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# Synthesis of Oxepanes and *trans*-Fused Bisoxepanes via Biomimetic, *endo*-Regioselective Tandem Oxacyclizations of Polyepoxides

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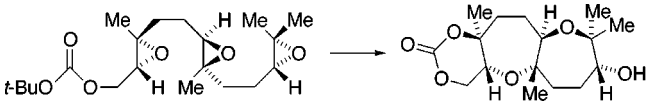
## ABSTRACT




**This communication describes the first examples of tandem *endo*-regioselective and stereospecific oxacyclizations of 1,5-diepoxides to oxepane products and a similar tandem oxacyclization of 1,5,9-triepoxides to fused bisoxepane cyclic carbonates. A mechanism for these biomimetic oxacyclizations is proposed in which the epoxides act as both electrophilic and nucleophilic reaction partners.**

Fused polycyclic ether natural products produced by marine organisms include structures such as the brevetoxins, ciguatoxin, and maitotoxin.[1] Likely pathways for polycyclic ether biosynthesis include tandem oxacyclizations of polyepoxides,[2] and the formation of adjacent chain (**1**) vs fused-ring polycyclic ethers (**2**, Figure 1) depends on the regioselectivity of nucleophilic addition to each epoxide. Although tandem *exo*-oxacyclizations of polyepoxides to form adjacent chain polycyclic ethers are well-known,[3] *endo*-regioselective oxacyclizations are less common, and the first stereospecific tandem *endo*-selective oxacyclization of a polyepoxide to fused polypyran was only recently reported.[4a] Herein we describe a strategy for tandem, *endo*-selective and stereospecific oxacyclizations of 1,5-diepoxides and 1,5,9-triepoxide substrates to form oxepane and *trans*-fused bisoxepanes in which epoxides serve as both electrophilic and nucleophilic reaction partners.[5,6]

To avoid competitive *exo*-oxacyclizations with nucleophilic hydroxyl or carboxylic acid substituents, we first prepared the 1,5-diepoxide **3** via Shi enantioselective ep-

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(1) Reviews: (a) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897. (b) Yasumoto, T.; Satake, M. *Chimia* **1998**, *52*, 63.

(2) (a) Westley, J. W.; Blount, J. F.; Evans, R. H.; Stempel, A.; Berger, J. *J. Antibiot.* **1974**, *27*, 597. (b) Cane, D. E.; Celmer, W. D.; Westley, J. W. *J. Am. Chem. Soc.* **1983**, *105*, 3594. (c) Chou, H.-N.; Shimizu, Y. *J. Am. Chem. Soc.* **1987**, *109*, 2184. (d) Lee, M. S.; Gin, G.-W.; Nakanishi, K.; Zagorski, M. G. *J. Am. Chem. Soc.* **1989**, *111*, 6234.

(3) Review: (a) Koert, U. *Synthesis* **1995**, 115. For recent examples, see: (b) Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 3448. (c) Xiong, Z.; Corey, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 4831. (d) For tandem oxacyclizations of poly(cyclic) sulfates, see: Beauchamp, T. J.; Powers, J. P.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1995**, *117*, 12873.

(4) (a) Previously reported tandem *endo*-oxacyclizations have been limited to low-yield formation of three six-membered rings from a 1,4,7-triepoxide: Tokiwano, T.; Fujiwara, K.; Murai, A. *Synlett* **2000**, 335. (b) An earlier approach from a 1,4-diepoxide proceeded via an unexpected double inversion to afford the *cis*-fused bispyran: Hayashi, N.; Fujiwara, K.; Murai, A. *Tetrahedron Lett.* **1996**, *37*, 6173.

(5) *endo*-Regioselectivity in *mono*oxacyclizations has been observed with antibody (ref 5a) or Co-salen catalysis (ref 5b), or more generally by placing cation-stabilizing or other directing substituents onto the epoxide (ref 5c−k). (a) Janda, K. D.; Shevlin, C. G.; Lerner, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 2659. (b) Wu, M. H.; Hansen, K. B.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2012. (c) Chen, R.; Rowand, D. A. *J. Am. Chem. Soc.* **1980**, *102*, 6609. (d) Cookson, R. C.; Liverton, N. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1589. (e) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5335. (f) Adiwidjaja, G.; Flörke, H.; Kirschning, A.; Schaumann, E. *Tetrahedron Lett.* **1995**, *36*, 8771. (g) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1996**, *118*, 8158. (h) Oishi, T.; Maeda, K.; Hirama, M. *J. Chem. Soc., Chem. Commun.* **1997**, 1289. (i) Neogi, P.; Doundoulakis, T.; Yazbak, A.; Sinha, S. C.; Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1998**, *120*, 11279. (j) Mukai, C.; Sugimoto, Y.; Ikeda, Y.; Hanaoka, M. *Tetrahedron* **1998**, *54*, 823. (k) Fujiwara, K.; Hayashi, N.; Tokiwano, T.; Murai, A. *Heterocycles* **1999**, *50*, 561. (l) Review of oxepane synthesis: Hoberg, J. O. *Tetrahedron* **1998**, *54*, 12631.

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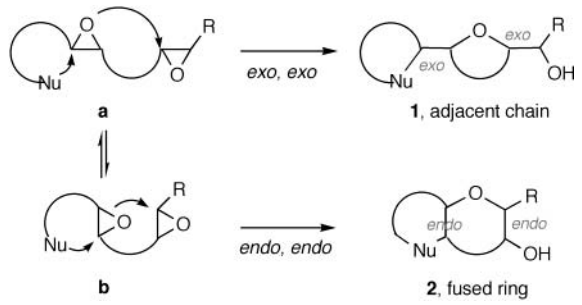
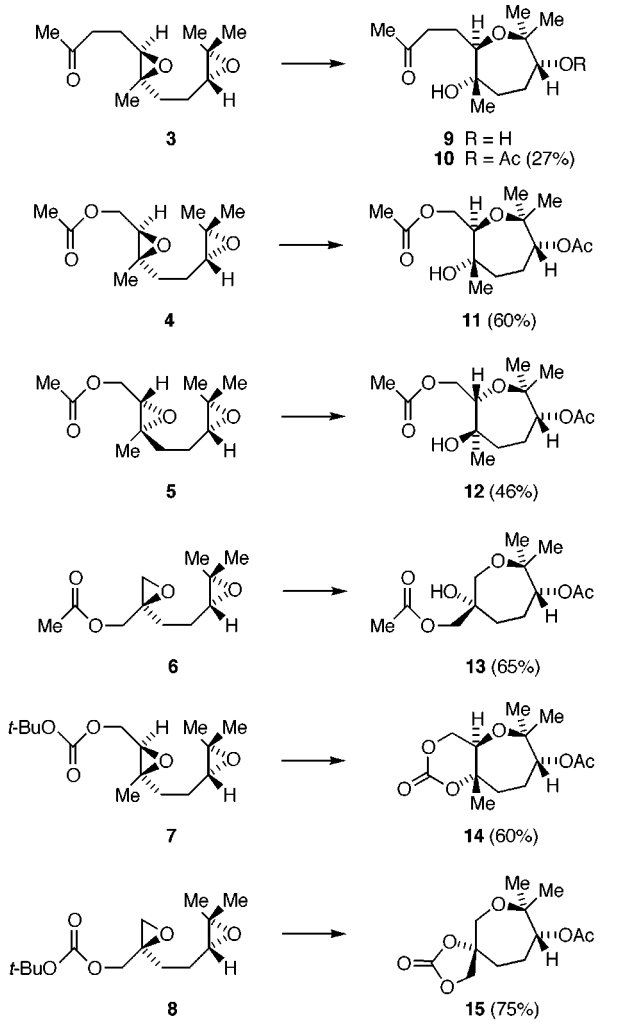



**Figure 1.** Regiochemical pathways for polycyclic ether formation.

oxidation[7] of both alkenes of commercially available geranylacetone. Upon screening several Lewis acids and reaction conditions, we found that reaction of diepoxide-ketone substrate **3** with $BF_3{\cdot}Et_2O$ in $CH_2Cl_2$ at −40 °C promoted rapid cyclization to provide oxepanediol **9** as the major cyclization product after aqueous workup (Scheme 1). This product was best purified after acetylation of the crude product mixture, which selectively derivatized the secondary alcohol to afford compound **10**. Better results were obtained with the diepoxide-acetate ester **4**,[8] which was subjected to similar reaction conditions to provide a good yield of the oxepane **11**. The regioselectivity of oxacyclization and relative stereochemistry of this product were unambiguously assigned by X-ray crystallographic analysis.[9] The stereospecificity of these oxacyclization transformations was demonstrated with the diastereomeric diepoxide-acetate substrate **5**,[8] which provided the corresponding oxepane diastereomer **12**. Diepoxide-acetate **6**[10] underwent oxacyclization in slightly better yield providing a different substituent pattern in the oxepane product **13**.

When the terminal functional group was changed from acetate to *tert*-butyl carbonate as in substrates **7** and **8**, the crude oxacyclization product mixtures were significantly cleaner and the isolated products were the fused and spiro

**Scheme 1.** *endo,endo*-Oxacyclizations of 1,5-Diepoxides




bicyclic carbonates **14**[11] and **15**, respectively. Note that the best yields were observed in cyclizations of substrates **6** and **8**, in which the carbonyl oxygen is only five atoms away from the more highly substituted carbon of the proximal epoxide.

Our working hypothesis for the mechanism of these bisepoxide oxacyclizations (Figure 2) involves Lewis acid activation of the terminal epoxide **16** (electrophile) followed by intramolecular addition of the internal epoxide (nucleophile) to give intermediate bicyclo[4.1.0]epoxonium ion **17** rather than the more highly strained [3.1.0] regioisomer **18**. The terminal carbonyl oxygen then participates in intramolecular nucleophilic addition to the more highly substituted carbon of epoxonium intermediate **17** to give **19**. Hydrolytic quench provides either the acyclic ketone **9**, esters **11** and

(6) Other examples in which epoxides have been utilized as nucleophiles in oxacyclization transformations include ref 4b and (a) David, F. *J. Org. Chem.* **1981**, *46*, 3512. (b) Tokumasu, M.; Sasaoka, A.; Takagi, R.; Hiraga, Y.; Ohtaka, K. *Chem. Commun.* **1997**, 875. (c) Alvarez, E.; Manta, E.; Martin, J. D.; Rodriguez, M. L.; Ruiz-Perez, C. *Tetrahedron Lett.* **1988**, *29*, 2093. (d) Alvarez, E.; Manta, E.; Martin, J. D.; Rodriguez, M. L.; Ruiz-Perez, C.; Zurita, D. *Tetrahedron Lett.* **1988**, *29*, 2097. (e) Alvarez, E.; Díaz, M. T.; Pérez, R.; Ravelo, J. L.; Regueiro, A.; Vera, J. A.; Zurita, D.; Martín, J. D. *J. Org. Chem.* **1994**, *59*, 2848.

(7) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224.

(8) Prepared from geraniol by a sequence of Sharpless enantioselective epoxidation of the 2,3-alkene (Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765), Shi epoxidation of the 6,7-alkene, and acetylation of the primary alcohol.

(9) Colorless crystals of **11** ($C_{14}H_{24}O_6$) were grown from slow diffusion of hexanes into a solution of **11** 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, $\beta$ = 99.446(4)°; $V$ = 785.49(9) Å$^3$; $Z$ = 2; $R_1$ = 0.0358, w$R_2$ = 0.1129, GoF 1.168.

(10) Prepared from 6-methyl-2-methylene-hept-5-en-1-ol (Takano, S.; Morimoto, M.; Satoh, S.; Ogasawara, K. *Chem. Lett.* **1984**, 1261) via sequential Sharpless enantioselective epoxidation of the 2-methylene and Shi epoxidation of the remaining 5,6-alkene followed by acetylation of the primary alcohol.

(11) Colorless crystals of **14** ($C_{13}H_{20}O_6$) were grown from slow evaporation of a solution of **14** 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, w$R_2$ = 0.0929, GoF 1.123.

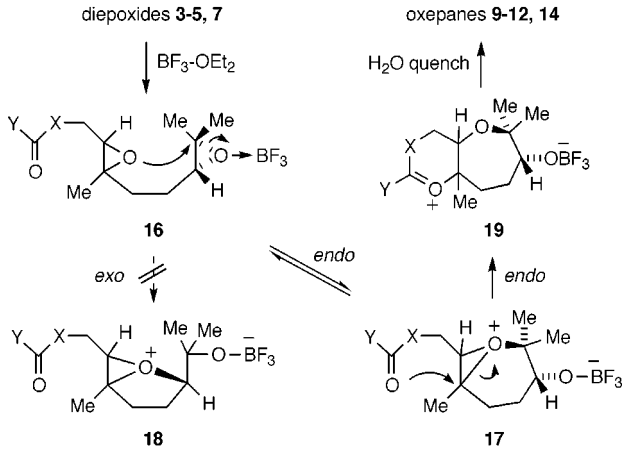
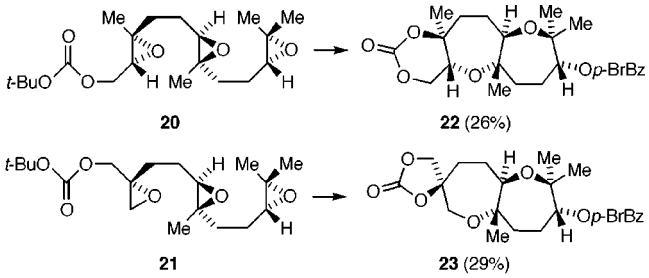



**Figure 2.** Mechanism of bisepoxide *endo,endo*-oxacyclization.

**12**, or cyclic carbonate **14**, depending on the nature of substituents X and Y.[12] Note that the mechanism indicates that the tertiary alcohols of the oxepane products **9**−**13** and the corresponding oxygen atoms of cyclic carbonates **14** and **15** originate from the carbonyl oxygen in each substrate **3**−**8**.

As a demonstration of this strategy to construct fused bisoxepane compounds, we explored tandem oxacyclization of triepoxide substrates **20**[13] and **21**[14] (Scheme 2), with the *tert*-butyl carbonate as the nucleophilic terminating functional group. Upon reaction with $BF_3{\cdot}Et_2O$, each triepoxide substrate afforded the respective tricyclic bisoxepanes **22** and **23** as the major products. X-ray crystallography[15] provided unambiguous determination of the atom connectivity of product **22** arising from triply *endo*-regioselective oxacyclization, as well as assignment of absolute and relative stereochemistry. The absolute configuration determined for

**Scheme 2.** Tandem Oxacyclization of 1,5,9-Triepoxide Carbonates **20** and **21**




Reaction conditions: 1 equiv. $BF_3$-$OEt_2$, $CH_2Cl_2$, -40°C, 20 min., $H_2O$ quench; then *p*-bromobenzoyl chloride, $Et_3N$, $CH_2Cl_2$.

**22** is also consistent with the mechanism depicted in Figure 2. Cyclization via an alternative mechanism, involving Lewis acid activation of the "left" epoxide and tandem nucleophilic addition of the "middle" and "right" epoxide oxygens at the less substituted carbon of each activated epoxonium ion, would have provided *ent*-**22**.

In conclusion, our results represent the first tandem *endo*-selective oxacyclization approach to the synthesis of oxepane and fused bisoxepane compounds from polyepoxide precursors obtained from acyclic polyenes. The nucleophilic terminating carbonyl group appears to play an essential role in the effective preference for *endo*-regioselective oxacyclizations. Preliminary experiments suggest that *endo*-regioselectivity in these biomimetic polyepoxide oxacyclizations is also dependent upon methyl or alkyl substitution at each site of nucleophilic addition, which is reminiscent of similar substituent requirements in polyene substrates for *endo*-selective, biomimetic tandem *carba*cyclizations.[16] Further studies on the scope of this methodology and applications to efficient and biomimetic syntheses of the brevetoxin family of polycyclic ether natural products are underway.

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**Supporting Information Available:** Representative experimental procedure for the tandem oxacyclization reaction; characterization data for compounds **3**−**8**, **10**−**15**, and **20**−**23**; thermal ellipsoid figures, X-ray crystallographic tables and X-ray CIF files for compounds **11**, **14**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) We have not excluded the possibility of a concerted oxacyclization process rather than the stepwise mechanism shown in Figure 2.

(13) Prepared from *E*,*E*-farnesol by a three-step sequence of Sharpless enantioselective epoxidation of the 2,3-alkene, Shi epoxidation of the remaining 6,7- and 10,11-alkenes, and *tert*-butyl carbonate derivatization of the primary alcohol.

(14) Prepared from 6,10-dimethyl-2-methyleneundeca-5,9-dien-1-ol [(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.] via sequential Sharpless enantioselective epoxidation of the 2-methylene, Shi epoxidation of the remaining 5,6- and 9,10-alkenes, and *tert*-butyl carbonate derivatization of the primary hydroxyl.

(15) Colorless crystals of **22** ($C_{23}H_{29}BrO_7$) were grown from slow diffusion of hexanes into a solution of **22** 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, $\beta = 94.1510(10)°$; $V = 1274.17(15)$ Å$^3$; $Z = 2$, $R_1 = 0.0448$, w$R_2 = 0.0575$, GoF 1.082.

(16) Reviews: (a) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, pp 341−409. (b) Abe, I.; Rohmer, M.; Prestwich, G. D. *Chem. Rev.* **1993**, *93*, 2189. For recent examples, see: (c) Johnson, W. S.; Plummer, M. S.; Reddy, S. P.; Bartlett, W. R. *J. Am. Chem. Soc.* **1993**, *115*, 515. (d) Corey, E. J.; Luo, G.; Lin, L. S. *J. Am. Chem. Soc.* **1997**, *119*, 9927. (e) Heinemann, C.; Demuth, M. *J. Am. Chem. Soc.* **1999**, *121*, 4894. (f) Ishihara, K.; Nakamura, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1999**, *121*, 4906. (g) Bogenstätter, M.; Limberg, A.; Overman, L. E.; Tomasi, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 12206.