Efficient Access to Polyfunctionalized and Polycyclic Furanoids: Control of the Off-template Centre *via* Acid Catalysis

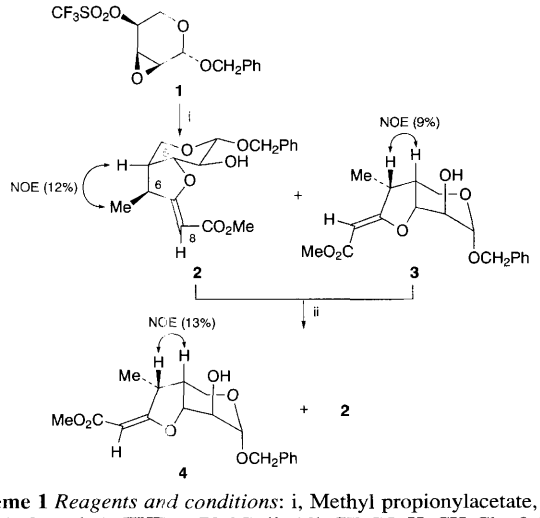
Taleb H. Al-Tel and Wolfgang Voelter*

Abteilung für Physikalische Biochemie des Physiologisch-chemischen Instituts der Universität Tübingen, Hoppe-Seyler-Straße 4, D-72076 Tübingen, Germany

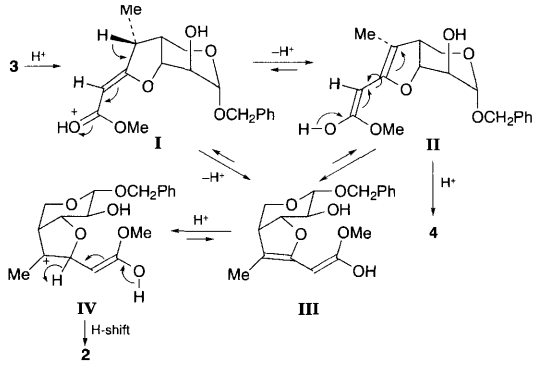
A mild and economic strategy for the synthesis of chiral and polyfunctionalized furanoids on carbohydrate templates is described; also a new methodology for the control of the substituents on the satellite ring through acid catalysis is achieved.

The occurrence of highly functionalized furanoid systems either as a key entity or key substructure of more complex molecules in various biologically active natural products[1] creates a need for their synthesis, and remarkable approaches have been developed in this direction.[2,3] We therefore investigated the nucleophilic addition of the ambident nucleophile of 1,3-dicarbonyl compounds to the ambident electrophile of type 1 directed towards both dihydrofuran (5-enol *endo-exo-tet* ring closure process)[4a] and tetrahydrofuran systems (C-alkylation followed by 5-enol *exo-exo-tet* ring closure process).[4b] In order to extend the scope of this new furanoid synthesis to more complex ring systems, we recently investigated the related reaction with substituted acyclic and cyclic β-dicarbonyl compounds with the *cis* oriented epoxy triflates **1** and **5**. Our expectation was that the steric bias and the inherent chirality of the pyranose ring should result in an unusual annulation reaction in which new polycyclic and polyfunctionalized tetrahydrofuran systems could be achieved *via* a regio- and stereo-controlled fashion, economically and under mild conditions. In this regard, we needed to introduce an alkyl group at C-6, since the entire class of polyether antibiotics contains at least one methyl moiety on a tetrahydrofuran ring.[1] Usually, the 'off-template' substituents have been introduced by taking advantage of the conformationally locked bicyclic system. In such reactions, diastereoselective alkylation of an enolate[5] or diastereoselective epoxidation of a double bond in the satellite ring followed by nucleophilic opening of the resultant oxirane are involved.[6] Alkylation of the enolate of our α,β-unsaturated ester was expected to yield an α-alkyl-β,γ-unsaturated ester.[7] These tedious strategies can be circumvented by our approach. The dianion of methyl propionyl acetate is reacted with benzyl 2,3-anhydro-β-L-ribopyranoside **1** in THF at −78 °C to afford a 1 : 1 mixture of the diastereoisomers **2**† and **3**‡ in 90% combined yield (Scheme 1). Interestingly, in **2** the non-bonded interactions override the anomeric effect forcing it into the $^1C_4$ conformation, while **3** exists in the $^4C_1$ form. This is evident from the ^{1}H NMR spectra: H-1 in **2** resonates at δ 4.26 but in **3** at δ 4.61. $J_{1,2}$ for **2** is 7.6 Hz but in **3** it is 2.4 Hz. The stereochemistry around C-6 was unambiguously assigned through NOE and ^{1}H NMR data: H-6 in **2** shows a coupling of 11.2 Hz to H-4 while in **3** it is 6.5 Hz. This indicates that in **2** H-6 and H-4 are *trans* to each other (*exo*-methyl) and in **3** they are *cis*-oriented (*endo*-methyl). Furthermore, the $^1C_4$ conformation of compound **2** is unambiguously confirmed by extensive NOE experiments. Reciprocating NOE interactions were observed between H-1, H-3 and H-5_{ax} (δ 3.64) on one hand and saturation of H-2 resulted in an NOE enhancement of H-6 (19%) on the other. Also irradiation of H-5_{eq} (δ 3.88) gives NOE interactions with H-6 (11%) and Me-6 (7%). The formation of a 1 : 1 mixture of **2** and **3** resulted in the loss of 50% of our required intermediate. Interestingly, treatment of the mixture of both **2** and **3** with 1% CF_3CO_2H in CH_2Cl_2 quantitatively epimerizes to a 9 : 1 mixture of (6*S*)-**2** and (6*R*)-**4**, respectively; however, if the pure compound **2** is treated with 1% CF_3CO_2H under the same reaction conditions no epimerization is observed from which the conclusion can be drawn that **2** is the thermodynamically preferred compound (Scheme 1). To the best of our knowledge, this is the first report of such configurational and/or conformational changes.[8] As proposed in Scheme 2, we suggest that by proton addition to **3**, the intermediate **I**[9] is formed which could rearrange to the dienol **II** leading after rotation around C7–C8 to the (*E*)-isomer **4** (10%) or under conformational change isomerizes to **III**. Alternatively, **III** could be formed directly by deprotonation of **I**. Subsequently, protonation of **III** would yield the tertiary carbonium ion **IV**, which after rearrangement and proton shift results in the (*Z*)-isomer **2** (90%).

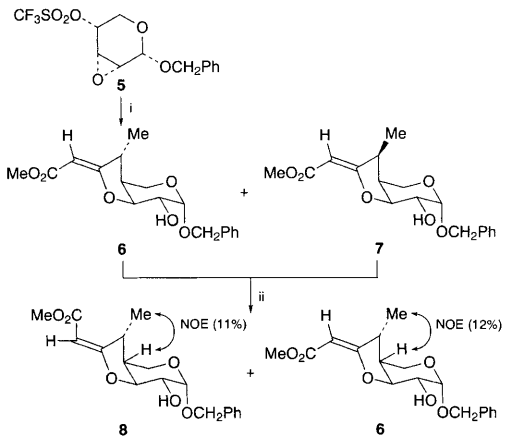
A similar reaction with benzyl 2,3-anhydro-α-D-ribopyranoid **5** resulted in a 1 : 1 epimeric mixture of compounds **6** and **7** in 95% combined yield (Scheme 3). In this case, both products adopt the $^4C_1$ conformation as concluded from the chemical shifts and the coupling constants of their anomeric protons. Treatment of the diastereoisomeric mixture with 1% CF_3CO_2H in CH_2Cl_2 gave **8** and **6** in 15 and 80% yields, respectively. On the other hand, the pure compound **6** yielded under identical reaction conditions only traces of **8**, thereby indicating that **6** is the thermodynamically preferred compound (Scheme 3). These experiments demonstrate that **7** should produce **8** under a configurational change. The stereostructures of **6** and **8** are



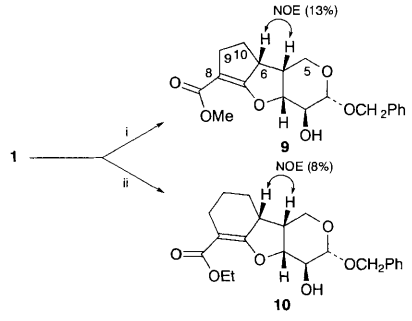
Scheme 1 *Reagents and conditions*: i, Methyl propionylacetate, NaH, Bu^nLi (3 equiv.), THF. −78 °C; ii, 1% CF_3CO_2H–CH_2Cl_2, 0 °C → room temp., 3–5 h



Scheme 2 Proposed mechanism for the rearrangement of compound **3** to **2** and **4** under acid catalysis



Scheme 3 *Reagents and conditions*: i, Methyl propionylacetate, NaH, Bu^{n}Li (3 equiv.), THF, −78 °C; ii, 1% CF_3CO_2H–CH_2Cl_2, 0 °C → room temp., 3–5 h



Scheme 4 *Reagents and conditions*: i, 2-Carboxymethyl cyclopentanone, NaH, Bu^{n}Li (3.5 equiv.), THF, −78 → 30 °C, 2–3 h; ii, 2-carboxyethyl cyclohexanone, NaH, Bu^{n}Li (3.5 equiv.), THF, −78 → 30 °C, 2–3 h

assigned from the ^{1}H NMR spectra as well as NOE experiments. Both **6** and **8** have *endo*-methyl groups as indicated from the couplings between H-6 and H-4, $J_{4,6}$ 11.5, and 13.4 Hz, respectively.

Since the entire class of prostaglandins[2f,3,10] and the antitumour agent phyllanthocin[3,11] contain cyclopentane, cyclohexane rings, respectively, fused to a substituted THF system, we were interested to expand the scope of this methodology to substructures providing entries to complex polycyclic furanoid systems with the future aim to use these chiral synthons for natural product syntheses. Thus, the *cis*-fused tricyclic furanoids **9** and **10** (Scheme 4) were synthesized in 75 and 74% yields by the reaction of the dianions of 2-carbomethoxy cyclopentanone and 2-carboethoxy cyclohexanone, respectively with the anhydropyranoside **1**. Interestingly, in each case only one tricyclic furanoid is obtained. Although the ^{1}H NMR signals of the furanoids **9**§ and **10** in $CDCl_3$ at 400 MHz exhibit considerable overlap, their absolute stereochemistry could be determined from unequivocally assigned resonances. Couplings of 6.5 and 6.6 Hz between H-4 and H-6 in the tricyclic furanoids **9** and **10**, respectively, indicated that both protons are in a *cis*-relationship. These assigned spectral data are also confirmed by NOE experiments.

In summary, the resulting chiral polycyclic systems are potentially useful intermediates for a general approach to related natural products such as the insect antifeedant bisabolangelon[10a] or marine Laurencia metabolites.[2a] Although our new strategy has been specifically demonstrated with cyclopentanone and cyclohexanone precursors, it is most likely not limited to these ring systems.

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Footnotes

† *NMR data* for **2**: δ_H (400 MHz, $CDCl_3$) 7.23–7.20 (5H, m, C_6H_5), 4.80 (1H, d, *J* 11.8 Hz, OC*H*HPh), 4.81 (1H, d, *J* 1.5 Hz, 8-H), 4.56 (1H, d, *J* 11.8 Hz, OCH*H*Ph), 4.53 (1H, t, *J* 7.4 Hz, 3-H), 4.26 (1H, d, *J* 7.6 Hz, 1-H), 3.88 (1H, dd, *J* 2.0, 12.7 Hz, 5-H), 3.64 (1H, dd, *J* 7.2, 12.7 Hz, 5′-H), 3.59 (3H, s, OMe), 3.51 (1H, t, *J* 7.6 Hz, 2-H), 2.85 (1H, dddd, *J* 1.5, 6.6, 11.2, 13.2 Hz, 6-H), 2.00 (1H, ddd, *J* 2.0, 7.1, 11.5 Hz, 4-H), 1.10 (3H, d, *J* 6.7 Hz, 6-Me); δ_c (100 MHz, $CDCl_3$) 174.9, 166.4 (*C*O_2Me, 7-C), 137.0, 128.4, 127.9, 127.8 (C_6H_5), 101.4 (C-1), 88.9 (8-C), 85.3 (3-C), 70.5 (O*C*H_2Ph), 60.8 (5-C), 60.8 (2-C), 50.77 (OMe), 43.9 (6-C), 39.3 (4-C), 15.3 (6-Me).

‡ *NMR data* for **3**: δ_H (400 MHz, $CDCl_3$) 7.21–7.15 (5H, m, C_6H_5), 4.73 (1H, d, *J* 1.5 Hz, 8-H), 4.65 (1H, d, *J* 12.5 Hz, OC*H*HPh), 4.61 (1H, d, *J* 2.4 Hz, 1-H), 4.48 (1H, t, *J* 3.9 Hz, 3-H), 4.28 (1H, d, *J* 12.5 Hz, OCH*H*Ph), 4.13 (1H, t, *J* 3.2 Hz, 2-H), 3.60 (3H, s, OMe), 3.48 (1H, dd, *J* 6.5, 13.3 Hz, 5-H), 3.39 (1H, dd, *J* 6.9, 13.3 Hz, 5′-H), 2.90 (1H, dddd, *J* 1.5, 6.5, 13.5 Hz, H-6), 2.60 (1H, m, 4-H), 1.03 (3H, d, *J* 7.3 Hz, 6-Me); δ_c (100 MHz, $CDCl_3$) 176.0, 167.4 (*C*O_2Me, 7-C), 138.6, 128.9, 127.9, 127.4 (C_6H_5), 99.3 (1-C), 88.1 (8-C), 83.7 (3-C), 69.0 (O*C*H_2Ph), 55.8 (5-C), 55.8 (2-C), 51.0 (OMe), 41.3 (4-C), 35.1 (6-C), 11.7 (6-Me).

§ *NMR data* for **9**: δ_H (400 MHz, $CDCl_3$) 7.23–7.15 (5H, m, C_6H_5), 4.85 (1H, bs, 3-H), 4.77 (1H, s, 1-H), 4.2 (1H, bs, 2-H), 4.67 (1H, d, *J* 12.4 Hz, OC*H*HPh), 4.30 (1H, d, *J* 12.4 Hz, OCH*H*Ph), 3.64 (3H, s, OMe), 3.60 (1H, d, *J* 12.1 Hz, 5-H), 3.40 (1H, dd, *J* 6.6, 12.1 Hz, 5′-H), 3.35 (1H, m, 6-H), 2.71 (2H, m), 2.51 (1H, bd, *J* 6.5 Hz, 4-H), 1.75 (1H, m), 1.41 (1H, m); δ_c (100 MHz, $CDCl_3$) 174.2, 165.0 (*C*O_2Me, 7-C), 137.8, 128.3, 127.2, 126.8 (C_6H_5), 98.1 (1-C), 95.2 (8-C), 91.2 (3-C), 68.4 (O*C*H_2Ph), 64.2 (2-C), 55.0 (5-C), 51.6 (6-C), 51.1 (OMe), 31.4 (4-C), 31.4 (9-C), 21.8 (10-C).

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