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Synthesis of *trans*-fused tetrahydropyrans via intramolecular cyclization of α-bromo-γ′-hydroxy ketones

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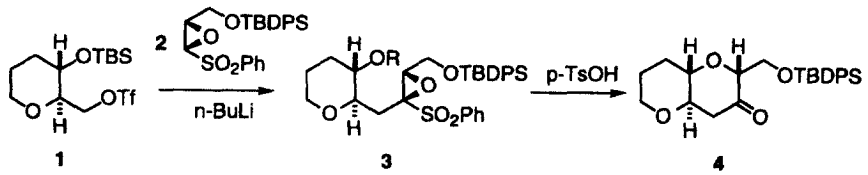
Abstract

A practical method for the synthesis of *trans*-fused polytetrahydropyrans using racemic *cis*- and *trans*-epoxy sulfones was developed. Four diastereoisomers, obtained by the reaction of an optically active triflate and the oxiranyl anions generated from racemic *cis*- and *trans*-epoxy sulfones, were transformed into α-bromo-γ′-hydroxy ketones, and the DBU-induced intramolecular cyclization gave tetrahydropyranones.

Keywords: epoxides; cyclization; tetrahydropyrans; oxiranyl anion.

Polytetrahydropyran ring systems are the most frequently encountered cyclic units and they form the rigid backbone of marine toxins such as brevetoxins, maitotoxin, and yessotoxin.[1] The synthesis of such fused systems is currently receiving a great deal of attention and diverse approaches have been developed with increasing emphasis on iterative strategies.[2] In a previous communication, we reported a new strategy for the synthesis of *trans*-fused polytetrahydropyrans based on an oxiranyl anion strategy, wherein epoxy sulfone **3**, prepared from the optically active triflate **1** and the optically active *cis*-epoxy sulfone **2**, stereospecifically cyclized in a 6-*endo* manner to give bicyclic ketone **4** (Scheme 1).[3]



Scheme 1.

However, synthesis of the optically active **2** required an eight-step manipulation starting from the Peterson reaction of (*S*)-pentylideneglyceraldehyde and phenyl trimethylsilylmethyl sulfone.[4] We then explored an alternative method to synthesize ketone **4** using racemic *cis*- and *trans*-epoxy sulfones which

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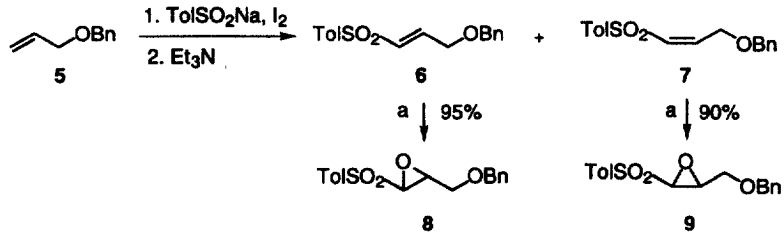
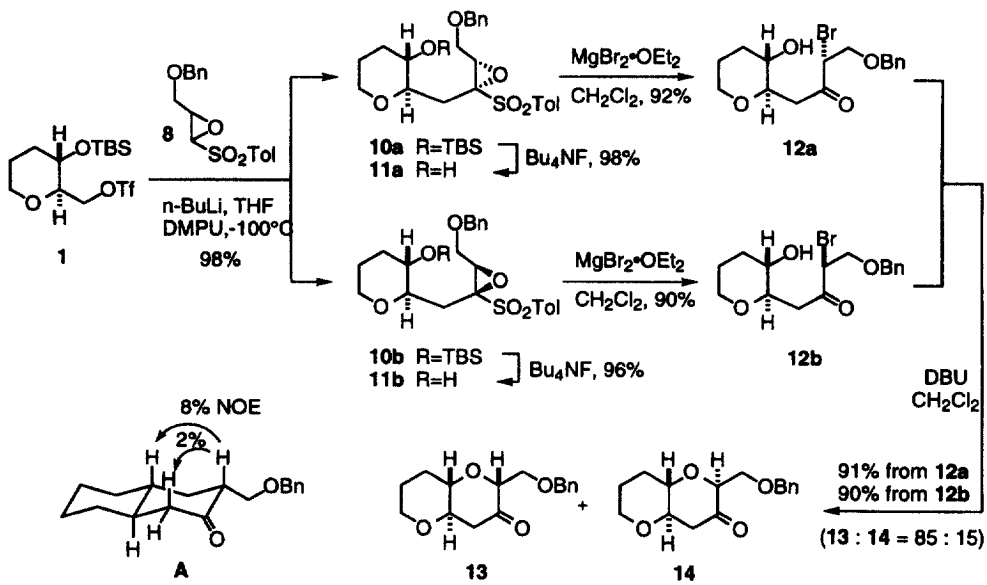
could be easily obtained from allyl benzyl ether in only three steps. We report herein a practical synthesis of **4** employing racemic *cis*- and *trans*-epoxy sulfones.

Racemic *cis*- and *trans*-epoxy sulfones were prepared from allyl benzyl ether **5** (Scheme 2). Reaction of **5** with sodium *p*-toluenesulfinate in the presence of iodine followed by treatment with triethylamine gave **6** and **7** in 83% yield as a 3:1 separable mixture. Epoxidation of each isomer with lithium *t*-butyl peroxide afforded *trans*- and *cis*-epoxy sulfones **8** and **9**, respectively.[5]



Scheme 2. Reaction conditions: (a) *n*-BuLi, *t*-BuOOH, THF, –78°C, 30 min; 0°C, 20 h

The monocyclic triflate **1** was prepared in 93% yield from (2*R*,3*S*)-3-hydroxy-2-hydroxymethyltetrahydropyran by the regioselective triflation of the primary hydroxyl group and silylation of the secondary hydroxyl group using a one-pot procedure.[4] Coupling reaction of **1** with the oxiranyl anion generated from the racemic *trans*-epoxy sulfone **8** was carried out by an internal quenching method. A mixture of **1** and **8** in THF–DMPU at –100°C was treated with *n*-butyllithium to give a separable 1:1 mixture of diastereoisomers **10a** and **10b** (Scheme 3). The stereochemistry of the epoxide of each isomer, which is not crucial for the final tetrahydropyran ring formation, was established at a later stage (vide infra).



Scheme 3.

The attempted 6-*endo* cyclization of **10a,b** and the corresponding desilylated compounds **11a,b** with various acids such as PPTS, *p*-TsOH, and $BF_3 \cdot OEt_2$ was unsuccessful and resulted in the recovery of the starting material (Scheme 3). Reaction of **11a,b** with $MgBr_2 \cdot OEt_2$ gave α-bromo-γ′-hydroxy ketones **12a,b**, respectively, instead of the expected cyclized product.[6] The stereoselectivity of this reaction is

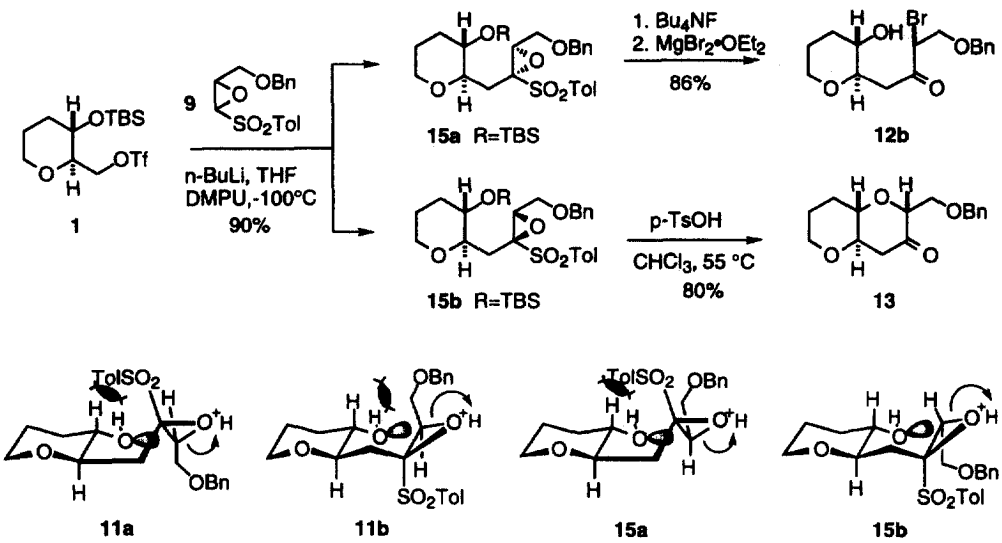


Figure 1. Presumed transition states of hydroxy epoxy sulfones **11a,b** and **15a,b**

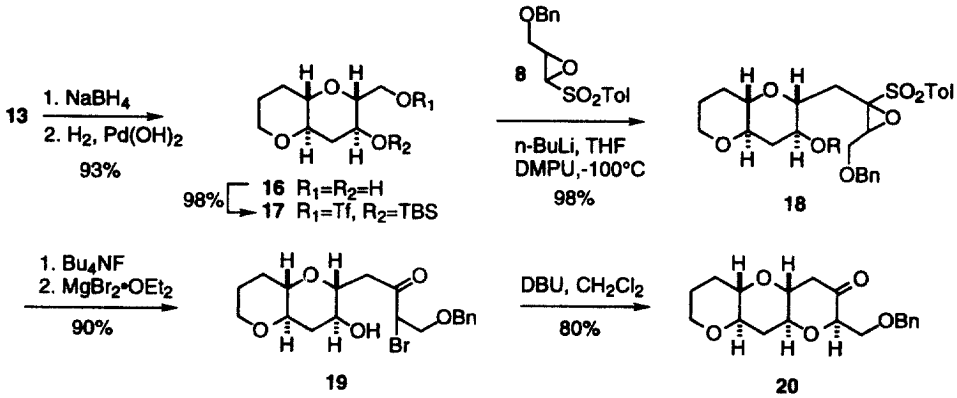
more than 97:3 and the stereocenter of the bromine-attached carbon was assigned based on an S_N2-type ring-opening of epoxide. Exposure of **11a** to other Lewis acids such as $TiCl_4$ and $ZnCl_2$ led to the formation of the corresponding chloroketone in high yield. It is noteworthy that the formation of hemiketals of **12a,b** was not observed in these reaction conditions.

Then, we envisioned the intramolecular cyclization of hydroxy bromoketones **12a,b**. Interestingly, such a simple approach has not been reported so far. We expected that both isomers would provide the same product **13** because the cyclization product **14**, having an axial side chain, could isomerize to a thermodynamically more stable isomer under the base-induced cyclization conditions. After several attempts with different bases, it was found that reaction of **12a,b** with DBU led to a clean cyclization to give the same 85:15 diastereomeric mixture of products, respectively. Chromatographic separation gave the bicyclic ketones **13** and **14** in 77 and 14%, respectively. These results indicated that racemic *trans*-epoxy sulfone **8** could be used as a building block for tetrahydropyran synthesis. In practice, **13** was prepared from **1** in 68% overall yield without separation of the isomers **10a** and **10b**. The stereochemistry of the major isomer **13** was determined by the NOE measurements (**A**) to have a thermodynamically stable *anti–syn* configuration. Isomerization of the minor isomer **14** to the isomer **13** was effected by treatment with DBU in 78% yield.

We next turned our attention to utilization of racemic *cis*-epoxy sulfone **9** for the tetrahydropyran synthesis. The coupling reaction of **1** and **9** proceeded uneventfully to give a separable 1:1 mixture of **15a**:**15b** in 90% yield. The NMR data of **15b** were in good accordance with those of **3** prepared from the optically active **2**, indicating that **15b** is a β-epoxy isomer. The desilylated compound of **15a** was found to be intact under the 6-*endo* cyclization conditions with *p*-TsOH and $BF_3 \cdot OEt_2$. Treatment with $MgBr_2 \cdot OEt_2$ gave a bromoketone which was identical to **12b** obtained from *trans*-epoxy sulfone **11b**. Therefore, the stereochemistry of **11b** was assigned to be a β-epoxy isomer at this stage. By contrast, the isomer **15b**, which has the same stereochemistry as **3**, cyclized easily upon treatment with *p*-TsOH and afforded **13** in 80% yield as a single isomer. This indicates that only isomer **15b** can adopt a chair-like six-membered transition state that has no serious nonbonded interactions like those of the other isomers as shown in Fig. 1. Moreover, reaction of **15b** with $MgBr_2 \cdot OEt_2$ afforded the expected bromoketone **12a**.

The reduction of **13** with sodium borohydride followed by debenzylation gave the bicyclic diol **16**, from which point the original steps can be repeated (Scheme 4). Thus, the coupling reaction of the

oxiranyl anion generated from racemic *trans*-epoxy sulfone **8** with triflate **17** gave **18** in 98% yield as a 1:1 diastereoisomeric mixture.



Scheme 4.

The mixture was, without separation, subjected to desilylation followed by treatment with $MgBr_2 \cdot OEt_2$ to give bromoketone **19** in 90% yield. Cyclization with DBU proceeded in 94% yield with an 85:15 selectivity and the *trans*-fused tricyclic ketone **20** was isolated in 80% yield. The overall yield of the desired ketone **20** from **16** was 76% including an additional isomerization reaction of the isomer of **20**. These results constitute the first examples of tetrahydropyran formation by hydroxy-bromide cyclization.[7]

In conclusion, we have developed a practical method for the synthesis of a *trans*-fused polytetrahydropyran ring system utilizing both racemic *cis*- and *trans*-epoxy sulfones via the DBU-induced intramolecular cyclization of α-bromo-γ′-hydroxy ketones.

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