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Expeditious Entries to Chiral Furanoids via Pyranose Annulation

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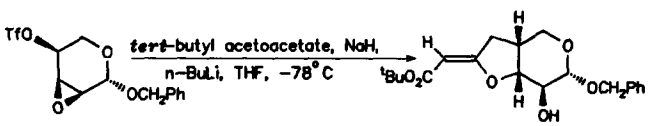
Abstract: A facile synthesis of polysubstituted (*Z*)-tetrahydrofurylidenes using anhydrosugars is described. The (*Z*)-compounds can be conveniently isomerized to the (*E*)-products. The regiochemistry of the annulation reaction can be reversed by judicious choice of the leaving groups.

Due to their frequent occurrence in nature, furanoids are important targets for synthesis either as final products or as useful intermediates. The entire class of polyether antibiotics has at least one furanoid ring.[1] Besides, they represent substructures of a number of bioactive marine[2,3] and terrestrial natural products.[3] Thus, there has been an upsurge in the development of new synthetic methods directed towards furanoid systems.[4,5] In continuation of our interest in pyranose annulation,[6] we describe here efficient approaches to chiral, highly functionalized α-alkylidene tetrahydrofurans via regio- and stereoselective annulation of a pyranose ring. We also demonstrate that two regioisomeric tetrahydrofurylidenes can be obtained from the same anhydrosugar by subtle changes in reaction conditions and the leaving group.

Our strategy banks upon a combination of two facts, namely (a) the nucleophilic displacement of a 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 a delocalized ketone enolate leading to the formation of a five-membered ring is observed under kinetic conditions.[7] Indeed, the dianion[8] of *tert*-butyl acetoacetate (**2**) reacted with benzyl 2,3-anhydro-ß-L-ribopyranoside (**1a**)[9] in THF at -78°C to afford the (*Z*)-tetrahydrofurylidene **3**[10] in 78% yield (Scheme 1, Table 1, entry 1). Encouraged by these results, we have studied the reaction of various sulfonates of anhydrosugars with the dianions of a number of ß-dicarbonyl

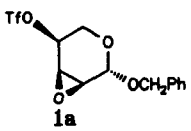
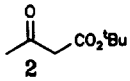
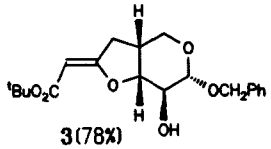
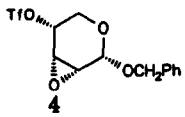
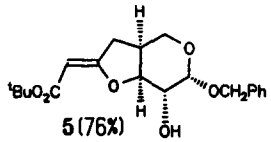
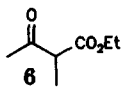
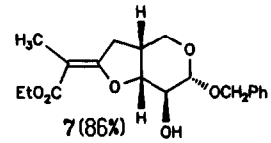
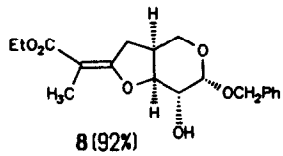
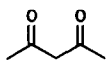
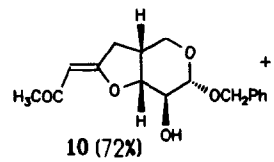
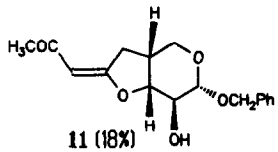
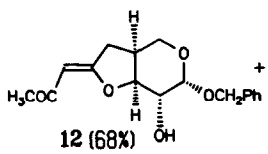
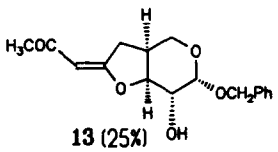
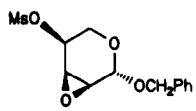
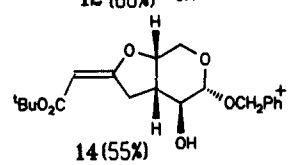
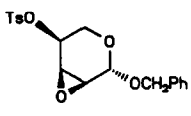


1a **3**

Scheme 1

compounds under different reaction conditions. Our results are summarized in Table 1. A similar reaction (entry 2) with benzyl 2,3-anhydro-α-D-ribopyranoside (**4**)[9] also afforded the (*Z*)-tetrahydrofurylidene **5**[11] as the major product. The reaction of the dianion of the α-methyl-ß-ketoester **6** with **1a** and **4** (entries 3 and 4) afforded the tetrahydrofurylidenes **7**[12] and **8**,[12] respectively. It is noteworthy that in the latter case the (*E*)-isomer **8** (entry 4) was obtained. Acetyl acetone (**9**) also reacts similarly (entries 5 and 6), but in both cases a small amount of (*E*)-product was also isolated (see Table 1). The fact that the relative reactivities of the oxirane and the sulfonate were delicately poised, was indicated by the reaction of the mesylate **1b** with the dianion of **2** (entry 7). The rate of this reaction was insignificant at -78°C, while at higher temperature (0°C), the regioisomeric tetrahydrofurylidenes **14**[13] and **3** were obtained in 2.5:1 ratio. This result also suggests that a fine tuning of the reactivities may permit, at will, the preparation of one regioisomer to the exclusion of the other. In fact, the only tetrahydrofurylidene isolated from the reaction of the tosylate **1c** was **14** (entry 7).

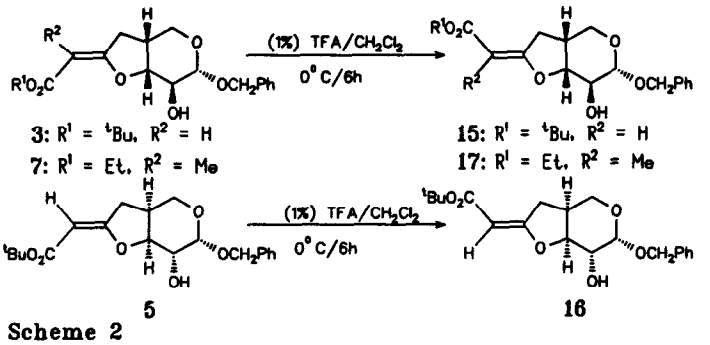
Table 1. Reactions of dianions of ß-dicarbonyl compounds with 4-sulfonyl-2,3-anhydropyranose derivatives.

Entry	Substrates	ß-Dicarbonyl compounds[a]	Cond.[b]	Product(s)
1	 **1a**	 **2**	A	 **3** (78%)
2	 **4**	**2**	A	 **5** (76%)
3	**1a**	 **6**	A	 **7** (86%)
4	**4**	**6**	A	 **8** (92%)
5	**1a**	 **9**	A	 **10** (72%) +  **11** (18%)
6	**4**	**9**	A	 **12** (68%) +  **13** (25%)
7	 **1b**	**2**	B	 **14** (55%) + **3** (22%)
8	 **1c**	**2**	C	**14** (58%, not optimized)

[a] See ref. 8 for the preparation. In each case a solution of the epoxysulfonates in THF was added to the dianion.

[b] A: THF/ -78°C/ 2h; B: THF/ 0°C/ 6h; C: THF/ 0°C→r.t./ 12h.

The compounds **3**, **5** and **7** could be quantitatively converted to the thermodynamically more stable (*E*)-isomers (**15**,[14] **16**[15] and **17**,[12] respectively) upon treatment with 1% TFA in CH_2Cl_2 at 0°C (Scheme 2). As expected,[16] the resonances of the vinylic and the allylic methylene protons in the ^1H NMR spectra shift to



Scheme 2

downfield during the (*Z*) to (*E*) isomerization. The reverse was true for the H-3 resonance. Further evidence for the double bond configuration was obtained from NOE difference measurements.

The application of our newly developed methodology towards the syntheses of natural products is being investigated.

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Malik, A.; Voelter, W. *Liebigs Ann. Chem.* **1990**, 389. (d) Fatima, A.; Zaman, F.; Voelter, W. Z. *Naturforsch.* **1991**, *46b*, 1227. (e) Al-Abed, Y.; Zaman, F.; Shekhani, M. S.; Fatima, A.; Voelter, W. *Tetrahedron Lett.* **1992**, *33*, 3305. (f) Al-Abed, Y.; Al-Tel, T. H.; Voelter, W. *Tetrahedron* **1993**, accepted for publication. (g) Al-Abed, Y.; Al-Tel, T. H.; Shekhani, M. S.; Voelter, W. *Carbohydrate Lett.*, submitted for publication.

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8. Weiler, L. *J. Am. Chem. Soc.* **1970**, *92*, 6702.
9. Kimmich, R.; Voelter, W. *Liebigs Ann. Chem.* **1981**, 1100, and references cited therein.
10. **3**: Yellow oil; $[\alpha]_D$ +82° (c = 0.66, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ: 4.77 (bs, 1H; *H*8), 4.75 (d, *J* = 12.1 Hz,1H; OC*H*HPh), 4.53 (t, *J* = 6.0 Hz, 1H; *H*3), 4.48 (d, J = 12.1 Hz, 1H; OCH*H*Ph), 4.42 (d, *J* = 6.0 Hz, 1H; *H*1), 3.70 (t, *J* = 6.0 Hz, 1H; *H*2), 3.70 (dd, *J* = 3.7, 12.4 Hz, 1H; *H*5'), 3.57 (dd, *J* = 4.1, 12.4 Hz, 1H; *H*5), 2.55 (m, 2H; *H*6,6'), 2.54 (m, 1H; *H*4), 1.34 (s, 9H; ^tBuO); ^{13}C NMR: 170.0 (*C*7), 165.6 ($CO_2{}^t$Bu), 127.0-137.0 (*Ph*), 100.6 (*C*1), 91.4 (*C*8), 86.3 (*C*3), 79.4 ($C(CH_3)_3$), 69.9 (CH_2Ph), 69.6 (*C*2), 60.6 (*C*5), 34.6 (*C*6), 34.6 (*C*4), 28.4 ($C(CH_3)_3$).
11. **5**: Amorphous solid; $[\alpha]_D$ +87° (c = 0.76, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ: 4.93 (d, *J* = 2.4 Hz, 1H; *H*1), 4.92 (s, 1H; *H*8), 4.85 (d, *J* = 11.8 Hz, 1H; OC*H*HPh), 4.78 (t, *J* = 6.5 Hz, 1H; *H*3), 4.64 (d, *J* = 11.8 Hz, 1H; OCH*H*Ph), 4.05 (dd, *J* = 4.6, 12.2 Hz, 1H; *H*5), 3.88 (bdd, *J* = 2.4, 6.5 Hz, 1H; *H*2), 3.56 (dd, *J* = 4.0, 12.2 Hz, 1H; *H*5'), 2.73 (m, 2H; *H*6,6'), 2.64 (m, 1H; *H*4), 1.39 (s, 9H; ^tBuO); ^{13}C NMR: 169.2 (*C*7), 165.2 ($CO_2{}^t$Bu), 128.0-137.0 (*Ph*), 97.5 (*C*1), 91.9 (*C*8), 85.1 (*C*3), 79.2 ($C(CH_3)_3$), 70.1 (CH_2Ph), 68.1 (*C*2), 59.7 (*C*5), 34.8 (*C*6), 34.4 (*C*4), 28.4 ($C(CH_3)_3$).
12. All the new products were characterized with the help of spectral data. The ^1H and ^{13}C NMR spectra of **7**, **8**, **10**, **11**, **12**, **13** and **17** are in full agreement with the assigned structures.
13. **14**: Amorphous powder; $[\alpha]_D$ +90° (c = 0.13, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ: 5.25 (t, *J* = 0.8 Hz, 1H; *H*8), 4.83 (d, *J* = 11.7 Hz, 1H; OC*H*HPh), 4.50 (d, *J* = 11.7 Hz, 1H; OCH*H*Ph), 4.23 (dd, 1H; *H*5), 4.21 (d, *J* = 7.5 Hz, 1H; *H*1), 4.2 (m, 1H; *H*4), 3.68 (dd, *J* = 2.5, 13.6 Hz, 1H; *H*5'), 3.53 (d, *J* = 18.1 Hz, 1H; *H*6), 3.23 (dt, *J* = 2.8, 7.5 Hz, 1H; *H*2), 2.85 (ddd, *J* = 2.3, 7.1, 18.1 Hz, 1H; *H*6'), 2.39 (d, $J_{H2,OH}$ = 2.8 Hz, 1H; O*H*), 2.30 (m, 1H; *H*3), 1.39 (s, 9H; ^tBuO); ^{13}C NMR: 173.1 (*C*7), 168.0 ($CO_2{}^t$Bu), 128.0-137.0 (*Ph*), 102.0 (*C*1), 94.9 (*C*8), 79.6 (*C*4), 79.2 ($C(CH_3)_3$), 70.5 (CH_2Ph), 70.2 (*C*2), 64.3 (*C*5), 41.3 (*C*3), 35.6 (*C*6), 28.4 ($C(CH_3)_3$).
14. **15**: Oil; $[\alpha]_D$ -19° (c = 0.27, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ: 5.30 (t, *J* = 1.7 Hz, 1H; *H*8), 4.79 (d, *J* = 11.7 Hz, 1H; OC*H*HPh), 4.49 (d, *J* = 11.7 Hz, 1H; OCH*H*Ph), 4.30 (d, *J* = 6.8 Hz, 1H; *H*1), 4.30 (t, *J* = 7.2 Hz, 1H; *H*3), 3.84 (dd, *J* = 3.8, 12.5 Hz, 1H; *H*5), 3.63 (dd, *J* = 4.4, 12.4 Hz, 1H; *H*5'), 3.49 (bt, *J* = 6.8 Hz, 1H; *H*2), 3.23 (ddd, *J* = 1.2, 8.5, 18.1 Hz, 1H; *H*6), 2.85 (ddd, *J*= 2.0, 9.9, 18.1 Hz, 1H; *H*6'), 2.53 (m, 1H; *H*4), 1.39 (s, 9H; ^tBuO); ^{13}C NMR: 172.4 (*C*7), 167.0 ($CO_2{}^t$Bu), 127.3-136.2 (*Ph*), 100.1 (*C*1), 93.3 (*C*8), 82.2 (*C*3), 78.6 ($C(CH_3)_3$), 70.1 (*C*2) 69.6 (CH_2Ph), 60.9 (*C*5), 35.5 (*C*4), 32.3 (*C*6), 27.7 ($C(CH_3)_3$).
15. **16**: Amorphous solid; $[\alpha]_D$ +159° (c = 0.62, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ: 5.20 (bs, 1H; *H*8), 4.70 (d, *J* = 3.3 Hz, 1H; *H*1), 4.66 (d, *J* = 11.8 Hz, 1H; OC*H*HPh), 4.41 (d, *J* = 11.8 Hz, 1H; OC*H*HPh), 4.33 (t, *J* = 6.9 Hz, 1H; *H*3), 3.87 (dd, *J* = 4.5, 12.2 Hz, 1H; *H*5), 3.50 (dt, *J* = 3.3, 7.2 Hz, 1H; *H*2), 3.44 (dd, *J* = 12.2, 3.5 Hz, 1H; *H*5'), 3.14 (ddd, *J* = 1.0, 8.2, 18.1 Hz, 1H; *H*6), 2.80 (ddd, *J* = 1.8, 9.2, 18.1 Hz, 1H; *H*6'), 2.45 (m, 1H; *H*4), 2.16 (d, $J_{H2,OH}$ = 7.4 Hz, 1H; O*H*), 1.32 (s, 9H; ^tBuO); ^{13}C NMR: 173.0 (*C*7), 167.8 ($CO_2{}^t$Bu), 128.1-136.8 (*Ph*), 97.3 (*C*1), 94.0 (*C*8), 82.5 (*C*3), 79.3 ($C(CH_3)_3$), 70.0 (CH_2Ph), 68.6 (*C*2) 59.5 (*C*5), 35.6 (*C*4), 33.1 (*C*6), 28.4 ($C(CH_3)_3$).
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