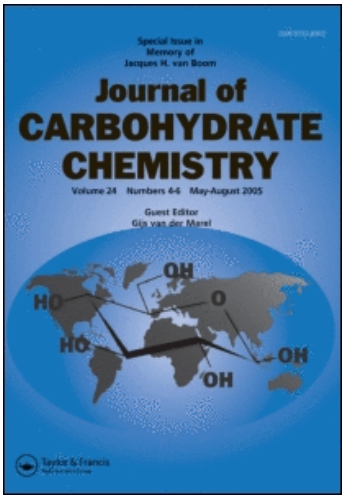


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# An Unusual Side Reaction in the Rearrangement of 3,4,6-Tri-*O*-Acetyl-1,2-*O*-(Allyloxyethylidene)-β-D-Mannopyranose with TMS-Triflate: Formation of an α(1→2)-Linked Disaccharide

Thisbe K. Lindhorst[a]
[a] Department of Organic Chemistry, University of Hamburg, Hamburg

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*COMMUNICATION*

# AN UNUSUAL SIDE REACTION IN THE REARRANGEMENT OF 3,4,6-TRI-*O*-ACETYL-1,2-*O*-(ALLYLOXYETHYLIDENE)-β-D-MANNOPYRANOSE WITH TMS-TRIFLATE: FORMATION OF AN α(1→2)-LINKED DISACCHARIDE

Thisbe K. Lindhorst

Department of Organic Chemistry, University of Hamburg,
Martin-Luther-King-Platz 6, D-20146 Hamburg

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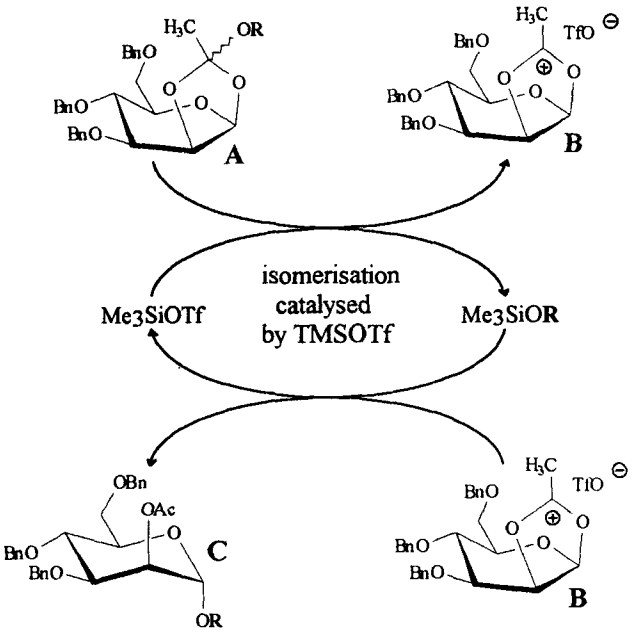
Sugar 1,2-orthoesters are versatile intermediates in carbohydrate synthesis. They are stable in neutral and basic medium but are readily hydrolysed under acidic conditions to form the corresponding 2-*O*-acetyl-protected reducing sugars.[1] The formation of the 2-OH-unprotected glycosyl actetates with trifluoroacetic acid has also been reported.[2] Furthermore 1,2-orthoacetates are known as glycosylating agents after activation by protic or Lewis acids.[3]

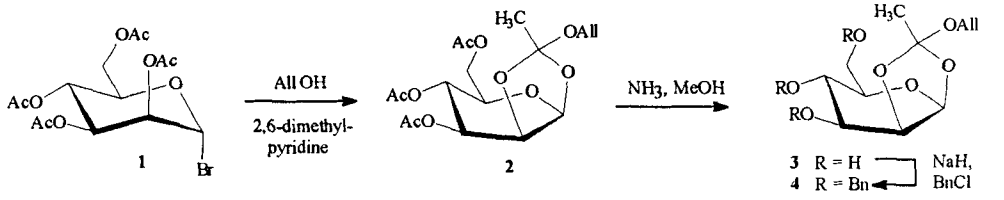
On the other hand orthoesters are often undesired side products in glycosylation reactions resulting from the nucleophilic attack at the centre of the intermediate acetoxonium ion.[4] This side reaction is especially favoured in the *manno*-series where the substituent adjacent to the anomeric centre is oriented in the axial position. Several methods have therefore been used for the isomerisation of 1,2-orthoacetates to the corresponding glycosides including the use of mercury salts.[5] An especially feasible method, introduced by Ogawa and coworkers in 1981,[6] applies trimethylsilyl trifluoromethanesulfonate (TMSOTf) as catalyst and has been regularly used since then.[7]

The catalytic role of TMSOTf ($Me_3SiOSO_2CF_3$) in the rearrangement reaction of sugar orthoacetates to glycosides can be understood as the attack of the Lewis acid at the alkoxy moiety of the dioxolane ring in **A** which results in the fomation of the 1,2-acetoxonium ion **B** (an example is depicted in Scheme 1). This can then be attacked by the silyl ether $Me_3SiOR$ to form the 1,2-*trans*-mannoside **C**. Accordingly, it is argued that the Lewis acid-catalysed glycosylation reaction with *O*-glycosyl trichloroacetimidates might proceed via orthoesters which rearrange to the desired glycosides in course of the reaction.[8]



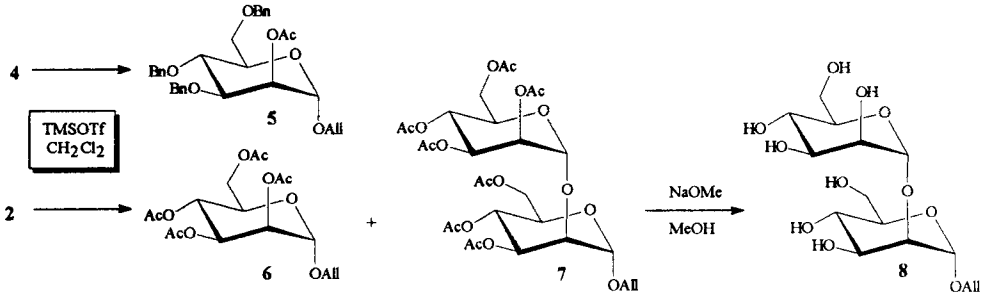

**Scheme 1**

This paper describes a new side reaction which occurs during the isomerisation of 3,4,6-tri-*O*-acetyl-1,2-*O*-(allyloxyethylidene)-β-D-mannopyranose (**2**) with TMSOTf. In the context of ongoing work on oligomannosylation reactions it was necessary to investigate the effect of TMSOTf on acetyl-protected mannose orthoacetates. Therefore, starting from the glycosyl bromide **1** the acetylated β-D-mannopyranose 1,2-allyl orthoester **2** was synthesized by direct treatment in allyl alcohol with 2,6-dimethylpyridine




**Scheme 2**

(2,6-lutidine) and obtained in 86% yield following published procedures[7b] (Scheme 2). The orthoacetate **2** can be deprotected to **3** and then benzylated to **4**[7b] in 61 % overall yield. As described in the literature,[7b] the benzylated orthoacetate **4** rearranges with TMSOTf to the allyl 2-*O*-acetyl-protected α-mannoside **5** in good yields around 80% (Scheme 3; for comparison of the NMR data see Table 1).




**Scheme 3**

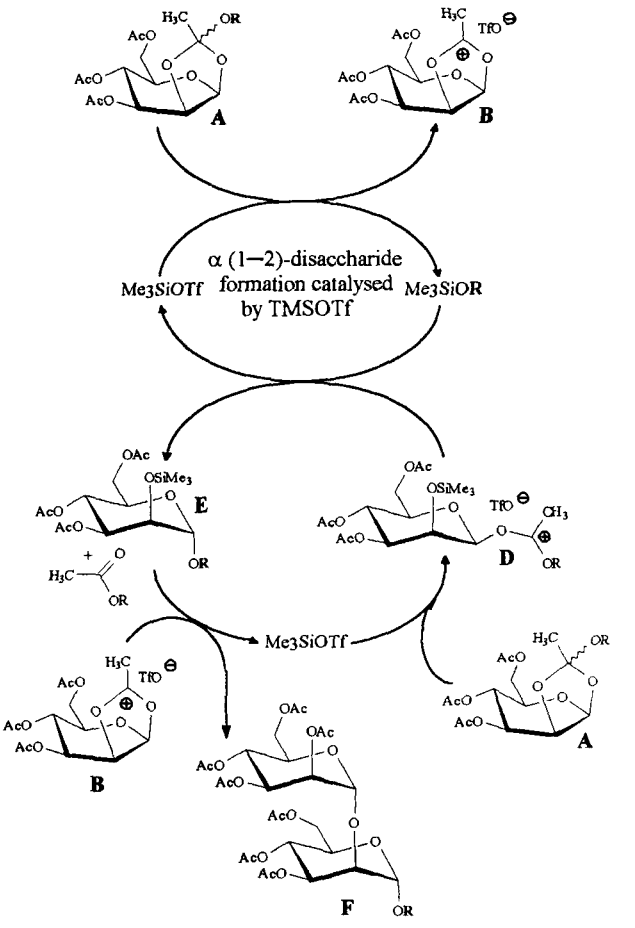
However, the same reaction carried out with the acetyl-protected orthoester **2** gave only 15 % of the known rearrangement product **6** ($R_f$ 0.59 in toluene/ethyl acetate, 1:1). A second slow moving product was detected by TLC which was not a hydrolysis product as could have been assumed from its low $R_f$ (0.33) but instead was identified as the mannobioside allyl 3,4,6-tri-*O*-acetyl-2-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-α-D-mannopyranoside (**7**) which was obtained in 30% isolated yield.

**Table 1.** $^1$H NMR Chemical shifts[a] of compounds **2-6**

| | **2** | **3** | **4** | **5** | **6** |
|---|---|---|---|---|---|
| H-1 | 5.42 (d) | 5.47 (d) | 5.24 (d) | 4.81 (d) | 4.87 (d) |
| H-2 | 4.55 (dd) | 4.51 (dd) | 4.40 (dd) | 5.36 (dd) | 5.25 (m) |
| H-3 | 5.08 (m) | 3.73-3.90 (4H) | 3.69-3.78 (3H) | 3.96 (dd) | 5.37 (dd) |
| H-4 | 5.23 (t) | 3.73-3.90 (4H) | 3.92 (t) | 3.87 (t) | 5.29 (t) |
| H-5 | 3.62 (ddd) | 3.30 (ddd) | 3.41 (ddd) | 3.69-3.81 | 4.02 (m) |
| H-6a | 4.08 (dd) | 3.73-3.90 (4H) | 3.69-3.78 (3H) | 3.69-3.81 | 4.12 (dd) |
| H-6b | 4.17 (dd) | 3.73-3.90 (4H) | 3.69-3.78 (3H) | 3.69-3.81 | 4.28 (dd) |
| OH-signals | | 4.42, 3.48, 2.72 | | | |

a. Recorded in $CDCl_3$ with TMS as an internal standard.

The $^1H$ NMR spectrum of 7 could be fully assigned by using $C_6D_6$ instead of $CDCl_3$ as solvent. The interpretation of the $^1H$-$^1H$ COSY is easily possible starting from the H-2 of the glycosidic linkage at 4.08 ppm. The gated decoupled $^{13}C$ NMR spectrum shows the heterocoupling constants for C-1 and C-1' with $J_{C\text{-}1,H\text{-}1}$ 170.7 and 172.6 Hz, respectively, proving the α-configuration of both glycosidic linkages.[9] Zémplen deprotection of the disaccharide gave the allyl mannobioside **8** with the correct NMR and FAB-MS spectrum.




**Scheme 4**

For the formation of an α(1→2)-linked disaccharide 7 from the orthoester **2** under TMSOTf-catalysis a mechanistic proposal can be made as depicted in Scheme 4. The orthoester **A** can be attacked by the Lewis acid at the OR-group resulting in the usual formation of the acetoxonium ion **B** and $Me_3SiOR$. In a second reaction pathway TMSOTf attacks the 2-oxygen atom of **A** which results in the formation of the ion **D**.This can in turn react with $Me_3SiOR$ to give the glycoside **E** and the acetate ester $H_3CCO_2R$. **E** can be regarded as an activated alcohol, suitable for the nucleophilic opening of the acetoxonium ion **B** and thus leading to the α(1→2)-linked disaccharide **F**.

The same product was formed when either catalytic or equimolar amounts of TMSOTf were used in the rearrangement reaction. The mannobioside 7 could also be obtained, probably by an analogous mechanism, when *t*BDMSOTf (*tert*-butyl-dimethylsilyl trifluoromethanesulfonate) or even triflic acid were used instead of TMSOTf. Similar side reactions during the glycosylation with sugar orthoesters have been mentioned in the literature which were also due to competing protonation at the 2-*O*-atom.[10] However, it is not completely understood why this reaction does not occur in the case of the 3,4,6-tri-*O*-benzylated orthoacetate **4**.

It should be noted that the herein described rearrangement reaction of **2** could even be regarded as an alternative synthesis of the allyl mannobioside **8** instead of a classical glycosylation approach.



## EXPERIMENTAL

**General methods.** The reactions were monitored by TLC (Merck silica gel plates $GF_{245}$), the products were purified by flash chromatography (Merck silica gel 60, 230-400 mesh), and characterized by NMR and mass spectrometry. The NMR spectra were recorded on a Bruker AMX 400 (400.14 MHz for $^{1}H$ and 100.67 MHz for $^{13}C$) and the FAB-MS experiments were carried out with a VG Analytical 70-250S mass spectrometer in the positive mode.

**Rearrangement of 3,4,6-tri-*O*-acetyl-1,2-*O*-(allyloxyethylidene)-β-D-manno-pyranose (2): allyl 2-*O*-acetyl-3,4,6-tri-*O*-acetyl-α-D-mannopyranoside (6) and allyl 3,4,6-tri-*O*-acetyl-2-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)-α-D-mannopy-ranoside (7).** The 1,2-orthoacetate **2** (500 mg, 1.28 mmol) was dissolved in anhydrous dichloromethane (10 mL) and stirred with molecular sieves (1 g, 4Å) under an inert atmosphere. Then the mixture was cooled to 0 °C and trimethylsilyl trifluoromethane-sulfonate (TMSOTf, 50μL, 0.27 mmol) was added. The reaction mixture was stirred at rt for 10 h , then it was filtered, diluted with dichloromethane (20 mL), neutralized with saturated sodium hydrogen carbonate solution, washed with water and the organic phase

was dried over $MgSO_4$. After filtration the solvent was evaporated and the remaining syrup purified on silica gel with toluene/ethyl acetae (1:1 v/v). The first fraction ($R_f$ 0.59) was **6** (76 mg, 0.195 mmol, 15%) and as the second fraction ($R_f$ 0.33) **7** (125 mg, 0.183 mmol, 29%) was obtained as white foam. When the same experiment was carried out with *t*BDMSOTf (100 µL) 55 mg (0.141 mmol, 11%) **6** and 129 mg (0.189 mmol, 30%) **7** were obtained. **7**: $^1$H NMR (400 MHz, $C_6D_6$) δ 5.78 (t, 1H, $J_{3,4} \approx J_{4,5} \approx 9.8$ Hz, H-4), 5.76 (dd, 1H, $J_{2',3'} = 3.1$, $J_{3',4'} = 10.2$ Hz, H-3'), 5.69 (m, 1H, $OCH_2$-C**H**=$CH_2$), 5.66 (t, 1H, $J_{4',5'} = 9.9$ Hz, H-4'), 5.62 (dd, 1H, $J_{2,3} = 3.1$, $J_{3,4} = 10.2$ Hz, H-3), 5.58 (dd, 1H, $J_{1',2'} = 2.0$, $J_{2',3'} = 3.1$ Hz, H-2'), 5.19 ($m_c$, 1H, O-$CH_2$-CH=C**H**$_2$), 5.12 (d, 1H, $J_{1,2} = 2.1$ Hz, H-1), 5.03 ($m_c$, 1H, O-$CH_2$-CH=C**H**$_2$), 4.92 (d, 1H, $J_{1',2'} = 2.0$ Hz, H-1'), 4.41, (m, 1H, H-5'), 4.34 (m, 2H, H-6a, H-6a'), 4.28 (dd, 1H, $J_{5',6b'} = 2.5$, $J_{6a',6b'} = 12.2$ Hz, H-6b'), 4.13 (dd, 1H, $J_{5,6b} = 5.4$, $J_{6a,6b} = 12.2$ Hz, H-6b), 4.08 (dd, 1H, $J_{1,2} = 2.0$, $J_{2,3} = 3.1$ Hz, H-2), 3.99 ($m_c$, 1H, O**C**$H_2$-CH=$CH_2$), 3.80 ($m_c$, 1H, O**C**$H_2$-CH=$CH_2$), 3.90 (m,1H, H-5), 2.06, 1.88, 1.76, 1.69, 1.63 (each s, each 3H, 5 OAc), 1.65 (s, 6H, 2 OAc) ppm; $^1$H NMR (400 MHz, $CDCl_3$) δ 5.90 ($m_c$, 1H, O-$CH_2$-C**H**=$CH_2$), 5.41 (dd, 1H, $J_{2,3} = 3.6$ Hz, $J_{3,4} = 10.2$ Hz, H-3), 5.37-5.27 (m, 5H, H-2', 3', 4, 4'), 4.98 (d, 1H, $J_{1,2} = 2.0$ Hz, H-1), 4.93 (d, 1H, $J_{1',2'} = 2.0$ Hz, H-1'), 4.27-4.07 (m, 8H, H-2, H-6a, 6b, 6a', 6b', 5 or 5', O-$CH_2$-CH=C**H**$_2$), 3.95 (m, 1H, H-5 or 5'), 2.15, 2.14, 2.09, 2.08, 2.04, 2.03, 2.01 (each s, each 3H, 7 OAc) ppm; $^{13}$C NMR ($CDCl_3$) δ 99.46, 99.19 (C-1, 1', $J_{C\text{-}1,H\text{-}1} = 172.6$, $J_{C\text{-}1',H\text{-}1'} = 170.7$ Hz,), 77.01, 70.35, 69.80, 69.20, 68.62, 68.43, 62,51, 62,17 (C-2, 2', 3, 3', 4, 4', 5, 5'), 66.40, 66.23 (C-6, 6'), 133.15 ($OCH_2$-**C**H=$CH_2$), 118.12 ($OCH_2$-CH=**C**$H_2$), 68.72 ($OCH_2$-CH=$CH_2$), 170.84, 1170.44, 170.35, 169.82, 169.71, 169.43, 169.39 (7 $OCOCH_3$), 21.43-20.62 (7 $OCOCH_3$) ppm.

**Allyl 2-*O*-(α-D-mannopyranosyl)-α-D-mannopyranoside (8).** The protected disaccharide **7** (58 mg, 0.085 mmol) was dissolved in anhydrous methanol (5 mL) and treated with a catalytic amount of a 1N sodium methanolate solution. The mixture was stirred at rt till the reaction was complete according to TLC. Then it was neutralized with ion exchanger (Dowex $H^+$ W50x8), fitered, and concentrated. Flash chromatography with ethyl acetate/methanol/water (7:2:1 v/v) gave **8** (27 mg, 0.071 mmol, 83%) as a colourless syrup: $^1$H NMR ($CD_3OD$) δ 5.84 ($m_c$, 1H, $OCH_2$-C**H**=$CH_2$), 5.19 ($m_c$, 1H, $OCH_2$-

CH=CH$_2$), 5.07 (m$_c$, 1H, OCH$_2$-CH=CH$_2$), 5.00, 4.88 (s, d, each 1H, H-1, 1'), 4.10 (m$_c$, 1H, OCH$_2$-CH=CH$_2$), 3.90 (m$_c$, 2H, OCH$_2$-CH=CH$_2$, H-2), 3.78-33.69 (m, 4H, ring-H), 3.65-3.39 (m, 7H, ring-H) ppm; FAB-MS: Calcd for $C_{15}H_{26}O_{11}$: 382.15. Found *m/z* 405.2 ($M+Na^+$).

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## REFERENCES

1. a) N. E. Franks and R. Montgomery, *Carbohydr. Res.*, **6**, 286 (1968); b) H. Paulsen, M. Springer, F. Reck, E. Meinjohanns, I. Brockhausen and H. Schachter, *Liebigs Ann.*, 53 (1995); c) H. Paulsen, M. Springer, F. Reck, I. Brockhausen and H. Schachter, *ibid.*, 67 (1995); d) A. B. Charette, N. Turcotte and B.Côté, *J. Carbohydr. Chem.*, **13**, 421 (1994).
2. H. Franzyk, M. Meldal, H. Paulsen and K. Bock, *J. Chem. Soc. Perkin Trans. I*, 2883 (1995).
3. a) G. Wulff and G. Röhle, *Angew. Chem.*, **86**, 173 (1974), *Angew. Chem. Int. Ed. Engl.*, **13**, 157 (1974); b) N. K. Kochetkov, A. F. Bochkov, T. A. Sokolovskaya and V. J. Snyatkova, *Carbohydr. Res.*, **16**, 17 (1971); c) A. F. Bochkov and N. K. Kochetkov, *Carbohydr. Res.*, **39**, 355 (1975).
4. G. Wulff and W. Schmidt, *Carbohydr. Res.*, **53**, 33 (1977).
5. a) N. K. Kochetkov, A. Y. Khorlin and A. F. Bochkov, *Tetrahedron*, **23**, 693 (1967); b) A. F. Bochkov and Y. V. Voznyi, *Carbohydr. Res.*, **32**, 1 (1967); c) U. E. Udodong, R. Madsen, C. Roberts and B. Fraser-Reid, *J. Am. Chem. Soc.*, **115**, 7886 (1993); d) J. R. Merritt, E. Naisang and B. Fraser-Reid, *J. Org. Chem.*, **59**, 4443 (1994).
6. T. Ogawa, K. Beppu and S. Nakabayashi, *Carbohydr. Res.*, **93**, C6 (1981).
7. a) T. Ogawa and T. Nukuda, *Carbohydr. Res.*, **136**, 135 (1985); b) H. Paulsen and B. Helpap, *Carbohydr. Res.*, **216**, 289 (1991).
8. R. R. Schmidt and W. Kinzy, *Adv. Carbohydr. Chem. Biochem.*, **50**, 21 (1994).
9. a) K. Bock, I. Lundt and C. Pedersen, *Tetrahedron Lett.*, **14**, 1073 (1973); b) K. Bock and C. Pedersen, *J. Chem. Soc. Perkin Trans. II*, 293 (1974).
10. A. F. Bochkov, V. I. Betanely and N. K. Kochetkov, *Carbohydr. Res.*, **30**, 418 (1973).