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Note

An efficient synthesis of D-mannoheptulose via oxidation of an olefinated sugar with potassium permanganate in aqueous acetone

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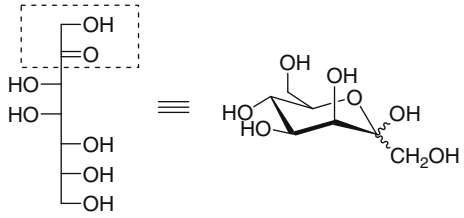
ABSTRACT

An efficient three-step synthesis of D-mannoheptulose was successfully accomplished from 2,3,4,5,6-penta-*O*-benzyl-D-mannose. First, an olefinated sugar was prepared from 2,3,4,5,6-penta-*O*-benzyl-D-mannose via a Wittig reaction. Second, the key step, a 2-hydroxyoxirane product was unexpectedly obtained by oxidation of the olefinated sugar with potassium permanganate in aqueous acetone. Finally D-mannoheptulose was synthesized through debenzylation and hydrolysis in an overall yield of 39%.

D-Mannoheptulose, which can be extracted from avocado, is a rare seven-carbon sugar with a number of potential pharmacological functions, including inhibition of insulin secretion (hypoglycemia),[1] obesity therapy,[2] and anti-cancer activity.[3] The C-1 and C-2 segment of D-mannoheptulose is an α-hydroxy ketone (α-ketol, Scheme 1), which could be considered as the product resulting from the oxidation of olefinated sugar derivatives with permanganate.

The synthesis of α-hydroxy ketone compounds is a topic of interest because of their use in organic synthesis, and their widespread occurrence in numerous important natural products such as botrytinone[4] and adriamycin acetate.[5] The oxidation of olefins to oxygen-containing compounds is one of the most important synthetic transformations, and asymmetric dihydroxylation[6] and epoxidation[7] reactions are the most well-studied ones. However, the preparation of α-hydroxy ketones through the direct oxidation of olefins has rarely been investigated.[8]

Because the introduction of olefins in many functionalized compounds can easily be achieved, a direct method for the synthesis of α-ketols (Scheme 2) appears quite desirable. Previously, oxidation of simple internal and terminal alkenes utilizing stoichiometric amounts of $KMnO_4$ in aqueous and catalytic HOAc,[9] $KMnO_4$–$CuSO_4{\cdot}5H_2O$,[10] isobutylaldehyde–O_2 and catalytic OsO_4–Ni(mac)$_2$,[11] or regioselective ruthenium-catalyzed two-step ketohydroxylation,[12] was found to be less than optimal, affording the desired α-hydroxy ketols in only 49–67% yields.



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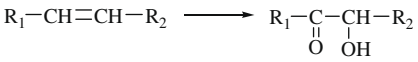
Scheme 1. Structure of D-mannoheptulose.

The oxidation of olefin bonds by permanganate ion is an important reaction in organic chemistry, and in neutral or slightly basic solutions α-hydroxy ketones are produced. Our study began with the elongation of carbon chain of 2,3,4,5,6-penta-*O*-benzyl-D-mannose (**2**) through a Wittig reaction to prepare the olefinated sugar **3** (Scheme 3). Aldehyde **2** could be easily obtained from mannose in three steps in an overall yield of 56%.[13] In the oxidation step, using a previously reported procedure for the preparation of α-ketols with $KMnO_4$ in aqueous acetone and acetic acid,[14] we unexpectedly prepared the 2-hydroxyoxirane **4**, which is isomeric to the α-ketol, in 53% yield. Compound **4** was stable in solution for about



Scheme 2.

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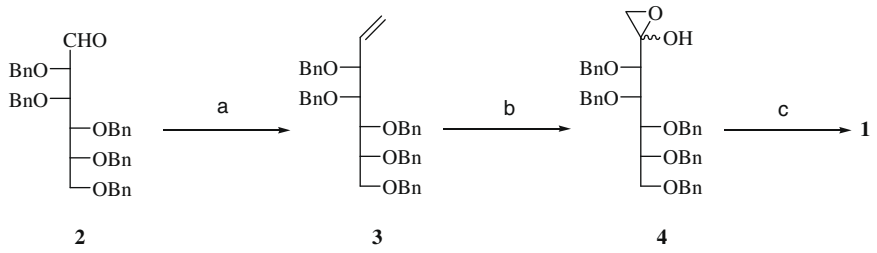
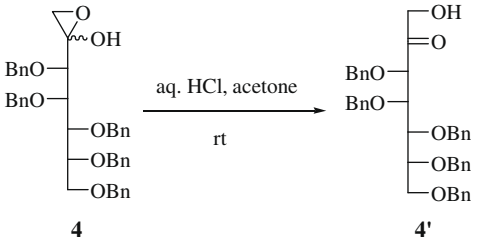


Scheme 3. Reagents and conditions: (a) $Ph_3P^+CH_3Br^-$, *n*-BuLi–hexane, toluene, rt; (b) $KMnO_4$, HOAc, acetone, H_2O, 0 °C to rt; and (c) (1) Pd–C, H_2 (g), 1–2 atm, rt; (2) aq H_2SO_4, 60 °C.



Scheme 4.

one week, and under acid conditions, could be converted to the α-ketol, namely, 3,4,5,6,7-penta-*O*-benzyl-D-mannoheptulose (**4′**, Scheme 4). Finally, D-mannoheptulose (**1**) was obtained in 85% yield through hydrogenation of 2-hydroxyoxirane **4**, followed by removal of the benzyl groups by Pd–C and hydrolysis in dilute sulfuric acid.

The structures of compounds **1**, **3**, and **4** were characterized by NMR spectroscopy and mass spectrometry. The ^1H and ^{13}C NMR spectra of the olefinated sugar **3** displayed distinct olefinic signals at δ_H 5.3–6.0 ppm and δ_C 119.4 and 118.2 ppm, respectively. The molecular weight of the oxidized product **4** was confirmed by mass spectrometry; however, to our surprise the ^{13}C NMR spectrum did not show a singlet for a carbonyl group. After hydrolysis of **4** under acidic condition, the singlets at δ_H 5.69 ppm and δ_C 103.3 ppm disappeared, and the product (**4′**) showed the expected signals for the α-ketol (δ_C 206.5 ppm). Furthermore, the 2-hydroxyoxirane structure of compound **4** was confirmed by ^{13}C–^1H COSY 2D NMR, which showed that the singlet at δ_C 75.1 ppm (C-1) correlated with the signal peaks at δ_H 5.69 ppm and δ_H 4.76 ppm. Moreover, in the ^{13}C spectrum, the signal at δ_C 103.3 ppm arose from the C-2, which was connected to two oxygens. In addition, a broad peak at δ_H 2.65 ppm was from the C-2 hydroxyl group and this signal disappeared after adding D_2O. After D-mannoheptulose was obtained following hydrogenation and hydrolysis, the ^{13}C NMR spectrum of D-mannoheptulose revealed that it existed in a ring structure, given the signal at δ_C 100.3 ppm, which arose from the anomeric carbon.

Owing to the speed of the reaction and the complex reagent system, the mechanism of the permanganate oxidation of olefinated sugar **3** to 2-hydroxyoxirane **4** is poorly understood. The oxidation mechanisms for different organic substrates suggested by various authors are not similar. In an earlier work Bonini[14a] suggested that the preservation of the silyl and acetyl groups on the hydroxy functions of the substrates was important for the prevention of the formation of over-oxidized products, and was advantageous for the conversion of the olefin to the α-ketol. In our case, the formation of the 2-hydroxyoxirane product probably results from the influence of the benzyl groups on the hydroxyl group of the olefinated sugar. Similar results were obtained by oxidation of a pentabenzylated olefin obtained from 2,3,4,5,6-penta-*O*-benzyl-D-glucose.

1. Experimental

1.1. General methods

All solvents were dried using standard procedures. The melting point (mp) was determined on a WRS-1B digital apparatus and was uncorrected. The optical rotation was measured on a Shen-Guang WZZ-2B polarimeter at 20 °C using a 1-dm cell. ^1H and ^{13}C NMR spectra were recorded on a Bruker ARX 300 spectrometer (300 and 75 MHz for ^1H and ^{13}C, respectively) in $CDCl_3$, $CDCl_3$–D_2O or D_2O at 298 K. Chemical shift data are given in δ measured downfield from Me_4Si at 0.00 ppm. Mass spectrometry was carried out on a Finnigan HPLC-ESI-MS spectrometer. Analytical RP-HPLC was carried out on a Hypersil APS NH_2 column (5 μm, 4.6 × 250 mm) at 80 °C. The mobile phase employed for elution was MeCN–H_2O = 85:15 at a flow rate of 2.0 L/min.

1.2. 1,2-Dideoxy-3,4,5,6,7-penta-*O*-benzyl-D-*manno*-hept-1-enitol (3)

To a suspension of methyltriphenylphosphonium bromide (7.10 g, 19.9 mmol) in dry toluene (120 mL) was added dropwise a 1.6 M solution of *n*-BuLi in hexane (12 mL, 19.2 mmol) under N_2 at 0 °C. The solution was stirred for 2 h, at rt and then a solution of 2,3,4,5,6-penta-*O*-benzyl-D-mannose (**2**) (4.16 g, 6.6 mmol) in dry toluene (30 mL) was added in one portion, and the mixture was stirred for 48 h at rt. The reaction was quenched by the addition of acetone (20 mL), the mixture was diluted with $CHCl_3$ and extracted with $CHCl_3$ (2 × 100 mL), and the organic layers were combined, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography on silica gel (EtOAc–petroleum ether, 1:8) to afford **3** (3.65 g, 88%) as a yellow syrup: ^1H NMR (300 MHz, $CDCl_3$), δ: 3.67–3.73 (dd, 1H, J = 5.7, 11.1 Hz), 3.83–3.88 (m, 2H), 4.00–4.07 (m, 2H), 4.17 (d, 1H, J = 11.7 Hz), 4.42–4.74 (m, 10H, $PhCH_2$), 5.32 (dd, 1H, J = 2.9, 17.7 Hz), 5.37 (dd, 1H, J 2.9, 9.8 Hz), 5.92–6.01 (ddd, 1H, J = 8.0, 9.8, 17.7 Hz), 7.00–7.29 (m, 25H, Ph); ^{13}CNMR (75 MHz, $CDCl_3$), δ: 69.6, 69.9, 71.7, 73.2, 74.2, 74.3, 78.7, 78.9, 80.8, 81.4, 119.4, 126.8–128.2 (25C), 128.2, 138.4–138.9 (5C); HRMS calcd for $C_{42}H_{45}O_5$ $[M+H]^+$ 629.32615. Found: 629.32225.

1.3. 2-Hydroxyoxirane-3,4,5,6,7-penta-*O*-benzyl-D-manno-heptitol (4)

The olefinated sugar **3** (1.85 g, 2.9 mmol) was added to a solution of acetone (28.0 mL), H_2O (5.3 mL), and HOAc (1.2 mL). A solution of $KMnO_4$ (0.69 g, 4.3 mmol) in acetone (9.5 mL) and H_2O (4.3 mL) was added dropwise at 0 °C, and the resulting mixture was stirred at 0 °C for 1.0 h and at rt for 0.5 h. EtOH was added until effervescence stopped. The crude was filtered over Celite and washed several times with CH_2Cl_2. The filtrate was concentrated, diluted with $CHCl_3$ (2 × 60 mL), and washed with a saturated

aqueous solution of $NaHCO_3$ until pH 8. The organic layer was then washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography on silica gel (EtOAc–petroleum ether, 1:8) to afford **4** (1.0 g, 53%) as a yellow syrup: ^{1}H NMR (300 MHz, $CDCl_3$), δ: 2.65 (br, 2.65, 1H, 2-OH), 3.68–3.73 (m, 2H), 3.84–3.89 (m, 3H), 4.07 (dd, 1H, J = 3.3, 7.1 Hz), 4.27 (dd, 1H, J = 5.7, 11.7 Hz), 4.34–4.45 (m, 4H), 4.70–4.76 (m, 6H), 5.69 (s, 1H), 7.21–7.48 (m, 25H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$), δ: 62.3, 69.3, 72.3, 73.5, 73.7, 75.1, 76.9, 78.3, 78.7, 78.7, 79.9, 103.3, 127.1–129.8 (25C), 137.4-138.8 (5C); ESI-MS: m/z = 683.28 $[M+Na]^+$, 699.27 $[M+K]^+$; HRMS calcd for $C_{42}H_{45}O_7$ $[M+H]^+$ 661.31598. Found: 661.31490.

1.4. 3,4,5,6,7-Penta-*O*-benzyl-D-mannoheptulose (4′)

A suspension of **4** (1.0 g, 1.5 mmol) and 3 M hydrochloric acid (10 mL) in acetone (10 mL) was stirred at rt for 3 h. The mixture was diluted and extracted with $CHCl_3$ (2 × 100 mL), the organic layers were washed with a saturated aqueous solution of $NaHCO_3$, dried (Na_2SO_4), and concentrated. The residue was purified by chromatography on silica gel (EtOAc–petroleum ether, 1:8) to afford **4'** (0.95 g, 95%) as a yellow syrup: ^{1}H NMR (300 MHz, $CDCl_3$), δ:3.66–3.73 (m, 2H), 3.74–3.76 (m, 2H), 3.81–3.83 (m, 2H), 3.85–3.88 (m, 2H), 4.12–4.68 (m, 10H, $PhCH_2$), 7.20–7.41 (m, 25H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$), δ: 60.3, 63.9, 69.5, 72.2, 72.5, 73.1, 73.4, 73.7, 78.4, 78.8, 79.5, 127.6–128.9 (25C), 137.6–138.0 (5C), 206.5 (C-2); HRMS calcd for $C_{42}H_{45}O_7$ $[M+H]^+$ 661.31598. Found: 661.32470.

1.5. D-Mannoheptulose (1)

A suspension of **4** (2.0 g, 3.0 mmol) and 10% Pd–C (1.5 g) in EtOAc–EtOH (1:1, 20 mL) was stirred at rt under 1–2 atm H_2 for 48 h. After removing the Pd–C by filtration, the filtrate was concentrated and then dissolved in 0.5 M sulfuric acid (30 mL), and the mixture was maintained at 60 °C for 12 h, neutralized with barium carbonate until pH 7, filtered, and concentrated to dryness. The residue was purified by chromatography on silica gel (MeOH–Et_3N–H_2O, 6:2:1) and then crystallized from methanol to afford **1** (0.53 g, 85%) as a white solid: mp 148–150 °C, lit.[15] mp 151 °C; $[\alpha]_D^{20}$ = +29.0 (c 1.0, H_2O), lit[15] $[\alpha]_D^{20}$ = +29.1 (c 1.0, H_2O); ^{13}C NMR (75 MHz, $CDCl_3$), δ: 63.6, 66.6, 69.4, 72.5, 73.4, 75.5, 100.3 (C-2); ESI-MS: m/z = 211.06 $[M+H]^+$; the purity of **1** as checked by RP-HPLC was 99.5%.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.carres.2009.06.020.

References

1. Xu, L. Z.; Weber, I. T.; Harrison, R. W.; Gidh-Jain, M.; Pilkis, S. J. *Biochemistry* **1995**, *34*, 6083–6092.
2. Ferrer, J.; Gomis, R.; Fernandez Alvarez, J.; Casamitjana, R.; Vilardell, E. *Diabetes* **1993**, *42*, 1273–1280.
3. Board, M.; Colquhoun, A.; Newsholme, E. A. *Cancer Res.* **1995**, *55*, 3278–3285.
4. Li, X. F.; Zhang, D. H.; Lee, U.; Li, X. G.; Cheng, J. G.; Zhu, W. L.; Jung, J. H.; Choi, H. D.; Son, B. W. *J. Nat. Prod.* **2007**, *70*, 307–309.
5. Taatjes, D. J.; Gaudiano, G.; Resing, K.; Koch, T. H. *J. Med. Chem.* **1997**, *40*, 1276–1286.
6. (a) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; 2nd ed.; Wiley: New York, Weinheim, 2000; p 357; (b) Bolm, C.; Hildebrand, J. P.; Muniz, K. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed., 2nd ed.; Wiley: New York, Weinheim, 2000; p 399.
7. (a) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed., 2nd ed.; Wiley: New York, Weinheim, 2000; p 231; (b) Katsuki, T. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed., 2nd ed.; Wiley: New York, Weinheim, 2000; p 287; (c) Jacobsen, E. N.; Wu, M. H.. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Heidelberg, 1999; Vol. II, p 649.
8. (a) Lohray, B. B.; Bhushan, V.; Kumar, R. K. *J. Org. Chem.* **1994**, *59*, 1375–1380; (b) Sharpless, K. B.; Akashi, K. *J. Am. Chem. Soc.* **1976**, *98*, 1986–1987.
9. Srinivasan, N. S.; Lee, D. G. *Synthesis* **1979**, 520.
10. Baskaran, S.; Das, S. J.; Chandrasekaran, S. *J. Org. Chem.* **1989**, *54*, 5182–5184.
11. Takai, T.; Yamada, T.; Mukaiyama, T. *Chem. Lett.* **1991**, 1499.
12. (a) Plietker, B. *Eur. J. Org. Chem.* **2005**, 1919–1929; (b) Plietker, B. *Org. Lett.* **2004**, *6*, 289–291; (c) Plietker, B. *J. Org. Chem.* **2004**, *69*, 8287–8296; (d) Plietker, B.; Niggemann, M. *Org. Biomol. Chem.* **2004**, *2*, 2403–2407; (e) Plietker, B. *J. Org. Chem.* **2003**, *68*, 7123–7125.
13. López-Herrera, F. J.; Sarabia-Garcia, F. *Tetrahedron* **1997**, *53*, 3325–3346.
14. (a) Bonini, C.; Chiummiento, L.; Funicello, M.; Lupattelli, P.; Pullez, M. *Eur. J. Org. Chem.* **2006**, 80–83; (b) Bonini, C.; Chiummiento, L.; Pullez, M.; Solladié, G.; Colobert, F. *J. Org. Chem.* **2004**, *69*, 5015–5022.
15. Kampf, A.; Dimant, E. *Carbohydr. Res.* **1974**, *32*, 380–382.