Reiterative Synthesis of *trans*-Fused Polytetrahydropyrans Using the Oxiranyl Anion

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Abstract: The oxiranyl anion is a very unstable nucleophilic epoxide. This previously uncommon nucleophile has now been used for the synthesis of polycyclic ethers. Alkylation of an oxiranyl anion, a three-carbon building block, with a triflate derived from tetrahydropyranmethanol followed by acid-catalyzed 6-*endo* cyclization provides a *trans*-fused bicyclic compound. Reiterative application of this procedure enables the rapid construction of *trans*-fused polytetrahydropyrans.

Keywords: C–C coupling · cyclizations · oxiranyl anion · synthetic methods · tetrahydropyrans

After the discovery of brevetoxin B,[1] many polycyclic ether biotoxins, which show strong biological activities by interacting with cation channels of cellular membranes,[2] were isolated from marine dinoflagellates. These highly complex molecules are characterized by having *trans*-fused polyoxacycles ranging in size from five- to nine-membered. The *trans*-fused tetrahydropyran ring system is the most frequently encountered cyclic unit and forms a rigid backbone for the biotoxins (Figure 1).

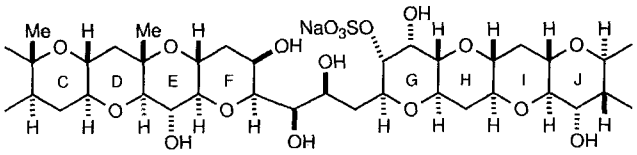

Figure 1. Partial structure of maitotoxin.

Synthesis of such fused systems is currently receiving a great deal of attention and a variety of approaches have been explored with an increasing emphasis on iterative strategies.[3] This article describes our strategic principle of *trans*-fused tetrahydropyran synthesis as well as a brief overview of other approaches that have contributed to the reiterative synthesis.

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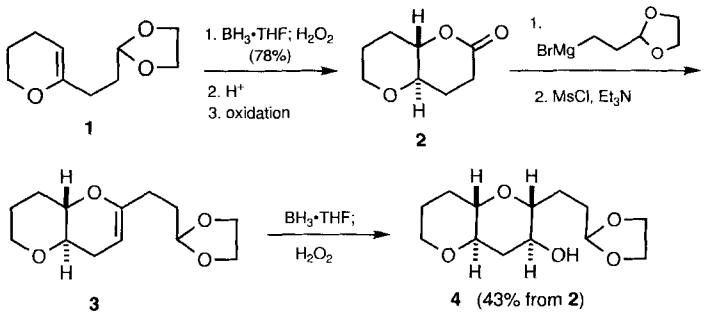
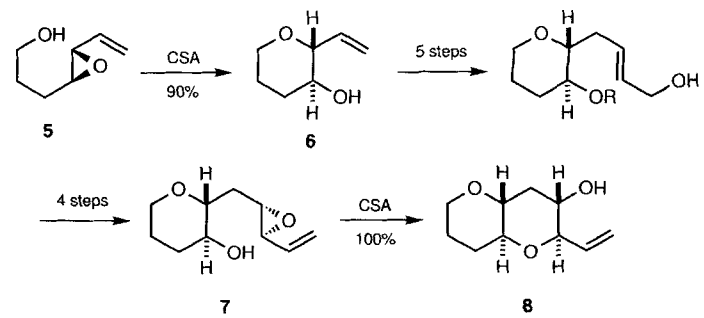
A method for effecting the annulation of a pyran ring to an existing pyran ring structure was first demonstrated by Kozikowski et al.[4] The dihydropyran **1** was transformed into lactone **2** by stereoselective hydroboration followed by acid treatment and oxidation (Scheme 1). The carbon chain was extended by the Grignard reaction, and the resulting lactol was dehydrated to the bicyclic dihydropyran **3**. The second hydroboration afforded an alcohol **4** as a nearly single isomer. The *syn*-specific hydroboration process plays an important role in introducing the secondary hydroxyl group of the pyran ring *trans* to the carbon chain. Later, this process was effectively applied to seven-membered enol ethers by other groups.[5]



Scheme 1.

The ring-selective synthesis of tetrahydropyrans was achieved by Nicolaou et al, who used the acid-catalyzed cyclization of *trans*-hydroxy epoxides **5** and **7** (Scheme 2).[6] The π orbital adjacent to the epoxide unit serves as a director functionality that controls the 6-*endo* over the usually favored 5-*exo* modes of



Scheme 2.

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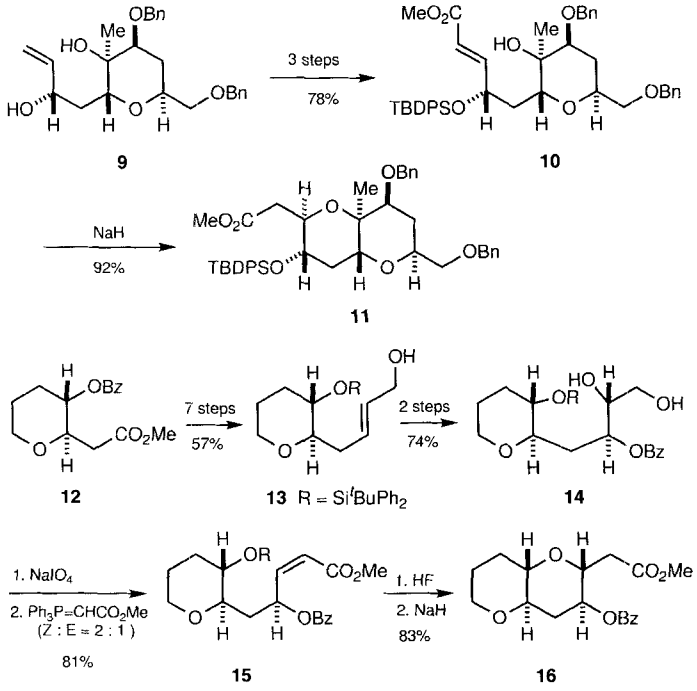
epoxide opening.[7] Acid treatment of **5** gave the *trans*-disubstituted tetrahydropyran **6**. The *trans* stereochemistry of the epoxide is critical to the exclusive 6-*endo* cyclization. Elaboration of the vinyl group to the olefinic epoxide **7** requires nine steps including *trans*-allylic alcohol formation and Sharpless asymmetric epoxidation. This strategy was successfully employed in the fragment synthesis of brevetoxin B.[8]

A methodology based on the intramolecular hetero-Michael addition of appropriately functionalized hydroxy γ-silyloxy-α,β-unsaturated ester **10** to the tetrahydropyran **11** has been demonstrated by Nicolaou et al. (Scheme 3).[9] Later, Martin et al.

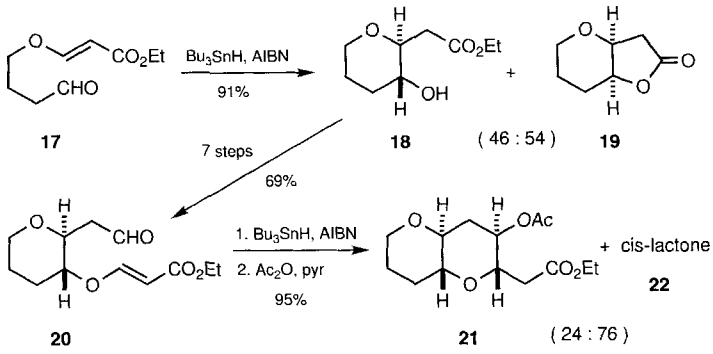


Scheme 3.

applied this procedure to alkoxy γ-benzoyloxy-α,β-unsaturated ester **15**.[10] The stereocontrolled introduction of the benzoyloxy group of **14** was carried out by the asymmetric epoxidation of **13** followed by the regioselective addition of benzoic acid. The bicyclic ring system **16** was stereospecifically constructed by means of the Michael addition reaction of the (*Z*) isomer **15** (R = H) under kinetically controlled conditions. This iterative procedure requires a large number of steps, which leads to lower overall yields.

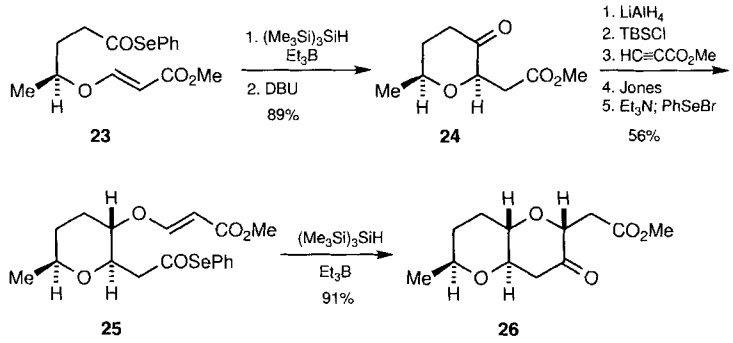
The synthetic approach by intramolecular C–C bond formation may employ cyclization at the annulation sites. β-Alkoxyacrylates are efficient radical acceptors during the intramolecular addition of alkyl and alkoxy radicals.[11, 12] Under standard conditions for radical generation, the substituted aldehydes **17** and **20** cyclized to tetrahydropyran derivatives **18** and **21**, respectively, in high yields (Scheme 4).[12] However, the lack of stereoselectivity of the stannyloxyalkyl radical addition limits the applicability of this reaction.

Formation of diastereoisomers can be avoided by employing an acyl radical instead of an alkoxy radical. Based on this idea, Evans et al. have developed an efficient reiterative method.[13]



Scheme 4.

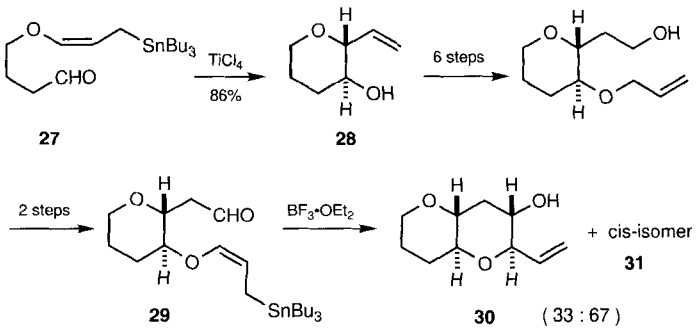
Intramolecular addition of the acyl radical, generated from acyl selenide **23** by treatment with tris(trimethylsilyl)silane and triethylborane, to the acrylate provided tetrahydropyran-3-one **24** as the major isomer (5.7:1, Scheme 5). After transformation of



Scheme 5.

24 into **25**, which is a latent version of the original material, the radical cyclization was repeated to give **26** in a 19:1 stereoselectivity. The excellent stereocontrol obtained for the second radical cyclization is in sharp contrast to the modest diastereoselectivity obtained in the monocyclic system.

Another strategy used to construct tetrahydropyran rings in such a way that new C–C bonds could be formed at annulation sites is the intramolecular allylstannane–aldehyde condensation approach.[14] Yamamoto et al. reported that the Lewis-acid mediated cyclization of ω-stannyl ether aldehyde **27** predominantly gave the cyclic ether **28** (*trans*:*cis* = 83:17; Scheme 6).[15] The advanced cyclization precursor **29** was treat-



Scheme 6.

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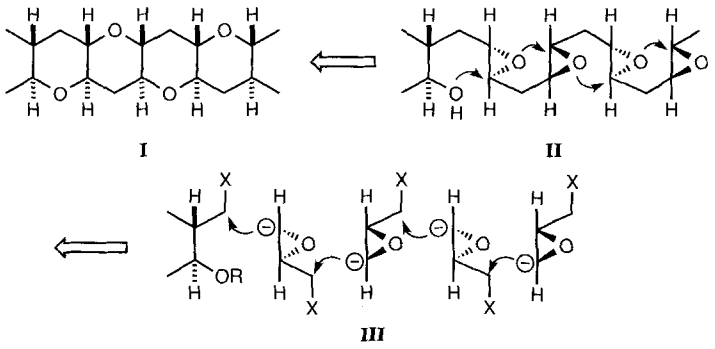
ed with boron trifluoride etherate to yield a 33:67 mixture of the *trans* (**30**) and *cis* isomers.[16] Although the cyclization to the six-membered cyclic ether proceeded in a nonstereoselective way, perfect control was accomplished in the case of the seven-membered systems.[16, 17] It is interesting to note that an allylboronate derivative corresponding to **27** was reported to undergo ready cyclization to a *cis*-fused tetrahydropyran with >95% selectivity in moderate yield.[18]

Our strategy[19] is based on the biosynthesis of polycyclic ethers.[20] The regio- and stereoselective 6-*endo* mode of ring opening of epoxide **II** would be an attractive access to the *trans*-fused tetrahydropyran system **I** (Scheme 7), which was first



Scheme 7.

demonstrated by Nicolaou's group[6] as previously described, because such a cyclization is considered to be a key step in the biosynthesis. Moreover, it is interesting to carry out a reaction that contradicts Baldwin's rules of cyclization reactions.[7] The next problem is how to synthesize the polyepoxide precursor **II** made up of a single carbon chain. In a proposal for the biosynthesis of brevetoxin B, it has been suggested that the hypothetical building block of the tetrahydropyran rings of brevetoxin B may be a three-carbon unit derived from a succinate or its equivalent (Figure 2).[21] This suggestion inspired us to attempt to

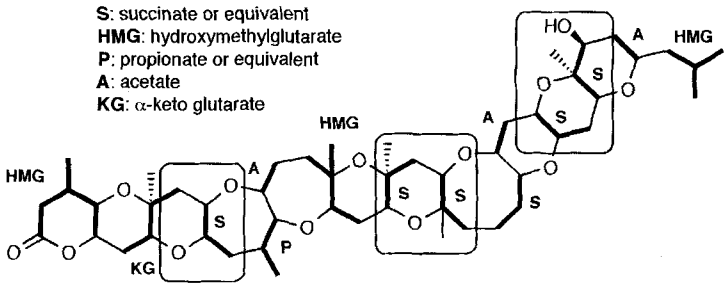
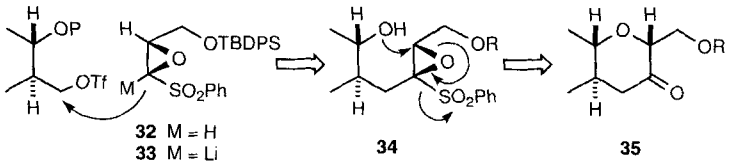


Figure 2. Hypothetical building blocks of brevetoxin B.

mimic nature by using the coupling reaction of the oxiranyl anion **III** as a three-carbon building block. This new approach is very challenging because the reaction of epoxides as a nucleophile is uncommon while epoxides are widely recognized as extremely useful electrophiles.

Based on this concept, a synthetic reagent corresponding to the oxiranyl anion **III** was sought. Oxiranyl anions have been known as extremely unstable intermediates, but several methods for generating the anions have been reported: deprotonation of epoxides having an anion-stabilizing group such as silyl,[22] sulfonyl,[23] and unsaturated functional groups,[24] desilylation of epoxy silanes with fluoride,[25] desulfinylation of epoxy sulfoxides,[26] and transmetalation of trialkylstannyl-substituted epoxides.[27] By considering the synthetic potential for further chemical transformations, sulfonyl-stabilized oxiranyllithium **33** was chosen, which could be easily generated from **32** by deprotonation with *n*-butyllithium.[23]

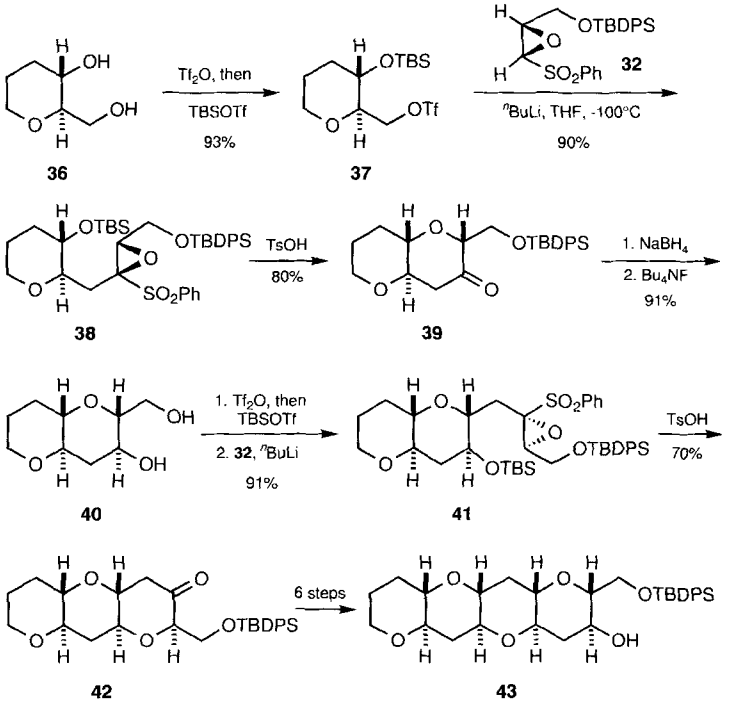
A general strategy for constructing a tetrahydropyran ring is shown in Scheme 8. Alkylation of the anion **33** with a suitable electrophile would give the substituted epoxy sulfone **34**. Theo-



Scheme 8.

retically, epoxide **34** could suffer ring closure through the 5-*exo* or 6-*endo* mode of cyclization leading to a tetrahydrofuran or a tetrahydropyran system, respectively; however, the electron-withdrawing ability of the sulfonyl group would work against the adjacent C–O bond breaking in an acid-catalyzed epoxide ring-opening process and, consequently, favor the *endo*-mode pathway to give tetrahydropyranone **35** after elimination of phenylsulfinic acid. This idea is complementary to that of the π-orbital-assisted 6-*endo* cyclization developed by Nicolaou et al.[6]

Regioselective activation and protection of the starting monocyclic diol **36** as triflate **37** were carried out using a one-pot process (Scheme 9). The coupling reaction of **37** and oxiranyl-



Scheme 9.

lithium **33** is a major hurdle in our strategy, because a sulfonyl-stabilized *cis*-oxiranyl anion is very unstable even at $-105\,^{\circ}C$ as reported by Jackson et al.[23] The crucial C–C bond formation was smoothly performed by treating a mixture of epoxy sulfone **32** (1.7 equiv) and triflate **37** (1.0 equiv) with *n*-butyllithium (1.7 equiv) at -100 to $-90\,^{\circ}C$ for 30 min to afford **38** in high yield. This procedure effectively minimizes the decomposition of the unstable oxiranyl anions.[28] Desilylation of the secondary alcohol and the following key cyclization reaction were accomplished in one step by treatment of **38** with *p*-toluenesulfonic acid to give the bicyclic ketone **39** as a single isomer. It is noteworthy that other stereoisomers with respect to the epoxy sulfone moiety did not cyclize under the various acidic conditions. The reduction of **39** with sodium borohydride (selectivity 97:3) followed by deprotection provided the bicyclic diol **40**, from which point the original steps can be repeated. A tetracyclic product **43** has been obtained from a monocyclic template **36** using three iterations of this five-step synthesis sequence.

The advantages of using the sulfonyl-stabilized oxiranyl anion are threefold: efficiency of the C–C bond formation, control of the 6-*endo* mode of cyclization, and facilitation of the secondary hydroxyl regeneration. The oxiranyl anion strategy allowed the rapid construction of *trans*-fused tetrahydropyran ring systems.

Oxiranyl anions are unique reactive nucleophiles and the coupling reaction with electrophiles represents an extraordinary means by which epoxides can be directly incorporated into organic molecules. Use of the functionalized oxiranyl anions as synthons may be advantageous in other areas of organic synthesis.

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