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 in the monosaccharide residue to octahydroxy carbasugar present in the year 2000, 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 have attracted a lot of attention as new types of carbohydrate mimics.\(^2,3\) An advantageous feature of the cycloheptane and cyclooctane polyols\(^3,5\) 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\(^6,7\) 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 cyclooctatetraene with dimethylcarbamoyl chloride as described by Shechter and coworkers.\(^8\) We visualized 8 as a “functionally locked” COT with differentiated olefinic bonds and a “masked” C-9 cycloocto-carbasugar from which the eight-membered ring can be extracted through oxidative C\(_2\)-C\(_9\) bond scission. Baeyer-Villiger oxidation in 8 was smooth and led to the formation of \(\delta\)-lactone 9. Scheme 1.\(^8\) Catalytic Os\(_8\)O\(_{12}\) dihydroxylation in 9 proceeded with complete regio- and stereo-selectivity to furnish the \(\ex\)-1,2-diol 10.\(^9\) Attempted acetylation of the diol 10 led to an unanticipated but interesting rearrangement to the \(\gamma\)-lactone 12 having \(\ex\)-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-\(\ci\)-diene tetrol 14, which could also be obtained directly from 10 through hydride reduction. Catalytic hydrogenation of 13 to 15 and hydrogenolysis furnished 16 the first of the desired cyclooctane polyols. Scheme 1.\(^8\) Bicyclic \(\gamma\)-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-\(\gamma\)-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 \(\gamma\)-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 structure\(^2\) not only revealed an open \(\alpha\)-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.
through stereoselective double cis-dihydroxylation of the diene moiety in 13. Prolonged exposure of 13 to catalytic OsO4-NMNO 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 1H NMR analysis and in particular the J312-313 and J31-16 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.

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Notes and references
8 All new compounds reported here were racemic and characterized on the basis of spectroscopic data (IR, 1H and 13C 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.rsc.org/suppdata/cc/b2/b208918a/.

(63: 30: 7), Scheme 3. 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 1H NMR (COSY) data and more specifically from the trans coupling (JH1-H16) 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 stereostructure of the next major product 24 was readily hydrolysed to furnish the pentahydroxy-cyclooctanoids 29. The three acetonide stereostructures of 29, having a trans disposition, are given as ESI.

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