occurred as expected, affording an 80:20 mixture of compound **24** and the methyl ester[6a] **27**, respectively, in a combined isolated yield of 90%. This mixture was then hydrolyzed with PPTS/acetone/H_2O, which gave an 80:20 mixture of **25** and the known[6c] latanoprost acid ester **28**. The next step led, by efficient hydrolysis of the esters (91.5% yield), to the latanoprost acid **26**. Selective alkylation of **26** with 2-iodopropane provided a 76.4% yield of latanoprost, in which the (15*S*)-**1** isomer could not be detected. However, a few percent of the 5,6-*trans* diastereomer of **1** were present in the product. Preparative HPLC purification of **1** on silica gel gave latanoprost in better than 99.9% purity and 65% yield from acid **26**.[27]

Conclusions

A new synthesis of latanoprost (**1**) was designed and carried out. High-purity latanoprost was obtained in 15.8% overall yield in eight synthetic steps from sulfone **4** or in 26.5% yield and six steps from prostaglandin intermediate **21**. The occurrence of the (15*S*)-**1** diastereomer has been an "Achilles heel" of most existing syntheses of **1**. Therefore, the present method for latanoprost synthesis targeted a very high enantiomeric purity at C(15) of the product. The α chain in a carefully selected, novel derivative of the (–)-Corey lactone was elongated first, followed by the attachment of a novel, enantiomerically pure ω chain synthon. This ensured the absence of an appreciable quantity of the undesired (15*S*)-**1** diastereomer in the synthesized prostaglandin. The crystalline nature of our starting material (sulfone **4**) eliminates the need for the troublesome ester protecting groups at the C(11)-hydroxy, such as a benzoate or a *p*-phenylbenzoate, which were previously used by others to impart crystallinity and thus facilitate purifications during the course of prostaglandin synthesis.[2,4,6] We also describe a variation of the new synthesis of latanoprost, where the laboratory scale synthesis is further adapted to a multigram scale by carrying out a series of transformations, in parallel and in one pot, with two prostaglandin compounds: (a) a compound protected at C(1) with the 4-methyl-OBO group and (b) a compound protected with an ester group at the same position. The absence of (15*S*)-**1** in the crude final product substantially facilitated the preparative HPLC purification of **1** from the (5*E*) diastereomer. This resulted in pure latanoprost obtained from the prostaglandin precursor **21** in 25% yield.

Importantly, in the course of the present synthesis, a new prostaglandin sulfone intermediate **21**, which may find application in the synthesis of diverse prostaglandin analogs, was introduced. A practical synthesis of novel, enantiomerically pure ω chain synthons **17**, **18**, and **19** has also been carried out, employing diol **12**, which was obtained from derivatives of the D-mannitol chiral pool.

Experimental Section

The starting material, (3a*R*,4*S*,5*R*,6a*S*)-4-(hydroxymethyl)-5-(triethylsilyloxy)hexahydrocyclopenta[*b*]furan-2-one (**2**), is commercially available[28] under the name "(–)-Triethylsilyloxy Corey-diol": $[\alpha]_D^{20} = -47.5$ (c = 1.00, $CHCl_3$). 1-(4-Iodobutyl)-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (**7**) was obtained as described by Matsamura et al.[14] (*R*)-2,3-*O*-Isopropylideneglyceraldehyde (**9**) was obtained from D-mannitol according to the known procedure and was distilled immediately before use (b.p. 47–51 °C/20 Torr).[19]

(3a*R*,4*R*,5*R*,6a*S*)-4-(Phenylthio)methyl-5-(triethylsilyloxy)hexahydrocyclopenta[*b*]furan-2-one (3): To a solution of (3a*R*,4*S*,5*R*,6a*S*)-4-(hydroxymethyl)-5-(triethylsilyloxy)-hexahydro-cyclopenta[*b*]-furan-2-one (**2**, 11.45 g, 40 mmol) in CH_2Cl_2 (40 mL), stirred under Ar at room temperature, THF (20 mL) and PPh_3 (13.1 g, 50 mmol) were added. After the solids dissolved, the solution was cooled to 15 °C, and benzenethiol (5.51 g, 50 mmol) was added. The mixture was stirred for 5 min, after which time a solution of DIAD (95%, 10.4 mL, 50 mmol) in THF (20 mL) was slowly added by syringe. Stirring was continued while the mixture was allowed to gradually warm to 25 °C. After 15 h, THF (25 mL) was added, and the mixture was heated at 40 °C for 9 h and then stirred at room temperature for 16 h. Afterwards, the solvents were evaporated to give an oil (41 g), which was subjected to flash chromatography on silica gel (230–400 mesh, 440 g). Elution with hexanes/EtOAc/CH_2Cl_2 (75:12.5:12.5) gave sulfide **3** (10.84 g, 71.6% yield) as a colorless, viscous oil. $[\alpha]_D^{25} = -31.0$ (c = 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.56 (q, J = 8.0 Hz, 6 H), 0.92 (t, J = 8.0 Hz, 9 H), 2.00 (m, 1 H), 2.08 (m, 1 H), 2.22 (m, 1 H), 2.45–2.85 (m, 4 H), 3.02 (dd, J = 13.2, 5.9 Hz, 1 H), 4.08 (q, J = 5.0 Hz, 1 H), 4.95 (ddd, J = 7.0, 6.8, 2.8 Hz, 1 H), 7.31 (m, 5 H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 4.6 (3 C), 6.7 (3 C), 35.8, 36.1, 40.6, 41.8, 54.0, 76.3, 83.1, 126.2, 129.0 (2 C), 129.1 (2 C), 135.4, 176.9 ppm;

EI-MS: *m*/*z* (%) = 379 [M + H] (2). $C_{20}H_{30}O_3SSi$ (378.6): calcd. C 63.45, H 7.99, S 8.47; found C 63.37, H 8.03, S 8.46.

(3a*R*,4*R*,5*R*,6a*S*)-4-(Phenylsulfonyl)methyl-5-(triethylsilyloxy)-hexahydro-cyclopenta[*b*]furan-2-one (4): (a) Sulfide **3** (9.55 g, 25.2 mmol) was dissolved in CH_2Cl_2 (150 mL). The flask was cooled in a H_2O bath at 17 °C. Upon vigorous stirring, a suspension of magnesium monoperoxyphthalate hexahydrate (MMPP·6H_2O, 80% pure, 89.7 g, ca. 145 mmol) in H_2O (230 mL) was added over 2 min. Vigorous stirring was continued for 65 min, after which time saturated aqueous $NaHCO_3$ (350 mL) was added dropwise over 20 min. Stirring was continued for another 15 min. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (40 mL). The organic phases were combined and extracted with saturated aqueous $NaHCO_3$ (300 mL). The phases were separated, and the aqueous phase was re-extracted with CH_2Cl_2 (40 mL). The organic phases were combined, extracted with 10% aqueous $Na_2S_2O_3$ (500 mL) and saturated aqueous $NaHCO_3$ (300 mL). The organic layer was dried with $MgSO_4$ (50 g). The drying agent was filtered and then washed with CH_2Cl_2 (50 mL). The filtrates were combined, concentrated in vacuo, and dried in vacuo (1 Torr, 30 °C, 30 min), affording compound **4** as a colorless, solidifying oil (9.81 g, 94.8% yield). $[\alpha]_D^{25}$ = +24.9 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.53 (q, *J* = 8.0 Hz, 6 H), 0.89 (t, *J* = 8.0 Hz, 9 H), 1.98 (m, 1 H), 2.15 (m, 1 H), 2.33 (m, 1 H), 2.62–2.98 (m, 4 H), 3.18 (dd, *J* = 13.9, 4.4 Hz, 1 H), 4.01 (q, *J* = 5.1 Hz, 1 H), 4.98 (ddd, *J* = 7.1, 6.8, 3.5 Hz, 1 H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 4.6 (3 C), 6.7 (3 C), 35.8, 40.4, 41.9, 49.4, 58.5, 76.7, 82.6, 127.7 (2 C), 129.4 (2 C), 133.9, 139.0, 176.6 ppm; HRMS (ESI): calcd. for $C_{20}H_{31}O_5SSi$ [M + H]$^+$ 411.1656; found 411.1676; $C_{20}H_{30}O_5SSi$ (410.6): calcd. C 58.50, H 7.36, S 7.81; found C 58.36, H 7.22, S 8.01.

(b) In another series of two reactions, compound **2** (211.2 g) gave sulfone **4** (179.5 g, 69.2% yield as a solidifying oil), as described above. This sample of **4** was crystallized from EtOAc/hexanes (1:1, 400 mL). The white precipitate thus obtained was then recrystallised from Et_2O/hexanes (3:1). This gave crystalline sulfone **4** (141.25 g, 46.7% yield from **2**) as white needles; m.p. 75–76 °C, other analytical data were identical with that described above for compound **4**. Chiral HPLC analysis [Chiralcel OD 10 μm, 250 × 4.6 mm column, *n*-hexanes/2-propanol (85:15), and 1.0 mL/min] gave only one peak for the crystallized sample of compound **4**.

(2*R*/*S*,3a*R*,4*R*,5*R*,6a*S*)-4-[(Phenylsulfonyl)methyl]-5-(triethylosilyloxy)hexahydro-2*H*-cyclopenta[*b*]furan-2-ol (5): To a solution of lactone **4** (9.26 g, 22.55 mmol) in THF (120 mL), stirred under Ar at –75 °C, DIBALH (1.4 M toluene solution, 35.4 mL, 49.6 mmol) was added dropwise over 5 min. Stirring at –75 °C was continued for 2 h, and then MeOH (9.5 mL, 234 mmol) was added slowly (foaming!) with vigorous stirring. The mixture was warmed to –5 °C, and H_2O (130 mL) was added dropwise, followed by aqueous $NaHSO_4$ (2 M, 100 mL). Stirring was continued for 5 min, EtOAc (100 mL) was added, and the phases were separated. The aqueous layer was extracted with EtOAc (2 × 80 mL). The organic layers were combined, washed with brine (2 × 200 mL), dried with Na_2SO_4 (50 g), filtered, and concentrated under reduced pressure. The viscous, colorless oil thus obtained (10.1 g) was purified by flash chromatography on silica gel (200 g). Elution with 42–50% EtOAc/hexanes + 0.02% C_5H_5N gave hemiacetal **5** (3:1 mixture of epimers) as a colorless, viscous oil (8.50 g, 91.3% yield). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.52 (q, 6 H), 0.89 (t, 9 H), 1.62 (m, 0.75 H), 1.98–2.37 (m, 4 H), 2.62 (m, 1.25 H), 2.90–3.04 (m, 1.75 H), 3.23 (dd, *J* = 14.1, 4.4 Hz, 0.25 H), 3.36 (dd, *J* = 14.0, 3.1 Hz, 0.75 H), 3.78 (ddd, *J* = 8.8, 8.6, 5.8 Hz, 0.75 H), 3.98 (br. q, *J* = 5.1 Hz, 0.25 H), 4.60 (m, 1.25 H), 5.48 (ddd, *J* = 6.4, 4.5, 1.7 Hz, 0.25 H), 5.62 (dd, *J* = 3.7, 3.5 Hz, 0.75 H), 7.91 (m, 2 H), 7.61 (m, 3 H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 4.45,4.73, 6.63, 6.73, 40.36, 40.68, 40.99, 42.54, 44.18, 46.43, 48.45, 49.08, 59.04, 59.80, 77.39, 78.46, 79.90, 83.62, 100.42 and 101.22 (hemiacetal), 127.61, 127.80, 129.19, 129.23, 133.54, 133.66, 139.28, 139.58 ppm; $C_{20}H_{32}O_5SSi$ (412.6): calcd. C 58.22, H 7.82, S 7.77; found C 57.98, H 7.78, S 8.05.

[4-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]oct-1-yl)butyl]triphenylphosphonium Iodide (8): A mixture of iodide **7** (15.8 g, 50.6 mmol), PPh_3 (14.6 g, 55.66 mmol), sulfolane (20 mL), and anhydrous pyridine (0.1 mL) was stirred under Ar at 80 °C for 70 min. After cooling to 40 °C, $CHCl_3$ containing 0.3% of pyridine (70 mL) was added. The resulting solution was added dropwise to a mixture of Et_2O (1.5 L) and EtOAc (0.6 L), vigorously stirred under Ar. Stirring was continued for 30 min, and then the solution was decanted. The remaining precipitate was dissolved in $CHCl_3$ containing 0.2% pyridine (75 mL). The solution thus obtained was added dropwise to the mixture of Et_2O (1.2 L) and EtOAc (0.5 L), vigorously stirred under Ar. The stirring was continued for 20 min at 25 °C. The solution was decanted, and the precipitate was washed with Et_2O (100 mL) and dried (1 Torr, 25 °C, 1.5 h). The crude product (28.95 g) was dissolved in MeOH containing 0.04% pyridine (35 mL), EtOAc containing 0.04% pyridine (65 mL) was added, and the mixture was stored at 4 °C. The crystals were filtered and dried (1 Torr, 25 °C, 1 h) to give phosphonium iodide **8** (14.01 g, 48.3% yield) as colorless thick prisms. M.p. 130–134 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.78 (s, 3 H), 1.58–1.80 (m, 6 H), 3.45 (m, 2 H), 3.79 (s, 6 H), 7.70–7.88 (m, 15 H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.5, 21.7 (d, *J* = 4.0 Hz), 22.7 (d, *J* = 50.8 Hz), 24.0 (d, *J* = 16.8 Hz), 30.2, 34.7, 72.3 (3 × C), 108.5, 117.8 (3 × C, d, *J* = 86 Hz), 130.5 (6 × C, d, *J* = 12.4 Hz), 133.5 (6 × C, d, *J* = 10.0 Hz), 135.1 (3 × C, d, *J* = 2.8 Hz) ppm.

(*S*)-4-Phenylbutane-1,2-diol (12). (a) By Asymmetric Synthesis: A mixture of *tert*-butyl alcohol (450 mL), distilled H_2O (450 mL), $(DHQ)_2AQN$ (Aldrich, 95%, 990 mg, 1.1 mmol), K_2CO_3 (38.7 g, 280 mmol), $K_3Fe(CN)_6$ (93.1 g, 280 mmol), and $K_2OsO_2(OH)_4$ (133 mg, 0.33 mmol) was vigorously stirred at room temperature for 1.5 h. The mixture was cooled to 0 °C, 4-phenyl-1-butene (13.52 mL, 11.90 g, 90.0 mmol) was added, and stirring at 0 °C was continued for 17 h. $Na_2S_2O_5$ (130 g) was added in a few portions, and the mixture was warmed to room temperature over 1 h. The product was extracted with EtOAc twice (400 mL and 100 mL). The combined organic phases were dried with anhydrous Na_2SO_4 (100 g) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (350 g). Elution with EtOAc gave diol **12** (14.70 g, 98% yield, 65.3% *ee*) as a viscous oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.72 (m, 2 H), 2.70 (m, 2 H), 3.31 (br. s, 2 H) 3.42 (dd, *J* = 11.2, 7.7 Hz, 1 H), 3.61 (dd, *J* = 11.2, 2.9 Hz, 1 H), 3.69 (m, 1 H), 7.13–7.31 (m, 5 H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 31.8, 34.6, 66.6, 71.5, 125.8, 128.2 (2 C), 128.3 (2 C), 141.5 ppm; chiral HPLC: Chiralcel OD, 10 μm, (250 + 20) × 4.6 mm column, hexanes/2-propanol, 80:20 (v/v), 1.0 mL/min, R_t 8.47 min (17.2% yield), R_t 11.06 min (81.9% yield), 65.3% *ee*. Racemic diol **12**, used as a standard for HPLC, was prepared from 4-phenyl-1-butene by a dihydroxylation reaction as described above, in which DABCO was used in place of $(DHQ)_2AQN$.

(b) Chiral-Pool Synthesis. (*E*/*Z*,4*S*)-2,2-Dimethyl-4-styryl-1,3-dioxolane (10): To a suspension of benzyltriphenylphosphonium bromide (189.4 g, 0.437 mol) in THF (1.2 L), vigorously stirred under Ar at 0 °C, hexyllithium (2.5 M solution in hexanes, 170 mL,

0.425 mol) was added dropwise while the temperature was maintained below 5 °C. The temperature of the mixture was then allowed to increase to 15 °C during 1 h. The mixture was stirred at 15 °C for 30 min, and then it was cooled to 0 °C. A solution of freshly distilled (*R*)-2,3-*O*-isopropylideneglyceraldehyde (**9**, 52.3 g, 0.402 mol) in THF (150 mL), cooled to <5 °C, was added dropwise. The mixture was stirred at 20 °C for 2 h, and then MeOH (10 mL) was slowly added. The suspension thus formed was filtered through Celite (100 g), which was additionally washed with hexanes/EtOAc (2:1, 2 × 200 mL). The filtrates were combined, concentrated, and subjected to flash chromatography on silica gel (500 g). Elution with hexanes/EtOAc (1:1) gave dioxolane **10** (50.9 g, 62% yield) as a colorless, viscous oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.39 (s, 2.3 H), 1.43 (s, 0.7 H), 1.47 (br. s, 3 H), 3.68 (m, 1 H), 4.08 (m, 0.3 H), 4.16 (m, 0.7 H), 4.67 (m, 0.3 H), 4.92 (m, 0.7 H), 5.70 (dd, *J* = 11.6, 9.0 Hz, 0.7 H), 6.16 (dd, *J* = 15.8, 7.6 Hz, 0.3 H), 6.70 (m, 1 H), 7.23–7.42 (m, 5 H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.89, 25.94, 26.75, 26.86, 69.51, 69.70, 72.41, 77.24, 109.37, 109.43, 126.61, 126.71, 127.52, 127.98, 128.29, 128.57, 128.70, 129.20, 133.38, 133.97, 136.13, 136.24 ppm.

(4*S*)-2,2-Dimethyl-4-phenethyl-1,3-dioxolane (11): The (*E*/*Z*) mixture of dioxolanes (4*S*)-**10** (50.0 g) was dissolved in MeOH (0.5 L), and the solution was hydrogenated in a Parr reactor over 10% Pd/C (5.0 g) under a pressure of 10 bar at 30 °C for 24 h. The catalyst was filtered, washed with MeOH (3 × 50 mL), the solvent was evaporated under reduced pressure, and the residue was dried in vacuo to give dioxolane **11** (49.9 g, 98.8% yield) as a colorless oil. $[\alpha]_D^{20}$ = +3.8 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.36 (br. s, 3 H), 1.43 (br. s, 3 H), 1.88 (m, 2 H), 2.70 (m, 2 H), 3.52 (dd, *J* = 7.5, 7.0 Hz, 1 H), 4.05 (m, 2 H), 7.14–7.33 (m, 5 H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.73, 26.99, 32.02, 35.33, 69.31, 75.35, 108.71, 125.95, 128.35, 125.41, 141.53 ppm.

(*S*)-4-Phenylbutan-1,2-diol (12): A solution of dioxolane **11** (49.8 g, 0.241 mol) in MeOH (600 mL) was treated with PTSA (0.5 g), and the mixture was stirred at 40 °C for 4 h. Et_3N (2 mL) was added, the solvent was evaporated, and the residue was subjected to flash chromatography on silica gel (500 g). Elution with EtOAc afforded diol **12** (40.0 g, 99% yield, 99.3% *ee*) as a colorless oil, which solidified at 4 °C. M.p. 34–36 °C; $[\alpha]_D^{20}$ = –13.6 (*c* = 1.00, $CHCl_3$); $[\alpha]_D^{20}$ = –33.1 (*c* = 1.00, EtOH); ^{1}H NMR (200 MHz, $CDCl_3$) was identical with that given for **12** above; chiral HPLC: Chiralcel OD, 10 μm, (250+20) × 4.6 mm column, hexanes/2-propanol, 80:20 (v/v), 1.0 mL/min, R_t 8.5 min (0.33% yield), R_t 11.1 min (98.86% yield), 99.3% *ee*. For HPLC calibration, *rac*-4-phenyl-1,2-butanediol was used.

(*S*)-4-Phenyl-1-(*p*-tolylsulfonyloxy)butan-2-ol (13). (a) By Asymmetric Synthesis: To a solution of (*S*)-4-phenyl-1,2-butanediol (**12**, 13.58 g, 81.7 mmol, 65% *ee*) in anhydrous CH_2Cl_2 (190 mL), stirred under Ar, was added Bu_2SnO (720 mg, 2.89 mmol). The suspension was stirred for 5 min prior to adding Et_3N (11.40 mL, 8.276 g, 81.79 mmol). The mixture was cooled to 0 °C, and *p*-toluenesulfonyl chloride (16.03 g, 84.08 mmol) was added. The mixture was stirred at 0 °C for 5 min, gradually warmed to room temperature over 1.5 h, and then left overnight at 4 °C. The mixture was then concentrated to 100 mL and purified by flash chromatography on silica gel (500 g). Elution with 25% EtOAc/hexanes gave nonracemic tosylate **13** (20.1 g, 76.8% yield) as a colorless, viscous oil. This sample of **13** (19.85 g) was crystallized from Et_2O (60 mL), leading to crystals (10.51 g). This sample was further recrystallised from Et_2O twice, affording compound **13** (4.77 g, 18.45% yield, 99.26% *ee*) as needles. M.p. 68–69 °C; $[\alpha]_D^{25}$ = +0.70 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.73 (m, 2 H), 2.19 (d, *J* = 4.6 Hz, 1 H), 2.45 (s, 3 H), 2.70 (m, 2 H), 3.85 (m, 2 H), 4.02 (dd, *J* = 9.5, 2.9 Hz, 1 H), 7.11–7.37 (m, 7 H), 7.79 (ddd, *J* = 8.4, 2.0, 1.8 Hz, 2 H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 21.6, 31.3, 34.1, 68.5, 73.8, 125.9, 127.8 (2 C), 128.2 (2 C), 128.3 (2 C), 129.8 (2 C), 132.4, 140.9, 144.9 ppm; chiral HPLC: Chiralcel OD, 10 μm, (250+20) × 4.6 mm column, hexanes/2-propanol, 80:20 (v/v), 1.0 mL/min, R_t 13.28 min (99.59% yield), R_t 15.53 min (0.37% yield), 99.26% *ee*; $C_{17}H_{20}O_4S$ (272.4): calcd. C 63.73, H 6.29, S 10.01; found C 63.79, H 6.19, S 10.16.

(b) Chiral-Pool Synthesis: Diol **12** (40 g, 99.3% *ee*) was monotosylated as described above for the asymmetric dihydroxylation product. The usual workup and flash chromatography on silica gel (1 kg, elution with 25% EtOAc/hexanes) gave compound **13** (60 g, 77.8% yield) as a colorless, viscous oil. Crystallization from Et_2O (210 mL) gave *p*-toluenesulfonate **13** (52 g, 67.4% yield) as colorless needles. $[\alpha]_D^{20}$ = +1.0 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) was identical with that given above for compound **13**, obtained from the asymmetric synthesis; chiral HPLC: Chiralcel OD, 10 μm, (250+20) × 4.6 mm column, hexanes/2-propanol, 80:20 (v/v), 1.0 mL/min, R_t 13.2 min (98.370% yield), R_t 15.9 min (0.039% yield), 99.92% *ee*.

(*S*)-4-Phenyl-1-(*p*-tolylsulfonyloxy)-2-(triethylsilyloxy)butane (14): (a) By Asymmetric Synthesis: To a solution of *p*-toluenesulfonate **13** (4.537 g, 14.16 mmol, 99.26% *ee*) in anhydrous DMF (38 mL), stirred under Ar at 0 °C, imidazole (1.07 g, 15.7 mmol) and Et_3N (2.0 mL, 1.45 g, 14.3 mmol) were added, followed by chlorotriethylsilane (2.52 mL, 2.26 g, 15.0 mmol). Stirring at 0 °C was continued for 1 h and then at room temperature for 20 min. The mixture was diluted with hexanes (100 mL) and washed with saturated aqueous $NaHCO_3$ (90 mL). The aqueous layer was extracted with hexanes (2 × 40 mL). The organic phases were combined, washed with saturated aqueous $NaHCO_3$ (100 mL), dried with Na_2SO_4 (20 g), and concentrated in vacuo. The residue thus obtained (7.0 g) was purified by flash chromatography on silica gel (185 g). Elution with 10% EtOAc/hexanes gave triethylsilyl derivative **14** (6.127 g, 99.5% yield, 99.26% *ee*) as a colorless, viscous oil. $[\alpha]_D^{25}$ = +4.9 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.56 (q, 8.0 Hz, 6 H), 0.91 (t, *J* = 8.0 Hz, 9 H), 1.74 (m, 2 H), 2.44 (s, 3 H), 2.60 (m, 2 H), 3.90 (br. s, 3 H), 7.09–7.36 (m, 7 H), 7.78 (ddd, *J* = 8.4, 2.0, 1.8 Hz, 2 H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 4.8 (3 C), 6.8 (3 C), 21.6, 31.0, 35.8, 69.4, 72.8, 125.8, 127.8 (2 C), 128.1 (2 C), 128.3 (2 C), 129.7 (2 C), 132.7, 141.4, 144.7 ppm; $C_{23}H_{34}O_4SSi$ (434.7): calcd. C 63.55, H 7.88, S 7.38; found C 63.62, H 7.72, S 7.40.

(b) Chiral-Pool Synthesis: Crystalline compound **13** (10.0 g, 99.92% *ee*) was silylated with chlorotriethylsilane according to the procedure described above, to give triethylsilyl derivative **14** (13.43 g, 99% yield, 99.92% *ee*); ^{1}H NMR (200 MHz, $CDCl_3$) was identical to that described above for compound **14**.

(*S*)-4-Phenyl-1-iodo-2-(triethylsilyloxy)butane (15). (a) By Asymmetric Synthesis: To a solution of tosylate **14** (3.145 g, 7.23 mmol, 99.26% *ee*) in anhydrous DMF (30 mL), vigorously stirred under Ar at room temperature, was added sodium iodide (4.60 g, 30.7 mmol), and the mixture was heated and stirred at about 80 °C for 2 h. After cooling to about 40 °C, saturated aqueous $NaHCO_3$ (70 mL) was added, and the mixture was extracted with hexanes (70 mL and 2 × 40 mL). The combined hexanes solutions were washed with saturated aqueous $NaHCO_3$ (70 mL), dried (Na_2SO_4, 16 g), and concentrated in vacuo to give a yellow oil (2.88 g), which was subjected to flash chromatography on silica gel (100 g). Elution with 3–10% EtOAc/hexanes afforded iodide **15** (2.423 g, 85.8% yield, 99.2% *ee*) as a colorless oil {$[\alpha]_D^{20}$ = –9.1 (*c* = 1.00, $CHCl_3$);

^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.62 (q, J = 7.6 Hz, 6 H), 0.98 (t, J = 7.6 Hz, 9 H), 1.78 (m, 2 H), 2.65 (m, 2 H), 3.23 (dd, J = 5.1, 0.6 Hz, 2 H), 3.66 (m, 1 H), 7.14–7.33 (m, 5 H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 5.05 (3 C), 6.90 (3 C), 13.25, 31.26, 38.61, 71.01, 125.73, 128.16 (2 C), 128.25 (2 C), 141.58 ppm; HRMS (ESI): calcd. for $C_{16}H_{27}IONaSi$ $[M + Na]^+$ 413.0768; found 413.0764} and recovered **14** [317 mg, 10.1% yield, ^{1}H NMR (200 MHz, $CDCl_3$) was identical to that cited above for this compound]}.

(b) Chiral-Pool Synthesis: Tosylate **14**, obtained from the chiral-pool synthesis (13.2 g, 99.92% *ee*) was treated with NaI in DMF for 2.5 h, essentially as described above, but the temperature was very strictly maintained within the 75–80 °C range. Workup and chromatography as described above gave iodide **15** (10.55 g, 89% yield, 99.92% *ee*); ^{1}H NMR (200 MHz, $CDCl_3$) was identical to that cited above for this compound.

(*S*)-2-Hydroxy-1-iodo-4-phenylbutane (16). Chiral-Pool Synthesis: Compound **15** (3.52 g, 9.0 mmol, 99.2% *ee*) was dissolved in acetone (20 mL). H_2O (2 mL) was added. This solution was stirred at 20 °C, and pyridinium *p*-toluenesulfonate (200 mg) was added. After 20 h, the mixture was poured into 3% aqueous $NaHCO_3$ (150 mL), and the mixture was extracted with Et_2O/EtOAc (1:1, 100 mL). The phases were separated, the organic phase was dried with Na_2SO_4 (15 g), and the drying agent was filtered and washed with EtOAc (20 mL). The filtrates were combined and concentrated in vacuo, and the oil thus obtained was purified by flash chromatography on silica gel (120 g). Elution with 15% EtOAc/hexanes gave pure fractions by TLC, which were concentrated in vacuo to 10 mL and allowed to crystallize at 0 °C for 2 h. The crystals were filtered and dried, giving compound **16** (1.80 g, 72.3% yield, 99.85% *ee*) as white needles. M.p. 76–77 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.87 (m, 2 H), 2.74 (m, 2 H), 3.24 (dd, J = 10.2, 6.8 Hz, 1 H), 3.38 (dd, J = 10.1, 3.5 Hz, 1 H), 3.52 (m, 1 H), 7.15–7.34 (m, 5 H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 16.59, 31.91, 38.14, 70.12, 126.07, 128.42 (2 C), 128.50 (2 C), 141.26 ppm; $C_{10}H_{13}IO$ (276.1): calcd. C 43.50, H 4.75, I 45.96; found C 43.49, H 4.61, I 46.00; chiral HPLC: Chiralcel OD, 10 μm, (250+20) × 4.6 mm column, hexanes/2-propanol, 85:15 (v/v), 1.0 mL/min, R_t 8.2 min (99.867% yield), R_t 11.1 (0.073% yield), 99.85% *ee*.

(*S*)-1,2-Epoxy-4-phenylbutane (17). Chiral-Pool Synthesis: Crystalline compound **16** (1.61 g, 5.84 mmol, 99.85% *ee*) was dissolved in THF (12 mL). H_2O (1.5 mL) and solid KOH (1.95 g) were added. The mixture was stirred at 20 °C under Ar for 7 h, and then transferred to a separatory funnel containing brine (50 mL), H_2O (100 mL), and Et_2O (120 mL). After extraction, the phases were separated, and the organic phase was extracted with H_2O (150 mL) and then dried with Na_2SO_4 (20 g). The drying agent was filtered and washed with Et_2O (20 mL). The filtrates were combined and concentrated in vacuo at 0 °C and then dried (10 °C, 5 Torr, 15 min), affording epoxide **17** (0.70 g, 81% yield, 99.85% *ee*). $[a]_D^{20}$ = –22.5 (c = 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.79–1.92 (m, 2 H), 2.47 (dd, J = 4.9, 2.6 Hz, 1 H), 2.66–2.87 (m, 3 H), 2.91–3.00 (m, 1 H), 7.15–7.34 (m, 5 H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 32.25, 34.29, 47.25, 51.79, 126.02, 128.38, 128.45, 141.26 ppm; $C_{10}H_{12}O$ (148.2) calcd. C 81.04, H 8.16; found C 81.25, H 8.20.

(2*RIS*,4*S*)-4-(2-Phenylethyl)-1,3,2-dioxathiolane 2-Oxide (18). Chiral-Pool Synthesis: Diol **12** (13.4 g, 80.6 mmol, 99.92% *ee*) was dissolved in CH_2Cl_2 (600 mL). Diisopropylethylamine (28.2 mL, 20.92 g, 161.9 mmol) was added, and the mixture was cooled to 5 °C. Subsequently, thionyl chloride (6.20 mL, 10.11 g, 85 mmol) was carefully introduced under the surface of the stirred solution over 10 min such that the temperature was maintained at 0–5 °C, and stirring was continued for another 1 h. The mixture was poured into pH 7.2 phosphate buffer (0.1 M, 500 mL) and stirred at 0 °C. The organic phase was separated, washed with 2% aqueous NaCl (500 mL), dried with Na_2SO_4, and concentrated under reduced pressure, yielding cyclic sulfite **18** [16.5 g, 96% yield, 2 diastereomers (1:1)] as a thick oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.83–2.38 (m, 2 H), 2.62–2.97 (m, 2 H), 3.90 (dd, J = 8.1, 6.8 Hz, 0.5 H), 4.24–4.52 (m, 1 H), 4.62 (dd, J = 8.5, 6.4 Hz, 0.5 H), 4.87–5.00 (m, 0.5 H), 7.16–7.35 (m, 5 H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 31.58, 31.99, 34.09, 35.13, 70.20, 71.50, 79.41, 82.98, 126.45, 126.49, 128.42, 128.46, 128.6, 128.70, 140.06, 140.16 ppm.

(2*RIS*,4*S*)-4-(2-Phenylethyl)-1,3,2-dioxathiolane 2,2-Dioxide (19). Chiral-Pool Synthesis: Sulfite **18** (7.8 g, 36.7 mmol) was dissolved in acetonitrile (100 mL) and sodium periodate (11.0 g), $RuCl_3 \cdot 3H_2O$ (81 mg), and H_2O (20 mL) were added to the stirred solution. The reaction mixture was warmed to 40 °C over 10 min, after which time the oxidation was complete (TLC, hexanes/EtOAc, 2:1). The mixture was cooled to 20 °C, Et_2O (100 mL) and H_2O (80 mL) were added, and after extraction, the phases were separated. The aqueous phase was extracted with Et_2O (2 × 200 mL). The Et_2O layers were combined, dried with Na_2SO_4, filtered, and concentrated in vacuo to give a dark solid (7.9 g), which was crystallized from Et_2O (20 mL), affording cyclic sulfate **19** (3.50 g, 42% yield, 100% *ee*) as white crystals. M.p. 50–51 °C; $[a]_D^{20}$ = –42.9 (c = 1, MeOH); IR (KBr): $\tilde{\nu}$ = 651, 702, 757, 783, 853 (s), 965 (s), 1013, 1038, 1210 (s), 1381 (s), 1602 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.93–2.11 (m, 1 H), 2.19–2.37 (m, 1 H), 2.65–2.94 (m, 2 H), 4.28 (t, J = 8.1 Hz, 1 H), 4.60 (dd, J = 9.0, 6.0 Hz, 1 H), 4.85–4.98 (m, 1 H), 7.16–7.38 (m, 5 H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 30.73, 33.86, 72.68, 81.99, 126.68, 128.31, 128.76, 139.07 ppm; $C_{10}H_{12}O_4S$ (228.3): calcd. C 52.62, H 5.30, S 14.05; found C 52.66, H 5.34, S 14.09; chiral HPLC: Chiralcel OD, 10 μm, (250+20) × 4.6 mm column, hexanes/2-propanol, 85:15 (v/v), 1.0 mL/min, R_t 41.0 min (100% yield), the other peak was not detected; chiralcel AD, 10 μm, (250+20) × 4.6 mm column, hexanes/2-propanol, 85:15 (v/v), 1.0 mL/min, R_t 10.5 min (100% yield), the other peak was not detected, 100% *ee*.

(1*R*,3S,4*R*,5*R*)-4-[(*Z*)-6-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)hex-2-enyl]-5-[(phenylsulfonyl)methyl]cyclopentan-1,3-diol (20a) and a Mixture of (1*S*,2*R*,3*R*,4*R*)-2-[(*Z*)-6-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)hex-2-enyl]-3-[(phenylsulfonyl)methyl]-4-(triethylsilyloxy)cyclopentanol (20b) and (1*R*,2*R*,3*R*,4*S*)-3-[(*Z*)-6-(4-Methyl-2,6,7-trioxabicyclo[2.2.2]octan-1-yl)hex-2-enyl]-2-[(phenylsulfonyl)methyl]-4-(triethylsilyloxy)cyclopentanol (20c): To a suspension of phosphonium iodide **8** (7.98 g, 13.9 mmol), stirred under Ar at 0 °C in anhydrous THF (25 mL), *t*BuOK (3.85 g, 34 mmol, Fluka > 97%) was added in a few portions. After 5 min, the cooling bath was removed, and anhydrous THF (10 mL) was added. The mixture was vigorously stirred and warmed to 20 °C over 20 min. The reaction mixture was cooled to 0 °C, and a solution of hemiacetal **5** (mixture of epimers, 2.70 g, 6.54 mmol) in anhydrous THF (10 mL) was added. After 15 min, the cooling bath was removed, and the mixture warmed to 20 °C. After stirring for 80 min, Al(*t*BuO)$_3$ (420 mg, 1.7 mmol) was added, and stirring at 20 °C was continued for another 5 h. The reaction mixture was cooled to 0 °C, and 3% aqueous pyridine (10 mL) and saturated aqueous $NaHCO_3$ (70 mL) were slowly added. The mixture was extracted with EtOAc (3 × 50 mL). The organic layers were combined and washed with brine (2 × 50 mL). Pyridine (3 drops) was added, and the solution was dried with Na_2SO_4 (25 g) at 4 °C and then concentrated in vacuo to give an oil (8.2 g). This sample was

purified by flash chromatography on silica gel (250 g). Elution with EtOAc/hexanes (70:30) + 0.15% pyridine gave a mixture (35:65) of **20b** and **20c** (584 mg, 15.4% yield) as a colorless glass; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.57 (q, J = 8.0 Hz, 6 H), 0.79 (s, 1.95 H), 0.80 (s, 1.05 H), 0.93 (t, J = 8.0 Hz, 9 H), 1.34–1.54 (m, 3.5 H), 1.56–1.78 (m, 3 H), 1.82–2.20 (m, 6.6 H), 3.01 (dd, J = 14.4, 11.2 Hz, 0.65 H), 3.32 (dd, J = 14.4, 2.6 Hz, 0.65 H), 3.56 (m, 0.65 H), 3.88 (s, 3.9 H), 3.89 (s, 2.1 H), 3.90 (m, 0.35 H), 4.13 (m, 1.30 H), 5.15–5.38 (m, 2 H), 7.54–7.74 (m, 3 H), 7.93–7.99 (m, 2 H) ppm. Further elution with EtOAc/hexanes (84:16) + 0.15% pyridine gave 3.597 g of a glassy solid, slightly contaminated with Ph_3PO. Trituration of this solid with Et_2O twice (8 mL and 4 mL) afforded compound **20a** (2.0 g, 65.5% yield) as a glassy solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.80 (s, 3 H), 1.36–1.52 (m, 3 H), 1.61 (m, 2 H), 1.8–2.29 (m, 8 H), 3.05 (dd, J = 14.3, 11.0 Hz, 1 H), 3.33 (dd, J = 14.3, 2.6 Hz, 1 H), 3.53 (br. s, 1 H), 3.88 (s, 6 H), 4.09 (m, 1 H), 4.31 (m, 1 H), 5.17–5.39 (m, 2 H), 7.47–7.74 (m, 3 H), 7.93–7.99 (m, 2 H) ppm.

1-<(*Z*)-6-{(1*R*,2*R*,3*R*,5*S*)-2-[(Phenylsulfonyl)methyl]-3,5-bis(triethylsilyloxy)cyclopentyl}hex-4-enyl>-4-methyl-2,6,7-trioxabicyclo-[2.2.2]octane (21): (a) A solution of cyclopentanediol **20a** (279 mg, 0.58 mmol) in anhydrous DMF (10 mL) was stirred under Ar at 0 °C. Imidazole (160 mg, 2.34 mmol) and Et_3N (300 μL, 2.15 mmol) were added, followed by chlorotriethylsilane (420 μL, 2.5 mmol). After 2.5 h, pyridine (0.5 mL) was added, followed by saturated aqueous $NaHCO_3$ (60 mL). The mixture was extracted with EtOAc/hexanes (1:1, 3 × 20 mL). The solutions were combined, washed with saturated aqueous $NaHCO_3$ (60 mL), dried with anhydrous Na_2SO_4 (12 g), and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (60 g). Elution with 18% EtOAc/hexanes +0.007% pyridine, followed by vacuum drying (1 Torr, 25 °C, 3 h) gave compound **21** (361 mg, 87% yield) as a glassy solid. $[\alpha]_D^{22}$ = +9.3 (c = 1.00, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.55 (q, J = 8.0 Hz, 12 H), 0.80 (s, 3 H), 0.92 (t, J = 8.0 Hz, 18 H), 1.39–1.72 (m, 6 H), 1.84 (m, 1 H), 1.98 (m, 1 H), 2.16 (m, 4 H), 3.19 (br. d, J = 5.3 Hz, CH_2SO_2Ph, 2 H), 3.89 (s, 6 H), 4.14 (m, 2 H), 5.33 (m, 2 H), 7.50–7.68 (m, 3 H), 7.89–7.95 (m, 2 H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 4.69 (3 C), 4.82 (3 C), 6.77 (3 C), 6.82 (3 C), 14.49, 23.15, 25.18, 26.94, 30.12, 36.16, 43.65, 46.73, 47.15, 57.40, 71.40, 72.47 (3 C), 74.74, 108.95, 127.95 (2 C), 128.54, 129.08 (2 C), 130.28, 133.38, 140.27 ppm; $C_{36}H_{62}O_7SSi_2$ (695.1): calcd. C 62.20, H 8.99; found C 62.04, H 8.68. (b) The mixture of **20b** and **20c** described above (558 mg, 0.961 mmol) was dissolved in DMF and treated with imidazole, Et_3N, and chlorotriethylsilane as described in section (a) above. After workup, the crude product was stored at 4 °C overnight, after which time it was subjected to chromatography, as described above, giving compound **21** (67% yield); ^{1}H NMR (200 MHz, $CDCl_3$) data was identical with the data cited above for **21**.

1-{(*Z*)-6-[(1*R*,2*R*,3*R*,5*S*)-2-[(1*R*/1*S*,3*S*)-3-Triethylsilyloxy-5-phenyl-1-(phenylsulfonyl)pentyl]-3,5-bis(triethylsilyloxy)cyclopentyl]hex-4-enyl}-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (22) and 2,2-Bis(hydroxymethyl)propyl-(*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-2-[(1*R*/1*S*,3*S*)-3-triethylsilyloxy-5-phenyl-1-(phenylsulfonyl)pentyl]-3,5-bis(triethylsilyloxy)cyclopentyl]hept-5-enoate (23): To a solution of sulfone **21** (2.29, 3.29 mmol) in anhydrous THF (15 mL), vigorously stirred under Ar at –78 °C, lithium bis(trimethylsilyl)amide (LHMDS, 1.0 M solution in THF, 14 mL, 14 mmol) was added over 3 min. After 20 min, the mixture was warmed to 0 °C and stirred for 10 min. The mixture was then cooled to –78 °C, and a solution of iodide **15** (4.96 g, 12.7 mmol, 99.2% *ee*) in anhydrous THF (4 mL) was added dropwise. After 10 min, the temperature was raised to 0 °C, and the mixture was stirred at 0 °C for 80 min, at which time it was warmed to room temperature. After 5 h of stirring, the mixture was cooled to –78 °C, and 1% pyridine in brine/saturated aqueous $NaHCO_3$ (1:1, 4 mL) was added dropwise, followed by EtOAc/CH_2Cl_2 (6:1, 50 mL). The cooling bath was changed to a H_2O bath at 10 °C. 1% Pyridine in brine/saturated aqueous $NaHCO_3$ (1:1, 50 mL) was added, and the mixture was extracted twice with EtOAc/CH_2Cl_2 (1:1, 60 mL and 30 mL). The organic phases were combined, washed with 1% pyridine in brine/saturated aqueous $NaHCO_3$ (1:1, 50 mL), dried with anhydrous Na_2SO_4 (15 g), filtered, concentrated, and dried under vacuum to give a yellow oil (6.92 g), which was purified by flash chromatography on silica gel (250 g, 0.1% pyridine in 5–99% EtOAc/hexanes). This procedure gave iodide **15** [3.76 g, 99.2% *ee*, ^{1}H NMR (200 MHz, $CDCl_3$) was identical with that of an original sample], sulfone **22** [1.456 g, 46.2% yield, a 5:2 mixture of isomers as a colorless glassy solid. The composition of this mixture was established based on the integration in the ^{1}H NMR (500 MHz, $CDCl_3$) spectrum; NMR spectroscopic data for the individual components (13*R*)-**22** and (13*S*)-**22** are cited below. $C_{52}H_{88}O_8SSi_3$ (957.6): calcd. C 65.22, H 9.26, S 3.35; found C 65.58, H 9.37, S 3.55], recovered substrate **21** [165 mg, 7.2% yield as a colorless glass; ^{1}H NMR (200 MHz, $CDCl_3$) was identical with that of an original sample], and ester **23** [453 mg, 13.5% yield, a 5:2 mixture of isomers as a yellowish, thick oil; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.57 (m, 18 H), 0.83 (s, 3 H), 0.94 (m, 27 H), 1.40–1.82 (m, 5 H), 1.90 (m, 2 H), 1.98–2.45 (m, 10 H), 3.10 (br. s, 1 H), 3.22 (m, 0.29 H), 3.47 (m, 0.71 H), 3.55 (br. s, 4 H), 3.87 (m, 1 H), 3.89 (br. s, 1 H), 4.18 (m, 4 H), 4.41 (m, 0.29 H), 4.53 (m, 0.71 H), 5.26–5.53 (m, 2 H), 7.08–7.33 (m, 5 H), 7.46–7.72 (m, 3 H), 7.84–7.94 (m, 2 H) ppm]. A sample of **22** (90 mg, 5:2 mixture of epimers) was separated by repeated chromatography on silica gel LiChroprep (25–40 μm, 7 g). Elution with 10% EtOAc/hexanes with 0.1% pyridine gave the more mobile major isomer, 1-{(*Z*)-6-[(1*R*,2*R*,3*R*,5*S*)-2-[(1*R*,3*S*)-3-(triethylsilyloxy)-5-phenyl-1-(phenylsulfonyl)pentyl]-3,5-bis(triethylsilyloxy)-cyclopentyl]hex-4-enyl}-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane {[(13*R*)-**22**, 26.6 mg) as a colorless viscous oil; ^{1}H NMR (500 MHz, $CDCl_3$ + 1% C_5D_5N): δ = 0.572 (m, 18 H), 0.798 (s, 3 H), 0.940 (m, 27 H), 1.560 (m, 4 H), 1.654 (m, 3 H), 1.730 (m, 2 H), 1.992 (m, 1 H), 2.074–2.238 (m, 5 H), 2.362 (ddd, J = 10.1, 8.2, 1.9 Hz, 1 H), 2.494 (ddd, J = 13.6, 11.0, 5.2 Hz, 1 H), 2.584 (ddd, J = 13.6, 11.0, 6.1 Hz, 1 H), 3.471 (ddd, J = 7.2, 5.2, 2.0 Hz, 1 H), 3.898 (s, 6 H), 3.92 (m, 1 H), 4.168 (m, 1 H), 4.582 (m, 1 H), 5.402 (m, 2 H), 7.132 (br. d, J = 7.1 Hz, 2 H), 7.181 (br. t, J = 7.3 Hz, 1 H), 7.276 (br. t, J = 7.6 Hz, 2 H), 7.532 (br. t, J = 7.8 Hz, 2 H), 7.594 (ddd, J = 7.4, 2.0, 1.6 Hz, 1 H), 7.886 (bdd, J = 7.2, 1.5 Hz, 2 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$ + 1% C_5D_5N): δ = 4.96 (3 C), 5.04 (3 C), 5.22 (3 C), 6.87 (6 C), 6.93 (3 C), 14.51, 23.21, 25.69, 27.24, 30.16, 31.11, 34.35, 36.30, 39.07, 44.14, 45.78, 50.44, 60.74, 69.04, 71.09, 72.52 (3 C), 73.03, 109.02, 125.67, 128.22 (2 C), 128.28 (2 C), 128.37 (2 C), 128.54, 128.91 (2 C), 130.20, 133.10, 140.13, 142.17 ppm] and the minor isomer, 1-{(*Z*)-6-[(1*R*,2*R*,3*R*,5*S*)-2-[(1*S*,3*S*)-3-(triethylsilyloxy)-5-phenyl-1-(phenylsulfonyl)pentyl]-3,5-bis(triethylsilyloxy)cyclopentyl]hex-4-enyl}-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane {[(13*S*)-**22**, 17.9 mg] as a colorless viscous oil; ^{1}H NMR (500 MHz, $CDCl_3$ + 1% C_5D_5N): δ = 0.580 (m, 18 H), 0.783 (s, 3 H), 0.950 (m, 17 H), 1.420–1.609 (m, 6 H), 1.677 (m, 3 H), 1.805 (quintet, J = 7.1 Hz, 1 H), 1.924–2.374 (m, 7 H), 2.475 (ddd, J = 13.8, 11.4, 4.8 Hz, 1 H), 3.240 (ddd, J = 7.0, 4.8, 1.9 Hz, 1 H), 3.882 (s, 6 H), 3.896 (m, 1 H), 4.183 (dd, J = 9.9, 5.1 Hz, 1 H), 4.484 (ddd, J = 12.6, 7.8, 5.9 Hz, 1 H), 5.265 (bdd, J = 5.0, 4.4 Hz, 2 H), 7.027 (dddd, J = 7.0, 2.2, 1.8, 1.4 Hz, 2 H), 7.161 (dd, J = 7.4, 1.4 Hz, 1 H), 7.239 (dddd, J = 7.4, 7.0, 2.2, 1.6 Hz, 2 H), 7.494 (dddd, J = 7.6, 7.1, 1.6, 1.2 Hz, 2 H), 7.550 (dd, J = 7.5,

1.3 Hz, 1 H), 7.912 (dddd, *J* = 7.1, 2.0, 1.5, 1.2 Hz, 2 H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$ + 1% C_5D_5N): δ = 4.97 (3 C), 4.99 (3 C), 5.05 (3 C), 6.86 (3 C), 6.92 (3 C), 6.94 (3 C), 14.53, 23.17, 25.70, 26.18, 27.07, 29.65, 30.16, 30.37, 34.93, 36.29, 37.74, 43.57, 46.32, 51.51, 61.23, 69.49, 71.86, 72.53, 73.64, 109.05, 125.61, 128.13, 128.16 (2 C), 128.19 (2 C), 128.90 (2 C), 128.92 (2 C), 130.48, 133.31, 139.44, 142.10 ppm}.

1-{(*Z*)-6-[(1*R*,2*R*,3*R*,5*S*)-2-[(*R*)-3-(Triethylsilyloxy)-5-phenylpentyl]-3,5-bis(triethylsilyloxy)cyclopentyl]hex-4-enyl}-4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (24): Sulfone **22** (116 mg, 0.121 mmol, 5:2 mixture of epimers) was dissolved in anhydrous MeOH (5 mL), and $NaHPO_4$ (150 mg, 1.06 mmol) was added. The mixture was stirred under Ar at room temperature for 20 min, cooled to 0 °C, and 10% Na/Hg amalgam (360 mg, 1.5 mmol Na) was added. Stirring at 0 °C was continued for 1 h. The cooling bath was removed, and the reaction mixture was warmed to 20 °C with continued stirring. After another 40 min, the mixture was cooled to 0 °C and, with vigorous stirring, saturated aqueous solution of NH_4Cl (3.0 mL) was added dropwise. The mixture was stirred for 10 min, H_2O (3 mL) was added, and stirring was continued for another 15 min. The mixture was transferred to a separatory funnel containing saturated aqueous NH_4Cl (40 mL) and 1% pyridine/EtOAc (40 mL). The phases were separated (mercury was carefully collected). The aqueous phase was extracted with EtOAc (30 mL). The combined organic phases were dried with Na_2SO_4 (10 g), filtered, concentrated, and dried in vacuo (1 Torr, 40 min, 25 °C), affording compound **24** (106 mg, 99% yield) as a glassy solid. $[\alpha]_D^{20}$ = +10 (*c* = 1.00, $CHCl_3$ + 0.1% Et_3N); ^{1}H NMR (200 MHz, $CDCl_3$ + 0.1% C_5H_5N): δ = 0.60 (m, 18 H), 0.79 (s, 3 H), 0.96 (m, 27 H), 1.30–1.61 (m, 8 H), 1.65–1.82 (m, 5 H), 2.01–2.32 (m, 5 H), 2.68 (m, 2 H), 3.73 (m, 2 H), 3.88 (s, 6 H), 4.09 (bdd, *J* = 11.5, 5.8 Hz, 1 H), 5.39 (m, 2 H), 7.20 (m, 3 H), 7.28 (m, 2 H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$ + 0.1% C_5H_5N): δ = 4.87 (3 C), 4.90 (3 C), 5.09 (3 C), 6.85 (3 C), 6.86 (3 C), 6.97 (3 C), 14.49, 23.22, 25.74, 27.00, 27.93, 30.11, 31.66, 34.35, 36.21, 39.08, 44.19, 48.15, 50.10, 71.72, 72.34, 72.47 (3 C), 76.23, 108.96, 125.51, 128.23 (2 C), 128.26 (2 C), 129.32, 129.71, 142.73 ppm; $C_{46}H_{84}O_6Si_3$ (817.4): calcd. C 67.59, H 10.36; found C 67.62, H 10.40.

2,2-Bis(hydroxymethyl)propyl (*Z*)-7-{(1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-[(*R*)-3-hydroxy-5-phenylpentyl]cyclopentyl}hept-5-enoate (25): To a solution of orthoester **24** (378 mg, 0.462 mmol) in acetone (11 mL), stirred under Ar at 18 °C, H_2O (1.5 mL) was added, followed by PPTS (210 mg, 0.836 mmol). Stirring was continued for 5 h, and then the mixture was concentrated to 1.5 mL, and EtOAc (40 mL), brine (30 mL), and saturated aqueous $NaHCO_3$ (20 mL) were added. After extraction, the aqueous layer was washed with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (50 mL), dried with anhydrous Na_2SO_4 (7 g), filtered, and concentrated in vacuo. The residue was subjected to flash chromatography on silica gel (14 g). Elution with 5% MeOH/EtOAc gave ester **25** (217 mg, 95% yield) as a colorless glass. $[\alpha]_D^{20}$ = +29.7 (*c* = 1.8, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.85 (s, 3 H), 1.36 (m, 2 H), 1.48–1.88 (m, 11 H), 2.02–2.39 (m, 6 H), 2.71 (m, 2 H), 3.42 (br. s, 4 H), 3.55 (s, 4 H), 3.63 (m, 1 H), 3.95 (m, 1 H), 4.12 (br. s, 2 H), 5.41 (m, 2 H), 7.18 (m, 3 H), 7.28 (m, 2 H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$ + 1% C_5D_5N): δ = 16.88, 24.80, 26.52, 27.02, 29.61, 32.15, 33.54, 35.74, 39.05, 40.51, 42.51, 51.70, 52.63, 61.41, 66.55, 67.00, 71.15, 74.53, 78.53, 125.78, 128.39 (2 C), 128.42 (2 C), 129.21, 129.77, 142.23, 174.56 ppm; HRMS (ESI): calcd. for $C_{28}H_{44}O_7Na$ $[M + Na]^+$ 515.2979; found 515.2962.

(*Z*)-7-{(1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-[(*R*)-3-hydroxy-5-phenylpentyl]cyclopentyl}hept-5-enoic Acid (26): To a solution of ester **25** (120 mg, 0.243 mmol) in MeOH (5 mL), stirred under Ar, H_2O (0.5 mL) was added, followed by $LiOH·H_2O$ (240 mg, 5.72 mmol). After 8 h, the mixture was transferred to a separatory funnel containing saturated aqueous NH_4Cl (50 mL), aqueous $NaHSO_4$ (2 M, 30 mL), and EtOAc (50 mL). The phases were separated, aqueous $NaHSO_4$ (2 M, 20 mL) was added to the aqueous phase, and the mixture was extracted with EtOAc (30 mL). The EtOAc phases were combined, washed with a mixture of saturated aqueous NH_4Cl (20 mL) and aqueous $NaHSO_4$ (2 M, 10 mL) and dried with anhydrous Na_2SO_4 (10 g). The drying agent was filtered and washed with EtOAc (10 mL). The filtrates were combined, concentrated, and dried in vacuo (1 Torr, 25 °C, 3 h), affording acid **26** (94.1 mg, 99% yield) as a thick, pale yellow oil. $[\alpha]_D^{20}$ = +29.7 (*c* = 1.00, MeOH); ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.35 (m, 2 H), 1.45–1.86 (m, 10 H), 2.07–2.37 (m, 7 H), 2.71 (m, 2 H), 3.66 (m, 1 H), 3.94 (m, 1 H), 4.14 (m, 1 H), 5.42 (m, 2 H), 5.70 (br. s, 3 H), 7.21 (m, 5 H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$): δ = 24.82, 26.50, 26.68, 29.23, 32.10, 33.49, 35.38, 38.86, 42.44, 51.62, 52.32, 71.33, 74.28, 78.42, 125.74, 128.35 (2 C), 128.41 (2 C), 129.44, 129.50, 142.21, 177.10 ppm; HRMS (ESI): calcd. for $C_{23}H_{34}O_5Na$ $[M + Na]^+$ 413.2298; found 413.2279.

Isopropyl (*Z*)-7-{(1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-[(*R*)-3-hydroxy-5-phenylpentyl]cyclopentyl}hept-5-enoate (Latanoprost, 1): Acid **26** (20.0 mg, 0.051 mmol) was dissolved in acetone (2.0 mL). To this solution, stirred under Ar, DBU (100 μL, 102 mg, 0.67 mmol) was added, followed after 3 min by 2-iodopropane (100 μL, 170 mg, 1.0 mmol). Stirring was continued at 20 °C for 14 h. Subsequently, the mixture was concentrated to about 0.5 mL, 4% aqueous citric acid (4 mL) and EtOAc (10 mL) were added, and the mixture was transferred to a separatory funnel containing EtOAc (20 mL), brine (30 mL), and 4% aqueous citric acid (10 mL). The phases were separated, and the aqueous phase was re-extracted with EtOAc (10 mL). The organic phases were combined and extracted with a mixture of brine (20 mL) and saturated aqueous $NaHCO_3$ (20 mL). The organic phase thus obtained was dried with anhydrous Na_2SO_4 (7 g). The drying agent was filtered and washed with EtOAc (5 mL). The organic phases were combined, concentrated in vacuo, and dried in vacuo (1 Torr, 20 °C, 1 h), giving a colorless, thick oil, which was chromatographed on LiChroprep silica gel (25–40 μm, 4.0 g). Elution with 20% hexanes/EtOAc gave **1** as an oil, showing 91% HPLC purity [ca. 9% (5*E*)-**1**]. This sample was further purified by preparative HPLC on silica gel to give latanoprost (**1**, 14.0 mg, 63.2% yield) as a thick, colorless oil. HPLC purity 99.83%; $[\alpha]_D^{20}$ = +32.0 (*c* = 1.00, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) and ^{13}C NMR (125 MHz, $CDCl_3$) fully assigned spectra of compound **1** are given in Table S1 in the Supporting Information. HRMS (ESI): calcd. for $C_{26}H_{40}O_5Na$ $[M + Na]^+$ 455.2768; found 455.2756; $C_{26}H_{40}O_5$ (432.6): calcd. C 72.19, H 9.32; found C 71.96, H 9.27.

Supporting Information (see also the footnote on the first page of this article): Experimental details and characterization data for all compounds reported in this manuscript not included in the Experimental Section, experimental details for larger scale experiments, and tables with ^{1}H and ^{13}C NMR assignments for latanoprost (**1**), (15*S*)-**1**, and (5*E*)-**1**.

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