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A SELECTIVE SYNTHESIS OF PROTECTED α-D-GLUCOFURANURONO-6,3-LACTONE CHLORIDE USING BISMUTH (III) CHLORIDE AS CATALYST

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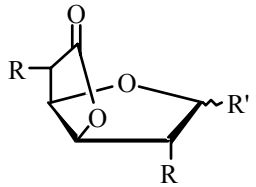
A new and specific route for the synthesis of peracetylated-α–glucofuranurono-6,3-lactone chloride has been described using bismuth (III) chloride and methyltrichlorosilane as chlorinating agents.

INTRODUCTION

In sugar chemistry, a selective synthesis of an anomer is of great importance. Halogenation at the anomeric position of glucofuranurono-6,3-lactone has been intensively studied.[1-6] The different halogenated compounds described in the literature, starting from 1905, are summarized in Table 1. Most of the published synthesis led to an anomeric mixture or to the β-halogenated glucofuranurono-lactone. Only one article refers to the synthesis of the α-chlorinated derivative. Indeed, in 1968, Goodman *et al*.[5] have published a procedure for the chlorination of the β-triacetylated derivative **3** using titanium chloride. The final compound was described as the α-chlorinated derivative **2** evidenced solely by data such as melting point and index of rotation.

Table 1

Compounds described in the literature and in this work



1 R = OAc ; R' = Br.
Neuberg *et al*. (1905).[1] Contested by Goebel *et al*. (1933).[2]
2 R = OAc ; R' = Cl
*Goebel *et al*. (1933),[2] anomeric form non determinated.
**Korytnyk *et al*. (1959),[3] β-anomer.
Contested by Momose *et al*. (1966)[4] and by ourselves.
***Goodman (1968),[5] α-anomer. Contested by ourselves.
3 R = R' = OAc.
4 R = OBz ; R' = Cl.
Momose *et al*. (1966).[4]
5 R = OBz ; R' = OAc.
6 R = OAc ; R' = OH.

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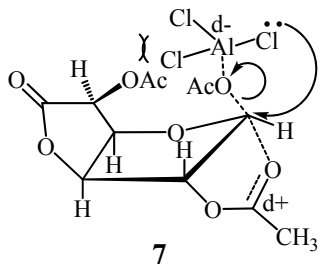
However, the results were often contested and the final compounds were not always identified, due to the lack of method of analysis.

RESULTS AND DISCUSSION

We have carried out the halogenation of the glucurono-6,3-lactone using aluminium chloride as chlorinating agent. Treatement of derivative **3** with aluminium chloride in methylene chloride or chloroform gave an anomeric α/β-ratio (1/4) of compound **6,** free on the anomeric position and the unreacted starting material **3.** However, the treatment of the benzoyl derivative **5** with aluminium chloride gave the β-anomer in quantitative yield. It seems that the protecting groups are involved in the reaction with $AlCl_3$. The free orbital of aluminium coordinates with the anomeric oxygen, involving the transfer of the acetoxy group on the aluminium, leading to the complex **7** (Scheme 1).



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Scheme 1 – Complexation between aluminium chloride and the anomeric oxygen.

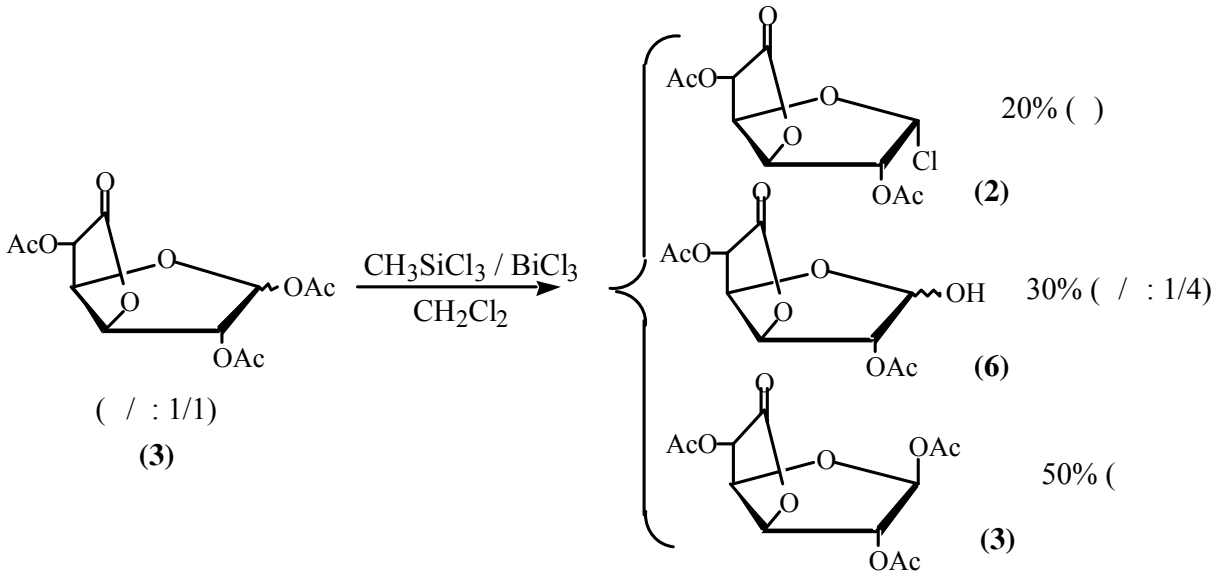
In the case of the triacetylated compound, the chloride derivative was not obtained, the folding of the lactone bridge impeding the transfer of the chlorine ion (Scheme 1). The two anomers of the benzoyl compound **5** have shown a reactivity toward aluminium chloride. In the case of the α-anomer, this result can be explained by the formation of an orthoester between the C-5 benzoate and the anomeric acetate. In the case of the β-anomer the orthoester was obtained with the C-2 benzoate.[7]

In this article, we describe a specific route for the synthesis of the α-glucofuranurono-6,3-lactone chloride derivative using a halogenation method for non primary alcohols. This method, which consists of using the couple methyltrichlorosilane/bismuth chloride, was introduced by Dubac *et al.*[8] and adapted by Montero *et al.*[9] for the halogenation of peracetylated sugars at the anomeric position.

Following the procedure described in these articles, three compounds were obtained starting from an anomeric α/β- ratio (1/1) of 1,2,5-tri-*O*-acetyl-D-glucofuranurono-6,3-lactone (scheme 2):

- 2, 5-di-*O*-acetyl-1-chloro-α-D-glucofuranurono-6,3-lactone **2** (yield : 20%)
- 2, 5-di-*O*-acetyl-α/β-D-glucofuranurono-6,3-lactone **6** (yield : 30%)
- 1, 2, 5-tri-*O*-acetyl-β-D-glucofuranurono-6,3-lactone **3** (yield : 50%)

Only the α-anomer of the triacetylated glucofuranuronolactone **3** reacted with the halogenating mixture of methyltrichlorosilane/bismuth chloride to give the α-chlorinated derivative **2** and compound **6,** deprotected on the anomeric position. Compound **6** under the same halogenating conditions gave no reaction.



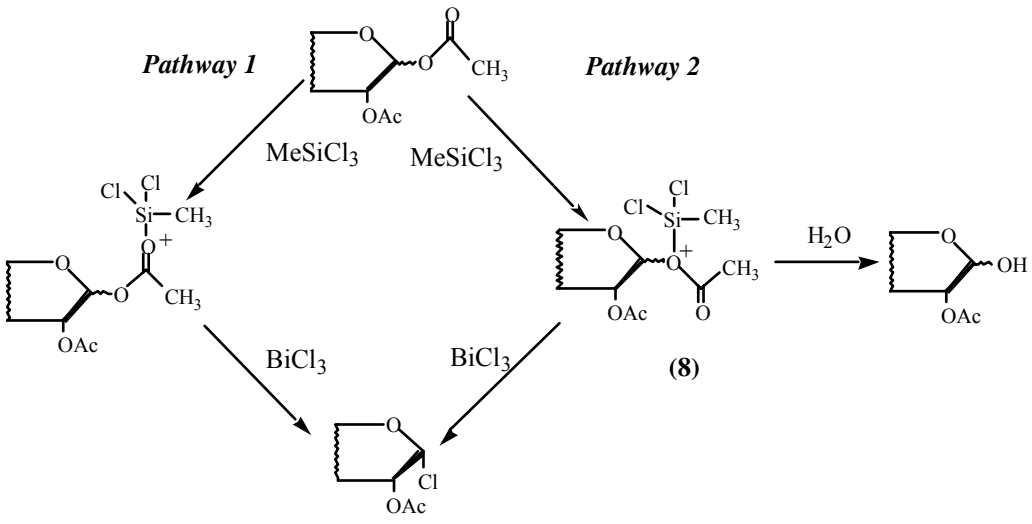
Scheme 2 – Compounds obtained by halogenation of the lactone using $SiMeCl_3/BiCl_3$.

Proton NMR data, with a coupling constant J_{H1-H2} of 4.4 Hz characteristic of a *cis*-orientation between protons H_1 and H_2 in furanose sugars, confirmed that only the α-anomer of the derivative **2** was synthesized during the halogenation. The melting point and the index of rotation of the compound were also determinated (see experimental section).

Then, the same halogenation method was applied using different protecting groups on the C-2 and C-5 hydroxyl. The anomeric mixture of 1-*O*-acetyl-2,5-di-*O*-benzoyl-glucofuranurono-6,3-lactone **5** was first prepared and then reacted with $SiCH_3Cl_3/BiCl_3$ in methylene chloride. After stirring for three hours at room temperature, the β-chloride derivative **4** was obtained in 46% yield. NMR spectrum of the mixture showed that the starting material which reacted was the β-acetylated anomer. The β-chloride derivative was obtained quantitatively when the chlorinating agent was aluminium chloride. The coupling constant J_{H1-H2}, almost equal to zero, proved the β-configuration of the chlorinated derivative.

It is evident that the protecting groups on the C-2 and C-5 of the lactone play a prominent part in the anomeric form of the halogenated compound.

A mechanism for the halogenation of acetylated sugars, in which the silicon from the halogenating agent has an affinity for the oxygen of the anomeric carbonyl acetate, has been proposed (pathway 1, scheme 3).[9] However, in our case, another mechanism has to be considered. The mechanism of halogenation by methyltrichlorosilane using bismuth chloride as catalytic agent that we propose is similar to the one proposed by Dubac.[8] It assumes that the silicon, which has a good affinity for the oxygen at the anomeric position, gives the intermediate **8.** Due to its instability, this compound, after being washed with water, gave the hydroxyl derivative. In the presence of $BiCl_4^-$ as chlorinating agent, the chlorinated derivative was obtained (pathway 2, scheme 3).



Scheme 3 – Mechanisms for the halogenation of the lactone.

With acetate as protecting group, the chlorinating agent has shown a selectivity toward the α-acetylated anomer to give selectively the α-chlorinated anomer. This selectivity was reversed when benzoate was used as protecting group. This difference in reactivity can be explained by the study of the Chem 3D representation of compounds **3** and **5.**[10]

In the case of derivative **3**, a folding of the lactone bridge was shown on the furanose sugars. This folding resulted from the endo position of the C-5 acetate. This conformation lead to a bigger steric hindrance for the β-anomer, and thus, the formation of the silylated derivative **8** was more difficult (Figure 1).

In reverse, for the derivative **5**, the C-5 benzoate bulky group adopts an exo conformation and separates the lactone bridge from the furanose cycle, which can explain the reactivity of the β-derivative (Figure 2).

In both case, the halogenated derivative was obtained in low yield. This could be explained by the voluminous size of the bismuth, the last compound stable of the periodical table. The bismuth cannot get close to the anomeric position and the displacement of the acetate group cannot take place.

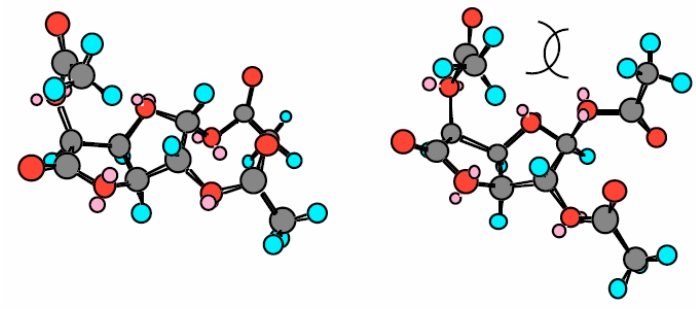


Fig. 1 – Chem 3D representation of the two anomers of the 1,2,5-tri-*O*-acetyl-D-glucofuranurono-6,3-lactone **3.**

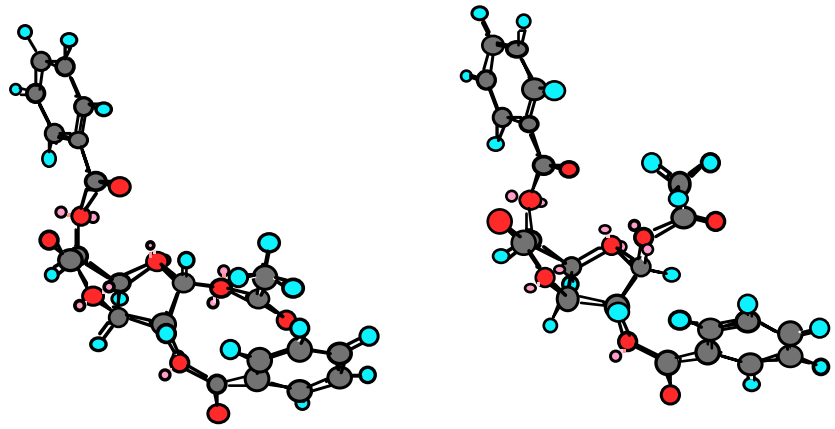


Fig. 2 – Chem 3D representation of the two anomers of the 1-*O*-acetyl-2,5-di-*O*-benzoyl-D-glucofuranurono-6,3-lactone **5.**

EXPERIMENTAL

Reactions were monitored by TLC using aluminium-coated plates with silica gel 60 F_{250} (Merck) and visualized by UV light (254 nm) and/or by charring with H2SO4 (aqueous 20% spray solution). Column chromatography was performed with Merck silica gel 60 H. ^{1}H and ^{13}C NMR spectra were recorded with a 400 MHz Bruker spectrometer. Chemical shifts are quoted in parts per million (ppm), referenced to the residual solvent peak. Mass spectra were measured with a JMS-DX 300 Jeol spectrometer in the FAB^{+} ion mode. Specific rotations were measured with sodium-D light at 20°C using a Perkin-Elmer spectrometer.

2,5-di-*O*-acetyl-1-chloro-α-glucofuranurono-6,3-lactone (2).

To a solution of **3** (0.5 g, 1.65 mmol) in 3 mL of methylene chloride under nitrogen was added 0.01 g of bismuth chloride (0.082 mmol) and 0.85 ml of methyltrichlorosilane(6.63 mmol). After stirring at room temperature for 24 h, 30 mL of methylene chloride were added and the organic layer was washed with a saturated aqueous $NaHCO_3$ solution then with water until neutral pH, dried and concentrated under reduced pressure. The α-anomer was obtained after chromatography on silica gel (AcOEt/hexane : 1/2) in 20% yield.
TLC: Rf = 0.7 (AcOEt/hexane : 1/1);
mp = 85-90°C;
$[\alpha]^{20}_{D}$ = + 136° (c = 0.5 g/100mL, $CHCl_3$);
^{1}H NMR ($CDCl_3$) δ = 6.49 (d, 1H, H_l, J_{H1-H2} = 4.4 Hz); 5.18 (dd, 1H, H_2, J_{H2-H1} = 4.4 Hz, J_{H2-H3} = 1.9 Hz); 5.07 (dd, 1H, H_3, J_{H3-H2} = 1.9 Hz, J_{H3-H4} = 4.5 Hz); 5.14 (dd, 1H, H_4, J_{H4-H3} = 4.5 Hz, J_{H4-H5} = 5.8 Hz); 5.47 (d, 1H, H_5, J_{H5-H4} = 5.8 Hz); 2.10 and 2.25 (2s, 6H, 2Ac).
^{13}C NMR ($CDC1_3$) δ = 94.0 (C1); 77.5 (C2); 81.5 (C3); 74.0 (C4); 66.5 (C5); 19.5 and 20.2 (CO**C**H_3); 168.5, 169.0, 170.0 (**C**O and **C**OCH_3);
MS (NBA ; FAB^{+}) m/z (%) : 279$[M+H]^{+}$; 243$[M-CI+H]^{+}$; 185$[M-CI-AcOH+H]^{+}$.

2,5-di-*O*-acetyl-glucofuranurono-6,3-lactone (6) was also separated from above mixture (30% yield)**:**
β-anomer : mp = 128-130 °C; $[\alpha]^{20}_{D}$ =+70° (c = 0.43 g/100 mL ; MeOH); ^{1}H NMR (DMSO/D_2O, 400 MHz) δ = 5.30 (s, 1H, H_1); 5.50 (d, 1H, H_5, J_{H4-H5} = 6.6 Hz); 5.15 (m, 1H, H_2); 2.10 and 2.25 (2s, 6H, 2 Ac); ^{13} C NMR (DMSO/D_2O, 400 MHz) δ = 168.6, 169.2, 170.0 (**C**O and **C**OCH_3); 99.4 (Cl); 82.0 (C2); 74.2 (C3); 77.5 (C4); 66.39 (C5); 18.4 and 19.1 (CO**C**H3).
α-anomer : ^{1}H NMR (DMSO/D_2O, 400 MHz) δ = 5.51 (d, 1H, H_l; J_{H1-H2} = 4.2 Hz); 5.20 (dd, 1H, H_2, J_{H2-H1} = 4.2

Hz , J_{H2-H3} = 2.7 Hz); 4.81-5.02 (m, 2H, H_3, H_4); 5.15 (d, 1H, H_5, J_{H4-H5} = 5.1 Hz); 2.10 and 2.25 (2s, 6H, 2Ac); ^{13}C NMR (DMSO/D2O, 400 MHz) δ = 168.5, 169.2, 170.0 (**C**O and **C**OCH_3); 95.05 (Cl); 85.3 (C3); 74.1 (C2); 71.9 (C4); 66.4 (C5); 18.05 and 19.65 (CO**C**H_3).

2,5-di-*O*-benzoyl-1-chloro-β-glucofuranurono-6,3-lactone (**4**)

Method 1: Chlorination using $AlCl_3$

To a solution of **5** (0.7 g, 1.64 mmol) in 5 mL of methylene chloride was added 0.22 g of aluminium chloride (1.64 mmol). After stirring at room temperature for 3 h, a saturated aqueous $NaHCO_3$ solution was added and the aqueous phase was extracted 3 times with 15 mL of methylene chloride. The organic layer was washed with water until neutral pH, dried and concentrated under reduced pressure. Compound **4** was obtained quantitatively as a yellow powder.

Method 2: Chlorination using $BiCl_3$.

To a solution of **5** (0.2 g, 0.47 mmol) in 1 mL of methylene chloride was added 0.22 g of bismuth chloride (1.64 mmol) and 30 mL of methyltrichlorosilane (1.88 mmol). After stirring at room temperature for 24 h, 10 mL of a saturated aqueous $NaHCO_3$ solution was added and the aqueous phase was extracted 3 times with 15 mL of methylene chloride. The organic layer was washed with an aqueous solution of HCl 0.5 N then with water until neutral pH, dried and concentrated under reduced pressure. Compound **4** was obtained in 46 % yield.

TLC : Rf = 0.55 (CH_2Cl_2);
mp = 132-135 °C;
$[\alpha]^{20}_D$ = +48° (c = 0.83 g/100 mL; $CHCl_3$);
^1H NMR ($CDC1_3$) δ = 6.25 (d, 1H, H_1, J_{H1-H2} = 0.7 Hz); 5.03 (dd, 1H, H_2, J_{H2-H1} = 0.7 Hz, J_{H2-H3} = 4.4 Hz) ; 5.01-5.15 (m, 2H, H_3, H_4) ; 5.91 (s, 1H, H_5) ; 7.45-8.25 (m, 10H, Hϕ); ^{13}C NMR ($CDC1_3$) δ = 96.1 (C1); 78.0 (C2); 84.3 (C3); 84.2 (C4); 71.4 (C5);
MS (GT; FAB^+) m/z (%): 405 $[M+H]^+$; 427 $[M+Na]^+$; 370 $[M-Cl+H]^+$.

CONCLUSIONS

In conclusion, we have shown that the α-selectivity for the halogenation of the peracetylated glucurono-6,3-lactone can be obtained using methyltrichlorosilane and bismuth chloride. These reagents are known to be efficient for the halogenation of the anomeric position of peracetylated sugars. In our case we have shown selectivity for the α-anomeric form but the modest yields obtained can be explained by the conformation of the lactone. It is possible that, for the same reason, the α-anomer **2** could not be obtained by treatement of the lactone with aluminium chloride.

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