

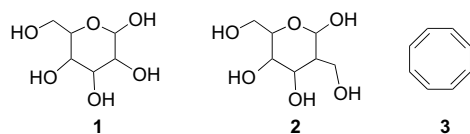
From cyclic polyenes to carbohydrates: synthesis of the hexose sugar β -allose and its 2C-branched homologue from cyclooctatetraene

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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.

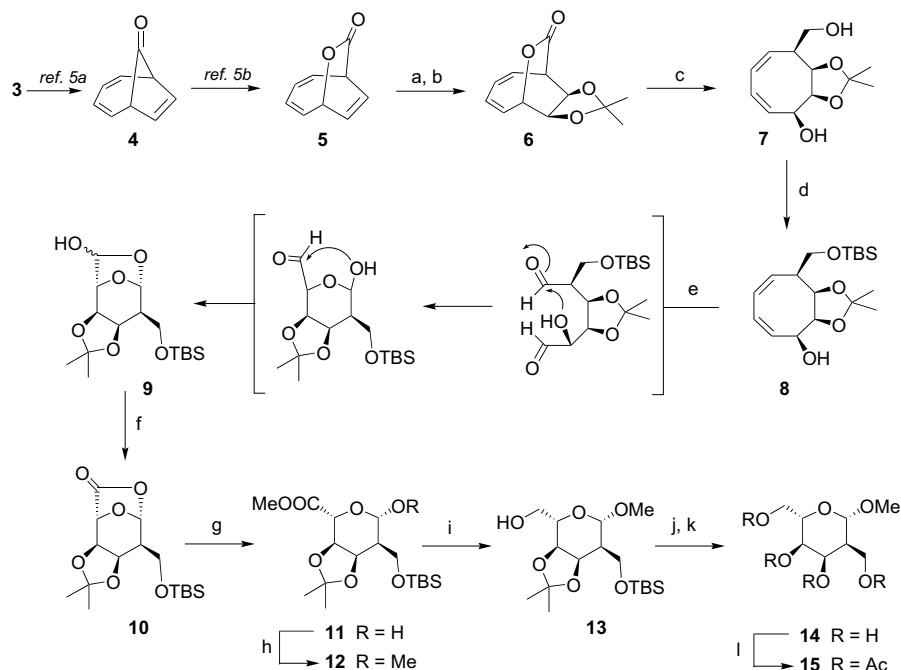
Hexose sugars **1** are among nature's premier and ubiquitous building blocks that are essential for the sustenance of diverse biological systems and processes.¹ Though many hexose sugars are readily available and are plentiful, their architecture with a network of hydroxyl functionalities, and stereochemical 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



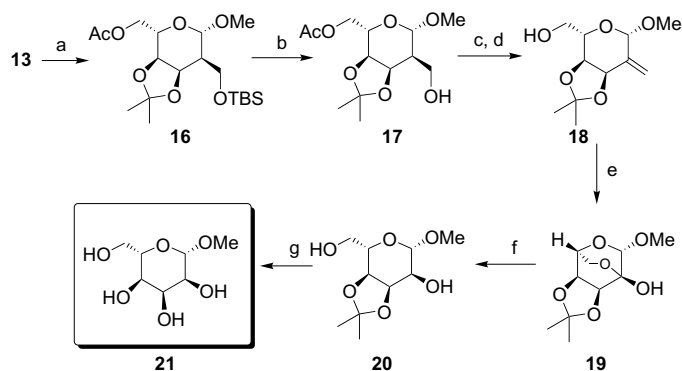
Our synthetic approach to hexose sugars emanated from bicyclo[4.2.1]nona-2,4,7-trien-9-one **4**, a 'functionally locked' cyclooctatetraene, readily available from **3** in a single pot operation as described by Shechter and co-workers.^{5a} Baeyer–Villiger oxidation of **4** led to the lactone **5** and further catalytic OsO₄ 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 determination⁷ unambiguously secured its formulation.

Next, the 2C-branched precursor **13** was elaborated to the rare hexose β -allose. Protection of the C₅-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

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Scheme 1. Reagents and conditions: (a) OsO₄, NMMO, 75%; (b) 2,2-dimethoxypropane, acetone, CSA, 65%; (c) LiAlH₄, THF, 80%; (d) TBSCl, Im, DMF, 54%; (e) O₃, DCM–MeOH, DMS; (f) PCC, NaOAc, DCM, 40% for two steps; (g) NaOMe, MeOH; (h) MeI, Ag₂O, 73% for two steps; (i) LiAlH₄, THF, 85%; (j) TBAF, THF, 70%; (k) Amberlyst-15, MeOH, 65%; (l) Ac₂O, py, DMAP, 90%.



Scheme 2. Reagents and conditions: (a) Ac₂O, DMAP, DCM, 92%; (b) TBAF, THF, 74%; (c) MsCl, Et₃N, DCM, 65%; (d) KO^tBu, DMSO, 70%; (e) O₃, DCM, DMS, 75%; (f) NaBH₄, MeOH, 80%; (g) Amberlyst-15, MeOH, 60%.

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

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.

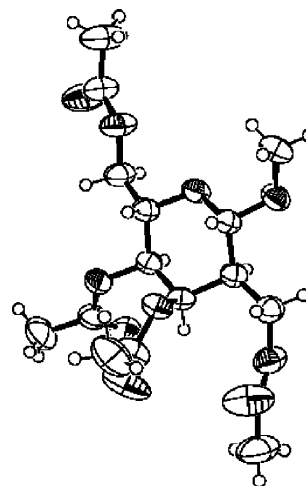
Acknowledgements

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6. All compounds reported here are racemic and all new compounds were characterized on the basis of their IR, ^1H and ^{13}C NMR and mass spectral data. Selected spectral data: Compound **10**: IR (cm^{-1}) 1802; ^1H NMR (300 MHz, CDCl_3) δ 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}C NMR (75 MHz, CDCl_3) δ 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**: ^1H NMR (500 MHz, CDCl_3) δ 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}C NMR (75 MHz, CDCl_3) δ 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**: ^1H NMR (500 MHz, CD_3OD) δ 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}C NMR (75 MHz, CD_3OD) δ 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 (cm^{-1}) 3470, 937; ^1H NMR (300 MHz, CDCl_3) δ 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}C NMR (75 MHz, CDCl_3) δ 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 (cm^{-1}): 3412; ^1H NMR (300 MHz, CDCl_3) δ 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}C NMR (75 MHz, CDCl_3) δ 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 (M^++Na^+); HRMS for $\text{C}_{10}\text{H}_{16}\text{O}_6\text{Na}$. Calcd: 255.0845. Found: 255.0846. Compound **21**: IR (cm^{-1}) 3371; ^1H NMR (300 MHz, D_2O) δ 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}C NMR (75 MHz, D_2O) δ 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 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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