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# Stereocontrolled construction of tetrasubstituted tetrahydrofurans: synthesis of 2,5-anhydro D-glucitol ☆

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ABSTRACT

A highly stereoselective construction of 2,3,4,5-tetrasubstituted tetrahydrofurans has been accomplished by an unusual intramolecular 5-*endo-tet* cyclization of 2,3-epoxy alcohols involving hydroxyl nucleophile. The method has been utilized for the synthesis of 2,5-anhydro D-glucitol through two different approaches starting from the chiral molecule, L(+)-diethyl tartarate or from the non-chiral compound, allyl bromide or *cis*-but-2-ene-1,4-diol. This synthetic method is a useful example of *5-endo-tet* cyclization of 2,3-epoxy alcohols.



The presence of tetrahydrofuran (THF) moiety in a wide variety of natural products[1] has attracted the attention of synthetic organic chemists and several novel methods for their synthesis have been developed.[2] The conformation and stereochemistry of the tetrahydrofuranoid structure are very important for the bioactivity of the natural products having this structure. Aurodox and efrotomycin are two of the most important members of the elfamycin family of the antibiotics which possess tetrasubstituted THF ring as the core structure.[3] Dolle and Nicolaou constructed[4] the intermediate fragment having THF ring for the preparation of these antibiotics, involving the sequence of *5-exo-tet* cyclization of an epoxide system according to Baldwin's rules.[5] We report in this communication a useful example of the 5-*endo-tet* cyclization mode[6] as a method to prepare tetrasubstituted THF ring system from 2,3-epoxy alcohols and the application of the method for the synthesis of 2,5-anhydro D-glucitol (**1**). Compound **1** can be utilized as an important intermediate for the synthesis of THF ring containing natural products. Previously some methods were developed for the synthesis of **1**.[7] However, the present method constitutes a novel approach for synthesis of this compound.

The retrosynthetic analysis (Scheme 1) demonstrates that the compound **1** can be obtained from the intermediate **2** (by 5-*endo-tet* cyclization) which can be prepared from the α,β-unsaturated ester **3** generated from L(+)-diethyl tartarate (**5**) via the formation of the alcohol **4**.

We initiated the synthesis of 2,5-anhydro glucitol (**1**) with commercially available L(+)-diethyl tartarate (**5**) (Scheme 2). Out of four contiguous stereocenters of **1** two stereocenters were manipulated from this compound. Compound **5** was converted into **3** following the reported methods.[8] Subsequent reduction of the latter with DIBAL-H produced the allylic alcohol **9** which is a suitable entity for Sharpless epoxidation to generate the other two chiral centers present in **1**. Thus the treatment of **9** with $Ti(O^iPr)_4$ (0.2 equiv), (+)-DIPT (0.3 equiv), and TBHP (2.5 equiv) in $CH_2Cl_2$ at −20 °C afforded the desired epoxy alcohol **2** which was chirally pure after purification. All the products of this synthetic sequence were obtained in high yields.

The deprotection and cyclization of **2** were attempted with both protic acid, *p*-TSA and Lewis acid, $BF_3{\cdot}OEt_2$ using ethylene glycol. It was observed that with *p*-TSA the *endo-tet* cyclization product **7** was obtained in low yield along with side products. However, when $BF_3{\cdot}OEt_2$ was used, compound **7** was obtained in high yield (72%) within 3 h (Scheme 3). On continuation of the reaction for 12 h the cyclized and deprotected product 2,5-anhydro D-glucitol (**1**) was obtained.

The alternative retrosynthetic analysis (Scheme 4) indicates that 2,5-anhydro D-glucitol (**1**) can be prepared from the epoxy alcohol **8** (by 5-*endo-tet* cyclization) which in turn can be obtained from the allylic alcohol **10** generated from allylic bromide **11** or *cis*-but-2-ene-1,4-diol (**12**). This synthetic approach constitutes the preparation of **1** starting from non-chiral molecules.

Allyl bromide (**11**) or *cis*-but-2-ene-1,4-diol (**12**) was initially converted into the allyl alcohol (**10**) following the reported methods.[9,10] This allylic alcohol (**10**) underwent Sharpless epoxidation to form the epoxide **13** which was oxidized to the corresponding aldehyde **14** with IBX in DMSO and $CH_2Cl_2$ (Scheme 5). Subsequent homologation of **14** (not isolated) by Wittig method using ethoxycarboxymethylene triphenylphosphorane afforded the

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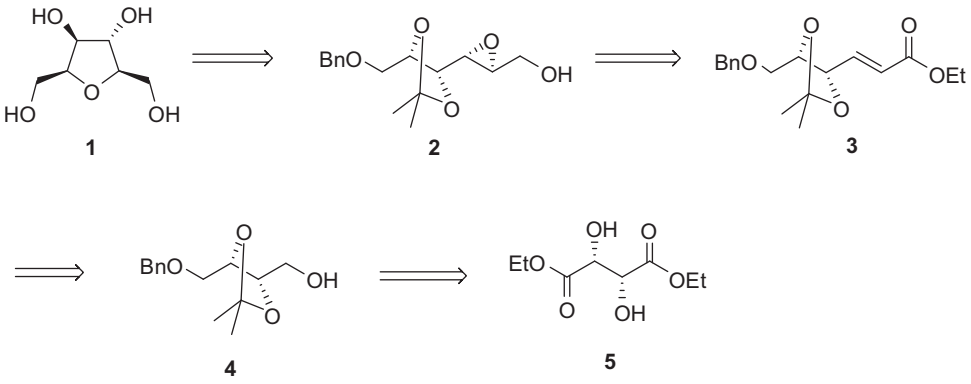
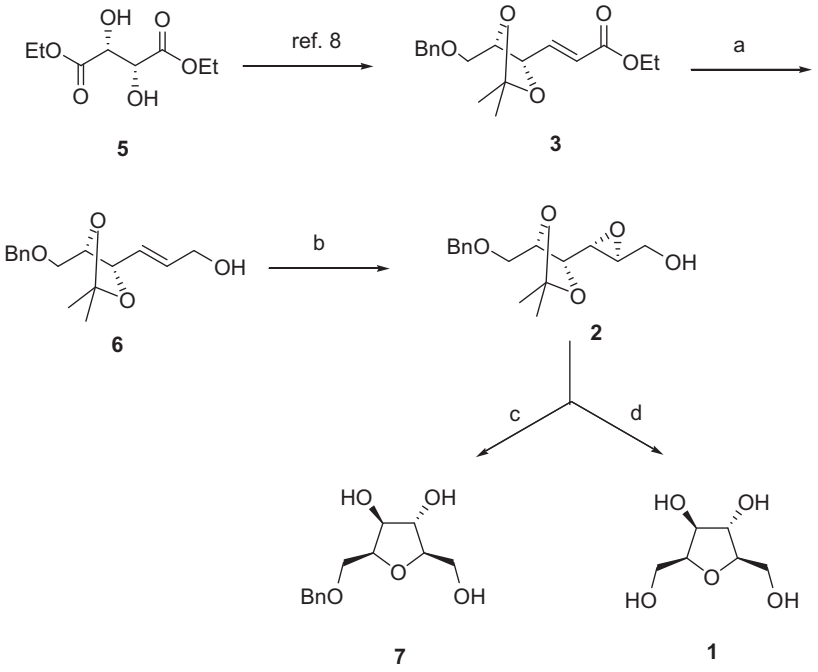
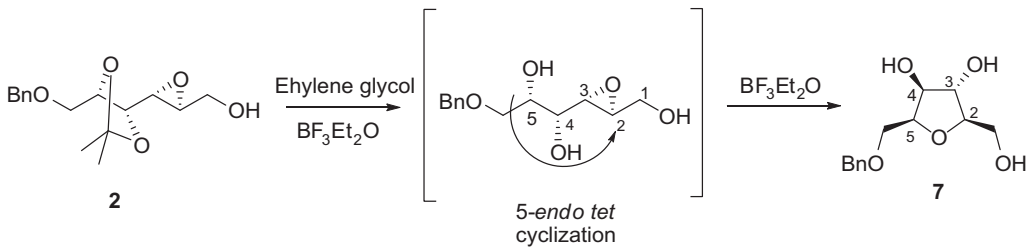


**Scheme 1.** Retrosynthetic analysis of 2,5-anhydro D-glucitol **1**.

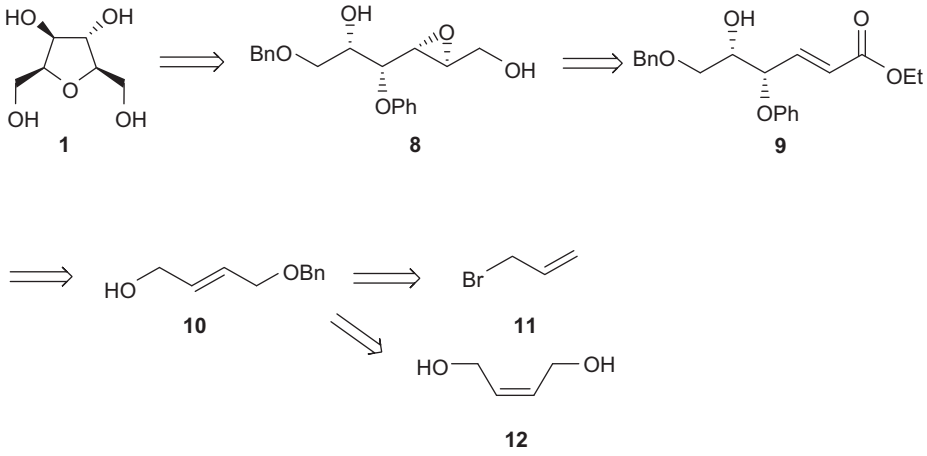


**Scheme 2.** Synthesis of tetrasubstituted tetrahydrofurans **1** and **7**. Reagents and conditions: (a) DIBAL-H, $CH_2Cl_2$, −78 to −10 °C, 0.5 h, 82%; (b) $Ti(^iOPr)_4$ (0.2 equiv), (+)-DIPT (0.3 equiv), TBHP (2.5 equiv), $CH_2Cl_2$, −20 °C, 12 h, 82%; (c) ethylene glycol, $BF_3{\cdot}Et_2O$, $CH_2Cl_2$, −0 °C to rt, 3.5 h, 72%; (d) ethylene glycol, $BF_3{\cdot}Et_2O$, $CH_2Cl_2$, −0 °C to rt, 12 h, 67%.

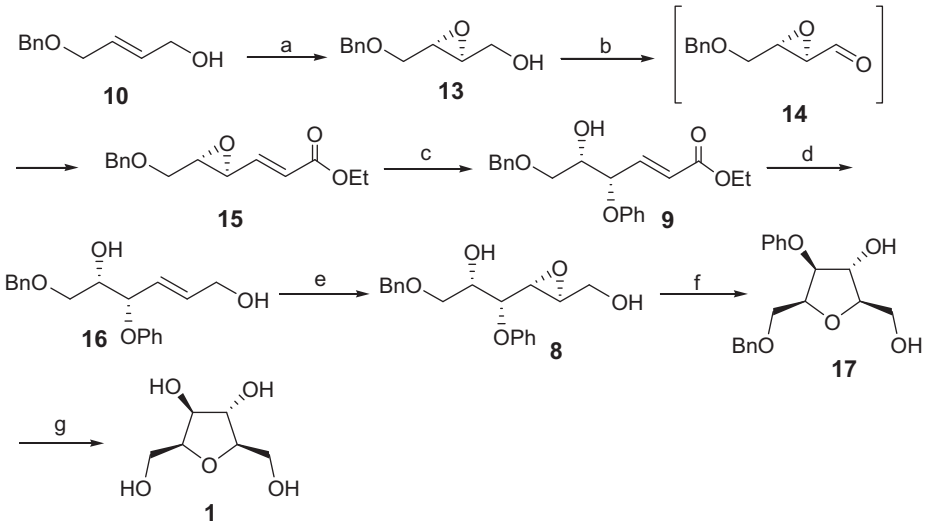


**Scheme 3.** Conversion of **2** into **7**.

α,β-unsaturated ester **15**. The opening of the epoxide ring of **15** to form the compound **9** was carried out by utilizing the method of double inversion for retention of configuration of the *syn*-centers.[11] This conversion was successful by using triphenyl borate, pinacol, and $[Pd(PPh_3)_4]$ at room temperature. Subsequent reduction of **9** with DIBAL-H to form the allylic alcohol **16** followed by asymmetric epoxidation afforded the desired epoxy alcohol **8**. Compound **8** underwent 5-*endo-tet* cyclization (as shown in Scheme 3) by reaction with CSA in $CH_2Cl_2$ to form the tetrasubstituted tetrahydrofuran **17**. Deprotection of both phenyl and benzyl groups of **17** was achieved by treatment with ammonium formate and Pd/C in hydrogen atmosphere to yield 2,5-anhydro D-glucitol (**1**). The spectral properties of the compound were found to be identical to those reported earlier.[7a]




**Scheme 4.** Alternative retrosynthetic analysis of 2,5-anhydro D-glucitol **1**.




**Scheme 5.** Alternative synthesis of 2,5-anhydro D-glucitol **1**. Reagents and conditions: (a) $Ti(^{i}OPr)_4$ (0.2 equiv), (+)-DIPT (0.3 equiv), TBHP (2.5 equiv), $CH_2Cl_2$, −20 °C, 4 h, 93%, ee 97%; (b) (i) IBX, DMSO, $CH_2Cl_2$, 0 °C to rt, 3 h; (ii) $PPh_3CHCOOEt$, $CH_2Cl_2$, rt, 2 h, 82% (in two steps); (c) $[Pd(PPh_3)_4]$, pinacol, $B(OPh)_3$, THF, rt, 30 min, 89%; (d) DIBAL-H, $CH_2Cl_2$, −78 °C, 3 h, 83%; (e) $Ti(^{i}OPr)_4$, (+)-DET, TBHP, $CH_2Cl_2$, −20 °C, 78%, ee 96%; (f) CSA, $CH_2Cl_2$, 0 °C, 20 min, 72%; (g) ammonium formate, Pd/C, MeOH, reflux, 4 h, 67%.

The THF derivative **7** was formed from the epoxy alcohol derived from **2** (Scheme 3) and the other related compound **17** from **8** (Scheme 5) by 5-*endo-tet* cyclization. The epoxide ring in each compound (**2** or **8**) is in α-orientation. It is activated by the Lewis or protic acid and the hydroxyl nucleophile at C-5 attacks the C-2 position from the opposite direction of the epoxide ring to open it. Thus the cyclization takes place resulting in the formation of a THF derivative with the inversion of configuration at C-2 without disturbing the remaining stereogenic centers.

In conclusion, we have developed a highly stereoselective synthesis of tetrasubstituted tetrahydrofurans following two approaches starting from a chiral or a non-chiral molecule by applying intramolecular 5-*endo-tet* cyclization of 2,3-epoxy alcohols involving hydroxyl nucleophile. This synthetic method is a useful example of the 5-*endo-tet* mode of cyclization. In our approach the *syn*-opening of the epoxide ring has been accomplished to generate the required 2,3-epoxy alcohol.

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