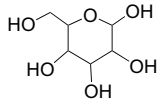
From cyclic polyenes to carbohydrates: synthesis of the hexose sugar β-allose and its 2C-branched homologue from cyclooctatetraene

Goverdhan Mehta* and Kotapalli Pallavi

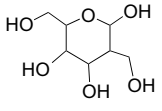
Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India

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]



1



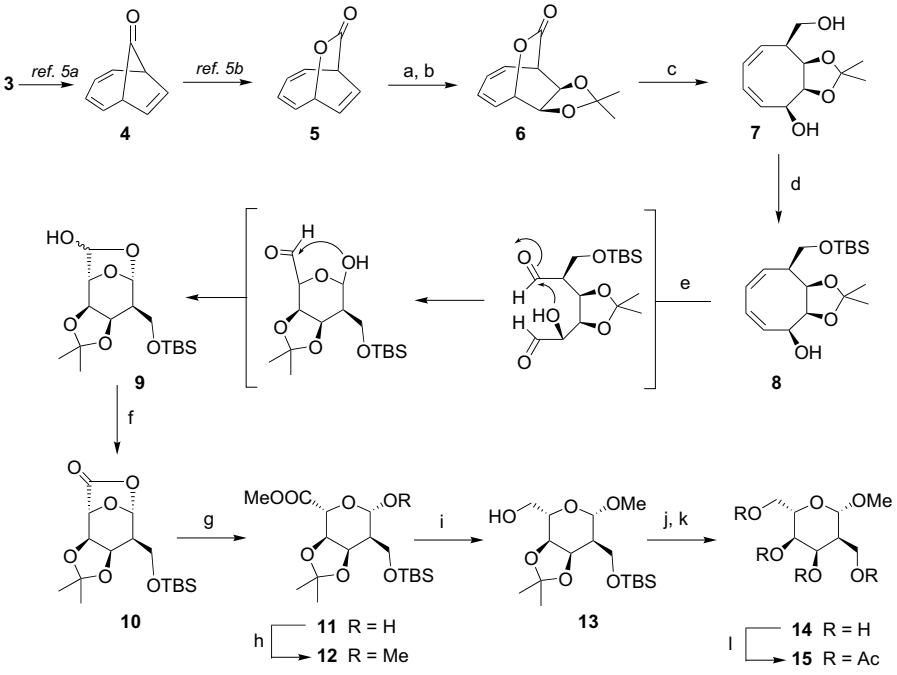
2

3

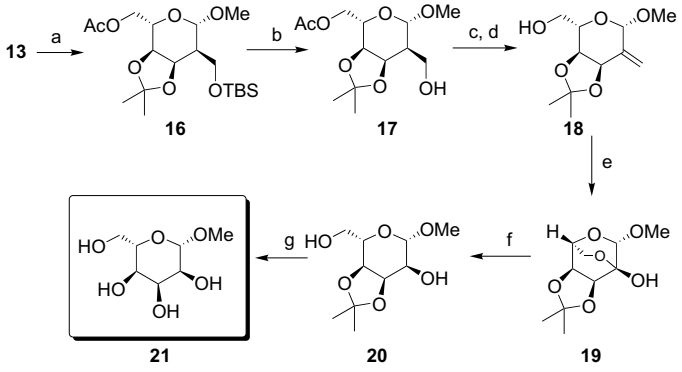
* Corresponding author. Tel.: +91-80-22932850; fax: +91-80-236009-36; e-mail: gm@orgchem.iisc.ernet.in

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



Scheme 1. Reagents and conditions: (a) OsO_4, NMMO, 75%; (b) 2,2-dimethoxypropane, acetone, CSA, 65%; (c) $LiAlH_4$, THF, 80%; (d) TBSCl, Im, DMF, 54%; (e) O_3, DCM–MeOH, DMS; (f) PCC, NaOAc, DCM, 40% for two steps; (g) NaOMe, MeOH; (h) MeI, Ag_2O, 73% for two steps; (i) $LiAlH_4$, THF, 85%; (j) TBAF, THF, 70%; (k) Amberlyst-15, MeOH, 65%; (l) Ac_2O, py, DMAP, 90%.



Scheme 2. Reagents and conditions: (a) Ac_2O, DMAP, DCM, 92%; (b) TBAF, THF, 74%; (c) MsCl, Et_3N, DCM, 65%; (d) KO^{t}Bu, DMSO, 70%; (e) O_3, DCM, DMS, 75%; (f) $NaBH_4$, 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.

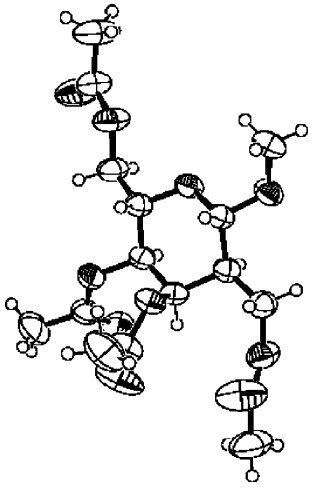
Acknowledgements

This research was supported by the Chemical and Biology Unit of JNCASR, Bangalore, India. One of us (K.P.) would like to thank CSIR (India) for the award of a research fellowship.

References and notes

1. (a) Collins, P. M.; Ferrier, R. J. *Monosaccharides: Their Chemistry and Their Roles in Natural Products*. 1st ed.; Wiley, 1995 (b) Bashkin, J. K. *Chem. Rev.* **2000**, *100*, 4265; (c) Dwek, R. A.; Butters, T. D. *Chem. Rev.* **2002**, *102*, 283.
2. (a) Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A., III; Sharpless, K. B.; Walker, F. J. *Science* **1983**, *220*, 949; (b) Vogel, P.; Fattori, D.; Gasparini, F.; Le Drian, C. *Synlett* **1990**, 173; (c) Hudlicky, T.; Entwistle, D. A.; Pitzer, K. K.; Thorpe, A. *Chem. Rev.* **1996**, *96*, 1195; (d) Takeuchi, M.; Taniguchi, T.; Ogasawara, K. *Synthesis* **1999**, 341; (e) Taniguchi, T.; Takeuchi, M.; Kadota, K.; ElAzab, A. S.; Ogasawara, K. *Synthesis* **1999**, 1325; (f) Honzumi, M.; Taniguchi, T.; Ogasawara, K. *Org. Lett.* **2001**, *3*, 1355.
3. (a) Yoshimura, J. *Adv. Carbohydr. Chem. Biochem.* **1984**, *42*, 69; (b) Wagner, J.; Vogel, P. *Tetrahedron* **1991**, *47*, 9641; (c) Beyer, J.; Madsen, R. *J. Am. Chem. Soc.* **1998**,

120, 12137; (d) Kato, K.; Yamamura, S. *Nucleosides Nucleotides* **1999**, *18*, 657.
4. (a) Fukami, H.; Koh, H.-S.; Sakata, T.; Nakajima, M. *Tetrahedron Lett.* **1967**, 4771; (b) Brimacombe, J. S.; Hunedy, F.; Husain, A. *J. Chem. Soc. C.* **1970**, 1273; (c) Singh, U. P.; Brown, R. K. *Can. J. Chem.* **1971**, *49*, 1179; (d) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 835; (e) Vogel, P.; Auberson, Y. *Helv. Chim. Acta* **1989**, *72*, 278; (f) Malleron, A.; David, S. *New J. Chem.* **1996**, *20*, 153.
5. (a) Antkowiak, T. A.; Sanders, D. C.; Trimitsis, G. B.; Press, J. B.; Shechter, H. *J. Am. Chem. Soc.* **1972**, *94*, 5366; (b) Mehta, G.; Pallavi, K. *Chem. Commun.* **2002**, 2828.
6. All compounds reported here are racemic and all new compounds were characterized on the basis of their IR, ^{1}H and ^{13}C NMR and mass spectral data. Selected spectral data: Compound **10**: IR (cm^{-1}) 1802; ^{1}H 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 $(M+1)^+$. Compound **12**: ^{1}H 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**: ^{1}H 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 $(M+Na)^+$; HRMS for $C_8H_{16}O_6Na$. Calcd: 231.0845. Found: 231.0864. Compound **18**: IR (cm^{-1}) 3470, 937; ^{1}H 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 $(M+Na)^+$; HRMS for $C_{11}H_{18}O_5Na$. Calcd: 253.1053. Found: 253.1091. Compound **19**: IR (cm^{-1}): 3412; ^{1}H 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 $C_{10}H_{16}O_6Na$. Calcd: 255.0845. Found: 255.0846. Compound **21**: IR (cm^{-1}) 3371; ^{1}H 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 $(M+Na)^+$; HRMS for $C_7H_{14}O_6Na$. 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 Kα 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. $C_{16}H_{24}O_{10}$, 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(0 0 0) = 800.0, $\mu = 0.11$ mm^{-1}. Total number of l.s. parameters = 331, $R1 = 0.0472$ for 3179 Fo > 4sig(Fo) 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:



8. Bock, K.; Pedersen, C. *Adv. Carbohydr. Chem. Biochem.* **1983**, *41*, 27.