C-Furanoside Synthesis via Intramolecular Cyclization

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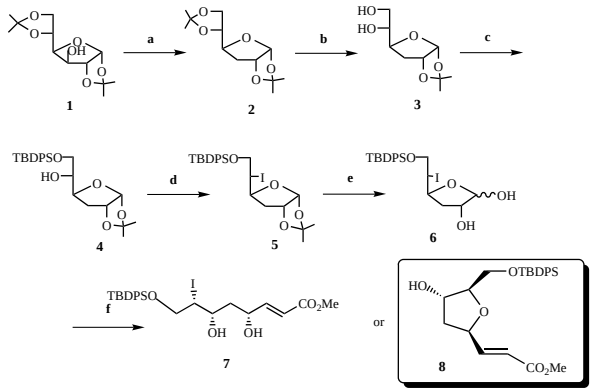
Abstract. Polysubstituted C-furanoside **8**, with the correct absolute configuration is readily available from diacetone-D-glucose. This C-furanoside after deprotection should be a useful synthon for natural product synthesis.

Key words: C-furanoside, intramolecular cyclization, absolute configuration steady-state NOE, diacetone-D-glucose

C-Furanosides are found in many natural products as polyether antibiotics,[1] acetogenins[2a] as well as C-glycosides,[2b] in a wide range of stereochemical complexity. Due to their biological importance, the synthesis of such valuable compounds has attracted the attention of organic synthetic chemists. A variety of different approaches towards these furanosides, has been developed,[3,4] using the "chiral pool"[5] and other strategies with substituents both at C-2 and C-5. Non-natural tetrahydrofurans might be interesting from a biological point of view, especially, on account of their applications as potential synthons in different classes of natural compounds including phosphoglycerides and analogues.[6,7] These tetrahydrofuran analogues, in which the Protein Activating Factor (PAF) moiety is restricted as a part of the heterocyclic skeleton, have been shown to be very potent agonists of PAF.[8]

Carbohydrates have been used extensively as precursors in C-furanoside synthesis. Ring closure by attack of an OH or OR-group at an activated double bond, normally the most applied method to prepare the furan moiety, has been used in few cases within the carbohydrates.[9] A general method to create hydroxylated furans from carbohydrates is the nucleophilic attack of an OH-group on a suitably introduced leaving group. Wittig reactions with sugars have been described in the literature and, depending on the reaction conditions and the reagents employed, open-chain[10] or C-furanoside[11] derivatives can be obtained. We have found that the reaction of diol **6** in the presence of 3 equivalents of methoxycarbonylmethylene triphenylphosphorane gave quantitatively **8** (Scheme 1). The use of cyclic chiral precursors such as **8** presents certain potential advantages such as a considerable degree of stereocontrol of the three asymmetric centers.

In the course of our ongoing research on the total synthesis of isoprostaglandins,[12] we have investigated the intramolecular nucleophilic cyclization of iodo derivative **6** under Wittig conditions. Hence, the observed results (Scheme 1) are different with regards to the amount of methoxycarbonylmethylene triphenylphosphorane used and also the temperature applied during the Wittig reaction.

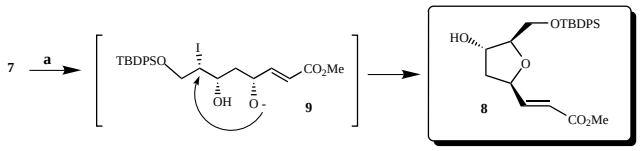


a) NaH/THF/imidazole/CS_2/MeI then Bu_3SnH/toluene reflux, 3 h, 85%. b) aq. AcOH 70%, 7 h, 92%. c) TBDPSCl/DMF/imidazole, 2 h at 0°C then rt, 100%. d) I_2/Ph_3P/imidazole/xylene, 15 min at reflux, 91% e) aq. H_2SO_4 10%, THF-dioxane (3:1), 4 h, 80%. f) $Ph_3P{=}CHCO_2Me$ 2 eq. in dry THF, 11 h at rt, 75% of **7** or $Ph_3P{=}CHCO_2Me$ 3 eq. in dry THF, 24 h at reflux, 100% of **8**.

Scheme 1

The synthesis of **8** (Scheme 1) starts with the commercial 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **1**, which was transformed to the corresponding 3-deoxy-sugar **2** in 85% yield using the Barton-McCombie procedure.[13] A selective deprotection of the isopropylidene group in 5,6 position was accomplished in the presence of 70% aq. acetic acid in 92% yield. Protection of the primary alcohol at C-6 of derivative **3** using 1.1 eq. of *tert*-butyldiphenylsilyl chloride in freshly distilled DMF in the presence of 2.8 eq. of imidazole led to the pure mono silyl ether **4** in 100% yield. Introduction of iodine at C-5 was carried out using the procedure that we have developed earlier[14] (I_2, Ph_3P, imidazole, xylene) and led to compound **5** in 91% yield. Hydrolysis of the isopropylidene group in 1,2 position was achieved in the presence of 10% aq. sulfuric acid in THF-dioxane (3:1) to afford the diol **6** in 80% yield.

Finally, when **6** was stirred at room temperature with two equivalents of methoxycarbonylmethylene triphenylphosphorane in dry THF for 11h 75% of **7**[15] was obtained, whereas, using three equivalents of the Wittig reagent and refluxing the solution for 24 h 100% of the C-furanoside **8**[16] was produced in 55% overall yield after 6 steps.



Scheme 2

The mechanism that we propose for the formation of the C-furanoside **8** is shown in the Scheme 2. After formation of derivative **7** and under the basic conditions of the Wittig reaction, alcoholate **9** was generated *in situ* followed by intramolecular nucleophilic cyclization on the iodo leaving group to afford the C-furanoside **8**. We have confirmed the structure of this compound **8** by a NMR studies in 1D (^{1}H and ^{13}C) and 2D (HQMC and HMBC) and elemental analysis.

Finally, we have determined and confirmed the *4R,6S,7R* configuration of compound **8** (Figure 1 and Table 1) by steady-state NOE difference spectroscopy (DNOES) experiments, which have previously been employed by our group.[17] Concerning the relative configuration of the chains situated at C-7 and C-4, the irradiation of 7-H (to 3.94 ppm) induced a NOE of 1.0% on 4-H (to 4.74 ppm). This result is in agreement with a relative *cis* configuration between these two chains. The irradiation of 6-H (to 4.44 ppm) induced a NOE of 0.4% on 8-H (to 3.59 ppm) and of 3.9% on 5'-H (to 1.87 ppm), and the irradiation of 3-H (to 6.92 ppm) also induced a NOE of 0.1% on 5'-H (to 1.87 ppm). These observations allowed us to confirm the relative *trans* configuration of the hydroxyl group and the chains situated in C-7 and C-4 positions.

Table 1 : Experimental steady-state value (NOE%) for compound **8** ($CDCl_3$)

Protons irradiated	3-H	4-H	5-H	5'-H	6-H	7-H	8-H
3-H	Irr.	0.24	-	0.12	-	-	0.05
4-H	1.7	Irr.	1.8	-	0.07	0.87	-
5-H	0.09	1.49	Irr.	~	0.89	0.35	-
5'-H	0.67	-	~	Irr.	4.0	0.53	0.16
6-H	0.08	0.19	-	3.9	Irr.	1.09	0.45
7-H	-	1.05	-	-	0.86	Irr.	0.88
8-H	-	-	-	-	0.23	1.0	Irr.

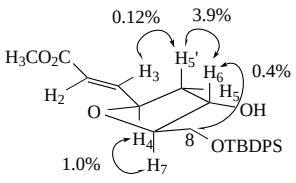


Figure 1

In conclusion, we consider this intramolecular nucleophilic cyclization, as a useful straightforward way to obtain chiral C-furanoside **8** substituted at C-2, C-3, C-5 with the *4R,6S,7R* configuration. This C-furanoside after deprotection should be a useful synthon for natural product synthesis.

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(15) Compound **7**: To a solution of diol **6** (564 mg, 1.1 mmol) in dry THF (15 ml) was added methoxycarbonylmethylene triphenylphosphorane (730 mg, 2.2 mmol). The reaction mixture was stirred for 11 h at room temperature. Concentration under reduced pressure followed by purification by flash chromatography (Silica gel, Hex-EtOAc 8:2) gave **7** (468 mg, 75%)
^{1}H-NMR (360 MHz, $CDCl_3$) δ : 7.62-7.6 (m, 4H, Ph), 7.37-7.46 (m, 6H, Ph), 6.87-6.92 (dd, J=15.8 and 4.7 Hz, 1H, H-3), 6.07-6.11 (dd, J=1.4 Hz, 1H, H-2), 4.54-4.57 (m, 2H, H-4),

4.12-4.16 (m, 1H, H-7), 3.96-4.03 (m, 1H, H-8), 3.72 (s, 3H, OCH_3), 3.58-3.60 (d, J=10.8, and 5.9 Hz, 1H, H-6), 1.68-1.86 (m, 1H, H-5), 1.07 (s, 9H, $(\underline{CH_3})_3C$). **^{13}C-NMR** (90 MHz, $CDCl_3$) δ : 167 (C-1), 149.2 (C-3), 135.7 (Ph); 132.7 (Ph); 132.3 (Ph), 130.1 (Ph), 128 (Ph), 120.1 (C-2), 71.4 (C-4), 70.1 (C-6), 67.5 (C-8), 51.7 (OCH_3), 42.7 (C-7) 42.5 (C-5). 26.9 (*t*-Bu), 19.2 (*t*-Bu) **IR** (film) (υ_{max}): 3515 (OH), 1730 (C=O), 1650 (C=C) **Anal.Calcd**. For $C_{25}H_{33}O_5ISi$ C, 52.82; H, 5.85; O, 14.07; Found C, 52.82; H, 5.87; O, 14.02.

(16) Compound **8 :** To a solution of diol **6** (110 mg, 0.22 mmol) in dry THF (10 ml) was added methoxycarbonylmethylene triphenylphosphorane (220 mg, 0.66 mmol). The reaction mixture was stirred for 24 h at 80°C. Concentration under reduced pressure followed by purification by flash chromatography (Silica gel, Hex-EtOAc 8:2) gave **8** (95.2 mg, 100%) **^{1}H-NMR** (360 MHz, $CDCl_3$) δ : 7.63-7.65 (m, 4H, Ph), 7.36-7.43 (m, 6H, Ph), 6.89-6.95 (dd, J=15.6 and 3.6 Hz, 1H, H-3), 6.03-6.08 (dd, J=1.7 Hz, 1H, H-2), 4.72-4.75 (m, 2H, H-4), 4.42-4.46 (m, 2H, H-6), 3.92-3.96 (m, 1H, H-7), 3.71-3.78 (m, 1H, H-8), 3.71 (s, 3H, OCH_3), 3.57-3.62 (dd, J=10.8, and 5.9 Hz, 1H, H-8), 2.02-2.11 (ddd, J=12.9, 5.9 and 2 Hz, 1H, H-5), 1.85-1.90 (ddd, J=9.9 and 5.7 Hz, 1H, H-5), 1.02-1.05 (s, 9H, $(\underline{CH_3})_3C$). **^{13}C-NMR** (90 MHz, $CDCl_3$) δ : 166.84 (C-1), 147.43 (C-3), 135.54 (Ph); 133.02 (Ph), 129.84 (Ph), 127.87 (Ph), 120.34 (C-2), 87.31 (C-7), 76.91 (C-4), 73.91 (C-6), 64.53 (C-8), 51.57 (OCH_3), 40.77 (C-5). 26.84 (*t*-Bu), 19.2 (*t*-Bu) **IR** (film) (υ_{max}): 1720 (C=O), 1650 (C=C) **Anal.Calcd**. For $C_{25}H_{32}O_5Si$ C, 68.15; H, 7.33; O, 18.17; Found C, 68.02; H, 7.36; O, 18.15.

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