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Convergent synthesis of (1→2)- and (1→4)-*C*-linked imino disaccharides†

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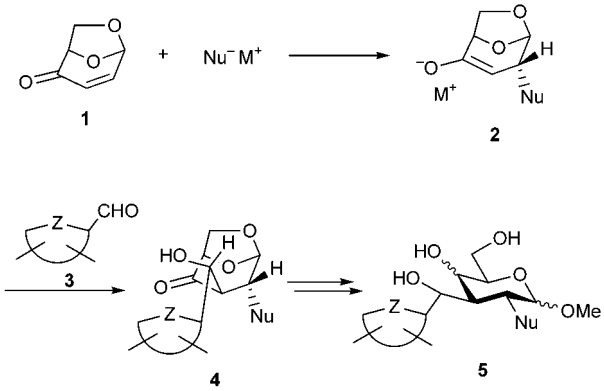
A convergent synthesis of (1→2)- and (1→4)-*C*-linked imino disaccharides was achieved by applying Nozaki–Kishi coupling of a hydroxyproline-derived carbaldehyde with isolevoglucosenone or levoglucosenone derived enol triflates.

Carbohydrate mimetics are potentially useful tools to study cellular interactions,[1] the biosynthesis of glycoproteins, the metabolism of glycoconjugates,[2] and the mechanisms of digestion.[3] Inhibitors of the enzymes involved in these processes such as the glycosidases and the glycosyltransferases are potential anti-cancer, antiviral, and antidiabetic agents, as well as insect antifeedant agents.[4] Disaccharide mimetics such as *C*-disaccharides and dideoxyiminoalditol *C*-linked to monosaccharides have emerged as a new class of specific glycosidase inhibitors and may represent non-hydrolyzable epitopes.[5–7] Recently we disclosed an efficient and versatile approach to the syntheses of (1→3)-*C*-disaccharides and (1→3)-*C*-linked imino disaccharides **5** based on the cross-aldolisation of the aldehydes **3** with the nucleophile 1,4-adducts **2** of isolevoglucosenone **1** (Scheme 1).[8,9] We report here that (1→4)- and (1→2)-*C*-disaccharides can be prepared starting from **1** and levoglucosenone **17** with **3**, respectively.

Adduct **6** of benzyl alcohol with isolevoglucosenone was enolized, without elimination of benzylate anion, on treatment with LiHMDS in 95:5 THF–HMPA at −78 °C (Scheme 2).[9] Quenching of the corresponding lithium enolate with 2-[bis(trifluoromethylsulfonyl)amino]-5-chloropyridine provided the enol triflate **7** in 87% yield.[10] Nozaki–Kishi coupling of **7** and aldehyde **8** led to allylic alcohols **9** and **10** isolated in 62 and 17% yield, respectively.[11,12]‡ Interestingly, the reaction was accelerated by ultrasound and O_2. Under N_2 atmosphere, ultrasound shortened the reaction time from 30 to 2 h. While in the presence of a catalytic amount of O_2 (5 mol% with respect to $CrCl_2$, concentration of O_2 lower than 10%), the reaction time was reduced further to less than 1 h. Moreover, O_2 suppressed the formation of **11**, resulting from H_2O quenching of the alkenylchromium species, from 36 to less than 10%.

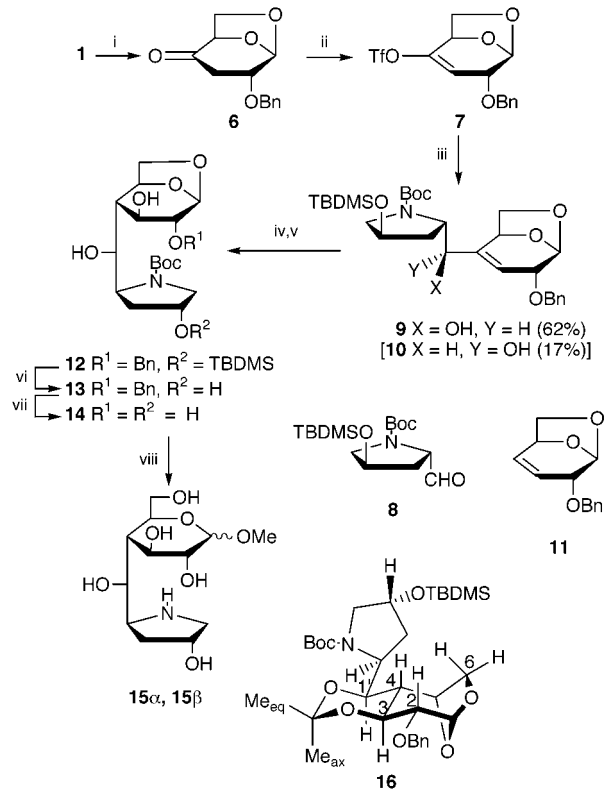


Scheme 1

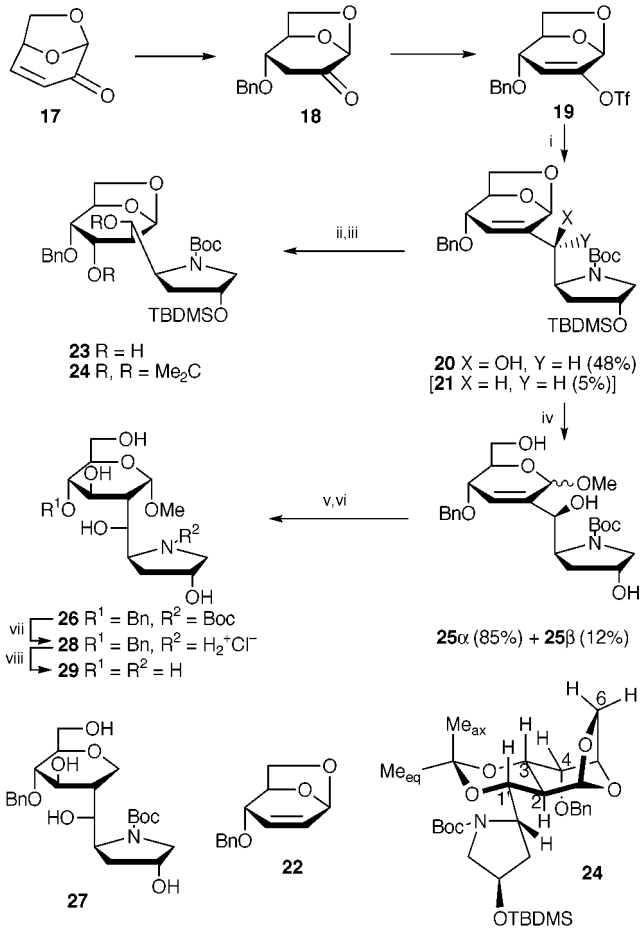
† Spectral data for **15α**, **15β** and **29** are available from the RSC web site, see http://www.rsc.org/suppdata/cc/1999/1873/

Hydroboration of **9** with $BH_3{\cdot}SMe_2$ in THF at 50 °C followed by H_2O_2/NaOH work-up furnished the D-glucose derivative **12** in 57% yield. Desilylation with Bu_4NF in THF gave triol **13** (97%), which was debenzylated to give tetrol **14** (94%). Treatment of **14** in refluxing MeOH saturated with gaseous HCl for 2 days produced a 2:1 mixture of **15α** and **15β** in 83% yield.

The D-*gluco* configuration of the methyl pyranosides **15α** and **15β** was determined from their ^1H NMR spectra.[13] The configuration of the hydroxymethano linker was established by converting diol **12** into the corresponding acetonide **16** [$(MeO)_2CMe_2$, acetone, TsOH, Drierite, 25 °C, 68% yield], the structure of which was established by its NOESY and ^1H NMR spectra. The coupling constants, ^3J(H-3, H-4) = 10.9 Hz, ^3J(H-4, H-1′) = 11.2 Hz and ^3J(H-2, H-3) = 7.2 Hz, show the antiperiplanar orientation between these proton pairs. Furthermore, NOEs were observed between signals attributed to H_{syn}-6, H-2, H-4, and between those attributed to Me_{axial}, H-1′, H-3. Thus, the *Re* face of aldehyde **8** is preferred for the alkenylchromium addition, which is in accord with the Felkin–Anh Model.[14]



Scheme 2 *Reagents and conditions*: i, BnOH, Et_3N, 25 °C; ii, LiHMDS, HMPA–THF, 2-[bis(trifluoromethylsulfonyl)amino]-5-chloropyridine, −78 °C, 87%; iii, **8**, $CrCl_2$, $NiCl_2$, O_2, DMF, ultrasound, 25 °C; iv, $BH_3{\cdot}SMe_2$, THF, 50 °C, v, H_2O_2, NaOH, 57% for 2 steps; vi, Bu_4NF, THF, 97%; vii, H_2, 10% Pd-C, MeOH, 25 °C, 94%; viii, MeOH, HCl, reflux, 2 days, 83%.



Scheme 3 *Reagents and conditions*: i, **8**, $CrCl_2$, $NiCl_2$, O_2, DMF, ultrasound, 25 °C; ii, $BH_3{\cdot}SMe_2$, THF, reflux; iii, H_2O_2, NaOH, 37% for 2 steps; iv, MeOH, TsOH, 25 °C; v, $BH_3{\cdot}SMe_2$, THF; vi, H_2O_2, NaOH, 46% for 2 steps; vii, MeOH, HCl, reflux, 92%; viii, H_2, 10% Pd-C, MeOH, 25 °C, 95%.

In parallel with the synthesis of (1→4)-*C*-disaccharides, (1→2)-*C*-disaccharides and analogues can be obtained starting from levoglucosenone **17** (Scheme 3). Benzyl alcohol adduct **18** was converted (as above) into triflate **19** in 90% yield.[15] In the Nozaki–Kishi coupling reaction, **19** was found to be less reactive than triflate **7**. It required activation with ultrasound and a catalytic amount of O_2 to react (best results with 5 mol% O_2 with respect to $CrCl_2$, 0.3 mol% $NiCl_2$). This led to alcohol **20** isolated in 48% yield, together with dehydroxylated product **21** (5% yield) and side product **22** (8% yield).‡ Hydroboration of **20** followed by oxidative work-up provided diol **23** in modest yield (37%). The ^{1}H NMR and NOESY spectra of acetonide **24** (obtained under the same conditions as those for **16**) showed coupling constants ^3J(H-2, H-3) = 10.7 Hz, ^3J(H-1′, H-2) = 10.7 Hz, ^3J(H-3, H-4) = 3.6 Hz, and NOEs between proton pairs H_{syn}-6/H-3, H-3/H-1′ H-3/Me_{axial} and H-1′/Me_{axial}. These establish the D-*altro* configuration of the anhydrohexose moiety and the (*R*) configuration of the hydroxymethano linker demonstrating again that the *Re* face of **8** was preferred for the nucleophilic addition.[16] Hydroboration took place from the *exo* face of the bicyclic system probably because of steric hindrance from the *endo* hydrogen at C6. The allylic acetal was readily opened by acidic methanolysis, which provided glycosides **25α** and **25β** isolated in 85 and 12% yield, respectively. Hydroboration of **25α** gave alcohol **26** (46%) and the anhydroglucitol derivative **27** (10%).[16] Under reflux in MeOH saturated with HCl, **28** was obtained in 92% yield. Hydrogenation liberated the (1→2)-*C*-linked imino disaccharide **29** (95%).

The stereoselective methods presented above should be applicable to the preparation of a large variety of (1→2)- and (1→4)-*C*-disaccharides and analogues employing the same starting materials as those for the synthesis of (1→3)-*C*-disaccharides, and thus make possible the exploration of their structure–activity relationships.[17]

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Notes and references

‡ *Selected data* for **9**: colorless oil; $[\alpha]_D^{25}$ −107 (*c* 1.2, $CHCl_3$); δ_H(400 MHz, $CDCl_3$, 323 K) 7.38–7.25 (m, 5H, Ph), 5.54 (m, 2H, H-1, H-3), 4.76 [d, ^3J (H-5, H_{exo}-6) 3.6, H-5], 4.65 and 4.62 (2d, 2H, ^2J 11.5, PhCH_2O), 4.38 (p, ^3J 3.6, H-4′), 4.37 (m, H-1′), 4.31 (m, H-2′), 3.71 (m, 2H, H-6), 3.55 [d, ^3J(H-2, H-3) 3.9, H-2), 3.48 (d, ^2J 11.2 , H-5′a), 3.35 [dd, ^2J 11.2 , ^3J(H-4′, H-5′b) 4.2, H-5′b] 1.92 (m, 2H, H-3′), 1.48 [s, 9H, $(CH_3)_3$CO], 0.86 [s, 9H, $(CH_3)_3$CSi], 0.04 [s, 6H, $(CH_3)_3$Si]. For **20**: $[\alpha]_D^{25}$+24 (*c* 0.94, $CHCl_3$); δ_H(400 MHz, $CDCl_3$, 323 K) 7.44–7.26 (m, 5H, Ph), 5.69 (m, H-3), 5.64 (s, H-1), 4.77 [dtd, ^3J(H-5, H_{exo}-6) 6.6, ^4J(H-3, H-5) = ^3J(H-5, H_{endo}-6) = 1.7, ^3J(H-4, H-5) 1.1, H-5), 4.68 (s, 2H, PhCH_2O), 4.52 (m, H-1′), 4.32 (m, H-4′), 4.20 (m, H-2′), 3.87 (dd, ^2J 7.6, ^3J 6.6, H_{exo}-6), 3.58 [dt, ^3J(H-3, H-4) 3.9, ^3J(H-4, H-5) = ^5J (H-4, H-1′) = 1.1, H-4], 3.46 (m, H-5′a), 3.36 (dd, ^2J 11.2, ^3J 4.2, H-5′b), 3.31 (dd, ^2J 7.6 ,^3J 1.7, H_{endo}-6), 1.89 (m, 2H, H-3′), 1.49 [s, 9H, $(CH_3)_3$CO], 0.88 [s, 9H, $(CH_3)_3$CSi], 0.06 [s, 6H, $(CH_3)_2$Si].

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