From cyclic polyenes to carbohydrates: synthesis of the hexose sugar β-allose and its 2C-branched homologue from cyclooctatetraene

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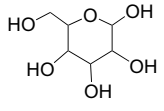
Abstract—In an unconventional but interesting synthetic enterprise, the commercially available hydrocarbon cyclooctatetraene (COT) has been elaborated to the rare hexose sugar (DL)-β-allose and its 2C-branched analogue. The synthetic sequence delineated here is notable for its high regio- and stereoselectivity and is flexible enough to enable access to polyoxygenated systems, hexose sugars, and their siblings from a cyclic polyene precursor.

Hexose sugars **1** are among nature's premier and ubiquitous building blocks that are essential for the sustenance of diverse biological systems and processes.[1] Though many hexose sugars are readily available and are plentiful, their architecture with a network of hydroxyl functionalities, and stereochemical nuances has always posed an attractive ongoing challenge to synthetic chemists.[2] During the last few decades, a variety of new and interesting strategies have been developed for the synthesis of hexose sugars and their C-branched siblings. Branched hexose sugars (e.g., **2**) are interesting in their own right as they constitute the glycosidic component of many antibiotics and have also received a great deal of attention from synthetic chemists.[3] While many synthetic approaches to hexose sugars and their branched analogues have been explored,[2,3] the possibility of employing a cyclic polyene like cyclooctatetraene **3** (COT) for their synthesis appealed to us as an esoteric and interesting proposition. Herein, we report the transformation of COT **3** into a rare hexose sugar (DL)-β-allose and its 2C-branched sibling.[4]



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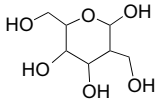

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Our synthetic approach to hexose sugars emanated from bicyclo[4.2.1]nona-2,4,7-trien-9-one **4**, a 'functionally locked' cyclooctatetraene, readily available from **3** in a single pot operation as described by Shechter and coworkers.[5a] Baeyer–Villiger oxidation of **4** led to the lactone **5** and further catalytic OsO_4 dihydroxylation, and acetonide protection led to **6** with complete regio- and stereocontrol, Scheme 1.[5b,6] LAH reduction of **6** led to the cyclooctadienediol **7** in which the primary hydroxyl group was selectively protected as the TBS derivative **8**. Ozonolysis of **8** and PCC oxidation of the resulting product led to the bicyclic lactone **10** through the intermediacy of the lactol **9** as depicted in Scheme 1.[6] Methoxide mediated lactone opening in **10** furnished **11** and the anomeric hydroxyl group was protected as the methyl ether **12**. LAH reduction of **12** revealed the branched sugar **13** and further deprotections led to (DL)-methyl-2-deoxy-2C-hydroxymethyl-β-allose **14**. The branched hexose **14** was transformed to the tetraacetate **15** and its X-ray crystal structure determination[7] unambiguously secured its formulation.

Next, the 2C-branched precursor **13** was elaborated to the rare hexose β-allose. Protection of the C_5-hydroxylmethyl as an acetate **16** and TBS deprotection furnished **17**, Scheme 2.[6] The primary hydroxyl group in **17** was transformed to the terminal olefin **18** via mesylate formation and base mediated elimination. Ozonolysis of **18** furnished the intermediate hemiacetal **19**, which was reduced with sodium borohydride to furnish **20**, Scheme 2.[6] Acetonide deprotection in **20** delivered