

Ladder Polyether Synthesis via Epoxide-Opening Cascades Using a Disappearing Directing Group

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The ladder polyether natural products (Figure 1) are associated with a number of marine phenomena, including the Red Tide. Twenty years ago, Nakanishi proposed an intriguing explanation for the structural and stereochemical similarities found in all known members of this family—the transformation of a polyepoxide into a ladder polyether via a cascade of epoxide-opening events.¹ However, this two-decade-old hypothesis remains unconfirmed, and the existing epoxide ring-opening cascades provide only limited information regarding the validity of this proposal. Nevertheless, McDonald and Murai have reported especially impressive cascades that afford *trans-syn-trans*-fused polycyclic systems containing as many as five oxygen heterocycles.² To control the regioselectivity of epoxide opening, however, all of these utilize one or more directing groups that are not removed after the cascade. Furthermore, the four-ring system found in the majority of the ladder polyether natural products, a tetrad of tetrahydropyran rings, has not been synthesized using an epoxide-opening cascade.^{3,4}

Herein we report the first epoxide ring-opening cascades that (a) afford ladder polyethers containing *no* directing groups at the end of the cascade, (b) overcome the inherent bias for formation of a tetrahydrofuran (5-*exo*) over a tetrahydropyran (6-*endo*) in the opening of a *trans*-disubstituted epoxide by a pendant hydroxyl group,⁵ and (c) yield the distinctive tetrahydropyran tetrad of the ladder polyether natural products. All of the above are made possible by trimethylsilyl (Me₃Si) directing groups that *disappear* during the course of the cascades.

Previously we reported a Me₃Si-based, iterative strategy for the synthesis of tetrahydropyran (THP) ladder polyether subunits.⁶ In this approach, Shi's method⁷ effected highly stereoselective epoxidation of trisubstituted alkenylsilanes, and Et₂O·BF₃ promoted highly regioselective (>95% 6-*endo*) and highly diastereoselective (>95% inversion) intramolecular opening of the resulting epoxysilanes by a hydroxyl group.

We have since found that the corresponding polyenes and polyepoxides can be prepared using analogous methods, but in contrast, Lewis and Brønsted acids do *not* promote the desired cascades (Scheme 1). For example, diene **1** undergoes highly stereoselective, reagent-controlled Shi epoxidation, but when diepoxide **2** is treated with Et₂O·BF₃, an undesired bis-THF (**3**) forms, and no THP-containing products (e.g., **4**) are detected.

A thorough evaluation of reaction conditions ultimately revealed that very different results are obtained when Brønsted bases in hydroxylic solvents are employed.⁸ Exposure of diepoxide **2** to excess Cs₂CO₃ in methanol afforded the desired two-ring system, in the form of THP diad **4**. Despite the low overall yield, the fortuitous loss of one of the Me₃Si groups dramatically changed the course of these investigations.

Two further modifications greatly improved the efficiency and scope of this strategy (Scheme 2). Construction of one THP prior to the cascade increased the overall yield substantially, and the addition of CsF effected the removal of *all* Me₃Si groups. In the

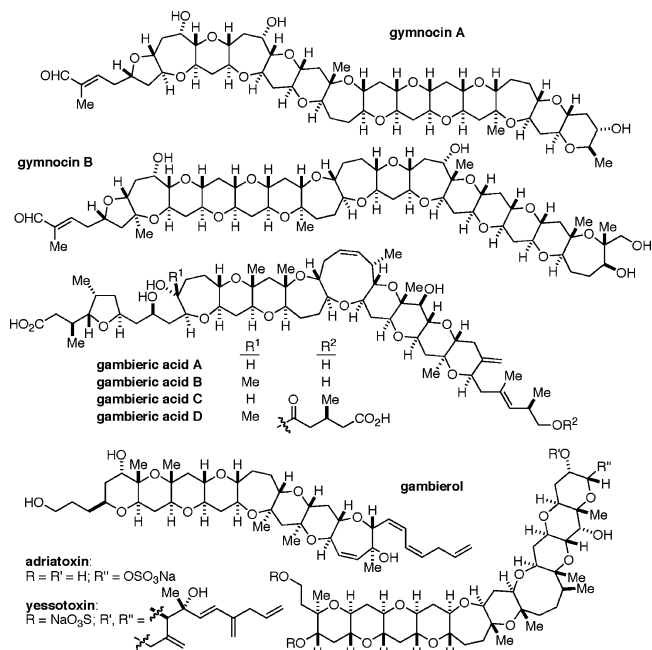
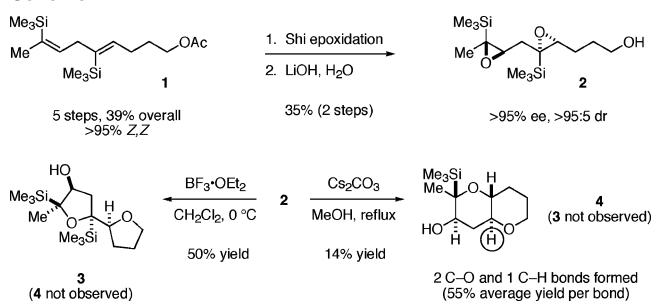


Figure 1. The ladder polyether natural products that contain one or more tetrads of tetrahydropyran rings.

Scheme 1

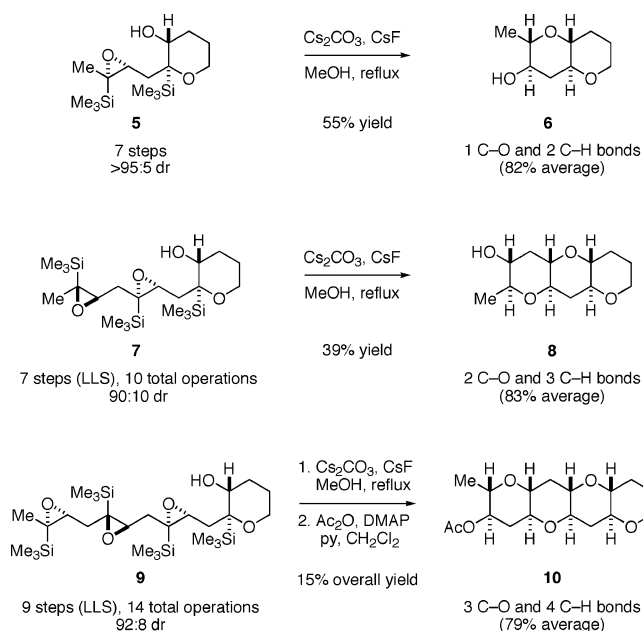


conversion of **5** to THP diad **6**, one C–O bond and two C–H bonds were formed in an average of 82% yield for each event.

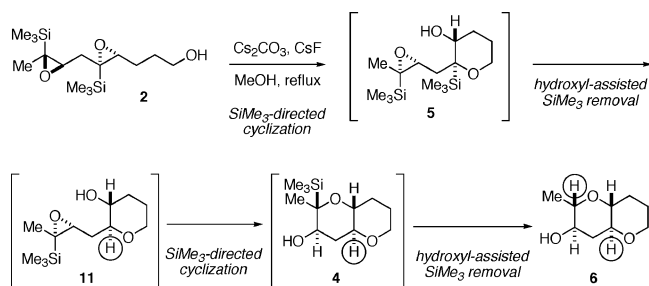
These phenomena are also observed in similar efficiency in the conversion of diepoxide **7** to THP triad **8**, which we had previously prepared in iterative fashion in 18 linear steps.^{6a} The transformation of triepoxide **9** into THP tetrad **10** represents the shortest synthesis of the signature subunit of the ladder polyether natural product family (Figure 1) and, more significantly, the first by way of an epoxide-opening cascade.

Featuring a “disappearing” directing group (Me₃Si), these cascades are conducted under conditions that differ significantly from those used in previously reported cascades (Lewis acids, generally in aprotic solvents²), and we believe that they proceed by the sequence of events shown in Scheme 3. The Me₃Si group

Scheme 2

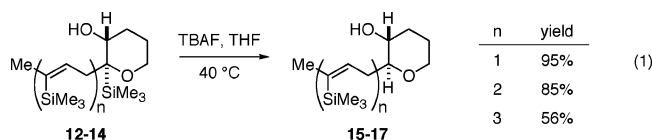


Scheme 3



biases the regioselectivity of epoxide opening in the conversion of **2** to **5** and is removed (giving **11**) before the next epoxide-opening event that, in this example, leads to THP diad **4**. We have yet to observe the formation of any THP-containing products that possess a Me_3Si group at the junction of two THP rings. Protodesilylation likely involves transfer to the adjacent hydroxyl group⁹ and subsequent cleavage of the resulting silyl ether, giving the end product of the cascade (**6**).

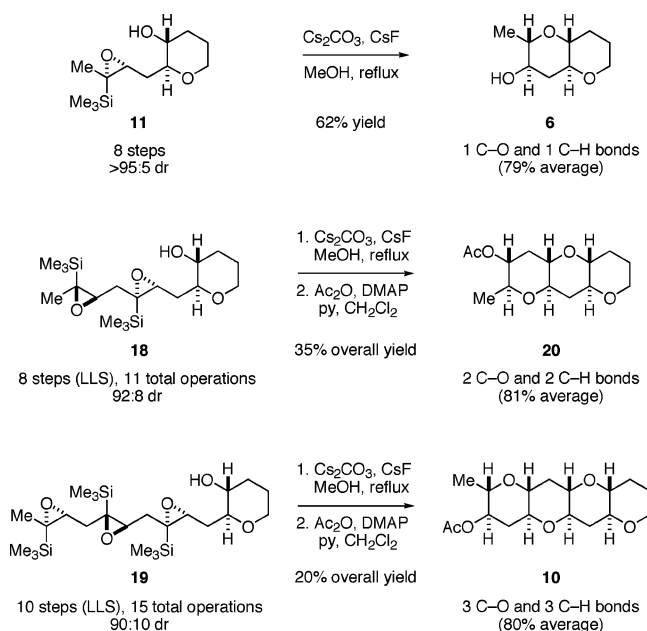
To test this model further, we prepared the one remaining intermediate proposed in Scheme 3 (**11**) by selective removal of the Me_3Si group adjacent to the hydroxyl group in **12** in the presence of the alkenyl Me_3Si group (eq 1). Homologues **16** and **17** were prepared in a similar fashion.



Shi epoxidation (see Supporting Information) of these three compounds provided **11**, **18**, and **19**. As before, all Me_3Si groups disappeared during the cascades ($\text{Cs}_2\text{CO}_3/\text{CsF}$ in MeOH, Scheme 4), leading to the THP diad (**6**), triad (**10**), and tetrad (**10**), in an average yield of 80% per C-X bond formed.

In summary, the combination of a Me_3Si group, a Brønsted base, a fluoride source, and a hydroxylic solvent enables the first construction of the THP tetrad found in the majority of the ladder polyether natural products by way of a cascade of epoxide-opening

Scheme 4



events that emulates Nakanishi's proposed biosynthetic pathway. Further development of these and related cascades is ongoing.

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Supporting Information Available: Experimental procedures and data for all new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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