Endo-Oxacyclizations of Polyepoxides: Biomimetic Synthesis of Fused Polycyclic Ethers

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Boron trifluoride-etherate promotes the endo-selective oxacyclization of polyepoxides derived from various acyclic terpenoid polyalkenes, including geraniol, farnesol, and geranylgeraniol, providing an efficient and stereoselective synthesis of substituted oxepanes and fused polyoxepanes. The mechanism of the oxacyclization reaction probably involves intramolecular nucleophilic addition of epoxide oxygen to open another epoxide that is activated as an electrophile by the Lewis acid. These oxacyclizations proceed stereospecifically with inversion of configuration upon opening of each epoxide to provide trans-fused polycyclic products. The oxacyclization cascade is terminated by a tethered nucleophile, which may be the carbonyl oxygen of a ketone, ester, or carbonate, or a trisubstituted alkene. The best oxacyclization yields are generally observed with *tert*-butyl carbonate as the terminating nucleophile, although in some cases the oxacyclization products include formation of *tert*-butyl ethers as a minor product. The oxacyclization transformations described herein may mimic ring-forming steps in the biosynthesis of trans-syn-trans-fused polycyclic ether marine natural products.

Introduction

A variety of marine natural product structures consist of multiple cyclic ether structures.[2] Trans-syn-trans-fused polycyclic ether structures are present in a large family of dinoflagellate-derived natural products, with the simplest member of these structurally complex compounds represented by hemibrevetoxin B (**3**, Figure 1).[3,4] The production of these compounds in nature is associated with dinoflagellate blooms ("red tide" phenomenon), which can result in massive kills of fish and other marine animals in temperate waters in both the Atlantic and Pacific Oceans.[5] Human exposure to these compounds can cause symptoms ranging from diarrhea to extreme cardiovascular and neurotoxic effects at exposures as low as a few parts per billion in contaminated seawater or seafood. However, some fused polycyclic ether compounds also exhibit potent antifungal activity,[6] and the demonstrated activation of sodium ion channels by brevetoxins and the resulting increase in sodium ion transport[7] may

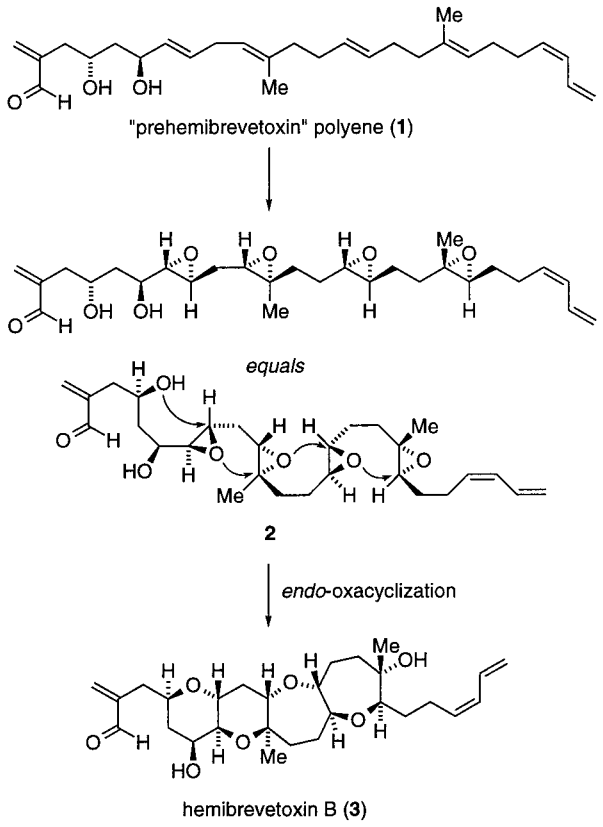

Figure 1. Proposed biosynthesis of hemibrevetoxin from an acyclic polyene.

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also have beneficial and highly potent antibiotic effects similar to those of ionophoric polyethers.

Hemibrevetoxin B (**3**) is a relatively simple member of this class of polycyclic ether natural products and has been synthesized by several laboratories, albeit with long step counts in each case (38−60 steps).[8] However, nature probably synthesizes hemibrevetoxin and structurally related natural products in a much more efficient fashion, constructing several rings and multiple stereocenters via a tandem oxacyclization transformation. In the mid-1980s, Shimizu and Nakanishi[9] independently proposed a general scheme for brevetoxin biosynthesis (Figure 1): an all *trans*-polyene precursor **1** is biosynthesized, followed by multiple enzyme-catalyzed epoxidations of the alkenes to polyepoxide **2**. While the absolute sense of epoxidation is identical for each alkene, perhaps the most interesting step is the endo-regioselective tandem oxacyclization to form the fused polycyclic ether structure **3**, a reaction that would normally proceed with exo-regioselectivity due to both kinetic and stereoelectronic factors.[10]

We plan to mimic the efficient biosynthesis of polycyclic ether natural products by a nonenzymatic strategy featuring tandem oxacyclizations from acyclic polyene precursors. The principal challenge to this strategy is achieving endo-regioselectivity in oxacyclization transformations. Cascades of exo-selective oxacyclizations of polyepoxides to afford chain polycyclic ethers are well precedented, particularly when promoted by protic acids.[11] A good nucleophile (usually an alcohol or carboxylic acid) intramolecularly adds to the nearest protonated epoxide at the proximal position to generate a new hydroxyl group upon oxacyclization (**4** to **5**, Figure 2). However, various substituent effects[12] have been employed to elicit endo-selectivity as well as the use of catalytic antibodies[13] or Co-salen catalysis.[14]

Prior to our initial communication[15] there was only one report of cascade endo-selective oxacyclization.[16] Murai demonstrated the formation of polypyrans via lanthanum triflate-promoted oxacyclizations of 1-hydroxy-4,7-di-

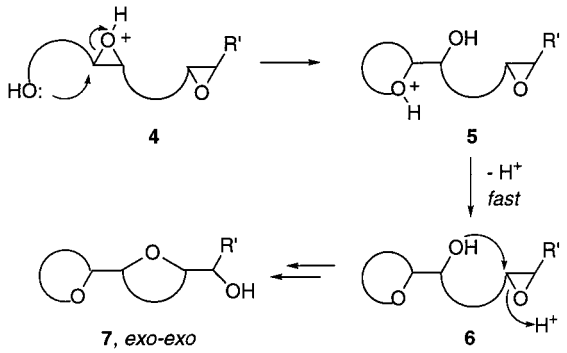

Figure 2. Tandem exo-cyclizations of polyepoxides.

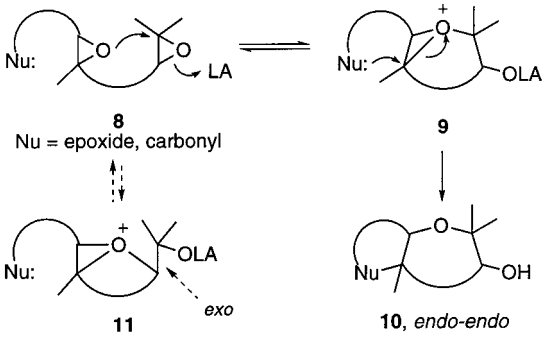

Figure 3. Tandem endo-oxacyclizations of polyepoxides.

epoxides and a 1-hydroxy-4,7,10-triepoxide substrate, but this synthesis required introduction of chelating substituents in order to provide endo-regioselectivity. Although single endo-oxacyclizations had been reported with larger ring sizes,[12j,k] the tandem oxacyclizations reported were limited to formation of six-membered rings, and the triepoxide substrate provided the tricyclic polypyran product in less than 10% yield.

Our mechanistically unique strategy for tandem, endo-selective oxacyclizations of polyepoxide substrates is to diminish the reactivity of the oxygen nucleophile, with epoxides serving as nucleophiles (at oxygen) as well as electrophiles (at carbon).[17] Thus, activation of one epoxide as an electrophile in **8** (Figure 3) is followed by nucleophilic addition of a second epoxide to form an epoxonium

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ion intermediate **9**. The reverse reaction may be facile and, thus, controlled by thermodynamic rather than exclusively kinetic factors. The attack of an external nucleophile (another epoxide or carbonyl oxygen) finally terminates the ring-forming reaction (**9** to **10**). Endo-regioselectivity might be due in part to the difference in stability between the two bicyclic oxonium ions **11** vs **9**, with the smaller ring size in **11** (from exo-cyclization) more strained than the intermediate **9** arising from initial endo-cyclization. We also anticipated that endo-selectivity might be favored in substrates bearing alkyl substitution at each site of nucleophilic attack.

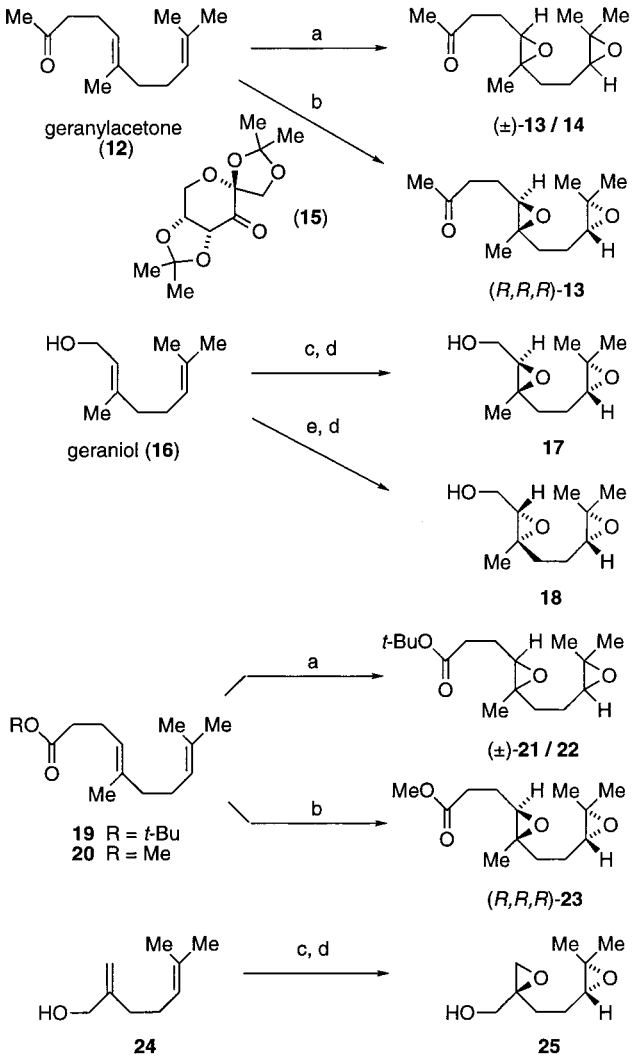
Results and Discussion

Stereoselective Synthesis and Oxacyclization Reactions of 1,5-Diepoxides: Initial Studies. Our studies began with diepoxides derived from terpene-derived 1,5-dienes, including geranylacetone and geraniol. Although peroxycarboxylic acid epoxidation of geranylacetone (**12**) provided an inseparable 1:1 mixture of diastereomeric diepoxides **13** and **14**, the Shi enantioselective double epoxidation[18] of both alkenes of geranylacetone provided an inseparable mixture of diastereomers favoring **13** in a 3.7:1 ratio in quantitative yield (Scheme 1). Enantioselective epoxidation of both alkenes of geraniol **16** was best obtained by Sharpless enantioselective epoxidation[19] of the alkene nearest the hydroxyl group (88% ee), followed by Shi epoxidation of the remaining alkene, providing a 4.6:1 mixture of diastereomers with the major diastereomer **17** produced in 98% ee as determined by HPLC analysis (Chiralpak OD-H).[20] Furthermore, a diastereomeric diepoxide **18** could be produced using the opposite catalytic tartrate enantiomer for the Sharpless epoxidation and the Shi ketone epoxidation catalyst **15**. The *tert*-butyl ester of geranylacetic acid (**19**)[21] was insoluble in the polar solvent medium required for Shi epoxidation, but the corresponding methyl ester **20**[22] could be stereoselectively epoxidized to give diepoxide **23** with high diastereo- and enantioselectivity. Diepoxide substrate **25** was prepared from sequential Sharpless and Shi epoxidations of 2-methylene-6-methyl-5-hepten-1-ol (**24**).[23]

Oxacyclization studies were first conducted with geranylacetone-derived diepoxide mixture **13/14**. A variety of Lewis acids were initially explored, including $SnCl_4$ and $Yb(OTf)_3$, which both gave complex mixtures, before we observed that reaction of **13/14** with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 promoted rapid formation of a mixture of compounds determined to be oxepanediol **26** and a diastereomer in a 1:1 inseparable mixture after aqueous workup. The corresponding reaction with the 3.7:1 mixture of diepoxides favoring **13** afforded oxepanediol **26**, which was purified after acylation of secondary alcohol to provide monoacetate **27** as a 3.7:1 inseparable mixture of diastereomers (Scheme 2). We also explored $B(C_6F_5)_3$ catalysis, which converted diepoxyketone **13** to oxepanediol **26** in a slightly better yield. Structure assignments for **26** were based on the observation that only one of the alcohols underwent acylation, as indicated by the presence of one new acetate methyl ^1H NMR resonance, as well as IR stretches in the carbonyl region. Alternative structures **28** and **29** would have been present predominantly in the cyclic hemiketal form; thus, the ketone C=O IR stretch would have been absent or relatively weak. Structure **30** with two tertiary alcohols was also excluded by the presence of the ^1H NMR doublet of doublets at 4.83 ppm, which was assigned to H-9 of structure **27**.

The primary hydroxyl group of the geraniol-derived diepoxide **17** (5.7:1 dr) was protected as acetate ester **31** and then subjected to $BF_3{\cdot}OEt_2$-promoted oxacyclization to provide the corresponding oxepane **33** in 60% isolated

Scheme 1. Stereoselective Epoxidations of 1,5-Dienes[a]



[a] Reagents and Conditions: (a) *m*-CPBA, CH_2Cl_2 (100%). (b) 0.6 equiv **15**, Oxone, MeCN/DMM/H_2O, pH 10.5, 0 °C (from **12**, 100% yield, 3.7:1 dr; from **19**, 61%). (c) 5 mol % Ti(O-*i*-Pr)$_4$, 6 mol % (−)-DET, TBHP, CH_2Cl_2, −25 °C (from **16**, 100% yield, 88% ee; from **24**, 77% yield). (d) 0.3 equiv **15**, Oxone, MeCN/DMM/H_2O, pH 10.5, 0 °C (93% yield, 4.6:1 dr **17**:**18**, 98% ee for **17**; 85% yield, 5.7:1 dr **18**:**17**, 99% ee for **18**; 85% yield of **25**). (e) 5 mol % Ti(O-*i*-Pr)$_4$, 6 mol % (+)-DET, TBHP, CH_2Cl_2, −25 °C (100% yield, 88% ee).

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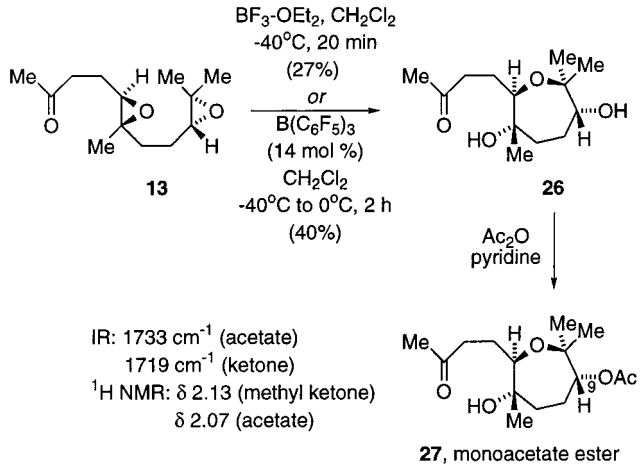
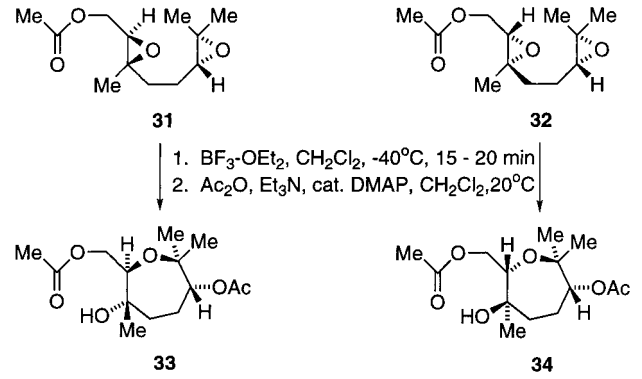
Scheme 2. Endo,Endo-Oxacyclization of Diepoxyketone 13



Scheme 3. Endo,Endo-Oxacyclization of Geraniol-Derived Diepoxides 31 and 32



yield after acylation of the crude reaction mixture, along with diastereomer **34** in 10% yield (Scheme 3). For this substrate, $B(C_6F_5)_3$-catalyzed cyclization provided only 20% yield of **33**. Unambiguous confirmation of the atom connectivity and relative stereochemistry was obtained by X-ray diffraction of a single crystal of **33**.[24] As a demonstration of the stereospecificity of the oxacyclization process, the diastereomeric diepoxide **18** (4.6:1 dr) was also acylated to **32** and cyclized with $BF_3{\cdot}OEt_2$, which after acylation of the crude reaction mixture resulted in predominant formation of oxepane **34** in 46% isolated yield and diastereomer **33** isolated in 9% yield.

We sought to determine if the carbonyl-containing side chains of substrates **13**, **31**, and **32** were serving as terminating nucleophiles, as we had originally hypothesized,[25] to provide the tertiary hydroxyls in products **26**, **33**, and **34**. Alternatively, these tertiary hydroxyls might instead have arisen from stereoselective addition of water upon aqueous quenching. However, diepoxide substrates tethered to a carbonate functional group would be expected to provide a cyclic carbonate fused to the oxepane ring if the carbonyl was terminating the tandem oxacyclization reaction. The first experiment with methyl carbonate diepoxide **35** afforded a mixture of two major products, one of which was characterized after acylation as the expected bicyclic carbonate **36** (Scheme 4). The atom connectivity and relative stereochemistry of **36** were unambiguously determined by X-ray crystallography.[26] The other product, **37**, clearly retained the acyclic methyl carbonate side chain but appeared to be a cyclic oxepane product. Exchange of the acyclic carbonate of **37** for acetate showed that the resulting compound **38** was similar to but slightly different from oxepane **33**, and the presence of covalently bound fluorine was then confirmed by ^{19}F NMR spectroscopy of **37**. However, the *tert*-butyl carbonate **39** cleanly underwent endo,endo-oxacyclization to provide bicyclic product **40** in good yield, which was converted by acylation into the identical compound **36** produced by oxacyclization of the methyl carbonate diepoxide substrate **35**. Close inspection of the byproducts arising from oxacyclization of **39** revealed the formation of the *tert*-butyl ether **41** as a minor side product, which apparently results from *tert*-butyl group transfer from the acyclic carbonate. On one occasion, a trace amount (<5%) of the fluoride corresponding to **37** was obtained from oxacyclization of *tert*-butyl carbonate diepoxide substrate **39**.

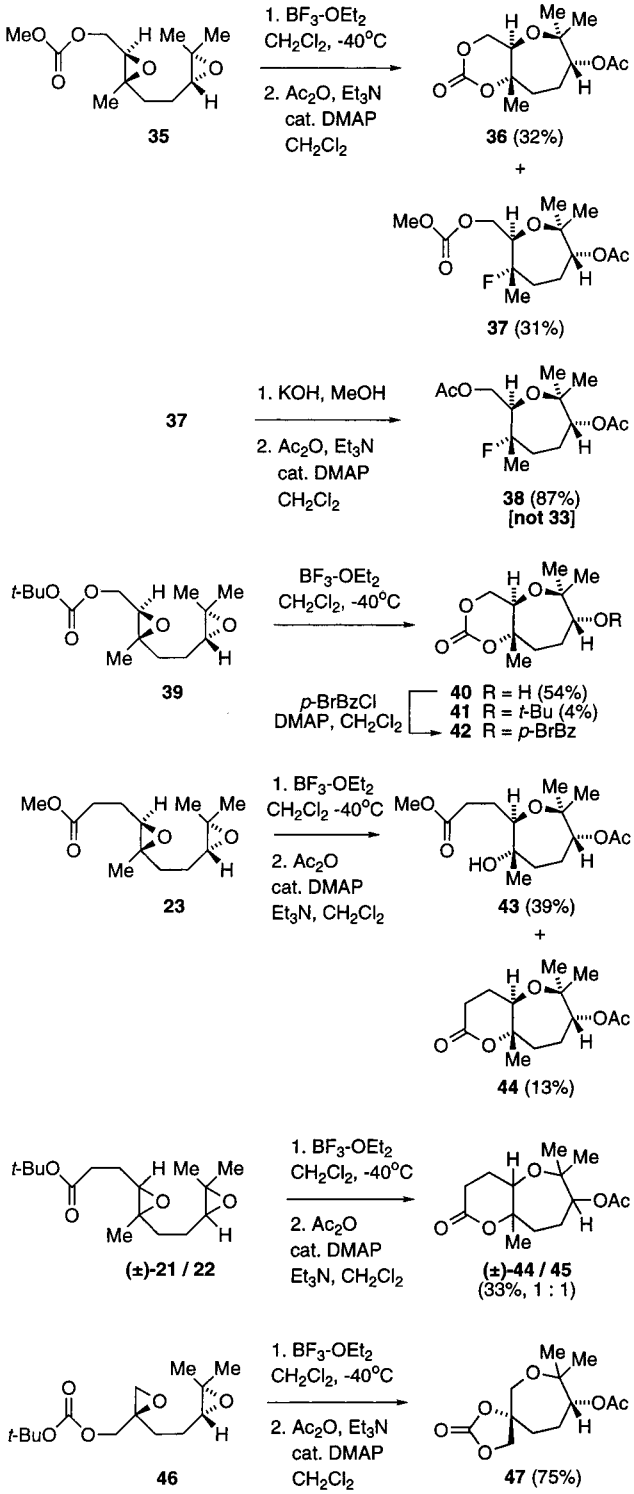
Similar oxacyclization results were observed with the geranylacetic acid-derived diepoxides. The methyl ester diepoxide **23** afforded two products after acylation, the oxepane **43** and a single isomer of the bicyclic lactone **44**. As the *tert*-butyl ester diepoxide was produced as racemic mixture of diastereomers **21/22**, oxacyclization provided the lactone **44** combined with a stereoisomeric product **45**; however, the open-chain *tert*-butyl ester−oxepane corresponding to **43** was not found. These results indicate that intramolecular oxygen participation occurs in the course of oxacyclization, although the hydrolysis product (lactone vs acyclic ester) is partially dependent on the nature of the ester substituent (*tert*-butyl vs methyl). The oxygen of the carbonyl side chain could also be positioned five atoms away from the tertiary center of the proximal epoxide, demonstrated by oxacyclization of *tert*-butyl carbonate diepoxide **46** (from **25**) to provide spirocyclic carbonate-oxepane **47** in 75% yield.

(24) Colorless crystals of **33** ($C_{14}H_{24}O_6$) were grown from slow diffusion of hexanes into a solution of **33** in CH_2Cl_2. Data collection was conducted at 298 K on a monoclinic crystal, $P2_1$; a = 6.7703(3) Å, b = 15.9227(12) Å, c = 7.3866(5) Å, β = 99.446(4)°; V = 785.49(9) Å^3; Z = 2; R_1 = 0.0358, wR_2 = 0.1129, GOF = 1.168.

(25) The participation of carbonyl oxygens in stereospecific oxacyclizations of monoepoxides tethered to ketones and carboxylic esters has been demonstrated. (a) Scheidegger, U.; Schaffner, K.; Jeger, O. *Helv. Chim. Acta* **1962**, *45*, 400. (b) Demole, E.; Wuest, H. *Helv. Chim. Acta* **1967**, *50*, 1314. (c) Wasserman, H. H.; Barber, E. H. *J. Am. Chem. Soc.* **1969**, *91*, 3674. (d) Costa, M. C.; Tavares, R.; Motherwell, W. B.; Marcelo Curto, M. J. *Tetrahedron Lett.* **1994**, *35*, 8839. (e) Boeckman, R. K.; Rico Ferreira, M.; Mitchell, L. H.; Shao, P. *J. Am. Chem. Soc.* **2002**, *124*, 190.

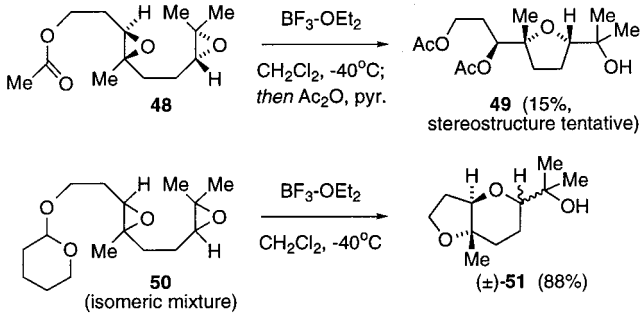
(26) Colorless crystals of **36** ($C_{13}H_{20}O_6$) were grown from slow evaporation of a solution of **36** in a mixture of hexanes and CH_2Cl_2. Data collection was conducted at 100 K on an orthorhombic crystal, $P2_12_12_1$; a = 8.0614(8) Å, b = 10.6645(11) Å, c = 16.1512(16) Å; V = 1388.5(2) Å^3; Z = 4; R_1 = 0.0419, wR_2 = 0.0929, GOF = 1.123.

Scheme 4. Demonstrated Intramolecular Participation of Carbonyl Oxygen in Endo,Endo-Oxacyclizations of Carbonate and Ester-Substituted Diepoxides



Oxacyclizations of 1,5-Diepoxide Substrates that Afford Five- and/or Six-Membered Ring Products. Several other substrates were briefly explored that demonstrated the limitations of this methodology. For instance, BF_3−etherate-promoted reaction of substrate **48** (from double Shi epoxidation of homogeraniol[27] and alcohol acylation) gave a complex mixture, with the only characterizable compound found to be the tetrahydrofuran product **49** (Scheme 5). In this case, it appears that the placement of the carbonyl oxygen of the acetate is now too distant from the tertiary center of the proximal epoxide to favor endo-regioselectivity. However, the tetrahydropyranyloxy diepoxide **50** (prepared by double *m*-CPBA epoxidation of the THP derivative of homogeraniol) afforded the bicyclic product **51**, consistent with initial endo-selective tetrahydrofuran formation followed by exo-cyclization to close the six-membered ring.

Scheme 5. Oxacyclizations of Diepoxides Derived from Homogeraniol



The effect of alkyl substituents on the epoxide moieties was also explored with 1,5-diepoxide substrates **52**,[28] **53**, **56**,[29] and **58**.[30] Although we had anticipated that oxacyclization of substrate **52** would have occurred with sequential exo- and endo-selectivity (with each nucleophilic addition occurring at the more substituted carbon of each epoxide), we instead observed formation of *meso*-tetrahydrofuran diol **54** as the major product (Scheme 6). Similar results were obtained with bis-*tert*-butyl carbonate substrate **53**. The reaction rates for these reactions (based on TLC analysis) were much slower than those for substrates previously described. Thus, it is possible that formation of products **54** and **55** resulted only upon aqueous quenching of the reaction mixture, upon either TLC analysis of an aliquot or workup of the entire reaction mixture. Indeed, compound **54** is formed in 65% isolated yield from the reaction of diepoxide **52** with aqueous perchloric acid in THF. Substrate **56** bearing one trisubstituted epoxide and one disubstituted epoxide also afforded tetrahydrofuran **57** as the major product upon BF_3-promoted reaction and acylation of free hydroxyl groups (which assisted in product characterization). Substrate **58** (two disubstituted epoxides) gave an unusual product (assigned as structure **60**), which exhibited NMR characteristics of six-membered ring formation but a mass spectrum consistent with a dimeric structure.

Tri- and Tetracyclization Reactions. We subsequently demonstrated this strategy in formation of trans-fused bisoxepane compounds from multiple oxacycliza-

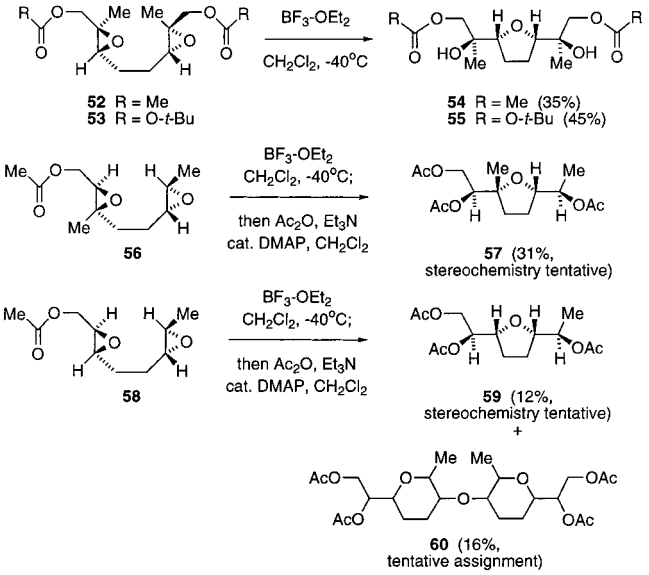
(27) Leopold, E. J. *Org. Synth.* **1985**, *64*, 164.

(28) The diepoxide diol precursor to substrates **52** and **53** is known: (a) Hoye, T. R.; Jenkins, S. A. *J. Am. Chem. Soc.* **1987**, *109*, 6196−6198. (b) Lindel, T.; Franck, B. *Tetrahedron Lett.* **1995**, *36*, 9465−9468.

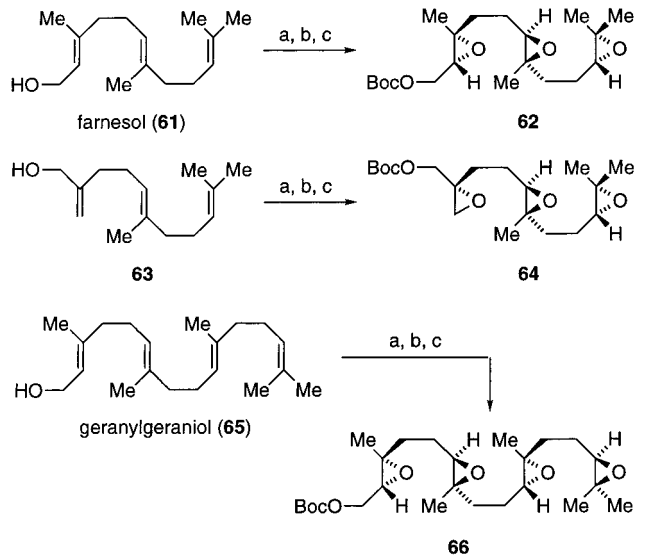
(29) Prepared from *trans*-5-hepten-2-one (Cane, D. E.; Thomas, P. J. *J. Am. Chem. Soc.* **1984**, *106*, 5295. Jung, M. E.; Angelica, S.; D'Amico, D. C. *J. Org. Chem.* **1997**, *62*, 9182) in four steps: (1) trimethyl phosphonoacetate, NaOMe, THF, reflux; (2) $LiAlH_4$, THF; (3) Shi epoxidation; (4) Ac_2O, Et_3N, catalytic DMAP, CH_2Cl_2.

(30) Prepared from *trans*-4-hexenal (Oppolzer, W.; Siles, S.; Snowden, R. L.; Bakker, B. H.; Petrzilka, M. *Tetrahedron* **1985**, *41*, 3497) in four steps: (1) (triphenylphosphoranylidene)acetaldehyde, C_6H_6, reflux; (2) $NaBH_4$, MeOH; (3) Shi epoxidation; (4) Ac_2O, Et_3N, catalytic DMAP, CH_2Cl_2.

Scheme 6. Oxacyclizations of 1,5-Diepoxide Substrates 52, 53, 56, and 58



Scheme 7. Enantioselective Epoxidations of Hydroxytrienes and Hydroxytetraenes[a]



[a] Reagents and Conditions: (a) 5 mol % Ti(O-*i*-Pr)$_4$, 6 mol % (−)-DET, TBHP, CH_2Cl_2, −25 °C. (b) 0.6 equiv **15**, Oxone, MeCN/DMM/H_2O, pH 10.5, 0 °C. (c) (*t*-BuOCO)$_2$O, Et_3N, catalytic DMAP, CH_2Cl_2 (**62**, 60%, 3 steps; **64**, 42%, 3 steps; **66**, 30%, 3 steps).

tions of tri- and tetraepoxide substrates. Given our experiences described above, we began with two 1,5,9-trienes that were appropriately substituted with alkyl substituents. Sharpless enantioselective epoxidation of the 2,3-alkene of farnesol (**61**) followed by Shi epoxidations on the remaining alkenes and derivatization of the primary alcohol provided the triepoxide **62** (Scheme 7). Similar conversions of hydroxytriene **63**[31] and geranylgeraniol **65** afforded the respective triepoxide **64** and tetraepoxide **66**. The *tert*-butyl carbonate (Boc) terminating substituent was introduced in all three substrates

(31) (a) Ogiso, A.; Kitasawa, E.; Kurabayashi, M.; Sato, A.; Takahashi, S.; Noguchi, H.; Kuwano, H.; Kobayashi, S.; Mishima, H. *Chem. Pharm. Bull.* **1978**, *26*, 7. (b) Koohang, A.; Coates, R. M.; Owen, D.; Poulter, C. D. *J. Org. Chem.* **1999**, *64*, 6.

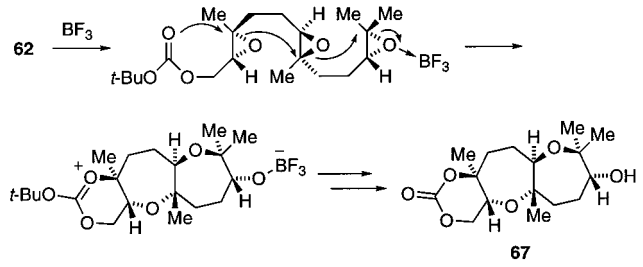
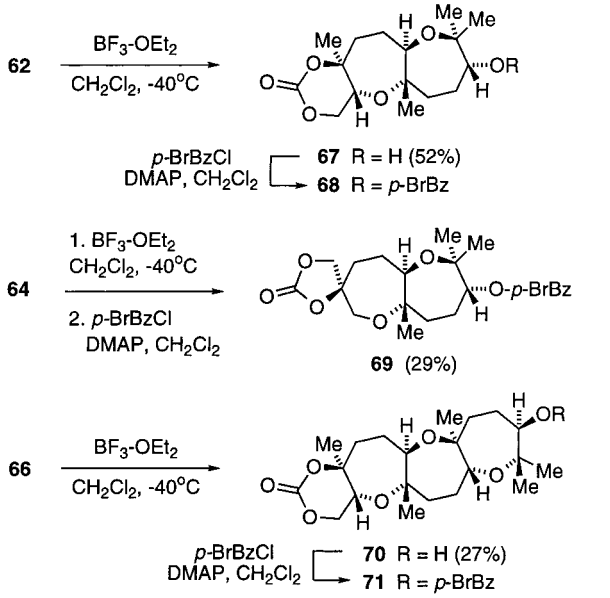


Figure 4. Mechanism 1: tandem endo,endo,endo-oxacyclization via nucleophilic addition at tertiary centers.

Scheme 8. Tandem Endo-Oxacyclizations of Tri- and Tetraepoxides



on the basis of our experience with oxacyclizations of substrates **39** and **46**.

The reaction of triepoxide substrate **62** with $BF_3{\cdot}OEt_2$ was optimized to provide the tricyclic product **67** in 52% yield,[32] which was derivatized at the secondary alcohol as a crystalline *p*-bromobenzoate (*p*-BrBz) ester **68** (Scheme 8). The atom connectivity and relative and absolute configuration of compound **68** were unambiguously determined by X-ray diffraction analysis.[33] Likewise, the triepoxide substrate **64** provided the spirocarbonate bisoxepane **69** as the major characterized product, and the tetraepoxide **66** could be effectively converted into the tetracyclic product **70**. This compound contains trans-ring fusions between the each of the three oxepane rings as well as the cyclic carbonate and adjacent oxepane, reminiscent of the trans-syn-trans stereostructure of brevetoxins and structurally related fused polycyclic ether marine natural products.

Crystals of suitable quality for X-ray diffraction analysis were obtained from compound **68**. The presence of the

(32) In the course of optimizing the oxacyclization of **62**, we searched for but have not yet found the *tert*-butyl ether byproduct corresponding to **67** with R = *tert*-butyl. In general, the material balance appears to be a mixture of several very minor products that are less polar than the polycyclic ether product. No epoxide-containing byproducts seem to be present on the basis of an absence of resonances at ca. 3.0 ppm in the crude ^{1}H NMR spectra.

(33) Colorless crystals of **68** ($C_{23}H_{29}BrO_7$) were grown from slow diffusion of hexanes into a solution of **68** in CH_2Cl_2. Data collection was conducted at 100 K on a monoclinic crystal, $P2_1$; a = 10.3128(7) Å, b = 10.7363(7) Å, c = 11.5382(8) Å, β = 94.1510(10)°; V = 1274.17(15) Å^3; Z = 2, R_1 = 0.0448, wR_2 = 0.0575, GOF = 1.082.

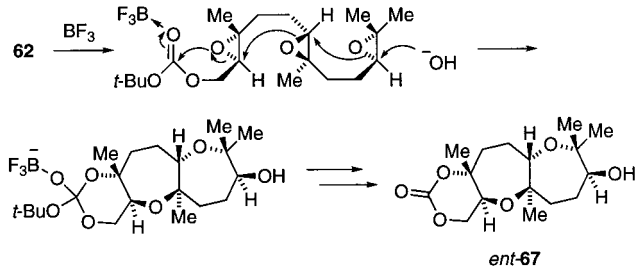


Figure 5. Mechanism 2: tandem endo,endo,endo-oxacyclization via nucleophilic addition at secondary centers.

p-bromobenzoate permitted not only determination of the atom connectivity and relative stereochemistry but also confirmation of the absolute stereochemistry for product **68**. The unambiguous assignment of the absolute stereochemistry for **68** has important mechanistic implications for the tandem oxacyclization reaction. For instance, the proposed mechanism (Figure 4) featuring BF_3 activation of the terminal epoxide, a cascade of intramolecular nucleophilic additions by the other epoxide oxygens, and termination by the carbonate oxygen nucleophile is consistent with the stereostructure determined for **68** (*p*-bromobenzoate ester of **67**).

In contrast, an alternative mechanism (Figure 5) could be considered, particularly in the case of inadvertent addition of water. This mechanism features nucleophilic addition of water or hydroxide to the less substituted carbon of the terminal epoxide, generating a tertiary alcohol that might react with the same regiochemistry at the neighboring epoxide, until the reaction is terminated by intramolecular alkoxide addition to the carbonate *carbon*. However, this alternative mechanism is conclusively disproven by the crystallographic determination of the absolute stereochemistry of **68**, rather than the enantiomer *ent*-**68** (from acylation of *ent*-**67**, mechanism 2, Figure 5).

Although the tetracyclic bromobenzoate **71** did not yield crystals suitable for X-ray diffraction analysis,[34] the structural and stereochemical assignment of **71** is based on careful comparison of the ^1H and ^{13}C NMR spectra of **71** with the bicyclic acetate **36**, the bromobenzoate analogue **42**, and tricyclic product **68**, with the assignments of **36** and **68** secured by crystallography. Coupling constants and chemical shifts are similar for hydrogen atoms located at the same relative positions in each compound, indicating similar ring conformations for compounds **36**, **42**, **68**, and **71**. Specifically, the hydrogen atoms located at the ring fusions between oxepanes in **68** and **71** exhibit similar chemical shifts and coupling constants (Figure 6). In addition, the crystal structures of bicyclic acetate **36** and tricyclic bromobenzoate **68** show that the terminal ester substituent is in a pseudoaxial position, and the hydrogen atom attached to the carbon at this terminus of each polycyclic product **36**, **42**, **68**, and **71** exhibits similar NMR chemical shifts for each compound.

We observed that Shi enantioselective epoxidation of farnesol (**61**) proceeded more rapidly with the 6,7- and

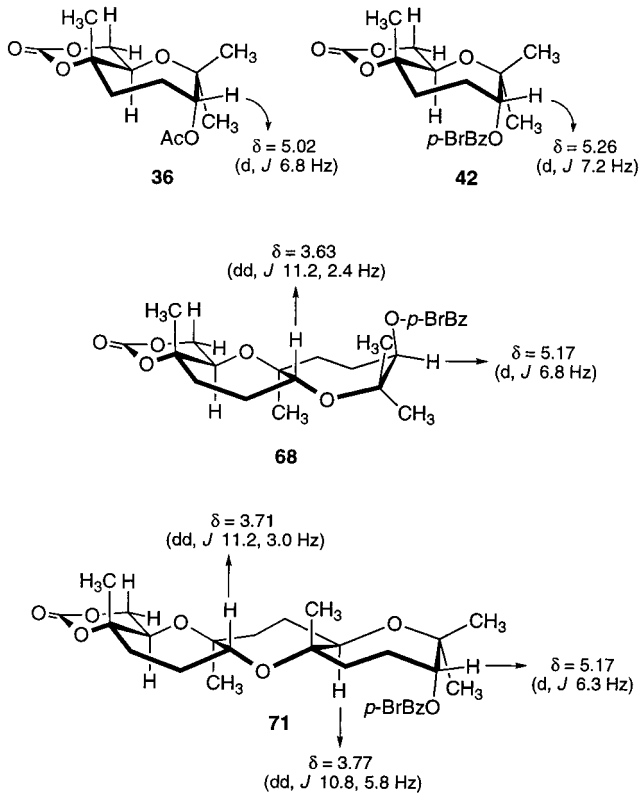
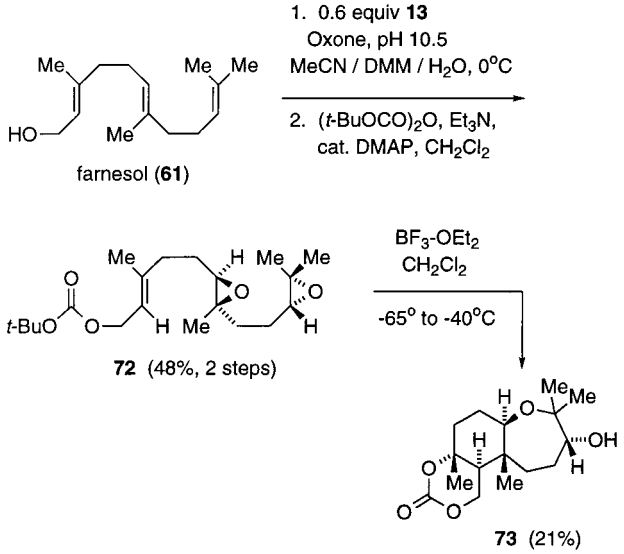


Figure 6. Key ^1H NMR assignments for compounds **36**, **42**, **68**, and **71**.

Scheme 9. Synthesis and Tandem Endo-Polycyclization of Alkene-Diepoxide 72



10,11-alkenes, thus providing easy access to the diepoxide-alkene substrate **72**. To test a hypothesis combining biomimetic alkene and epoxide cyclizations, we subjected the *tert*-butyl carbonate derivative **72** to our standard cyclization conditions to obtain a major tricyclic product. X-ray crystallographic structure determination unambiguously confirmed the atom connectivity and stereochemistry of compound **73** (Scheme 9).[35,36]

Conclusions

A biomimetic strategy has been developed to synthesize trans-fused polyoxepanes via tandem endo-regioselective

(34) After this manuscript was submitted, we obtained colorless crystals of **71** ($C_{28}H_{37}BrO_8$) from slow diffusion of heptane into a solution of **71** in CH_2Cl_2. Data collection was conducted at 100 K on an orthorhombic crystal, $P2_12_12_1$; a = 7.08380(10) Å, b = 12.1709(3) Å, c = 32.0281(7) Å; V = 2761.34(10) Å^3; Z = 4; R_1 = 0.0439, wR_2 = 0.0560, GOF = 1.011.

and trans-stereoselective oxacyclization of 1,5-, 1,5,9-, and 1,5,9,13-polyepoxides by reaction with Lewis acids. Despite some limitations with regard to substituent patterns and the nature of the nucleophilic terminating group,[37] such tandem oxacyclizations have great potential in providing efficient syntheses of structurally complex polycyclic ether natural products, particularly when one considers the ease of substrate synthesis.

Experimental Section

General. ^{1}H NMR and ^{13}C NMR spectra were recorded at either 300 MHz on a Varian Mercury-300 or 400 MHz on an Inova-400 spectrometer. NMR spectra were recorded on solutions in deuterated chloroform ($CDCl_3$), with residual chloroform (δ 7.26 ppm for ^{1}H NMR and δ 77.23 ppm for ^{13}C NMR) taken as the internal standard, and were reported in parts per million (ppm). Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. IR spectra were collected on a Mattson Genesis II FT-IR spectrometer as neat films. Mass spectra (low- and high-resolution FAB) were recorded on a VG 70-S Nier Johason Mass Spectrometer. Elemental analyses were performed by Atlantic Microlab, Inc, Norcross, GA. Analytical Thin Layer Chromatography (TLC) was performed on precoated glass-backed plates purchased from Whatman (silica gel 60 F_{254}; 0.25 mm thickness). Flash column chromatography was carried out with silica gel 60 (230−400 mesh ASTM) from EM Science.

All reactions were carried out with anhydrous solvents in oven- or flame-dried and nitrogen- or argon-charged glassware. All anhydrous solvents except as mentioned were freshly distilled. All the solvents used in workup extraction procedures and chromatography were used as received from commercial suppliers without prior purification. During reaction workup, the reaction mixture was usually diluted to three times the original volume and washed with an equal volume of water and/or aqueous solutions as needed. Purified and redistilled boron trifluoride diethyl etherate (BF_3·OEt_2) was purchased from Aldrich. All other reagents were purchased from Aldrich.

Representative Procedures for Synthesis of Polyepoxide Substrates: (*R*,*R*,*R*)-Diepoxide-acetate (31). To a 250 mL three-neck round-bottom flask were added buffer (0.05 M $Na_2B_4O_7$·$10H_2O$ in 4×10^{-4} M aqueous Na_2(EDTA), 30 mL), acetonitrile (15 mL), dimethoxymethane (30 mL), (2*R*,3*R*)-3-methyl-3-(4-methyl-3-pentenyl)oxiranemethanol ((+)-2,3-epoxygeraniol,[19] 509 mg, 2.92 mmol), tetrabutylammonium hydrogen sulfate (73 mg, 0.215 mmol), and 1,2:4,5-di-*O*-isopropylidene-D-*erythro*-2,3-hexodiuro-2,6-pyranose (Shi's catalyst, **15**,[18] 280 mg, 1.08 mmol). The reaction mixture was cooled with an ice bath. A solution of Oxone (2.55 g, 4.15 mmol) in aqueous Na_2 (EDTA) (4×10^{-4} M, 20.0 mL) and a solution of K_2CO_3 (2.49 g, 18.0 mmol) in water (20.0 mL) were added dropwise through two separate addition funnels over a period of 1.5 h. The pH value of the reaction mixture was kept between 10.3 and 10.5. At this point, the reaction was immediately quenched by addition of EtOAc and water. The mixture was extracted with EtOAc, washed with brine, and dried over $MgSO_4$. After removal of volatiles by rotary evaporation, the crude product **17** was dissolved in anhydrous CH_2Cl_2 (20 mL) and sequentially treated with DMAP (10 mg), triethylamine (2.10 mL, 15 mmol), and acetic anhydride (0.55 mL, 6.0 mmol). The reaction mixture was stirred for 1 h at room temperature and then washed with water (2×7 mL) and brine (7 mL); the organic layer was dried over $MgSO_4$ and then concentrated to give the crude acetylated product. Purification by silica gel flash chromatography (6:1 hexanes/EtOAc) provided compound **31** (630 mg, 93% yield). The enantiomeric excess was determined on the basis of the corresponding benzoate ester derived from **17** to be 98% ee by HPLC analysis. Conditions for HPLC analysis: column, Chiralpak OD(H) 0.46 cm $\phi \times$ 25 cm; eluent, 9:1 hexanes/2-propanol; flow rate, 1.0 mL/min; 254 nm; temp = 25 °C; *R*,*R*,*R*-isomer, t_R = 6.97 min; *S*,*S*,*S*-isomer, t_R = 16.0 min). IR (neat) 2964, 2930, 1744, 1378, 1235, 1037 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.31 (AB dd, J = 12.0, 4.5 Hz, 1H), 4.04 (AB dd, J = 12.0, 6.9 Hz, 1H), 3.01 (dd, J = 6.9, 4.5 Hz, 1H), 2.70 (m, 1H), 2.09 (s, 3H), 1.90−1.76 (m, 1H), 1.72−1.49 (m, 3H), 1.33 (s, 3H), 1.30 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.06, 63.83, 63.45, 60.33, 59.49, 58.68, 34.97, 25.00, 24.54, 20.99, 18.86, 17.20. Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.16; H, 8.86.

(*R*,*R*,*R*)-Diepoxide-*tert*-butyl Carbonate (39). Diepoxyalcohol **17** (135 mg, 0.725 mmol, prepared as described above) was dissolved in anhydrous CH_2Cl_2 (20 mL) and sequentially treated with DMAP (5 mg), triethylamine (0.53 mL, 3.75 mmol), and di-*tert*-butyl dicarbonate (288 mg, 1.32 mmol). The reaction mixture was stirred for 1 h at room temperature and then washed with water (2×2 mL) and brine (2 mL); the organic layer was dried over $MgSO_4$ and then concentrated to give the crude Boc-protected product. Purification by silica gel flash chromatography provided compound **39** (191 mg, 92%) as a colorless oil: IR (neat) 2977, 2932, 1744, 1459, 1373, 1279, 1257, 1164, 1095 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06−4.17 (m, 2H), 2.99 (t, J = 5.4 Hz, 1H), 2.66 (t, J = 6.0 Hz, 1H), 1.80−1.72 (m, 1H), 1.69−1.50 (m, 3H), 1.43 (s, 9H), 1.27 (s, 3H), 1.24 (s, 3H), 1.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 82.4, 65.3, 63.5, 60.0, 58.9, 58.3, 34.6, 27.6, 24.7, 24.2, 18.5, 16.8. Anal. Calcd for $C_{15}H_{26}O_5$: C, 62.91; H, 9.15. Found: C, 63.00; H, 9.19.

(*R*,*R*,*R*,*R*,*R*)-Triepoxide-*tert*-butyl Carbonate (62): IR (neat) 2971, 2932, 1743, 1460, 1279, 1164, 861 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (AB dd, J = 11.6, 5.2 Hz, 1H), 4.11 (AB dd, J = 12.0, 6.0 Hz, 1H), 3.01 (t, J = 5.6 Hz, 1H), 2.74−2.66 (m, 2H), 1.82−1.70 (m, 2H), 1.70−1.54 (m, 6H), 1.47 (s, 9H), 1.31 (s, 3H), 1.28 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.43, 82.81, 65.56, 63.97, 62.64, 60.58, 60.26, 59.21, 58.61, 35.32, 34.82, 27.88, 25.01, 24.74, 24.32, 18.82, 17.12, 16.77.

(*R*,*R*,*R*,*R*,*R*,*R*)-Tetraepoxide-*tert*-butyl Carbonate (66): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (dd, J = 12.0, 5.2 Hz, 1H), 4.11 (dd, J = 12.0, 6.0 Hz, 1H), 3.03 (t, J = 5.6 Hz, 1H), 2.74−2.64 (m, 3H), 1.80−1.50 (m, 12H), 1.47 (s, 9H), 1.30 (s, 3H), 1.28 (s, 3H), 1.24 (s, 3H), 1.24 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (100 MHz) δ 153.1, 82.6, 65.3, 63.9, 63.7, 62.5, 62.4, 60.3, 60.0, 59.0, 58.3, 35.1, 35.0, 34.6, 27.6, 24.7, 24.5, 24.3, 24.1, 18.6, 16.9, 16.5 (2C).

Representative Procedures for BF_3-Catalyzed Endo-Oxacyclizations: Oxepane-Fused Cyclic Carbonate (40), the Byproduct *tert*-Butyl Ether (41), and the Derived Acetate (36) and *p*-Bromobenzoate Esters (42). Diepoxide-*tert*-butyl carbonate **39** (248 mg, 0.87 mmol) was added to a 50 mL, oven-dried, round-bottom flask containing a magnetic stir bar, and anhydrous CH_2Cl_2 (5 mL) was added under an inert atmosphere. The solution was stirred and cooled to −40

(35) Colorless crystals of **73** ($C_{16}H_{26}O_5$) were grown from slow evaporation of a solution of **73** in CD_2Cl_2. Data collection was conducted at 100 K on an orthorhombic crystal, $P2_12_12_1$; a = 7.19550(10) Å, b = 11.12840(10) Å, c = 18.5031(2) Å; V = 1481.62(3) Å^3; Z = 4; R_1 = 0.0271, wR_2 = 0.0602, GOF = 1.006.

(36) Several natural products exhibit similar cyclohexane structures trans-fused to oxepanes, which might be derived from compound **73**: (a) Sipholenols: Carmely, S.; Kashman, Y. *J. Org. Chem.* **1983**, *48*, 3517. (b) Sodwanones: Rudi, A.; Goldberg, I.; Stein, Z.; Benayahu, Y.; Schleyer, M.; Kashman, Y. *Tetrahedron Lett.* **1993**, *34*, 3943. (c) Raspacionin: Cimino, G.; Epifanio, R.; Madaio, A.; Puliti, R.; Trivellone, E. *J. Nat. Prod.* **1993**, *56*, 1622. (d) Rudi, A.; Yosief, T.; Schleyer, M.; Kashman, Y. *Tetrahedron* **1999**, *55*, 5555. (e) Review: Fernández, J. J.; Souto, M. L.; Norte, M. *Nat. Prod. Rep.* **2000**, *17*, 235.

(37) Endo-selective polyene *carbo*cyclizations to fused polycyclohexanoid products exhibit similar substrate requirements. For recent examples, see: (a) Corey, E. J.; Luo, G. L.; Lin, L. S. *Angew. Chem., Int. Ed.* **1998**, *37*, 1126. (b) Sen, S. E.; Zhang, Y. Z.; Smith, S. M. *J. Org. Chem.* **1998**, *63*, 4459. (c) Zoretic, P. A.; Fang, H.; Ribeiro, A. A. *J. Org. Chem.* **1998**, *63*, 7213. (d) Aggarwal, V. K.; Bethel, P. A.; Giles, R. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3315. (e) Yang, D.; Ye, X.-Y.; Gu, S.; Xu, M. *J. Am. Chem. Soc.* **1999**, *121*, 5579. (f) Bender, J. A.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 7443. (g) Bogenstätter, M.; Limberg, A.; Overman, L. E.; Tomasi, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 12206. (h) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2001**, *123*, 1505. (i) Goeller, F.; Heinemann, C.; Demuth, M. *Synthesis* **2001**, 1114.

°C, and precooled $BF_3{\cdot}OEt_2$ in CH_2Cl_2 (4.5 mL of a 0.2 M solution freshly prepared from redistilled $BF_3{\cdot}OEt_2$ and anhydrous CH_2Cl_2) was added dropwise. The reaction mixture was stirred for 30 min while maintaining the temperature between −40 and −50 °C, and the reaction was then quenched with saturated aqueous $NaHCO_3$ (2 mL). The reaction mixture was allowed to warm to room temperature and washed with CH_2Cl_2 (3 × 15 mL), and the combined organic layers were dried over $MgSO_4$. The mixture was purified by silica gel flash chromatography (gradient elution from 10:1 to 1:3 hexanes/ethyl acetate), to obtain 107 mg (54%) of the alcohol **40** and a less polar fraction, which was repurified by flash chromatography (2:1 pentane/ether) to furnish the *tert*-butyl ether **41** (10 mg, 4% yield). Data for alcohol **40**: mp 151 °C dec; IR (neat) 3431 (br), 2975, 2935, 1720, 1461, 1404, 1382, 1344, 1257, 1232, 1153, 1131, 1099, 1081, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.29 (dd, J = 10.8, 6.4 Hz, 1H), 4.11 (dd, J = 10.8, 6.8 Hz, 1H), 3.93 (t, J = 10.8 Hz, 1H), 3.88 (d, J = 6.8 Hz, 1H), 2.80 (br s, 1H), 2.26 (td, J = 13.3, 2.8 Hz, 1H), 1.94−1.84 (m, 1H), 1.76−1.62 (m, 1H), 1.70 (t, J = 13.2 Hz, 1H), 1.39 (s, 3H), 1.23 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (100 MHz) δ 148.7, 84.2, 79.8, 74.5, 66.8, 64.1, 32.9, 27.8, 24.4, 22.0, 18.9. Partial data for *tert*-butyl ether byproduct **41**: IR (neat) 2977, 2937, 2874, 1759, 1463, 1404, 1381, 1366, 1349, 1289, 1253, 1225, 1209, 1190, 1152, 1130, 1102, 1072, 1020 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.22 (dd, J = 11.0, 6.8 Hz, 1H), 4.12 (t, J = 11.0, 6.8 Hz, 1H), 3.95 (t, J = 10.8 Hz, 1H), 3.56 (d, J = 7.2 Hz, 1H), 2.3 (td, J = 13.4, 3.2 Hz, 1H), 1.82−1.62 (m, 3H), 1.41 (s, 3H), 1.17 (s, 12H), 1.12 (s, 3H); ^{13}C NMR (100 MHz) δ 148.4, 83.7, 80.6, 74.7, 74.2, 66.9, 64.2, 33.3, 28.3, 28.0, 24.6, 23.4, 19.0.

In a smaller scale experiment, diepoxide-*tert*-butyl carbonate **39** (85 mg, 0.3 mmol) was cyclized to **40** by reaction with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 (1.0 mL of a 0.30 M solution) in CH_2Cl_2 (5 mL) for 20 min while maintaining the temperature between −40 and −50 °C. After aqueous extractive workup as described above and removal of volatiles by rotary evaporation, the crude product **40** was dissolved in anhydrous CH_2Cl_2 (10 mL) and sequentially treated with DMAP (1 mg), triethylamine (0.42 mL, 3 mmol), and acetic anhydride (0.11 mL, 1.2 mmol). The reaction mixture was stirred for 1 h at room temperature and then washed with water (2 × 1.5 mL) and brine (1.5 mL); the organic layer was dried over $MgSO_4$ and then concentrated to give the crude acetylated product. Purification by silica gel flash chromatography (gradient elution from 9:1 to 4:1 hexanes/EtOAc) provided compound **36** (48 mg, 60%). Data for **36**: mp 119−121 °C; $[\alpha]^{23}{}_D$ −13.28 (*c* 1.02, $CHCl_3$); IR (KBr) 3133, 2361, 2339, 1756, 1629, 1401, 1245, 1106 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.02 (d, J = 6.8 Hz, 1H), 4.19 (dd, J = 9.6, 6.0 Hz, 1H), 4.12−4.00 (m, 2H), 2.16 (s, 3H), 2.08−1.92 (m, 2H), 1.84−1.74 (m, 2H), 1.46 (d, J = 0.8 Hz, 3H), 1.21 (s, 3H), 1.18 (m, 3H); ^{13}C (100 MHz) δ 169.90, 148.08, 83.43, 79.34, 77.03, 66.87, 65.07, 34.08, 28.16, 22.34, 22.06, 21.15, 19.05. Anal. Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40. Found: C, 57.26; H, 7.40. The *p*-bromobenzoate ester **42** was prepared similarly, except that *p*-bromobenzoyl chloride was used instead of acetic anhydride. Partial data on **42**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (dt, J = 8.8, 2.0 Hz, 1H), 7.62 (dt, J = 8.8, 2.0 Hz, 1H), 5.26 (d, J = 7.2 Hz, 1H), 4.25 (dd, J = 10.2, 6.0 Hz, 1H), 4.15 (dd, J = 10.4, 6.0 Hz, 1H), 4.05 (t, J = 10.2 Hz, 1H), 2.20−1.78 (m, 4H), 1.49 (s, 3H), 1.26 (s, 3H), 1.22 (s, 3H).

Fused Bisoxepane-Cyclic Carbonate (67). Boron trifluoride dietherate (4.7 mL of an approximately 0.2 M solution in CH_2Cl_2, 0.94 mmol) was added dropwise to a cooled solution (−40 °C) of triepoxide **62** (346 mg, 0.93 mmol) in anhydrous CH_2Cl_2 (14 mL). The reaction was monitored by TLC (1:1 hexanes/ethyl acetate) and quenched after 30 min by addition of 3 mL of saturated sodium bicarbonate. After the reaction mixture was warmed to room temperature, the contents of the flask were poured into an aqueous saturated $NaHCO_3$ solution and extracted with dichloromethane. The organic layers were combined, dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. After column chromatography (gradient elution from 10:1 to 1:3 hexanes/ethyl acetate), the tricyclic alcohol product **67** was isolated (152 mg, 52% yield): IR (neat) 3449 (br), 2977, 2936, 2877, 1752, 1453, 1406, 1382, 1359, 1272, 1254, 1203, 1153, 1104, 1069, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.16−3.95 (m, 3H), 3.73 (br s, 1H), 3.63 (dd, J = 11.2, 2.4 Hz, 1H), 2.14 (br s, 1H), 2.14−1.72 (m, 6H), 1.50−1.34 (m, 2H), 1.39 (s, 3H), 1.23 (s, 3H), 1.19 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (100 MHz) δ 149.1, 83.2, 80.8, 78.1, 77.5, 75.7, 66.8, 63.4, 37.1, 34.7, 28.5, 27.9, 25.3, 22.0, 21.6, 16.1. Data for *p*-bromobenzoate ester **(68**, derived from **67)**: mp 203−205 °C; $[\alpha]^{23}{}_D$ −10.2 (*c* 0.98, $CHCl_3$); IR (KBr neat) 3130, 2985, 2359, 1750, 1724, 1271, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.4 Hz, 2H), 7.63 (d, J = 9.2 Hz, 2H), 5.17 (d, J = 6.8 Hz, 1H), 4.22−4.12 (m, 2H), 4.08−4.02 (m, 1H), 3.63 (dd, J = 11.2, 2.4 Hz, 1H), 2.25 (dq, J = 16.0, 2.8 Hz, 1H), 2.12−1.96 (m, 3H), 1.94−1.70 (m, 2H), 1.62−1.50 (m, 2H), 1.46 (s, 3H), 1.31 (s, 3H), 1.20 (s, 3H), 1.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.72, 148.82, 132.18, 130.95, 129.06, 128.64, 83.10, 80.60, 79.20, 78.66, 78.13, 66.90, 63.74, 38.14, 36.12, 28.53, 28.16, 23.18, 22.62, 21.91, 16.43.

Fused Trisoxepane-Cyclic Carbonate (70): IR (neat) 3475 (br), 2975, 2935, 2873, 1750, 1462, 1404, 1381, 1302, 1252, 1212, 1134, 1104, 1069, 992, 886, 769, 737, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.20 (dd, J = 10.4, 6.4 Hz, 1H), 4.05 (t, J = 10.4 Hz, 1H), 3.92 (dd, J = 10.4, 6.4 Hz, 1H), 3.78 (bs, 1H), 3.74 (dt, J = 11.2, 5.2 Hz, 1H), 3.61 (dd, J = 11.6, 3.2 Hz, 1H), 2.05−1.61 (m, 12H), 1.46 (s, 3H), 1.27 (s, 3H), 1.23 (s, 3H), 1.20 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (100 MHz) δ 148.3, 83.6, 81.6, 80.0, 78.4, 77.9, 76.4, 72.9, 67.0, 66.5, 40.3, 36.2, 35.4, 28.6, 27.5, 26.8, 25.6, 22.0, 20.4, 18.8, 15.8; FABMS *m*/*z* 405.4 ($M + Li^+$); HRMS (FAB) calcd for $C_{21}H_{34}O_7Li$ ($M + Li^+$) 405.2465, found 405.2485.

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Supporting Information Available: Characterization data for compounds **13**, **21**−**23**, **27**, **32**−**34**, **43**−**47**, **49**, **51**, **54**, **57**, **59**−**60**, **64**, **69**, **71**−**73**; thermal ellipsoid figures, X-ray crystallographic tables, and X-ray CIF files for compounds **33**, **36**, **68**, **71**, and **73**; and ^1H NMR spectra for compounds **40**−**42**, **54**, **62**, **64**, **66**−**73**. This material is available free of charge via the Internet at http://pubs.acs.org.

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