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Biomimetic Synthesis of Fused Polypyrans: Oxacyclization Stereo- and Regioselectivity Is a Function of the Nucleophile†

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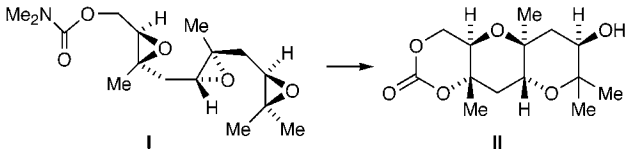
ABSTRACT



The stereoselectivity of Lewis acid-induced *endo*-regioselective oxacyclizations of 1,4-diepoxides is dependent upon the nature of the terminating nucleophile. For instance, the *tert*-butyl carbonate-substituted diepoxide of 3,6-dimethylhepta-2,5-dien-1-ol provides a *cis*-fused bicyclic product, whereas the *N*,*N*-dimethylcarbamate derivative affords the *trans*-fused diastereomer. Stereospecific and regioselective conversion of the tertiary carbamate-terminated 1,4,7-triepoxide (I) to tricyclic all-*trans*-fused polypyran (II) is also demonstrated.

The red tide phenomenon has been intensively studied by the scientific community due to its economic, environmental, and health impacts. Red tide contamination occurs in warm waters of the Atlantic Ocean and is associated with the production of a family of fused polycyclic ether natural products from the reddish blooms of marine dinoflagellates.[1] A similar phenomenon, ciguatera, is observed in waters of the Pacific Ocean. Representative fused polycyclic ether toxins include the brevetoxins, ciguatoxin, gambierol, yessotoxin, and maitotoxin.

The challenges presented by the molecular complexity of these fused polycyclic ether natural products have encouraged numerous groups to explore their chemical synthesis. These syntheses have generally been based on sequential formation of each oxacyclic ring,[2−6] whereas the biosynthesis may involve stereoselective polyepoxidation of an acyclic polyene with formation of the fused polycyclic ether skeleton in a single step via a cascade of *endo*-regioselective oxacyclizations (Figure 1).[7] We previously reported the stereoselective

† Dedicated to Prof. Fredric M. Menger on the occasion of his 65th birthday.

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(1) (a) Shimizu, Y. In *Marine Natural Products*; Scheuer; P. J., Ed.; Academic Press: New York, 1978; Vol. 1, Chapter 1. (b) Tayler, D. L.; Seliger; H. H. In *Toxic Dinoflagellate Blooms*; Elsevier/North-Holland, New York, 1979. (c) Baden, D. G.; Bikkazi, G.; Decker, S. J.; Foldes, F. F.; Leung, I. *Toxicon* **1984**, *22*, 75. (d) Scheuer, P. J. *Tetrahedron* **1994**, *50*, 3. (e) Lewis, R. J. *Toxicon* **2001**, *39*, 97.

(2) Total syntheses of hemibrevetoxin B: (a) Nicolaou, K. C.; Raja Reddy, K.; Skokotas, G.; Sato, F.; Xiao, X.-Y.; Hwang, C.-K. *J. Am. Chem. Soc.* **1993**, *115*, 3558. (b) Kadota, I.; Jung-Youl, P.; Koumura, N.; Pollaud, G.; Matsukawa, Y.; Yamamoto, Y. *Tetrahedron Lett.* **1995**, *36*, 5777. (c) Morimoto, M.; Matsukura, H.; Nakata, T. *Tetrahedron Lett.* **1996**, *37*, 6365. (d) Mori, Y.; Yaegashi, K.; Furukawa, H. *J. Am. Chem. Soc.* **1997**, *119*, 4557. (e) Kadota, I.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 6597. (f) Rainier, J. D.; Allwein, S. P.; Cox, J. M. *J. Org. Chem.* **2001**, *66*, 1380.

(3) Total synthesis of brevetoxin B: (a) Nicolaou, K. C.; Theodorakis, E. A.; Rutjes, F. P. J. T.; Tiebes, J.; Sato, M.; Untersteller, E.; Xiao,X.-Y. *J. Am. Chem. Soc.* **1995**, *117*, 1171. (b) Nicolaou, K. C.; Rutjes, F. P. J. T.; Theodorakis, E. A.; Tiebes, J.; Sato, M.; Untersteller, E. *J. Am. Chem. Soc.* **1995**, *117*, 1173. (c) Nicolaou, K. C.; Hwang, C.-K.; Duggan, M. E.; Nugiel, D. A.; Abe, Y.; Reddy, K. B.; DeFrees, S. A.; Reddy, D. R.; Awartani, R. A.; Conley, S. R.; Rutjes, F. P. J. T.; Theodorakis, E. A. *J. Am. Chem. Soc.* **1995**, *117*, 10227. (d) Nicolaou, K. C.; Theodorakis, E. A.; Rutjes, F. P. J. T.; Sato, M.; Tiebes, J.; Xiao, X.-Y.; Hwang, C.-K.; Duggan, M. E.; Yang, Z.; Couladouros, E. A.; Sato, F.; Shin, J.; He, H.-M.; Bleckman, T. *J. Am. Chem. Soc.* **1995**, *117*, 10239. (e) Nicolaou, K. C.; Rutjes, F. P. J. T.; Theodorakis, E. A.; Tiebes, J.; Sato, M.; Untersteller, E. *J. Am. Chem. Soc.* **1995**, *117*, 10252.

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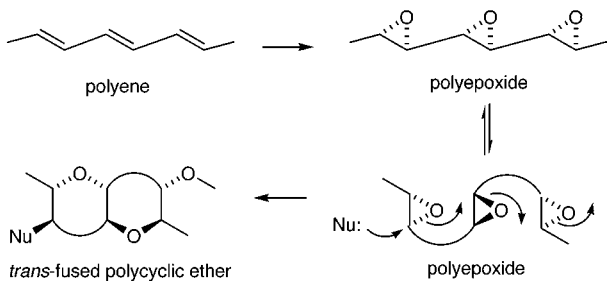
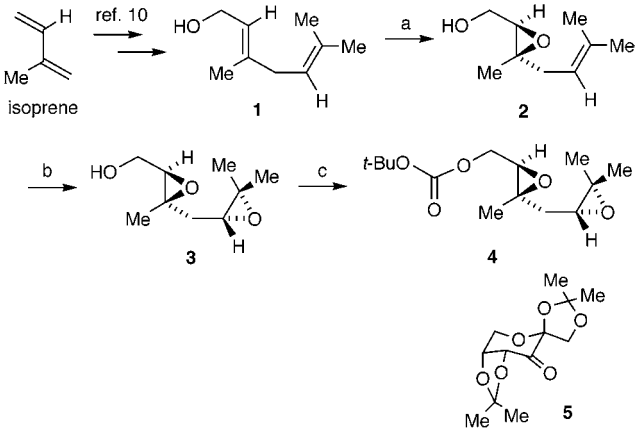


Figure 1. Biosynthesis hypothesis for fused polycyclic ether natural products.

construction of *trans*-fused seven-membered cyclic ethers (polyoxepanes) by Lewis acid activation of 1,5,...-polyepoxides derived from the acyclic isoprenoid polyenes geraniol, farnesol, and geranylgeraniol.[8] In the course of extending this strategy to the synthesis of six-membered cyclic ethers (polypyrans) from the corresponding 1,4- and 1,4,7-polyepoxides,[9] we have uncovered novel aspects of the mechanism of polyepoxide oxacyclizations with critical implications for the stereo- and regioselectivity of the oxacyclization process.

Our studies began with synthesis of the 1,4-diepoxide precursor from the known dienyl alcohol **1** (Scheme 1), obtained from isoprene in three steps.[10,11] The alkenes were

Scheme 1. Stereoselective Synthesis of Diepoxide- *tert*-Butyl Carbonate (**4**)[a]



[a] Key: (a) D-(−)-DIPT, Ti(O-*i*-Pr)$_4$, *t*-BuOOH, CH_2Cl_2, −18 °C (100%); (b) **5**, Oxone, dimethoxymethane/CH_3CN/H_2O, pH = 11.4, 0 °C (70%; dr 85:15); (c) $(Boc)_2O$, N^3-Me-imidazole, toluene, 0 °C to rt (91%).

sequentially epoxidized, first with hydroxyl-directed Sharpless asymmetric epoxidation to **2**,[12,13] followed by the asymmetric epoxidation method developed by Shi for isolated alkenes.[14] As we had earlier observed that a carbonyl group was required as a terminating nucleophile in tandem *endo*-selective oxacyclizations,[8] the primary alcohol of the resulting 1,4-diepoxide **3** was derivatized as the *tert*-butyl carbonate[15] to provide the substrate **4** in 64% overall yield (three steps).

Reaction of the diepoxide *tert*-butyl carbonate **4** with 1 equiv of BF_3•OEt_2 at −40 °C gave only a trace amount of the desired *trans*-fused product **10**, with the *cis*-fused diastereomer **11** as the major product, along with the *tert*-butyl ether (**12**, also *cis*-fused) as a minor product (Table 1, entry 1). The production of *tert*-butyl ether byproduct **12** was diminished by conducting the reaction in refluxing CH_2Cl_2 at relatively dilute concentration (0.05 M, entry 2). Crystallographic analysis of **11**[16] revealed *cis*-ring fusion of the cyclic carbonate−pyran products, resulting from apparent retention of configuration at the carbon undergoing nucleophilic addition of the carbonyl oxygen, rather than the expected *trans*-fused product **10** from inversion of configuration.[17]

(4) Total synthesis of brevetoxin A: (a) Nicolaou, K. C.; Bunnage, M. E.; McGarry, D. G.; Shi, S.; Somers, P. K.; Wallace, P. A.; Chu, X.-J.; Agrios, K. A.; Gunzner, J. L.; Yang, Z. *Chem. Eur. J.* **1999**, 5, 599. (b) Nicolaou, K. C.; Wallace, P. A.; Shi, S.; Ouellette, M. A.; Bunnage, M. E.; Gunzner, J. L.; Agrios, K. A.; Shi, G.-Q.; Gartner, P.; Yang, Z. *Chem. Eur. J.* **1999**, 5, 618. (c) Nicolaou, K. C.; Shi, G.-Q.; Gunzner, J. L.; Gartner, P.; Wallace, P. A.; Ouellette, M. A.; Shi, S.; Bunnage, M. E.; Agrios, K. A.; Veale, C. A.; Hwang, C.-K.; Hutchinson, J.; Prasad, C. V. C.; Ogilvie, W. W.; Yang, Z. *Chem. Eur. J.* **1999**, 5, 628. (d) Nicolaou, K. C.; Gunzner, J. L.; Shi, G.-Q.; Agrios, K. A.; Gartner, P.; Yang, Z. *Chem. Eur. J.* **1999**, 5, 646.

(5) Total synthesis of ciguatoxin CTX 3C: Hirama, M.; Oishi, T.; Uehara, H.; Inoue, M.; Maruyama, M.; Oguri, H.; Satake, M. *Science* **2001**, *294*, 1904.

(6) Total synthesis of gambierol: (a) Fuwa, H.; Sasaki, M.; Satake, M.; Tachibana, K. *Org. Lett.* **2002**, *4*, 2981. (b) Fuwa, H.; Kainuma, N.; Tachibana, K.; Sasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14983. (c) Kadota, I.; Takamura, H.; Sato, K.; Ohno, A.; Matsuda, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 46.

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(8) (a) McDonald, F. E.; Wang, X.; Do, B.; Hardcastle, K. I. *Org. Lett.* **2000**, *2*, 2917. (b) McDonald, F. E.; Bravo, F.; Wang, X.; Wei, X.; Toganoh, M.; Rodríguez, J. R.; Do, B.; Neiwert, W. A.; Hardcastle, K. I. *J. Org. Chem.* **2002**, *67*, 2515.

(9) Shortly before our first work in this area was submitted for publication (ref 8a), Tokiwano et al. reported the La(OTf)$_3$-promoted *endo*-selective oxacyclization to *trans-syn-trans*-fused bis- and tristetrahydropyrans. However, regioselective oxacyclization requires the presence of chelating alkoxymethyl substituents at each epoxide, which adds an undesirable degree of complexity to substrate synthesis as well as product structures, which are also produced in yields lower than those generally reported by our strategy. See: Tokiwano, T.; Fujiwara, K.; Murai, A. *Synlett* **2000**, 335.

(10) (a) Preparation of 4-chloro-3-methyl-(*E*)-propen-1-ol in three steps: Lambertin, F.; Wende, M.; Quirin, M. J.; Taran, M.; Delmond, B. *Eur. J. Org. Chem.* **1999**, *1489*, 9. (b) Preparation of (3*E*)-3,6-dimethyl-2,5-heptadien-1-ol (**1**): Mori, K.; Okada, K. *Tetrahedron* **1985**, *41*, 557.

(11) A minor modification was introduced from the procedure described in ref 10a: the reaction of isoprene with *tert*-butyl hypochlorite in acetic acid at −10 °C gave directly the 1,4 addition of chlorine and acetate in 99:1 *E*/*Z* ratio (GC/MS).

(12) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

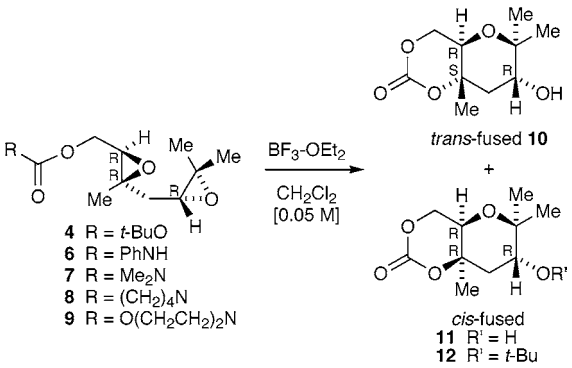
(13) The enantioselectivity was determined to be 95:5 er for the benzoate derivative of **2** by HPLC analysis. See the Supporting Information for details.

(14) (a) Wang, Z.; Tu, Y.; Frohn, M.; Zhang, J.; Shi, Y. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (b) Cao, G.-A.; Wang, Z.-X.; Tu, Y.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 4425. (c) Zhu, Y.; Tu, Y.; Tu, H.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 7819. (d) Shi, Y.; Wang, Z.-X. *J. Org. Chem.* **1998**, *63*, 3099.

(15) Basel, Y.;Hassner, A. *J. Org. Chem.* **2000**, *65*, 6368.

(16) See the Supporting Information for essential data and thermal ellipsoid diagrams for compounds **10**−**12** and **18**. The detailed crystallographic data can be obtained from the Cambridge Crystallographic Data Center (CCDC) free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html. Compound **10**: CCDC 202087. Compound **11**: CCDC 202085. Compound **12**: CCDC 202086. Compound **18**: CCDC 202088.

Table 1. Oxacyclizations of 1,4-Diepoxide Substrates

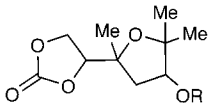


entry	substrate[a]	*T* (°C)	time (min)	products (isolated yield)
1	**4**	−40	10	**10** (<4%), **11** (56%), **12** (12%)
2	**4**	+40	2	**11** (65%), **12** (4%)
3	**4** (0.5 M)	−40	10	**11** (42%), **12** (10%)
4	**6**	−40	10[b]	**11** (70%)
5	**7**	−40	10[b]	**10** (35%), **11** (10%)
6	**7**	+20	2[b]	**10** (55%), **11** (21%)
7	**8**	−40	10[b]	**10** (32%), **11** (8.5%)
8	**9**	−40	10[b]	**10** (34%), **11** (13%)

[a] Concentration was 0.05 M of substrate in CH_2Cl_2, unless otherwise stated. [b] The reaction mixture was subsequently stirred with aq $NaHCO_3$ for 2 h to hydrolyze iminium ions.

Under the assumption that the *cis*-fused product **11** was formed via the intermediacy of a carbocation intermediate (resulting in retention of configuration at the site of carbonyl oxygen addition), we considered that increasing the nucleophilicity of the terminating carbonyl might favor inversion of stereoselectivity. With this aim, other derivatives were tested, including carbamates **6** and **7**.[18] Although the *N*-phenylcarbamate **6** also provided the *cis*-fused product **11** (Table 1, entry 4) after hydrolysis of the initial iminocarbonate, the *N*,*N*-dimethylcarbamate **7** afforded the *trans*-fused bicyclic product **10** as the major product (entry 5). X-ray crystallography analysis of **10**[16] confirmed the structural and stereochemical assignment, consistent with stereochemistry inversion occurring at the site of carbonyl oxygen addition. The reaction was optimized to furnish a 55% yield of **10** when conducted at room temperature[19] (entry 6), with an additional 21% yield of the *cis*-fused byproduct **11**. Similar results were obtained with the *N*-pyrrolidinocarbamate **8** and *N*-morpholinocarbamate derivatives **9** (entries 7 and 8).

(17) Minor byproducts obtained from cyclization of **4** included a regioisomeric five-membered cyclic carbonate **i** attached to a tetrahydrofuranol ring (4% isolated yield for Table 1, entry 1). At higher concentration (Table 1, entry 3), byproduct **i** was isolated in 6% yield along with the corresponding *tert*-butyl ether **ii** (7% yield). Minor traces (<5%) of byproduct **i** were observed by ^{1}H NMR from cyclization of **7**.



(18) Compound **6** was prepared by reaction of diepoxyalcohol **3** with phenyl isocyanate and Et_3N in CH_2Cl_2. Compounds **7**−**9** were prepared by reacting a THF solution of **3** with either *n*-BuLi (for **7**) or NaH (for **8** and **9**) and the corresponding carbamoyl chloride.

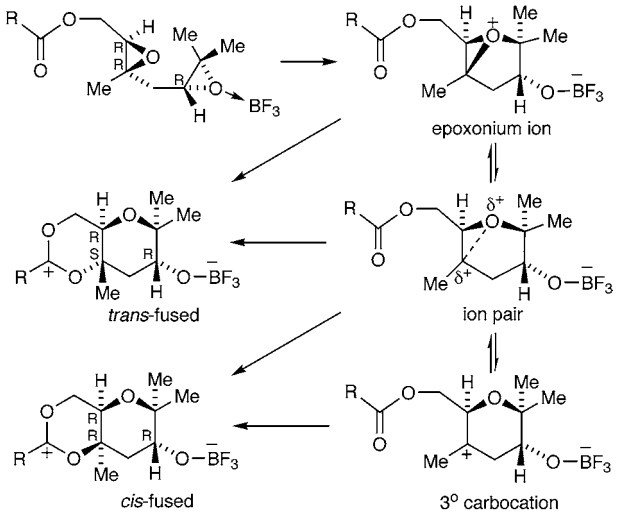


Figure 2. Possible mechanism for oxacyclization process.

The dependence of ring fusion stereochemistry on the nature of the nucleophile (*tert*-butyl carbonate gives *cis*-fusion, *N*,*N*-dimethyl carbamate gives *trans*-fusion) may be explained by the mechanism of Figure 2, in which the nucleophile intercepts at different points in the continuum between epoxonium ion at one extreme and tertiary carbocation at the other. We propose that *cis*-fused products arise from nucleophilic addition in the continuum closer to the tertiary carbocation, whereas the *trans*-fused products are favored with a better nucleophile, i.e., the tertiary carbamate, which intercepts a tight ion-pair intermediate[20] nearer in structure to the epoxonium ion.

With these results in hand, we explored the formation of the fused tricyclic product from the corresponding 1,4,7-triepoxide. The synthesis of the triepoxide precursors was initiated from epoxide **2** (see Scheme 1), which after protection of the alcohol was subjected to regioselective allylic oxidation to provide **13** (Scheme 2).[21] Sharpless asymmetric epoxidation and conversion of the hydroxyl to the bromide **14** was followed by substitution with 1-lithio-2-methyl-1-propene[22] and desilylation to afford diepoxy alcohol **15** in good yield. This compound was converted into the triepoxide substrates **16** and **17** by a sequence involving protection of the hydroxyl group and Shi epoxidation of the remaining alkene.

As expected from the earlier results with diepoxide cyclizations, the BF_3·OEt_2-promoted oxacyclization of the

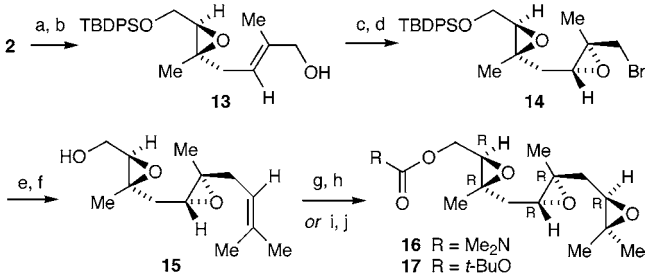
(19) Temperatures for the cyclizations of **4** and **7** were optimized by exploring a range from −95 to +40 °C, with only the best results shown in the tables. Although formation of the *tert*-butyl ether byproduct **12** relative to alcohol **11** is diminished at higher temperatures, the stereo- and regioselectivity for fused bicyclic products **11** and **12** vs byproducts **i** and **ii** remains constant. For cyclizations of **7**, optimized results are obtained with a short reaction time (Table 1, entry 6), as more side products are formed with the longer reaction times required for lower temperature experiments.

(20) (a) Sneen, R. A. *Acc. Chem. Res.* **1973**, *6*, 46. (b) Jencks, W. P. *Acc. Chem. Res.* **1980**, *13*, 161. We thank Prof. Peter Beak for suggesting ion-pair phenomena as a mechanistic explanation for these results.

(21) Umbreit, M. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1977**, *99*, 5526.

(22) Corey, E. J.; Kania, R. S. *J. Am. Chem. Soc.* **1996**, *118*, 1229.

Scheme 2. Stereoselective Syntheses of Triepoxides[a]



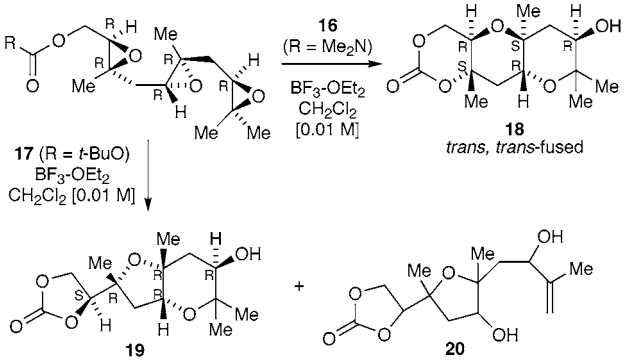
[a] Key: (a) TBDPSCl, imidazole, CH_2Cl_2 (100%); (b) SeO_2 (10 mol %), *t*-BuOOH/H_2O, CH_2Cl_2; then $NaBH_4$, MeOH, 0 °C (75%); (c) D-(−)-DIPT, Ti(O-*i*-Pr)$_4$, *t*-BuOOH, CH_2Cl_2, −18 °C (100%); (d) CBr_4, PPh_3, CH_2Cl_2, 0 °C (98%); (e) Me_2C=CHLi, THF/HMPA, −94 °C (85%); (f) Bu_4NF, THF, 0 °C (100%); (g) *n*-BuLi, THF, then $ClC(O)NMe_2$ (90%); (h) 0.3 equiv of **5**, Oxone, dimethoxymethane/CH_3CN/H_2O, pH = 11.4, 0 °C (90%); (i) 0.3 equiv of **5**, Oxone, dimethoxymethane/CH_3CN/H_2O, pH = 11.4, 0 °C; (j) $(Boc)_2O$, N^3-Me-imidazole, toluene, 0 °C to rt (70%, two steps).

dimethylcarbamate triepoxide **16** gave the desired all-fused *trans,trans* tricyclic product **18** as the major characterizable product in 31% isolated yield (Table 2, entry 1). This product results from inversion of configuration in each ring-forming event, and the structural assignment was secured by X-ray crystallography.[16] The corresponding reaction of the *tert*-butyl carbonate triepoxide **17** was also explored under a variety of reaction conditions. In this case, the major tricyclic product was determined to be structure **19** (Table 2, entry 2), resulting from a combination of exocyclization and endocyclization processes. Although crystalline samples of this product could not be obtained for X-ray diffraction analysis, NOESY NMR spectroscopy is consistent with the structure depicted for **19**, which has a *cis*-ring fusion between the five- and six-membered cyclic ethers.[23] When the cyclization reaction was conducted at higher temperature (Table 2, entry 3), a small amount of the all-fused *trans,trans* tricyclic product **18** was found along with **19** as the major tricyclic product and the elimination product **20** as a principal byproduct (stereochemistry not determined for **20**).

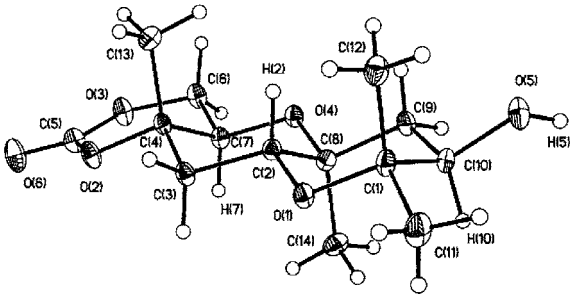
In summary, we have demonstrated that the choice of the terminal nucleophile can drive the cascade *endo*-oxacyclization of 1,4-diepoxides to proceed with retention or inversion of configuration at the ring fusion. For 1,4,7-diepoxides, this dependence of stereoselectivity on the nature of the nucleophile is also accompanied by different regioselectivity in the cyclization of the epoxide proximal to the carbonyl nucleophile. Current research is directed toward the application of this biomimetic synthesis strategy to the efficient construction of polypyran and structurally related polycyclic ether natural products.

(23) See the Supporting Information for details on chemical degradation and NOESY experiments resulting in the structural assignment for compound **19**.

Table 2. Oxacyclizations of 1,4,7-Triepoxide Substrates



entry	substrate	T (°C)	time (min)	products (isolated yield)
1	**16** R = Me_2N	+20	2	**18** (31%)
2	**17** R = *t*-BuO	-40	10	**19** (23%)
3	**17**	+40	2	**18** (4.5%), **19** (20%), **20** (29%)



thermal ellipsoid diagram of compound **18**

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Supporting Information Available: Experimental procedures; characterization data; thermal ellipsoid figures and essential data for compounds **10**−**12** and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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