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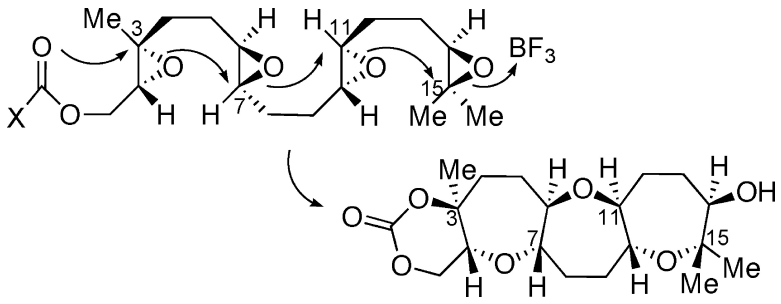

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Biomimetic Synthesis of *trans,syn,trans*-Fused Polyoxepanes: Remarkable Substituent Effects on the *endo*-Regioselective Oxacyclization of Polyepoxides

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trans,syn,trans-Fused polycyclic ether structures are found in many biologically active marine natural products.[1] These compounds have received much attention from the synthetic community and many elegant methods toward their synthesis have been described.[2] However, these syntheses generally rely on iterative strategies in which each cyclic ether is formed over a stepwise series of operations. Our laboratory has previously described the biomimetic synthesis of *trans,syn,trans*-fused polyoxepanes[3] and polypyrans[4] via Lewis acid-intitiated *endo*-regioselective tandem oxacyclization of polyepoxides.

Our mechanistic hypothesis (Figure 1) for tandem *endo*-oxacyclization involves Lewis acid activation **1** followed by nucleophilic addition of 6,7-epoxide to give fused bicyclic epoxonium ion **2**. Subsequent epoxide additions occur as shown for **2** → **3**, until the oxacyclization cascade is terminated by a tethered carbonyl nucleophile, to provide all-*trans,syn,trans*-polycyclic ether product, i.e., **4**.

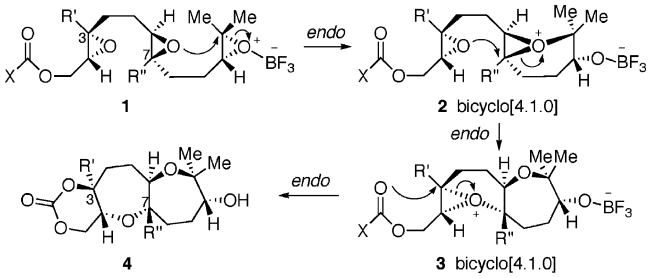


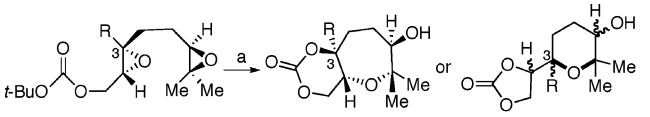
Figure 1. Proposed mechanism of Lewis acid-initiated oxacyclization.

From previous work by Coxon and others[5] on regioselective hydroxyepoxide oxacyclizations, we anticipated that Lewis acid-initiated oxacyclization of disubstituted epoxides would not yield the *endo*-regiochemistry required for *trans,syn,trans*-fused polycyclic ethers, but would instead give the undesired *exo*-oxacyclization product. For this reason all previous examples from our laboratory had utilized alkyl substitution (i.e., R′ = R″ = Me)[3,4] to overcome the kinetic and stereoelectronic bias toward *exo*-oxacyclization. However, alkyl substitution is not found at all ring junctions in the naturally occurring fused polycyclic ethers. Herein we report the extension of our Lewis acid-initiated oxacyclization reaction to include 6,7-disubstituted epoxides (R′ = Me, R″ = H), and further disclose the application of 3-silyl epoxides (R′ = $SiMe_3$, R″ = Me) to achieve *endo*-regiochemistry.

Preliminary experiments with the diepoxide **5** from 3-desmethylgeraniol (Scheme 1) confirmed the preference for *exo*-cyclization predicted by Coxon[5] to give **7** in low yield.[6] However further experimentation revealed that 3-silyl diepoxide **8**[7,8] favored regioselective tandem *endo*-oxacyclization to afford **9**[9] in good yield.

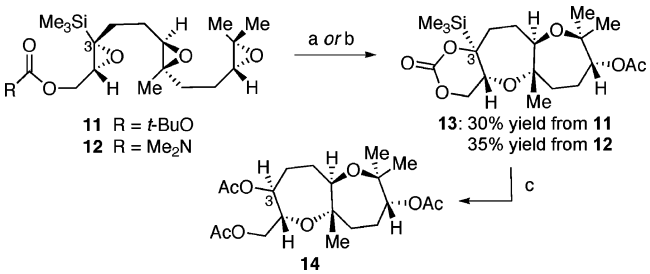
We next investigated 3-silyl triepoxides **11** and **12**[6−8] (Scheme 2), which upon treatment with freshly distilled BF_3-OEt_2 at

Scheme 1. 2,3-Epoxysilane Oxacyclization[a]



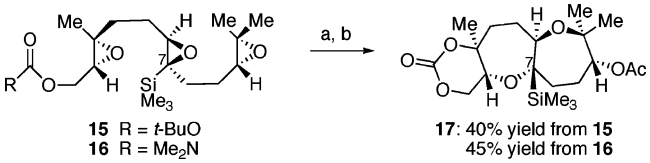
[a] Conditions: (a) BF_3-OEt_2, CH_2Cl_2, −40 °C.

Scheme 2. 2,3-Epoxysilane Oxacyclization/Protiodesilylation[a]



[a] Conditions: (a) **11**, BF_3-OEt_2, CH_2Cl_2, −40 °C; Ac_2O, pyridine. (b) **12**, BF_3-OEt_2, CH_2Cl_2, −40 °C; Ac_2O, pyridine; CF_3CO_2H. (c) Bu_4NF, THF; Ac_2O, pyridine.

Scheme 3. 6,7-Epoxysilane Oxacyclization[a]



[a] Conditions: (a) BF_3-OEt_2, CH_2Cl_2, −40 °C. (b) Ac_2O, pyridine.

−40 °C provided the *trans,syn,trans*-fused dioxepane product **13**. The more nucleophilic dimethylcarbamate consistently gives superior yields over the *tert*-butyl carbonate in these oxacyclization reactions (vide infra). Treatment of **13** with TBAF followed by peracylation gave ring-opened dioxepane **14**, corresponding to protiodesilylation at C-3 accompanied by cyclic carbonate removal.[9]

On the basis of Coxon's observations,[5] we expected silyl substitution at the 6,7-epoxide would also be required to achieve *endo*-oxacyclization (Figure 1, R′ = Me, R″ = $SiMe_3$). The reactions of both **15** and **16** with BF_3-OEt_2 gave the bisoxepane-carbonate **17** as the major product (Scheme 3).[6] However, 7-silyl substituted dioxepane **17** could not be protiodesilylated or functionalized under a variety of conditions, apparently as a neighboring hydroxyl group was not available to assist silicon migration from carbon.

These results led us to directly investigate the cyclization regioselectivity of 6,7-disubstituted epoxides (Figure 1, R′ = Me, R″ = H; Scheme 4). In contrast to expectations,[5] both substrates **18** and **19**[10] provided the all-*endo* oxacyclization product best characterized as the ester derivative **20**.[11] The structure of **20** was confirmed by single-crystal X-ray analysis.[6] Likewise, oxacycliza-

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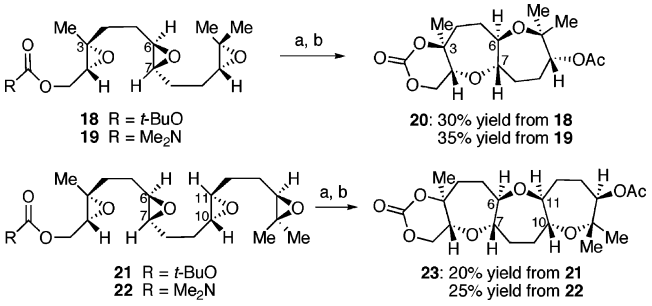
Scheme 4. Oxacyclizations of Disubstituted Epoxide Substrates[a]



[a] Conditions: (a) BF_3-OEt_2, CH_2Cl_2, −40 °C. (b) Ac_2O, pyridine.

tion of substrates **21** and **22**[10] bearing two "internal" disubstituted epoxides also resulted in the formation of *trans,syn,trans*-fused tetracyclic product **23**.[12]

The general *endo*-regioselectivity of substrates **18**, **19**, **21**, and **22** is consistent with the idea of nucleophile-driven regiochemical control (Figure 2)[3] where the nature of the nucleophile (i.e., epoxide vs carbonyl) drives the regioselectivity of oxacyclization with disubstituted epoxide electrophiles. In the case of the 2,3-epoxide nucleophile addition to either C6 or C7 of epoxonium ion **24**, *endo*-cyclization is observed due to formation of fused bicyclo[4.1.0] intermediate **25** rather than bicyclo[3.1.0] **26** which would have arisen from *exo* addition. We speculate that **25** is favored due to minimization of ring strain in formation of [4.1.0] epoxonium ion **25** relative to **26**.

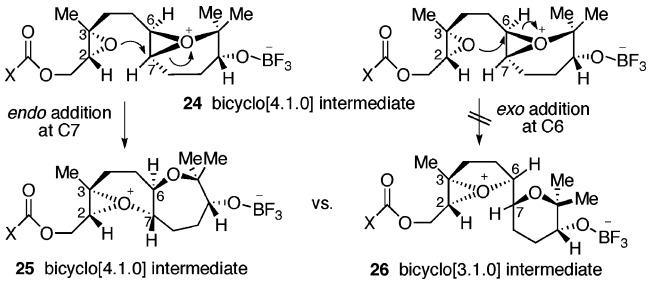


Figure 2. Rationale for regioselectivity directed by epoxide nucleophile.

With carbonyl nucleophiles (i.e., *tert*-butyl carbonate and *N,N*-dimethylcarbamate) there is little ring strain associated with either intermediate **29** or **30**,[3a,b] and the kinetically anticipated *exo* product arising from **28** (H at C-3) predominates in substrates with 2,3-disubstituted epoxide electrophiles. To achieve the *endo*-oxacyclization to **29** via **27** in the terminal cyclization, either an alkyl substituent (R′ = Me) or removable surrogate such as R′ = $SiMe_3$ is essential (Figure 3).

In conclusion, we have discovered that "internal" disubstituted epoxides are viable substrates in Lewis acid-initiated oxacyclization

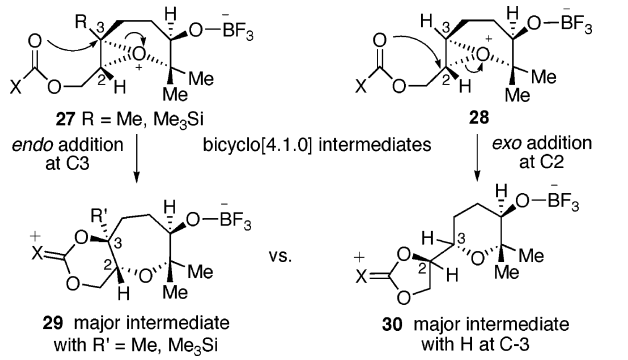


Figure 3. Rationale for regioselectivity in terminal cyclization step.

of polyepoxides. We note the reaction yields for oxacyclization of substrates **21** and **22**, 20% and 25% respectively, are similar to that of the geranylgeraniol-derived tetraepoxide substrate previously reported (27% yield[3b]). We have further demonstrated the utility of 2,3-epoxysilanes (**8**, **11**, **12**) to serve as a regioselectivity-directing surrogate in this tandem oxacyclization reaction, which can be efficiently removed. These findings greatly expand the scope of biomimetic oxacyclization methodology so that naturally occurring, non-terpene-derived polycyclic ethers can now be efficiently prepared by our approach.

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Supporting Information Available: Experimental procedures and spectroscopic data for the preparation of all polyepoxide substrates and their cyclization products; thermal ellipsoid figures and essential data for crystal structures of a derivative of compound **9**, and compound **20**. X-ray crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Compound **9** also undergoes efficient protiodesilylation (Supporting Information). Careful studies of the protiodesilylation of **9** and **13** reveal that carbonate opening precedes protiodesilylation. The liberated primary alcohol then assists in protiodesilylation via Brook-type silicon migration.
(10) The polyalkene precursors were generated by iterative ortho ester Claisen rearrangement: Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.
(11) The structure of compound **20** was confirmed by single-crystal X-ray analysis.
(12) The structure of compound **23** was confirmed by NOESY spectroscopy.

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