

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

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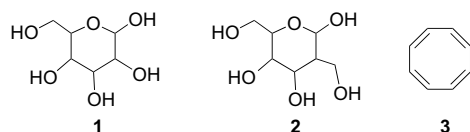
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**Abstract**—In an unconventional but interesting synthetic enterprise, the commercially available hydrocarbon cyclooctatetraene (COT) has been elaborated to the rare hexose sugar (DL)- $\beta$ -allose and its 2C-branched analogue. The synthetic sequence 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.

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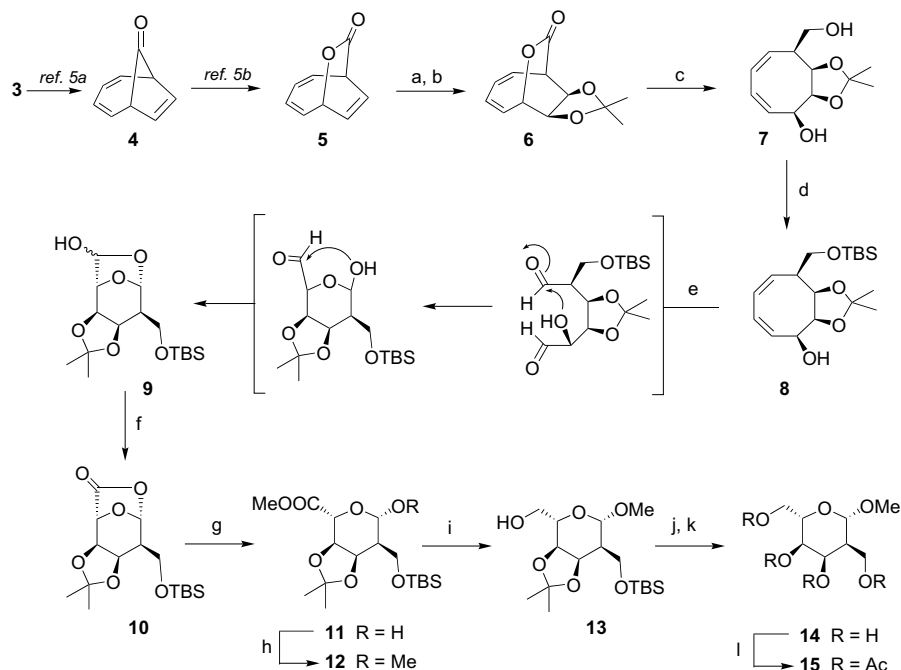
Hexose sugars **1** are among nature's premier and ubiquitous building blocks that are essential for the sustenance of diverse biological systems and processes.<sup>1</sup> Though many hexose sugars are readily available and are plentiful, their architecture with a network of hydroxyl functionalities, and stereochemical nuances has always posed an attractive ongoing challenge to synthetic chemists.<sup>2</sup> 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.<sup>3</sup> While many synthetic approaches to hexose sugars and their branched analogues have been explored,<sup>2,3</sup> 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)- $\beta$ -allose and its 2C-branched sibling.<sup>4</sup>



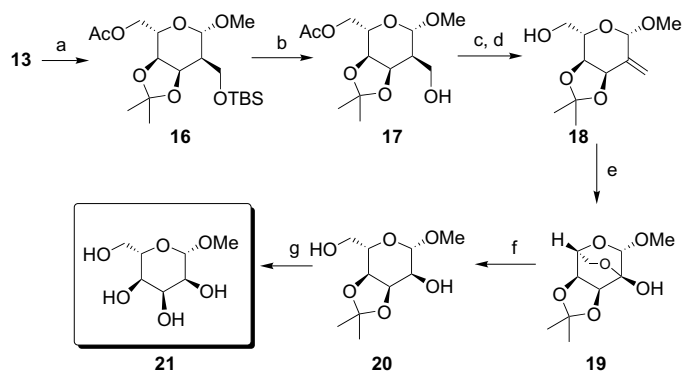
Our synthetic approach to hexose sugars emanated from bicyclo[4.2.1]nona-2,4,7-trien-9-one **4**, a 'functionally locked' cyclooctatetraene, readily available from **3** in a single pot operation as described by Shechter and co-workers.<sup>5a</sup> Baeyer–Villiger oxidation of **4** led to the lactone **5** and further catalytic OsO<sub>4</sub> dihydroxylation, and acetonide protection led to **6** with complete regio- and stereocontrol, Scheme 1.<sup>5b,6</sup> 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.<sup>6</sup> 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- $\beta$ -allose **14**. The branched hexose **14** was transformed to the tetraacetate **15** and its X-ray crystal structure determination<sup>7</sup> unambiguously secured its formulation.

Next, the 2C-branched precursor **13** was elaborated to the rare hexose  $\beta$ -allose. Protection of the C<sub>5</sub>-hydroxylmethyl as an acetate **16** and TBS deprotection furnished **17**, Scheme 2.<sup>6</sup> 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.<sup>6</sup> Acetonide deprotection in **20** delivered

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**Scheme 1.** Reagents and conditions: (a) OsO<sub>4</sub>, NMMO, 75%; (b) 2,2-dimethoxypropane, acetone, CSA, 65%; (c) LiAlH<sub>4</sub>, THF, 80%; (d) TBSCl, Im, DMF, 54%; (e) O<sub>3</sub>, DCM–MeOH, DMS; (f) PCC, NaOAc, DCM, 40% for two steps; (g) NaOMe, MeOH; (h) MeI, Ag<sub>2</sub>O, 73% for two steps; (i) LiAlH<sub>4</sub>, THF, 85%; (j) TBAF, THF, 70%; (k) Amberlyst-15, MeOH, 65%; (l) Ac<sub>2</sub>O, py, DMAP, 90%.



**Scheme 2.** Reagents and conditions: (a) Ac<sub>2</sub>O, DMAP, DCM, 92%; (b) TBAF, THF, 74%; (c) MsCl, Et<sub>3</sub>N, DCM, 65%; (d) KO<sup>t</sup>Bu, DMSO, 70%; (e) O<sub>3</sub>, DCM, DMS, 75%; (f) NaBH<sub>4</sub>, MeOH, 80%; (g) Amberlyst-15, MeOH, 60%.

(DL)-methyl-β-allopyranoside **21** whose spectral characteristics were identical with those reported in the literature.<sup>8</sup>

In short, we have accomplished an interesting elaboration of a commercially available polyene (COT) into β-allose and a 2C-branched congener through a strategy that should be amenable for adaptation to access other hexose sugars and some densely oxygenated systems.

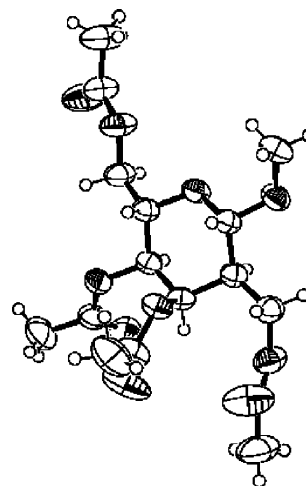
#### Acknowledgements

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6. All compounds reported here are racemic and all new compounds were characterized on the basis of their IR,  $^1\text{H}$  and  $^{13}\text{C}$  NMR and mass spectral data. Selected spectral data: Compound **10**: IR ( $\text{cm}^{-1}$ ) 1802;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  6.04 (s, 1H), 4.56–4.51 (m, 2H), 4.24 (d,  $J = 7.2$  Hz, 1H), 3.90 (dd,  $J = 10.8, 5.7$  Hz, 1H), 3.72 (t,  $J = 10.5$  Hz, 1H), 2.34–2.26 (m, 1H), 1.47 (s, 3H), 1.30 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  107.6, 109.6, 104.5, 73.8, 69.8, 69.4, 60.1, 40.9, 25.9, 25.8 (3C), 24.5, 18.2, –5.5, –5.4; Mass (EI, 70 eV):  $m/z$  345 ( $\text{M}+1$ ) $^+$ . Compound **12**:  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  4.58 (dd,  $J = 5.5, 4.0$  Hz, 1H), 4.40 (d,  $J = 9.0$  Hz, 1H), 4.34 (dd,  $J = 7.5, 5.5$  Hz, 1H), 4.06 (d,  $J = 7.0$  Hz, 1H), 3.83–3.79 (m, 1H), 3.79 (s, 3H), 3.70 (t,  $J = 10.0$  Hz, 1H), 3.47 (s, 3H), 2.12–2.09 (m, 1H), 1.50 (s, 3H), 1.36 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  170.2, 109.5, 100.6, 74.7, 72.5, 72.2, 59.5, 56.5, 52.4, 43.5, 27.9, 25.8 (3C), 25.6, 18.3, –5.6, –5.5. Compound **14**:  $^1\text{H}$  NMR (500 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  4.58 (d,  $J = 9.0$  Hz, 1H), 4.17 (t,  $J = 3.0$  Hz, 1H), 3.90–3.86 (m, 1H), 3.75–3.69 (m, 4H), 3.44 (s, 3H), 3.46 (dd,  $J = 9.5, 3.0$  Hz, 1H), 1.73–1.68 (m, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CD}_3\text{OD}$ )  $\delta$  101.7, 75.3, 70.0, 69.7, 63.3, 60.2, 56.9, 48.9; LRMS:  $m/z$  231.1 ( $\text{M}+\text{Na}$ ) $^+$ ; HRMS for  $\text{C}_8\text{H}_{16}\text{O}_6\text{Na}$ . Calcd: 231.0845. Found: 231.0864. Compound **18**: IR ( $\text{cm}^{-1}$ ) 3470, 937;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.51 (s, 1H), 5.43 (s, 1H), 5.08 (s, 1H), 4.80 (d,  $J = 6.0$  Hz, 1H), 4.16 (t,  $J = 7.2$  Hz, 1H), 3.84 (br d,  $J = 10.8$  Hz, 1H), 3.71 (br d,  $J = 5.4$  Hz, 1H), 3.65–3.60 (m, 1H), 3.53 (s, 3H), 1.50 (s, 3H), 1.38 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  139.0, 117.6, 109.9, 100.3, 75.9, 75.4, 73.3, 63.1, 56.2, 27.7, 25.7; LRMS:  $m/z$  253.1052 ( $\text{M}+\text{Na}$ ) $^+$ ; HRMS for  $\text{C}_{11}\text{H}_{18}\text{O}_5\text{Na}$ . Calcd: 253.1053. Found: 253.1091. Compound **19**: IR ( $\text{cm}^{-1}$ ): 3412;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  4.93 (s, 1H), 4.41 (d 1/2 ABq,  $J = 7.8, 1.2$  Hz, 1H), 4.37 (1/2 ABq,  $J = 8.1$  Hz, 1H), 4.27 (dd,  $J = 9.9, 1.8$  Hz, 1H), 4.04 (d,  $J = 1.5$  Hz, 1H), 3.81 (d,  $J = 9.9$  Hz, 1H), 3.54 (s, 3H), 1.53 (s, 3H), 1.38 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  110.9, 98.9, 92.3, 75.7, 75.4, 68.5, 65.0, 55.9, 25.7, 24.5; LRMS:  $m/z$  255.0563 ( $\text{M}^++\text{Na}^+$ ); HRMS for  $\text{C}_{10}\text{H}_{16}\text{O}_6\text{Na}$ . Calcd: 255.0845. Found: 255.0846. Compound **21**: IR ( $\text{cm}^{-1}$ ) 3371;  $^1\text{H}$  NMR (300 MHz,  $\text{D}_2\text{O}$ )  $\delta$  4.42 (d,  $J = 8.7$  Hz, 1H), 3.96 (t,  $J = 3.3$  Hz, 1H), 3.72 (dd,  $J = 12.0, 1.8$  Hz, 1H), 3.63–3.58 (m, 1H), 3.49 (dd as t,  $J = 6.3$  Hz, 1H), 3.42 (dd,  $J = 9.6, 2.7$  Hz, 1H), 3.37 (s, 3H), 3.25 (dd,  $J = 8.4, 3.3$  Hz, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{D}_2\text{O}$ )  $\delta$  101.7, 74.1, 71.6, 70.8, 67.4, 61.7, 57.6; LRMS:  $m/z$  217.0528 ( $\text{M}+\text{Na}$ ) $^+$ ; HRMS for  $\text{C}_7\text{H}_{14}\text{O}_6\text{Na}$ . Calcd: 217.0688. Found: 217.0704.
7. *X-ray data for 15*: X-ray data were collected at 293 K on a SMART CCD-BRUKER diffractometer with graphite monochromated Mo  $\text{K}\alpha$  radiation ( $\lambda = 0.7107$  Å). Structure was solved by direct methods (SIR92). Refinement was by full-matrix least-squares procedures on  $F^2$  using SHELXL-97. The nonhydrogen atoms were refined anisotropically whereas hydrogen atoms were refined isotropically.  $\text{C}_{16}\text{H}_{24}\text{O}_{10}$ , MW = 376.36, colorless crystal, crystal system: monoclinic, space group:  $P2(1)/n$ , cell parameters:  $a = 8.9525$  (4) Å,  $b = 20.7773$  (10) Å,  $c = 11.2568$  (5) Å,  $\beta = 111.037$  (1),  $V = 1954.30$  Å $^3$ ,  $Z = 4$ ,  $D_c = 1.279$  g  $\text{cm}^{-3}$ ,  $F(000) = 800.0$ ,  $\mu = 0.11$  mm $^{-1}$ . Total number of l.s. parameters = 331,  $R1 = 0.0472$  for 3179  $F_o > 4\text{sig}(F_o)$  and 0.0576 for all 3981 data.  $wR2 = 0.1400$ , GOF = 1.024, restrained GOF = 1.024 for all data. Crystallographic data has been deposited with Cambridge Crystallographic Data Centre. CCDC 232049. ORTEP diagram of **15** is shown below:



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