A Facile Approach to Polysubstituted Chiral Dihydrofurans on Carbohydrate Templates

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A one-step procedure from *cis*-oriented epoxy pyranose triflates and monoanions of 1,3-dicarbonyl compounds to polyfunctionalized dihydrofurans is described.

Furanoid ring systems of rich stereochemical complexity are important structural units in a wide variety of naturally occuring substances.[1] Therefore, the synthesis of chiral tetrahydrofuran[2a] and dihydrofuran[2b] derivatives has attracted increasing attention, and a whole series of new synthetic methods have been recently developed. In connection with the synthesis of natural products *via* pyranose annulation, we needed a stereospecific and mild method for the construction of ring systems on carbohydrates.[3] Due to their ready accessibility and versatility towards chemical transformations, the epoxy triflates **1** and **4** are key intermediates for the preperation of a large variety of chiral building blocks bearing the stereochemical and the functional code of the intended synthetic target.[3] In this context and based on our earlier investigations,[3a] the nucleophilic addition of the dianions of β-dicarbonyl compounds to **1** and **4** was found to be based on two facts, namely (*a*) the C-alkylation of the trifluoromethanesulfonyl group is enormously facile compared to the nucleophilic opening of an oxirane, and (*b*) due to almost complete exclusion of the thermodynamically preferred C-alkylation, the O-alkylation of the ketone enolate *via* 5-enol *exo-exo*-tet ring closure (Scheme 1)[3a,4] leading to tetrahydrofurylidene is observed under kinetic conditions.

The monoanions of β-dicarbonyl compounds allow expeditious entries to polysubstituted chiral dihydrofuran derivatives *via* the nucleophilic attack at the triflate group of the epoxy sugars **1** and **4** followed by O-alkylation of the oxirane ring. Thus, the conversion of benzyl 4-*O*-trifluoromethanesulfonyl-2,3-anhydro-β-L-ribopyranoside **1** to the dihydrofuran **3**† is conveniently carried out by the addition of 5 equiv. of the monoanion of *tert*-butyl acetoacetate **2** in THF to the *cis*-oriented epoxy triflate **1**. Only a single dihydrofuran isomer is produced from the intermediate **I**, which should exist in a diastereoisomeric mixture (Scheme 2). All attempts to isolate the intermediate **I** failed. The process seems to involve a fast proton transfer from the intermediate **I** to the unreacted anion, leading to intermediate **II**, followed by a 5-enol *endo-exo*-tet ring closure[4] to deliver the desired dihydrofuran **3** in 78% yield. However, due to stereoelectronic factors, no transformation to the cyclopropanated sugar **III** (involving the disfavoured 3-enol *exo-exo*-tet ring-closure process)[4] was observed as was received by nucleophilic epoxide ring opening by the acetonitrile carbanion.[3d-f]

Following the same procedure, the stereoisomeric dihydrofuran **5**‡ was obtained in 85% yield (Table 1, entry 2) from the pyranoside **4**. The stereostructures of the furanoids **3** and **5** were deduced from their ^{1}H NMR spectra. The resonances of H-3 of compounds **3** and **5** are observed as double doublets at δ 4.45 (*J* 8.4, 10.3 Hz) and δ 4.66 (*J* 4.9, 9.6 Hz), respectively. Compound **3** adopts the $^1C_4$ and the furanoid **5** the $^4C_1$ conformation, as concluded from the chemical shifts and the coupling constants of their anomeric protons.[3b] H-1 of **3** appears as a doublet (*J* 6.3 Hz) at δ 4.53 while that of **5** resonates as a doublet (*J* 3.3 Hz) at δ 4.8. Additionally, the *exo*-methyl groups in **3** and **5** appear as doublets at δ 2.11 (*J* 1.5 Hz) and δ 2.10 (*J* 1.1 Hz), respectively, due to the homoallylic coupling with H-4. In order to extend this new dihydrofuran synthesis to more complex systems, we investigated related reactions with branched β-dicarbonyl systems. The *cis*-fused furanoids **9**, **10** and **12**, **13**§ (Table 1, entries 4–7) are prepared analogously as mentioned earlier by reacting methyl propionyl acetate **8** and ethyl isobutyryl acetate **11** with the two anhydroriboses **1** and **4**. The general applicability of this method is also tested with the symmetrical dione acetylacetone **6** and the trione **14** (di-*tert*-butyl 1,3-acetonedicarboxylate Table 1, entries 3 and 8) leading to the branched furanoids **7** and **15**,¶ respectively. The reaction can be performed also with aromatic β-dicarbonyl compounds leading to the phenyl-substituted dihydrofuran **17**, a potential intermediate for a highly substituted tetralone system, (Table 1, entry 9).[5]

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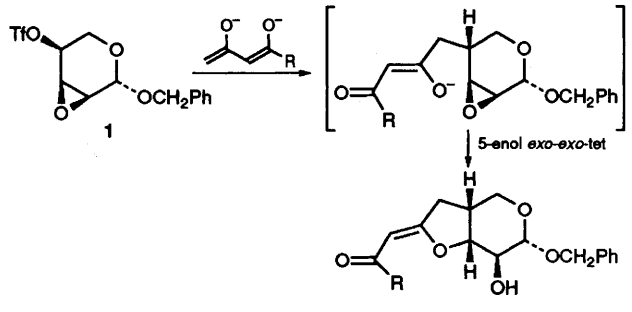
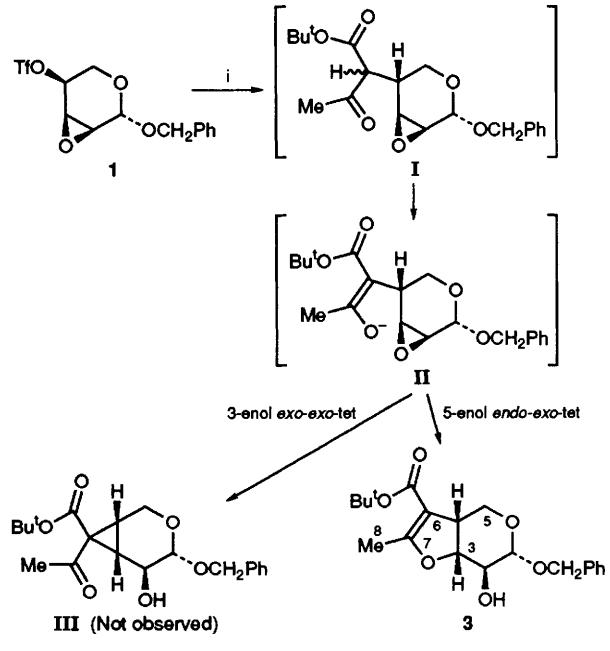
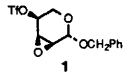
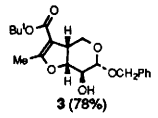
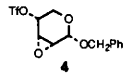
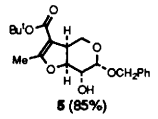
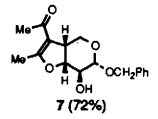
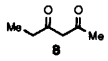
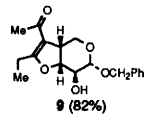
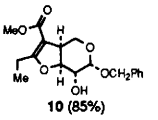
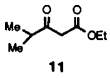
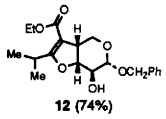
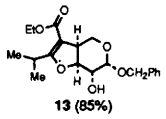
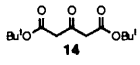
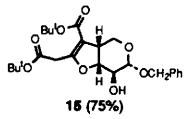
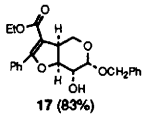


Scheme 1 Tetrahydrofurylidene formation from epoxy pyranose triflate **1** and 1,3-dicarbonyl compounds



Scheme 2 *Reagents and conditions*: i, 5 equiv. NaH, 15-crown-5, THF, 5 equiv. *tert*-butyl acetoacetate, 0 °C → room temperature, 2–3 h

Table 1 Reaction products from β-dicarbonyl compounds with epoxy triflates **1** and **4**

Entry	Substrate	Reagent	Product[a] (% yield)[b]
1	 **1**	 **2**	 **3** (78%)
2	 **4**	**2**	 **5** (85%)
3	**1**	 **6**	 **7** (72%)
4	**1**	 **8**	 **9** (82%)
5	**4**	**8**	 **10** (85%)
6	**1**	 **11**	 **12** (74%)
7	**4**	**11**	 **13** (85%)
8	**1**	 **14**	 **15** (75%)
9	**4**	 **16**	 **17** (83%)

[a] All reactions are carried out in THF at 0 °C → room temperature for 2–3 h. [b] After purification on silica gel chromatography

Footnotes

† *Selected NMR data* for **3**: δ_H (400 MHz, $CDCl_3$) 3.59 (1 H, m, 4-H), 3.76 (1 H, t, *J* 11.8 Hz, 5-H), 3.78 (1 H, ddd, *J* 3.4, 6.3, 9.0 Hz, 2-H), 3.90 (1 H, dd, *J* 6.9, 11.8 Hz, 5′-H), 4.45 (1 H, dd, *J* 8.4, 10.3 Hz, 3-H), 4.53 (1 H, d, *J* 6.3 Hz, 1-H), δ_c (100 MHz, $CDCl_3$), 99.9 (1-C).

‡ *Selected NMR data* for **5**: δ_H (400 MHz, $CDCl_3$) 3.23 (1 H, m, 4-*H*), 3.70 (1 H, dd, *J* 3.6, 11.7 Hz, 5-H), 3.93 (1 H, dd, *J* 4.5, 8.6 Hz, 2-*H*), 4.00 (1 H, dd, *J* 4.5, 11.7 Hz, 5′-H), 4.66 (1 H, dd, *J* 4.9, 9.6 Hz, 3-H), 4.80 (1H, d, *J* 3.3 Hz, 1-H); δ_C (100 MHz, $CDCl_3$) 95.4 (1-C).

§ *Selected NMR data* for **13**: δ_H (400 MHz, $CDCl_3$) 3.27 (1 H, m, 4-H) 3.72 (1 H, dd, *J* 3.7, 11.7 Hz, 5-H), 3.90 (1 H, dd, *J* 4.6, 8.6 Hz, 2-H), 4.00 (1 H, dd, *J* 4.4, 11.7 Hz, 5′-H) 4.66 (1 H, dd, *J* 5.0, 9.7 Hz, 3-H), 4.77 (1H, d, *J* 4.5 Hz, 1-H); δ_C (100 MHz, $CDCl_3$) 95.7 (1-C).

¶ *Selected NMR data* for **15**: δ_H (400 MHz, $CDCl_3$) 3.42 (1 H, dd, *J* 1.2, 16.3 Hz, 8-H), 3.60 (1 H, br t, *J* 8.7 Hz, 4-H), 3.64 (1 H, d, *J* 16.3, 8′-H), 3.88 (3 H, m, 5-H, 5′-H, 2-H), 4.53 (1 H, dd, *J* 8.7, 10.2 Hz, 3-H), 4.55 (1 H, d, *J* 6.3 Hz, 1-H); δ_C (100 MHz, $CDCl_3$) 99.9 (1-C).

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