Enantioselective Synthesis of α,*β*,α′-Trisubstituted Cyclic Ethers†

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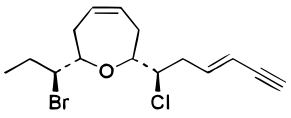
A synthetic strategy for the preparation of trisusbstituted cyclic ethers is presented, in which the stereochemistry at the carbon atoms adjacent to the oxygen of the ether was controlled by means of a hetero Diels−Alder reaction between a monoactivated diene and a chiral aldehyde. The adducts were transformed into linear ethers, which were then used for the preparation of cis and trans cyclic ethers of different sizes. A *cis*-oxepane, *cis*-oxonane, and *cis*-oxocane and a *trans*-oxocane were prepared as examples of the scope of the strategy.

Introduction

During the last years, cyclic ethers have attracted considerable attention due to their occurrence in several groups of natural compounds exhibiting important biological activities.[1] These units can be found isolated in monocyclic or polycyclic compounds, fused with other cyclic ethers, or forming spiro systems.[2] In nature, monocyclic compounds with ring sizes ranging from 5 to 9 atoms are known. Most have cis stereochemistry at the positions adjacent to the oxygen atom of the ether (α, α′ positions), such as isolaurepinnancin (**1**)[3] and laurencin (**2**),[4] although trans compounds such as obtusenin (**3**)[5] have also been obtained.



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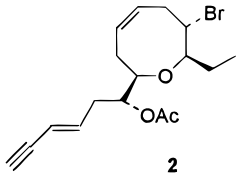

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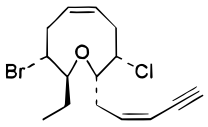

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A number of synthetic approaches have been devised in order to construct the cyclic ether moiety, using a carbon−carbon[6] or a carbon−oxygen[7] cyclization step or modifying cyclic precursors.[8]

Recently,[9] we presented an approach to cyclic ethers of different ring sizes in racemic form, using a hetero Diels−Alder reaction between a monoactivated diene and an aldehyde as the key step in the control of the relative stereochemistry of the centers adjacent to the oxygen atom, followed by ozonolysis and intramolecular alkylation of the resulting linear ether (Figure 1).

In this paper, we wish to present the extension of the methodology to enantiomerically pure, polysubstituted compounds.

Results and Discussion

To induce the desired chirality, we decided to use a chiral aldehyde instead of chiral dienes or chiral catalysts, since different aldehydes bearing chiral centers at the α position are available in both enantiomeric forms by literature procedures and have been used successfully in hetero Diels−Alder reactions.[10] We chose the aldehyde R-(+)-**5**[11] since previous work by Danishefsky and colleagues[12] has shown that it undergoes hetero Diels−Alder reaction with mono- and diactivated dienes with a high yield and high endo-Cram selectivity.

† Dedicated to Prof. A. G. González with respect and admiration on the occasion of his 80th birthday.

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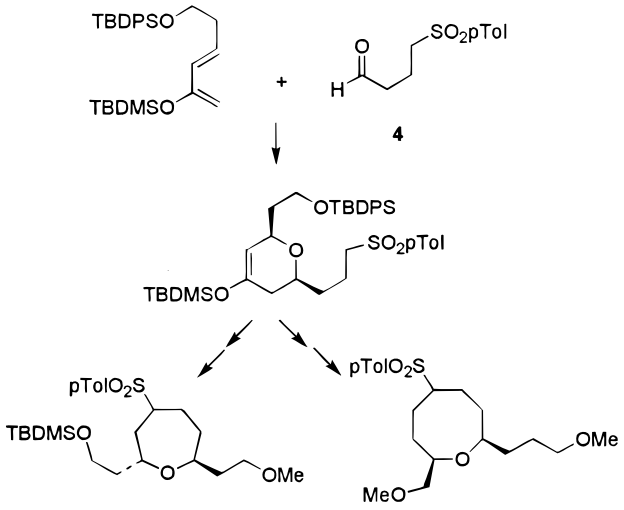


Figure 1. Strategy used in the synthesis of racemic oxepanes and oxocanes.[9]

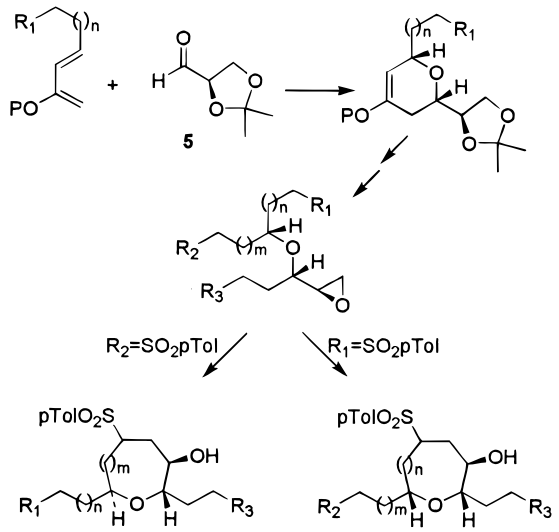
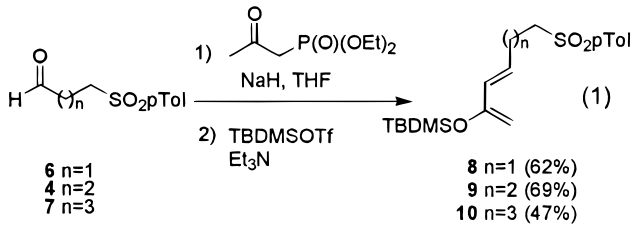


Figure 2. Proposed strategy for the synthesis of enantiomerically pure cis and trans cyclic ethers.

Our strategy is depicted in Figure 2. The cycloadduct is opened to give a linear ether, and the acetonide is transformed into an epoxide. The placing of the carbanion stabilizing group (a sulfone) in either of the two side chains of the upper part of the molecule should allow us to control the relative stereochemistry of the two centers at the α and α′ position to the oxygen atom of the ether. The size of the ring obtained depends on the length of the chain carrying the sulfone and the regioselectivity of the attack of the carbanion to the epoxide in the cyclization step. Such chemistry has previously been used to construct five- and six-membered rings and an endo preference in the attack has been observed.[13]

To test our ideas, we started by preparing a few examples of cis-substituted cyclic ethers. For these compounds, the sulfone should be located in the side chain coming from the diene in the cycloaddition (R_1 in Figure 2), and thus it could be present from the beginning of the synthesis.

The dienes chosen (**8**−**10**) were prepared from the corresponding aldehydes as shown in eq 1.[14]



Synthesis of the *cis*-Oxepane. We first tested the reaction of the aldehyde **5** with the diene **8**, which has the suitable side chain for the preparation of the oxepane ring. The hetero Diels−Alder reaction between **8** and **5** was carried out using boron trifluoride etherate as catalyst, according to our previous experiment.[15] The best results were obtained when the reaction took place at −25 °C, at which temperature only two of the four possible isomers (**11** and **12**) were obtained in a 2.6:1 ratio and in an 82% isolated yield. The study of the relative stereochemistry at the newly created chiral centers in the major product was carried out using the corresponding ketone **13**, obtained by treatment of the cycloadduct, after HPLC separation, with tetrabutylammonium fluoride (TBAF).

A complete spectroscopic study of this pyrone allowed us to identify all relevant signals in the NMR spectrum, and a ROESY[16] experiment indicated that this compound was the cis isomer since correlation was observed between the two protons geminal to the oxygen atom of the pyrone. The absolute stereochemistry could not be ascertained at this point and was tentatively assigned as shown on the basis of the previously observed tendency of the aldehyde **5** to react through an endo approach to the diene.[12] It should be noted that, according to a lanthanide-induced shift (LIS)[17] study using $Eu(hfc)_3$, no racemization took place during the cycloaddition reaction since only one enantiomer was observed to the detection limits of 400 MHz NMR.[18]

The enolsilyl ether moiety present in the cycloadducts was too labile to allow an efficient separation, and thus it was decided to continue with the mixture. The cycloaddition products were treated with ozone followed by

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(14) The aldehydes were prepared according to literature procedures or by simple modification of commercial compounds. See the Supporting Information section.

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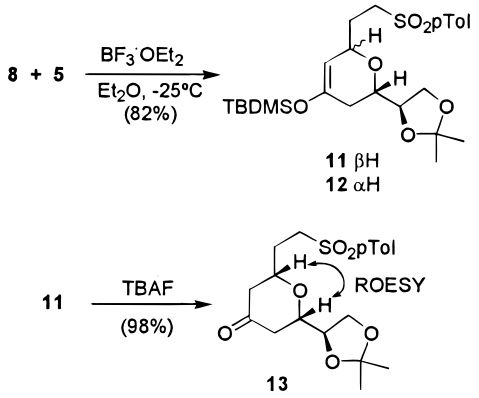
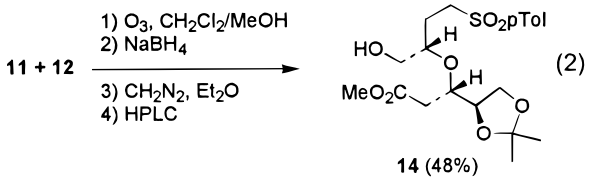
(17) Parker, D. *Chem. Rev.* **1991**, *91*, 1441.

(18) The LIS studies were conducted comparing the displacement of the signals with that of a racemic mixture, prepared by mixing the enantiomers obtained using aldehyde **5** and its enantiomer in the cycloaddition reaction.

Scheme 1



$NaBH_4$ reduction, and the resulting crude was methylated using diazomethane as shown in eq 2. At this

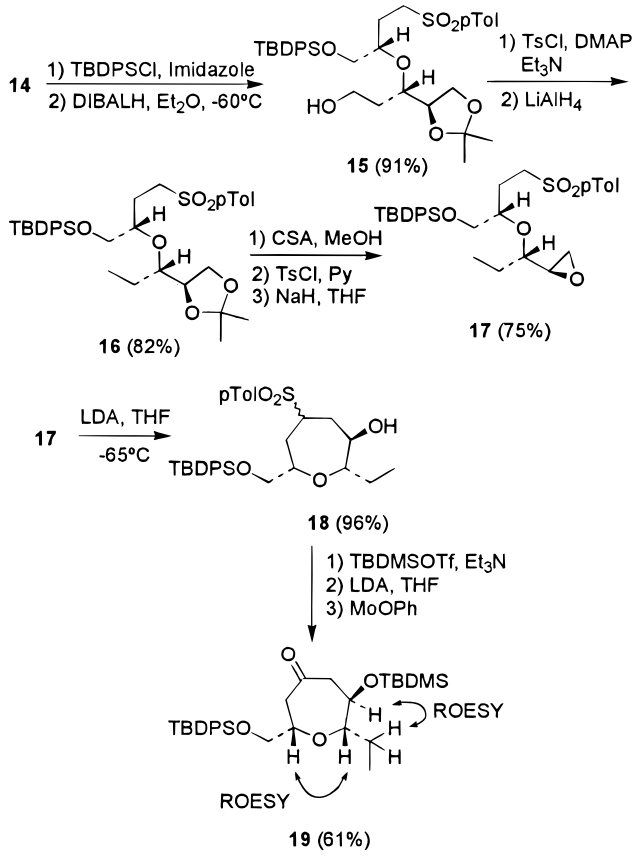


point, the two compounds were readily separated by HPLC and the rest of the synthesis was carried out using only the major compound **14**, obtained in a 48% yield from **11** + **12**.

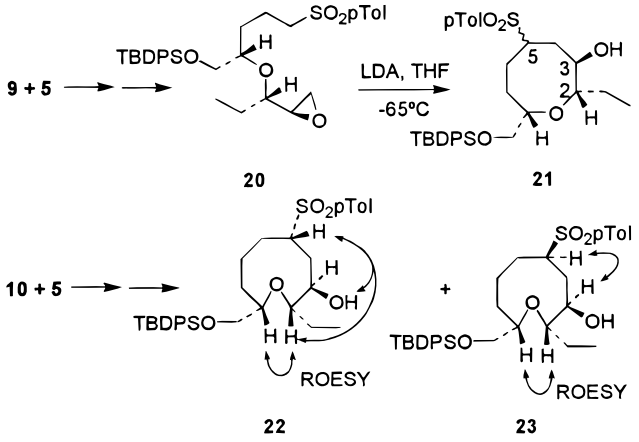
The hydroxyl group in **14** was protected as its *tert*-butyldiphenylsilyl ether and the ester reduced with DIBALH to the alcohol **15** in 91% yield (two steps). At this point, the hydroxyl group in **15** (Scheme 2) could be protected with a different group for possible transformation at a later stage, but since at this stage we only wanted to demonstrate the usefulness of our synthetic scheme, we decided to simplify the molecule by treating the corresponding tosylate with $LiAlH_4$, yielding **16** (82%). In the following steps, the acetonide was transformed into an epoxide by deprotection with camphorsulfonic acid, tosylation of the primary alcohol, and treatment with sodium hydride. The epoxide **17**, obtained in a 75% isolated yield from **16**, is the linear ether depicted in Figure 2 with the entire functionality required for its transformation into an oxepane. This transformation was achieved in a 96% yield by treating **17** with 4 equiv of LDA at −65 °C in THF. No compound coming from an exo attack on the epoxide could be detected. The oxepane **18** was obtained as a 1:1 mixture of epimers at the sulfone, and this was proven by treatment of the tertbutyldimethylsilyl protected compounds with LDA and MoOPh,[19] yielding the ketone **19** in a 61% yield from **18** as a single compound. The spectroscopic data (ROESY) indicated that the absolute stereochemistry of the cyclic ether was indeed the expected one, that is, for the major isomer of the cycloaddition reaction, the one coming from the endo-Cram approach of the aldehyde to the diene.

Synthesis of the *cis*-Oxocane and *cis*-Oxonane. Once the viability of this approach for the preparation of oxepanes was demonstrated, we wanted to test its scope in the synthesis of larger rings. The cycloaddition of diene **9** with **5**, using the same procedure, and on the same scale, described for the cycloadducts of **8** with **5**, proceeded with higher selectivity giving a 7:1 ratio of cis: trans isomers in an 82% yield (Scheme 3).

Scheme 2



Scheme 3



The other two possible isomers were observed only as traces. Following the same synthetic sequence as described for the oxepane, the linear ether **20** was obtained in a 26% overall yield from the cycloadducts. The cyclization step was carried out by addition of 4 equiv of LDA at −65 °C to a THF solution of **20** (0.1−0.7 mmol scale), and thus **21** was obtained in a 60% yield together with unreacted material, as a 9:1 mixture of epimers at the carbon atom bearing the sulfone, the major isomer being the (5*S*)-sulfone, according to the correlations found in the ROESY experiment. Changing the temperature or reaction time did not lead to improvement of the yield, only to decomposition of the products. Again, no compound coming from an exo attack of the carbanion on the

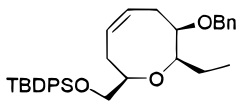
(19) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 188.

epoxide was detected. The mixture of epimers **21** was partially separated and the stereochemistry at the major isomer studied. The correlations found in the ROESY experiment showed that the major compound in the cycloaddition reaction was the one coming from an endo-Cram approach of the aldehyde to the diene. When the diene **10** was used, the hetero Diels−Alder reaction, under the same experimental conditions used for diene **8**, yielded 76% of an 8.3:1 mixture of cis:trans cycloadducts (the other two possible isomers being detected only as very minor components of the crude reaction mixture). It is interesting to note that the longer the chain carrying the sulfone, the better the ratio of the cycloadducts obtained. After the same transformations used for the synthesis of the oxepane and oxocane rings were carried out, the cyclization of the linear epoxy ether (4 equiv of LDA at −65 °C) gave a 45% yield of a 3.5:1 mixture of two compounds (**22** and **23**) and unreacted material. As described for the oxocanes, the yield could not be increased by changing the reaction conditions. In this case, compounds **22** and **23** exhibited very different chromatographic behavior (different R_f in TLC, different t_R in HPLC). After separation and by spectroscopic studies, it was concluded that they were the expected oxonane epimers at the sulfone-bearing carbon, both coming from an endo-Cram cycloaddition as observed by the ROESY correlations. The difference in their properties could be due to the greater flexibility of the oxonane ring and the possibility of intramolecular hydrogen bonding in one of the isomers. When the hydroxyl group in both compounds was protected as TBDMS ether, their chromatographic properties were almost identical, as observed for the other epimers with smaller ring sizes.

The preparation of the oxepane, oxocane, and oxonane ring systems with cis stereochemistry at the positions adjacent to the oxygen atom of the ether validates the usefulness of our approach.

Formal Synthesis of (+)-Laurencin.[20] As a further demonstration of the utility of this approach for the synthesis of mediocyclic ethers, we decided to carry out the synthesis of a natural product with a cis cyclic ether skeleton.

The compound chosen was (+)-laurencin (**2**), of which, at the time this work was being conducted, two enantioselective syntheses had been reported.[21] We decided to prepare, using our methodology, compound **24**, an intermediate in the synthesis of Holmes and co-workers, making it a formal synthesis of (+)-laurencin, if successful. The absolute stereochemistry of the selected compound at the carbons adjacent to the oxygen atom of the ether was opposite to the one obtained in our previous preparation of the oxocane ring. Thus, it was necessary to start the synthesis using **25**,[22] the enantiomer of **5**, as the aldehyde in the hetero Diels−Alder reaction (Scheme 4).



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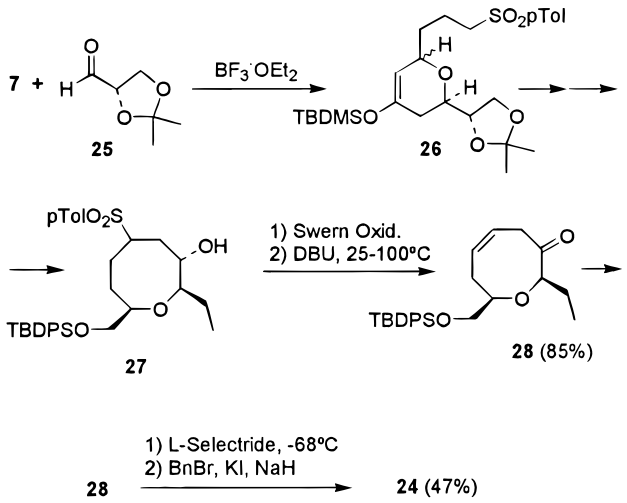
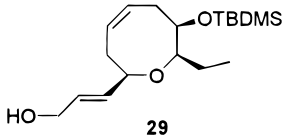
Scheme 4



Working as previously described, **27**, enantiomer of **21**, was obtained with a similar yield. The introduction of the double bond in the oxocane ring was accomplished by Swern oxidation of the hydroxyl group, elimination of the sulfone with DBU at room temperature, and then deconjugation of the α,β-unsaturated ketone by heating the mixture at 100 °C,[21a] giving **28** in an 85% yield. Reduction of **28** with L-Selectride at −68 °C gave a 94% yield of the alcohol with the desired β orientation, as determined by ROESY experiments. The benzylation of the hydroxyl with benzyl bromide furnished **24**, whose spectroscopic data were totally consistent with the proposed structure. These data, however, were different from those reported by Holmes and co-workers for their intermediate in the synthesis of (+)-laurencin. We then learned of the problems encountered by the authors in that paper, which was later retracted,[23,24] and thus the preparation of **24** was not sufficient to claim a formal synthesis.

Fortunately, in the meantime, Overman and co-workers reported on a new synthesis of (+)-laurencin[25] in which one of the intermediates (**29**) was easily accessible from **28**. The preparation of **29** was carried out as shown in Scheme 5.



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Deprotection of **28** (98% yield) followed by Swern oxidation gave the corresponding aldehyde, which was converted into **30**, using a Wittig−Horner reaction, in an 85% yield (two steps). In the latter reaction it is important to use an excess of triethylphosphonoacetate since a slight excess of base produces an intramolecular Michael addition of the enolate of the ketone to the α,β-

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(21) (a) Tsushima, K.; Murai, A. *Tetrahedron Lett.* **1992**, *33*, 4345. (b) Robinson, R. A.; Clark, J. S.; Holmes, A. B. *J. Am. Chem. Soc.* **1993**, *115*, 10400.

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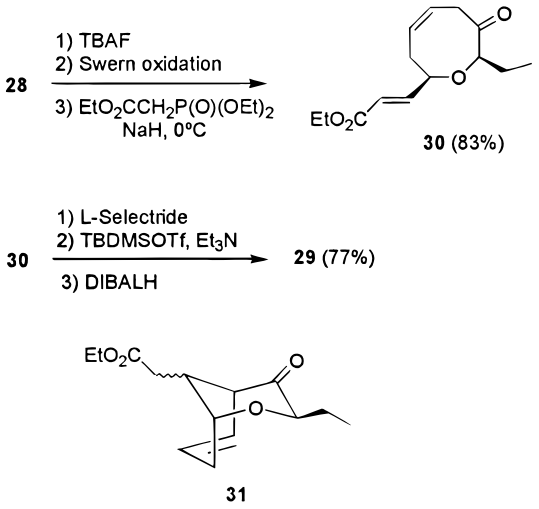
(23) Burton, J. W.; Clark, J. S.; Bendall, J.; Derrer, S.; Stork, T.; Holmes, A. B. *J. Am. Chem. Soc.* **1996**, *118*, 6806.

(24) We thank Prof. Holmes for informing us of the inconsistencies found in his paper prior to the publication of the retraction.

(25) Bratz, M.; Bullock, W. H.; Overman, L. E.; Takemoto, T. *J. Am. Chem. Soc.* **1995**, *117*, 5958.

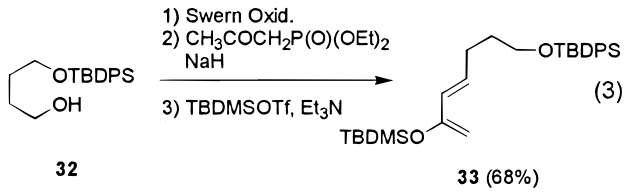
Scheme 5



unsaturated ester, giving **31** as the major product, 43% yield, as a mixture of epimers. The preparation of **29** was accomplished by L-Selectride reduction of **30** followed by protection of the hydroxyl group and DIBALH reduction of the ester (77% from **30**). This compound exhibits spectroscopic and physical data[20] identical to those reported by Overman and co-workers[25] for their intermediate in the synthesis of (+)-laurencin. A LIS study of **29** using $Eu(hfc)_3$ and comparison with its enantiomer, prepared by using the same synthetic sequence starting with aldehyde **5**, showed only one isomer to the detection limits of the NMR. Thus, we have accomplished a formal synthesis of (+)-laurencin, demonstrating the viability of our synthetic scheme. It should be noted also that the reduction product of **28** presents spectroscopic data identical to those reported in the recent papers on the synthesis of (+)-laurencin by Holmes[26] and in the formal synthesis of (+)-laurencin reported by Hoffmann.[27]

Synthesis of a *trans*-oxocane. After completing the formal synthesis of (+)-laurencin, we turned our attention to the preparation of cyclic ethers with trans stereochemistry at the positions adjacent to the oxygen atom. According to our synthetic scheme (Figure 2), the sulfone group should be located in the side chain coming from the ozonolysis of the dihydropyrane after the hetero Diels–Alder reaction (R_2 in Figure 2) and thus it must be introduced at a later stage in the synthesis.

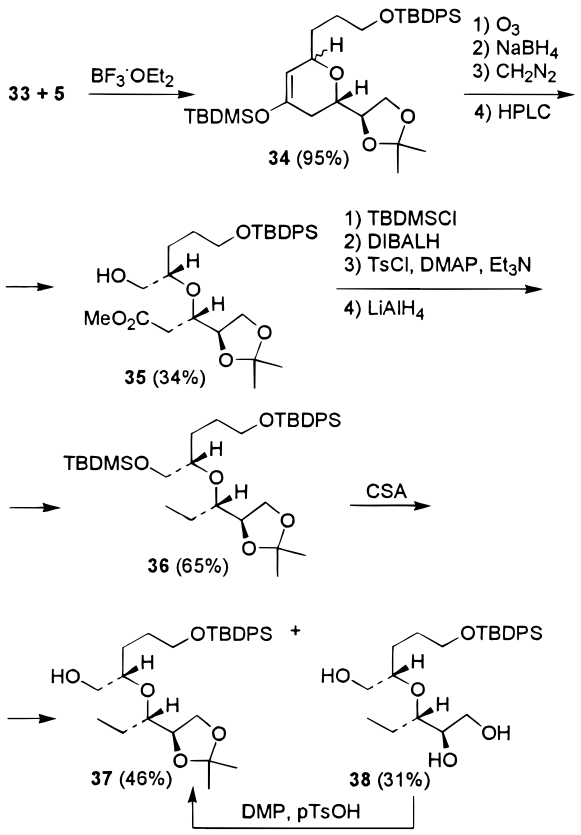
The diene **33** needed for this synthesis was prepared in a 68% overall yield from **32**, as shown in eq 3.



(3)

The reaction of **33** and **5** (Scheme 6) under boron trifluoride etherate catalysis gave a 4.3:1 mixture of cycloadducts (**34**) in a 95% yield. The ozonolysis, followed by sodium borohydride reduction, treatment with diazomethane, and HPLC separation of the major isomer, gave

Scheme 6



35 in a 34% overall yield. The alcohol was protected as the TBDMS ether, and the ester was transformed into an ethyl group affording **36** (65% yield). Treatment with camphorsulfonic acid to remove the TBDMS silyl group gave compounds **37** and **38**, but the diol **38** was easily reprotected under the standard conditions. To effect closure of the mediocyclic ether ring, we needed to incorporate a sulfone group into the molecule, and it was also necessary to define the size of the ring to be formed since this depended on the length of the side chain bearing the sulfone. As an example, we chose to form a *trans*-oxocane, and thus the chain had to be extended by two carbons.

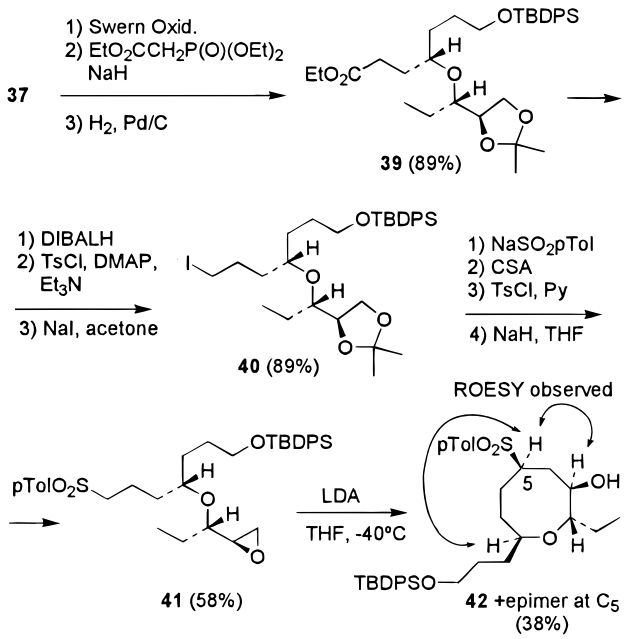
This was accomplished by oxidation of the alcohol, Wittig–Horner olefination with triethylphosphonoacetate/NaH, and catalytic hydrogenation of the double bond to give **39** in an 89% yield after the three steps. No epimerization was observed to the detection limits of NMR during these reactions. The ester was reduced, and the resulting alcohol was tosylated and treated with sodium iodide, giving the iodide **40** (89% yield). The sulfone group was then introduced by displacement of the iodine with *p*-toluensulfinic acid sodium salt in high yield (98%), and the acetonide was transformed into an epoxide (59% yield). The cyclization of the epoxysulfone **41** using 7 equiv of LDA at −40 °C gave the *trans*-oxocane **42** in a 38% yield as a 5.6:1 mixture of epimers at the carbon atom bearing the sulfone (C_5), together with unreacted material. The stereochemistry was confirmed by ROESY experiments on the major compound, as depicted in Scheme 7.

Conclusions

The preparation of the *cis*-oxepane **19**, *cis*-oxocanes **21** and **29**, *cis*-oxonanes **22** and **23**, and *trans*-oxocane **42**,

(26) Burton, J. W.; Clark, J. S.; Derrer, S.; Stork, T. C.; Bendall, J. G.; Holmes, A. B. *J. Am. Chem. Soc.* **1997**, *119*, 7483.
(27) Krüger, J.; Hoffmann, R. W. *J. Am. Chem. Soc.* **1997**, *119*, 7499.

Scheme 7



in enantiomerically pure form, demonstrated the versatility of the strategy based on the highly regioselective intramolecular alkylation of α-lithiosulfones with epoxides, in which the chiral centers adjacent to the oxygen atom have been established via a hetero Diels−Alder reaction.

Experimental Section

Material and Methods. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, in $CDCl_3$ or C_6D_6 as solvent, and chemical shifts are quoted in ppm and reported relative to tetramethylsilane. Flash column chromatography was performed on Merck silica gel 60 (260−400 mesh). Analytical thin-layer chromatography (TLC) was carried out on Merck precoated 0.25 mm thick plates of Merck Kieselgel 60 F_{254}. Reactions requiring anhydrous conditions were carried out under an atmosphere of dry argon. Anhydrous THF was distilled from sodium in a recycling still. Other solvents were purified by standard techniques. Ether refers to diethyl ether.

3(*E*)-2-((*tert*-Butyldimethylsilyl)oxy)-6-(tolyl-4-sulfonyl)-hexa-1,3-diene (8). Step a. To a suspension of NaH (679 mg, 80% in mineral oil, 22.64 mmol) in THF (160 mL) at 0 °C under argon was added diethyl (2-oxopropyl)phosphonate (22.63 mmol, 4.35 mL) with stirring. After 0.5 h, 3-(tolyl-4-sulfonyl)-propionaldehyde (4 g, 18.9 mmol) was added and the reaction was allowed to reach room temperature (1 h). Then water and ice were added and the solution was neutralized with 1% aqueous HCl and extracted with ether (2 × 100 mL). The organic phases were dried (Na_2SO_4), concentrated, and purified by column chromatography (silica gel, 40% ethyl acetate in hexane) to yield **3(*E*)-6-(tolyl-4-sulfonyl)hex-3-en-2-one** (3.71 g, 78%) as a clear oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.17 (s, 3H), 2.43 (s, 3H), 2.61 (m, 2H), 3.19 (m, 2H), 6.01 (dt, J = 16.0, 1.5 Hz, 1H), 6.62 (dt, J = 16.0, 6.7 Hz, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.75 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.5, 25.6, 26.9, 54.3, 128.0, 130.0, 132.5, 135.6, 142.2, 145.0, 187.0; IR ($CHCl_3$) 1690, 1670, 1310 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 253 (MH^+, 1), 155 (7), 97 (100); HRMS (EI) *m*/*z* calcd for $C_{13}H_{16}O_3S$ 252.08202, found 252.08296.

Step b. *tert*-Butyldimethylsilyl triflate (2.35 mL, 10.13 mmol) was added to a stirred solution of 3(*E*)-6-(tolyl-4-sulfonyl)hex-3-en-2-one (2.32 g, 9.20 mmol) in triethylamine (TEA) (6.5 mL) at 0 °C under an argon atmosphere. The reaction was stirred at room temperature until TLC showed the complete disappearance of the starting material (1 h). Then ether (50 mL) and a saturated solution of $NaHCO_3$ were added. The phases were separated, and the aqueous one was extracted with ether (2 × 100 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and chromatographed on silica gel (15% ethyl acetate in hexane) to yield 2.68 g of **8** (80%) as a clear oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.13 (s, 6H), 0.93 (s, 9H), 2.46 (s, 3H), 2.49 (m, 2H), 3.12 (m, 2H), 4.20 (s, 1H), 4.23 (s, 1H), 5.84 (m, 2H), 7.36 (d, J = 8.1 Hz, 2H), 7.78 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.8, 18.1, 21.5, 25.4, 25.6, 55.5, 95.2, 125.7, 128.1, 129.8, 130.3, 135.9, 144.7, 154.1; IR ($CHCl_3$) 1640, 1590, 1310 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 309 (49), 211 (10).

Hetero Diels−Alder Reaction of 8 and 5. To a solution of **8** (2.4 g, 6.5 mmol) in anhydrous ether (60 mL) was added under argon *R*-(+)-2,3-*O*-isopropylideneglyceraldehyde (**5**) (850 mg, 6.5 mmol) in 10 mL of ether. The reaction was cooled to −25 °C, and BF_3•OEt_2 (0.82 mL) was added. After 15 min, TEA (1.8 mL) was added and the reaction was allowed to reach room temperature. Water was added, and the mixture was extracted with ether (3 × 75 mL). The combined organic phases were dried (Na_2SO_4), concentrated, and chromatographed (silica gel, 20% EtOAc in hexane), yielding 2.66 g of the Diels−Alder adducts (82%) as a 2.6:1 mixture. A fraction of the mixture was separated by HPLC and a small amount of the minor isomer (**12**) was obtained pure.

(2*S*,6*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-2-[4(*R*)-2,2-dimethyl[1,3]dioxolan-4-yl]-6-[2-(tolyl-4-sulfonyl)ethyl]-3,6-dihydro-2*H*-pyran (11): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.10 (s, 3H), 0.11 (s, 3H), 0.88 (s, 9H), 1.31 (s, 3H), 1.35 (s, 3H), 1.73−1.79 (m, 1H), 1.98 (m, 1H), 2.03 (m, 2H), 2.42 (s, 3H), 3.14 (m, 2H), 3.44 (m, 1H), 3.80 (dd, J = 8.3, 5.0 Hz, 1H), 3.89 (m, 1H), 4.0 (dd, J = 8.3, 6.2 Hz, 1H), 4.21 (m, 1H), 4.57 (bs, 1H), 7.33 (d, J = 7.9 Hz, 2H), 7.75 (d, J = 8.3 Hz, 2H).

(2*S*,6*R*)-4-((*tert*- Butyldimethylsilyl)oxy)-2-[4(*R*)-2,2-dimethyl[1,3]dioxolan-4-yl]-6-[2-(tolyl-4-sulfonyl)ethyl]-3,6-dihydro-2*H*-pyran (12): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.13 (s, 3H), 0.14 (s, 3H), 0.91 (s, 9H), 1.34 (s, 3H), 1.37 (s, 3H), 1.98−1.81 (m, 2H), 2.17−2.01 (m, 2H), 2.46 (s, 3H), 3.12 (m, 1H), 3.24 (m, 1H), 3.53 (m, 1H), 3.70 (dd, J = 7.4, 4.7 Hz, 1H), 4.02 (m, 2H), 4.24 (m, 1H), 4.72 (bs, 1H), 7.37 (d, J = 7.9 Hz, 2H), 7.89 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.6, −4.4, 18.0, 21.6, 25.2, 25.6, 26.5, 27.7, 31.9, 53.3, 67.0, 70.7, 72.3, 104.0, 109.5, 128.0, 130.0, 136.2, 144.7, 148.9; IR ($CHCl_3$) 1670, 1600, 1310 cm^{-1}.

(2*S*,6*S*)-2-[4(*R*)-2,2-Dimethyl[1,3]dioxolan-4-yl]-6-[2-(tolyl-4-sulfonyl)-ethyl]tetrahydropyran-4-one (13). To a solution of compound **11** (50 mg, 0.1 mmol) in anhydrous THF (2 mL) at 0 °C under an argon atmosphere, a small amount of tetrabutylammonium fluoride hydrate (TBAF) was added. After 10 min, ice and an aqueous saturated solution of NaCl were added and the mixture was extracted with ether (3 × 50 mL). The organic phases were dried ($MgSO_4$), concentrated, and chromatographed on silica gel (20% EtOAc in hexane), yielding 47 mg (98%) of **13** as a white solid: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35 (s, 3H), 1.39 (s, 3H), 1.98 (m, 2H), 2.24 (dd, J = 14.4, 11.6 Hz, 1H), 2.36 (m, 2H), 2.47 (s, 3H), 2.54 (dt, J = 14.7, 2.2 Hz, 1H), 3.20 (m, 1H), 3.27 (m, 1H), 3.50 (m, 1H), 3.68 (m, 1H), 3.83 (m, 1H), 4.08 (m, 2H), 7.38 (d, J = 8.0 Hz, 2H), 7.79 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 25.0, 26.5, 29.3, 43.5, 47.4, 52.6, 66.5, 75.0, 77.4, 77.6, 110.0, 128.0, 130.0, 136.0, 144.9, 205.1; IR ($CHCl_3$) 1715, 1590, 1310 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 383 (MH^+, 2), 367 (31), 281 (7). Anal. Calcd for $C_{19}H_{26}O_6S$: C, 59.66; H, 6.86; S, 8.37. Found: C, 59.60; H, 6.73; S, 8.22.

Methyl 3(*S*)-3-[4(*R*)-2,2-Dimethyl[1,3]dioxolan-4-yl]-3-[1(*S*)-(hydroxymethyl)-3-(tolyl-4-sulfonyl)propoxy]propionate (14). Ozone was bubbled into a cooled (−78 °C) three-neck flask containing a solution of the mixture of isomers **11** and **12** (2.6 g, 5.24 mmol) in 100 mL of CH_2Cl_2/MeOH (80:20), until a blue color persisted. The ozone flow was then replaced by argon until the color disappeared and $NaBH_4$ (198 mg, 5.24 mmol) was added, continuing the stirring for 1 h. Then another portion of $NaBH_4$ (198 mg) was added, and the solution was allowed to reach room temperature. After being stirred for 18 h, the solution was concentrated, the residue was diluted with

EtOAc, and an aqueous solution of NaCl was added. The aqueous layer was neutralized with 10% HCl, extracted with EtOAc (2 × 75 mL), dried ($MgSO_4$), and concentrated. The crude extract was dissolved in ether (10 mL) and cooled to 0 °C. Then an ethereal solution of CH_2N_2 was added until TLC showed total transformation of the products. The solvent was removed in vacuo, and the residue was chromatographed on silica gel (70% EtOAc in hexanes), yielding 1.57 g of the mixture of hydroxyesters. The mixture was separated by HPLC (85% EtOAc in hexane, 5.2 mL/min) giving 410 mg of the minor isomer (t_R 22.2 min) and 1.10 g (48%) of **14** (t_R 24.3 min): $[\alpha]^{25}_D$ −33.2 ($CHCl_3$, *c* 1.37); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (s, 3H), 1.40 (s, 3H), 1.90 (m, 2H), 2.45 (s, 3H), 2.57 (m, 2H), 3.22 (dd, J = 8.0, 7.3 Hz, 2H), 3.43 (m, 1H), 3.63 (dd, J = 8.4, 6.3 Hz, 1H), 3.69 (m, 1H), 3.70 (s, 3H), 3.80 (m, 1H), 4.02 (m, 2H), 4.23 (m, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.78 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 24.6, 25.0, 26.1, 35.4, 52.1, 52.3, 64.1, 65.6, 74.3, 75.8, 76.6, 109.5, 128.0, 129.9, 136.1, 144.7, 173.2; IR ($CHCl_3$) 3450, 1720, 1600, 1310 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 415 (9), 383 (19). Anal. Calcd for $C_{20}H_{30}O_8S$: C, 55.79; H, 7.03; S, 7.43. Found: C, 55.98; H, 7.21; S, 7.18.

3(*S*)-3-[1(*S*)-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-3-(tolyl-4-sulfonyl)propoxy]-3-[4(*R*)-2,2-dimethyl[1,3]dioxolan-4-yl]propan-1-ol (15). Step a. To a solution of **14** (380 mg, 0.88 mmol) in CH_2Cl_2 (109 mL) was added imidazole (181 mg, 2.56 mmol) and *tert*-butyldiphenylsilyl chloride (0.25 mL, 0.97 mmol). The reaction was stirred at room temperature until TLC showed disappearance of the starting material. Then ice and a saturated aqueous solution of NaCl were added, and the mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$), concentrated, and chromatographed on silica gel (30% EtOAc in hexane) yielding 590 mg (98%) of the protected compound: $[\alpha]^{25}_D$ −12.7 ($CHCl_3$, *c* 0.935); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.00 (s, 9H), 1.32 (s, 3H), 1.36 (s, 3H), 1.85 (m, 1H), 2.05 (m, 1H), 2.39−2.48 (m, 2H), 2.43 (s, 3H), 3.18 (t, J = 7.9 Hz, 2H), 3.38 (m, 1H), 3.50 (s, 3H), 3.63 (m, 3H), 3.79 (m, 1H), 3.95 (dd, J = 8.0, 6.9 Hz, 1H), 4.05 (m, 1H), 7.32−7.45 (m, 8H), 7.60 (m, 4H), 7.78 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.0, 21.5, 24.9, 25.2, 26.1, 26.7, 36.8, 51.4, 51.9, 64.7, 65.7, 75.3, 76.6, 76.7, 109.3, 127.7, 128.0, 129.8, 132.9, 133.0, 135.4, 136.0, 144.5, 171.3; IR ($CHCl_3$) 1730, 1600, 1310 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 553 (3), 385 (16), 273 (24), 101 (100). Anal. Calcd for $C_{36}H_{48}O_8SiS$: C, 64.64; H, 7.24; S, 4.78. Found: C, 64.49; H, 7.27; S, 4.47.

Step b. The previous compound (590 mg, 0.88 mmol) was dissolved in ether (10 mL) and cooled to −60 °C under argon. Then DIBALH (4.4 mL, 1 M in hexanes) was added and the stirring was continued until TLC showed the end of the reaction (30 min). The reaction was poured into an aqueous solution of potassium sodium tartrate and was vigorously stirred until the phases became clear. After phase separation, the aqueous phase was extracted with ether (3 × 20 mL), and the combined organic extracts were dried ($MgSO_4$), concentrated, and chromatographed on silica gel (40% EtOAc in hexane) yielding 526 mg (93%) of **15**: $[\alpha]^{25}_D$ −14.8 ($CHCl_3$, *c* 1.15); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.03 (s, 9H), 1.32 (s, 3H), 1.37 (s, 3H), 1.63 (dt, J = 5.9, 5.8 Hz, 2H), 1.95 (m, 2H), 2.44 (s, 3H), 3.15 (m, 2H), 3.53−3.71 (m, 7H), 3.94 (dd, J = 8.0, 6.7 Hz, 1H), 4.05 (m, 1H), 7.32−7.46 (m, 8H), 7.61 (m, 4H), 7.76 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.1, 21.6, 24.9, 25.4, 26.3, 26.8, 33.7, 52.3, 59.3, 65.1, 65.7, 75.9, 76.5, 77.2, 109.1, 127.8, 128.1, 129.8, 129.9, 132.8, 135.6, 136.1, 144.6; IR ($CHCl_3$) 3500, 1600, 1310 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 525 (1), 465 (4), 347 (54). Anal. Calcd for $C_{35}H_{48}O_7SiS$: C, 65.60; H, 7.56; S, 4.99. Found: C, 65.84; H, 7.67; S, 4.69.

2(*S*)-1-((*tert*-Butyldiphenylsilyl)oxy)-4-(tolyl-4-sulfonyl)-2-[1(*S*)-[4(*R*)-2,2-dimethyl-[1,3]dioxolan-4-yl]propoxy]butane (16). To a solution of **15** (525 mg, 0.82 mmol) in CH_2Cl_2 (10 mL) were added (dimethylamino)pyridine (104 mg, 0.82 mmol), TEA (0.11 mL, 0.82 mmol), and tosyl chloride (235 mg, 1.23 mmol). The reaction was stirred at room temperature for 12 h, and then iced water was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic phases were dried ($MgSO_4$), concentrated, and filtered through a short column of silica gel (20% EtOAc in hexane) yielding the corresponding tosylate which was immediately used in the following reaction. The tosylate, dissolved in 5 mL of ether, was added to a suspension of $LiAlH_4$ (31 mg, 0.82 mmol) in ether (3 mL) at 0 °C under an atmosphere of argon. After being refluxed until TLC showed that no tosylate remained, the reaction was cooled and water (0.03 mL), 10% aqueous NaOH solution (0.09 mL), and more water (0.09 mL) were added. The suspension was stirred for 20 min, filtered through Celite, concentrated, and chromatographed on silica gel (20% EtOAc in hexane) yielding 420 mg (82%) of **16**: $[\alpha]^{25}_D$ −3.7 ($CHCl_3$, *c* 0.87); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.78 (t, J = 7.4 Hz, 3H) 1.01 (s, 9H), 1.25−1.44 (m, 2H), 1.33 (s, 3H), 1.35 (s, 3H), 1.93 (m, 1H), 2.06 (m, 1H), 2.44 (s, 3H), 3.22 (m, 2H), 3.35 (ddd, J = 5.3, 5.2, 5.0 Hz, 1H), 3.45 (m, 1H), 3.62 (m, 2H), 3.67 (dd, J = 7.6, 7.5 Hz, 1H), 3.89 (dd, J = 7.6, 6.7 Hz, 1H), 4.01 (m, 1H), 7.33−7.46 (m, 8H), 7.62 (m, 4H), 7.79 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 9.3, 19.0, 21.5, 24.1, 25.1, 25.3, 26.4, 26.7, 52.2, 65.0, 65.5, 76.4, 76.8, 78.5, 108.7, 127.7, 128.1, 129.8, 133.0, 133.1, 135.5, 136.2, 144.4; IR ($CHCl_3$) 1600, 1310 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 609 (1), 567 (12), 465 (10). Anal. Calcd for $C_{35}H_{48}O_6SiS$: C, 67.28; H, 7.75; S, 5.12. Found: C, 67.62; H, 7.81; S, 5.01.

2(*S*)-1-((*tert*-Butyldiphenylsilyl)oxy)-2-[1(*S*)-[1(*R*)-oxiranyl]propoxy]-4-(tolyl-4-sulfonyl)butane (17). Step a. To a solution of **16** (310 mg, 0.50 mmol) in MeOH (5 mL) was added camphorsulfonic acid (12 mg, 0.05 mmol). After stirring of the reaction at 4 °C for 12 h, one drop of TEA was added and MeOH was removed under reduced pressure. The residue was chromatographed on silica gel (45% EtOAc in hexane) yielding 35 mg of unreacted **16** and 245 mg (85%) of the corresponding deprotected diol: $[\alpha]^{25}_D$ −7.83 ($CHCl_3$, *c* 1.15); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.79 (t, J = 7.5 Hz, 3H), 1.01 (s, 9H), 1.35 (m, 1H), 1.49 (m, 1H), 1.93 (m, 1H), 2.12 (m, 1H), 2.44 (s, 3H), 3.24 (m, 2H), 3.36 (m, 1H), 3.44 (m, 1H), 3.65 (m, 5H), 7.33−7.46 (m, 8H), 7.61 (m, 4H), 7.78 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 9.6, 19.0, 21.6, 23.3, 25.1, 26.7, 51.9, 62.7, 65.0, 72.0, 76.4, 81.2, 127.7, 128.0, 129.8, 129.9, 132.9, 133.0, 135.5, 135.9, 144.6; IR ($CHCl_3$) 3450, 1600, 1310 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 527 (4), 347 (37), 199 (87). Anal. Calcd for $C_{32}H_{44}O_6SiS$: C, 65.72; H, 7.59; S, 5.47. Found: C, 65.89; H, 7.60; S, 5.07.

Step b. Pyridine (0.2 mL) and tosyl chloride (88 mg, 0.46 mmol) were added to a flask containing the deprotected diol (245 mg) described before. The mixture was kept at room temperature for 16 h, and then ice was added and the reaction was extracted with ether (3 × 15 mL). The extract was dried ($MgSO_4$) and concentrated. The crude tosylate obtained was added to a suspension of NaH (19 mg of 80% suspension in mineral oil, 0.63 mmol) in THF (8 mL) at 0 °C. After the mixture was stirred for 30 min, ice and a 1% aqueous solution of HCl were added, the organic layer was extracted with ether (3 × 15 mL), and the combined organic extracts were dried ($MgSO_4$), concentrated, and chromatographed on silica gel (20% EtOAC in hexane) yielding 209 mg of **17** (88%): $[\alpha]^{25}_D$ −23.8 ($CHCl_3$, *c* 1.2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.85 (t, J = 7.4 Hz, 3H) 1.01 (s, 9H), 1.41−1.58 (m, 2H), 1.85 (m, 1H), 2.04 (m, 1H), 2.45 (s, 3H), 2.56 (m, 1H), 2.69 (m, 1H), 2.77 (m, 1H), 3.13 (m, 1H), 3.21 (dd, J = 8.1, 7.9 Hz, 2H), 3.41 (dd, J = 10.1, 6.2 Hz, 1H), 3.54 (m, 1H), 3.60 (dd, J = 10.1, 4.7 Hz, 1H), 7.34−7.47 (m, 8H), 7.61 (m, 4H), 7.79 (d, J = 4.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 9.3, 19.0, 21.6, 25.8, 26.0, 26.7, 44.8, 52.3, 53.0, 65.0, 76.9, 77.9, 127.7, 128.1, 129.8, 132.9, 133.1, 135.5, 136.1, 144.4; IR ($CHCl_3$) 1600, 1310 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 510 (2), 347 (10). Anal. Calcd for $C_{32}H_{42}O_5SiS$: C, 67.81; H, 7.48; S, 5.65. Found: C, 67.63; H 7.47; S, 5.55.

(2*S*,6*R*,7*S*)-6-((*tert*-Butyldimethylsilyl)oxy)-2-(((*tert*-butyldiphenylsilyl)oxy)methyl)-7-ethyloxepan-4-one (19). Step a. To a solution of **17** (24 mg, 0.042 mmol) in 9 mL of THF at −65 °C under atmosphere of argon, was added LDA (0.7 mL, 0.17 mmol, 0.24 M in THF). After the mixture was stirred for 25 min, 2 mL of a saturated aqueous solution of

NH_4Cl was added and the mixture was extracted with ether (3 × 10 mL), dried ($MgSO_4$), concentrated, and chromatographed on silica gel (25% EtOAc in hexane) yielding 23 mg (96%) of an inseparable mixture of epimers **18**.

Step b. To a solution of **18** (23 mg, 0.04 mmol) in TEA (0.1 mL) at 0 °C under argon was added *tert*-butyldimethylsilyl triflate (19 μL, 0.08 mmol). The reaction was stirred at room temperature for 15 min, and then ether (5 mL) and a saturated aqueous solution of $NaHCO_3$ (5 mL) were added. The layers were separated, and the aqueous phase was extracted with ether (3 × 10 mL); the combined organic extracts were dried ($MgSO_4$), concentrated, and chromatographed on silica gel (10% EtOAc in hexane), yielding 25 mg (92%) of the corresponding protected epimers. Those compounds (25 mg, 0.037 mmol) were dissolved in THF (1 mL) and cooled to −78 °C under an argon atmosphere, and then LDA (0.92 mL, 0.22 mmol, 0.24 M in THF) was added. After the reaction was stirred for 10 min, a solution of MoOPh (48 mg, 0.11 mmol) in THF (2 mL) was added, and after 5 min, 1 mL of saturated aqueous solution of Na_2SO_3 was added and the mixture was poured into water and extracted with ether (3 × 10 mL). The combined organic extracts were washed with 0.6 N HCl (5 mL) and saturated aqueous NaCl (5 mL), dried ($MgSO_4$), concentrated, and chromatographed on silica gel (5% EtOAc in hexane) yielding 12 mg (61%) of **19** as a single compound: $[\alpha]^{25}_D$ −31.8 ($CHCl_3$, *c* 0.67); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.08 (s, 3H), 0.10 (s, 3H), 0.90 (s, 9H), 0.98 (t, *J* = 7.4 Hz, 2H), 1.06 (s, 9H), 1.37 (m, 1H), 1.66 (m, 1H), 2.45 (dd, *J* = 16.4, 10.8 Hz, 1H), 2.70 (dd, *J* = 16.4, 3.6 Hz, 1H), 2.74 (dd, *J* = 12.2, 2.4 Hz, 1H), 2.86 (dd, *J* = 12.1, 9.4 Hz, 1H), 3.41 (m, 1H), 3.52 (dd, *J* = 10.4, 5.4 Hz, 1H), 3.65 (m, 1H), 3.70 (dd, *J* = 10.4, 6.1 Hz, 1H), 4.11 (m, 1H), 7.37−7.46 (m, 6H), 7.68 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.8, −4.5, 10.3, 17.9, 19.2, 25.7, 26.5, 26.8, 47.8, 50.0, 66.8, 72.3, 76.7, 88.8, 127.7, 129.6, 129.7, 133.3, 133.4, 135.5, 135.6, 207.8.

(2*S*,3*R*,5*S*,8*S*)-8-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2-ethyl-5-(tolyl-4-sulfonyl)oxocan-3-ol (21). Major epimer at C_5: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, *J* = 7.3, Hz, 3H), 1.03 (s, 9H), 1.32 (m, 1H), 1.75 (m, 3H), 1.90 (m, 1H), 2.05 (m, 1H), 2.13 (ddd, *J* = 14.8, 9.3, 1.9 Hz, 1H), 2.27 (ddd, *J* = 14.8, 4.8, 1.6 Hz, 1H), 2.46 (s, 3H), 3.06 (dt, *J* = 8.5, 3.0 Hz, 1H), 3.30 (m, 1H), 3.45 (dd, *J* = 10.0, 6.6 Hz, 1H), 3.58 (m, 1H), 3.66 (dd, *J* = 10.0, 5.5 Hz, 1H), 3.77 (m, 1H), 7.40 (m, 8H), 7.64 (m, 4H), 7.76 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 10.3, 19.1, 21.6, 23.7, 26.8, 27.7, 27.8, 31.1, 59.4, 66.0, 72.6, 80.4, 81.2, 127.6, 127.7, 129.0, 129.6, 129.7, 129.8, 133.4, 133.5, 134.6, 135.6, 144.5; IR ($CHCl_3$) 3710, 1600, 1300 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 523 (3), 337 (7), 273 (36). Anal. Calcd for $C_{33}H_{44}O_5SSi$: C, 68.24; H, 7.64; S, 5.51. Found: C, 68.10; H, 7.68; S, 5.63.

(2*S*,3*R*,5*S*,9*S*)-9-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2-ethyl-5-(tolyl-4-sulfonyl)oxonan-3-ol (22): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.92 (t, *J* = 7.4 Hz, 3H), 1.04 (s, 9H), 1.38−1.80 (m, 8H), 2.26 (m, 2H), 2.48 (s, 3H), 3.18 (m, 1H), 3.25 (m, 1H), 3.40 (m, 2H), 3.61 (m, 2H), 3.78 (m, 1H), 7.35−7.44 (m, 8H), 7.64 (m, 4H), 7.78 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 9.3, 16.5, 19.2, 21.7, 24.5, 25.7, 26.8, 27.2, 29.2, 58.1, 64.9, 70.7, 78.2, 127.6, 127.6, 129.2, 129.7, 129.9, 133.5, 133.5, 133.7, 135.6, 135.6, 145.0.

(2*S*,3*R*,5*R*,9*S*)-9-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2-ethyl-5-(tolyl-4-sulfonyl)oxonan-3-ol (23): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.76 (t, *J* = 7.4 Hz, 3H), 1.04 (s, 9H), 1.13−1.27 (m, 1H), 1.51−1.64 (m, 5H), 1.75−1.99 (m, 4H), 2.35 (bs, *J* = 15.2 Hz, 1H), 2.46 (s, 3H), 3.18 (m, 1H), 3.27 (m, 1H), 3.38 (dd, *J* = 10.1, 6.8 Hz, 1H), 3.46 (m, 1H), 3.61 (dd, *J* = 10.2, 5.0 Hz, 1H), 3.84 (m, 1H), 7.33−7.46 (m, 8H), 7.65 (d, *J* = 6.7 Hz, 4H), 7.78 (d, *J* = 7.8 Hz, 2H).

(2*R*,8*R*)-8-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-2-ethyl-7,8-dihydro-4*H*-oxocin-3-one (28). Step a. To a solution of DMSO (25 μL, 0.35 mmol) in CH_2Cl_2 (2 mL) under argon at −78 °C was slowly added a solution of oxalyl chloride (24 μL, 0.28 mmol) in CH_2Cl_2 (0.5 mL). After 30 min the alcohol **27**, mixture of epimers at C_5 (134 mg, 0.23 mmol), was added in CH_2Cl_2 (1 mL). After the mixture was stirred for 1 h, TEA (0.16 mL) was added, and the reaction was allowed to reach room temperature. Water was added, and the reaction was extracted with ether. The combined organic extracts were washed with 5 mL each of 1% aqueous solution of HCl, 5% Na_2CO_3, and saturated solution of NaCl. The solution was dried ($MgSO_4$), concentrated, and purified by column chromatography (silica gel, 20% EtOAc in hexanes) yielding 125 mg (94%) of the corresponding ketone **(2*R*,5*R*,8*R*)-8-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-ethyl-5-(tolyl-4-sulfonyl)-oxocan-3-one** (major epimer at C_5): $[\alpha]^{25}_D$ +46.2 ($CHCl_3$, *c* 1.41); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.91 (t, *J* = 7.4 Hz, 3H), 1.06 (s, 9H), 1.35 (m, 1H), 1.45−1.60 (m, 2H), 1.82 (m, 1H), 2.03 (m, 2H), 2.46 (s, 3H), 2.49 (bs, 1H), 3.08 (m, 1H), 3.19 (dd, *J* = 12.4, 9.9 Hz, 1H), 3.39 (dd, *J* = 8.3, 5.7 Hz, 1H), 3.57 (m, 2H), 3.76 (m, 1H), 7.35−7.64 (m, 8H), 7.66 (m, 4H), 7.73 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 9.6, 19.2, 20.9, 21.7, 25.5, 25.6, 26.8, 35.6, 64.3, 65.3, 80.7, 87.3, 127.7, 128.9, 129.8, 129.9, 133.2, 133.8, 135.5, 145.0, 215.1; IR ($CHCl_3$) 1710, 1600, 1310 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 521 (27), 365 (85). Anal. Calcd for $C_{33}H_{42}O_5SiS$: C, 68.48; H, 7.32; S, 5.53. Found: C, 68.76; H, 7.54; S, 5.14.

Step b. DBU (48 μL, 0.32 mmol) was added to a solution of the previously described ketone (124 mg, 0.21 mmol) in toluene (5 mL) at room temperature under an argon atmosphere. The reaction mixture was stirred for 2 h, and then another 48 μL of DBU (0.32 mmol) was added and the reaction heated at 100 °C for 3 h. After cooling, ice and a saturated aqueous solution of NaCl were added and the reaction was extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), concentrated, and chromatographed (silica gel, 15% EtOAc in hexanes), yielding 82 mg (90%) of **28**: $[\alpha]^{25}_D$ +281 ($CHCl_3$, *c* 1.65); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.90 (t, *J* = 7.4 Hz, 3H), 1.07 (s, 9H), 1.54 (m, 1H), 1.69 (m, 1H), 2,36 (m, 2H), 2.76 (dd, *J* = 12.2, 6.8 Hz, 1H), 3.50 (m, 1H), 3.58 (dd, *J* = 10.1, 6.8 Hz, 1H), 3.71 (dd, *J* = 8.6, 4.3 Hz, 1H), 3.78 (dd, *J* = 10.1, 5.7 Hz, 1H), 3.87 (dd, *J* = 12.2, 7.4 Hz, 1H), 5.61 (dt, *J* = 10.6, 7.2 Hz, 1H), 5.77 (m, 1H), 7.37−7.45 (m, 6H), 7.67 (d, *J* = 6.9 Hz, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 10.0, 19.2, 26.1, 26.8, 29.9, 41.0, 66.2, 84.1, 87.1, 125.8, 127.7, 128.6, 129.7, 133.4, 133.5, 135.6, 135.7, 214.0; IR ($CHCl_3$) 1705, 1310 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 365 (57), 323 (9). Anal. Calcd for $C_{26}H_{34}O_3Si$: C, 73.89; H, 8.11. Found: C, 73.51; H, 7.99.

(2*R*,3*R*,8*R*)-8-(((*tert*-Butyldiphenylsilyl)oxy)methyl)-3-(benzyloxy)-2-ethyl-3,4,7,8-tetrahydro-2*H*-oxocin (24). Step a. To a solution of **28** (39.2 mg, 0.092 mmol) in THF (1 mL) at −78 °C under argon was added L-Selectride (0.18 mL, 1 M in THF). After 30 min, TLC showed total conversion of the starting material, and EtOH (0.1 mL), water (1 drop), a 10% aqueous solution of NaOH (2 drops), and 30% H_2O_2 (3 drops) were added. The reaction was allowed to reach room temperature, and a saturated aqueous solution of K_2CO_3 was added. The aqueous layer was extracted with ether (3 × 5 mL), and the combined organic extracts were dried ($MgSO_4$), concentrated, and chromatographed (silica gel, 20% EtOAc in hexanes), yielding 37 mg (94%) of the corresponding alcohol **(2*R*,3*R*,8*R*)-8-(((*tert*-butyldiphenylsilyl)oxy)methyl)-2-ethyl-3,4,7,8-tetrahydro-2*H*-oxocin-3-ol**: $[\alpha]^{25}_D$ +3.5 ($CHCl_3$, *c* 1.465); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.87 (t, *J* = 7.4 Hz, 3H), 1.07 (s, 9H), 1.37−1.45 (m, 1H), 1.60−1.68 (m, 1H), 1.72 (bs, 1H), 2.27−2.42 (m, 3H), 2.53 (m, 1H), 3.40 (dd, *J* = 9.2, 4.4 Hz, 1H), 3.53 (m, 2H), 3.65 (m, 1H), 3.73 (dd, *J* = 12.8, 8.3 Hz, 1H), 5.70−5.81 (m, 2H), 7.36−7.45 (m, 6H), 7.68 (m, 4H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 10.5, 19.2, 25.9, 26.9, 30.4, 33.5, 66.4, 74.3, 81.1, 82.3, 127.6, 127.7, 129.1, 129.5, 129.6, 133.6, 135.6; MS (EI) *m*/*z* (rel intensity) 424 (M^+, 1), 414 (19), 289 (100).

Step b. To a solution of the previously reported alcohol (8.4 mg, 0.02 mmol) in THF (1.5 mL) at 0 °C was added DMF (0.05 mL) and NaH (1 mg, 80% in mineral oil, 0.03 mmol). The reaction was kept at room temperature for 20 min, and then benzyl bromide (5 μL, 0.04 mmol) and potassium iodide (3.3 mg, 0.02 mmol) were added. After 20 h ice was added and the reaction was extracted with ether (3 × 5 mL). The combined extracts were dried, concentrated, and chromatographed on silica gel (4% EtOAc in hexanes) yielding 5 mg (50%) of **24**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.78 (t, *J* = 7.4 Hz, 3H), 1.05 (s,

9H), 1.20−1.34 (m, 1H), 1.61−1.71 (m, 1H), 2.26−2.44 (m, 3H), 2.68 (ddd, J = 11.1, 10.9, 10.7 Hz, 1H), 3.31−3.44 (m, 3H), 3.52 (dd, J = 9.9, 8.0 Hz, 1H), 3.80 (dd, J = 10.0, 5.1 Hz, 1H), 4.43 (d, J = 12.4 Hz, 1H), 4.66 (d, J = 12.4 Hz, 1H), 5.67 (m, 1H), 5.84 (m, 1H), 7.29−7.41 (m, 11H), 7.66 (m, 4H); ^{1}H NMR (C_6D_6, 400 MHz) δ 0.92 (t, J = 7.4 Hz, 3H), 1.23 (s, 9H), 1.38−1.51 (m, 1H), 1.91−2.02 (m, 1H), 2.27 (m, 2H), 2.46 (m, 1H), 2.90 (ddd, J = 11.0, 10.9, 10.9 Hz, 1H), 3.28 (m, 1H), 3.41 (m, 2H), 3.70 (dd, J = 10.1, 6.3 Hz, 1H), 3.97 (dd, J = 10.2, 5.4 Hz, 1H), 4.28 (d, J = 11.9 Hz, 1H), 4.56 (d, J = 11.9 Hz, 1H), 5.60 (m, 1H), 5.80 (m, 1H), 7.11−7.39 (m, 11H), 7.87 (m, 4H).

(2*R*,8*R*)-2-Ethyl-8-(2-(methoxycarbonyl)vinyl)-7,8-dihydro-4*H*-oxocin-3-one (30). Step a. To a solution of **28** (100 mg, 0.24 mmol) in THF (3 mL) at 0 °C under argon was added TBAF (31 mg, 0.12 mmol). After 3 h, the reaction was quenched with ice and a saturated aqueous solution of NaCl. After extraction with ether (3 × 15 mL), the combined extracts were dried ($MgSO_4$), concentrated, and chromatographed on silica gel (40% EtOAc in hexanes), yielding 42 mg (98%) of the corresponding alcohol, as a white solid: $[\alpha]^{25}_D$ +568 ($CHCl_3$, c 0.81); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.96 (t, J = 7.4 Hz, 3H), 1.63−1.76 (m, 2H), 2.05 (m, 1H), 2.25−2.32 (m, 2H), 2.80 (dd, J = 12.3, 6.7 Hz, 1H), 3.55−3.64 (m, 3H), 3.81 (dd, J = 8.2, 4.5 Hz, 1H), 3.87 (dd, J = 12.3, 7.5 Hz, 1H), 5.64 (m, 1H), 5.81 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 10.0, 26.1, 29.9, 41.0, 65.9, 84.1, 86.8, 126.0, 128.1, 213.1; MS (EI) m/z (rel intensity) 156 (3), 125 (4), 84 (100). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.25; H, 8.89.

Step b. Following the procedure given for the Swern oxidation of **27**, from the alcohol previously described (38 mg, 0.20 mmol), DMSO (22 μL, 0.31 mmol) and oxalyl chloride (0.12 μL, 0.24 mmol), the expected aldehyde was obtained and it was used without further purification.

Step c. To a suspension of NaH (7.2 mg, 80% in mineral oil, 0.24 mmol) in THF (2 mL) was added triethyl phosphonoacetate (0.07 mL, 0.36 mmol) at 0 °C under argon. After 30 min this solution was added to a solution of the aldehyde in THF (1 mL). The reaction was followed by TLC until completion (15 min). Then ice was added and the solution was neutralized with 1% aqueous HCl. The two phases were separated, and the aqueous one was extracted with ether (3 × 10 mL). The combined extracts were dried and concentrated, and the resulting crude was purified by column chromatography (silica gel, 10% EtOAc in hexanes), yielding 51 mg (85%) of **30**: $[\alpha]^{25}_D$ +518 ($CHCl_3$, c 0.74); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.98 (t, J = 7.4 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H), 1.63 (m, 1H), 1.73 (m, 1H), 2.35 (m, 1H), 2.43 (m, 1H), 2.83 (dd, J = 12.9, 6.3 Hz, 1H), 3.79 (dd, J = 8.7, 4.3 Hz, 1H), 3.86 (m, 1H), 4.18 (m, 1H), 4.22 (q, J = 7.1 Hz, 2H), 5.70 (m, 2H), 6.13 (dd, J = 15.6, 1.8 Hz, 1H), 6.91 (dd, J = 15.6, 4.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 10.0, 14.2, 26.2, 32.5, 41.4, 60.5, 81.4, 86.9, 121.0, 126.7, 127.1, 147.0, 166.4, 213.5; IR ($CHCl_3$) 1712, 1660 cm^{-1}; MS (EI) m/z (rel intensity) 252 (M^+, 2), 166 (29). Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.66; H, 7.68.

(2*R*,3*R*,8*R*)-3-((*tert*-Butyldimethylsilyl)oxy)-2-ethyl-8-(3-hydroxy-1(*E*)-propenyl)-3,4,7,8-tetrahydro-2*H*-oxocin (29). Step a. Following the procedure given for the L-Selectride reduction of **28**, ketone **30** (11 mg, 0.04 mmol) afforded, after column chromatography (silica gel, 20% EtOAc in hexanes), 9.7 mg (87%) of the corresponding alcohol **(2*R*,3*R*,8*R*)-2-ethyl-3-hydroxy-8-(2-(methoxycarbonyl)vinyl)-3,4,7,8-tetrahydro-2*H*-oxocin:** $[\alpha]^{25}_D$ +60.0 ($CHCl_3$, c 0.87); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.92 (t, J = 7.4 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H), 1.47 (m, 1H), 1.74 (m, 1H), 2.36 (m, 3H), 2.55 (m, 1H), 3.50 (dddd, J = 9.4, 5.5, 4.2, 1.3 Hz, 1H), 3.72 (m, 1H), 4.14 (m, 1H), 4.21 (q, J = 7.2 Hz, 2H), 5.80 (m, 2H), 6.10 (dd, J = 15.6, 1.8 Hz, 1H), 6.90 (dd, J = 15.6, 4.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 10.4, 14.2, 25.9, 33.3, 33.5, 60.4, 74.3, 78.9, 82.7, 120.6, 128.4, 129.9, 147.8, 166.6; IR ($CHCl_3$) 3689, 1712 cm^{-1}; MS (EI) m/z (rel intensity) 255 (MH^+, 6), 209 (10), 129 (46). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.10; H, 8.72. Found: C, 66.20; H, 8.64.

Step b. To a solution of the alcohol (8 mg, 0.031 mmol) in CH_2Cl_2 (1 mL) at 0 °C under argon were added TEA (7 μL, 0.05 mmol) and *tert*-butyldimethylsilyl triflate (11 μL, 0.05 mmol). After 5 min the reaction was allowed to reach room temperature and was followed by TLC. When it was finished (1 h), ether (5 mL) and saturated aqueous solution of $NaHCO_3$ (5 mL) were added, the phases were decanted, and the aqueous one was extracted with ether (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$), concentrated, and chromatographed (silica gel, 3% EtOAc in hexanes), yielding 11 mg (93%) of the protected alcohol. **(2*R*,3*R*,8*R*)-3-((*tert*-butyldimethylsilyl)oxy)-2-ethyl-8-(2-(methoxycarbonyl)vinyl)-3,4,7,8-tetrahydro-2*H*-oxocin:** $[\alpha]^{25}_D$ +42.3 ($CHCl_3$, c 0.68); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.07 (s, 3H), 0.09 (s, 3H), 0.89 (t, J = 7.4 Hz, 3H), 0.92 (s, 9H), 1.30 (m, 1H), 1,31 (t, J = 7.1 Hz, 3H), 1.65 (m, 1H), 2.16 (m, 2H), 2.48 (m, 1H), 2.72 (dd, J = 10.9, 10.6 Hz, 1H), 3.42 (dt, J = 9.7, 2.7 Hz, 1H), 3.74 (ddd, J = 10.8, 4.9, 2.5 Hz, 1H), 3.90 (dd, J = 10.4, 4.0 Hz, 1H), 4.21 (dq, J = 7.1, 1.7 Hz, 2H), 5.77 (m, 2H), 6.13 (dd, J = 15.6, 1.6 Hz, 1H), 6.94 (dd, J = 15.6, 4.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.8, −4.1, 10.8, 14.3, 18.3, 25.9, 26.0, 33.6, 34.4, 60.3, 75.9, 80.7, 84.4, 120.3, 128.8, 130.1, 148.8, 166.9; MS (EI) m/z (rel intensity) 323 (5), 311 (30), 197 (43), 145 (100).

Step c. Following the procedure given for the DIBALH reduction of TBDPS-protected **14**, the ethyl ester described before (11 mg, 0.04 mmol) afforded, after column chromatography (3% EtOAc in hexane), 6.5 mg (95%) of **29**, whose spectroscopic and physical data were identical to those described in the literature:[25] $[\alpha]^{25}_D$ −5.3 ($CHCl_3$, c 1.21) [lit. $[\alpha]^{25}_D$ −6.3 ($CHCl_3$, c 0.85)]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.06 (s, 3H), 0.08 (s, 3H), 0.91 (c, 12H), 1.28 (m, 1H), 1.64 (m, 2H), 2.10 (m, 2H), 2.49 (m, 1H), 2.74 (q, J = 10.9 Hz, 1H), 3.43 (dt, J = 9.8, 3.0 Hz, 1H), 3.74 (m, 2H), 4.16 (d, J = 4.0 Hz, 2H), 5.67−5.92 (m, 4H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ −4.7, −4.2, 10.9, 18.3, 26.0, 33.6, 35.1, 63.3, 76.1, 81.8, 84.1, 128.9, 129.4, 129.5, 133.4.

Hetero Diels−Alder Reaction of 33 and 5. Following the same procedure described for the reaction of **8** and **5**, using **33** (6.0 g, 12.5 mmol), **5** (1.62 g, 12.5 mmol), $BF_3{\cdot}OEt_2$ (1.58 mL), and TEA (3.5 mL, 25.0 mmol) at −65 °C, 7.3 g of a 4.3:1 mixture of two adducts **34** (95%) was obtained. A fraction of the mixture was purified by HPLC (μ-Porasil 300 × 19 mm column, 8% EtOAc in hexanes, 4 mL/min). The major isomer was **(2*S*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-6-[3-((*tert*-butyldiphenylsilyloxy) propyl]-2-[4(*R*)-2,2-dimethyl-[1,3]-dioxolan-4-yl]-3,6-dihydro-2*H*-pyran:** t_R = 22.4 min; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.16 (s, 3H), 0.17 (s, 3H), 0.95 (s, 9H), 1.07 (s, 9H), 1.38 (s, 3H), 1.43 (s, 3H), 1.55−1.69 (m, 4H), 2.13 (m, 2H), 3.50 (ddd, J = 7.0 Hz, 1H), 3.50 (t, J = 6.2 Hz, 2H), 3.92 (dd, J = 8.0, 5.0 Hz, 1H), 3.98 (dd, J = 6.1, 5.1 Hz, 1H), 4.07 (dd, J = 8.0, 6.1 Hz, 1H), 4.13 (m, 1H), 4.76 (bs, 1H), 7.37−7.43 (m, 6H), 7.68 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.6, −4.3, 18.0, 19.2, 25.4, 25.6, 26.8, 26.9, 28.2, 32.6, 33.2, 63.9, 67.3, 74.1, 75.3, 78.1, 106.6, 109.3, 127.6, 129.5, 134.1, 135.6, 148.5. The minor isomer was **(2*S*,6*S*)-4-((*tert*-Butyldimethylsilyl)oxy)-6-[3-((*tert*-butyldiphenylsilyl)oxy)-propyl]-2-[4(*R*)-2,2-dimethyl-[1,3]dioxolan-4-yl]-3,6-dihydro-2*H*-pyran:** t_R = 24.3 min; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.16 (s, 9H), 0.94 (s, 9H), 1.06 (s, 9H), 1.37 (s, 3H), 1.42 (s, 3H), 1.48−1.74 (m, 4H), 2.09−2.16 (m, 2H), 3.64 (m, 1H), 3.69 (t, J = 5.8 Hz, 2H), 3.86 (dd, J = 7.8, 5.4 Hz, 1H), 4.02 (dd, J = 12.5, 6.3 Hz, 1H), 4.09 (m, 1H), 4.19 (bs, 1H), 4.82 (bs, 1H), 7.37−7.45 (m, 6H), 7.67 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −4.5, −4.3, 18.0, 19.2, 25.3, 25.6, 26.7, 26.9, 29.2, 31.2, 32.5, 63.7, 67.5, 69.7, 72.3, 77.6, 106.0, 109.4, 127.6, 129.5, 134.0, 135.6, 147.6.

Methyl 3(*S*)-3-[1(*S*)-4-((*tert*-Butyldiphenylsilyl)oxy)-1-(hydroxymethyl)butoxy]-3-[4(*R*)-2,2-dimethyl-[1,3]dioxolan-4-yl]propionate (35). Following the procedure described in the preparation of **14**, from the mixture of epimers **34** (3.44 g, 5.63 mmol), after ozonolysis, esterification, and HPLC separation, 1.0 g (34% overall yield) of **35** was obtained: $[\alpha]^{25}_D$ +1.5 ($CHCl_3$, c 1.68); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.06 (s, 9H), 1.34 (s, 3H), 1.41 (s, 3H), 1.50−1.65 (m, 5H), 2.65 (d, J = 5.5 Hz, 2H), 3.36 (m, 1H), 3.46 (m, 1H), 3.58 (m, 1H), 3.66 (m, 2H), 3.73 (s, 3H), 3.76 (dd, J = 8.3, 6.1 Hz, 1H), 3.96 (ddd, J = 5.5, 5.5, 5.5 Hz, 1H), 4.03 (dd, J = 8.2, 6.6 Hz, 1H), 4.11

(dd, J = 11.9, 6.1 Hz, 1H), 7.37−7.45 (m, 6H), 7.66 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 19.2, 25.0, 26.4, 26.9, 27.9, 28.5, 35.9, 52.0, 63.8, 64.9, 66.4, 75.1, 76.6, 79.8, 109.5, 127.6, 129.6, 133.9, 135.5, 173.0; IR ($CHCl_3$) 3450, 1720 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 530 (4), 430 (10), 386 (28). Anal. Calcd for $C_{30}H_{44}O_7Si$: C, 66.14; H, 8.15. Found: C, 66.04; H, 8.36.

2(*S*)-1-((*tert*-Butyldimethylsilyl)oxy)-5-((*tert*-butyldiphenylsilyl)oxy)-2-[1(S)-1-(4(*R*)-2,2-dimethyl[1,3]dioxolan-4-yl)propoxy]pentane (36). Following a procedure similar to that described for the preparation of **16**, using TBDMS instead of TBDPS as protecting group in the first step, 1.25 g of **36** was prepared in 4 steps and in a 65% overall yield: $[\alpha]^{25}_D$ +7.2 ($CHCl_3$, *c* 0.98); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.06 (s, 6H), 0.91 (s, 9H), 0.97 (t, J = 7.5 Hz, 3H), 1.06 (s, 9H), 1.35 (s, 3H), 1.40 (s, 3H), 1.57−167 (m, 6H), 3.49−3.55 (m, 3H), 3.60 (m, 1H), 3.66 (m, 2H), 3.84 (dd, J = 7.4, 6.9 Hz, 1H), 4.02 (m, 2H), 7.37−7.43 (m, 6H), 7.68 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ −5.4, 9.1, 18.3, 19.2, 24.3, 25.4, 25.9, 26.6, 26.9, 28.2, 28.4, 64.2, 65.3, 66.6, 77.1, 78.5, 79.0, 108.7, 127.6, 129.5, 134.0, 135.6; MS (EI) *m*/*z* (rel intensity) 600 (1), 543 (1), 283 (20), 159 (52). Anal. Calcd for $C_{35}H_{58}O_5Si_2$: C, 68.36; H, 9.51. Found: C, 68.19; H, 9.70.

2(*S*)-5-((*tert*-Butyldiphenylsilyl)oxy)-2-[1(*S*)-1-(4(*R*)-2,2-dimethyl[1,3]dioxolan-4-yl)propoxy]pentan-1-ol (37). To a stirred solution of **36** (1.19 g, 1.94 mmol) in MeOH (10 mL) at 0 °C was added camphorsulfonic acid (22 mg, 0.1 mmol). After 3 h, TEA was added (3 drops) and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (30% EtOAc in hexanes) yielding 450 mg of **37** (46%) and 280 mg of **38** (31%). Compound **37**: $[\alpha]^{25}_D$ +22.4 ($CHCl_3$, *c* 1.195); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.98 (t, J = 7.5 Hz, 3H), 1.07 (s, 9H), 1.36 (s, 3H), 1.41 (s, 3H), 1.53−1.74 (m, 6H), 3.51 (m, 2H), 3.57 (m, 1H), 3.65 (m, 3H), 3.85 (dd, J = 7.7, 6.8 Hz, 1H), 4.02 (dd, J = 7.8, 6.4 Hz, 1H), 4.08 (dd, J = 12.2, 6.3 Hz, 1H), 7.37−7.46 (m, 6H), 7.67 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 9.0, 19.2, 23.9, 25.3, 26.6, 26.8, 27.2, 28.3, 63.8, 64.2, 66.4, 76.7, 77.7, 78.1, 108.9, 127.6, 129.6, 133.8, 135.5; IR ($CHCl_3$) 3600, 3450 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 485 (3), 399 (3), 283 (82). Anal. Calcd for $C_{29}H_{44}O_5Si$: C, 69.56; H, 8.86. Found: C, 69.13; H, 8.86.

Ethyl 4(*S*)-7-((*tert*-Butyldiphenylsilyl)oxy)-4-[1(*S*)-1-(4(*R*)-2,2-dimethyl[1,3]dioxolan-4-yl)propoxy]heptanoate (39). Step a. Following the procedure given for the Swern oxidation of **27**, alcohol **37** (450 mg, 0.9 mmol) afforded the expected aldehyde, which was used in the subsequent reaction without purification.

Step b. To a suspension of NaH (81 mg, 80% in mineral oil, 2.7 mmol) in THF (5 mL) was added triethylphosphonoacetate (0.8 mL, 4.05 mmol) at 0 °C under argon. After 30 min, 2.4 mL of this solution was added to a solution of the previously prepared aldehyde in THF (10 mL). After 30 min, TLC showed that no starting material remained, and ice and 10 mL of a 1% aqueous solution of HCl were added. The reaction was extracted with ether (3 × 20 mL), and the combined ethereal extracts were dried ($MgSO_4$), concentrated, and chromatographed (silica gel, 10% EtOAc in hexanes), yielding 465 mg (91%) of the expected α,β-unsaturated ester **ethyl 4(*S*)-7-((*tert*-butyldiphenylsilyl)oxy)-4-[1(*S*)-1-(4(*R*)-2,2-dimethyl-[1,3]dioxolan-4-yl)propoxy]hept-2-enoate:** $[\alpha]^{25}_D$ −2.8 ($CHCl_3$, *c* 0.78); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.92 (t, J = 7.4 Hz, 3H), 1.06 (s, 9H), 1.32 (t, J = 7.2 Hz, 3H), 1.35 (s, 3H), 1.40 (s, 3H), 1.47 (m, 2H), 1.51−1.67 (m, 3H), 1.75 (m, 1H), 3.47 (m, 1H), 3.67 (m, 2H), 3.86 (dd, J = 7.6, 7.5 Hz, 1H), 3.98 (dd, J = 7.5, 6.4 Hz, 1H), 4.06 (m, 1H), 4.16 (m, 1H), 4.22 (q, J = 7.2 Hz, 2H), 5.95 (d, J = 15.8 Hz, 1H), 6.79 (dd, J = 15.8, 7.3 Hz, 1H), 7.36−7.45 (m, 6H), 7.67 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 9.6, 14.2, 19.2, 24.7, 25.2, 26.6, 26.9, 28.0, 31.4, 60.4, 63.7, 65.7, 77.6, 77.7, 78.4, 108.7, 122.2, 127.6, 129.5, 133.9, 135.5, 148.8, 166.2; IR ($CHCl_3$) 1710, 1650 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 511 (7), 409 (6), 331 (6), 283 (21). Anal. Calcd for $C_{33}H_{48}O_6Si$: C, 69.68; H, 8.51. Found: C, 69.75; H, 8.61.

Step c. To a suspension of 10% Pd on carbon (40 mg) in EtOAc (5 mL), under an H_2 atmosphere, was added the unsaturated ester previously obtained (393 mg, 0.69 mmol) in EtOAc (2 mL). After 4 h the catalyst was filtered out and the solution was concentrated and chromatographed on silica gel (5% EtOAc in hexanes) affording 387 mg (98% yield) of **39**: $[\alpha]^{25}_D$ +24.8 ($CHCl_3$, *c* 0.96); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.96 (t, J = 7.5 Hz, 3H), 1.08 (s, 9H), 1.27 (t, J = 7.1 Hz, 3H), 1.35 (s, 3H), 1.40 (s, 3H), 1.45−1.70 (m, 6H), 1.71−1.79 (m, 1H), 1.81−1.90 (m, 1H), 2.39 (m, 2H), 3.45 (m, 2H), 3.69 (t, J = 5.9 Hz, 2H), 3.83 (dd, J = 6.7, 6.4 Hz, 1H), 4.02 (m, 2H), 4.14 (q, J = 7.1 Hz, 2H), 7.37−7.44 (m, 6H), 7.68 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.8, 14.2, 19.2, 23.5, 25.4, 26.6, 26.8, 28.0, 29.0, 29.6, 30.1, 60.2, 63.9, 66.7, 75.8, 76.6, 77.0, 108.7, 127.6, 129.5, 133.9, 135.5, 173.7; IR ($CHCl_3$) 1720 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 555 (3), 513 (35), 411 (26). Anal. Calcd for $C_{33}H_{50}O_6Si$: C, 69.43; H, 8.84. Found: C, 69.05; H, 9.06.

4(*S*)-1-((*tert*-Butyldiphenylsilyl)oxy)-4-[1(*S*)-1-(4(*R*)-2,2-dimethyl[1,3]dioxolan-4-yl)propoxy]-7-iodoheptane (40). Step a. Following the procedure given for the DIBALH reduction of TBDPS-protected **14**, second step in the preparation of compound **15**, ethyl ester **39** (376 mg, 0.66 mmol) afforded, after column chromatography (silica gel, 25% EtOAc in hexanes), 340 mg (98%) of the corresponding alcohol **4(*R*)-7-((*tert*-butyldiphenylsilyl)oxy)-4-[1(*S*)-1-(4(*R*)-2,2-dimethyl[1,3]dioxolan-4-yl)propoxy]heptan-1-ol**: $[\alpha]^{25}_D$ +22.0 ($CHCl_3$, *c* 0.855); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.96 (t, J = 7.5 Hz, 3H), 1.07 (s, 9H), 1.35 (s, 3H), 1.40 (s, 3H), 1.47−1.71 (m, 10H), 3.47 (m, 2H), 3.64 (m, 2H), 3.68 (t, J = 5.8 Hz, 2H), 3.83 (m, 1H), 4.03 (m, 2H), 7.37−7.45 (m, 6H), 7.68 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.9, 19.2, 23.7, 25.3, 26.6, 26.8, 28.2, 28.3, 29.5, 30.3, 63.1, 64.0, 66.8, 76.6, 77.0, 77.4, 108.8, 127.6, 129.5, 134.0, 135.5; IR ($CHCl_3$) 3400 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 513 (2), 311 (100). Anal. Calcd for $C_{31}H_{48}O_5Si$: C, 70.41; H, 9.16. Found: C, 70.47; H, 9.25.

Step b. To a solution of the alcohol previously prepared (335 mg, 0.63 mmol) in CH_2Cl_2 (6 mL) at 0 °C were added DMAP (86 mg, 0.7 mmol), TEA (0.10 mL, 0.7 mmol), and tosyl chloride (174 mg, 0.91 mmol). The reaction was stirred at room temperature for 12 h, and then ice was added and the reaction was extracted with CH_2Cl_2 (3 × 10 mL). The ethereal extracts were dried ($MgSO_4$), concentrated, and quickly filtered on silica gel (15% EtOAc in hexanes) to give 427 mg (98% yield) of the corresponding tosylate, which was used immediately in the subsequent transformation.

Step c. To a solution of the tosylate (427 mg) in anhydrous acetone (6 mL) was added NaI (369 mg, 2.46 mmol), and the reaction was stirred for 14 h at room temperature. The solvent was removed in vacuo, water was added to the residue, and the resulting suspension was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with a saturated aqueous solution of $Na_2S_2O_3$, concentrated, and chromatographed on silica gel (5% EtOAc in hexanes) yielding 375 mg of **40** (93%): $[\alpha]^{25}_D$ +15.5 ($CHCl_3$, *c* 1.375); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.98 (t, J = 7.4 Hz, 3H), 1.10 (s, 9H), 1.37 (s, 3H), 1.42 (s, 3H), 1.50−1.70 (m, 8H), 1.82−1.97 (m, 2H), 3.21 (t, J = 6.9 Hz, 2H), 3.47 (m, 2H), 3.71 (t, J = 5.7 Hz, 2H), 3.84 (dd, J = 6.9, 6.3 Hz, 1H), 4.04 (m, 2H), 7.44 (m, 6H), 7.70 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 7.2, 8.9, 19.1, 23.7, 25.3, 26.6, 26.8, 28.1, 29.2, 29.7, 34.8, 63.9, 66.6, 76.1, 76.7, 77.3, 108.7, 127.6, 129.5, 133.9, 135.5; MS (EI) *m*/*z* (rel intensity) 623 (1), 479 (13), 437 (29), 283 (68). Anal. Calcd for $C_{31}H_{47}O_4SiI$: C, 58.29; H, 7.42. Found: C, 58.12; H, 7.48.

4(S)-1-((*tert*-Butyldiphenylsilyl)oxy)-4-[1(*S*)-1-(2(*R*)-oxiranyl)propoxy]-7-(tolyl-4-sulfonyl)heptane (41). Step a. In a two-neck flask equipped with a reflux condenser were placed **40** (180 mg, 0.28 mmol), DMF (3 mL), and *p*-toluenesulfinic acid sodium salt (72 mg, 0.4 mmol). The mixture was stirred at 65 °C for 2 h, and then it was cooled, poured into 50 mL of water, and vigorously stirred for 30 min. The two phases were decanted, and the aqueous one was extracted with ether (3 × 10 mL). The combined organic extracts were washed with a saturated aqueous solution of $Na_2S_2O_3$ (5 mL), dried ($MgSO_4$), concentrated, and chromatographed on silica gel (15% hexanes in EtOAc), yielding 183 mg (98%) of the corresponding sulfone **4(*S*)-1-((*tert*-butyldiphenylsilyl)oxy)-4-[1(*S*)-1-(4-(*R*)-2,2-dimethyl[1,3]dioxolan-4-yl)propoxy]-7-(tolyl-4-sulfonyl)heptane**: $[\alpha]^{25}_D$ +17.05 ($CHCl_3$, *c* 1.12); ^{1}H NMR

($CDCl_3$, 400 MHz) δ 0.86 (t, J = 7.4 Hz, 3H), 1.06 (s, 9H), 1.33 (s, 3H), 1.37 (s, 3H), 1.41−1.62 (m, 8H), 1.69−1.83 (m, 2H), 2.44 (s, 3H), 3.07 (t, J = 8.0 Hz, 2H), 3.36 (m, 2H), 3.65 (t, J = 6.0 Hz, 2H), 3.76 (m, 1H), 3.97 (m, 2H), 7.34−7.45 (m, 8H), 7.66 (m, 4H), 7.78 (d, J = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 8.7, 19.0, 19.1, 21.5, 23.5, 25.3, 26.6, 26.8, 28.0, 29.6, 32.5, 56.5, 63.8, 66.6, 76.2, 76.5, 77.1, 108.7, 127.6, 128.1, 129.5, 129.8, 133.8, 135.5, 136.1, 144.5; IR ($CHCl_3$) 1590, 1310 cm^{-1}; MS (EI) *m*/*z* (rel intensity) 651 (2), 609 (71), 449 (39). Anal. Calcd for $C_{38}H_{54}O_6SiS$: C, 68.43; H, 8.17. Found: C, 68.18; H, 8.52.

Step b. Following the three-step procedure described for the preparation of **17** from **16**, starting from 67 mg of the compound reported above, 36 mg of the epoxysulfone **41** was obtained (59% yield): $[\alpha]^{25}_D$ −1.0 ($CHCl_3$ *c* 0.89); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.89 (t, J = 7.4 Hz, 3H), 1.05 (s, 9H), 1.45−1.63 (m, 7H), 1.65−1.83 (m, 3H), 2.44 (s, 3H), 2.58 (dd, J = 5.2, 2.5 Hz, 1H), 2.67 (dd, J = 5.0, 4.1 Hz, 1H), 2.77 (m, 1H), 2.98 (ddd, J = 5.9, 5.9, 5.6 Hz, 1H), 3.07 (t, J = 7.9 Hz, 2H), 3.33 (m, 1H), 3.65 (m, 2H), 7.34−7.45 (m, 8H), 7.66 (m, 4H), 7.78 (d, J = 8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 9.4, 18.8, 19.2, 21.6, 26.0, 26.8, 28.2, 30.4, 32.4, 45.7, 53.2, 56.5, 63.8, 77.3, 78.1, 127.6, 128.1, 129.6, 129.8, 133.9, 135.5, 136.1, 144.6; MS (EI) *m*/*z* (rel intensity) 551 (8), 449 (5), 283 (66). Anal. Calcd for $C_{35}H_{48}O_5SiS$: C, 69.04; H, 7.95; S, 5.26. Found: C, 69.23; H, 7.95; S, 5.14.

(2*S*,3*R*,5*R*,8*S*)-8-((3-*tert*-Butyldiphenylsilyl)oxy)propyl-2-ethyl-5-(tolyl-4-sulfonyl)oxocan-3-ol (42). To a solution of **41** (23.7 mg, 0.038 mmol) in THF (7 mL) at −65 °C under argon was added LDA (1.15 mL, 0.27 mmol, 0.24 M in THF). The reaction was stirred at −40 °C for 30 min, and then 2 mL of a saturated aqueous solution of NH_4Cl was added and the reaction was extracted with ether (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), concentrated, and chromatographed on silica gel (25% hexanes in EtOAc) yielding 9 mg (38%) of a mixture (85:15) of *trans*-oxocane epimers at the sulfone-bearing carbon and unreacted compound **41** (12 mg). A pure fraction of the major isomer was isolated by HPLC (μ Porasil, 300 × 19 mm, 30% EtOAC in hexanes, 3 mL/min, t_R = 9.7 min): ^{1}H NMR (C_6D_6, 400 MHz) δ 0.81−0.95 (m, 1H), 0.99 (t, J = 7.4 Hz, 3H), 1.21 (s, 9H), 1.33−1.44 (m, 4H), 1.45−1.65 (m, 3H), 1.70−1.89 (m, 3H), 1.92 (s, 3H), 2.77 (dd, J = 14.2, 4.0 Hz, 1H), 3.18 (m, 1H), 3.25 (m, 1H), 3.42 (m, 1H), 3.62 (m, 2H), 3.89 (m, 1H), 6.82 (d, J = 8.0 Hz, 2H), 7.28 (m, 6H), 7.81 (m, 6H); ^{13}C NMR (C_6D_6, 100 MHz) δ 7.5, 19.4, 21.1, 25.8, 27.1, 27.2, 27.4, 29.8, 30.6, 33.3, 60.0, 64.0, 70.9, 73.5, 78.0, 127.9, 128.1, 129.3, 129.7, 130.0, 134.3, 135.9, 143.8.

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Supporting Information Available: Experimental procedures for the synthesis of **4**, **7**, **9**, **10**, **31**, and **33**, ^{1}H NMR spectra for **11** and **23**, and ^{1}H and ^{13}C NMR spectra for **21** and new compounds for which no elemental analysis could be obtained (40 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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