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A SYNTHESIS OF 2-(TRIMETHYLSILYL)ETHYL α-D-MANNOPYRANOSIDE

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Abstract The first high yield synthesis is reported of 2-(trimethylsilyl)ethyl α-D-mannopyranoside, using 2-*O*-benzoylated mannosyl donors, as precursors.

The success of the chemical synthesis of complex oligosaccharides depends on the availability of mono- and oligosaccharide building blocks that: 1. can dictate the stereoselectivity of glycosylation, 2. permit chain extention at desired position(s), and 3. allow deprotection with a minimum number of chemical transformations. In this regard the 2-(trimethylsilyl)ethyl (SE) glycosides[1] proved to be particularly valuable.[2] This is due to the stability of the glycosidic bond of the SE glycosides under a variety of reaction conditions, thus permitting diverse functional group manipulations. On the other hand, the SE glycosides can be converted to glycosyl donors[3] such as glycosyl acetates and glycosyl chlorides.[1,4a] Hydrolytic conditions can lead to glycosyl hemiacetals,[1,4b] which may be used as precursors to other activated, glycose derivatives.[2a,b,f] Further transformations include conversion into trimethylsilyl and methoxymethyl glycosides[4c] under moderately acidic conditions.

The published syntheses of the SE glycosides of the commonly occurring hexopyranoses utilize the Koenigs-Knorr procedure.[1] A remarkable exception is the SE glycoside of D-mannopyranose, which was prepared by the Fischer-glycosidation method. In Magnusson's protocol, 2-(trimethylsilyl)ethyl α-D-mannopyranoside (**1**) was obtained in admixture with the β anomer (**2**), in 18 % yield, in the milligram scale.[1b] Compound **1** could be purified through its acetate[1b] **3**. Scale-up of this protocol would be difficult, considering the high cost of the precursor alcohol 2-(trimethylsilyl)ethanol (SEOH), and the additional steps needed for the separation of the anomeric mixture. Since D-mannose is a major constituent of many biologically important glycoconjugates,[5] e. g. mammalian glycoproteins, and bacterial, capsular polysaccharides, compound **1** can be an important synthetic intermediate. Here we describe our experiments towards its synthesis.

As presumed at the outset of this work, reaction of the chloride[6] **5** or the corresponding bromide[2b] with SEOH failed to give the desired glycoside in an acceptable yield. In both cases, the major product was the hemiacetal[7] **7** (43 %).[8] It appeared to us, that the formation of **7** is *not* due to direct hydrolysis of **5** but rather to a secondary reaction, such as decomposition of an intermediate orthoester.[9]

We surmised, that the relative rates of the reactions leading to the desired glycoside *versus* the other products can be controlled by the array of the protecting groups. We reasoned, that a mannosyl donor, less reactive than compound **5**, can favourably influence the product distribution. Indeed, reaction of the *O*-benzoylated chloride[10] **6** with SEOH [AgOTf (2 eq[11]), 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP, 0.8 eq), CH_2Cl_2, at 25 °C], afforded the target glycoside[7] **4** as the major product. However, the yield (48 %) was less

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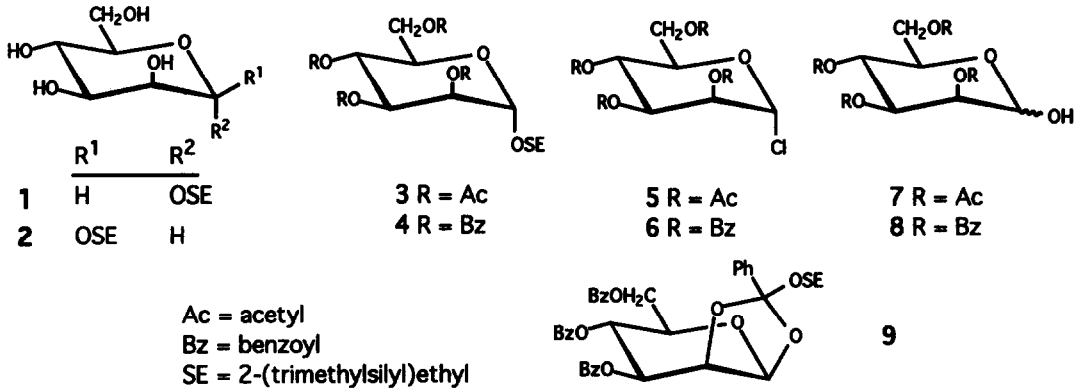
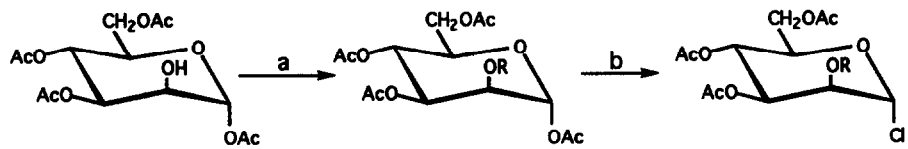


than acceptable.[12] In this reaction the major side-product was the hemiacetal[7] **8** (32 %). When the reaction was carried out at between -20 and -10 °C, orthoester[7] **9** predominated, accompanied by small amounts of the glycoside **4**, and the hemiacetal **8**, while at 0 °C the major product was **8**, and only trace amounts of **9** were detected (TLC). Zemplen deacylation of **4** afforded the target glycoside[7] **1**. The examples just described clearly demonstrated the crucial importance of the protecting group scenario. In addition, they indicated that subzero temperatures are unfavourable for the *O*-glycoside formation. Since the substituent at the carbon atom adjacent to the anomeric center is the most critical in glycosylation reactions, we hypothesized, that a mannosyl donor having a (substituted) benzoyl group at the *O*-2 position only, and acetyl groups elsewhere can be the donor of choice. Thus, we prepared mannosyl chlorides[7] **14-16** from tetra-acetate[2b] **10** by way of the mono-*O*-benzoates[7] **11-13** (Scheme), and tested their reaction with SEOH under promotion by AgOTf. All three donors afforded the desired

Scheme [a]



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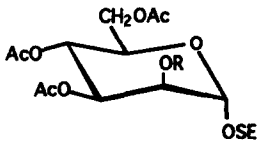
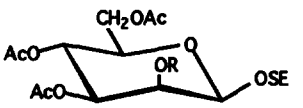
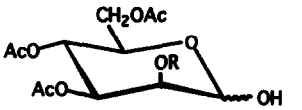
11 R = 4-NO4-C6H4CO 14
12 R = C6H5CO 15
13 R = 4-MeO-C6H4CO 16

[a]Reagents: (a) 4-NO_2-C_6H_4COCl/Py for **11**, C_6H_5COCl/Py for **12**, 4-MeO-C_6H_4COCl/Py for **13**; (b) CH_3OCHCl_2, $ZnCl_2$. Et_2O, CH_2Cl_2 (Ref. 2b).

α glycoside[7] (**17**, **18**, and **19**), the isomeric β glycoside[7] (**20**, **21**, and **22**), and the hemiacetal[7] (**23**, **24**, and **25**) in comparable ratios, in high overall yields. (Table) Interestingly, the highest yield was obtained with the





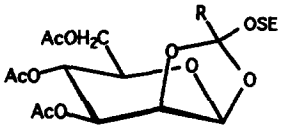


R = 4-$NO_2C_6H_4CO$	17	20	23
R = C_6H_5CO	18	21	24
R = 4-$MeOC_6H_4CO$	19	22	25

Table Reaction of mannosyl donors **14-16** with 2-(trimethylsilyl)ethanol[a]

Donor	Promoter/donor ratio[b]	Products[c]		
14	3.8	**17** (67)	**20** (5)	**23** (22)
15	2.3	**18** (72)	**21** (3)	**24** (23)
16	4.0	**19** (62)	**22** (2)	**25** (24)

[a]Molar ratio of donor/SEOH: 1.5-4, promoter: AgOTf, base:2,6-di-*tert*-butyl-4-methylpyridine[11] (0.8 eq), solvent: CH_2Cl_2, temperature: 25°C, reaction time: 10-30 min. [b]At the initiation of the reaction. [c]Yields are in parentheses.



26 R = C_6H_5
27 R = 4-$NO_2C_6H_4$

donor **15** having an unsubstituted benzoyl group at *O*-2.[13] Although the promoter/donor ratio was not optimized, it appeared to us that it should be at least 2 for the preferential formation of the *O*-glycosides. When the reaction of the chloride **15** with SEOH was initiated at -20 °C, orthoester[7] **26** could be detected as the major intermediate *before* the complete disappearance of the chloride **15**. Upon increasing the reaction temperature to -10 °C, conversion of **26** to the hemiacetal **24** but *not* to the glycoside **18** was observed. Further, when the reaction of the nitrobenzoate **14** with SEOH was conducted in the presence of an equimolar amount of AgOTf, orthoester **27** was the major product. These observations, together with the formation of compound **9** as described above suggest, that the initial products in the reaction between a mannosyl donor and SEOH are an orthoester and the required glycoside, in a ratio which is critically influenced by the temperature and by the promoter/donor ratio. The mannosyl orthoester is eventually transformed to the corresponding hemiacetal.

We have thus shown that a proper ensemble of protecting groups in a mannosyl donor can efficiently offset abortive reactions and can promote the formation of the target glycoside. We established conditions for the preparation of 2-(trimethylsilylethyl) α-D-mannopyranoside in the multigram scale, using easily available starting materials.

References and notes

1 (a) Lipshutz, B. H.; Pegram, J. J.; Morey, M. C. *Tetrahedron Lett.* **1981**, *22*, 4603. (b) Jansson, K.; Ahlfors, S.: Frejd, T.; Kihlberg, J.; Magnusson, G. *J. Org. Chem.* **1986**, *53*, 5629. (c) For a recent review, see: Magnusson, G. *Trends Glycosci. Glycotechnol.* **1992**, *4*, 358

2 (a) Pozsgay, V.; Glaudemans, C. P. J.; Robbins, J. B.; Schneerson, R. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 255. (b) Pozsgay, V.; Glaudemans, C. P. J.; Robbins, J. B.; Schneerson, R. *Tetrahedron* **1992**, *48*, 10249. (c) Ray, A. K.; Nilsson, U.; Magnusson, G. *J. Am. Chem. Soc*, **1992**, *46*, 59. (d) Ogawa, Y.; Wakida, M.; Ishida, H.; Kiso, M.; Hasegawa, A. *Carbohydr. Res.* **1992**, *242*, 303. (e) Caro, H-N.; Martin-Lomas, M.; Barnabe, M. *Carbohydr. Res.* **1992**, *240*, 119. (f) Pozsgay, V.; Glaudemans, C. P. J.; Robbins, J. B.; Schneerson, R. *Carbohydr. Res.* **1993**, *244*, 259.

3 For leading reviews, see: (a) Kanie, O.; Hindsgaul, O. *Curr. Opin. Struct. Biol.* **1992**, *2*, 674. (b) Lockhoff, O. in *Methoden der organischen Chemie (Houben-Weyl)*; Hagemann, H.; Klamann, D., Eds.; G. Thieme Verlag; Stuttgart, **1992**; Vol. E 14a/3; p 621.

4 (a) Jansson, K.; Frejd, T.; Kihlberg, J.; Magnusson, G. *Tetrahedron Lett.* **1986**, *27*, 753. (b) Jansson, K.; Frejd, T.; Kihlberg, J.; Magnusson, G. *Tetrahedron Lett.* **1988**, *29*, 361. (c) Kartha, K. P. R.; Kiso, M.; Hasegawa, A. *J. Carbohydr. Chem.* **1989**, *8*, 675. (d) Jansson, K.; Noori, G; Magnusson, G. *J. Org. Chem.* **1990**, *55*, 3181. (e) Jansson, K.; Magnusson, G. *Tetrahedron*, **1990**, *46*, 59. (f) Kartha, K. P. R., Jennings, H. J. *Tetrahedron Lett.* **1990**, *31*, 2537.

5 *Glycoconjugates, Composition, Structure and Function* (Allen, H. J.; Kisalius, E. C. Eds.), Marcel Dekker, Inc. **1992**.

6 (a) Gross, H.; Farkas, I.; *Chem. Ber.* **1960**, *93*, 95. (b) Bonner, W. A. *J. Am. Chem. Soc.* **1958**, *80*, 3372. (c) Brauns, D. H. *J. Res. Nat. Bur. Standards* **1931**, *7*, 581. (d) Pacsu, E. *Chem. Ber.* **1928**, *61*, 1508.

7 All new compounds gave elemental analytical, NMR, FAB and CI MS data, which are consistent with the proposed structures. Selected physical constants [mp; $[\alpha]_D$ for $CHCl_3$ solutions; ^{1}H-NMR ($CDCl_3$); and ^{13}C-NMR ($CDCl_3$) data]: **1**, Decomposes above 165 °C; +75°. **4**, -50°; 5.13 (^3J 1.9 Hz, H-1), 5.68 (H-2), 5.96 (H-3), 6.09 (H-4); 97.1 ($^1J_{C\text{-}1,H\text{-}1}$ 171 Hz, C-1). **7**, +20°; 5.30 [H-4(α)], 5.42 [H-3(α)]; 92.1 [$^1J_{C\text{-}1,H\text{-}1}$ 173 Hz, C-1(α)], 92.8 [$^1J_{C\text{-}1,H\text{-}1}$ 162 Hz, C-1(β)]. **8**, +8°; 5.33 [0.05 H, H-1(β)], 5.54 [0.95 H, H-1(α)], 5.75 [H-2(α)], 6.02 [H-3(α)], 6.19 [H-4(α)]. **9**, -99°; 5.08 (H-2), 5.65 (H-3), 5.78 (H-1), 5.92 (H-4); 97.8 ($^1J_{C\text{-}1,H\text{-}1}$ 176 Hz, C-1). **11**, 150-152 °C; -92°. **13**, 128-130 °C; -100°. **14**, -12°. **15**, 75-77 °C; +3°; 5.54 (H-4), 5.63 (H-2), 5.73 (H-3), 6.14 (H-1); 88.9 ($^1J_{C\text{-}1,H\text{-}1}$ 184 Hz, C-1). **16**, -21°, 5.52 (H-4), 5.59 (H-2), 5.71 (H-3), 6.13 (H-1); 88.8 ($^1J_{C\text{-}1,H\text{-}1}$ 184 Hz, C-1). **17**, -27°; 5.00 (H-1), 5.4 (H-4), 5.47-5.53 (H-2,3); 96.7 (C-1). **18**, -14°; 4.89 (H-1), 5.40-5.52 (H-2,3,4); 96.9 (C-1). **19**, -33°; 4.97 (H-1), 5.39-5.50 (H-2,3,4); 97.1 ($^1J_{C\text{-}1,H\text{-}1}$ 172 Hz, C-1). **20**, -90°; 4.79 (H-1), 5.18 (H-3), 5.35 (H-4), 5.68 (H-2); 98.0 ($^1J_{C\text{-}1,H\text{-}1}$ 158 Hz, C-1). **21**, NMR data for C_6D_6 solutions: 4.26 (H-1), 5.25 (H-3), 5.67 (H-4), 5.90 (H-2); 98.8 (C-1). **22**, -89°; 4.75 (H-1), 5.14 (H-3), 5.36 (H-4), 5.66 (H-2); 98.4 ($^1J_{C\text{-}1,H\text{-}1}$ 156 Hz, C-1). **23**, -83°, 5.41 (H-1), 5.42-5.59 (H-2,3,4), 91.7 [$^1J_{C\text{-}1,H\text{-}1}$ 172 Hz, C-1(α)], 92.7 [$^1J_{C\text{-}1,H\text{-}1}$ 160 Hz, C-1(β)]. **24**, -46°; 5.39 (H-1), 5.45-5.58 (H-2,3,4); 92.1 ($^1J_{C\text{-}1,H\text{-}1}$ 173 Hz, C-1). **25**, -80°; 5.37 (H-1), 5.42-5.56 (H-2,3,4); 92.1 [$^1J_{C\text{-}1,H\text{-}1}$ 173 Hz, C-1(α)], 93.1 [$^1J_{C\text{-}1,H\text{-}1}$ 161 Hz, C-1(β)]. **26**, 78-80 °C; -79°; 4.79 (H-2), 5.19-5.27 (H-3,4), 5.59 (H-1); 97.5 ($^1J_{C\text{-}1,H\text{-}1}$ 178 Hz, C-1). **27**, 118-120 °C; 4.83 (H-2), 5.14-5.24 (H-3,4), 5.63 (H-1); 97.5 ($^1J_{C\text{-}1,H\text{-}1}$ 176 Hz, C-1).

8 At least four other products were formed, when the reaction was performed under base-deficient conditions [AgOTf; 2,6-di-*tert*-butyl-4-methylpyridine, 0.8 eq, CH_2Cl_2; -40 to 25 °C], including the desired glycoside[1b] **3**, in admixture with a compound which was tentatively identified as trimethylsilyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside. Further products were indirectly identified as 2-(trimethylsilyl)ethyl 3,4,6- and 2,4,6-tri-*O*-acetyl-α-D-mannopyranoside.

9 The formation of the hemiacetal **7** from a glycosylsulfonium intermediate seems unlikely, due to the non-nucleophilic nature of the base employed. *Cf.* van Boeckel, C. A. A.; Beetz, T.; Vos, J. N.; de Jong, A. J. M.; van Aelst, S. F.; van den Bosch, R. H.; Mertens, J. M. R.; van der Vlugt, F. A. *J. Carbohydr. Chem.* **1985**, *4*, 293.

10 Pozsgay, V.; Coxon, B.; Yeh, H. *Bioorg. Med. Chem.* **1993**, In press.

11 Molar ratios are based on the donor throughout this paper.

12 Under similar conditions, 2,3,4-tri-*O*-benzoyl-α-*L*-rhamnopyranosyl chloride could be cleanly converted to the corresponding, α-L SE glycoside in 86 % yield.[2b] A re-examination of this procedure showed the concomitant formation of 2-(trimethylsilyl)ethyl 2,3,4-tri-*O*-benzoyl-β-L-rhamnopyranoside {1 %; $[\alpha]_D$ +190°, ($CHCl_3$); ^{1}H NMR ($CDCl_3$): 4.89 (H-1), 5.55 (H-3), 5.62 (H-4), 5.91 (H-2); ^{13}C NMR ($CDCl_3$): 98.4 ($^1J_{C\text{-}1,H\text{-}1}$ 155 Hz, C-1)}, and 2,3,4-tri-*O*-benzoyl-L-rhamnopyranose {10-15 %, depending on small variations of the experimental conditions; $[\alpha]_D$ +207°, ($CHCl_3$); ^{1}H NMR ($CDCl_3$): 5.48 (H-1), 5.70 (H-4), 5.73 (H-2), 5.95 (H-3); ^{13}C NMR ($CDCl_3$): 92.0 ($^1J_{C\text{-}1,H\text{-}1}$ 173 Hz, C-1)}.

13 Typical procedure: Silver trifluoromethanesulfonate (10.0 g, 39 mM) was added to a stirred mixture of **15** (7.26 g, 16.9 mM), 2,6-di-*tert*-butyl-4-methylpyridine (2.8 g), 2-(trimethylsilyl)ethanol (3.6 mL, 25 mM), and 4A molecular sieves (2 g) in CH_2Cl_2 (60 mL) at 25 °C. After 10 min the mixture was treated with aq $NaHCO_3$, then filtered. The CH_2Cl_2 phase was washed with H_2O, dried (Na_2SO_4) and concentrated. The residue was chromatographed on silica gel (3:1 hexane-EtOAc) to give **18** as a syrup (6.52 g, 72%). De-*O*-acylation of **18** (NaOMe/MeOH) followed by crystalization of the residue from di-isopropyl ether-hexane afforded **1** in 90% yield.

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