

The formation of symmetrical glycosyl glycuronates by direct oxidation of partially protected methyl α -D-glycopyranosides

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Dedicated to Professor Domenico Spinelli on his 70th birthday
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Abstract

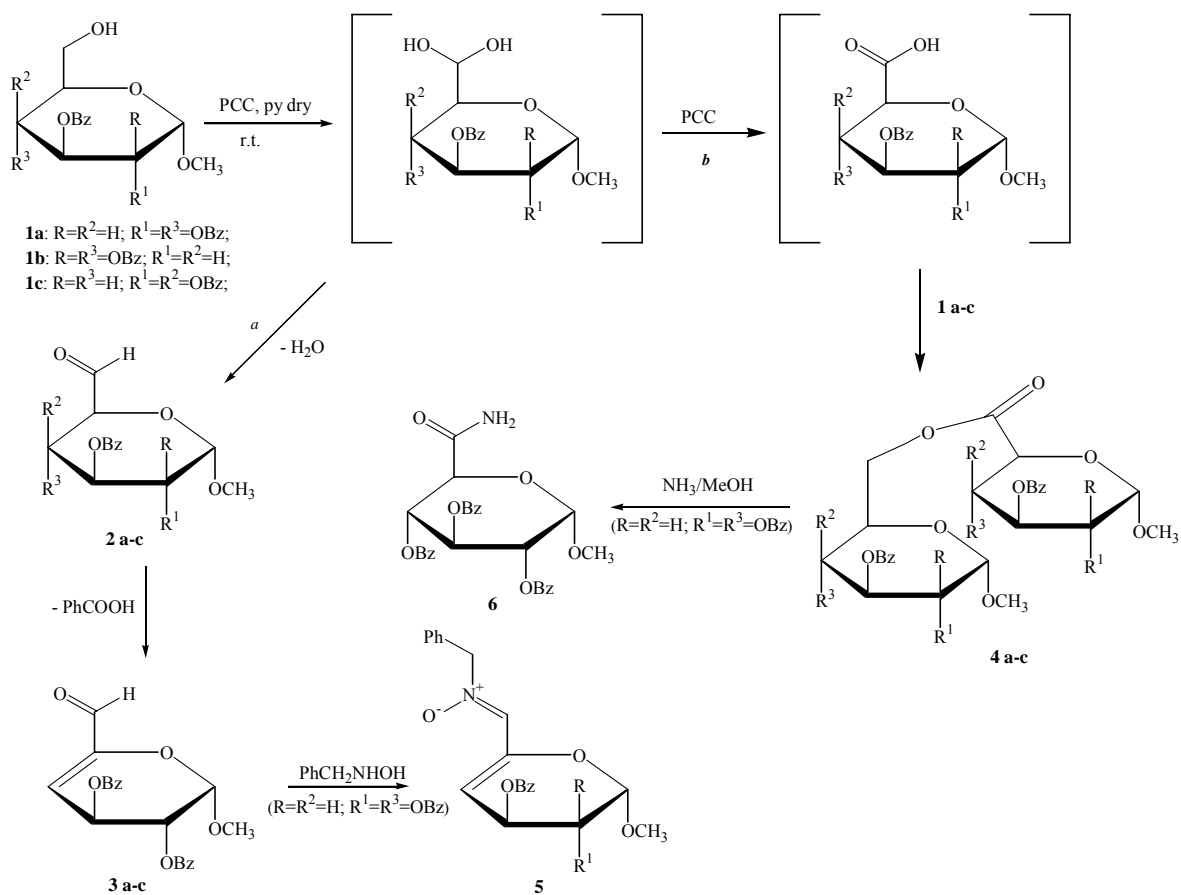
The formation of symmetrical glycuronates by oxidation of methyl α -D-2,3,4-tri-*O*-benzoyl glycopyranosides with pyridine dichlorochromate is described. A key intermediate in the process is represented by the initially formed aldehydes which react further through two competing reaction pathways leading to the glycals and to the symmetrical esters. The symmetrical glycuronates are formed by oxidation of the corresponding hemiacetal intermediates. The absolute configuration of the chiral centers at position 2-, 3-, and 4- of the glycopyranosides does not affect the two competing reaction paths.

Keywords: Glycopyranosides oxidation, symmetrical glycosyl glycuronates, sugar nitrones

Introduction

In the course of our studies concerning the synthesis of analogues of antiviral nucleoside drugs¹ we planned the formation of chiral nitrones **5** from the fully protected glycopyranoside **1a** through its stable 4,5- glucal, **3a**, achievable through a previously reported² procedure (**Scheme**, path *a*). The project aimed at exploiting new approaches to the enantioselective synthesis of isoxazolidino-nucleosides³ after the modification of the hexose ring through conventional chemistry.

Methyl α -D-2,3,4-tri-*O*-benzoyl glucopyranoside **1a** was obtained in three steps, from the corresponding methyl α -D-glucopyranoside, by tritylation in pyridine (75% yield) followed by benzylation in the same solvent (88% yield) and final de-blocking with trifluoroacetic acid at 0° C (85% yield). The corresponding *N*-benzyl nitrone **5** was obtained in satisfactory yield (**Scheme**).



Scheme

The apparent limitation of the method was represented by the modest yields of the oxidation step (**Scheme**, path a) which were in contrast with a previous report² on the oxidation of the same species protected at the positions 2, 3 and 4 with an acetyl group. However, a species having the structure of the glucuronate **4a** was obtained in 45% isolated yield from the reaction mixture. The structural assignment was based on ¹H- NMR and FAB- mass spectrometric data, and on the chemical information provided by the formation of methyl α-D-glucuronamide **6** after conventional ammonia/methanol de-blocking (**Scheme**).

Table. Isolated yields (%) of compounds **3a–c** and **4a–c**

Reagents	Aldehyde	Ester
1a	3a (40)	4a (45)
1b	3b (40)	4b (47)
1c	3c (38)	4c (42)

The generalization of this peculiar oxidation process was checked with other glycopyranosides under the same experimental conditions. Manno- (**1b**) and galacto-pyranosides (**1c**) afforded the glycuronates **4b** and **4c**, with 47 and 42% yields, respectively, together with the glycals **3b,c** (Table).

From the data reported in the table it can be assumed that the formation of the ester (**Scheme**, path *b*) is an independent process competing with the formation of the α,β -unsaturated aldehyde moiety of the glycals (**Scheme**, path *a*). Whatever the mechanism, in fact, no unsaturated glucuronides were formed. The elimination of a benzoic acid unit from positions -4 and -5 of the investigated glyco-pyranosides does not depend on the absolute configuration of the chiral centers involved in the process. It is, in fact, taken by the galacto- and gluco- isomers, affording the same glycal. The formation of the symmetrical esters is probably owing to the oxidation of intermediate hemiacetals originating from the interaction of the unreacted glycopyranosides **1a-c** with the primarily formed aldehydes (**Scheme**).

To the best of our knowledge, the formation of symmetric glycuronides by oxidation of the corresponding glycopyranoside has never been described before, whereas it has been shown⁴ that even in the case of simple cyclic or acyclic alcohols, the reaction sequence alcohol \rightarrow aldehyde \rightarrow hemiacetal \rightarrow symmetrical ester was preferred to the commonly accepted oxidation of alcohols to carboxylic acids, followed by esterification.

This reaction pathway, which is not usually recognized, can be in operation as a competitive process in the oxidation of glycopyranosides to 4,5-glycals and represents a valuable *one-pot* alternative to the conventional access to symmetrical glycopyranoside uronates. Moreover, the oxidation of the starting compounds proceeds with excellent isolated yields.

Experimental Section

General Procedures. NMR spectra were measured at 300 MHz; coupling constants, *J*, are in Hz. FAB-MS spectra were obtained in 3-nitrobenzyl alcohol matrix (*m*-NBA).

Methyl α -D-2,3,4-tri-*O*-benzoylglycopyranosides (**1a-c**) (0.198 g; 0.39 mmol) and pyridinium chlorochromate (PCC) (0.13 g; 0.59 mmol) were placed in 15 ml of dry CH₂Cl₂ under dry nitrogen. Molecular sieves were added to this suspension. The reaction mixture was stirred for a week. Then 10 ml of diethyl ether was added and the suspension was filtered through a column of silica gel. The colorless filtrate was concentrated in vacuo and the residue purified by flash chromatography (petroleum, b.p. 40–60 °C / Et₂O, 9:1 v/v). Two products (**3a-c** and **4a-c**) were isolated.

3a. δ_{H} (CDCl₃): 3.56 (s, 3H, OCH₃); 5.42 (d, 1H, H₁, *J*_{1,2}=2.4); 5.61 (dd, 1H, H₂, *J*_{2,1}=2.4, *J*_{2,3}=8.4); 6.08 (d, 1H, H₄, *J*_{4,3}=2.8); 6.19 (dd, 1H, H₃, *J*_{3,2}=8.4, *J*_{3,4}=2.8); 8.10–7.30 (m, 10H, Ar); 9.31 (s 1H, CHO); FAB-MS (+), *m*-NBA *m/z*: 383 [M+H]⁺(13%); 261 [M-BzOH]⁺ (100%). Anal. Calcd. for C₂₁H₁₈O₇; C 65.96, H 4.74, O 29.29; found; C 66.28 H 4.26%.

3b. δ_{H} (CDCl₃): 3.60 (s, 3H, OCH₃); 5.34 (d, 1H, $J_{1,2}=2.7$); 5.70 (ddd, 1H, H₂, $J_{2,1}=2.7$, $J_{2,3}=2.3$, $J_{2,4}=1.9$); 6.04 (dd, 1H, H₄, $J_{4,2}=1.9$, $J_{4,3}=4.6$); 6.09 (dd, 1H, H₃, $J_{3,2}=2.3$, $J_{3,4}=4.6$); 8.05–7.34 (m, 10H, Ar); 9.31 (s 1H, CHO); FAB-MS (+), *m*-NBA m/z : 383 [M+H]⁺ (34%); 261 [M-BzOH]⁺ (100%). Anal. Calcd. for C₂₁H₁₈O₇; C 65.96, H 4.74, O 29.29: found; C 65.44, H 5.02%.

3c. δ_{H} (CDCl₃): 3.56 (s, 3H, OCH₃); 5.42 (d, 1H, H₁, $J_{1,2}=2.8$); 5.62 (dd, 1H, H₂, $J_{2,1}=2.8$, $J_{2,3}=8.6$); 6.08 (d, 1H, H₄, $J_{4,3}=2.6$); 6.19 (dd, 1H, H₃, $J_{3,2}=8.6$, $J_{3,4}=2.6$); 8.15–7.35 (m, 10H, Ar); 9.31 (s 1H, CHO); FAB-MS (+), *m*-NBA m/z : 383 [M+H]⁺ (23%); 261 [M-BzOH]⁺ (100%). Anal. Calcd. for C₂₁H₁₈O₇; C 65.96, H 4.74, O 29.29: found; C 65.83 H 5.28%.

4a. δ_{H} (CDCl₃): 3.20 (s, 3H, OCH₃); 3.45 (s, 3H, OCH₃); 4.25–4.30 (m, 2H, H₅, H_{6A}); 4.40 (m, 1H, H_{6B}); 4.60 (d, 1H, H₁, $J_{1,2}=9.83$); 4.75 (d, 1H, H₁, $J_{1,2}=3.64$); 5.15 (dd, 1H, H₂, $J_{2,1}=3.64$, $J_{2,3}=9.44$); 5.30 (m, 2H, H₅+H₄); 5.50 (t, 1H, H₄, $J_{4,3}=J_{4,5}=9.44$); 5.70 (t, 1H, H₂, $J_{2,3}=J_{2,1}=9.83$); 6.10 (t, 1H, H₃, $J_{3,2}=J_{3,4}=9.44$); 6.20 (t, 1H, H₃, $J_{3,2}=J_{3,4}=9.83$); 8.05–7.20 ppm (m, 30H, Ar); FAB-MS (+), *m*-NBA m/z : 1031 [M+Na]⁺ (50%); 1009 [M+H]⁺ (15%); 977 [M+H - MeOH]⁺ (100%). Anal. Calcd. for C₅₆H₄₈O₁₈; C 66.66, H 4.80, O 28.54: found; C 67.11 H 5.04%.

4b. δ_{H} (CDCl₃): 3.29 (s, 3H, OCH₃); 3.48 (s, 3H, OCH₃); 4.19 (d, 1H, H_{6A}, $J_{6A,6B}=7.50$); 4.27 (d, 1H, H_{6B}, $J_{6B,6A}=7.50$); 4.38 (d, 1H, H₁, $J_{1,2}=1.43$); 4.42 (d, 1H, H₅, $J_{5,4}=9.28$); 4.54 (dd, 1H, H₄, $J_{4,3}=6.07$, $J_{4,5}=4.29$); 5.07 (d, 1H, H₁, $J_{1,2}=2.14$); 5.52 (dd, 1H, H₂, $J_{2,1}=1.43$, $J_{2,3}=3.21$); 5.63 (t, 1H, H₂, $J_{2,1}=J_{2,3}=2.14$); 5.74 (t, 1H, H₄, $J_{4,3}=J_{4,5}=9.28$); 5.76 (dd, 1H, H₃, $J_{3,2}=3.21$, $J_{3,4}=9.28$); 5.91 (m, 2H, H₅, H₃); 7.24–8.06 (m, 30H, Ar); FAB-MS (+), *m*-NBA m/z : 1031 [M+Na]⁺ (43%); 1009 [M+H]⁺ (27%); 977 [M+H - MeOH]⁺ (100%). Anal. Calcd. for C₅₆H₄₈O₁₈: C 66.66, H 4.80, O 28.54: found; C 67.03 H 4.22

4c. δ_{H} (CDCl₃): 3.43 (s, 3H, OCH₃); 3.49 (s, 3H, OCH₃); 4.22 (dd, 1H, H_{6A}, $J_{6A,6B}=11.34$, $J_{6A,5}=6.65$); 4.31 (dd, 1H, H_{6B}, $J_{6B,6A}=11.34$, $J_{6B,5}=6.65$); 4.44 (t, 1H, H₅, $J_{5,6A}=J_{5,6B}=6.65$); 4.90 (d, 1H, H₅, $J_{5,4}=1.56$); 5.22 (d, 1H, H₁, $J_{1,2}=3.52$); 5.40 (d, 1H, H₁, $J_{1,2}=3.52$); 5.57 (dd, 1H, H₂, $J_{2,1}=3.52$, $J_{2,3}=10.56$); 5.66 (dd, 1H, H₂, $J_{2,1}=3.52$, $J_{2,3}=10.96$); 5.92 (d, 1H, H₄, $J_{4,3}=3.13$); 5.94 (dd, 1H, H₃, $J_{3,2}=10.96$, $J_{3,4}=3.13$); 5.97 (dd, 1H, H₃, $J_{2,3}=10.56$, $J_{3,4}=3.52$); 6.20 (dd, 1H, H₄, $J_{4,3}=3.52$, $J_{4,5}=1.56$); 8.02–7.01 (m, 30H, Ar); FAB-MS (+), *m*-NBA m/z : 1031 [M+Na]⁺ (30%); 1009 [M+H]⁺ (33%); 977 [M+H - MeOH]⁺ (100%). Anal. Calcd. for C₅₆H₄₈O₁₈; C 66.66, H 4.80, O 28.54: found, C 66.18 H 5.13%.

5. δ_{H} (CDCl₃): 3.24 (3H, s, OCH₃); 4.92 (s, 2H, CH₂); 5.20 (d, 1H, H₁, $J_{1,2}=2.3$); 5.48 (dd, 1H, H₂, $J_{2,1}=2.3$, $J_{2,3}=7.2$); 6.18 (dd, 1H, H₃, $J_{3,2}=7.3$, $J_{3,4}=4.0$); 6.97 (s, 1H, H_A); 7.21 (d, 1H, H₄, $J_{4,3}=4.1$); 7.26–8.00 (m, 15H, Ar); FAB-MS (+), *m*-NBA m/z : 510 [M+Na]⁺ (22%); 488 [M+H]⁺ (52%); 310 (100%). Anal. Calcd. for C₂₈H₂₅NO₇; C 68.98, H 5.17, N 2.87, O 22.97: found; C 68.83, H 4.99, N 2.92%.

6. ⁵FAB-MS (+), *m*-NBA C₇H₁₃NO₆, m/z : 230 [M+Na]⁺ (33%); 208 [M+H]⁺ (48%); 176 [M+H - MeOH]⁺ (100%).

Acknowledgements

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