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Alkene Substituents for Selective Activation of *endo*-Regioselective Polyepoxide Oxacyclizations

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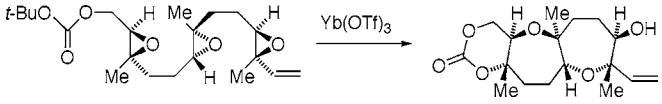
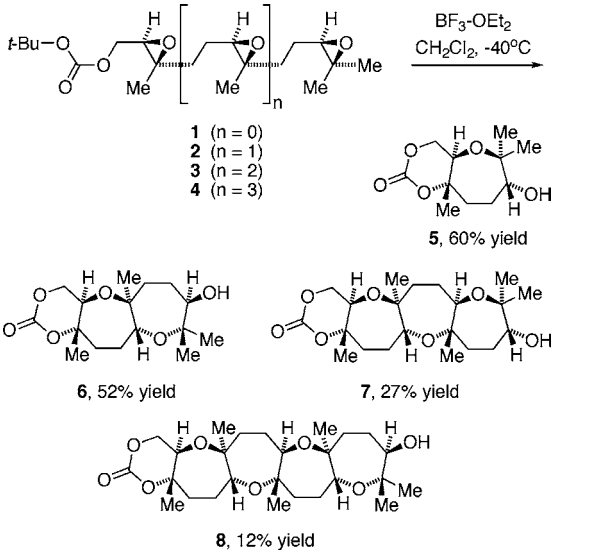
ABSTRACT



The presence of an alkenyl substituent on the terminal epoxide of a polyepoxide substrate enhances the yield of all-*endo*-regioselective tandem oxacyclization to *trans-syn-trans*-fused polycyclic ethers. For a substrate in which the epoxide and alkene functional groups are separated by two methylene substituents, a novel bromonium ion-induced *endo*-regioselective cyclization to bromooxepane is also described.

We recently demonstrated that the synthesis of fused polycyclic ethers (both polyoxepanes[1] and polypyrans[2]) can be achieved in a biomimetic and *endo*-regioselective fashion by addition of a Lewis acid to the corresponding polyepoxide. Boron trifluoride etherate was shown to be the best activator for the oxacyclization cascade, and the reaction required nucleophilic termination by a carbonyl oxygen such as carbonate or carbamate. However, the polyoxacyclization yield decreased with increasing the number of epoxides and, consequently, the number of rings formed. For instance, the geraniol and farnesol-derived polyepoxides **1** and **2** provided *trans-syn-trans*-fused oxacyclic products **5** and **6** in 60 and 52% isolated yields, respectively (Scheme 1), but only a 27% yield of **7** was obtained for the tetraoxacyclization of the tetraepoxide **3** derived from geranylgeraniol.[1b] The reaction was also explored in the pentaepoxide case **4**,[3−5] which afforded the pentacyclic product **8** in a single operation, but only in 12% isolated yield, thus setting the limits of the method.

Scheme 1. *endo*-Selective Polyepoxide Cyclizations



We anticipated that some of the mass balance was lost in activations of epoxides other than the terminal epoxide. With this consideration in mind, we envisioned that the introduction of an activating group at the terminal epoxide could increase the yield of the polyoxacyclization. As the activator,

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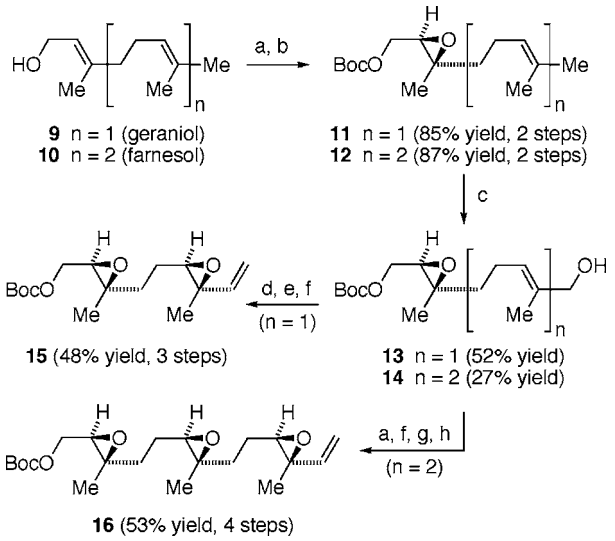
we chose the vinyl group, which not only better stabilizes the incipient positive charge at the terminal quaternary position[6] but might also act as a coordination site for an appropriate Lewis acid. In addition, the alkene functional group provides the opportunity for postcyclization transformations at the polycyclic ether terminus.

The cyclization precursors were synthesized as shown in Scheme 2. Geraniol (**9**) and farnesol (**10**) were each selectively epoxidized by Sharpless catalytic asymmetric epoxidation,[7] followed by protection of the alcohol as the Boc carbonate.[8] The terminal (*E*)-methyl substituents of **11** and **12** underwent Sharpless allylic oxidation with catalytic selenium dioxide[9] to afford the corresponding allylic alcohols **13** and **14**. Not surprisingly, the diene **12** was converted into **14** in significantly lower yield than observed for the monoalkene substrate **11**. Two slightly different routes were explored for the formation of polyepoxide substrates: from **13**, oxidation of the allylic alcohol with IBX and subsequent Wittig methylenation was followed by Shi epoxidation[10] of the conjugated diene to afford diepoxide **15** as the major product, although the yield for this final transformation (step f) was only 55% yield. From **14**, the allylic hydroxyl group was employed for Sharpless epoxidation of the terminal alkene, followed by Shi epoxidation of the internal alkene (in this case, step f gave 90% yield), and vinyl-substituted triepoxide **16** was then obtained by alcohol oxidation and Wittig methylenation, in this case using potassium *tert*-butoxide as a base.[11]

Scheme 2. Synthesis of Vinyl-Substituted Di- and Triepoxides **15** and **16**[a]



[a] Conditions: (a) D-(−)-DIPT, Ti(O-*i*-Pr)$_4$, *t*-BuOOH, CH_2Cl_2, −18 °C, 12 h. (b) $(Boc)_2O$, N^3-Me-imidazole, toluene, 0 to 20 °C, 12 h. (c) SeO_2 (10 mol %), *t*-BuOOH, H_2O/CH_2Cl_2, 0 to 20 °C, 36−96 h. (d) IBX, DMSO, 20 °C, 30 min. (e) $Ph_3P^+CH_3Br^-$, *n*-BuLi, THF, 20 °C, 12 h. (f) Shi ketone, Oxone, $(CH_3O)_2CH_2$/CH_3CN/H_2O, pH 11.4, 0 °C. (g) SO_3-py, DMSO, CH_2Cl_2, NEt_3, 0 °C, 3 h. (h) $Ph_3P^+CH_3Br^-$, *t*-BuOK, THF, 20 °C, 12 h.

In a continuing search for new methods to activate *endo*-regioselective epoxide cyclizations, we also explored halonium-promoted cyclization of epoxyalkene **11**. We were pleased to observe that bromonium di-sym-collidine perchlorate[14] afforded predominantly *endo*,*endo*-selective cyclization to provide bromooxepanes **19**/**20** as a separable mixture of diastereomers (Scheme 3).[12,15,16]

In conclusion, we note that the presence of terminal alkene in polycyclic products **17** and **18** might be exploited in

We proceeded to the optimization of cyclization conditions, first with diepoxide substrate **15**. Boron trifluoride etherate as a Lewis acid produced the desired bicyclic product **17** from tandem *endo*,*endo*-regioselective cyclization in 65% yield (Table 1, entry 1), which slightly improves the 60% yield obtained with the Boc-protected geraniol diepoxide (vide supra). This result is explained only by the better stabilization of the positive charge that effects the vinyl group in compound **15** in comparison with the methyl group, as boron trifluoride, once coordinated to the epoxide, lacks another free coordination site. Other Lewis acids with the potential for coordination to multiple sites were explored, in particular lanthanide Lewis acids. Lanthanum(III) triflate afforded the cyclized product **17** in 63% yield (entry 4), a result similar to that obtained with boron trifluoride. However, both gadolinium(III) triflate (77% yield of the bicyclic product, entry 5) and ytterbium(III) triflate (73%, entry 3) considerably increased the yield of the cyclization to provide **17**,[12] thus demonstrating the validity of our approach.[13] From the triepoxide substrate **16**, the use of gadolinium(III) triflate resulted in the formation of the all-*trans*-*syn*-*trans*-fused tricyclic product **18** in 45% yield (entry 6), whereas ytterbium(III) triflate proved to be a better choice, affording compound **18** in 56% yield (entry 7).

(3) Boc-protected pentaepoxide alcohol **4** was synthesized from the corresponding pentaene alcohol in a sequence of reactions similar to the ones described for geraniol, farnesol, and geranylgeraniol derivatives in ref 1. The pentaene alcohol, in turn, was prepared by coupling of the organobarium reagent derived from farnesyl chloride (see ref 4) with 8-bromo-1-*O*-*tert*-butyldiphenylsilyl-3,7-dimethyl-octa-2,6-dien-1-ol (ref 5). See Supporting Information for details.

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(11) Use of *n*-butyllithium or phenyllithium in the Wittig reaction leading to **16** considerably reduced the yield of the methylenation to 20−25%.

(12) See Supporting Information for essential data and thermal ellipsoid diagrams for crystal structures obtained for compounds *ent*-**17** and **19**.

(13) Cyclization of diepoxide **1** (Scheme 1) under the optimized conditions (ytterbium(III) triflate) gave the bicyclic product **5** in 52% yield, demonstrating that the vinyl substituent in substrate **15** plays a significant role in enhancing the cyclization yield.

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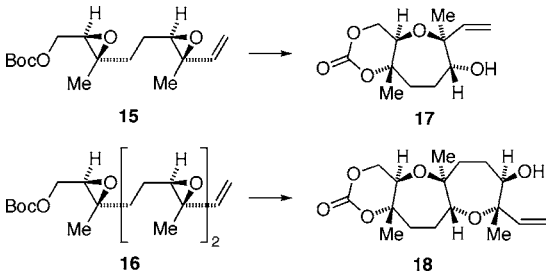
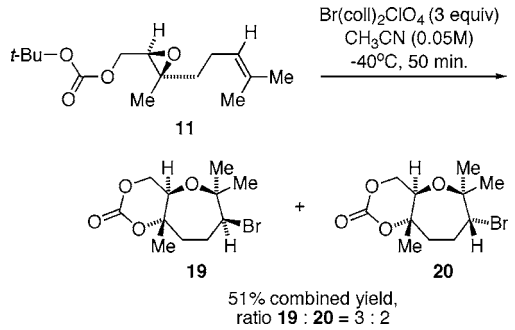
Table 1. Lewis Acid-Promoted Oxacyclizations of Polyepoxide Substrates **15** and **16**



entry	substrate	product	Lewis acid	conditions	isolated yield
1	**15**	**17**	$BF_3{-}OEt_2$ (1 equiv)	−40 °C, 10 min[a]	65%
2	**15**	**17**	$Yb(OTf)_3$ (1 equiv)	−40 to 20 °C, 4 h[a]	59%
3	**15**	**17**	$Yb(OTf)_3$ (3 equiv)	20 °C, 1 h[a]	73%
4	**15**	**17**	$La(OTf)_3$ (3 equiv)	20 °C, 2.5 h[a]	63%
5	**15**	**17**	$Gd(OTf)_3$ (3 equiv)	20 °C, 1 h[a]	77%
6	**16**	**18**	$Gd(OTf)_3$ (5 equiv)	20 °C, 4 h[b]	47%
7	**16**	**18**	$Yb(OTf)_3$ (6 equiv)	20 °C, 2 h[c]	56%

[a] Solvent: CH_2Cl_2, 0.05 M. [b] CH_2Cl_2, 0.01 M. [c] CH_2Cl_2, 0.04 M.

Scheme 3. *endo*,*endo*-Bromocyclization of Epoxyalkene **11**



postcyclization functionalization.[17] Further applications of vinyl-substituted polyepoxide substrates to polycyclic ether formation are in progress, including studies with transition-metal catalysts for selective epoxide activation. We also note that bromooxepane units similar to **19** and **20** are found in the armatol family of natural products.[18]

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Supporting Information Available: Experimental procedures and characterization data for new compounds and crystallographic data for compounds *ent*-**17** and **19** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) In addition to CH_2Cl_2 as a solvent, the bromocyclization of **11** could also be conducted in CH_3CN with a similar outcome (51% combined yield of **19** and **20**, 3:2 ratio). Toluene, DMF, THF, and Et_2O were not suitable solvents for this transformation.

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