Tetrahedron Vol. 46, No. 1, pp. 59-64, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

2-TRIMETHYLSILYLETHYL GLYCOSIDES. TREATMENT WITH ELECTROPHILIC REAGENTS TO GIVE TRIMETHYLSILYL- AND METHOXYMETHYL GLUCOPYRANOSIDES AND GLUCOPYRANOSYL CHLORIDE

*Karl Jansson and Göran Magnusson**
Organic Chemistry 2, Chemical Center, The Lund Institute of Technology
P.O. Box 124, S-221 00 Lund, Sweden

(*Received in Canada* 29 *March* 1989)

Abstract: Treatment of 2-trimethylsilylethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**1**) with trimethylsilyl trifluoromethanesulfonate, trifluoromethanesulfonic acid, or borontrifluoride etherate in the presence of dimethoxymethane gave methoxymethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside in 54, 62, and 66% yield, respectively. In the absence of dimethoxymethane, trimethylsilyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside was formed in 78% yield. Treatment of **1** with 1,1-dichloromethylmethyl ether in the presence of zinc chloride gave 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl chloride in 98% yield.

Introduction.

The stereospecific synthesis of β glucopyranosides is in most cases based on the intermediacy of a 1,2-acyloxonium ion that directs the attack of a nucleophilic alcohol moiety to the β side of the pyranosidic ring. The anomeric oxygen of the product emanates therefore from the attacking alcohol. A little explored alternative is to alkylate the anomeric oxygen of a β glucopyranoside and let the intermediate oxonium ion collapse into a new glucoside with retainment of the original anomeric oxygen atom in its original configuration.

We now report that 2-trimethylsilylethyl (TMSET) 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside[1,2] (**1**) may be transformed into the corresponding trimethylsilyl and methoxymethyl[3] glucosides **2** and **5** with conservation of the anomeric stereostructure. Furthermore, **1** was found to undergo quantitative transformation at room temperature to the corresponding α-glucopyranosyl chloride[4] **6**. These reactions are all based on the pronounced ability of the anomeric oxygen of TMSET glycosides to react with electrophilic reagents. This is in contrast to methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside which did not give **2** and **5** under similar reaction conditions[5] and that gave **6** in lower yield by prolonged heating of the reaction mixture[6,7].

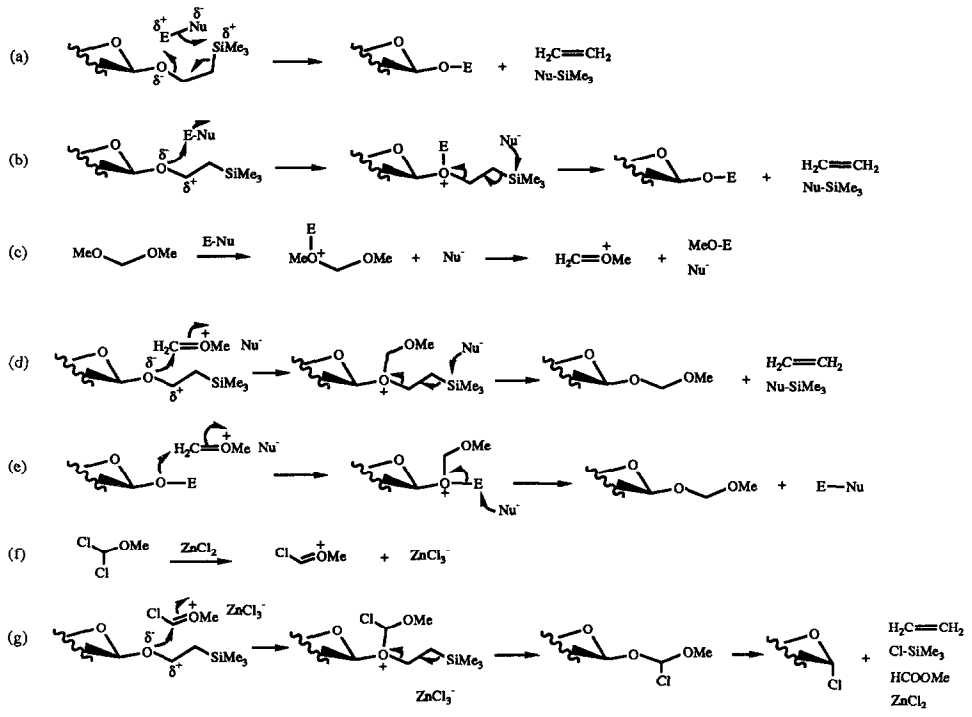
It was recently demonstrated[1] that a range of mono—tetrasaccharidic 2-trimethylsilylethyl (TMSET) glycosides are suitable anomerically protected derivatives for glycoside synthesis and that they can be transformed in one high-yielding step either into the corresponding 1-*O*-acyl sugars (with conservation of the anomeric configuration) or into hemiacetals.

Results and Discussion.

The anomeric oxygen of TMSET glycosides carries an increased electron density as a result of the ability of silicon to stabilize a positive charge on a carbon in the β-position[8] (the β-effect). TMSET glycosides therefore react rapidly with many electrophilic reagents[1] (E-Nu, Scheme 1). The reaction may proceed either by a concerted (path a) or a step-wise (path b) route. The intermediate oxonium ion of path b is expected to be short-lived because the positive charge β to the silicon-carbon bond makes the silicon prone to nucleophilic attack (even by weak nucleophiles such as trifluoromethanesulfonate anion as in the preparation of **2**; see Experimental) with concomitant fragmentation into the Sugar-O-E product. It is at present not possible to discern which of the routes that predominates.

TMSET glycosides fragment as discussed above, by concomitant expulsion of ethylene gas, which effectively drives the reaction towards completion. This high reactivity contrasts that of methyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside, which was inert under similar reaction conditions[5].

Mixed acetal glycosides are well known in the form of trehaloses. In addition, synthetic derivatives have been

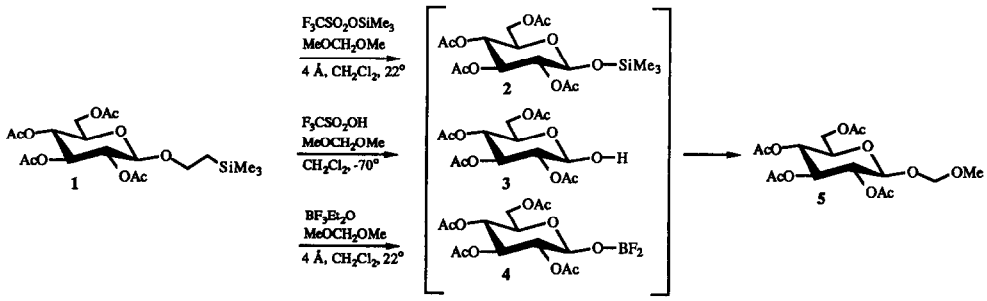


Scheme 1

reported: deBelder et al.[9] prepared tetrahydropyranyl glycosides and Dettinger et al.[10] reported the synthesis of 1-ethoxyethyl β/α glycosides from the corresponding hemiacetal sugars. Recently, Tietze et al.[3] prepared a series of 1-alkoxyalkyl β glycosides in connection with the development of new types of cytostatic anticancer agents. They used trimethylsilyl trifluoromethanesulfonate (TMS-triflate) at -70° for the synthesis of methoxymethyl glycosides from the corresponding trimethylsilyl glycosides (e.g. **2**; prepared by silylation of hemiacetals with trimethylsilyl chloride and separation of the anomeric mixture by crystallisation).

We now report our investigations of the reaction of trimethylsilylethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**1**) with TMS-triflate, triflic acid, and borontrifluoride etherate, respectively in the presence and absence of dimethoxymethane. (Scheme 2). The methoxymethyl glucoside **5** was the main product when the reaction was conducted in the presence of dimethoxymethane (cf. Experimental). Treatment of **1** with TMS-triflate/molecular sieve in the absence of dimethoxymethane permitted the isolation of the TMS glucoside **2** as the pure β anomer in 78% yield, albeit by a rather cumbersome procedure (cf. Experimental). It was earlier shown that treatment of TMSET glycosides with proton acids gave high yields of the corresponding hemiacetal sugars (e.g. **3**) as a mixture of anomers[1]. Furthermore, TMSET glycosides react with borontrifluoride etherate in solvents of low basicity to produce a new type of carbohydrate derivatives (e.g. **4**) carrying an anomeric OBF_2 (or related) substituent[1]. In summary, treating **1** under reaction conditions similar to those shown in Scheme 2, but omitting the dimethoxymethane, resulted in the formation of **2**, **3**, and **4** which are possible intermediates in the transformation of **1** into **5** (Scheme 2). Compounds **2**, **3**, and **4** correspond to the sugar-O-E derivative shown in Scheme 1.

In an attempt to show the intermediacy of **3** (as the β anomer) in the transformation of **1** into **5**, **1** was treated with triflic acid at -70° for several hours, followed by addition of acetyl bromide/pyridine in order to trap **3** as its acetate. However, only a small amount (ca 2% yield) of a β/α mixture of glucose pentaacetate was formed. Treatment of β-glucose pentaacetate under similar conditions did not cause anomerization. Most probably, anomerization occurred before the addition of acetyl bromide. If **3** is an intermediate *en route* to **5**, it must react rapidly with the methylenoxymethyl cation (Scheme 1, path c and e) to avoid anomerization. In a separate experiment, a β/α

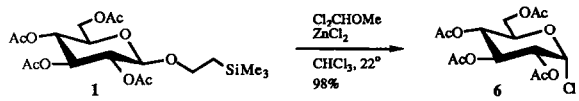


Scheme 2

mixture of **3** was treated with TMS triflate/dimethoxymethane/molecular sieve in dichloromethane at room temperature, which rapidly gave a β/α mixture of **5**. For reasons stated above, it was not possible to decide whether the formation of **5** proceeded directly *via* reaction of the TMSET glycoside with methylenoxymethyl cation (Scheme 1, path d) or if intermediate sugar-O-E derivatives were also involved (path e).

When the molecular sieve was omitted, **5** was formed as a β/α mixture. The reaction may proceed, at least partly, via the TMS glycoside **2**, which was isolated from the reaction mixture in low yield. If dimethoxymethane was omitted, **2** was produced in 78% yield.

Treatment of **1** with triflic acid/dimethoxymethane in dichloromethane at -70° gave **5** in 62% yield. The reaction may proceed, at least partly, via the hemiacetal sugar **3**,



Scheme 3

A similar electrophilic species (chloromethylenoxymethyl cation) was generated by treatment of 1,1-dichloromethyl methyl ether with zinc chloride (Scheme 1, path f). Further reaction with **1** gave the corresponding α chloro sugar **6**. Zinc chloride is not reactive enough to cause the formation of a Sugar-O-E species according to path a or b[1]. Therefore, direct attack of the chloromethylenoxymethyl cation on **1** is plausible, leading to the 1-chloro-1-methoxymethyl glycoside according to path g. The break-down of the latter would occur either by direct chloride ion attack from the α side or via participation of a 2-acetoxy group, thus generating an acetoxonium ion which reacts with chloride ion to give the thermodynamically unstable β-chloro sugar. The latter would equilibrate in the presence of chloride ion to give the α-chloro sugar. With methyl glycosides, a direct reaction with a chloromethylenoxymethyl cation was suggested[6].

Summary of reactions.

Treatment of **1** with TMS triflate/dimethoxymethane/molecular sieve in dichloromethane at room temperature produced, after chromatography, methoxymethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**5**) in 54% yield. which was formed as a byproduct. It could be obtained in virtually quantitative yield by treatment of **1** with proton acids[1]. Furthermore, treatment of a β/α mixture (ca 1:4) of **3** with TMS triflate/dimethoxymethane/molecular sieve in dichloromethane at room temperature rapidly gave a β/α mixture (ca 1:4) of **5**.

Treatment of **1** with borontrifluoride etherate/dimethoxymethane/molecular sieve at room temperature gave **5** in 66% yield. When the molecular sieve was omitted, a β/α mixture (6:4) of **5** was obtained. The reaction probably proceeded mainly according to path d (Scheme 1). However, the intermediacy of **4** can not be ruled out even if it is expected to have a low reactivity towards the methylenoxymethyl cation.

Treatment of **1** with 1,1-dichloromethyl methyl ether/zinc chloride in chloroform at room temperature gave, after chromatography, 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl chloride (**6**) in 98% yield (Scheme 3). The reaction probably proceeded via direct attack of chloromethylenoxymethyl cation on **1** as suggested for methyl glycosides. With the latter, the reaction requires prolonged heating to go to completion and the yields were lower[5,6,7] than with **1**.

Experimental section

General. Borontrifluoride etherate (BF_3Et_2O), trimethylsilyl trifluoromethanesulfonate (TMS triflate), and trifluoromethanesulfonic acid (triflic acid) were distilled and kept in sealed ampoules before use. The molecular sieve (Union Carbide, 4Å, pellets, 1.6 mm) was crushed in a mortar and flame-dried in a test tube until no more water condensed on the tube wall. The dried material should contain a small amount of fine powder, which helped to avoid side-reactions. Too much of powdered material seems to retard the reactions. Gas chromatographic analysis was performed with a 9.7 m polyphenylmethylsiloxane (50%) RSL-300 capillary column. Thin layer chromatography was performed on Kieselgel 60 F_{254} (Merck) and bands were detected by charring with 50% sulphuric acid. Compounds **2**, **3**, and **6** were detected as brown spots by heating before treatment with sulphuric acid[11]. Column chromatography was performed with Kieselgel 60 (Merck, 230-400 mesh). Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ with $CHCl_3$ as internal standard (δ 7.26 ppm) using a Varian XL 300 instrument. Optical rotations were measured with a Perkin-Elmer 141 polarimeter.

Trimethylsilyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (2). Crystalline trimethylsilylethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside[1] (**1**, 449 mg, 1 mmol) and molecular sieve (4Å, 3 g, crushed and flame-dried) were charged into a 25 mL round-bottom flask containing a magnetic stirring bar. The flask was evacuated and then filled with nitrogen. Dichloromethane (10 mL; dried by passage through alumina) was added and the mixture was stirred rapidly for 2 h. Trimethylsilyl trifluoromethanesulfonate (TMS triflate, 150 μL, 0.8 mmol) was added through a rubber septum with a syringe. The stirring was slowed down after 10 min in order to minimize the formation of finely powdered molecular sieve. A second aliquot of TMS triflate (150 μL) was added after 15 h and the mixture was stirred until the reaction was complete according to gas chromatography (23 h). The flask was cooled with ice and ethyldiisopropylamine (309 μL, 1.76 mmol), methanol (74 μL, 1.76 mmol) and isopropyl ether (3 mL) were added in order to destroy remaining TMS triflate and the mixture was allowed to attain room temperature. [The methanol addition was omitted in a separate experiment which led to the formation of trimethylsilyl 2,3,4-tri-*O*-acetyl-6-*O*-trimethylsilylacetyl-β-D-glucopyranoside (**7**, 19%).] The mixture was carefully concentrated until ca 1 mL of the solvent remained, dry Celite (ca 1.5 g) was added, followed by dry ether (10 mL) and the mixture was stirred for 10 min, then filtered through a dry column (13x4 cm) containing a 1 cm layer of sodium sulfate into a 100 mL flask filled with nitrogen. The filtrum was eluted with dry ether (30 mL) and the combined ethereal filtrate was concentrated to a volume of ca 10 mL and filtered. The solvent was removed to give crude **2** (446 mg, β/α: 94/6) containing ca 1% each of **1** and **7**. The crude material was dissolved in ether (5 mL) and hexane (6 mL) was added. The volume was reduced to ca 5 mL. When crystals started to form, the mixture was kept at -8° for 48 h. Filtration left pure **2** (330 mg, 78%), m.p. 102-103°, $[\alpha]_D^{22}$ -7° (*c* 1, chloroform) [Lit.[3]: m.p. 105°, $[\alpha]_D^{20}$, -6.8° (*c* 1, chloroform)]. ^{1}H-NMR δ 5.19 (t, 1 H, J 9.5 Hz, H-3), 5.05 (t, 1 H, J 9.8 Hz, H-4), 4.91, (dd, 1 H, J 9.6, 7.7 Hz, H-2), 4.74 (d, 1 H, J 7.7 Hz, H-1), 4.21, 4.12 (dABq, 1 H each, J 12.1, 5.5, 2.6 Hz, H-6), 3.71 (ddd, 1 H, J 9.9, 5.5, 2.6 Hz, H-5), 2.07, 2.03, 2.02, 2.00 (s, 3 H each, OAc), 0.16 (s, 9 H, $SiMe_3$).

Trimethylsilyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside (in crude **2**) had ^{1}H-NMR δ 5.49 (t, 1 H, J 9.8 Hz, H-3), 5.38 (d, 1 H, J 3.4 Hz, H-1), 5.04 (t, 1 H, J 10.2 Hz, H-4), 4.81 (dd, 1 H, J 10.1, 3.4 Hz, H-2), 4.26, 4.05 (dABq 1 H each, J 12.1, 4.7, 2.2 Hz, H-6), 4.15 (m, 1 H, H-5), 2.08, 2.05, 2.03, 2.01 (s, 3 H each, OAc), 0.16 (s, 9 H, $SiMe_3$).

Compound **7** had: m.p. 96-97° (ether/hexane), $[\alpha]_D^{20}$, +4° (*c* 1, chloroform)]. ^{1}H-NMR δ 5.18 (t, 1 H, J 9.6 Hz, H-3), 5.02 (t, 1 H, J 9.9 Hz, H-4), 4.90, (dd, 1 H, J 9.6, 7.6 Hz, H-2), 4.74 (d, 1 H, J 7.7 Hz, H-1), 4.21, 4.03 (dABq, 1 H each, J 12.2, 5.7, 2.4 Hz, H-6), 3.68 (ddd, 1 H, J 10.0, 5.7, 2.4 Hz, H-5), 2.03, 2.02, 1.99 (s, 3 H each, OAc), 1.91, 1.92 (ABq, 2 H, J 11.6 Hz, $SiCH_2COO$), 0.15, 0.12 (s, 9 H each, $SiMe_3$).

Methoxymethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (5).

(a) Crystalline trimethylsilylethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside[1] (**1**, 135 mg, 0.3 mmol) and molecular sieve (4Å, 0.9 g, crushed and flame-dried) were charged into a 10 mL round-bottom flask containing a magnetic stirring bar. The flask was evacuated and then filled with nitrogen. Dichloromethane (3 mL, dried by passage through alumina) was added and the mixture was stirred for 1 h at room temperature. Dimethoxymethane (82 μL, 0.9 mmol) and then TMS-triflate (62 μL, 0.33 mmol) were added with a syringe to the rapidly stirred reaction mixture. The stirring was slowed down after 10 min in order to minimize the formation of finely powdered molecular sieve. The reaction was monitored by TLC (SiO_2, ethyl acetate/hexane 2:3). After 41 h, the mixture was cooled in an ice-bath and

ethyldiisopropylamine (64 μL, 0.36 mmol) was added, followed by methanol (16 μL, 0.36 mmol) and isopropyl ether (1 mL). The mixture was allowed to attain room temperature. Dry Celite (ca 0.5 g) was added and the mixture was filtered. The filtrum was washed with dichloromethane/ethyl acetate (20 mL, 20:1) and the combined filtrate was washed with water, saturated aqueous sodium hydrogencarbonate and water, dried (sodium sulfate) and concentrated. The residue was chromatographed (SiO_2, ethyl acetate/heptane 1:1) to give **2** (7 mg, m.p. 101-102°) and **5** (63 mg, 54%) as the β anomers. Recrystallisation from ether/hexane gave pure **5** (50 mg, 42%) with m.p. 96-97°; $[\alpha]_D^{22}$, -85° (*c* 1.5, chloroform) [Lit.[3]: m.p. 96° (ether), $[\alpha]_D^{20}$, -91° (*c* 1, chloroform)]. ^{1}H-NMR δ 5.25 (t, 1 H, J 9.2 Hz, H-3), 5.12 (t, 1 H, J 9.2 Hz, H-4), 5.06, (dd, 1 H, J 9.2, 8.0 Hz, H-2), 4.80 (d, 1 H, J 8.0 Hz, H-1), 5.00, 4.60 (ABq, 1 H each, J 6.5 Hz, OCH_2O), 4.28, 4.13 (dABq, 1 H each, J 12.5, 4.5, 2.5 Hz, H-6), 3.73 (ddd, 1 H, J 9.2, 4.5, 2.5 Hz, H-5), 3.38 (s, 3 H, OCH_3), 2.09, 2.07, 2.04, 2.02 (s, 3 H each, OAc).

(b) Crystalline trimethylsilylethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside[1] (**1**, 135 mg, 0.3 mmol) was dissolved, under nitrogen, in dichloromethane (3 mL; dried by passage through alumina). Dimethoxymethane (82 μL, 0.9 mmol) was added and the mixture was cooled to ca -70°. Triflic acid (86 μL, 0.93 mmol) was added with a syringe and the mixture was stirred at -70° for 24 h. Ethyldiisopropylamine (197 μL, 1.12 mmol) was added to the cold solution, the mixture was diluted with dichloromethane at room temperature, then washed with water, saturated sodium hydrogencarbonate and water, dried (sodium sulfate) and concentrated. TLC analysis showed the presence of small amounts of **1** and **3** in addition to the main product **5**. The residue was chromatographed as above to give **5** (73 mg, 62%) as the β anomer. Recrystallisation gave pure **5** (57 mg, 48%) with m.p. 98-99°.

(c) Crystalline trimethylsilylethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside[1] (**1**, 135 mg, 0.3 mmol) and molecular sieve (4Å, 0.9 g, crushed and flame-dried) were charged into a 10 mL round-bottom flask containing a magnetic stirring bar. The flask was evacuated and then filled with nitrogen. Dichloromethane (3 mL; dried by passage through alumina) was added and the mixture was stirred for 1 h at room temperature. Dimethoxymethane (82 μL, 0.9 mmol) and then borontrifluoride etherate (43 μL, 0.34 mmol) were added with a syringe. The reaction was monitored by TLC (SiO_2, ethyl acetate/hexane 2:3). After 15 h, the mixture was filtered through a column of alumina (grade 2-3). The column was washed with ethyl acetate and the combined filtrates were concentrated. TLC and GC analysis showed the presence of small amounts of **1** and **2** in addition to the main product **5**. The residue was chromatographed as above to give **5** (78 mg, 66%) as a β anomer. Recrystallisation gave pure **5** (58 mg, 49%) with m.p. 96-97°.

(d) Same experiment as under (c) but without the molecular sieve. Chromatography gave a mixture (71 mg, 60%) of **5** and methoxymethyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside in the ratio 6:4. The α glycoside had ^{1}H-NMR δ 5.51 (t, 1 H, J 10.2 Hz, H-3), 5.30 (d, 1 H, J 3.8 Hz, H-1), 4.86, 4.61 (ABq, 1 H each, J 6.6 Hz, OCH_2O), 3.39 (s, 3 H, OCH_3).

2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranosyl chloride (6). Compound **1** (449 mg, 1 mmol) was dissolved, in chloroform (7 mL, dried by passage through alumina) under nitrogen. Zinc chloride (fused, 18 mg, 0.13 mmol) was added followed by dichloromethyl methyl ether (467 μL, 5 mmol). The mixture was stirred at room temperature and the reaction was monitored by TLC (SiO_2, ethyl acetate/hexane 1:1). After 19 h, the mixture was concentrated and purified by passage through silica (ethyl acetate/hexane 1:1), which gave crystalline **6** (359 mg, 98%). Recrystallisation (ether/hexane) gave **6** (334 mg, 91%) with m.p. 71-72°, $[\alpha]_D^{22}$, +163° (*c* 1, chloroform) [Lit.[4]: m.p. 75-76°, $[\alpha]_D^{20}$, +166° (*c* 2, chloroform)]. ^{1}H.NMR δ 6.29 (d, 1 H, J 3.9 Hz, H-1), 5.55 (t, 1 H, J 10.0 Hz, H-3), 5.13 (t, 1 H, J 9.7 Hz, H-4), 5.01 (dd, 1 H, J 10.1, 4.0 Hz, H-2), 4.30 (m, 2 H, H-5 and H-6), 4.12 (m, 1 H, H-6), 2.10, 2.09, 2.04, 2.03 (s, 3 H each, OAc).

Acknowledgements

This work was supported by The Swedish Natural Science Research Council and The National Swedish Board for Technical Development.

References and Notes

1 Jansson, K., Ahlfors, S., Frejd, T., Kihlberg, J., Magnusson, G., Dahmén, J., Noori, G., Stenvall, K. *J.Org. Chem.* **1988**, *53*, 5629-5647.

2 Lipshutz, B. H.; Pegram, J. J.; Morey, M. C. *Tetrahedron Lett.* **1981**, *22*, 4603-4606.

3 Tietze, L. F., Fischer, R., Guder, H.-J., Neumann, M. *Liebigs Ann. Chem.* **1987**, 847-856.

4 Lemieux, R. U. *Methods Carbohydr. Chem.* **1963**, *2*, 223-224

5 Jansson, K., Magnusson, G. unpublished results.

6 Gross, H., Farkas, I., Bognár, R. *Z. Chem.* **1978**, *18*, 201-210 and references cited.

7 Kovác, P., Whittaker, N. F., Glaudemans, C. P. J. *J. Carbohydr. Chem.* **1985**, *4*, 243-254.

8 Jarvie, A. W. P. *Organometal. Chem. Rev. (A)* **1970**, *6*, 153-207.

9 deBelder, A. N., Garegg, P. J., Lindberg, B., Petropavlovskii, G., Theander, O. *Acta Chem. Scand.* **1962**, *16*, 623-628.

10 Dettinger, H.-M., Lehmann, J., Wallenfels, K. *Carbohydr. Res.* **1980**, *87*, 63-70.

11 Magnusson, G., Noori, G., Dahmén, J., Frejd, T., Lave, T. *Acta Chem. Scand.* **1981**, *B 35*, 213-216.