A Practical Large-Scale Access to 1,6-Anhydro-β-D-hexopyranoses by a Solid-Supported Solvent-Free Microwave-Assisted Procedure

Vincent Bailliez, Renata M. de Figueiredo, Alain Olesker, Jeannine Cleophax*

Institut de Chimie des Substances Naturelles du C.N.R.S, Avenue de la Terrasse, 91198 Gif-sur-Yvette, France
Fax +33(1)69077247; E-mail: Jeannine.Cleophax@icsn.cnrs-gif.fr

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Abstract: Microwave irradiation of 6-*O*-tosyl or 2,6-di-*O*-tosyl peracetylated hexopyranoses absorbed on basic alumina in a dry medium afforded the corresponding 1,6-anhydro-β-D-hexopyranoses. A direct access to 1,6:3,4-dianhydro-β-D-altropyranose (**16**) from D-glucose is also described.

Key words: anhydrosugars, solid support synthesis, solvent-free reactions, microwave activation, ring closure

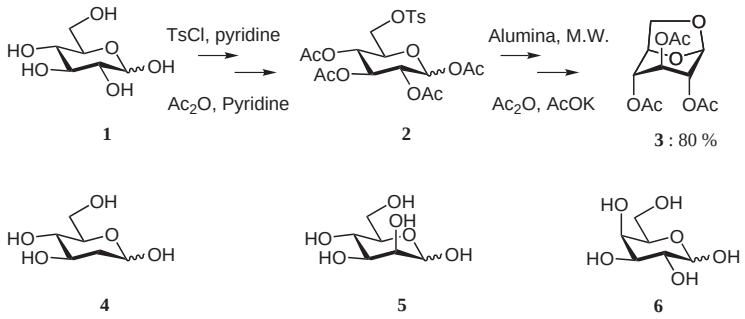
Among the carbohydrate derivatives, 1,6-anhydro-β-D-glycopyranoses are valuable intermediates in the synthesis of a large variety of biologically important natural products and their analogues.[1] They have been known since a long time,[2] especially the 1,6-anhydro-β-D-glucopyranose (levoglucosan), and used as synthons in the preparation of rare sugars,[3] diverse non-carbohydrate products,[4] and complex oligosaccharides.[5] Their bicyclic framework involves a $^1C_4$ locked conformation of the pyranose ring, where the 2,3,4-stereocentres are in opposite orientation with respect to the corresponding classical pyranosides. The reactivity (stereo- and regioselectivity) of the different sites of the sugar is therefore modified and this has been widely exploited, in particular by Cerny et al.[6] These derivatives have been obtained by two main pathways: 1) pyrolysis under vacuum or recently, using microwave irradiation of polysaccharides as starches and celluloses;[2b,7] and 2) by intramolecular cyclization of glycopyranoses with a good leaving group at either the primary[8] or the anomeric[9] position, or by treatment of protected glucopyranoses with various Lewis acids.[10]

In the synthesis of 1,6-anhydrosugars from monosaccharides, 6-*O*-sulfonylated pyranoses were used most often as starting materials. In spite of improvements accomplished in recent years by the work of Fraser-Reid,[8e] Nagarajan,[10d] and Descotes,[8d] a ready access to these 1,6-anhydrosugars is still of considerable interest.

In this paper, a mild, rapid, and solvent-free procedure for the preparation of 1,6-anhydro-β-D-hexopyranoses from mono- and ditosylates of D-pyranoses, absorbed on basic alumina, is described by classical thermal reaction (heating in an oil-bath) or irradiation under microwave.

In the literature, hydrolysis of various aliphatic and aromatic esters absorbed on neutral alumina, under microwave irradiation, has already been described.[11] The tertiary esters are, in general, more easily hydrolyzed than the secondary or primary esters, whereas for methyl 2,3,4,6-tetra-*O*-pivaloyl-α-D-glucopyranoside, only the 6 position was deprotected and no reaction was observed under classical heating. In the cases of peracetylated alkyl glycopyranosides absorbed on alumina, deacetylation did not occur, even by microwave irradiation.[11c]

We anticipated that on the acetyl 6-*O*-tosyl-2,3,4-tri-*O*-acetyl-α/β-D-glucopyranose (**2**), the most labile anomeric acetate could be probably more easily removed, followed by a ready 1,6-oxirane formation. And when **2**, readily prepared by selective tosylation at C-6 of D-glucose (**1**) followed by peracetylation,[12] was absorbed on various alumina and heated, in dry media by microwave irradiation, 1,6-anhydro-2,3,4-tri-*O*-acetyl-β-D-glucose (**3**)[8d,9c] was formed with a small amount of partially random deacetylated levoglucosan. Our hypothesis was confirmed since, in spite of some non-selective partial deacylation, no 3,6-anhydroglucopyranose derivatives were



Scheme 1

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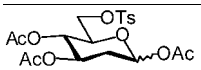
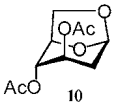
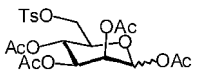
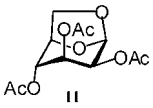
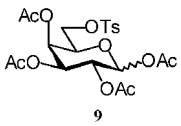
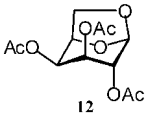
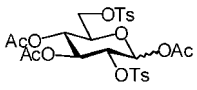
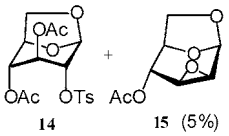
detected. The crude mixture was then eluted and reacetylated giving the 2,3,4-tri-*O*-acetyl-1,6-anhydro-β-D-glucopyranose (**3**) (Scheme 1).

With basic alumina (ICN, Brockmann Act. II–III), a good conversion (94%) was obtained by irradiation of **2** (absorbed on alumina, 1.5 g/1 g of **2**) under microwaves with a low power (300 W) at 110 °C over 7 minutes. After elution of the crude material and peracetylation of the mixture, the 2,3,4-tri-*O*-acetyllevoglucosan (**3**) was isolated by crystallization (70% for 1 to 3 g of starting material, 80% for 6 g). On a 1 to 6 g scale, the same process (same temperature, same time) using oil-bath heating gave nearly the same results (80% for 1 g, 85% for 6 g). As has been already observed, under microwave irradiation,[13] the method has been successfully extended up to a 38 g scale, always in 7 minutes, without loss of efficiency (85% yield).

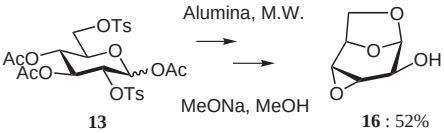
Our method has been applied to other hexoses as well: 2-deoxy-D-glucose (**4**), D-mannose (**5**), and D-galactose (**6**). The acetyl 2-deoxy-3,4-di-*O*-acetyl-6-*O*-tosyl-α/β-D-glucopyranose (**7**),[14] the acetyl 2,3,4-tri-*O*-acetyl-6-*O*-tosyl-α/β-D-mannopyranose (**8**)[8b] and the galactose derivative **9**[8d,15] were readily prepared in few steps by known procedures. They were converted to the corresponding 1,6-anhydro-β-D-derivatives **10**,[16] **11**,[8d] and **12**[8d] under the same conditions (Table 1). The relatively low yield of the 2-deoxy derivative **10** may be explained by the instability of that series.

Table 1 1,6-Anhydrosugars Prepared

Starting Material	Product	Yield (%)
 **7**	 **10**	45
 **8**	 **11**	64
 **9**	 **12**	86
 **13**	 **14** **15** (5%)	60

In the same way, irradiation of the acetyl 3,4-di-*O*-acetyl-2,6-di-*O*-tosyl-α/β-D-glucopyranose (**13**),[12b] absorbed on alumina with microwaves followed by reacetylation afforded the 3,4-di-*O*-acetyl-1,6-anhydro-2-*O*-tosyl-β-D-glucopyranose (**14**) in 60% yield with a low (about 5%) proportion of the 1,6:2,3-dianhydro-4-*O*-acetyl-β-D-mannopyranose (**15**). Cerny and co-workers[9b,17] have shown that from **14**, according to experimental conditions, the 1,6:2,3-dianhydro-β-D-mannopyranose and the more stable 1,6:3,4-dianhydro-β-D-altropyranose (**16**) could be formed selectively. These two derivatives have been largely used in the synthesis of aminodeoxy sugars.[5d,18]

With the objective of the selective preparation of the altro-epoxide **16**, we have modified the workup after irradiation. The crude eluted mixture was treated with NaOMe in MeOH–CH_2Cl_2 solution, giving exclusively **16** (52% from **13**) (Scheme 2) in 4 steps from D-glucose (**1**).



Scheme 2

In conclusion, we have developed an easy solvent-free procedure, under microwave irradiation, for the preparation of important 1,6-anhydroglycopyranose synthons in three or four steps from hexopyranoses. This method using a tosylate absorbed on alumina is simple, rapid, and inexpensive and can be extended to a large-scale.

1,6-Anhydrosugars 3, 10–12; General Procedure

To the corresponding tosylate **2**, **7**, **8**, or **9** dissolved in CH_2Cl_2 (10 mL for 10 mmol), was added basic alumina (ICN, Brockmann Act. II–III, 15 g for 1 g of tosylate). After evaporation under vacuum, the resulting powder was dried under 0.1 mm Hg and transferred to the reactor. This powder was irradiated under microwave (P 300 W, t = 7 min, T = max 110 °C), and the reaction mixture was eluted through a pad of Celite with a mixture of EtOAc–EtOH (9:1). The residue, after evaporation, was peracetylated with Ac_2O (10 equiv) and KOAc (1.1 equiv) for 15–20 min at 100 °C. The mixture was diluted with ice-water and extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and concentrated to dryness. The residue was recrystallized to furnish the corresponding per-*O*-acetyl-1,6-anhydro-β-D-glycopyranoses **3**, **10**, **11** or **12**, respectively. ^{1}H NMR spectra recorded were identical with those described in precedent syntheses. ^{13}C NMR spectra have been reported by Perlin and collaborators,[19] except for **10**.

2,3,4-Tri-*O*-acetyl-1,6-anhydro-β-D-glucopyranose (3)

Mp 107–109 °C (EtOH); $[\alpha]_D$ –60.0 (*c* = 1, $CHCl_3$) {Lit.[8d] mp 108–109 °C (EtOH); $[\alpha]_D$ –62.0 (*c* = 1, $CHCl_3$)}.

3,4-Di-*O*-acetyl-1,6-anhydro-2-deoxy-β-D-arabinohexopyranose (10)

$[\alpha]_D$ –109.0 (*c* = 1, $CHCl_3$) {Lit.[16] $[\alpha]_D$ –122.0 (*c* = 1.26, $CHCl_3$)}.

^{13}C NMR ($CDCl_3$): δ = 170.2 (2 CH_3CO), 99.7 (C-1), 73.3 (C-5), 70.8 (C-4), 67.2 (C-3), 64.8 (C-6), 33.1 (C-2), 21.1–20.9 (2 CH_3CO).

2,3,4-Tri-*O*-acetyl-1,6-anhydro-β-D-mannopyranose (11)

Mp 88–90 °C (EtOH); $[\alpha]_D$ –123.0 (*c* = 1.2, $CHCl_3$) {Lit.[8d] mp 89–90 °C (EtOH); $[\alpha]_D$ –123.5 (*c* = 1, $CHCl_3$)}.

2,3,4-Tri-*O*-acetyl-1,6-anhydro-β-D-galactopyranose (12)

Mp 77–79 °C (EtOH–Et_2O); $[\alpha]_D$ –5.0 (*c* = 1, $CHCl_3$) {Lit.[8d] mp 77–78 °C (EtOH–Et_2O); $[\alpha]_D$ –4.3 (*c* = 1, $CHCl_3$)}.

1,6:2,3- or 1,6:3,4-Dianhydrosugars 15 and 16; General Procedure

Isolation of 3,4-Di-O-acetyl-1,6-anhydro-2-*O*-tosyl-β-D-glycopyranose (**14**) and 4-*O*-Acetyl-1,6:2,3-dianhydro-β-D-mannopyranose (**15**):

To the ditosylate **13** dissolved in CH_2Cl_2 (10 mL for 10 mmol) was added basic alumina (ICN, Brockmann Act. II–III, 15 g for 1 g of **13**). After evaporation and drying under high vacuum (1 mm Hg), the powder was transferred to the reactor and irradiatedfor 6 min under microwaves (P 300 W, T = max 110 °C). The mixture was eluted through a pad of Celite with a mixture of EtOAc–EtOH (9:1) and concentrated to dryness. The residue was peracetylated with Ac_2O (10 equiv) and KOAc (1.1 equiv) for 15–20 min at 100 °C. After extraction and separation of the reaction product on silica gel, the derivatives **14** and **15** were identified by comparison of their ^1H and ^{13}C NMR spectra[20] (except the ^{13}C NMR spectrum of **14**, which is given below).

14

Mp 115–116 °C (EtOH); $[\alpha]_D$ –43.0 (*c* = 1, $CHCl_3$) {Lit.[17b] mp 116–117 °C (EtOH); $[\alpha]_D$ –44.0 (*c* = 1.5, $CHCl_3$)}.

^{13}C NMR ($CDCl_3$): δ = 170.1–168.6 (2 CH_3CO), 133.2–128.0 (4-$CH_3C_6H_4SO_2$), 99.6 (C-1), 74.7, 73.9 (C-2, C-5), 70.4 (C-4), 69.3 (C-3), 65.8 (C-6), 21.7 (4-$CH_3C_6H_4SO_2$), 20.9–20.7 (2 CH_3CO).

1,6:3,4-Dianhydro-β-D-altropyranose (**16**)

The residue from the above reaction workup was dissolved in CH_2Cl_2 (8 mL). To this solution was gradually added a solution of NaOMe (80 mg) in absolute MeOH (8 mL). After stirring for 12 h, the solution was diluted with CH_2Cl_2 (80 mL), filtered through a pad of silica gel and eluted with CH_2Cl_2–MeOH (9:1). The filtrate was concentrated under vacuum and the derivative **16** was isolated by crystallization (yield: 62% from **13**) and identified by its ^1H and ^{13}C NMR spectra.[20] By the same procedure, but with classical heating, the yield was 55%.

16

Mp 160–162 °C (EtOH); $[\alpha]_D$ –118.0 (*c* = 1.1, $CHCl_3$) {Lit.[17b] mp 160–162 °C; $[\alpha]_D$ –120.0 (*c* = 0.6, MeOH).

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