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A Cascade Cyclization Route to Adjacent Bistetrahydrofurans from Chiral Triepoxyfarnesyl Bromides

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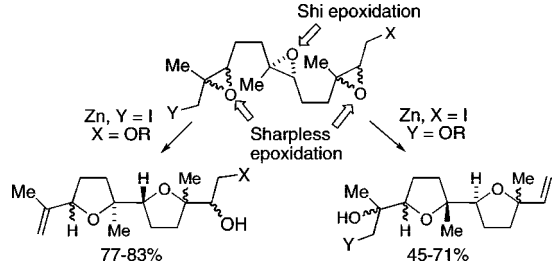
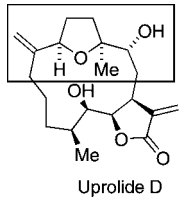
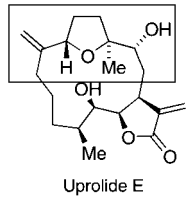


A number of isomeric bistetrahydrofuran analogues were prepared from triepoxy farnesyl bromides by a zinc-initiated reduction−elimination and in situ Lewis acid-promoted cascade cyclization.

Introduction

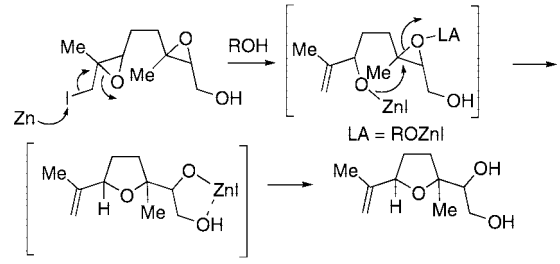
Tetrahydrofurans provide a structural motif for numerous bioactive natural products and a great deal of effort has been invested in devising methods for their synthesis.[1] Many acetogenins[2] and polyether ionophores,[3] a special subgroup of these natural products, possess connected bis- or less commonly tristetrahydrofuran moieties. The present contribution describes studies on the synthesis of bistetrahydrofurans related to ionophore-type natural products. The methodology that forms the basis of these studies was discovered in connection with experiments directed at the total synthesis of the cytotoxic marine cembranolides uprolides D and E.[4,5] In those investigations we were confronted with a need for an efficient route to tetrahydrofurans with vinyl and hydroxyethyl substituents at the 2- and 5-positions.


Uprolide D


Uprolide E

We examined a number of alternative possibilities for constructing the tetrahydrofuran ring of the foregoing natural products based upon internal epoxide cleavages. In the course of those investigations we discovered an efficient cascade sequence in which the zinc-initiated elimination of an iodomethyl epoxide generates the requisite vinyl group with formation of a Lewis-acidic iodozinc byproduct that catalyzes a subsequent internal 5-exo cyclization as depicted in Scheme 1.

SCHEME 1. Suggested Reaction Sequence for a Zinc-Initiated Iodo Epoxide Cascade Cyclization



Previous polyepoxide routes to tetrahydrofurans have typically employed acidic conditions to activate the epoxide toward internal cleavage by oxygen nucleophiles.[6] In contrast, the zinc methodology proceeds under nearly neutral conditions and produces unsymmetrical tetrahydrofurans with chemically distinct functionality at the 2- and 5-positions.

(1) For the most recent comprehensive review, see: Wolfe, J. P.; Hay, M. B. *Tetrahedron* **2007**, *63*, 261.
(2) Bermejo, A.; Figadere, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, 269.
(3) Faul, M. M.; Huff, B. E. *Chem. Rev.* **2005**, *105*, 4348.
(4) Marshall, J. A.; Chobanian, H. R. *Org. Lett.* **2003**, *5*, 1931.
(5) Rodriguez, A. D.; Soto, J. J.; Pina, I. C. *J. Nat. Prod.* **1995**, *58*, 1209.
(6) Cf. (a) Fukuyama, T.; Vranesic, B.; Negri, D. P.; Kishi, Y. *Tetrahedron Lett.* **1978**, 2741. (b) Hoye, T. R.; Ye, Z. *J. Am. Chem. Soc.* **1996**, *118*, 1801. (c) Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 9328.

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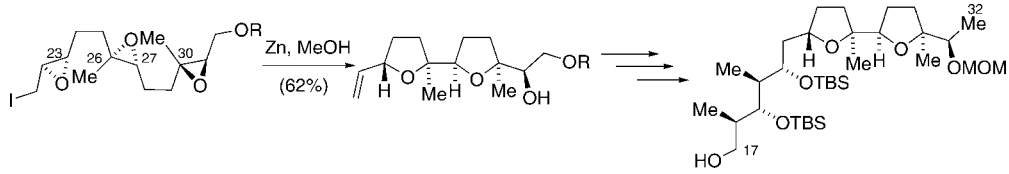
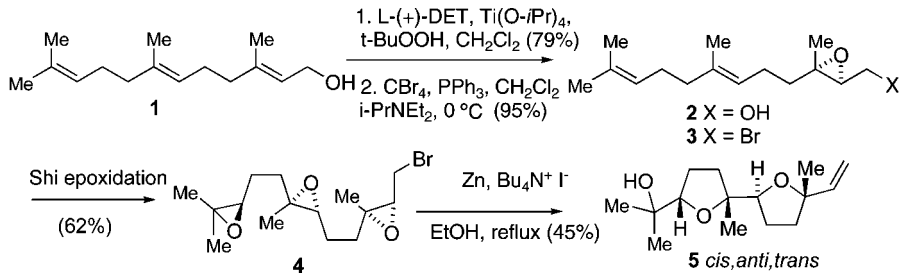
SCHEME 2. An Application of Zinc-Initiated Cascade Methodology to a Synthesis of the C17−C32 Segment of Ionomycin



SCHEME 3



We subsequently examined a single extended version of this methodology in which an iodomethyl triepoxide serves as the precursor of an adjacent bistetrahydrofuran segment of the polyether antibiotic ionomycin (Scheme 2).[7] Success with that application encouraged additional investigations to determine the potential of this novel extended sequence as a route to other bistetrahydrofurans. In the present report we describe the results of those investigations.

Results and Discussion

As a starting point for this project we selected the triepoxide **4**, which was readily prepared from farnesol (**1**) by Sharpless OH-directed asymmetric epoxidation with the ethyl L-(+)-tartrate ligand[8] and subsequent bis-Shi epoxidation[9] of the remaining two double bonds in the derived bromide **3** (Scheme 3). Purification of bromo epoxide **4** was greatly facilitated by treatment of the reaction mixture with $NaBH_4$ to reduce the Shi keto hexose catalyst to a more readily separable alcohol. Upon treatment with zinc dust and Bu_4NI in refluxing ethanol, bromo epoxide **4** was converted to the *cis*,*anti*,*trans*-bistetrahydrofuran **5** in 45% yield. Previously we found that bromo epoxides such as **4** are significantly more stable than the corresponding iodides, which tend to decompose upon storage. However, the zinc-initiated elimination reaction proceeds much more slowly with bromides than with iodides. Thus we employed a procedure for in situ conversion of the bromides to the more reactive iodides with Bu_4NI. In those earlier studies we found that DME, DMF, DMSO, MeCN, or Et_2O were ineffective as solvents for the cascade reaction. In the present investigation we confirmed that the reactions could be carried out in methanol or ethanol with comparable results, but the use of THF as a solvent or cosolvent proved unsatisfactory, resulting in low yields of impure products. Substitution of Mg for Zn resulted in recovery of the bromo epoxide **4** along with the corresponding iodide with no evidence for an elimination reaction. Treatment of the bromo epoxide **4** with TBAI and $ZnBr_2$, ZnI_2, or $MgBr_2$ in refluxing ethanol in the absence of Zn resulted in the formation of multiple decomposition products. Thus we conclude that the cascade sequence requires a special combination of reducing metal and in situ Lewis acid catalyst.

To probe potential stereochemical requirements of the reaction, we prepared the isomeric triepoxy bromide **8** from farnesol in a sequence parallel to that for **4** (Scheme 4). When subjected to the zinc-promoted cascade sequence this bromo epoxide afforded the *cis*,*anti*,*cis*-bistetrahydrofuran **9** in 63% yield. The improved yield in this cascade reaction may arise from a cis/trans preference in the initial ring formation, although we did not attempt to rigorously establish such a preference.

Our next series of experiments was conducted on the α,ω-difunctionalized farnesyl epoxide **11**. This intermediate was prepared from farnesol along the lines of McDonald and coworkers[10] by Sharpless asymmetric epoxidation followed by acetylation and Sharpless SeO_2-catalyzed allylic oxidation (Scheme 5). This latter reaction afforded a 60:40 mixture of the aforementioned primary allylic alcohol **11** and the internal secondary alcohol isomers **12**, along with small amounts of other byproducts. Separation of this mixture was facilitated by selective silylation of the primary alcohol **11** prior to chromatography and subsequent regeneration of the alcohol through treatment of the purified silyl ether **13** with TBAF. Upon Sharpless asymmetric epoxidation the allylic alcohol **11** gave the epoxide derivative **14**. This epoxy alcohol served as the starting point for a study to determine the effect of the ω-alcohol substituent on the efficiency of the cascade sequence. The first of these, the Boc ester **18**, was prepared from alcohol **14** as outlined in Scheme 5 by treatment with Boc anhydride. Shi epoxidation of the diepoxy ester **15** led to the triepoxide **16**, which was selectively cleaved to alcohol **17** and converted to the bromide **18**.[11]

For the terminal TBS ether analogue **21** (Scheme 6) we employed a double Shi epoxidation of the previously prepared dienyl epoxy acetate **13** and subsequent cleavage of the acetate **19** and bromide formation as described above. An analogous sequence of reactions was used to convert the diepoxy alcohol **14** to the DPS ether analogue **25** (Scheme 7).

(7) Marshall, J. A.; Mikowski, A. M. *Org. Lett.* **2006**, *8*, 4375.

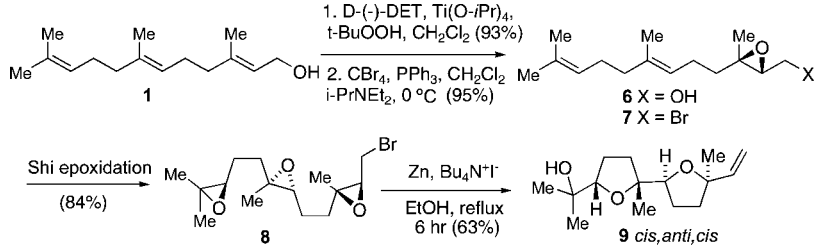
(8) (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. (b) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.

(9) (a) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (b) Tu, Y.; Frohn, M.; Wang, Z.-X.; Shi, Y. *Org. Syn.* **2003**, *80*, 1. (c) Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806.

(10) McDonald, F. E.; Bravo, F.; Wang, X.; Wei, X.; Toganoh, M.; Rodriguez, J. M.; Do, B.; Niewert, W. A.; Hardcastle, K. I. *J. Org. Chem.* **2002**, *67*, 2515.

(11) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Chem. Commun.* **1979**, 978.

SCHEME 4



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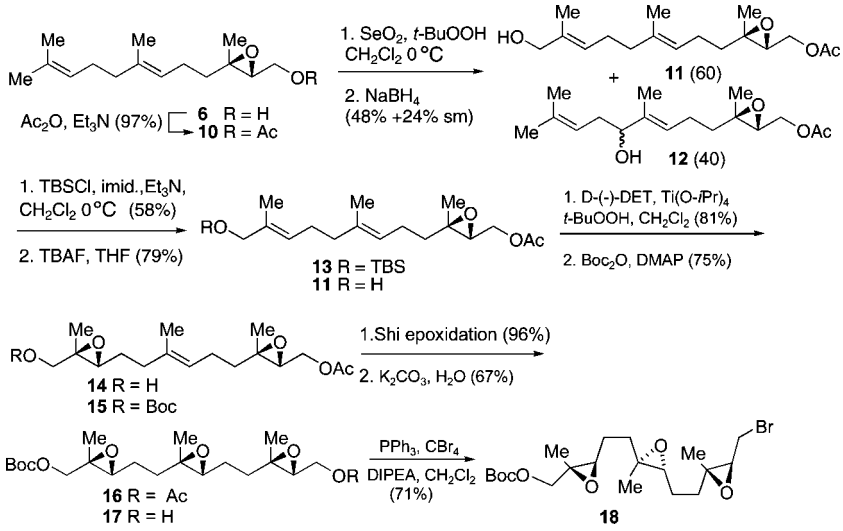

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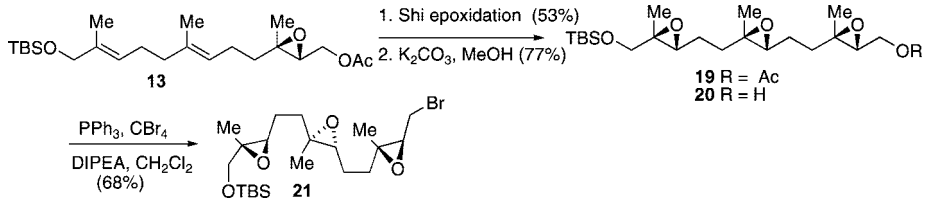


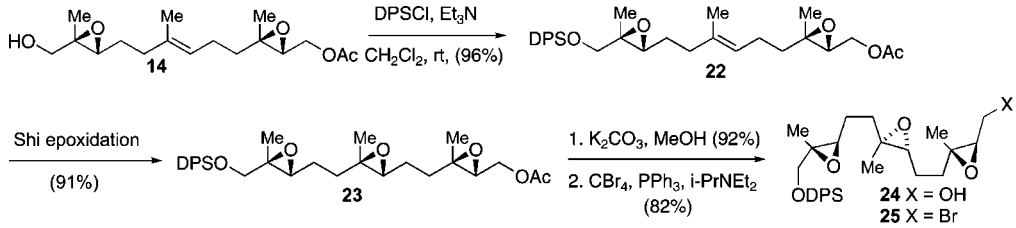
Each of the triepoxy bromide analogues **18**, **21**, and **25** was subjected to a Zn-initiated cascade cyclization to afford the corresponding, *cis*,*anti*,*cis*-bistetrahydrofurans **26**, **27**, and **28** (Scheme 8). We had expected the Boc derivative to coordinate with the halozinc Lewis acid salts formed in the initial step of the cascade thereby facilitating the second tetrahydrofuran ring formation (see Scheme 1). However, the yield of the bistetrahydrofuran product **26** was significantly lower than that of the other two analogues and an inseparable byproduct was formed. Presumably, as noted by McDonald and co-workers, the Boc grouping initiates a competing "left-to-right" cascade resulting in the formation of cyclic carbonates and related inseparable byproducts. Both silyl ethers **21** and **25** afforded the readily purified furan products **27** and **28** in satisfactory yield. Thus the cascade reaction does not appear to be appreciably facilitated by a coordinating terminal substituent.

The forgoing cascade cyclizations proceed in a "right-to-left" direction in which oxygen nucleophiles attack the secondary centers of the epoxide intermediates. In the next phase of these studies we examined a "left-to-right" cascade in which attack occurs at the tertiary centers of the two epoxide rings. The appropriate bromo substrates for these studies were prepared along the lines described above in which the Sharpless and Shi epoxidation methodology provide the requisite chiral epoxides (Scheme 9). To prepare the α,ω-difunctionalized farnesol precursor **35**, we adapted a sequence previously employed in our synthesis of the ionomycin segment (Scheme 2) starting from epoxide **29**. Conversion of alcohol **35** to the triepoxy bromide **38** then proceeded along the lines previously employed for triepoxy bromide **18**. The TBS analogue **39** was prepared analogously (Supporting Information).

By using the enantiomeric tartrate ligand for the various Sharpless epoxidation steps we also prepared the isomeric triepoxy bromides **42**/**43** and **46** (Supporting Information). Upon treatment with zinc dust and TBAI in refluxing ethanol all five of these substrates were cleanly converted to the expected bistetrahydrofurans **40**/**41**, **44**/**45**, and **47** (Scheme 10). The cyclizations were uniformly more efficient than the alternative "right-to-left" variations reflecting the more favorable disposition of the tertiary epoxide center to Lewis acid-catalyzed ring opening. It should be noted that the formation of both cis and trans 1,5-disubstituted tetrahydrofuran rings occurs with comparable efficiency in all of these cascade reactions.

The bistetrahydrofuran products of these cyclizations were produced as virtually single diastereomers in accord with the expected high enantioselectivity of the Sharpless and Shi

SCHEME 7



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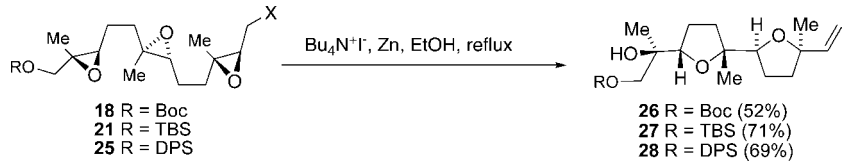
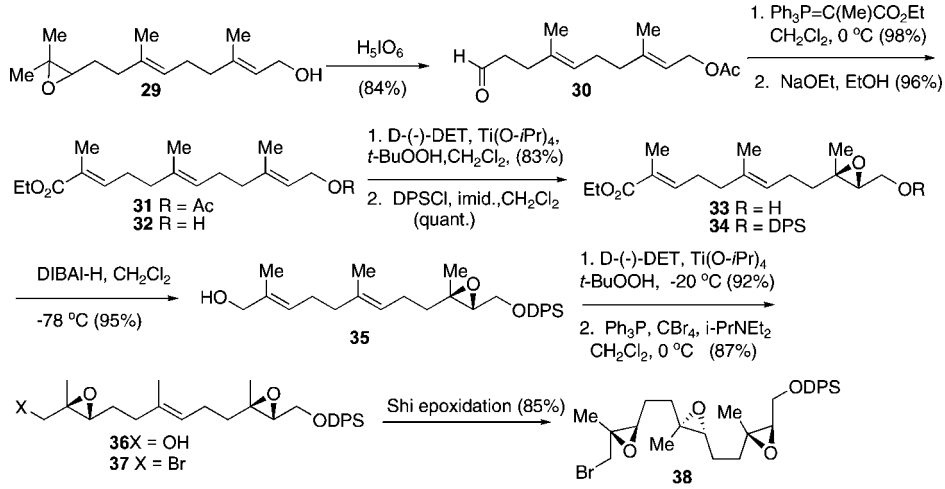


SCHEME 9



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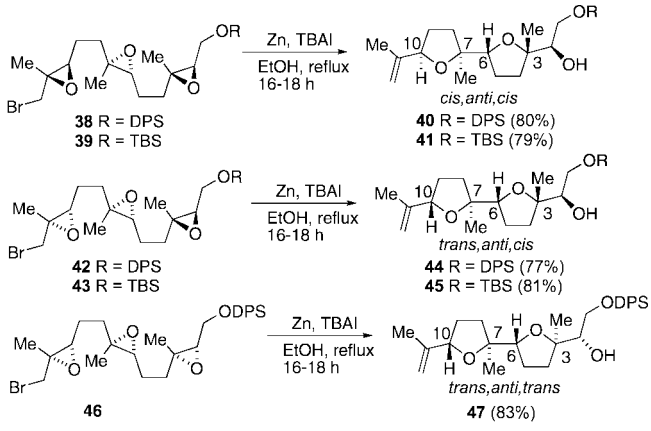

epoxidation reactions. The relative stereochemistry of the bistetrahydrofurans **40**, **44**, and **47** was confirmed by their 2D NOESY spectra (Supporting Information). All three showed cross-peaks indicative of a C6 H/C7 CH_3 interaction. The spectrum of the *cis*,*anti*,*cis* isomer **40** contained additional cross-peaks for the C3 CH_3/C6 H and C7 CH_3/C10 H substituents while the *trans*,*anti*,*cis* isomer **44** showed only one additional cross-peak for the C3 CH_3/C6 H.

The foregoing three-step cascade cyclization of farnesyl triepoxides to bistetrahydrofurans proceeds under mild, near-neutral condition with a high degree of stereocontrol. In the present study we prepared 3 of the 16 possible diasteroisomers starting from the readily available starting material *trans*,*trans*-farnesol. The remaining isomers should be available along similar lines through variations in the double bond geometry of the starting triene and the appropriate Sharpless tartrate ligand or Shi catalyst. We have shown that both 2,5-cis and -trans tetrahydrofuran rings form with nearly comparable ease but have not yet extended the methodology to syn related bistetrahydrofuran rings. A priori there is no reason to believe that such extensions would fail.

Experimental Section

(*E*,*E*,*R*,*R*)-2,3-Epoxy-3,7,11-trimethyl-6,10-dodecadien-1-ol (6). To a suspension of 4Å MS (0.57 g, 0.13 g/mmol substrate) in 39.2 mL of CH_2Cl_2 at −20 °C in a Cryobath was added D-(−)-diethyl tartrate (0.35 g, 1.72 mmol), followed by Ti(*i*-PrO)$_4$ (0.51 mL, 1.74 mmol). The mixture was stirred at −20 °C for 10 min, at which time *tert*-butyl hydroperoxide (1.1 mL, 5−6 M in decanes, ca. 6.60 mmol) was added dropwise. The mixture was stirred at −20 °C for 20 min, then a solution of *trans*,*trans*-farnesol (**1**) (1.03 g, 4.43 mmol) in 4.0 mL of CH_2Cl_2 was added dropwise over 15 min. The mixture was stirred at −20 °C for 1.5 h and then quenched with a minimal amount of water, diluted with EtOAc, warmed to rt, and filtered through Celite. The filtrate was concentrated under reduced pressure to ca. 25 mL. A solution of 30% NaOH/brine (1.9 mL) was added and the mixture was stirred vigorously for 20 min at rt.

The mixture was extracted with EtOAc. The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (gradient elution with hexanes to 20% EtOAc/hexanes) to afford epoxide **6** as a clear oil (0.98 g, 93%): $[\alpha]^{20}_D$ +5.8 (*c* 1.05, $CHCl_3$); lit.[12] $[\alpha]^{20}_D$ +6.53 (*c* 4.21, $CHCl_3$); IR (neat) ν 3425 (b), 1666, 1451, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.14−5.02 (m, 2H), 3.87−3.76 (m, 1H), 3.72−3.60 (m, 1H), 2.97 (dd, J = 4.2, 6.8 Hz, 1H), 2.12−2.01 (m, 4H), 2.00−1.92 (m, 2H), 1.74−1.61 (m, 1H), 1.66 (d, J = 1.1 Hz, 3H), 1.59 (s, 6H), 1.45 (ddd, J = 5.1, 8.8, 16.6 Hz, 1H), 1.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.0, 131.7, 124.4, 123.4, 63.3, 61.7, 61.5, 39.9, 38.7, 26.8, 25.9, 23.8, 17.9, 17.0, 16.2.

(*E*,*E*,2*S*,3*R*)-1-Bromo-2,3-epoxy-3,7,11-trimethyl-6,10-dodecadiene (7). To a magnetically stirred solution of epoxy alcohol **6** (0.52 g, 2.2 mmol) in 22 mL of CH_2Cl_2 at 0 °C was added diisopropylethylamine (2.29 mL, 13.2 mmol), PPh_3 (1.74 g, 6.6 mmol), and carbon tetrabromide (2.21 g, 6.6 mmol). The mixture was stirred overnight at 0 °C in a Cryocool bath. The reaction mixture was concentrated under reduced pressure and eluted through a short plug of silica gel. The plug was washed with 300 mL of 1:4 ethyl acetate in hexanes and the filtrate was concentrated under reduced pressure. Purification of the crude yellow syrup by flash chromatography on silica gel (gradient elution with hexanes to 2% EtOAc/hexanes) afforded bromide **7** as a clear pale-yellow oil (0.63 g, 95%): $[\alpha]^{20}_D$ −12.3 (*c* 1.70, $CHCl_3$); IR (neat) ν 1667, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.17−5.01 (m, 2H), 3.53 (dd, J = 5.9, 10.4 Hz, 1H), 3.23 (dd, J = 7.7, 10.4 Hz, 1H), 3.08 (dd, J = 5.9, 7.7 Hz, 1H), 2.17−2.01 (m, 4H), 2.01−1.93 (m, 2H), 1.78−1.68 (m, 1H), 1.67 (d, J = 1.1 Hz, 3H), 1.63−1.55 (m, 6H), 1.44 (ddd, J = 7.6, 9.0, 13.7 Hz, 1H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.1, 131.6, 124.4, 123.3, 63.3, 61.7, 39.9, 38.6, 30.0, 26.8, 25.9, 23.9, 17.9, 16.3, 16.2.

(2*S*,3*R*,6*R*,7*R*,10*R*)-1-Bromo-3,7,11-trimethyl-2,3;6,7;10,11-triepoxydodecane (8). To a magnetically stirred solution of bromide **7** (0.40 g, 1.6 mmol) in 40.7 mL of 2:1 dimethoxymethane: acetonitrile were added successively a buffer solution of $Na_2B_4O_7 \cdot 10H_2O$ (16.3 mL, 0.05 M in 0.4 mM aqueous Na_2EDTA), Bu_4NHSO_4 (57 mg, 0.17 mmol), and the D-fructose derived Shi catalyst (0.92 g, 3.6 mmol). The resulting mixture was stirred at room temperature for 5 min and then cooled to 0 °C in an ice bath. A solution of Oxone (4.59 g, 7.5 mmol) in 34.8 mL of 0.4 mM aqueous Na_2EDTA and a solution of K_2CO_3 (4.51 g, 32.6 mmol) in 34.8 mL of water were simultaneously added dropwise, using a syringe pump over 1.5 h at 0 °C. Once the two solutions were completely added, the reaction mixture was diluted with 50 mL of hexanes. The biphasic mixture was poured into a separatory funnel and NaCl was added until a slight slurry formed in the aqueous phase. The mixture was then extracted with hexanes. The combined organic phase was washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (elution gradient of hexanes to 2% EtOAc/hexanes, buffered with 0.5% Et_3N) afforded triepoxide **8** as a viscous, amber oil (0.46 g, 84%): $[\alpha]^{20}_D$ +0.3 (*c* 1.59, $CHCl_3$); IR (neat) ν 1459, 1249, 891, 651 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.54 (ddd, J = 4.9, 10.3, 14.5 Hz, 1H), 3.25 (ddd, J = 7.8, 10.4, 21.6 Hz, 1H), 3.11 (dt, J = 4.6, 5.6 Hz, 1H), 2.78 (dd, J = 4.1, 8.0 Hz, 1H), 2.70 (dd, J = 4.6, 7.6 Hz, 1H), 1.87−1.81 (m, 1H), 1.80−1.74 (m, 1H), 1.73−1.63 (m, 2H), 1.60 (ddd, J = 5.1, 7.6, 12.1 Hz, 4H), 1.33 (s, 3H), 1.30 (s, 3H), 1.28 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 64.0, 62.7, 62.5, 61.3, 60.7, 58.7, 35.4, 35.1, 29.8, 25.1, 24.8, 24.6, 18.9, 16.9, 16.4. Anal. Calcd for $C_{15}H_{25}BrO_3$: C, 54.06, H, 7.56. Found: C, 54.31; H, 7.43.

(3*S*,6*R*,7*S*,10*R*)-2,6,10-Trimethyl-3,6;7,10-diepoxy-11-dodecen-2-ol (9). Purified zinc dust[13] (158 mg, 2.42 mmol) and TBAI (133 mg, 0.35 mmol) were added to a stirring solution of bromide **8** (78 mg, 0.24 mmol) in 4.0 mL of absolute ethanol. The heterogeneous mixture was heated to reflux in an oil bath and stirred for 5.5 h. Halide exchange could be visually observed on a TLC plate under UV light. Upon reaction completion, as judged by TLC analysis, the reaction mixture was cooled to room temperature, diluted with EtOAc, and filtered through a short pad of Celite and the filtrate was concentrated under reduced pressure. The crude, yellow syrupy product mixture was dissolved in a minimal volume of CH_2Cl_2 and purified by flash chromatography on silica gel (gradient elution with hexanes to 7% EtOAc/hexanes) to afford bistetrahydrofuran **9** as a light-yellow syrup (38 mg, 63%): $[\alpha]^{20}_D$ +14.9 (*c* 1.32, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 5.90 (ddd, J = 9.4, 17.4, 27.9 Hz, 1H), 5.24−5.12 (m, 1H), 4.98 (dd, J = 1.2, 10.8 Hz, 1H), 4.08 (dd, J = 5.9, 9.4 Hz, 1H), 3.85 (dd, J = 5.3, 7.7 Hz, 1H), 2.19−2.05 (m, 2H), 2.01−1.86 (m, 3H), 1.84−1.76 (m, 1H), 1.58 (ddd, J = 3.6, 10.3, 11.6 Hz, 1H), 1.51 (ddd, J = 4.9, 8.6, 11.1 Hz, 1H), 1.31 (s, 3H), 1.24 (s, 3H), 1.15 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.7, 111.6, 85.6, 85.4, 84.3, 83.1, 71.8, 37.4, 31.4, 28.6, 27.9, 26.4, 26.2, 25.1, 24.8; HRMS (ESI, M + Na^+) calcd for $[C_{15}H_{26}O_3 + Na]^+$ 277.1780, found 277.1772.

Acknowledgment. We are indebted to Eli Lilly and Company for partial support of this investigation.

Supporting Information Available: Experimental procedures for all new compound not described in the print version and copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801188W

(12) Kigoshi, H.; Ojika, M.; Shizuri, Y.; Niwa, H.; Yamada, K. *Tetrahedron Lett.* **1982**, *23*, 5413.

(13) Zinc dust was purified by following the procedure described in the following: Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Butterworth-Heinemann Ltd: Boston, MA, 1994; p 360.