Synthesis of Furanylalkyl Hex- and Pentenopyranosid-4-uloses

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ABSTRACT

A few novel furanylalkyl hex- and pentenopyranones have been synthesized from the corresponding hexenopyranosides or hydroxymethylfurfural. In the hexose series, the reactions proceeded through monosilylation of the primary alcohol followed by oxidation of secondary alcohols. The pentenopyranones have been obtained by glycosidation of hydroxymethylfurfural oxidation product.

KEYWORDS

Hydroxymethylfurfural (HMF), silylation, oxidation, pyranone.

1. Introduction

The chemical synthesis of the carbohydrate domains of saccharides and glycoconjugates is now recognized as a major frontier for organic chemistry. Bioactive carbohydrates play a vital role in several life processes. Glycopyranosid-4-uloses, derived from glycals or hydroxymethylfurfural, are useful intermediates in many bioactive molecules such as anthracycline antibiotics with proven clinical effectiveness against leukemias, lymphomas, breast carcinomas, and sarcomas. They are also synthetic intermediates of sclerophylin A, a unique member of the cladiellin family which manifests strong cytotoxicity against the L1210 cell line.

Pyranones 1–3 (Fig. 1) seems to be the key intermediates for synthesis of iso-deoxynucleosides of type 4 (Scheme 1), a rare class of nucleosides showing significant and selective anti HIV activity as well as appearing as upstream precursors of interesting related nucleosides.

It has also been shown that carbohydrate molecules possessing the enone functionality are the preferred precursors for the synthesis of branched-chain and other rare sugars. As part of the development of new unsaturated pyran-3-ones, we report the synthesis of a number of new furanylalkyl hex- and pentenopyranosid-4-uloses.

2. Results and Discussion

In the hexose series, the synthetic route to the furanylalkyl hexenopyranosid-4-uloses is described in Scheme 1. The starting furanylalkyl hexenopyranosides 5a–d, as we recently reported, were prepared by allowing 3,4,6-tri-O-acetyl-D-glucal to react with an appropriate furanyl alcohol in the presence of a catalyst via Ferrier rearrangement.

The acetylated compounds 5a–d were deprotected using a mixture of methanol-water-triethylamine with excellent yields (75–92%) to form 6a–d. The α and β anomers were separated by chromatography on silica gel and characterized by 1H and 13C NMR.

The free primary hydroxyl group of 6b–d was then selectively protected as a tert-butyl dimethyl silyl ether under the silylation conditions described by Corey and Venkateswarlu to give monosilylated compounds 7b–d with yields varying from 70 to 90%. The reaction was carried out under kinetic control to avoid bis-silylation. The products 7b–d were characterized by 1H and 13C NMR. In the proton spectrum, the monosilylation of the primary alcohol was justified by the disappearance of the triplet at 2.36 ppm corresponding to the hydroxyl at position 6 (sugar nomenclature) in compounds 6a–d. The secondary alcohol was detected by a doublet at 2.62 ppm present in the spectra of compounds 6a–d and monosilylated compounds 7b–d.

Finally, oxidation with pyridinium chlorochromate (PCC) of 7b–d led to 8b–d in 68 to 86% yields. The structure of the pyranones was confirmed by 1H NMR which showed disappearance of the doublet due to the hydroxyl at position 4 and the appearance in the 13C NMR spectra of a signal with chemical shift 194 ppm, characteristic of the carbonyl carbon of α, β-unsaturated ketones.

In the pentose series, pyranones 11a–c could have been prepared starting from the corresponding furanylalkyl pentenopyranosides previously prepared by a similar process to the hexose series. However, we considered a direct glycosidation with 6-acetoxy-2H-pyran-3(6H)-one 10 (Scheme 2).
The starting compound 10 was synthesized from furfuryl alcohol 9a using the conditions of Hoffmann et al.\textsuperscript{15} The resulting compound was unstable in basic aqueous solution at room temperature and was stabilized as the acetate derivative using acetic anhydride and montmorillonite K-10, an acid catalyst known for acetylation of alcohols in carbohydrate chemistry.\textsuperscript{16}

Reactions of 10 with various furylcarbinols 9a–c, in the presence of a catalytic amount of ceric (IV) ammonium nitrate (CAN) in a direct glycosidation reaction, afforded 11a–c. These reactions proceeded in yields from 64 to 30%, decreasing with the length of the alkyl chain. Racemic mixtures were obtained and their structures were established by $^{1}$H and $^{13}$C NMR.

In the structures of hex- and pentenopyranosid-4-uloses 8 and 11, we note diene and dienophilic fragments. Thus, these compounds may be interesting for synthesis of tricyclic compounds via an intramolecular Diels-Alder cycloaddition. In fact Feringa et al.\textsuperscript{17} have particularly shown that for pyranones 1–3, the 6-alkoxysubstituant exerts complete stereocontrol in $\pi$ face selective additions of butadiene (Diels-Alder) or nitroethane (Michael) to this enone. Also of interest in this area, Horton’s\textsuperscript{18} and Herradon’s\textsuperscript{19} groups have discussed the total facial stereoselectivity induced by $\gamma$-substituents present on neighbouring unsaturated lactones.

3. Conclusion

Furanylalkyl hexenopyranosides and 6-acetoxy-2H-pyran-3(6H)-one were transformed into novel furanylalkyl hex- and pentenopyranosid-4-uloses with good yields. Their molecular structures were established using NMR methods. The prepared compounds may be of use in the synthesis of tricyclic compounds via intramolecular Diels-Alder cycloaddition.

4. Experimental

The 200 or 500 MHz $^1$H NMR and 50 MHz $^{13}$C NMR spectra were recorded with a Bruker AC spectrometer in CDCl$_3$, with TMS as an internal standard. Elemental analysis were performed in the CNRS Analysis Department of Solaize (France). Optical rotations were measured with a Perkin-Elmer 241 polarimeter in Villeurbanne (France). Thin-layer chromatography (TLC) was carried out on plates coated with silica gel 60 (40–63 µm) followed by spraying the plates with diluted sulfuric acid (25%). Mass spectra were recorded with a Finnigan Mat 95 XL spectrometer in Villeurbanne (France).

4. 1. General Procedure for the Preparation of Diol 6a–d

A solution of 5 (1.38 mmol) in a mixture (6.7 mL) of methanol-water-triethylamine (5-4-1) was stirred at room temperature for 3 hours. Thin-layer chromatography (3:2 CH$_2$Cl$_2$-AcOEt) showed the disappearance of the starting material 5. After filtration on celite and evaporation, the crude product was purified by silica gel column (1:2 petroleum ether-ethyl acetate) to give pure $\alpha$-anomers 6.

From the reaction of 5a was obtained 1’-(furan-2”-yl)methyl 2,3-dideoxy-$\alpha$-D-erythro-hex-2-enopyranoside 6a (75%) as a light
oil; \[\text{C}]_{D}^{20} +73.5 \text{ (c 1, CHCl3)}; R_0.2 \text{(1,2-diphenyl ether-ethyl acetate)}; \delta_0 (200 MHz, CDCl3) 2.75 (1H, s, br, -OH); 3.25 (1H, s, br, 4-(OH)); 3.76 (1H, m, 5-H), 3.82 (2H, s, br, 6a-H and 6b-H); 4.17 (1H, d, br, J_1 7.5 Hz, 4-H); 4.62 (1H, d, J_1 13.6 Hz, 1'-b-H); 4.68 (1H, d, J_1 \alpha 13.6 Hz, 1'a-H), 5.08 (1H, s, br, 1-H), 5.71 (1H, dt, J_1 3.4 Hz, 1' 24.4 Hz, J_1 10.0 Hz, 3-H), 5.96 (1H, d, J_1 2.0 Hz, 2-H), 6.35 (2H, s, br, 3'-H and 4'-H), 7.40 (1H, d, J_1 \alpha 1.4 Hz, 5'-H); \delta_0 (50 MHz, CDCl3) 61.9 (C-6), 62.5 (C-1'1'), 60.4 (C-4), 71.7 (C-5), 93.4 (C-1), 109.7 (C-3'), 110.5 (C-4'), 125.9 (C-3), 133.9 (C-2), 143.1 (C-5'), 151.3 (C-2'); MS (FAB) m/z 227 (M+H'); (HRMS Found: 227.0922 (M+H')). Calc. for C_{11}H_{14}O_{5} (226): 227.0919 (M+H').

From the reaction of 5b was obtained 1-"(furfuraldehyde-5')-methyl 2,3-dideoxy-d-erythro-hex-2-enopyranoside 6b (90%) as a light oil; \[\text{C}]_{D}^{20} +49.6 \text{ (c 2, CHCl3)}; R_0.15 \text{(1,2-diphenyl ether-ethyl acetate)}; \delta_0 (200 MHz, CDCl3) 2.95 (1H, s, br, 6-(OH)); 3.50 (1H, s, br, 4-(OH); 3.82 (2H, m, 4-H, 6a-H and 6b-H); 4.22 (1H, m, 5-H), 4.63 (1H, d, J_1 13.4 Hz, 1'-b-H); 4.77 (1H, d, J_1 \alpha 13.4 Hz, 1'a-H), 5.08 (1H, s, br, 1-H), 5.73 (1H, dd, J_1 \beta 2.4 Hz, J_1 10.2 Hz, 3-H), 5.97 (1H, d, J_1 \alpha 10.2 Hz, 2-H), 6.54 (1H, d, J_1 3.5 Hz, 5'-H), 7.19 (1H, d, J_1 \alpha 3.5 Hz, 4'-H), 9.95 (1H, s, CH(O)), \delta_0 (50 MHz, CDCl3) 61.9 (C-6), 62.4 (C-1'), 63.9 (C-2'), 67.2 (C-4'), 94.7 (C-1'), 111.6 (C-3'), 123.3 (C-4'), 126.4 (C-3'), 130.9 (C-2'), 152.3 (C-5'), 158.2 (C-8'), 177.8 (CHO); MS (FAB) m/z 255 (M+H'); (HRMS Found: 255.0864 (M+H')). Calc. for C_{14}H_{16}O_{5} (M = 254): 255.0868 (M+H').

From the reaction of 5e was obtained 2-"(furan-2'-yl)ethyl 2,3-dideoxy-d-erythro-hex-2-enopyranoside 6c (92%) as a light oil; \[\text{C}]_{D}^{20} +58 \text{ (c 1, CHCl3)}; R_0.34 \text{(1,2-diphenyl ether-ethyl acetate)}; \delta_0 (200 MHz, CDCl3) 2.50 (2H, s, br, 4-(OH) and 6-(OH)); 2.95 (2H, t, J_1 \beta 3.0 Hz, J_1 1.9 Hz, 1'-b-H), 6.78 (2H, s, br and 2'-b-H); 3.75 (1H, dd, J_1 \beta 6.8 Hz, J_1 \alpha 10.3 Hz, 6b-H), 3.82 (2H, m, 4-H and 6a-H), 3.99 (1H, d, J_1 \alpha 6.9 Hz, J_1 \beta 11.9 Hz, 6a-H), 4.09 (1H, d, J_1 \alpha 9.9 Hz, J_1 \beta 9.3 Hz, 6b-H), 4.18 (1H, s, br, 1-H), 4.95 (1H, d, J_1 \alpha 10.0 Hz, 2-H), 5.94 (1H, d, J_1 \beta 2.0 Hz, 1'-b-H), 6.08 (1H, d, J_1 \beta 3.0 Hz, 3'-H), 6.29 (1H, dd, J_1 \beta 2.0 Hz, J_1 2.4 Hz, 1'-b-H), 7.32 (1H, dd, J_1 \beta 0.7 Hz, J_1 \alpha 2.0 Hz, 5'-H); \delta_0 (50 MHz, CDCl3) 28.9 (C-2'), 62.3 (C-1'), 63.7 (C-4'), 66.7 (C-6'), 71.6 (C-5), 94.5 (C-1'), 109.1 (C-3'), 110.3 (C-4'), 125.9 (C-3'), 133.8 (C-2'), 141.2 (C-5'), 152.8 (C-2'); MS (FAB) m/z 241 (M+H'); (HRMS Found: 241.1077 (M+H')). Calc. for C_{14}H_{16}O_{5} (M = 240): 241.1076 (M+H').

From the reaction of 5d was obtained 3-("furan-2'-yl)propyl 2,3-dideoxy-d-erythro-hex-2-enopyranoside 6d (92%) as a colourless oil; \[\text{C}]_{D}^{20} +40 \text{ (c 1, CHCl3)}; R_0.34 \text{(3,2-dichloromethane-ethyl acetate)}; \delta_0 (200 MHz, CDCl3) 1.95 (2H, m, 2'-a-H and 2'-b-H), 2.36 (1H, t, J_1 \beta 4.0 Hz, J_1 3.4 Hz, 3'H), 2.47 (2H, t, J_1 \beta 7.5 Hz, J_1 6.0 Hz, 6-(OH); 2.62 (1H, d, J_1 \beta 7.5 Hz, 5-H), 2.73 (2H, t, J_1 \beta 7.5 Hz, J_1 7.4 Hz, 3'a-H and 3'b-H), 3.52 (1H, dd, J_1 \beta 3.4 Hz, J_1 \alpha 9.6 Hz, 9.6 Hz, 12.6 Hz, 1'-b-H), 3.72 (1H, m, 1'-a-H), 3.82 (3H, m, 4-H, 6a-H and 6b-H), 4.22 (1H, m, 5-H), 4.96 (1H, d, J_1 \beta 0.96 Hz, 1'-b-H), 5.75 (1H, dd, J_1 \beta 2.2 Hz, J_1 2.6 Hz, 1'-b, 10.2 Hz, 3'-H), 5.97 (1H, d, J_1 \beta 10.2 Hz, 2'-H), 6.00 (1H, dd, J_1 \beta 0.8 Hz, J_1 3.1 Hz, 3'-H), 6.28 (1H, dd, J_1 \beta 1.9 Hz, J_1 3.1 Hz, 4'-H), 7.31 (1H, dd, J_1 \beta 0.8 Hz, J_1 1.9 Hz, 5'-H); \delta_0 (50 MHz, CDCl3) 24.6 (C-2'), 28.2 (C-1'), 62.4 (C-1'), 63.8 (C-6'), 67.8 (C-4'), 71.6 (C-5), 94.5 (C-1), 105.1 (C-3'), 110.2 (C-4'), 126.1 (C-3), 133.6 (C-2'), 141.0 (C-5'), 155.8 (C-2'); (Found: C, 61.14; H, 7.15%). Calc. for C_{15}H_{18}O_{5} (M = 254.28): C, 61.40; H, 7.14%.
filtration on celite and evaporation, the crude product was purified by silica gel column (5:1 petroleum ether-acetone) to give the pure α-anomers 8.

From the reaction of 7b was obtained 2′-(furan-2′-yl)ethyl 6-O-(tert-butyldimethylsilyl)-2,3-dideoxy-α-D-glycero-hex-2-eno- pyranosid-4-ulose 8c (68%) as a yellow oil; [α]D 20 -20 (c 1.0, CHCl3); Rf 20 -59 (c 1.8, CHCl3); 41.1 (C-3), 113.0 (C-5), 128.1 (C-3'), 143.3 (C-4'), 41.4 (C-6), 62.2 (C-1), 126.8 (C-3'), 152.7 (C-2'), 194.5 (C-4'); (Found: C, 63.23; H, 6.02%. Calc. for [(CH3)2Si]3C(C(50 MHz, CDCl3) 20.8 (C-2), 28.8 (C-2'), 62.6 (C-1'), 67.2 (C-6), 193.3 (C-4). The 1H and 13C NMR spectra were in agreement with the reported data.}

4. 5. General Procedure for the Preparation of Furanylalyl Pentenopyranosid-4-uloses 11

Ceric (IV) ammonium nitrate (140 mg; 20 mmol %) in acetonitrile (4 mL) was added to a mixture of 10 (200 mg, 1.28 mmol) and furanic alcohol 9 (3.84 mmol, 3 equiv.). The mixture was stirred at room temperature in a 10 mL round-bottom flask under nitrogen atmosphere and the reaction was followed by thin-layer chromatography (5:0 CHCl3/ACOEt). After the disappearance of the starting compound 10 (5-24 hours), the mixture was quenched with water (5 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous MgSO4, concentrated and purified by silica gel column (2:1 petroleum ether-acetone) to afford a mixture of α- and β-anomers 11.

From the reaction of 9a was obtained 2′-(furan-2′-yl)methyl 2,3-dideoxy-α-D-glycero-pento- pyranosid-4-ulose 11a (64%) as a clear oil; [α]D 20 -15.3 (c 1, 5 mg/mL, CHCl3); Rf 20 -4 (c 2, CHCl3); 41.1 (C-3), 113.0 (C-5), 128.1 (C-3'), 143.3 (C-4'), 41.4 (C-6), 62.2 (C-1), 126.8 (C-3'), 152.7 (C-2'), 194.5 (C-4'); MS (FAB) m/z 533 (M+H+); (HRMS Found: 533.1793 (M+H+)). Calc. for C25H34O13Si (M = 532) 533.1784 (M+H+).

From the reaction of 9b was obtained 2′-(furan-2′-yl)ethyl 2,3-dideoxy-β-D-glycero-pento- pyranosid-4-ulose 11b (50%) as a clear oil; [α]D 20 -42 (c 1, 5 mg/mL, CHCl3); Rf 20 -4 (c 2, CHCl3); 41.1 (C-3), 113.0 (C-5), 128.1 (C-3'), 143.3 (C-4'), 41.4 (C-6), 62.2 (C-1), 126.8 (C-3'), 152.7 (C-2'), 194.5 (C-4'); (Found: C, 61.88; H, 5.30%.

From the reaction of 9c was obtained 3′-(furan-2′-yl)propyl 2,3-dideoxy-β-D-glycero-pento- pyranosid-4-ulose 11c (30%) as a clear oil; [α]D 20 -64 (c 1, 5 mg/mL, CHCl3); Rf 20 -4 (c 2, CHCl3); 41.1 (C-3), 113.0 (C-5), 128.1 (C-3'), 143.3 (C-4'), 41.4 (C-6), 62.2 (C-1), 126.8 (C-3'), 152.7 (C-2'), 194.5 (C-4'); (Found: C, 61.83; H, 5.19%).

From the reaction of 9d was obtained 3′-(furan-2′-yl)propyl 2,3-dideoxy-β-D-glycero-pento- pyranosid-4-ulose 11d (50%) as a clear oil; [α]D 20 -42 (c 1, 5 mg/mL, CHCl3); Rf 20 -4 (c 2, CHCl3); 41.1 (C-3), 113.0 (C-5), 128.1 (C-3'), 143.3 (C-4'), 41.4 (C-6), 62.2 (C-1), 126.8 (C-3'), 152.7 (C-2'), 194.5 (C-4'); (Found: C, 61.88; H, 5.30%.

From the reaction of 10a was prepared by the method of Hoffmann et al. 4 to 4.5 g (44 mmol) of furfuryl alcohol 9a, 9.8 g (75 mmol) of methacrolein-propionic acid (70%) in dichloromethane was added at 0°C. The crude product was purified by silica gel column (5:0 dichloromethane-acetone) to give 3.5 g of a mixture α- and β-anomers of 6-hydroxy-2,3-dihydro-6H-pyran-3-one.

Montmorillonite K-10 (7 g) was added to a suspension of 6-hydroxy-2,3-dihydro-6H-pyran-3-one (3.5 g, 30 mmol) in acetic anhydride (14 mL) at 0°C and the mixture stirred at room temperature for 12 hours until the completion of the reaction. The catalyst was filtered, washed with dichloromethane and the solvent evaporated. The crude product was purified by silica gel column (5:0.5 dichloromethane-acetone) to give 4 g of a mixture α- and β-anomers of 1-O-acetyl-2,3-dideoxy-D-pent-2- enopyranosid-4-ulose 10 (58%) as a yellow crystal; [α]D 20 -34.1 (c 2.0, CHCl3); 4.15 (1H, d, J1,2 7.7 Hz, 5-H), 4.38 (1H, d, J1,2 7.7 Hz, 5a-H), 6.10 (1H, d, J1,2 7.7 Hz, 1-H), 6.90 (1H, dd, J1,2 3.6 Hz, J5a,5b 10.4 Hz, 2-H); δ (50 MHz, CDCl3) 20.8 (CH3), 67.3 (C-5), 86.6 (C-1), 128.7 (C-3), 142.3 (C-2), 169.5 (CO2), 193.3 (C-4). The 1H and 13C NMR spectra were in agreement with the reported data.
$J_{3',2'} = 3.0$ Hz, $3''$-$H), 6.14 (1H, d, $J_{3',5'} = 1.8$ Hz, $J_{4',5'} = 3.0$ Hz, $4''$-$H), 6.28 (1H, dd, $J_{4',3'} = 10.3$ Hz, $3''$-$H), 7.30 (1H, s, br, $5''$-$H); \delta (50$ MHz, CDCl$_3$) 24.6 (C-$2'$), 28.1 (C-$3'$), 66.3 (C-$1'$), 68.5 (C-$5$), 93.3 (C-$1$), 105.3 (C-$3''$), 110.2 (C-$4''$), 127.7 (C-$3$), 141.0 (C-$5''$), 144.6 (C-$2$), 155.2 (C-$2''$), 194.7 (C-$4$); (Found: C, 64.54%; H, 6.14%. Calcd for C$_{12}$H$_{14}$O$_4$ (M = 222.23): C, 64.85%; H, 6.35%).

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