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A SERENDIPITOUS SYNTHESIS OF CYCLOKOJIBIOSE

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Abstract: *The fully protected kojibiosyl trichloroacetimidate* **5** *undergoes intramolecular cyclization accompanied by expulsion of the O-benzyl protecting group upon activation by a Lewis-acid to give the symmetrical, tricyclic compound* **6** *which is the first member of an as yet unreported group of cyclooligosaccharides.* Published by Elsevier Science Ltd

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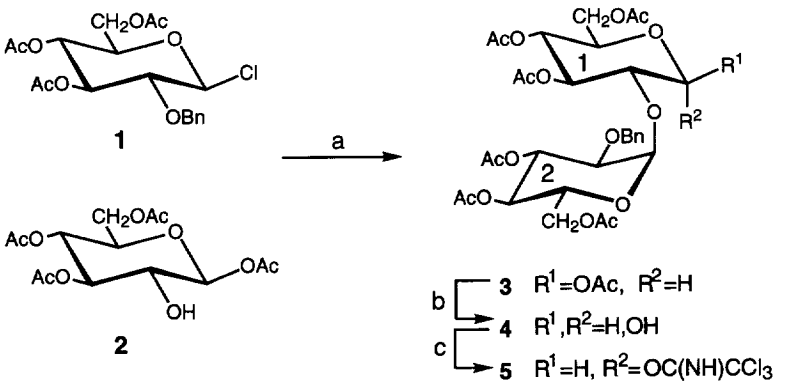
The ability of cyclic oligosaccharides consisting of D-glucopyranose residues (cyclodextrins) to form inclusion complexes with hydrophobic guest compounds made them challenging synthetic targets.[1] Cycloglycosylation strategies developed by Ogawa's group led to the total synthesis of cyclodextrins consisting of six[2] and eight[3] α-(1→4)-linked D-glucose residues. While the existence of smaller rings (degree of polymerization ≤ 5) in this series was questioned on the basis of potential energy calculations,[4] the recent successful synthesis of *cyclo*-α-(1→4)-glucopentaose[5] proved that α-(1→4)-linked small-ring cyclodextrins may, indeed, be constructed however, not without distorting the $^4C_1$ conformation of the pyranoid rings.[6] Other reported chemical syntheses of cyclodextrins include the preparation of α-(1→6)-linked cyclogluco-triose,[7] -tetraose,[8] and -hexaose,[7] and β-(1→6)-linked cycloglucobiose (cyclogentiobiose).[9]

In connection with our work on α-(1→2)-linked gluco-oligosaccharides[10] we report here a serendipitous synthesis of *cyclo*-α-(1→2)-glucobiose (cyclokojibiose) which is the first member of an as yet unreported group of cyclic oligosaccharides.

The protected kojibiose derivative **3**[11] was obtained in 70 % yield by the condensation of chloride **1**[10] with alcohol **2**[12] under promotion by $AgClO_4/Ag_2CO_3$. Regioselective deacetylation (NH_2NH_2/AcOH, Ref 13) of **3** afforded the hemiacetal **4**[11] (94 %) which was converted to the imidate **5**[11] under standard conditions[14] (87 %). (Scheme 1.) Most surprisingly, treatment of compound **5** with $BF_3 \cdot Et_2O$ in CH_2Cl_2 at 0 °C under rigorously anhydrous conditions either in the presence or the absence of an unreactive alcohol completely transformed compound **5** and the

Scheme 1.

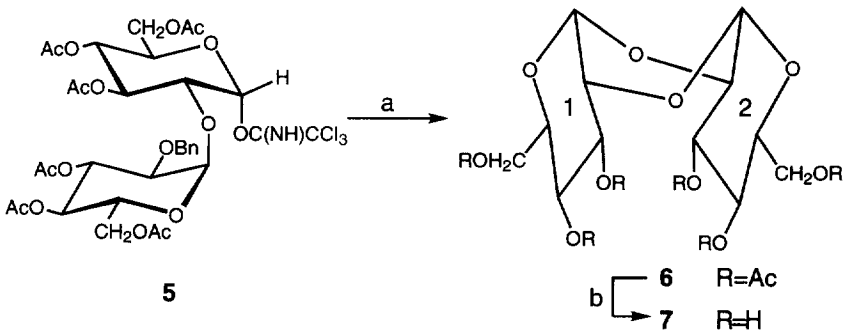


Reagents and conditions: (a) 1.3 equiv. **2**, 0.2 equiv. of $AgClO_4$, Ag_2CO_3 (excess), CH_2Cl_2, 4A molecular sieves, 25 °C, 24 h, 70%; (b) 1.3 equiv. of $NH_2NH_2 \cdot AcOH$, DMF, 25 °C, 3 h, 94%; (c) CCl_3CN (excess), 1,8-diazabicyclo-[5.4.0]undec-7-ene (cat), CH_2Cl_2, 0 °C, 1 h, 87%.

tricyclic compound **6**[11] could be isolated in 70 % yield. (Scheme 2.) Removal of the *O*-acetyl groups of **6** (NaOMe/MeOH, 80 %) afforded compound **7**.[11] The structure of **6** was established as follows. The most prominent peak in the chemical ionization mass spectrum at *m/z* 594 [$(M + NH_4)^+$] indicated that the losses from the parent compound **5** (MW 827) exceed that would correspond to the loss of the trichloroacetimidyl moiety [$CCl_3C(NH)OH$] only by 90 amu, which suggests the absence of the benzyl group. Indeed, the NMR spectra were devoid of aromatic signals and consistent with either an α-linked monosaccharide having three *O*-acetyl groups and no other functionalities or with a highly symmetrical, α-linked saccharidic structure. The ^1H NMR spectrum recorded at 500 MHz in $CDCl_3$ requires the presence of acetyl groups at O-3 and O-4. Since no acetyl group can be placed on O-2, the third acetyl group must be located at O-6. The low-field position (5.21 ppm, J=3.1 Hz) of the H-1 signal indicates an unusual environment for this part of the molecule which is further corroborated by the surprisingly high-field position (90.4 ppm) for C-1 in the ^{13}C NMR spectrum. Removal of the *O*-acetyl groups (→ **7**) shifted the H-3 and H-4 signals upfield as expected, while a shift in the opposite direction was observed for the H-1 signal to 5.33 ppm.

It is of importance to note that the intramolecular glycosylation reported in this work proceeded through a benzyl-protected, secondary hydroxyl group. This contrasts to cycloglycosylations reported earlier[2-9] which employed intermediates with a free hydroxyl group at

Scheme 2.



Reagents and conditions: (a) 5 equiv. of $BF_3 \cdot Et_2O$, CH_2Cl_2, 4A molecular sieves, 0 °C, 4 h 76%; (b) NaOMe (cat), MeOH, 25 °C, 3 h, 80%.

the site of the ring formation. Alternatively, this site was protected by the highly acid-labile trityl group.[15] While intramolecular expulsion of a benzyl group by a carbocation is not unprecedented[16] to our knowledge this is the first case of an anomeric carbon atom-mediated debenzylation. We propose that activation of **5** leads to a reactive intermediate in which the anomeric carbon atom C(11)[17] is placed in close proximity to the O(22) oxygen atom of the non-reducing end residue. The intermediate achieves stabilization by covalent bond formation between C(11) and O(22) and simultaneous expulsion of the benzyl group. This group is critical for the nucleophilicity of O(22) since no cycloglycosylation could be observed with the fully acetylated congener[18] of **5**.

X-ray crystallographic analysis and molecular modeling studies[19] of **6** indicate that the dioxane ring interconnecting the two monosaccharide units is in a boat conformation, the C(11)-C(12)-O(12)-C(21) and the C(11)-O(22)-C(22)-C(21) dihedral angles being +4.9° and -3.8°, respectively. The glucopyranose residues adopt a slightly distorted $^4C_1$ conformation. For example, the O(15)-C(11)-C(12)-C(13) dihedral angle is 47°, which is 11° smaller than the corresponding angle in methyl α-D-glucopyranoside.[20] Molecular models also show that **6** and **7** exhibit little flexibility. Their O(15)-C(15) bond is gauche to the C(11)-O(22) bond, and the *exo*-anomeric effect[21] is integrated for the dioxane ring. For the pyranose rings the anomeric effect is also integrated, but not the *exo*-anomeric effect, the H(11)-C(11)-O(22)-C(22) torsional angle being 67°.[22] The equivalent torsional angle on the other side H(21)-C(21)-O(12)-C(12) is -67°. It is likely that the combination of the stabilizing factors around the anomeric centers is sufficient to offset the unfavorable energy contributions of the dioxane moiety and the strained pyranose rings. However, the relative contributions of these effects is uncertain at this time.[23]

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(11) Analytical and mass spectral data were consistent with the structures presented. Selected NMR data (δ, $CDCl_3$, 20 °C except where noted otherwise) are given below. For compounds **3-5** the individual atoms are denoted by two numbers in parentheses following the atom symbol: the first one refers to the ring as defined in the Schemes, the second one refers to the individual atom of that ring. **3** δ_H 5.79 [d, J 7.7 Hz, H(11)], 5.09 [d, J 3.4 Hz, H(21)], δ_C 97.8 [C(21)], 92.7 [C(11)]; **4** δ_C 99.5 [C(11β)], 97.2 and 96.2 [C(21)], 90.4 [C(11α)]; **5** δ_H 6.57 [d, J 3.5 Hz, H(11)], 4.92 [d, J 3.3 Hz, H(21)], δ_C 98.4 [C(21)], 93.4 [C(11)]; **6** δ_H 5.60 (dd, $J_{2,3}$ 6.8 Hz, $J_{3,4}$ 8.8 Hz, H-3), 5.21 (d, $J_{1,2}$ 3.1 Hz, H-1), 4.96 (dd, $J_{4,5}$ 7.8 Hz, H-4), 4.27 (ddd, $J_{5,6}$ 2.8 Hz, $J_{5,6'}$ 4.8 Hz, H-5), 4.39 (dd, $J_{6,6'}$ -12.3 Hz, H-6'), 4.13 (dd, H-6), 3.99 (dd, H-2), δ_C 90.4 (C-1), 72.8, 72.0, 70.8, and 67.1 (C-2,3,4,5), 61.3 (C-6); **7** (D_2O) δ_H 5.33 (d, $J_{1,2}$ 3.3 Hz, H-1), 4.04 (d, $J_{2,3}$ 7.2 Hz, H-3), 3.93 (d, $J_{2,3}$ 7.2 Hz, H-2), 3.88 (ddd, $J_{5,6}$ 2.7 Hz, $J_{5,6'}$ 5.1 Hz, H-5), 3.53 (dd, $J_{4,5}$ 9.5 Hz, H-4), 3.83 (dd, $J_{6,6'}$ -12.4 Hz, H-6), 3.80 (dd, H-6'), δ_C 91.2 (C-1), 76.4 (C-2), 75.6 (C-5), 74.4 (C-3), 68.8 (C-4), 61.0 (C-6).

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(17) Atom numbering is defined in Ref. 11.

(18) This compound was obtained from **3** by successive hydrogenolysis, acetylation, followed by conversions *b* and *c* in Scheme 1.

(19) Molecular modeling was performed with the program Biosym Insight II, Ver. 2.3.0.

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(22) The *exo*-anomeric effect would require this angle to be *ca.* -60°. In methyl α-D-glucopyranoside the corresponding angle is, indeed, -54.4° (Ref. 20).

(23) For a discussion of the stabilizing factors in a related tricyclic saccharide harboring a *flexible* dioxane moiety, see: Bock, K.; Pedersen, C.; Defaye, J.; Gadelle, A. K. *Carbohydr. Res.* **1991**, *216*, 141-148.

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