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From hydrocarbons to polyols. Cyclooctatetraene to novel cyclooctitols†

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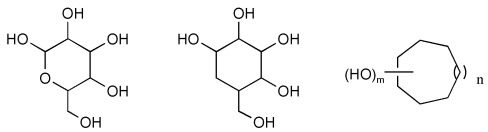
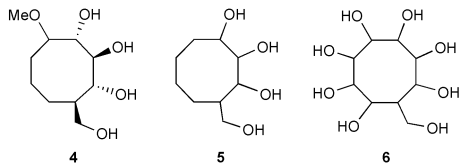
Received (in Cambridge, UK) 12th September 2002, Accepted 11th October 2002
First published as an Advance Article on the web 28th October 2002

Cyclooctatetraene (COT) derived bicyclo[4.2.1]nona-2,4,7-trien-9-one has been recognized as a cyclooctane carbasugar equivalent and elaborated to a range of cyclooctane polyols (cyclooctitols) through a flexible strategy with moderate regio- and stereo-control.

There is considerable current interest in the design of molecules that can mimic carbohydrates associated with important signalling and recognition events with improved efficacy, stability and specificity.[1] One of the commonly followed tactics in this regard has been the replacement of the ring oxygen atom in the monosaccharide residue by a methylene group. Thus, through a change from a aldopyranoside **1** to a carbasugar **2**, the vulnerability of the former to glycosidases is eliminated while retaining the core structure and essential network of hydroxyl functionalities for receptor recognition. Diverse synthetic strategies have been devised in recent years to access a range of carbasugars **2** and their structural variants to evaluate their biological properties, particularly the glycosidase inhibition profile.[2,3] In the last couple of years, higher analogues of carbasugars based on polyhydroxylated seven- and eight-membered rings have attracted a lot of attention as new types of potential glycomimics.[4,5] An advantageous feature of the cycloheptane[4] and cyclooctane polyols **3**[5,6] is that they offer

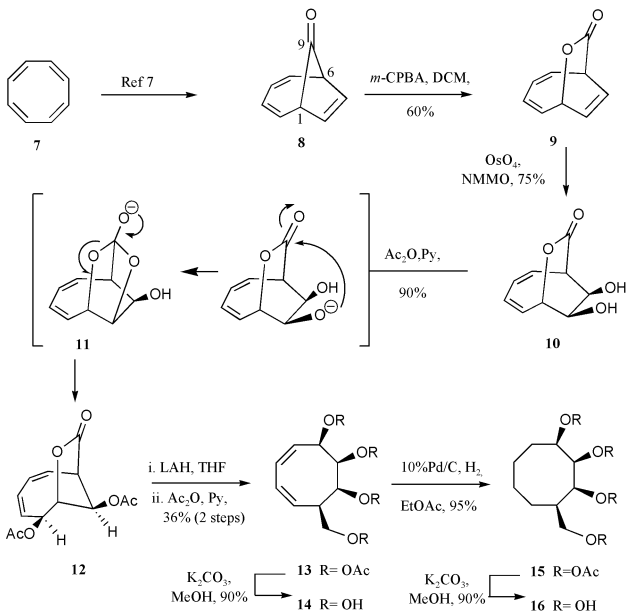


opportunities for new distributions of hydroxyl functionalities for biological interactions in a conformationally flexible environment compared to the classical conformations present in **1** and **2**. In particular, Sinay and coworkers[6c,h] in the year 2000 have reported the first synthesis of a cyclooctane homologue **4** of carbasugar **2** from glucose. In concurrent efforts in our laboratory, we have developed a versatile synthesis of cyclooctane based polyols (cyclooctitols) ranging from tetrahydroxy **5** to octahydroxy **6** from the commercially available hydrocarbon cyclooctatetraene **7** (COT) and these results form the theme of this letter.



Our synthetic approach to cyclooctitols emanated from COT **7** which was readily elaborated to bicyclo[4.2.1]nona-2,4,7-trien-9-one **8** in essentially a single-pot operation through the reaction of dilithium cyclooctatetraenide with dimethylcarbamoyl chloride as described by Shechter and coworkers.[7] We visualized **8** as a 'functionally locked' COT with differentiated olefinic bonds and a 'masked' C-9 cyclooctacarbasugar from which the eight-membered ring can be extracted through oxidative C_1–C_9 bond scission. Baeyer–Villiger oxidation in **8** was smooth and led to the formation of δ-lactone **9**, Scheme 1.[8] Catalytic OsO_4 dihydroxylation in **9** proceeded with complete regio- and stereo-selectivity to furnish the *exo*-1,2-diol **10**.[8] Attempted acetylation of the diol **10** led to an unanticipated but interesting rearrangement to the γ-lactone **12** having *exo*-1,3-diacetate functionality.[8] The stereospecific rearrangement of **10** to **12** can be rationalized as proceeding through the intermediacy of the tetrahedral intermediate **11**, Scheme 1. Reduction of **12** with $LiAlH_4$ and peracetylation of the resulting product for convenient isolation led to the 1,3-diene-tetraacetate **13**, Scheme 1.[8] Base hydrolysis of **13** furnished the all-*cis*-diene tetrol **14**, which could also be obtained directly from **10** through hydride reduction. Catalytic hydrogenation of **13** to **15** and hydrolysis furnished **16** the first of the desired cyclooctane polyols, Scheme 1.[8] Bicyclic γ-lactone **12** was further elaborated to amplify the network of hydroxyl functionalities. On controlled catalytic hydrogenation **12** furnished a 1:1 mixture of the dihydro- and tetrahydro-γ-lactones **17** and **18**, respectively, Scheme 2.[8] While $LiAlH_4$ on **17** furnished the unsaturated tetrol **19** and on further acetylation the tetraacetate **20**, the fully reduced γ-lactone on hydride reduction led to the above-described tetrol **16**, Scheme 2. Protection of the *vic*-diol functionality in **19** led to acetonide **21**[8] whose X-ray crystal structure[9] not only revealed an open α-face of the olefinic double bond but also secured all the earlier stereochemical assignments.

Hydroboration–oxidation of **21** and acetylation of the products furnished acetonide–triacetates **22**, **23** and **24**



Scheme 1

† Electronic supplementary information (ESI) available: spectroscopic characterization. See http://www.rsc.org/suppdata/cc/b2/b208918a/

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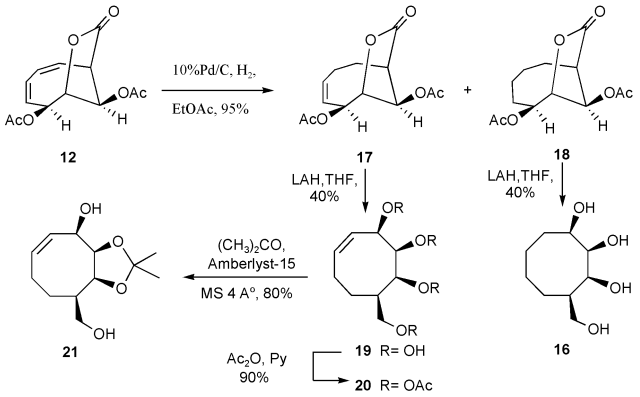
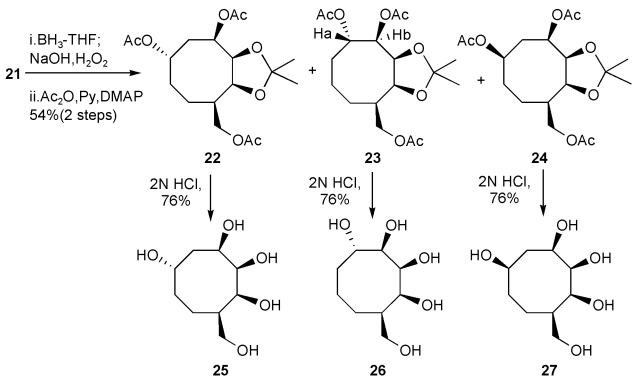


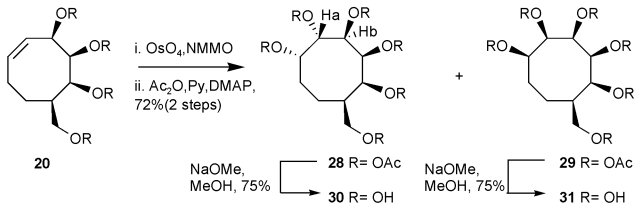
Scheme 2

(63 : 30 : 7), Scheme 3.[8] The stereostructure of the major product **22**, having a 'skipped methylene' hydroxyl pattern, was established through X-ray crystal structure determination.[9] The stereostructure of the next major product **23** followed from the incisive analysis of the ^{1}H NMR (COSY) data and more specifically from the *trans* coupling ($J_{H_a-H_b}$) of 9.6 Hz and was also confirmed by X-ray crystal structure determination.[9] The minor product **24** was readily recognized as the diastereomer of **22**.[8] The three acetonide–triacetates **22**–**24** were readily hydrolysed to furnish the pentahydroxy-cyclooctanoids **25**–**27**, Scheme 3. Interestingly, pentahydroxy **26** is a eight-membered carba analogue of α-talose. It is to be noted that the hydroboration of **21** proceeds with high stereoselectivity but with only 2 : 1 regioselectivity. Tetraacetate **20** was a suitable substrate for accessing the higher order cyclooctane polyols. OsO_4-mediated dihydroxylation of **20** followed by acetylation led to a 1 : 1 diastereomeric mixture of hexa-acetates **28** and **29** Scheme 4.[8] Stereostructures of **28** and **29** were determined through high-field 2D NMR experiments. For example, $J_{H_a-H_b}$ = 10 Hz in **28** was highly diagnostic of their *trans* disposition and was further confirmed by X-ray crystal structure determination.[9] Base hydrolysis of **28** and **29** furnished the hexahydroxy-cyclooctanes **30** and **31**, respectively, Scheme 4.[8] Interestingly, all the six oxygen functionalities in **29** are disposed on the β-face, imparting it a dipolarofacial character.

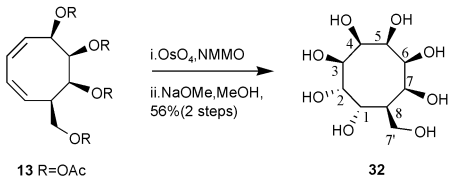
Finally, diene tetraacetate **13** was the substrate of choice for elaboration to the fully oxy-functionalized cyclooctane polyol



Scheme 3



Scheme 4



Scheme 5

through stereoselective double *cis*-dihydroxylation of the diene moiety in **13**. Prolonged exposure of **13** to catalytic OsO_4–NMMO milieu and base hydrolysis led to an octahydroxy compound **32**[8] through sequential stereoselective dihydroxylations, Scheme 5. The structure of cyclooctitol **32** was deduced through incisive high-field ^{1}H NMR (COSY) analysis and in particular the J_{H2-H3} and J_{H1-H8} *trans* coupling of 9.5 and 8.5 Hz, respectively, were decisive in securing its structure, Scheme 5. In addition the H-5 proton appeared as a broad singlet indicating that it is flanked by *cis* protons on either side. To our knowledge, a cyclooctane derivative bearing eight oxygen atoms has been prepared for the first time.

In summary, utilizing the commercially available cyclooctatetraene we have accomplished the synthesis of a range of cyclooctane based polyols (cyclooctitols) in a short and flexible sequence with moderate regio- and stereo-control. These new entities, homologues of carbasugars, have now become available for further transformations and biological evaluation.

K. P. thanks CSIR for the award of a Research Fellowship. We thank SIF and CCD facilities at IISc for help We acknowledge helpful correspondence with Professor Shechter, the Ohio State University, regarding the preparation of bicyclic ketone **8**.

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8 All new compounds reported here were racemic and characterized on the basis of spectroscopic data (IR, ^{1}H and ^{13}C NMR, mass).

9 Details of the X-ray crystal structure determination of **21**, **22**, **23** and **28** are given as ESI.† CCDC 193886–193889. See http://www.rsc.org/suppdata/cc/b2/b208918a/.