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THE SYNTHESIS OF *C*-FORMYL BRANCHED-CHAIN DEOXY-SUGARS BY CONVERSION OF NITRO GROUPS INTO CARBONYL GROUPS WITH TITANIUM(III) CHLORIDE[1]

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Formyl-branched deoxy-sugars (Type B)[2] have been accessible by two main routes. Ring contraction[3] of a suitable amino-pyranoside with nitrous acid gave *C*-formyl-deoxyfuranosides. Nucleophilic scission of sugar epoxides with either unsaturated organo-lithium reagents[4], or with 2-lithio-1,3-dithiane[5], gave deoxy-branched products that could be converted into *C*-deoxy-*C*-formyl derivatives.

Deoxy-nitromethyl branched-chain sugars may be obtained readily by condensation of nitromethane with a suitably protected glycosidulose in alkaline medium, followed by dehydration and subsequent reduction of the intermediate nitro-olefin[6]. In the carbohydrate field nitromethyl groups of Type A branched-chain derivatives have been converted into carbonyl compounds by oxidation with aqueous potassium permanganate[7], or *via* the classical Nef reaction for chain extension[8]. The facile conversion[9] of nitro groups into carbonyl groups with aqueous titanium trichloride, in combination with the nitromethane reaction on ketoses, presents a new convenient route to a variety of *C*-formyl-branched deoxy-sugars. Some examples of the procedure are described in this paper.

A solution of the nitronate salt of methyl 4,6-0-benzylidene-2,3-dideoxy-3-*C*-nitromethyl-α-D-*ribo*-hexopyranoside[6,10], **1**, (773 mg, 2.5 mmoles), prepared in anhydrous dimethylformamide (10 ml) at 0 °C by addition of sodium hydride (100 mg, 2.5 mmoles) as a 60 % dispersion in oil, was added dropwise to a mixture of 25 ml titanium trichloride (15 % in 4 % hydrochloric acid) and 25 ml aqueous ammonium acetate (35 %); pH 1. Extraction with dichloromethane after 5 min gave 71 % of methyl 4,6-0-benzylidene-2,3-dideoxy-3-*C*-formyl-α-D-*ribo*-hexopyranoside, **2**; m.p. 119–120 °C; $\nu_{max.}$ (KBr): 2840, 1720 cm^{-1} (CHO). Irradiation of a multiplet at δ 2.74 (H-3) in the 60 MHz nmr spectrum of **2**, caused the collapse of a quartet at δ 3.85 (H-4, $J_{3,4} = 4.5$ Hz; $J_{4,5} = 8.0$ Hz) to a doublet ($J_{4,5} = 8.0$Hz), and the collapse of the CHO doublet ($J_{3,3'} = 2.5$Hz) at δ 10.15 to a singlet. The relevant coupling constants for H-3 allowed assignment of the *allo*-configuration to **2**.

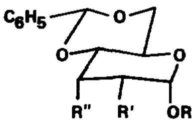
Treatment of **2** with methanolic sodium methoxide at 0 °C for 30 min caused epimerization at C-3 to give the energetically favored *gluco*-epimer, **3**. This epimerization was accompanied by an upfield shift of 0.3 ppm (from δ 10.15 for **2** to δ 9.85 for **3**) for the formyl-proton signal at 60 MHz. Since axial formyl protons are known[11] to occur at lower field than equatorial ones, the assignment of the *allo*-configuration to **2**, and the *gluco*-configuration to **3**, was substantiated.

Similarly, treatment of benzyl 2-acetamido-4,6-0-benzylidene-2,3-dideoxy-3-*C*-nitromethyl-α-D-allopyranoside (**4**)[6] with titanium trichloride gave a mixture of epimers (**5** and **6**), as judged by the occurrence of two formyl-proton signals at δ 10.07 (multiplet) and δ 9.62 (doublet, $J_{3,3'} = 4.8$ Hz) in the nmr spectrum. The pure *gluco*-epimer (**6**) was obtained in 61 % yield by refluxing the mixture in moist benzene containing potassium carbonate; m.p. 262–4 °C (dec); $\nu_{max.}$ 1735 cm^{-1}(CHO); δ ($CDCl_3$, 60 MHz): 9.62 (CHO).

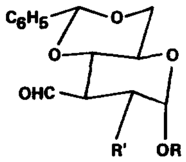
Titanium trichloride treatment of 5-0-acetyl-3-deoxy-1,2-0-isopropylidene-3-*C*-nitromethyl-α-D-ribofuranose (**7**)[6,12] gave the corresponding 3-*C*-formyl derivative (**8**) as a pure syrup that showed one spot on tlc; $\nu_{max.}$ 2760, 1735 (CHO), 1750 cm^{-1}(OAc); δ (60 MHz, $CDCl_3$): 9.80; m/e 229 (Calc. for $C_{10}H_{13}O_6$: 229.0712; found 229.0708) $(M-15)^+$. A crystalline semicarbazone was prepared from **8**; m.p. 182–183 °C.

Conversion of benzyl 2-acetamido-4,6-O-benzylidene-2,3-dideoxy-3-*C*-nitromethyl-α-D-*erythro*-hex-2-enopyranoside (**9**)[6] into the 3-*C*-formyl analog (**10**) with titanium trichloride proceeded in 98 % yield; m.p. 181–182 °C; δ (60 MHz, $CDCl_3$) 9.65. The α,β-unsaturated formyl group caused a downfield shift in the nmr signals for H-1 (δ 6.35 for **10**, *vs* δ 5.68 for **9**), and the NH (δ 11.77 for **10**, *vs* δ 9.09 for **9**).

The method seems to be applicable generally in the carbohydrate field.

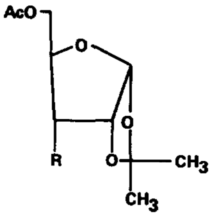


1 $R = CH_3$, $R' = H$, $R'' = CH_2NO_2$
2 $R = CH_3$, $R' = H$, $R'' = CHO$
4 $R = CH_2C_6H_5$, $R' = HNAc$, $R'' = CH_2NO_2$
5 $R = CH_2C_6H_5$, $R' = HNAc$, $R'' = CHO$

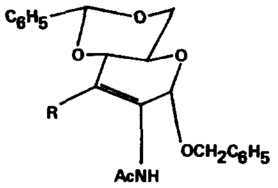


3 $R = CH_3$, $R' = H$

6 $R = CH_2C_6H_5$, $R' = HNAc$



7 $R = CH_2NO_2$
8 $R = CHO$



9 $R = CH_2NO_2$
10 $R = CHO$

REFERENCES AND FOOTNOTES

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