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Convenient syntheses of deoxypyranose sugars from glucuronolactone

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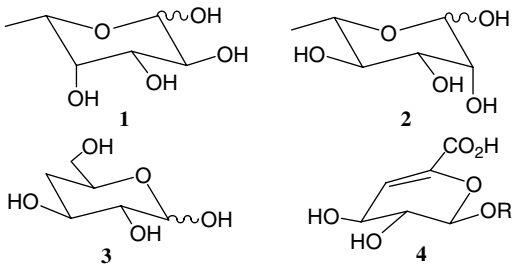
Abstract—One of the characteristic reactions of glucuronic acid derivatives is the base-catalysed elimination of a 4-(substituted) hydroxy group to generate a $\Delta_{4,5}$ pyranose. Following hydrogenation, proceeding mainly from the α-face provided the anomeric configuration is β, the initial C(5)-configuration is restored. This sequence affords access to a number of 4-deoxypyranoses: thus 4-deoxyglucoses are readily available by reduction at C(6). Conversion to a glycal, then cis-dihydroxylation at C(2)/C(3) leads to the D-*lyxo* configuration (found in neosidomycin). Finally a less obvious relationship to the KDO series is revealed, again by dihydroxylation.

Deoxypyranose sugars[1] are common in Nature, especially the 6-deoxy L-series sugars fucose **1** (mammals and higher organisms) and rhamnose **2** (plants and bacteria).



Access to pyranoses with *ring* deoxygenation, however, usually requires synthesis, and of the other positions, 4-deoxygenation is relatively the most difficult to achieve. Previously 4-deoxy-D-glucose **3** has been obtained via radical chemistry, for example, from a 4-thio derivative,[2] or by a sequence[3] from D-galactose involving selective acylation, then conversion to a 4-iodosugar and reduction.

The relative ease of base-catalysed elimination of 4-substituents from glucuronic acid (GlcA) derivatives is well known from early degradation studies on polysaccharides containing GlcA.[4] The resulting hexenuronic acids, viz. **4**, have been rather little used synthetically, but clearly they offer a convenient route to 4-deoxypyranoses provided good facial selectivity can be obtained on reduction. We now report the successful use of this approach for the synthesis of a number of deoxysugars.

The sequence to the key glycal intermediate (Scheme 1) began with glucuronolactone **5**, which was converted to tetraisobutyrate **6** via base-catalysed methanolysis followed by treatment with excess Pr^iCOCl and pyridine;[5] after recrystallisation, β-tetraester **6** was obtained in excellent anomeric purity in 50–60% yield. The advantages of the isobutyrate esters are several, namely, the crystallinity of key intermediates (v.i.), superior glycosidation, especially reduced transacylation,[5a] and a better yield in the later $NaBH_4$ reduction step. Numerous bases could effect elimination from **6**; the most convenient was DBU[6] (1.1 equiv, THF, 0–20 °C), which gave an excellent (96%) yield of unsaturated ester **7**. It was noteworthy that the 1α-ester corresponding to **6** did not undergo β-elimination easily. The trisubstituted double bond in **7** was not easily reduced by catalytic transfer hydrogenation, but classical hydrogenation in isopropanol led to clean reduction with 5β-ester **8** as the major product (5β:5α = 4:1). Recrystallisation from hexane gave pure 5β-CO_2Me product **8** in 58% yield.

For later adjustment of the stereochemistry at C(2) and C(3), **8** was converted to a glycal. Glycosyl bromide **9** was readily obtained from **8** using HBr·AcOH–CH_2Cl_2

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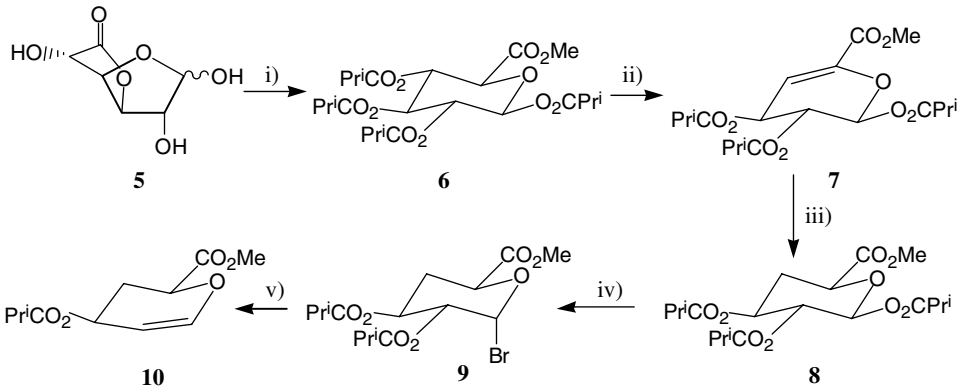


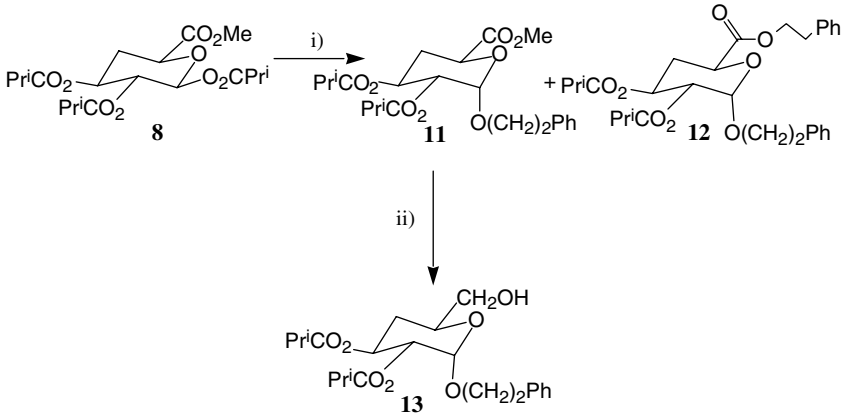
Scheme 1. Syntheses of 4-deoxyglucuronate ester **8** and derived glycal **10**. Reagents, yields: (i) Et_3N, MeOH, then AcOH, evap., Pr^iCOCl, pyridine, 59%; (ii) DBU, THF, 0–20 °C, 96%; (iii) H_2–Pd/C, Pr^iOH, remove 5α-isomer by crystallisation, 58%; (iv) HBr·AcOH, CH_2Cl_2, 80%; (v) Zn, vitamin B12, MeOH, 60%.

in the usual way; though **9** proved fairly unstable at 20 °C, it was readily converted to glycal **10**. In our hands the best procedure was the relatively recent[7] non-aqueous method employing Zn and catalytic vitamin B12 in MeOH: this is a fast, reproducible reaction. With the reactions summarised in Scheme 1, all key intermediates were in place.

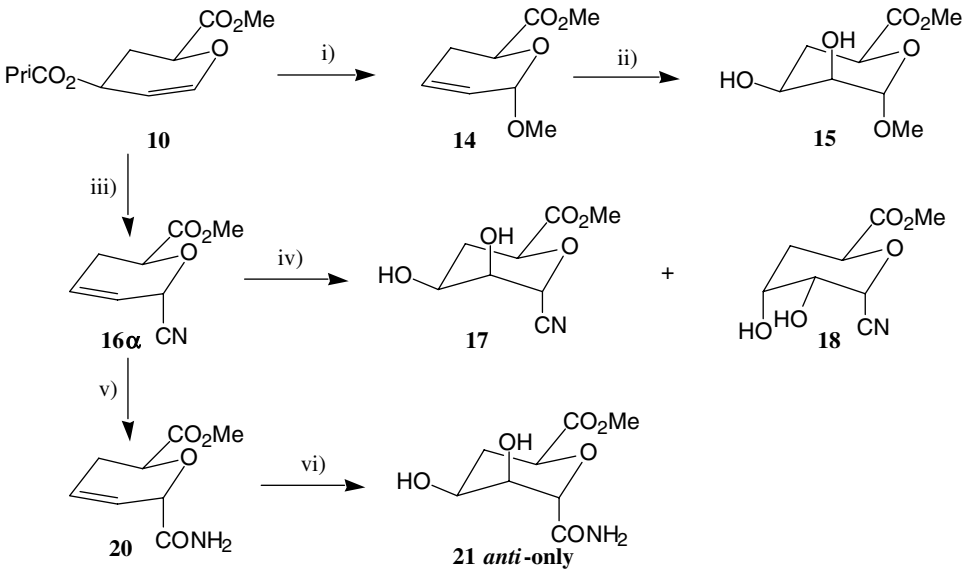
For entry to the 4-deoxyglucose series, (Scheme 2), 4-deoxyester **8** was first converted to a glycoside [$Ph(CH_2)_2OH$, TMSOTf], affording α-product **11** together with a small amount (ca. 10%) of the ester-exchanged product **12**. The 1α-configuration did not hinder the subsequent reduction, but this interesting result was in complete contrast to the TMSOTf-mediated glucuronidation of alcohols using **6**, where only the kinetic β-product was seen.[8] Clearly, the 4-deoxygenation has a profound influence here. Selective reduction of the 6-CO_2Me group with $NaBH_4$[9] then led to 4-deoxyglucoside **13** in good yield.

To obtain a dihydroxylation substrate, a Ferrier reaction[10] of **10** with methanol was performed, giving α-glycoside **14** in good yield, Scheme 3. Under the Upjohn conditions (catalytic OsO_4 with NMO as reoxidant),[11] this substrate afforded solely diol **15** by addition from the β-face, as expected for a 'non-directing' substituent[12,13] at C(1). This represents an entry to the D-*lyxo*-hexopyranose series as found in neosidomycin[14] and, at seven steps from **5** to **15**, is shorter than the previous route. In the previous synthesis of neosidomycin derivatives,[14] the acetonide of compound **15** was made and because of the close correspondence in NMR shifts and coupling constants [the acetonide showed δ 4.92 (1H, d, $J = 1.3$ Hz) and **15** showed δ 4.91 (1H, d, $J = 2.4$ Hz) for H-1 in each case] we are confident of the assignment of **15**. The acetonide J (H1–H2) value is consistent with an eq–eq coupling: in the same compound the ax–eq coupling [H-5 to H-4eq] was 5 Hz.[14] Also the dihydroxylation of normal (viz. 4-oxygenated) 2,3-dideoxypyranoses of 1α-configuration is known to give mainly mannoside products.[15]

Alternatively, conversion of **10** to a *C*-glycoside afforded convenient entries to other higher monosaccharides by dihydroxylation, with the facial preference of addition dependent on the new substituent added. Thus (Scheme 1) the Pd-catalysed reaction of **10** with Me_3SiCN[16] afforded very largely α-nitrile **16α** (α:β = 8:1) in a very good yield of 80%. The minor nitrile **16β** could be crystallised and a single crystal X-ray structure determination confirmed the stereochemistry, Figure 1.[17] Upjohn dihydr-



Scheme 2. Conversion to a 4-deoxyglucoside. Reagents and conditions: (i) TMSOTf, $Ph(CH_2)_2OH$, CH_2Cl_2, 0–20 °C, 59% **11** + 10% **12**; (ii) $NaBH_4$, 53%.



Scheme 3. Dihydroxylation studies. Reagents, yields: (i) MeOH, $BF_3{\cdot}Et_2O$, 52%; (ii) cat. OsO_4, *N*-methylmorpholine *N*-oxide, 41%; (iii) $Pd(OAc)_2$, Me_3SiCN, 80%, $\alpha{:}\beta = 8{:}1$; (iv) as (ii), or using quinuclidine-*N*-oxide (QNO) as reoxidant, 28%; (v) $TiCl_4$, AcOH, 40%; (vi) as (iv), 23%.

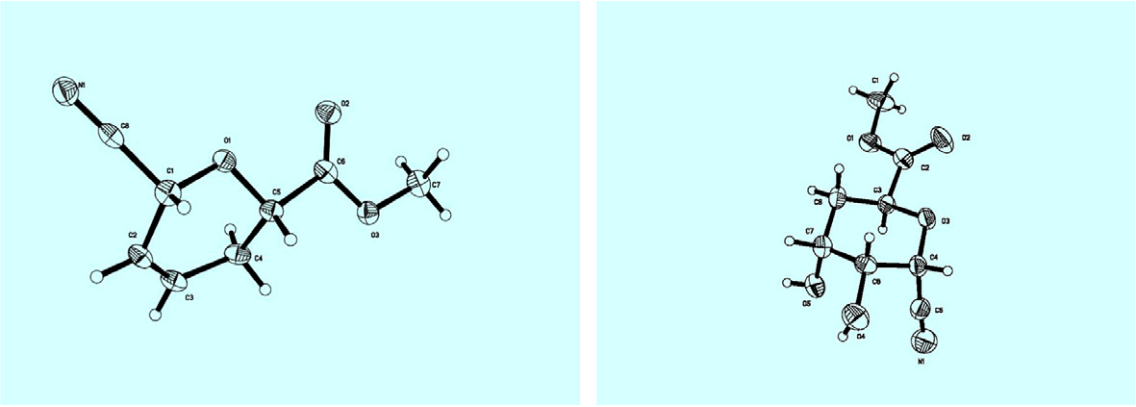
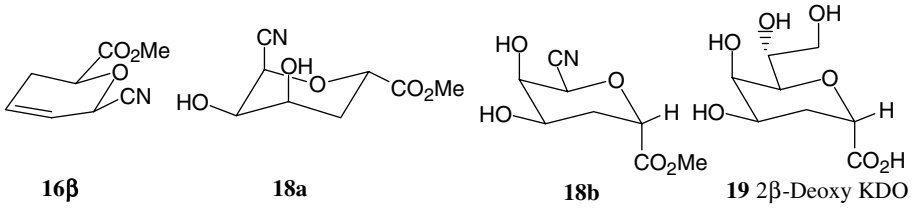


Figure 1. ORTEP representation for single crystal X-ray structures of **16β** and **18**.[17]

oxylation of **16α** gave a mixture of *anti* and *syn* diols **17** and **18** in a 3:2 ratio.

In contrast to the results of Donohoe[13] and others,[18] where allylic hydroxy or methoxy substituents usually direct dihydroxylation entirely to the opposite face, this is an interesting result. Either the nitrile substituent presents a relatively small bulk, so that appreciable *syn* dihydroxylation is sterically possible, or the nitrile may be exerting some directing effect. However, we found that both the yield and *syn*:*anti* ratio were virtually unaffected on using quinuclidine-*N*-oxide (QNO)[13,19] as reoxidant, so that currently we cannot offer a definite interpretation of this result.

By rotation, diol **18** may be drawn as **18a** whose alternative chair conformation is **18b** (v.s.): it can be seen that the absolute stereochemistry of **18b** is the same as that of 2β-deoxy KDO **19**,[20] with the nitrile replacing the 1,2-dihydroxyethyl side chain of the latter. Compound **19** is of considerable interest as an antibacterial agent since it is a potent inhibitor of CMP-KDO synthetase,[20,21] a key enzyme in Gram-negative bacterial cell wall assembly. A further X-ray structure determination[17] (Fig. 1) confirmed the stereochemistry of **18**. Unsurprisingly, the small nitrile substituent can adopt an axial setting, whereas the much bulkier 1,2-dihydroxyethyl side chain in **19** is known to be equatorial.[22]



Alternatively (Scheme 3), partial hydrolysis[23] of nitrile **16α** ($TiCl_3$, AcOH) afforded amide **20** in an acceptable (40%) yield. Dihydroxylation of **20** using either Upjohn conditions or QNO afforded a single product, namely *anti* diol **21**. Here the H(6)-proton [the carboxamide-bearing carbon is numbered C(6)] resonates at δ 4.10 (1H, d, $J = 1.6$ Hz), consistent with eq–eq coupling. This J value is strikingly similar to that in **15** and offers convincing evidence for the stereochemistry shown, though in this case we could not obtain a satisfactory crystalline sample. Apparently either the greater steric bulk of the amide over the nitrile directs the Os reagent entirely to the opposite face, or the amide NHs are insufficiently acidic to donate to Os, in contrast to the examples reported by Donohoe et al.[24] where a more acidic amide or carbamate NH was present. It is also noteworthy that examples featuring effective amide and carbamate donors have had the NH directly linked to the ring at the allylic position.[25] The *C*-glycosidic amide **20**, where the NH_2 unit is further away from the alkene, may have relatively unfavourable geometry to exert a donor effect.

In conclusion, we have demonstrated convenient routes from glucuronolactone to a variety of deoxypyranose sugars, including some of the potentially interesting biological activities. In addition the stereochemical preferences shown in the dihydroxylation reactions offer an interesting contribution to this topic.

Acknowledgements

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Supplementary data

Spectroscopic and analytical data for all new compounds reported, together with selected experimental procedures, are included in a supplementary file. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.127.

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