From hydrocarbons to polyols. Cyclooctatetraene to novel cyclooctitols†

Goverdhan Mehta* and Kotapalli Pallavi
Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India.
E-mail: gm@orgchem.iisc.ernet.in

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 to a carbasugar, 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 based on polyhydroxylated seven- and eight-membered rings. In the year 2000, Sinay and coworkers6-8 in the year 2000 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 cyclooctatetraene (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.5 We visualized 8 as a ‘functionally locked’ COT with differentiated olefinic bonds and a ‘masked’ C-9 cycloocta-carbasugar from which the eight-membered ring can be extracted through oxidative C1-C9 bond scission. Baeyer-Villiger oxidation in 8 was smooth and led to the formation of lactone 9. Catalytic OsO4 dihydroxylation in 9 proceeded with complete regio- and stereo-selectivity to furnish the exo-1,2-diol 10. Attempted acetylation of the diol 10 led to an unanticipated but interesting rearrangement to the γ-lactone 12 having exo-1,3-diacetate functionality. 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 LiAlH4 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 LiAlH4 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 whose X-ray crystal structure9 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

† Electronic supplementary information (ESI) available: spectroscopic characterization. See http://www.rsc.org/suppdata/cc/b2/b208918a/
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 through sequential stereoselective dihydroxylation. Scheme 5. The structure of cyclooctitol 32 was deduced through incisive high-field $^1$H NMR (COSY) analysis and in particular the $J_{	ext{H}2-	ext{H}3}$ and $J_{	ext{H}3-	ext{H}4}$ 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.

**Notes and references**


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 ESL1 CCDC 193886–193889. See http://www.rcsb.org/suppdata/cc/b2/b208918a/.