A New Strategy for the Reiterative Synthesis of *trans*-Fused Tetrahydropyrans *via* Alkylation of Oxiranyl Anion and 6-*endo* Cyclization

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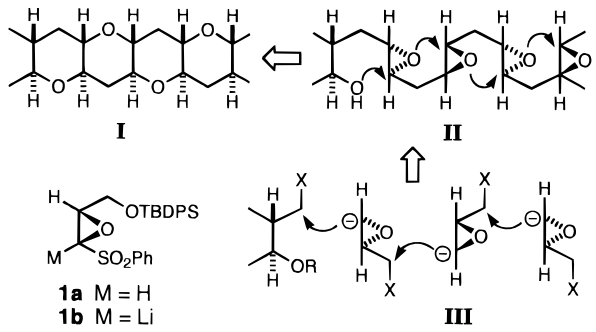
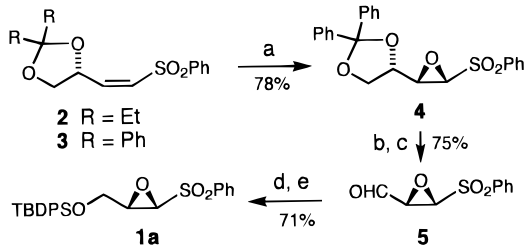
One of the most characteristic and interesting classes of marine toxins produced by dinoflagellates is the polycyclic ethers which show strong biological activities by interacting with the cation channels of cellular membranes.[1] *trans*-Fused tetrahydropyran rings are the most frequently encountered cyclic units and form a rigid backbone of this class of toxins. The synthesis of such a ring system (**I**) by Baldwin's rule[2] -disfavored 6-*endo* mode of cyclization of **II** is receiving attention[3] since such cyclization is considered to be a key step in the biosynthesis of polycyclic ethers.[4] Furthermore, in a proposal for the biosynthesis of brevetoxin B, it has been suggested that the hypothetical building block of tetrahydropyran rings may be a C_3 unit derived from a succinate or its equivalent.[5] This suggestion inspired us to attempt to mimic nature by using the coupling reaction of a C_3 oxiranyl anion **III** followed by 6-*endo* cyclization in a reiterative manner to construct a polycyclic framework (Scheme 1).

Although epoxides are widely recognized as extremely useful electrophiles,[6] the reaction of an epoxide as a nucleophile, i.e., oxiranyl anion, is less common. Several methods for generating oxiranyl anions have been reported: desilylation of epoxy silanes with fluoride,[7] desulfinylation of epoxy sulfoxides,[8] transmetalation of trialkylstannyl-substituted epoxides,[9] and deprotonation of epoxides having an anion-stabilizing group such as sulfonyl,[10] silyl,[11] and unsaturated functional groups.[12]

Scheme 1



Scheme 2[a]



[a] (a) *t*-BuOOH, *n*-BuLi, THF, −20 °C, 4 h; (b) TsOH, MeOH, 40 °C, 2 h; (c) $NaIO_4$, MeOH−H_2O, 15 min; (d) $NaBH_4$, MeOH, −20 °C, 0.5 h; (e) TBDPSCl, imidazole, DMF, 1.5 h.

These pioneering studies demonstrated that oxiranyl anions can be generated only at low temperature and that they react with very reactive electrophiles such as aldehydes, ketones, and chlorotrimethylsilanes. However, alkylation of oxiranyl anions has scarcely been studied.[10,11a] We recently found that alkyl triflates are reactive enough to couple with the anions.[13] In this communication, we report a new strategy for the synthesis of *trans*-fused tetrahydropyran systems using epoxy sulfone **1a** as the source of the C_3 oxiranyl anion **III**.

The synthesis of the key building block **1a** was initiated with the Peterson olefination between (*R*)-*O*-pentylideneglyceraldehyde and trimethylsilylmethyl phenyl sulfone[14] to provide *Z*-vinyl sulfone **2** along with the *E*-isomer (1:1 ratio) (Scheme 2). Epoxidation of **2** with lithium *tert*-butylperoxide proceeded with only 4:1 selectivity.[10a,15] In an attempt to enhance even further this selectivity, the diphenylmethylene ketal **3** was utilized in the reaction. One of the phenyl groups was expected to increase the steric bulk of the α-side of the molecule.[16] The epoxidation led to a higher ratio (12:1) of **4** to its isomer (78% total yield). Deprotection and recrystallization gave optically pure diol, which was treated with $NaIO_4$ to give **5** in 75% overall yield. Reduction and protection of the resulting alcohol as a silyl ether afforded epoxy sulfone **1a**.

The synthesis of the *trans*-fused tetrahydropyran system began from **6**[17] (Scheme 3). Regioselective activation and protection of two hydroxyl groups were carried out by a one-pot process. Treatment of a solution of **6** and 2,6-lutidine in methylene chloride with triflic anhydride (−78 °C, 30 min) followed by

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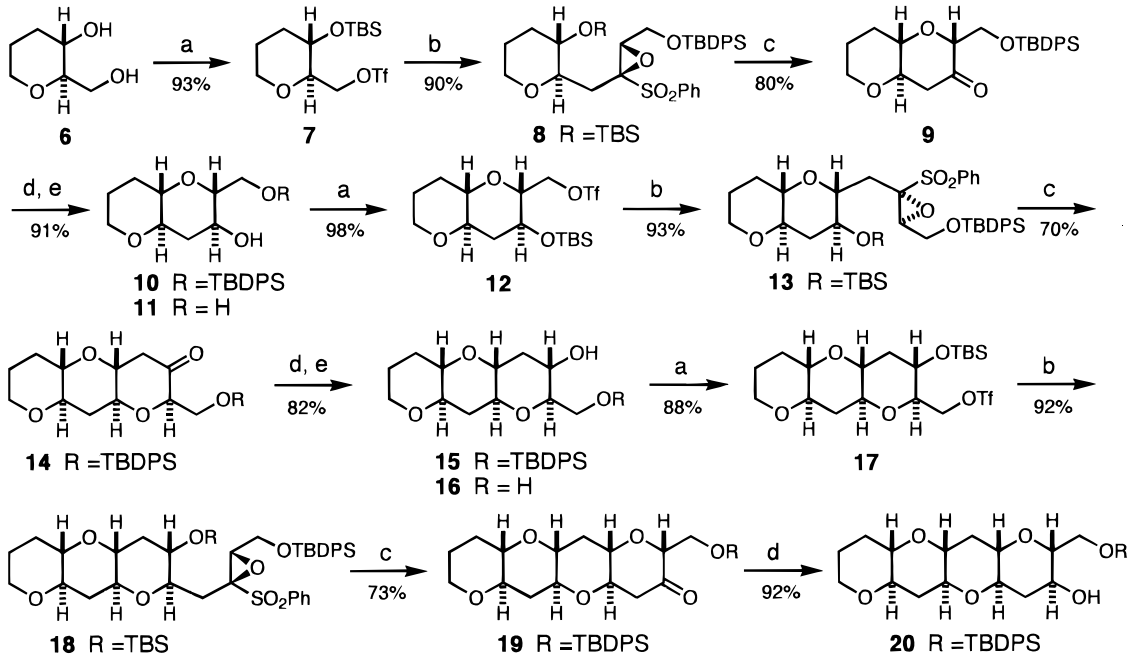
Scheme 3[a]



[a] (a) $(CF_3SO_2)_2O$, 2,6-lutidine, CH_2Cl_2, −78 °C, 30 min, then TBSOTf, −78 to 0 °C, 30 min; (b) **1a**, *n*-BuLi, THF, DMPU, −100 °C, 30 min; (c) *p*-TsOH·H_2O, $CHCl_3$, 55 °C, 6 h; (d) $NaBH_4$, MeOH−CH_2Cl_2, −78 °C, 2 h; (e) *n*-Bu_4NF, THF, rt, 1 h.

tert-butyldimethylsilyl triflate (−78 to 0 °C) gave **7** in 93% yield. The coupling reaction of **1b** and **7** is a major hurdle in our strategy, because a sulfone-stabilized *cis*-oxiranyl anion is very unstable and partially isomerizes to a *trans*-isomer even at −105 °C.[10a] This crucial C−C bond formation was smoothly performed by employing the following procedure: a mixture of epoxy sulfone **1a** (1.7 equiv) and triflate **7** (1 equiv) in THF was treated with *n*-butyllithium (1.7 equiv) at −100 to −90 °C for 30 min to afford **8** in 90% yield with a trace amount of isomer epimeric at the sulfone-bearing center. This procedure effectively minimizes the decomposition of the unstable oxiranyl anion.[13]

Theoretically, epoxide **8** (R = H) could suffer ring closure *via* a 5-*exo* or 6-*endo* mode of cyclization leading to a tetrahydofuran or a tetrahydropyran system, respectively, but the presence of a sulfonyl group would be expected to favor the *endo* mode pathway due to its electron-withdrawing ability.[18] This idea is complementary to that of the π-orbital-assisted cyclizations.[3a−e] Indeed, 6-*endo* cyclization of **8** was effected by heating with *p*-toluenesulfonic acid monohydrate in chloroform, thus furnishing the bicyclic system **9** in 80% yield with complete regio- and stereoselectivity; the stereochemistry was confirmed by NOE studies. Reduction of **9** with $NaBH_4$ gave the desired alcohol **10** in 92% yield and 94% ds. Successive desilylation provided diol **11**, from which point the original steps can be repeated.

The second cycle of the five-step operation afforded the tricyclic diol **16** in 52% overall yield from **11**. The second key coupling reaction of **12** with the oxiranyl anion **1b** and subsequent *endo* mode of cyclization proceeded uneventfully. The selectivity of the hydride reduction of **14** was 96% ds. Since **16** contains two hydroxyl groups, the sequence reported here was reiterated to construct the tetracyclic all-*trans*-fused framework **20** in 54% overall yield. The diastereomeric ratio of the final reduction was 97:3.

The reported processes represent a highly effective method for the construction of *trans*-fused tetrahydropyran ring systems. The advantages of using the sulfone-stabilized oxiranyl anion are 3-fold: efficiency of the C−C bond formation, control of the 6-*endo* mode of cyclization, and facilitation of the secondary hydroxyl regeneration. Applications of the present methodology to the synthesis of marine polycyclic ethers are in progress.

Supporting Information Available: Typical experimental procedures and characterization data for **1a** and **7**−**20** as well as NMR spectra (^{1}H, COSY, and DIFNOE) of **9**, **11**, **17**, and **19** (26 pages). See any current masthead page for ordering and Internet access instructions.

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