diffractometer with a smart CCD detector ($Mo_{K\alpha}$ radiation, $\lambda = 0.71073$ Å, ω scans, $3.6 \leq 2\theta \leq 60.74^\circ$). All in all 10263 reflections were detected (6663 independent reflections) and 5869 were classified as observed. The structure was solved by direct methods and refined against F^2. Hydrogen atoms were placed at calculated positions and refined dependent on the adjacent non-hydrogen atoms (riding model). The refinement of the 331 varied parameters converged to $R = 0.0425$ for 6663 reflections with $I > 2\sigma(I)$ and $wR2 = 0.0900$ for all reflections. Min./max. transmission 3.790/2.057 e Å^{-3}. The structure was solved with SIR-97[16] and refined with SHELXL-97.[17] Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-141108. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[14] In poorly solvating solvents the reaction of $TlTpms^{tBu}$ with $ZnBr_2$ leads to not only the expected C_{3v}-symmetrical species but also to a C_s-symmetrical compound that has yet to be identified.

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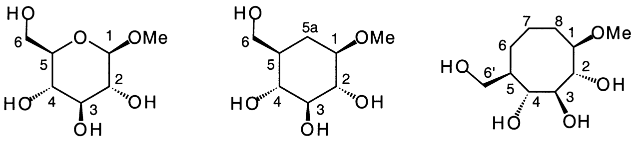
From Glucose to Cyclooctanic Carbaglucose: A New Class of Carbohydrate Mimetics

Wei Wang, Yongmin Zhang, Matthieu Sollogoub, and Pierre Sinaÿ*

Synthetic oligosaccharides have recently emerged as potential therapeutic agents.[1] A possible in vivo hydrolysis of such drugs by various glycosidases has stimulated the search for nonhydrolyzable oligosaccharide mimetics. One option is to replace the endocyclic oxygen atom of aldohexopyranosyl residues by a methylene group. The resulting 5a-carbasugars are hydrolytically stable analogues, and the chemical synthesis of the 5a-carbaaldohexopyranoside family has been largely developed.[2] An intriguing alternative is to use a cyclooctane ring as a framework for the OH groups of the carbohydrate. For instance, the replacement of the endocyclic oxygen atom in methyl β-D-glucopyranoside (**1**) by one methylene group would result in a cyclohexanic mimetic **2**, whereas the replacement by three methylene groups would give a novel type of cyclooctanic carbohydrate mimetic **3** (Scheme 1).

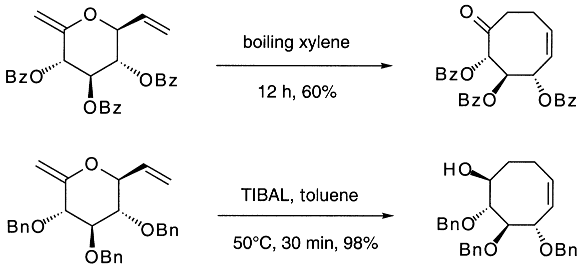


1 **2** **3**

Scheme 1. Methyl β-D-glucopyranoside (**1**) as well as the cyclohexanic (**2**) and cyclooctanic (**3**) analogues.

The rationale behind this proposal is that the conformation and conformational equilibration of cyclooctane derivatives[3] may offer interesting new distributions of hydroxy groups compared to those available through the classical pseudorotational itinerary[4] of pyranoid rings. The incorporation of these so far undescribed carbocyclic sugar mimetics in oligosaccharide chains is thus of interest in terms of the resulting biological responses, such as glycosidase inhibition, a feature which may benefit from the easy access to nonclassical conformers.

The thermal or triisobutylaluminum (TIBAL) promoted Claisen rearrangement of 2-methylene-6-vinyl-tetrahydropyran, which affords cyclooctanic derivatives by insertion of a C_2 unit, has been elegantly developed by Paquette et al.[5] for the synthesis of natural products with eight-membered rings. It has recently been applied in the carbohydrate field, either in the form of a thermal reaction,[6] or in the form of a smooth Al^{III}-catalyzed process[7] (Scheme 2).



4 **5**

Scheme 2. Thermal or TIBAL-catalyzed Claisen rearrangement of unsaturated monosaccharide derivatives. Bn = $PhCH_2$; Bz = PhCO.

As shown in Scheme 3, the cyclooctanol derivative **6**, the enantiomer of the previously prepared cyclooctanol **5**, was smoothly obtained in 96% yield from the TIBAL-catalyzed sigmatropic rearrangement of the gluco derivative **12**, which in turn was easily derived from methyl α-D-glucopyranoside in an eight-step sequence.

Methylation of **6** gave **13** which, upon regio- and stereoselective hydroboration, was converted in 60% yield into the cyclooctanol derivative **14** (Scheme 4). Oxidation of **14** gave the cyclooctanone **15**, and subsequent treatment with the Tebbe reagent $[Cp_2Ti(\mu\text{-}Cl)(\mu\text{-}CH_2)AlMe_2]$ generated the methylene derivative **16**. Regioselective hydroboration of **16** gave the cyclooctanic mimetic **17** and the α-L-ido isomer **18**, which were separated by flash chromatography on silica gel (Scheme 5).

The boat–chair conformation for compound **17** (Scheme 6) is assigned on the basis of the ^3J couplings in the ^1H NMR spectrum. The H1–H5 NOE confirms the β-D-gluco configuration. The interpretation of the NMR spectrum of the α-L-

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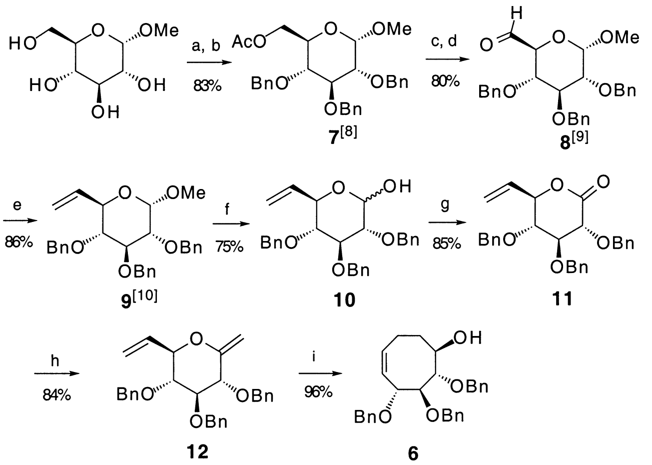
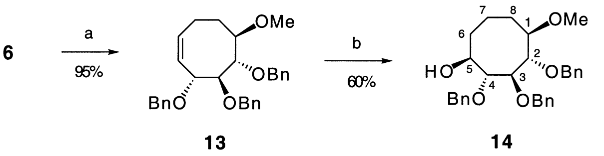
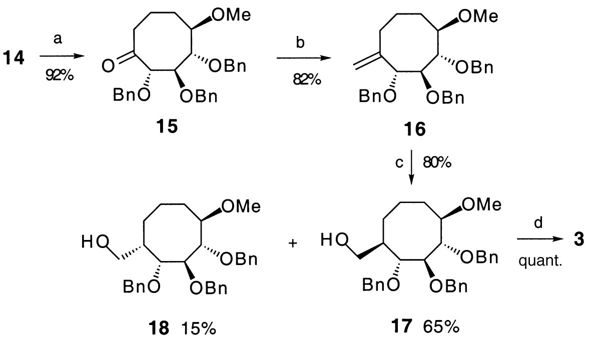


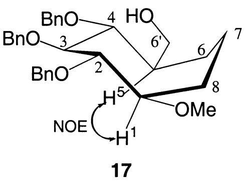
Scheme 3. a) BnBr (6 equiv), NaH (8 equiv), DMF, RT, 2.5 h, quant; b) TMSOTf (cat.), Ac_2O, CH_2Cl_2 (dry), −55 to −50 °C, 1.5 h; c) NaOMe/MeOH, 2 h, quant; d) PCC (1.1 equiv), 4 Å molecular sieves, CH_2Cl_2 (dry), 0 °C, 2 h; e) BuLi (3 equiv), Ph_3PCH_3Br (3 equiv), THF (dry), −78 °C to RT, 1.5 h; f) TfOH/AcOH/H_2O (1/28/5), 80 °C, 2.5 h; g) PCC (3 equiv), 4 Å MS, CH_2Cl_2 (dry), 0 °C to RT, 3 h; h) Tebbe reagent (3 equiv), Py/THF (1/1), −78 °C to RT, 30 min; i) iBu$_3$Al, toluene, 50 °C, 30 min. Abbreviations: RT = room temperature; TMS = trimethylsilyl; Tf = trifluoromethanesulfonyl; PCC = pyridinium chlorochromate; Py = pyridine.



Scheme 4. a) NaH, MeI (2.8 equiv), DMF, RT, 2 h; b) 1) $BH_3 \cdot THF$ (2 equiv), THF, RT, 1 h; 2) aq. NaOH (11 %), aq. H_2O_2 (35 %), 0 °C to RT, 1.5 h.



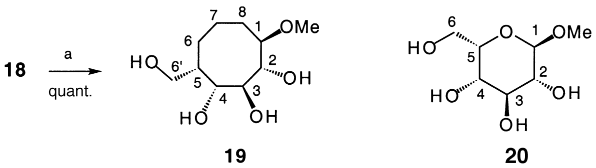
Scheme 5. a) PCC (3 equiv), dry CH_2Cl_2, 0 °C, 2 h; b) Tebbe reagent (2 equiv), Py/THF (1/1), −78 °C to RT, 20 min; c) 1) $BH_3 \cdot THF$ (2 equiv), THF, RT, 1 h; 2) aq. NaOH (11 %), aq. H_2O_2 (35 %), 0 °C to RT, 2 h; d) H_2, Pd/C, EtOAc, MeOH, RT, 2 h.



Scheme 6. The boat–chair conformation assigned to compound **17**.

ido isomer **18** is more complex and corresponds to the well known flexibility of idopyranosides.[11]

The two deprotected cyclooctanic sugar mimetics **3** and **19** were quantitatively obtained after catalytic hydrogenolysis of compounds **17** and **18** (Schemes 5 and 7), respectively. Compounds **3** and **19** represent the first two members of a new class of synthetic carbasugars, which are now available for various biological studies.



Scheme 7. Formation of **19**, a mimetic of methyl α-L-idopyranoside **20**, by deprotection of compound **18**: a) H_2 (170 kPa), Pd/C, ethyl acetate/methanol 1/1, RT, 2 h.

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