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Stereoselective synthesis of 2,2-bis(*C*-branched-chain)glucopyranosid-3-ulose *via* an autoxidation–Michael addition reaction†

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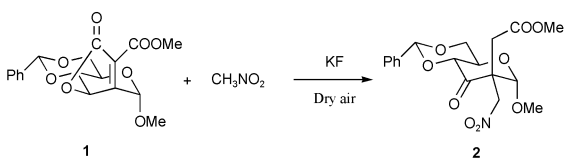
Received (in Cambridge, UK) 3rd June 2003, Accepted 27th June 2003
First published as an Advance Article on the web 4th July 2003

2,2-Bis(*C*-branched-chain)glucopyranosid-3-uloses, designed for the preparation of biologically active natural product *iridoid* derivatives, are synthesized selectively by the new reaction of butenolide-containing sugar with active methylene compounds, and the new reaction is clarified as autoxidation followed by Michael addition of carbanion.

Owing to their usefulness as intermediates for the synthesis of other non-sugar chiral molecules many different approaches have been established for the synthesis of branched chain sugars.[1] Branched chain glycosidulose can be used for construction of five- and six-membered carbocyclic rings into which two chiral carbons of sugar are incorporated by intramolecular aldol condensation,[2] and Robinson annulation,[3] Therefore they are useful in the synthesis of natural products which consist of annulated carbohydrates or where a highly functionalised enantiomerically pure cyclopentane or cyclohexane is required. Also, this type of branched chain sugar may be the synthon of monoterpenoid natural products of the *iridoids* class which have the cyclopentan-(*c*)-pyran structure.[4] In view of the importance of branched chain glycosiduloses, it is desirable to have a general, convenient methodology for their synthesis. However, none of the literature methods report a one-step synthesis of branched chain glycosidulose by a nucleophilic addition to a partially protected glycosidulose,[5] except that we recently synthesized 2-*C*-branched-chain glucopyranosid-3-ulose by the reaction of partially protected '2-oxoglucopyranoside' with diethyl malonate in one pot.[6] Further studies made us isolate glycoside lactone derivative **1** (butenolide-containing sugar,[7] Scheme 1) in good yield.[8] In order to get 2,2-bis(*C*-branched-chain)glucopyranosid-3-uloses for the preparation of *iridoid* derivatives and other biologically active substances. In this communication, we report on a general, convenient method for the one-step syntheses of 2,2-bis(*C*-branched-chain)glucopyranosid-3-uloses by the new reaction of **1** with various active methylene compounds.

Nitromethane was first used as a nucleophile and solvent to react with **1** at room temperature in the presence of KF to give 2-*C*-methoxycarbonylmethyl-2-*C*-nitromethyl-α-D-glycopyranoside-3-ulose **2** in 66% yield (Scheme 1). Further experiments were performed in various solvents and at different temperatures, indicating that besides nitromethane, DMF as a solvent is efficient at room temperature. The structure of **2** was definitely characterized by spectroscopic data. The high-resolution FAB mass spectrum indicated its formula to be $C_{18}H_{21}NO_9$ from the $M^+ + 1$ peak at *m*/*z* 396.1351 and the $M^- - 1$ peak at *m*/*z* 394.0989. In addition to showing NO_2 absorption at 1561 and 1386 cm^{-1}, the IR spectrum gave one carbonyl group absorption at 1741 cm^{-1}. However, the ^{13}C-NMR showed two carbonyl carbon signals at δ 197.1 (C-3) and 170.6 ($COOCH_3$), indicating the presence of two carbonyl groups. In the ^1H-NMR spectrum, the two protons assignable to methylene of newly formed CH_2COOCH_3, appeared as two doublets at δ 3.09 and 3.60 with coupling constant of 18.0 Hz, and the other two protons as two doublets at δ 4.88 and 5.00 (each J = 13.6 Hz) were ascribed to those of CH_2NO_2. The NOESY spectrum shows the correlation between the methylene of CH_2COOMe and H-1, and one proton in this methylene correlating with H-4 is also observed. All the assignments were based on 2D NMR spectra.



1 2

Scheme 1 Synthesis of 2-*C*-methoxycarbonylmethyl-2-*C*-nitromethyl-α-D-glycopyranoside-3-ulose **2** *via* an autoxidation–Michael addition reaction.

In order to investigate the generality of this method and to synthesize various 2,2-bis(*C*-branched-chain)glucopyranosid-3-uloses, the reaction was carried out with 2,4-pentanedione and ethyl acetoacetate in DMF and at room temperature. Surprisingly, 2,2-bis(*C*-branched-chain)glucopyranosid-3-uloses **3** and **4** were obtained in the form of ketals at C-3 positions (Table 1, entries 2 and 3). The two branched chains at the *C*-2 position of **3** or **4** may be easily opened by weak acid catalytic hydrolysis to yield 1,4-diketone and then readily cyclised to cyclopentaannulated sugar, which have applications in the synthesis of *iridoid* derivatives. Further, the new reaction was successfully extended to the synthesis of similar compounds from ethyl nitroacetate and nitroethane under the same conditions (Table 1, entries 4 and 5). In all cases the yields were higher than 60%. In addition, by-products such as Claisen condensation compounds in the reaction of esters and lactones with carbanions were not obtained in this case. All the products were spectroscopically characterized.‡ **3** and **6** gave crystals suitable for X-ray analyses§ after recrystallization from ethanol and acetone. Their crystal structures are depicted in Fig. 1.

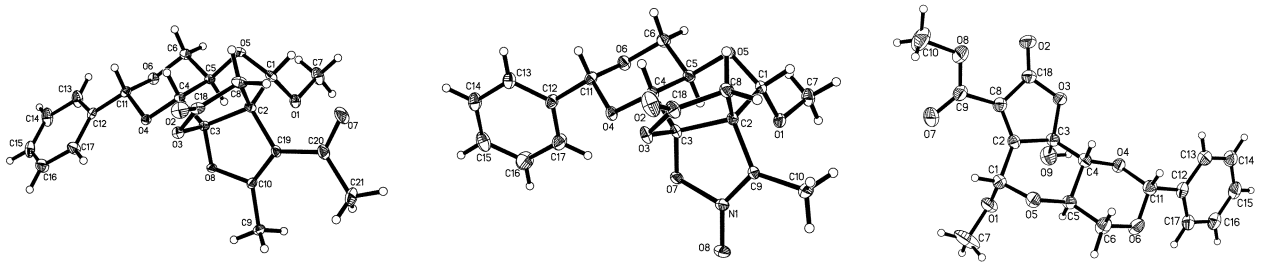
To uncover the novel reaction further, **1** in anhydrous DMF and baked KF was stirred in a dry atmosphere at room temperature. 30 h later, **7** (Scheme 2) was obtained in 68% yield, the crystal structure of which is shown in Fig. 1§, indicating the autoxidation of **1** to **7**. The reactions of **7** with various active methylene compounds were carried out under similar conditions to those described above to generate **2–6**, and gave identical results to when **1** was starting material. Thus, the reaction of **1** with carbanions can be rationalized by autoxidation of **1** followed by 1,4-Michael addition as the main steps. For instance, the reaction in Scheme 1 can be explained as shown in Scheme 2. **1** was autoxidized at the allyl position (C-3) into the corresponding compound **7** followed by 1,4-Michael addition with carbanion and decarboxylation to generate **2**.

In conclusion, we report a mild and convenient method for the stereoselective synthesis of 2,2-bis(*C*-branched-chain)glucopyranosid-3-uloses by a novel reaction. This new method is simple and selective, the mechanism of which is clarified as autoxidation followed by 1,4-Michael addition with carbanion. Application of this type of branched chain sugar for synthesis of *iridoid* derivatives and other biologically active substances is in progress.

We are grateful to NNSF of P. R. China (No. 20272054) for financial support of this research. We also thank Dr N.

† Electronic supplementary information (ESI) available: spectroscopic data for **2–7**. See http://www.rsc.org/suppdata/cc/b3/b306227a/

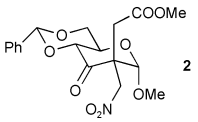
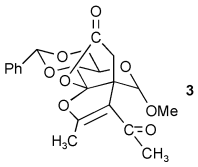
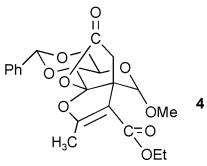
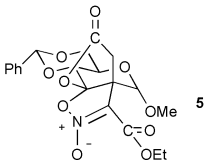
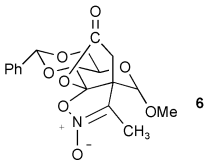
DOI: 10.1039/b306227a



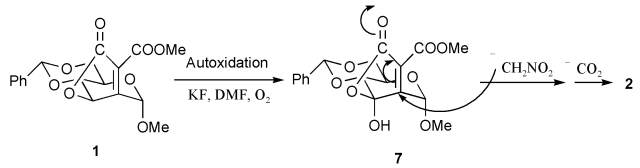
3 **6** **7**

Fig. 1 ORTEP of 2,2-bis(*C*-branched-chain)glucopyranosid-3-ulose **3**, **6**, and intermediate **7**.

Table 1 Synthesis of 2,2-bis(*C*-branched-chain)glucopyranosid-3-ulose in DMF and at room temperature[a]

Entry	Active methylene compounds	Rection time	Product	Yield (%)
1	CH_3NO_2	50 h	 **2**	62
2	$CH_3COCH_2COCH_3$	72 h	 **3**	65
3	CH_3COCH_2COOEt	72 h	 **4**	63
4	O_2NCH_2COOEt	75 h	 **5**	67
5	$CH_3CH_2NO_2$	8 days	 **6**	61

[a] General procedure: **1** (400 mg, 1.10 mmol) was dissolved in 2.5 mL of dry DMF, to which active methylene compound (4.0 equiv.) and KF (4.0 equiv.) were added. The mixture was stirred in a dry atmosphere and at room temperature (18–25 °C). The reaction was monitored by TLC. When **1** disappeared, the mixture was poured into water, extracted with EtOAc, dried over Na_2SO_4 and concentrated. The residue was crystallized from CH_3CH_2OH to give product as a white solid (61–67% yield).



1 **7**

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

Sugimoto (Division of Food Additives, NIHS, Kamiyoga 1-18-1, Setagaya, Tokyo 158-8501, Japan) for the MS measurements.

Notes and references

‡ *Selected data* for **2**: Mp 151–154 °C, IR (cm^{-1}, KBr): 1741 ($\nu_{C=O}$), 1561, 1433 ($\nu_{N=O}$); ^{1}H NMR (400 MHz, acetone-d_6) δ 3.09, 3.60 (d, each 1·H, J = 18.0 Hz, CH_2COOCH$_3$), 3.44 (s, 3H, OCH$_3$), 3.65 (s, 3H, COOCH$_3$), 4.03 (dt, 1H, J_1 = 4.8 Hz, J_2 = 10.0 Hz, H-5), 4.15 (t, 1H, J = 10 Hz, H-6a); 4.36 (dd, 1H, J_1 = 4.8 Hz, J_2 = 10.0 Hz, H-6b), 4.88, 5.00 (d, each 1H, J = 13.6 Hz, CH_2NO_2), 5.07 (s, 1H, H-1), 5.14 (d, 1H, J = 10.0 Hz, H-4), 5.74 (s, 1H, PhC*H*O$_2$), 7.37–7.39 (m, 3H, Ar*H*), 7.47–7.49 (m, 2H, Ar*H*); ^{13}C NMR (100 MHz, acetone-d_6): δ 37.1 (*C*H$_2$COOCH$_3$), 52.3 (COO*C*H$_3$), 56.0 (OCH$_3$), 56.5 (C-2), 68.2 (C-5), 69.2 (C-6), 74.9 (CH_2NO_2), 80.2 (C-4), 102.0 (Ph*C*HO$_2$), 104.7 (C-1), 127.1, 128.7, 129.7, 138.2 (Ph), 170.6 (*C*OOCH$_3$), 197.1 (C-3); HRMS (FAB): 396.1351 (M^+ + 1); Anal. calc. for $C_{18}H_{21}NO_9$: C, 54.68; H, 5.35; N, 3.54. Found: C, 54.64; H, 5.33; N, 3.53%.

§ *Crystal data* for **3**: $C_{21}H_{22}O_8$, M = 402.39, monoclinic, a = 8.8818(18), b = 8.5242(17), c = 13.488(3) Å, β = 103.36(3)°, V = 993.6(3) Å^3, $P2(1)$, Z = 2, D = 1.345 Mg m^{-3}, μ(Mo-Kα) = 0.104 mm^{-1}, θ range 1.55–24.99°, F(000) = 424, 2783 reflections collected, 2686 unique [R(int) = 0.0277], Final R indices [$I > 2\sigma(I)$]: R_1 = 0.0517, wR_2 = 0.1118. For **6**: $C_{18}H_{19}NO_8$, M = 377.34, orthorhombic, a = 11.070(2), b = 19.503(4), c = 8.6828(17) Å, V = 1877.1(6) Å^3, $P2(1)2(1)2(1)$, Z = 4, D = 1.335 Mg m^{-3}, μ(Mo-Kα) = 0.106 mm^{-1}, θ range 2.09–24.99°, F(000) = 792, 4806 reflections collected, 2744 unique [R(int) = 0.0520], final R indices [$I > 2\sigma(I)$]: R_1 = 0.0546, wR_2 = 0.1098, R indices (all data): R_1 = 0.0980, wR_2 = 0.1232. For **7**: $C_{18}H_{18}O_9$, M = 378.32, orthorhombic, a = 6.3659(13), b = 11.591(2), c = 23.782(5) Å, V = 1754.8(6) Å^3, Z = 4, D = 1.432 Mg m^{-3}, μ(Mo-Kα) = 0.116 mm^{-1}, θ range 1.71–27.53°, F(000) = 792, 5999 reflections collected, 3520 unique [R(int) = 0.0412], final R indices [$I > 2\sigma(I)$]: R_1 = 0.0557, wR_2 = 0.1064, R indices (all data): R_1 = 0.0993, wR_2 = 0.1184. CCDC 200166, 212059 and 212060. See http://www.rsc.org/suppdata/cc/b3/b306227a/ for crystallographic data in CIF or other electronic format.

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