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C-Glycofuranosides via Tandem Wittig-Michael Sequence Using a Thiazole-Armed Phosphorane. A Route to *C*-Furanosyl α-Hydroxy Propanals and Propionic Acids

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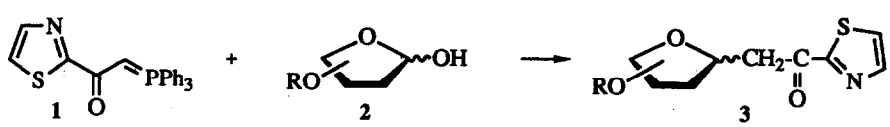
Key Words: *C*-glycosides, sugar hydroxy aldehydes, sugar hydroxy acids, 2-thiazolylcarbonylmethylene-triphenylphosphorane, *C*-glycosidation.

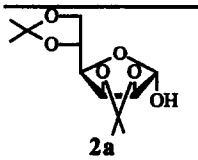
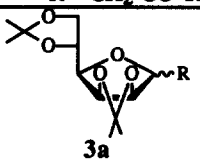
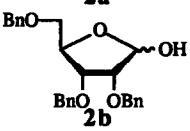
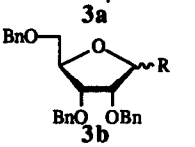
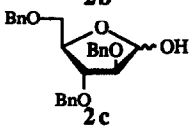
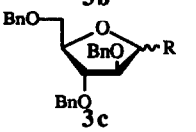
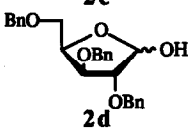
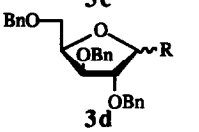
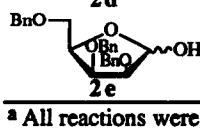
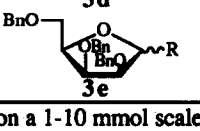
Abstract: *The reactions of 2-thiazolylcarbonylmethylenetriphenylphosphorane with five protected D-furanoses* (manno, ribo, arabino, xylo, *and* lyxo) *in refluxing toluene lead to mixtures of α- and β-1-C-(2-thiazolacyl)-glycosides (66 - 93 % overall yield). The β-linked C-glycoside derived from 2,3:5,6-di-O-isopropylidene-D-mannofuranose was reduced to* (R) *and* (S) *alcohols which after protection as O-benzyl ethers were transformed to α-alkoxy aldehydes by thiazole-to-formyl conversion; the aldehydes were oxidized to the corresponding α-alkoxy acids.*

Due to the potential biological properties of *C*-glycosides[1], new synthetic methodologies for the assemblage of a carbohydrate and a functionalized carbon-chain via carbon-carbon bond formation at the anomeric center are gaining increasing attention.[2] For instance, various reports have appeared[3] dealing with the installation of an acetate or acetonitrile moiety at C-1 of both furanoses and pyranoses using a Wittig-type reaction followed by spontaneous or base-catalyzed intramolecular cyclization (Michael-type addition) of the resultant activated alkene (Moffatt procedure).[4] Also the direct introduction of a pyruvate unit to give a sugar ketoacid[5] appears to be an interesting functionalization for the synthesis of more complex *C*-glyconjugates. No examples of this type of three carbon-chain extension have been so far reported to our knowledge. In exploratory work toward the development of a suitable Moffatt procedure, we employed the stabilized phosphorane[6] $Ph_3P{=}CHC(O)CO_2Et$, but no reaction was observed with either pyranoses and furanoses in different solvents (CH_3CN, THF, $CHCl_3$, $PhCH_3$) and 24 h refluxing. Attempts to exploit a Zn-promoted Wittig-type reaction[3i] using ethyl bromopyruvate failed to yield any *C*-glycofuranosides or pyranosides. Satisfactory results were obtained with the thiazole-armed carbonylphosphorane (2-TCMP, **1**). This newcomer to our family of thiazole-based reagents[7] has been already employed[8] for the installation of a masked pyruvate unit in polyalkoxy aldehydes via Wittig carbonylolefination and addition of an external nucleophile. We report here the results of 2-TCMP-based 1-*C*-functionalization of furanoses **2** by a tandem Wittig-internal Michael sequence and demonstrate the synthetic potential of the resultant 1-*C*-(2-thiazolacyl)-glycosides **3**.



An initial *C*-glycosidation model was generated from the readily available[9] 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**2a**). Optimized reaction conditions required 2 equiv. of 2-TCMP (**1**) in refluxing toluene for 16 h in the presence of 4 Å molecular sieves to give a mixture of α- and β-*C*-(2-thiazolacyl)-mannofuranosides[10] **3a** in very good isolated overall yield (Table 1). The vinylketone intermediate arising from the initial Wittig carbonylolefination of **2a** was not detected by tlc of the reaction mixture either after a partial and total conversion of **2a**. Successful *C*-glycosidation reactions by 2-TCMP (**1**) were carried out under the above conditions also with the four 2,3,5-tri-*O*-benzyl-D-pentofuranoses[11] **2b-e** (*ribo, arabino, xylo,* and *lyxo*) to give mixtures of the corresponding α- and β-C-glycosylmethyl ketones[10] **3b-e** in fairly good yields and without any epimerization at C-2 of the furanose ring. On the other hand, treatment of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (TBG) with 2-TCMP (**1**) under the above conditions[12] did not provide the corresponding *C*-glycosides, thus indicating that the 2-TCMP-based *C*-glycosidation of sugars is very likely limited to the furanose series.

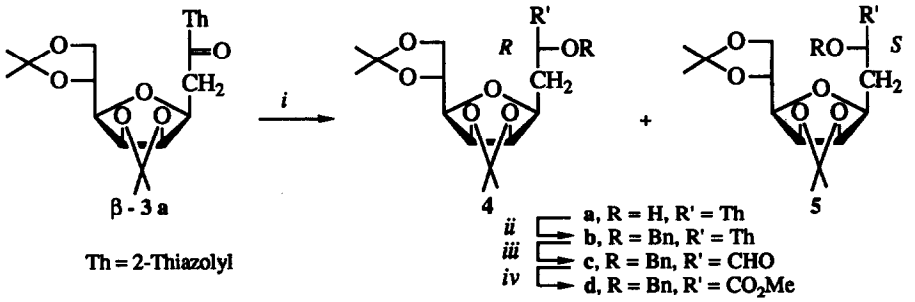
Table 1 Reactions of 2-TCMP (**1**) with Furanoses **2**[a]

Furanose 2	*C*-glycoside 3 R = CH_2-CO-Th	Time (h)	Yield (%)[b]	α/β ratio[c]
 **2a**	 **3a**	16	93	35:65
 **2b**	 **3b**	24	78	25:75
 **2c**	 **3c**	60	66	50:50
 **2d**	 **3d**	40	82	40:60
 **2e**	 **3e**	16	80	65:35

[a] All reactions were carried out on a 1-10 mmol scale of **2** and 2 equiv. of 2-TCMP (**1**) in refluxing toluene. [b] Isolated yield after flash chromatography. [c] Determined by ^{1}H NMR on the isolated anomeric mixtures.

Epimerization of the α– to the β–linked isomer was carried out on the mixture of 2-thiazolacyl C-glycosides **3a** isolated in a α/β ratio of 35 : 65 (Table 1); after 24 h in methanol containing 1 equiv. of KOH, the α/β equilibrium ratio[13] was 15:85. The individual α and β anomers were easily separated by silica gel chromatography and characterized. The reduction of the carbonyl of the β-linked 2-thiazolacyl *C*-glycoside β-**3a** with various metal hydride reducing agents afforded in each case mixtures of the alcohol epimers **4a** and **5a** with low selectivity although in good overall yields. The best results in favor of either diastereomer[14] were obtained with $LiAl(tBuO)_3H$ (**4a/5a**, 33/67, 93 %) and DIBALH (**4a/5a**, 63/37, 90 %). After separation by

chromatography, each alcohol was protected as the corresponding *O*-benzyl ether[15] **4b** and **5b** from which the aldehydes[15] **4c** and **5c** were revealed by the recently improved thiazole-to-formyl deblocking protocol[16] (*N*-methylation with TfOMe; reduction with $NaBH_4$; Cu(II)-assisted hydrolysis). These aldehydes were oxidized to carboxylic acids which were characterized as the corresponding methyl esters[15] **4d** and **5d**. Overall, diastereomeric *C*-glycosyl α-hydroxyalkylthiazoles **4a** and **5a** were transformed into *C*-glycosyl alkoxy propanals **4c** and **5c** and propionic acids **4d** and **5d** in very good yields and without epimerization.



Reagents and conditions: *i*. LiAl(*t*BuO)$_3$H, THF, -75 to -35°C, 5 h, 93%, (**4a** / **5a**, 33 /67); DIBALH, THF,- 80°C, 1 h, 90%, (**4a** / **5a**, 63 /37); *ii*: BnBr, NaH, DMF, r.t., 1 h; **4b**: 92%; **5b**: 94% *iii*: 1) MeOTf, CH_3CN, r.t., 10 min; 2) $NaBH_4$, CH_3OH, 0°C, 10 min; 3) $CuCl_2$ / CuO, CH_3CN / H_2O, r.t., 10 min; **4c**: 84%, **5c**: 78%; *iv*: 1)Ag_2O, THF / H_2O, r.t., 14 h; 2) CH_2N_2, CH_3OH / Et_2O; **4d**: 90%, **5d**: 92%.

In summary we have presented a practical method for installation of a highly fuctionalized three carbon-chain at the anomeric center of furanoses via 2-thiazolacyl *C*-glycosides **3**. We are currently investigating other chemoselective elaborations of these compounds toward *C*-glycosyl amino acids and *C*-glycopeptides.

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10. The anomeric configuration of *C*-glycosides **3** was established by ^1H (300 MHz) and ^{13}C (75 MHz) NMR ($CDCl_3$) as described in Ref. 4 and by analogy with the corresponding *O*-glycosides (see Bock, K.; Pedersen, C. *Adv. Carbohydr. Chem. Biochem.* **1983**, *41*, 27). Optical rotations were measured at 20°C for $CHCl_3$ solutions. α-**3a** had m.p. 139-140°C (AcOEt / hexane); β-**3b** had m.p. 57-58°C (hexane).

	α-3a	β-3a	α-3b	β-3b	α-3c	β-3c	α-3d	β-3d	α-3e	β-3e
$[\alpha]_D$	+27.1	+12.2	+23.1	-3.9	+11.7	+25.3	-37.4	-24.3	+28.7	-3.5
δ_{H-1}	4.72	4.14	4.79	4.70	4.77	4.69	4.85	4.58	4.69	4.79
δ_{C-1}	80.9	77.2	76.3	76.9	78.7	77.1	76.4	79.3	76.0	75.0
δ_{C-2}	85.2	81.0	77.8	80.7	86.8	83.0[a]	81.8	85.6	82.9	79.2[a]
δ_{C-3}	80.7	80.7	79.6	77.0	85.1	83.7	81.3	82.6	76.6	78.7[a]
δ_{C-4}	80.7	81.4	79.9	81.7	82.1	82.5[a]	78.6	80.1	79.1	78.4[a]
δ_{C-5}	73.2	73.1	70.0	70.2	70.2	70.5	68.3	68.3	68.7	69.9

[a] Assignment can be reversed.

11. Crude methyl α,β-D-ribo-, arabino-, and xylofuranoside were obtained by reacting the corresponding sugars with CH_3OH and conc. H_2SO_4 according to Barker, R.; Fletcher, H. G. *J. Org. Chem.* **1961**, *26*, 4605. After benzylation (BnBr, NaH, DMF), pure methyl α- and β-tribenzylfuranosides were isolated by flash chromatography. Hydrolysis (4 : 1 AcOH / 1M H_2SO_4, 100 °C, 0.5-1 h) of the anomeric mixtures afforded **2b-d**. Methyl α-D-lyxofuranoside (isolated by flash chromatography) was prepared according to Bishop, C. T.; Cooper, F. P. *Can. J. Chem.* **1963**, *41*, 2743. Benzylation and hydrolysis gave **2e**.
12. When *C*-glycosidation of TBG was carried out on heating under a nitrogen atmosphere at 180 °C with 2-TCMP (**1**) without solvent, a mixture of α- and β-*C*-glycosides was isolated in 20 % overall yield.
13. Under the same conditions, the α/β ratio of the other *C*-glycosides **3b-e** remained almost unchanged. This finding was not unexpected, see Ref. 4.
14. The absolute configuration of alcohols **4a** (*R*), $[\alpha]_D$ +26.0 ($CHCl_3$) and **5a** (*S*), $[\alpha]_D$ -27.5 ($CHCl_3$) was independently and unambiguously assigned by ^1H NMR analysis of the (*R*) and (*S*) MTPA esters of both epimers using the Kakisawa rule (Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092).
15. **4b**: $[\alpha]_D$ +24.4 ($CHCl_3$); **5b**: $[\alpha]_D$ -53.0 ($CHCl_3$); **4c**: $[\alpha]_D$ +8.5 ($CHCl_3$), δ_{CHO} 9.64 (d, J = 1.4 Hz); **5c**: $[\alpha]_D$ -51.7 ($CHCl_3$), δ_{CHO} 9.66 (d, J = 1.7 Hz); **4d**: $[\alpha]_D$ +23.0 ($CHCl_3$), δ_{OMe} 3.75; **5d**: $[\alpha]_D$ -63.6 ($CHCl_3$), δ_{OMe} 3.75.
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