Stereoselective synthesis of highly *O*-functionalized enantiopure 2,3,4-trisubstituted tetrahydrofurans by tandem debenzylative cyclization of glycal derived 2,3-epoxy alcohols†‡

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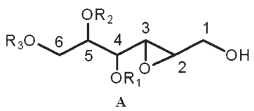
A new and highly efficient methodology for the construction of synthetically important highly *O*-functionalized enantiopure 2,3,4-trisubstituted tetrahydrofurans with three contiguous stereocenters is reported.

Functionalized tetrahydrofurans (oxolanes) are found in many naturally occurring compounds.[1–3] The dihydroxylated tetrahydrofuran unit is a common heterocyclic fragment present in natural products of great biological importance. Such units have constituted important synthons for the synthesis of pharmacologically important furanoid groups, such as cytotoxic anhydrophytosphingosine,[4] goniothalesdiol,[5] and the inhibitor of endogenous DNA polymerase of hepatitis B virus (HBV), virgutasin.[6] Polysubstituted tetrahydrofurans play an important role in organic chemistry due to the fact that they are important intermediates in the synthesis of novel nucleosides with potent chemotherapeutic activity such as tiazofurin and selenazofurin.[7] In addition, many anhydro-alditols (sugar derived tetrahydrofurans) are of great interest due to their industrial applications and biological properties, an example of which is SPAN-40,[8] a sorbitan fatty acid ester employed to use microbubbles for use in diagnostic ultrasound.

Moreover, oxolane units that occur widely in nature as constituents of marine and terrestrial organisms[9,10] exhibit remarkable antibiotic or cytotoxic effects, which have opened perspectives for selected clinical applications.[9] This circumstance has bought about a growing demand for cyclic ethers in general and tetrahydrofuran derived natural products in particular.[10,11] Since their supply cannot be met from natural sources alone, the invention of methods for stereoselective construction of tetrahydrofuran has received considerable attention.

Among the number of known methods available in the literature[12,13] intramolecular cyclization of epoxy alcohols is one of the useful strategies for the construction of the oxygen heterocycles. In fact, many biologically active compounds have been synthesized according to this strategy.[12,14] An epoxide may result in five or six membered oxygen heterocycles depending upon its mode of opening in a regioselective manner. Therefore regioselective cyclization has been paid considerable attention during the past decades.[15]

As a part of our ongoing effort to explore the utility of glycal derived 2,3-epoxy alcohols of general structure **A**,[16] we describe herein an efficient strategy for the synthesis of highly substituted enantiopure tetrahydrofurans starting from the glycal derived 2,3-epoxy alcohols.



A

Our idea for the synthesis of the tetrahydrofuran has emanated from the recent report by White *et al.* on the preparation of tetrahydrofuran by an intramolecular iodoetherification reaction involving the participation of secondary benzyl protected oxygen in cyclization followed by debenzylation.[17]

As it is well known that C-2 selective substitution reaction of 2,3-epoxy alcohol is extremely difficult.[18] Therefore, our retrosynthetic strategy (Fig. 1) involves the regioselective opening of the 2,3-epoxy ring at C-3 by intramolecular nucleophilic attack of the oxygen atom of the C-6 benzyloxy group to furnish the required THF derivative.

Scheme 1 unfolds the details of the route followed for the stereoselective synthesis of the highly functionalized tetrahydrofuran. The allylic alcohol **3** was prepared from glycal **1** in two steps by its Perlin hydrolysis[19] followed by Luche reduction[20] of aldehyde **2**. Catalytic Sharpless asymmetric epoxidation[21] of **3** afforded the enantiomerically pure epoxide **4** (>99% diastereoselectivity) in good yield.

Being aware of the report that heating D-glucitol with anhydrous pyridinium chloride at 120–160 °C over several hours affords the 1,4-anhydro-D-glucitol in fairly good yield,[8,22] our journey towards the goal started with the use of hydrazine salts. Initial attempt to achieve the goal proceeded by stirring of the epoxide **4** in refluxing ethanol in the presence of a catalytic amount of *t*-butyl hydrazine hydrochloride. After 6 h of continuous stirring we noticed 100% conversion of reactant **4** to furnish the product, **5**, whose structure was elucidated by preparing its acetyl derivative

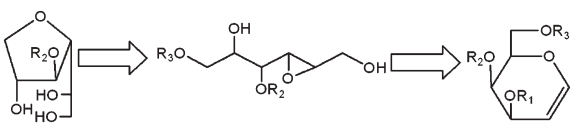


Fig. 1 Retro synthetic pathway.

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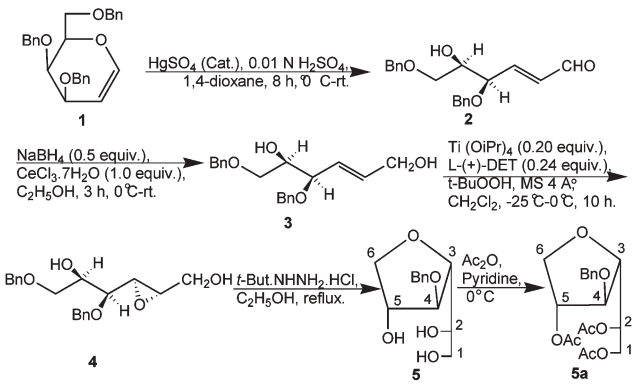
‡ Electronic supplementary information (ESI) available: Experimental procedure, ^{1}H and ^{13}C NMR spectra of all the THFs along with 2D NMR spectra of **5, 5a, 9, 9a**. See DOI: 10.1039/b606519h



Scheme 1 Synthetic route starting from tribenzylated galactal.

(**5a**). The structure of the chromatographically pure compound **5a** was established by the combined use of one and two dimensional NMR experiments (ESI‡).

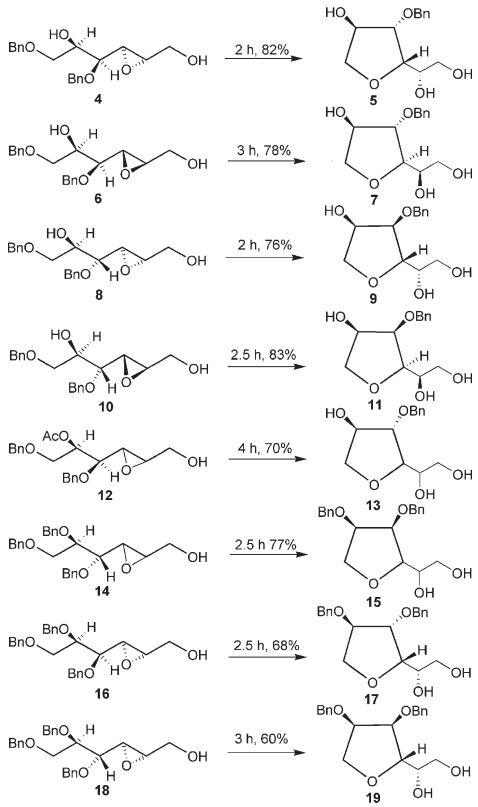
In the ^{1}H NMR spectrum the presence of five aromatic protons along with two benzylic methylene proton (AB spin system) signals clearly suggested the presence of one benzyl group in the system. The three methyl signals of the acetate at 1.86, 2.06 and 2.10 ppm, corresponded to the number of hydroxyl groups in **5**, indicated the opening of the epoxide ring during the course of the reaction. The differentiation of the two methylene carbon signals (C-1 and C-6) were carried out based on the corresponding downfield ^{13}C chemical shifts for the C-6 carbon (71.5 ppm) with respect to C-1 (63.1 ppm). Further, the long range heteronuclear correlations of the H-6 methylene protons with C-5, C-4 as well as with C-3 carbon atoms unequivocally supported the formation of the tetrahydrofuran like structure. Moreover, the HMBC correlations observed for the H-2, H-3 methine protons and H-1 methylene protons were found in accordance with the expected structure and explicitly confirmed the formation of the tetrahydrofuran derivative (**5a**). Further, the relative stereochemistry of the acetate product **5a** was deduced from the 2D NOESY spectrum, where the correlations indicated the H-3 and H-4 protons to be *cis* in nature.

After confirming the structure of **5**[23] the same transformation was carried out using piperazine salts[24] and hydrazine salts. Among them hydrazine salts (Table 1), especially phenyl hydrazine hydrochloride, were found to be the most effective in terms of the yield of the THF.

After optimizing the reaction a series of enantiomerically pure epoxides[21b] **6**, **8** and **10** were subjected to debenzylative stereoselective cyclization (Scheme 2) to afford their respective THFs **7**, **9** and **11**. The tetrahydrofuran **9** was acetylated and the structure of the acetate derivative **9a** was checked by the combined use of one and two dimensional NMR experiments. The 2D NOESY

Table 1 Results with different hydrazine salts

Salt No.	Amine salt	Time/h	Yield (%)
1	Hydrazine hydrochloride	6.0	55
2	*t*-Butyl hydrazine hydrochloride	4.0	60
3	Phenyl hydrazine hydrochloride	2.0	82
4	2,4-Difluoro phenyl hydrazine hydrochloride	1.5	62



Scheme 2 Debenzylative cyclizations of 2,3-epoxy alcohols.

spectrum of **9a** indicated that the H-3 and H-4 protons are *trans* in nature as expected.

Further, we were interested to notice whether there would be any change in the course of the reaction if the 5-OH group was protected. So, a 5-OH acyl protected diastereomeric mixture of epoxide **12** (dr 32 : 68) prepared by *m*-CPBA epoxidation of its corresponding allylic alcohol, was subjected to the above transformation, and was found to be intolerant of the reaction conditions resulting in the deacetylated diastereomeric mixture of tetrahydrofuran **13**. Then this transformation was performed with the 5-OH benzyl protected epoxide **14** (dr 28 : 72). To our delight expected tetrahydrofuran **15** was obtained in 77% yield. Later the same procedure was extended for the preparation of the dibenzyl protected tetrahydrofurans **17** and **19** from their respective enantiomerically pure epoxides **16** and **18**. In total the results obtained (Scheme 2) were general and satisfactory.

This transformation thus led to confirmation that irrespective of the nature of 5-OH, whether it is protected or unprotected, the ring opening of the 2,3-epoxy alcohols is highly regio- and stereoselective leading to highly functionalized tetrahydrofurans *via* intramolecular cyclization by nucleophilic attack of oxygen atom of the C-6 benzyloxy group followed by debenzylation.

Based on the above results it seems that the facile cleavage (Fig. 2) of the oxonium ion intermediate (**c**) resulted in the expected trisubstituted tetrahydrofuran. All the spectroscopic data are in accord with their structures.

In summary, a general method for the synthesis of 2,3,4-trisubstituted tetrahydrofurans (having 5-OH protected/unprotected) with high enantiomeric purity in good yield has been disclosed. To the best of our knowledge this is the first report on

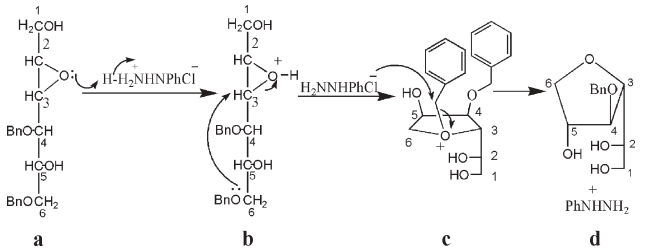


Fig. 2 Proposed mechanism.

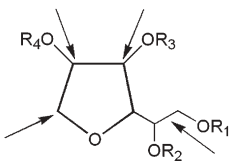


Fig. 3 Sites of diversification.

the illustrated chemistry described herein to obtain densely functionalized enantiomerically pure tetrahydrofurans. Moreover, the tetrahydrofurans synthesised above are unique due to the four point diversity (Fig. 3) and multiple stereocenters present in them. The utility of these templates (THFs) in the synthesis of biologically important natural products, including oligosaccharides, along with their analogues will be presented in due course.

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23 82% yield, mp 76–78 °C, $[\alpha]_D^{20}$ 53.12 (*c* 0.064, $CHCl_3$), column chromatography, 3 : 97 MeOH–$CHCl_3$ v/v, R_f 0.27 (1 : 9 MeOH–$CHCl_3$), ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.41 (brs, 3H, 3 × OH), 3.67–3.81 (m, 3H, H-1 and H-6a), 3.92 (brm, 1H, H-2), 4.02–4.06 (m, 3H, H-3, H-4, H-6b), 4.28 (brd, J = 2.4 Hz, 1H, H-5), 4.55 (d, J = 11.6 Hz, 1H, CH_2Ph), 4.63 (d, J = 12 Hz, 1H, CH_2Ph); 7.26-7.30 (m, 5H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 64.1 (C-1), 69.3 (C-2), 72.3 (CH_2Ph), 73.8 (C-6), 74.4 (C-5), 79.6 (C-3), 84.1 (C-4), 127.6 (ArC), 127.7 (ArC), 128.4 (ArC), 138.0 (qC); IR (KBr, cm^{-1}) 3393 (O–H str), 3018 (=C–H str), 2933, 2882 (C–H str), 1655, 1497, 1456 (C=C str), 1216, 1086 (C–O str); mass (ESI-MS) *m/z* 277 [M^+ + Na]; EI-HRMS: (M + H) calcd for $C_{13}H_{18}O_5$ + H 255.1241, found 255.1232.

24 Though THF was formed in this case, the separation of product became difficult as the R_f value of the tetrahydrofuran formed was the same as that of the amine salt.

