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Furan-Based Synthesis of *C*-Glycosyl Carboxylates

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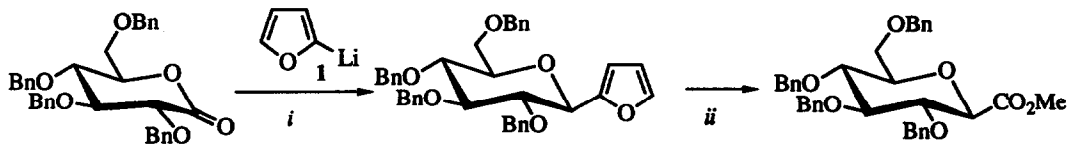
Key Words: Sugar lactones, sugar carboxylic acids, *C*-glycosides, furan, *C*-glycosidation, carboxylation

Abstract: *The installation of the 2-furyl ring at the anomeric carbon of 2,3,4,6-tetra-O-benzyl-D-glucopyranose and 2,3:5,6-di-O-isopropylidene-D-mannofuranose is carried out either by addition of 2-lithiofuran to the corresponding lactones either by direct C-glycosidation of the O-acetyl derivatives with furan; the resultant 2-furyl C-glycosides are converted to carboxylic acids by the oxidative cleavage of the furan nucleous.*

The various existing methods for the installation of the 2-furyl ring at the anomeric center of carbohydrates[1] and the oxidative cleavage of this heterocycle to the carboxylate group[2] indicate a route to *C*-glycosyl carboxylic acids, i.e. potential precursors to more complex *C*-glycosides of biological relevance.[3] Severe drawbacks that are apparent in other routes to sugar carboxylates, such as for instance via nitriles,[4,5] makes this approach quite attractive. Nevertheless the scope of the furan-based methodology wherein the glycosylation of the heterocycle and the conversion to acid were both examined, has not so far been described. We report here the initial results of our study in this topic.

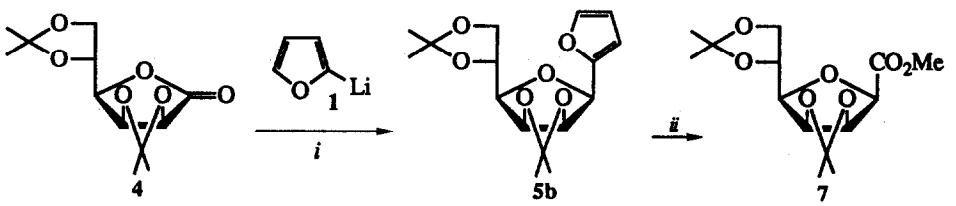
Following the quite promising approach to *C*-glycosyl aldehydes by addition of 2-lithiothiazole to sugar lactones,[6] we decided to employ these sugars toward *C*-glycosyl carboxylates as well. Initially we examined the reaction of 2-lithiofuran[7] (1) to 2,3,4,6-tetra-*O*-benzyl-D-gluconolactone[8] (2) since controversial results[1d,e] have been reported for this system. The addition of 1 to the sugar lactone 2 in THF at -78°C proceeded smoothly to give an anomeric mixture of 1-*C*-(2-furyl)-D-glucopyranose derivative which on treatment with triethylsilane (3 eq.) and trimethylsilyl triflate (TMSOTf, 1 eq.) at -40 °C afforded[9] exclusively the β-linked 2-furyl *C*-glycoside[1e] 3 in 77 % isolated yield. This stereoselectivity is well in agreement with a kinetically controlled axial hydride addition to an oxycarbenium intermediate.



2 3 6

Reagents and conditions : *i*, 1) THF, -78°C; 2) Et_3SiH (3 eq.), TMSOTf (1 eq.), CH_2Cl_2, -40°C, 15 min; *ii*, 1) O_3, CH_2Cl_2-MeOH, -78°C; 2) CH_2N_2, MeOH-Et_2O.

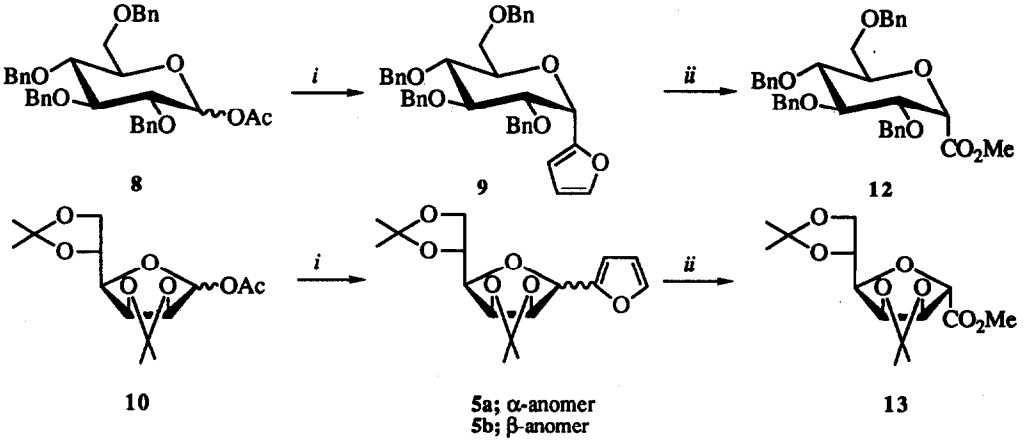
Then we extended the above procedure to 2,3:5,6-di-*O*-isopropylidene-D-mannono-1,4-lactone[10] (**4**) and observed also in this case the exclusive formation of the 2-(2,3:5,6-di-*O*-isopropylidene-β-D-mannofuranosyl)-furan[11] (**5b**) which was isolated in 60 % yield. In contrast to the Kraus and Molina report[1d], this result demonstrates that the furanose lactone **4** can be equally employed in the above *C*-glycosidation methodology.



Reagents and conditions : *i*, 1) THF, -78°C; 2) Et_3SiH (3 eq.), TMSOTf (1 eq.), CH_2Cl_2, -40°C, 15 min; *ii*, 1) O_3, CH_2Cl_2-MeOH, -78°C; 2) CH_2N_2, MeOH-Et_2O.

Although the oxidative cleavage of furan to carboxylic acid is attracting increasing attention in synthesis,[2] variable chemical yields (30-90 %) have been reported depending on the substrate and the oxidizing agent employed (O_3, RuO_2-$NaIO_4$).[12] The main problem in this operation is the compatibility of the hydroxyl protecting groups to the rather strong oxidizing conditions.[13] In this exploratory work we employed the ozonolysis in CH_2Cl_2-MeOH at -78 °C. Oxidative cleavage of β-linked 2-furyl *C*-glycosides **3** and **5b** under these conditions led after diazomethane esterification to the corresponding β-carboxylate glycosides **6** (40%)[14] and **7** (60%).[15] These yields were not improved by the use of RuO_2-$NaIO_4$ as oxidizing agent.

The direct *C*-glycosidation of furan was then examined. Although earlier reports described this reaction using pyridyl thioglycoside[1b] and *O*-trichloroacetimidate[1c] derivatives as glycosyl donors, we observed that the reaction proceeded smoothly by a mild activation of the anomeric center as *O*-acetate. Hence treatment of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-α,β-D-glucopyranose (**8**) with furan (3 eq.) in acetonitrile at -40°C in the presence of TMSOTf afforded the corresponding α-linked 2-furyl *C*-glycoside **9** which was isolated in 75 % yield. Also in this case the stereochemical outcome is in agreement with an axial attack of the nucleophile to an oxycarbenium ion intermediate.



Reagents and conditions : *i*, furan (3 eq.), TMSOTf (1.2 eq.), 4Å MS , CH_3CN, -40°C, 1 h. ; *ii* 1) O_3, CH_2Cl_2-MeOH, -78°C ; 2) CH_2N_2, MeOH-Et_2O.

However, under the same conditions 1-*O*-acetyl-2,3:5,6-di-*O*-isopropylidene-D-mannofuranose (**10**) afforded a 70 : 30 α/β mixture of 2-furyl *C*-glycosides **5** in only 30 % overall yield[16] from which the major isomer **5a**[17] was separated by flash chromatography. The oxidative cleavage of the furan nucleous of *C*-glycosides **9** and **5a** by ozonolysis and esterification by diazomethane afforded the corresponding α-linked *C*-glycosyl esters **12** (40%)[18] and **13** (60%).[19]

The furan-based installation of the carboxylate group at the anomeric center of two model pyranose and furanose sugars by two complementary routes leading to either α- or β-linked *C*-glycosyl esters is described. The scope of this methodology appears mainly conditioned in respect to chemical yields and compatibility with hydroxyl protecting groups by the furan-to-acid conversion step. The alternative route to *C*-glycosyl esters by oxidation of *C*-glycosyl aldehydes readily available via thiazole intermediates,[6] then becomes of interest.

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5. Synthetic applications of this route are seriously limited by the harsh conditions required for the hydrolysis of the nitrile to carboxylate.
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11. **5b**: syrup, $[\alpha]_D$ +42.7 ($CHCl_3$) ; ^1H NMR (300 MHz, $CDCl_3$) δ : 1.36, 1.39, 1.46 and 1.52 (4 s, 12 H, 4 CH_3), 3.58 (dd, 1 H, $J_{4,3}$ = 3.1, $J_{4,5}$ = 7.7 Hz, H-4), 4.12 (d, 2 H, $J_{6,5}$ = 5.1 Hz, 2 H-6), 4.48 (dt, 1 H, H-5), 4.61 (d, 1 H,$J_{1,2}$ = 3.1 Hz, H-1), 4.83-4.89 (m, 2 H, H-2, H-3), 6.36 (dd, 1 H, $J_{4,3}$ = 3.3, $J_{4,5}$ = 1.8 Hz, furan H-4), 6.59 (d, 1 H, furan H-3), 7.42 (d, 1 H, furan H-5).
12. Cleavage by O_3 : Danishefsky, S. J.; Maring, C. J. *J. Am. Chem. Soc.*, **1989**, *111*, 2193 (50%) ; Akita, H.; Koshiji, H.; Furuichi, A.; Horikoshi, K.; Oishi, T. *Chem. Pharm. Bull.* **1984**, *32*, 1242 (29%) ; Schmid, G.; Fukuyama, T.; Akasaka, K.; Kishi, Y. *J. Am. Chem. Soc.*, **1979**, *101*, 259 (55%).

Cleavage by RuO_2-$NaIO_4$: Danishefsky, S. J.; Pearson, W. H.; Segmuller, B. E. *J. Am. Chem. Soc.*, **1985**, *107*, 1280 (86%) ; Mukayama, T.; Tsuzuki, R.; Kato, J. *Chem. Lett.* **1985**, 837 (78%) ; DeNinno, M. P.; Danishefsky, S. J.; Schulte, G. *J. Am. Chem. Soc.*, **1988**, *110*, 3925 (90%).

13. For a high yield removal of benzyl ether protective groups by ozone, see Angibeaud, P.; Defaye, J.; Gadelle, A.; Utille, J. P. *J. Chem. Soc., Chem. Commun.* **1985**, 1123. For the oxidation of benzyl ethers to benzoates by RuO_2-$NaIO_4$, see Schuda, P. F.; Cichowicz, M. B.; Heimann, M. R. *Tetrahedron Lett.* **1983**, *24*, 3829.
14. **6**: syrup, $[\alpha]_D$ +17.5 ($CHCl_3$) ; ^1H NMR (300 MHz, $CDCl_3$) δ : 3.52 (ddd, 1 H, $J_{5,4}$ = 8.8, $J_{5,6}$ = 2.0, $J_{5,6'}$ = 4.2 Hz, H-5), 3.62 (dd, 1 H, $J_{4,3}$ = 9.0 Hz, H-4), 3.70 (dd, 1 H, $J_{3,2}$ = 8.4 Hz, H-3), 3.72 (m, 2 H, H-6), 3.81 (dd, 1 H, $J_{2,1}$ = 9.4 Hz, H-2), 3.90 (d, 1 H, H-1), 4.54 and 4.59 (2 d, 2 H, J = 12.0 Hz, PhCH_2), 4.55 and 4.77 (2 d, 2 H, J = 10.6 Hz, PhCH_2), 4.60 and 4.80 (2 d, 2 H, J = 11.0 Hz, PhCH_2), 4.90 (s, 2 H, PhCH_2), 7.11 - 7.37 (m, 20 H, 4 Ph).
15. **7**: syrup, $[\alpha]_D$ + 17.2 ($CHCl_3$) ; ^1H NMR (300 MHz, $CDCl_3$) δ : 1.33 and 1.38 (2 s, 6 H, 2 CH_3), 1.45 (s, 6 H, 2 CH_3), 3.52 (dd, 1 H, $J_{4,3}$ = 3.4, $J_{4,5}$ = 8.1 Hz, H-4), 3.80 (s, 3 H, OMe), 4.11 (dd, 1 H, $J_{6,6'}$ = 9.3, $J_{6,5}$ = 4.3 Hz, H-6), 4.14 (dd, 1 H, $J_{6',5}$ = 5.4 Hz, H-6'), 4.24 (d, 1 H, $J_{1,2}$ = 4.5 Hz, H-1), 4.51 (ddd, 1 H, H-5), 4.80 (dd, 1 H, $J_{3,2}$ = 5.9 Hz, H-3), 4.98 (dd, 1 H, H-2).
16. Similar results were obtained by *C*-glycosidation using the *O*-trichloroacetimidate derivative as glycosyl donor.
17. **5a**: syrup, $[\alpha]_D$ +5.0 ($CHCl_3$) ; ^1H NMR (300 MHz, $CDCl_3$) δ : 1.35 (s, 6 H, 2 CH_3), 1.43 and 1.55 (2 s, 6 H, 2 CH_3), 3.92 (dd, 1 H, $J_{4,3}$ = 3.6, $J_{4,5}$ = 8.4 Hz, H-4), 4.04 (dd, 1 H, $J_{6,5}$ = 4.3, $J_{6,6'}$ = 8.4 Hz, H-6), 4.10 (dd, 1 H, $J_{6',5}$ = 6.2 Hz, H-6'), 4.43 (ddd, 1 H, H-5), 4.90 (dd, 1 H, $J_{3,2}$ = 6.0 Hz, H-3), 5.01 (d, 1 H, H-2), 5.07 (s, 1 H, H-1), 6.24 (d, 1 H, $J_{3,4}$ = 3.1 Hz, furan H-3), 6.34 (dd, 1 H, $J_{4,5}$ = 1.8 Hz, furan H-4), 7.38 (d, 1 H, furan H-5).
18. **12**: syrup, $[\alpha]_D$ +49.7 ($CHCl_3$) ; ^1H NMR (300 MHz, $CDCl_3$) δ : 3.64 (dd, 1 H, $J_{4,3}$ = 8.7, $J_{4,5}$ = 9.6 Hz, H-4), 3.69 (m, 2 H, H-6), 3.76 (s, 3 H, OMe), 3.85 (dd, 1 H, $J_{2,3}$ = 8.8, $J_{2,1}$ = 6.7 Hz, H-2), 4.11 (dd, 1 H, H-3), 4.41 (ddd, 1 H, $J_{5,6}$ = $J_{5,6'}$ = 2.6 Hz, H-5), 4.49 and 4.60 (2 d, 2 H, J = 12.2 Hz, PhCH_2), 4.50 and 4.81 (2 d, 2 H, J = 11.0 Hz, PhCH_2), 4.68 and 4.72 (2 d, 2 H, J = 11.7 Hz, PhCH_2), 4.79 and 4.89 (2 d, 2 H, J = 11.0 Hz, PhCH_2), 7.13 - 7.36 (m, 20 H, 4 Ph).
19. **13**: mp 82°C (hexane), $[\alpha]_D$ -9.8 ($CHCl_3$) ; ^1H NMR (300 MHz, $CDCl_3$) δ : 1.35, 1.38, 1.45, and 1.51 (4 s, 12 H, 4 CH_3), 3.76 (s, 3 H, OMe), 4.00 (dd, 1 H, $J_{4,3}$ = 3.5, $J_{4,5}$ = 7.8 Hz, H-4), 4.10 (dd, 1 H, $J_{6,6'}$ = 8.4 , $J_{6,5}$ = 5.0 Hz, H-6), 4.13 (dd, 1 H, $J_{6',5}$ = 5.6 Hz, H-6'), 4.40 (ddd, 1 H, H-5), 4.55 (s, 1 H, H-1), 4.80 (dd, 1 H, $J_{3,2}$ = 5.8 Hz, H-3), 4.96 (d, 1 H, H-2).

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