Stereoselective Synthesis of New Higher Carbon Sugars from D-Xylose

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A simple, one-pot multi-step route for the synthesis of a higher carbon sugar **3** by the HDA reaction of a α,β-unsaturated ketone prepared in situ from protected D-xylose with PDC in C_6H_6 or CH_3CN, followed by the reduction to the C10 higher carbon sugar derivatives **4** and **5**, is described.

Introduction

In recent years, the so-called "higher carbon sugars" have been receiving increasing attention due to their prominent roles in biological processes. For example, members of these kinds of compounds such as octulosonic acid KDO, aminononulosonic acids (sialic acids) and others with constituents of natural products possess interesting biological properties,[1−2] with potential applications as antibiotic analogs and biological activators. Thus, the higher carbon sugars are interesting synthetic targets and several approaches towards their synthesis have been reported. Among the methods for coupling of simple monosaccharides are the Wittig reaction, the Horner−Emmons reaction,[3−9] radical addition[10] and related methods such as the hetero-Diels−Alder reaction,[11] enzymatic aldolization,[12] and crossed-aldol reactions.[13] Herein, we disclose a novel synthetic method for the 10 carbon sugar and its derivatives. These kinds of products are carbohydrate precursors which can be converted into higher carbon amino sugars and glycosidase inhibitors for further evaluation.

Results and Discussion

In our previous work, a number of new branched chain sugars and amino sugars were synthesized by oxidation and coupling reactions.[14] In this paper we report an efficient and convenient synthetic method for the C10 sugar, with reasonable yields obtained using a one-pot multi-step route, using PDC as the oxidant (Scheme 1). This novel method can be applied on a large scale to prepare the higher carbon sugars from D-xylose. PDC is commonly used to oxidize the hydroxyl group in carbohydrates, thus affording the corresponding ketone. Therefore, treatment of 5-*O*-benzoyl-1,2-isopropylidene-α-D-xylofuranose (**1**) with PDC in CH_2Cl_2 provides the ketone **2**. However, a new type of a higher carbon sugar **3** was obtained unexpectedly when CH_3CN was used instead of CH_2Cl_2. In order to study the transformation of the xylose derivative in CH_3CN, we monitored the products of the reaction at different times. After a reaction time of 3 hours or less, the major product was **2**, if the reaction time was prolonged to 6 hours, the only product obtained was **3**. If the reaction was allowed to proceed for longer than 6 h, the yield of **3** decreased. Nevertheless, product **2** was obtained only in the absence of acetic anhydride. It could be concluded that the time and solvent have a major influence on the product of the reaction (Table 1). The optimal reaction conditions were: treatment of **1** with PDC in CH_3CN at 80 °C in the presence of acetic anhydride for 6 h, thus giving compound **3** in good yields. Reduction of compound **3** by $NaBH_4$ stereoselectively gave a single product **4** in an excellent yield. The reduced product **5** was obtained stereoselectively (Scheme 1) after the catalytic hydrogenation of **4**.

Table 1. Reactions of compound **1** with PDC under various conditions

Solvent	Volume [mL][a]	Reaction time [h]	*T* [°C]	Product	Yield [%][b]
CH_2Cl_2	30	2	39	**2**	70.5
CH_2Cl_2	10	2	39	**2**	71.0
CH_2Cl_2	30	24	39	**2**	70.8
CH_3CN	30	3	80	**2**	77.5
CH_3CN	8	6	80	**3**	81.3
CH_3CN	8	10	80	**3**	74.4
C_6H_6	6	9	80	**3**	77.8
C_6H_6	6	5	80	**3**	18.5
C_6H_6	30	24	80	**3**	26.4
C_6H_6	30	3	80	**2**	88.0

[a] 1 g of substrate was used. [b] Crystallization yields.

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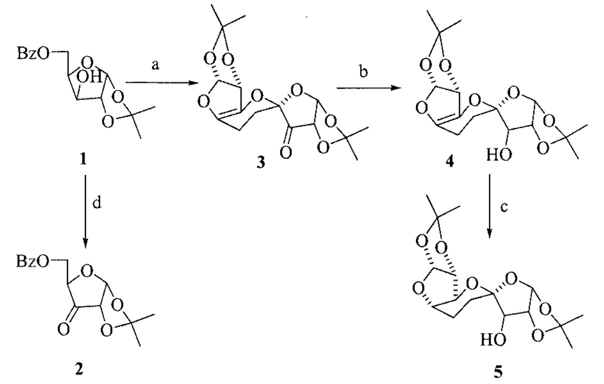
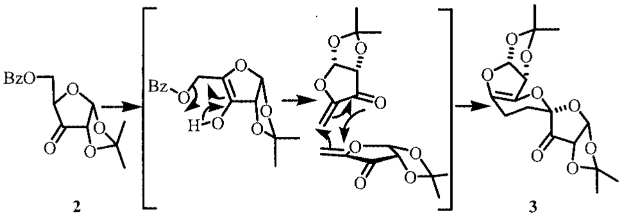


Scheme 1. a) PDC, CH_3CN, $(CH_3CO)_2O$, 80 °C, 6 h; b) $NaBH_4$, EtOH, room temp. 1 h; c) H_2/Pd−C, EtOH, 40 °C, 3 h; d) PDC, CH_2Cl_2, $(CH_3CO)_2O$, 40 °C, 2 h.

The IR spectra suggest that product **3** is a ketone. The molecular ion peak at $m/z = 340.1150$ in HR-MS indicate its molecular formula to be $C_{16}H_{20}O_8$. The ^{13}C NMR spectrum shows two anomeric carbons assigned to the signals at $\delta = 101.9$ and $\delta = 103.9$ ppm, a double bond at $\delta = 137.6$, $\delta 129.6$ ppm, and a new CH_2CH_2 bond at $\delta = 25.1$ and $\delta = 17.4$ ppm, as well as the presence of two isopropylidene groups. Therefore, it was concluded that compound **3** is comprised of two molecules of compound **2**.

A possible mechanism for the formation of **3** is outlined in Scheme 2, in which a hetero-Diels−Alder addition is involved.



Scheme 2. The possible reaction mechanism for the formation of **3**

The α,β-unsaturated ketone containing a six-membered ring was found to dimerize in the presence of Et_3N[15−16] and *s*-collidine.[17] In this reaction a five-membered ring with a α,β-unsaturated ketone structure formed in the presence of acetic anhydride. Thus, the reaction of compound **1** with PDC would be expected to result in the formation of 3-ketofuranose **2** at first. A PhCOOH group is then lost from 3-ketofuranose **2**, forming an α,β-unsaturated ketone. Two molecules of the α,β-unsaturated ketone undergo the hetero-Diels−Alder reaction,[18−21] affording the novel 10 carbon sugar **3** in situ.

To determine the stereochemistry of product **3**, its keto group was reduced stereoselectively by $NaBH_4$ affording **4** only, which is consistent with the presence of an isopropylidene group. The C=C double bond in compound **4** was reduced from the less hindered face by H_2 in the presence of Pd/C, thus stereoselectively yielding compound **5**. It was found that compound **4** and **5** crystallized as colorless needles by dissolving in diethyl ether and in ethanol, respectively. The structural information, as well as the stereochemistry of compound **4** was deduced by NMR spectroscopy, MS and X-ray crystallographic analysis.[22] The ORTEP drawing of **4** is shown in Figure 1. The configuration of spiro-carbon C4 is *S* as shown in Scheme 1. The high diastereoselectivity of the HDA reaction can be rationalized by the heterodiene and dienophile approaching each other from the less hindered *exo* face of the molecules. In compound **4**, the 3-OH group at C-3 has an α configuration. In agreement with steric factors, both **3** and **4** were reduced from the less hindered face of isopropylidene group. An ORTEP drawing of the hydrogenation product **5** is displayed in the Figure 2, together with the numbering scheme. In compound **5**, H-7 and H-8 are on the same side of the bond C7−C8. The X-ray diffraction analysis also indicates that molecular stacking occurs along a one-dimensional chain in the crystal.

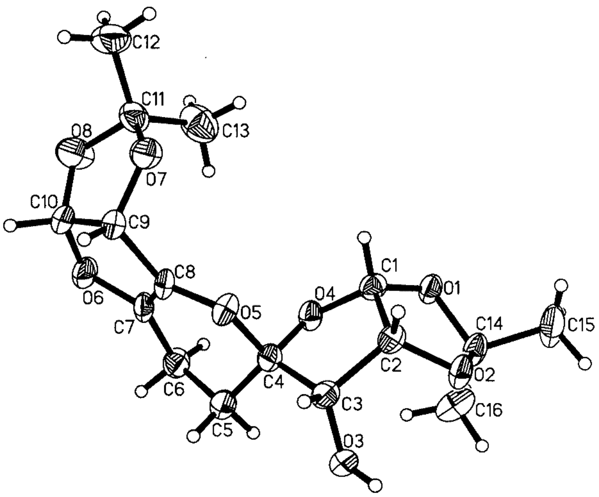


Figure 1. ORTEP diagram showing the X-ray structure of compound **4**

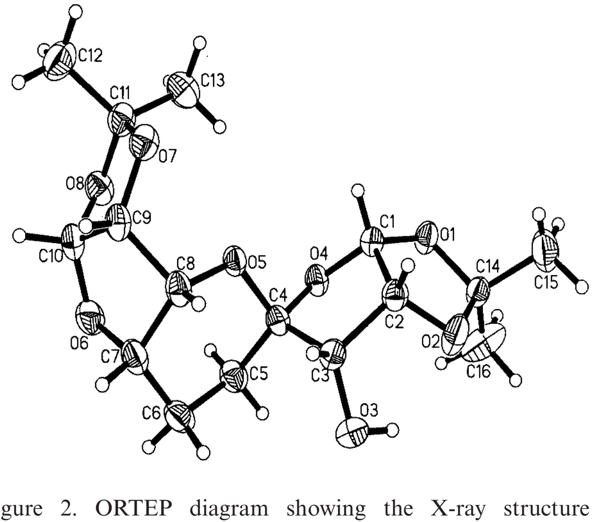


Figure 2. ORTEP diagram showing the X-ray structure of compound **5**

From the structures of compounds **4** and **5**, it could be seen that compound **3** has a double bond between C7 and C8 and a carbonyl group on C3. This confirms that compound **3** is formed by two molecules of compound **2** through a hetero-Diels−Alder reaction, as shown in Scheme 2.

Conclusion

In conclusion, we have developed a facile one-pot approach for the synthesis of the C10 higher carbon sugars under mild conditions with reasonable yields. The higher carbon sugars can be synthesized from D-xylose on a large scale both conveniently and economically. The higher carbon monosaccharides can be used in the synthesis of higher carbon amino sugars and glycosidase inhibitors, as well as new nucleosides with two anomeric carbons. Studies towards the synthesis of glycosidase inhibitors and new nucleoside are underway in our laboratory.

Experimental Section

General Remarks: Infrared spectra were recorded on a Bio-Rad FTS-40 spectrometer. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker AVANCE DPX-400 spectrometer with chemical shifts (δ) given in parts per million relative to tetramethylsilane as an internal standard. Melting points were determined by using open capillaries and are uncorrected.

Compound 3: A solution of **1** (10 g, 34 mmol) and PDC (8 g) in CH_3CN (80 mL) was stirred at 80 °C for 6 h in the presence of acetic anhydride (9 mL). After evaporation of the solvent under reduced pressure, the residue was dissolved in EtOAc (300 mL), filtered through a short silica-gel column, washed with saturated aqueous $NaHCO_3$ (3×50 mL) and the solvents evaporated. Recrystallization from diethyl ether yielded the product as a white flake (4.7 g, 81%). M.p. 166−168 °C. IR (KBr): $\tilde{\nu} = 1791$ cm^{-1} (C=O). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ = 1.40 (s, 3 H, CH_3), 1.44 (s, 3 H, CH_3), 1.46 (s, 3 H, CH_3), 1.50 (s, 3 H, CH_3), 1.96 (ddd, $^2J_{H,H} = 14.4$, $^3J_{H,H} = 6.4$, $^3J_{H,H} = 3.2$ Hz, 1 H, 5′-H), 2.17 (ddd, $^2J_{H,H} = 14.4$, $^3J_{H,H} = 10.8$, $^3J_{H,H} = 7.2$ Hz, 1 H, 5-H), 2.42 (m, 2 H, 6-H and 6′-H), 4.78 (d, $^3J_{H,H} = 4.0$ Hz, 1 H, 2-H), 5.17 (m, 1 H, 9-H), 5.94 (d, $^3J_{H,H} = 5.2$ Hz, 1 H, 10-H), 6.14 (d, $^3J_{H,H} = 4.0$ Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 17.4 (C-6), 25.1 (C-5), 27.2 (CH_3), 27.6 (CH_3), 27.7 (CH_3), 27.9 (CH_3), 76.4 (C-2), 80.4 (C-9), 100.2 (C-4), 101.9 (C-1), 103.9 (C-10), 112.9 (C-11), 116.1 (C-14), 129.6 (C-8), 137.6 (C-7), 201.2 (C-3) ppm. HRMS: *m/z* calcd. for $C_{16}H_{20}O_8$ [M]: 340.1158, found 340.1150. $C_{16}H_{20}O_8$ (340.33): calcd. C 56.47, H 5.92; found C 56.62, H 6.05.

Compound 4: A solution of **3** (1 g, 2.9 mmol) and $NaBH_4$ (0.11 g, 2.9 mmol) in ethanol (50 mL) was stirred at room temperature for 1 h. After evaporation of the solvent under reduced pressure, the residue was dissolved in water (60 mL), extracted with EtOAc (3×20 mL), dried (Na_2SO_4), and the solvents evaporated. After recrystallization from diethyl ether, the product was obtained as a colorless needle (0.97 g, 96%). M.p. 141−142 °C. IR (KBr): $\tilde{\nu} = 3520$ cm^{-1} (OH). ^{1}H NMR (400 MHz, [D$_6$]acetone, 25 °C, TMS): δ = 1.38 (s, 6 H, CH_3), 1.43 (s, 3 H, CH_3), 1.51 (s, 3 H, CH_3), 1.89 (m, 1 H, 5′-H), 2.21 (m, 3 H, 5-H, 6-H and 6′-H), 4.12 (d, $^3J_{H,H} = 5.6$ Hz, 1 H, 3-H), 4.87 (dd, $^3J_{H,H} = 5.6$, $^3J_{H,H} = 4.0$ Hz, 1 H, 2-H), 5.16 (m, 1 H, 9-H), 5.80 (d, $^3J_{H,H} = 3.6$ Hz, 1 H, 1-H), 5.92 (d, $^3J_{H,H} = 5.2$ Hz, 1 H, 10-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone, 25 °C, TMS): δ = 18.1 (C-6), 26.0 (C-5), 27.2 (CH_3), 27.3 (CH_3), 27.7 (CH_3), 28.0 (CH_3), 74.8 (C-3), 81.1 (C-2), 81.3 (C-9), 104.4 (C-1), 105.2 (C-10), 109.7 (C-4), 112.5 (C-11), 115.3 (C-14), 130.8 (C-8), 137.9 (C-7) ppm. HRMS: *m/z* calcd. for $C_{16}H_{22}O_8$ [M]: 342.1315, found 342.1341. $C_{16}H_{22}O_8$ (342.34): calcd. C 56.13, H 6.48; found C 56.01, H 6.67.

Compound 5: A solution of **4** (1 g, 2.9 mmol) in ethanol (60 mL) was hydrogenated (3 bars) for 3 h in the presence of 5% Pd/C (1 g). The reaction mixture was filtered through a short silica-gel column and the solvents evaporated. The residue was crystallized from ethanol to yield the product as colorless needles (0.9 g, 90%). M.p. 180−182 °C. IR (KBr): $\tilde{\nu} = 3534$ cm^{-1} (OH). ^{1}H NMR (400 MHz, [D$_6$]acetone, 25 °C, TMS): δ = 1.33 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3), 1.52 (s, 3 H, CH_3), 1.56 (s, 3 H, CH_3), 2.05−1.83 (m, 4 H, 5-H and 6-H), 3.86 (dd, $^3J_{H,H} = 3.6$, $^3J_{H,H} = 8.0$ Hz, 1 H, 7-H), 4.06 (dd, $^3J_{H,H} = 3.6$, $^3J_{H,H} = 5.6$ Hz, 1 H, 8-H), 4.16 (d, $^3J_{H,H} = 5.6$ Hz, 1 H, 3-H), 4.78 (dd, $^3J_{H,H} = 4.8$, $^3J_{H,H} = 5.6$ Hz, 1 H, 9-H), 4.84 (dd, $^3J_{H,H} = 4.0$, $^3J_{H,H} = 5.6$ Hz, 1 H, 2-H), 5.67 (d, $^3J_{H,H} = 4.8$ Hz, 1 H, 10-H), 5.88 (d, $^3J_{H,H} = 4$ Hz, 1 H, 1-H) ppm. ^{13}C NMR (100 MHz, [D$_6$]acetone, 25 °C, TMS): δ = 23.5 (C-6), 24.2 (C-5), 27.3 (CH_3), 27.6 (CH_3), 28.0 (CH_3), 28.7 (CH_3), 70.9 (C-3), 72.5 (C-8), 75.1 (C-7), 81.8 (C-2), 83.3 (C-9), 105.9 (C-10), 106.0 (C-1), 110.5 (C-4), 115.6 (C-14), 115.8 (C-11) ppm. HRMS: *m/z* calcd. for $C_{16}H_{25}O_8$ [M +1]: 345.1549, found 345.1568. $C_{16}H_{24}O_8$ (344.36): calcd. C 55.81, H 7.02; found C 55.90, H 6.84.

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[1] [1a] T. Iwasa, T. Kusuka, K. Suetomi, *J. Antibiot.* **1978**, *31*, 511−518. [1b] S. Harada, T. Kishi, *J. Antibiot.* **1978**, *31*, 519−524. [1c] S. Harada, E. Mizuta, T. Kishi, *Tetrahedron* **1981**, *37*, 1317−1327.

[2] [2a] A. Takatsuki, K. Arima, G. Tamura, *J. Antibiot.* **1971**, *24*, 215−223. [2b] A. Takatsuki, G. Tamura, *J. Antibiot.* **1971**, *24*, 224−231. [2c] A. Takatsuki, G. Tamura, *J. Antibiot.* **1971**, *24*, 232−238. [2d] A. Takatsuki, K. Kawamura, M. Okina, Y. Kodama, T. Ito, G. Tamura, *Agric. Biol. Chem.* **1977**, *41*, 2307−2309.

[3] [3a] D. R. Mootoo, B. Fraser-Reid, *J. Org. Chem.* **1987**, *52*, 4511−4517. [3b] D. R. Mootoo, B. Fraser-Reid, *J. Org. Chem.* **1989**, *54*, 5548−5550.

[4] M. Jørgensen, E. H. Iversen, R. Madsen, *J. Org. Chem.* **2001**, *66*, 4625−4629.

[5] S. Jarosz, S. Skóra, K. Szewczyk, Z. Ciunik, *Tetrahedron: Asymmetry* **2001**, *12*, 1895−1905.

[6] S. Jarosz, *J. Carbohydr. Chem.* **2001**, *20*, 93−107.

[7] J. Marco-Cotelles, E. D. Opazo, N. Arroyo, *Tetrahedron* **2001**, *57*, 4729−4739.

[8] H.-D. Junker, N. Phung, W.-D. Fessner, *Tetrahedron Lett.* **1999**, *40*, 7063−7066.

[9] S. Jarosz, P. Salański, M. Mach, *Tetrahedron* **1998**, *54*, 2583−2594.

[10] Y. Araki, T. Endo, Y. Arai, M. Tanji, Y. Ishido, *Tetrahedron Lett.* **1989**, *30*, 2829−2832.

[11] K. S. Kim, I. H. Cho, Y. H. Joo, I. Y. Yoo, J. H. Song, J. H. Ko, *Tetrahedron Lett.* **1992**, *33*, 4029−4032.

[12] O. Eyrisch, M. Keller, W.-D. Fessner, *Tetrahedron Lett.* **1994**, *35*, 9013−9016.

[13] A. H. Haines, A. J. Lamb, *Carbohydr. Res.* **2000**, *325*, 323−339.

[14] H.-M. Liu, F. Zhang, D.-P. Zou, *Chem. Commun.* **2003**, 2044−2045.

[15] R. E. Ireland, J. P. Daub, *J. Org. Chem.* **1983**, *48*, 1303−1312.

[16] E. Alvarez, R. Pérez, M. Rico, R. M. Rodríguez, J. D. Martín, *J. Org. Chem.* **1996**, *61*, 3003−3016.

[17] O. R. Martin, F. Xie, *Carbohydr. Res.* **1994**, *264*, 141−146.

[18] L.-S. Li, Y. Wu, Y.-J. Hu, L.-J. Xia, Y.-L. Wu, *Tetrahedron: Asymmetry* **1998**, *9*, 2271−2277.

[19] M. EI Sous, M. A. Rizzacasa, *Tetrahedron Lett.* **2000**, *41*, 8591−8594.

[20] A. N. Cuzzupe, C. A. Hutton, M. J. Lilly, R. K. Mann, K. J. McRae, S. C. Zammit, M. A. Rizzacasa, *J. Org. Chem.* **2001**, *66*, 2382−2393.

[21] G. Cravotto, G. M. Nano, G. Palmisano, S. Tagliapietra, *Tetrahedron: Asymmetry* **2001**, *12*, 707−709.

[22] Crystal data for **4**: $C_{16}H_{22}O_8$, $M = 342.34$, crystal dimensions: 0.30 × 0.30 × 0.20 mm, orthorhombic, space group: $P2(1)2(1)2(1)$, $a = 5.5760(11)$ Å, $b = 16.682(3)$ Å, $c = 17.832(4)$ Å, $V = 1658.7(6)$ Å^3, $Z = 4$, $\rho_{calcd.} = 1.371$ Mg·m^{-3}, $\mu(\text{Mo-}K_\alpha) = 0.110$ mm^{-1}, θ range 1.67−24.98°, $T = 291(2)$ K, $F(000) = 728$, 4272 reflections collect, 2451 unique [$R(\text{int}) = 0.0878$], final R indices [$I > 2\sigma(I)$]: $R1 = 0.0680$, $wR_2 = 0.1542$, R indices (all data): $R1 = 0.0848$, $wR_2 = 0.1628$. Crystal data for **5**: $C_{16}H_{24}O_8$, $M = 344.36$, crystal dimensions: 0.30 × 0.20 × 0.20 mm, orthorhombic, space group: $P2(1)2(1)2(1)$, $a = 5.5836(11)$ Å, $b = 16.183(3)$ Å, $c = 18.320(4)$ Å, $V = 1655.4(6)$ Å^3, $Z = 4$, $\rho_{calcd.} = 1.382$ Mg·m^{-3}, $\mu(\text{Mo-}K_\alpha) = 0.111$ mm^{-1}, θ range 1.68−27.54°, $T = 291(2)$ K, $F(000) = 736$, 2010 reflections collect, 2010 unique [$R(\text{int}) = 0.0000$], final R indices [$I > 2\sigma(I)$]: $R1 = 0.0403$, $wR_2 = 0.0791$, R indices (all data): $R1 = 0.0618$, $wR_2 = 0.0864$. CCDC-223650 (for **4**) and CCDC-223649 (for **5**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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