33. Stereoselective Glycosylation of Alcohols and Silyl Ethers Using Glycosyl Fluorides and Boron Trifluoride Etherate

by **Horst Kunz*** and **Wilfried Sager**

Institut für Organische Chemie der Universität Mainz, Joh.-Joachim-Becher-Weg 18–20, D-6500 Mainz

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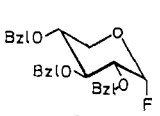
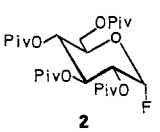
The stereoselective glycosylation of alcohols and their silyl ethers has been achieved using *O*-alkyl-, *O*-acyl-, and acetal-protected glycosyl fluorides of the pyranose and furanose series and boron trifluoride etherate in CH_2Cl_2.

There is much current interest in the glycosylation of alcohols and silyl ethers using glycosyl fluorides. *Mukaiyama* and coworkers [1] achieved stereoselective glycosylation using benzyl-protected glucopyranosyl fluoride in combination with the system tin chloride/silver perchlorate. Recently, *Noyori* and coworkers [2] have published a modification of this method consisting of the reaction of the benzyl-protected glucopyranosyl fluorides with alcohols and silyl ethers in the presence of either silicon tetrafluoride or trimethylsilyl trifluoromethane sulfonate. They observed a dependence of the anomeric configuration of the glycoside formed on the polarity of the medium (Et_2O or MeCN). However, both catalysts, silicon tetrafluoride and the silyltriflate, are very sensitive to hydrolysis, producing acids; furthermore, the former is highly volatile. In the course of the preparation of this manuscript, a third modification has been published in a preliminary paper [3] describing *inter alia* the application of BF_3 as a catalyst in reactions of alcohols with benzyl- and acetyl-protected glucopyranosyl fluorides.

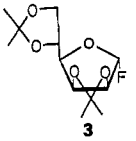
This prompted us to present our results [4] on glycosylations of glycosyl fluorides which avoid both a heterogeneous reaction and hydrolytically sensitive, volatile catalysts and thus offer a simple and practical way to exploit the hydrolytically stable glycosyl fluorides in glycosylations. We used boron trifluoride etherate ($BF_3 \cdot Et_2O$) as catalyst, this being not only easy to handle and convenient, but with which we also achieved stereoselective glycosylations.



1
Bzl = $C_6H_5CH_2$

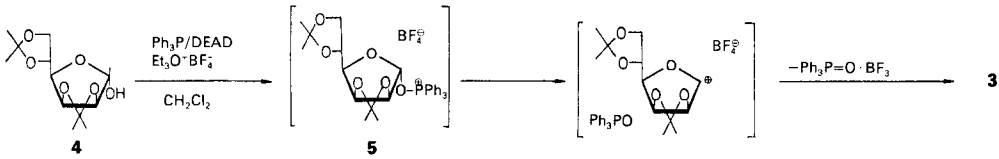


2
Piv = $(CH_3)_3CCO$



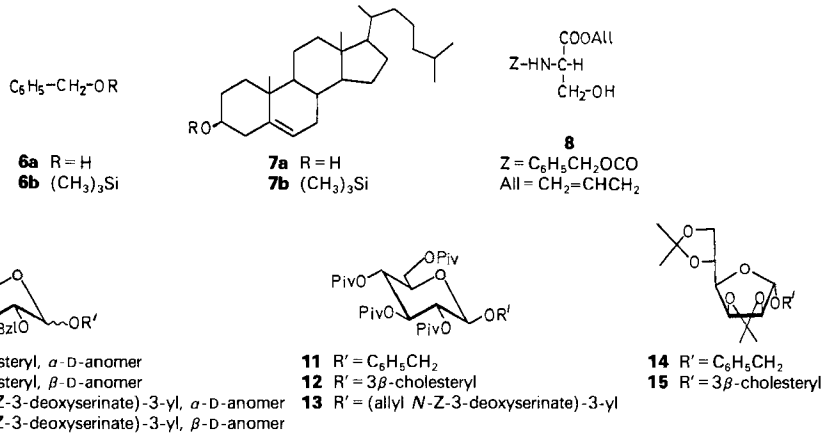
3

As models of glycosyl donors we chose the glycosyl fluorides **1**–**3**, *i.e.* different protected derivatives of the pyranose as well as of the furanose series. The *O*-benzyl-protected xylosyl fluoride **1** was synthesized from the corresponding 1-*O*-acetyl derivative on treatment with HF in CH_2Cl_2 at −70 °C. Similarily, the *O*-acyl-protected gluco-



syl fluoride **2** was obtained from the pentapivaloyl compound with liquid HF at −30 to −10°C.

In contrast, the acid sensitive acetal-protected mannofuranosyl fluoride **3** was prepared from diisopropylidene-mannofuranose **4** using triphenyl phosphine (Ph_3P), diethyl azodicarboxylate (DEAD) and triethyloxonium tetrafluoroborate [4a]. Presumably, this modification of the *Mitsunobu* reaction [5] [6] proceeds *via* the unstable oxyphosphonium salt **5** [7], which decomposes *via* the stabilized carbonium ion forming the fluoride **3**.



6a R = H
6b $(CH_3)_3Si$

7a R = H
7b $(CH_3)_3Si$

8
Z = $C_6H_5CH_2OCO$
All = CH_2=$CHCH_2$

9a R′ = 3β-cholesteryl, α-D-anomer
9b R′ = 3β-cholesteryl, β-D-anomer
10a R′ = (allyl *N*-Z-3-deoxyserinate)-3-yl, α-D-anomer
10b R′ = (allyl *N*-Z-3-deoxyserinate)-3-yl, β-D-anomer

11 R′ = $C_6H_5CH_2$
12 R′ = 3β-cholesteryl
13 R′ = (allyl *N*-Z-3-deoxyserinate)-3-yl

14 R′ = $C_6H_5CH_2$
15 R′ = 3β-cholesteryl

In the BF_3-catalysed reactions of the glycosyl fluorides **1–3** we used benzyl alcohol (**6a**), cholesterol (**7a**), their silyl ethers **6b** and **7b**, and *N*-(benzyloxycarbonyl)serine allyl ester (**8**) [8] as nucleophile. In order to trap the HF evolved in the reactions with alcohols, equimolar amounts of Et_3N were added to the reaction mixture. All reactions leading to the glycosides **9–15** were carried out in CH_2Cl_2 at room temperature *(Table)*. In reactions with **1** and **3**, catalytic amounts (up to 0.2 equiv.) of BF_3 are sufficient, whereas reactions with **2** require an excess of BF_3 (*ca.* 4.2 equiv.), due to complexation with the ester carbonyls. Generally, the fast reaction is complete with the silyl nucleophiles after 10 min and with the alcohols after *ca.* 30 min.

The glycosylation using 2,3,4-tri-*O*-benzyl-α-D-xylopyranosyl fluoride (**1**) shows remarkable stereoselectivity, but nevertheless yields mixtures of anomers **9a**/**9b**. This is in accord with the results formerly found with benzyl-protected glucose derivatives and tin [1] or silicon catalysts [2]. Interestingly, with the unpolar cholesterol nucleophiles **7**, the α-D-xyloside **9a** is preferentially formed, whereas with the polar Z-serine allyl ester **8** [8], the β-D-xyloside **10b** predominates. This suggests an influence of the aglycon polarity on the anomeric configuration of the glycoside formed, and parallels the effect of the solvent polarity observed in the reactions with the silyl catalysts [2]. On the other

Table. *Glycosylation of Alcohols and Silyl Ethers* **6-8** *Using the Glycosyl Fluorides* **1-3** *and* $BF_3 \cdot Et_2O$ *in* CH_2Cl_2 *at Room Temperature*

Glycosyl fluoride	Nucleophile	Glycoside[a])	
		α-D-anomer	β-D-anomer
1	**7a**	**9a** (66%): + 33.1° (c = 0.26)[b])	**9b** (11%): + 3.6° (c = 0.3)[b])
1	**7b**	**9a** (70%)[c])	**9b** (11%)[c])
1	**8**	**10a** (13%)[d]) [8]	**10b** (67%)[d]) [8]
2	**6b**		**11** (75%): − 20.9° (c = 1.05)[b]) [9]
2	**7a**		**12** (84%): − 14.6° (c = 1)[b]) [9]
2	**8**		**13** (85%): + 4.9° (c = 1.05)[b])
3	**6b**	**14** (54%): + 80.1° (c = 1)[e])	
3	**7b**	**15** (67%): + 34.1° (c = 0.3)[b])	

[a]) Yields of isolated compounds in parentheses.
[b]) $[\alpha]_D^{25}$ in $CHCl_3$.
[c]) Percentage from HPLC in petroleum ether/AcOEt 30:1.
[d]) Percentage from HPLC in $CHCl_3/Et_2O$ 19:1.
[e]) $[\alpha]_D^{25}$ in acetone.

hand, the striking difference in the stereoselectivity may be due to the different reactivity of the alcohols. Analogously to the observations *of Paulsen* [10], the more reactive serine derivative **8** gives the β-D-xyloside **10b** (inversion) whereas the less reactive cholesterol produces the α-D-xyloside (retention).

The method attains its full potential in glycosylations using acyl-protected glycosyl fluorides, *e.g.* 2,3,4,6-tetra-*O*-pivaloyl-α-D-glucopyranosyl fluoride (**2**). In this case, reaction occurs stereospecifically due to the directing influence of the 2-pivaloyloxy substituent [9], leading to the β-glycosides **11–13** in high yield. This complete stereoselectivity in combination with the high overall efficiency and the stability of the glycosyl fluorides themselves makes this homogeneous reaction a very potent alternative to the *Koenigs-Knorr* variants [11].

In the reaction of the 2,3:5,6-di-*O*-isopropylidene-α-D-mannofuranosyl fluoride (**3**), α-D-glycosides are formed highly stereoselectively. This example reveals an additional advantage of the method, namely the complete conservation of the acid-labile acetal protection during the mild glycosylation procedure. Small catalytic amounts of BF_3 are sufficient to produce a rapid glycosylation. This method, therefore, opens up a synthetic area not covered by classical glycoside syntheses which mostly require acidic conditions.

In conclusion, the glycosylation demonstrated here incorporates high stereoselectivity, mild reaction conditions, complete stability of the starting glycosyl fluorides, use of a stable and convenient catalyst, and the advantages of a homogeneous reaction.

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Experimental Part

General. Melting points were taken on a *Tottoli* apparatus *(Büchi)* and are uncorrected. TLC silica plates with fluorescent indicator were purchased from *E. Merck,* Darmstadt. NMR spectra were measured in $CDCl_3$ on *Jeol-JMN-60, Bruker-WH-90,* and *Bruker-WP-200* spectrometers relative to TMS as internal standard. EI-MS were obtained with a *Varian MAT CH 7A,* FD-MS with a *Varian MAT CH 711* mass spectrometer. Optical rotations were measured on a *Perkin-Elmer-241* polarimeter. HPLC chromatography was carried out on *Waters 6000 A* with a differential refractometer detector *(Knauer).*

*2,3,4-Tri-*O*-benzyl-α-*D*-xylopyranosyl Fluoride* (**1**). For 24 h, 2,3,4-tri-*O*-benzyl-D-xylopyranose [12] (2.65 g, 6.3 mmol) was treated with pyridine/Ac_2O 2:1 (15 ml). Then, the mixture was poured onto ice/H_2O (50 g), extracted with CH_2Cl_2 (50 ml), and the org. soln. washed in sequence with 50 ml of dil. HCl, $NaHCO_3$ soln., and H_2O. After drying over Na_2SO_4, evaporation yielded 2.9 g (*ca.* 100%) of *1-*O*-acetyl-2,3,4-tri-*O*-benzyl-*D*-xylopyranose.* Liquid HF (1 ml) was added to the soln. of this product in CH_2Cl_2 (25 ml) at −70°. After 30 min, the mixture was poured onto ice/H_2O (50 ml), extracted with CH_2Cl_2 (50 ml) and the org. layer washed with 50 ml of conc. $NaHCO_3$ soln. and H_2O. Drying over Na_2SO_4 and evaporation of the solvent gave 2.66 g (*ca.* 100%) of **1**, m.p. 59°, $[\alpha]_D^{22} = 6.2$ ($c = 1$, $CHCl_3$). ^{1}H-NMR (200 MHz): 5.45 (*dd*, $J_{1,F} = 53.1$, $J_{1,2} = 2.6$, H–C(1)). ^{19}F-NMR (84.67 MHz, fluorobenzene as standard): 18.79 ($J_{1,F} = 53.1$, $J_{2,F} = 25.5$). MS (FD): 421 ($M^+ - H$). Anal. calc. for $C_{26}H_{27}FO_4$ (422.5): C 73.92, H 6.44; found: C 73.51, H 6.11.

*2,3,4,6-Tetra-*O*-pivaloyl-α-*D*-glucopyranosyl Fluoride* (**2**). At −30°, 1,2,3,4,6-penta-*O*-pivaloyl-β-D-glucopyranose [9] (6 g, 0.1 mol) was dissolved in liq. HF (10 ml). During 80 min, the solution was allowed to warm to −10° and then poured onto ice/H_2O (50 g). Further isolation was carried out as described for **1**. The product **2** was recrystallized twice from acetone: 3.8 g (74%), m.p. 128° $[\alpha]_D^{25} = 75.6$ ($c = 1$, $CHCl_3$). ^{1}H-NMR (90 MHz): 5.73 (*dd*, $J_{1,F} = 53.11$, $J_{1,2} = 2.93$, H–C(1)); 4.91 (*ddd*, $J_{2,F} = 23.76$, $J_{1,2} = 2.93$, $J_{2,3} = 9.68$ H–C(2)). ^{13}C-NMR (22.63 MHz): 103.61 (*d*, $J_{C(1),F} = 227.96$, C(1)). ^{19}F-NMR (84.67 MHz, fluorobenzene as standard): −19.73 (*dd*, $J_{1,F} = 53.11$, $J_{2,F} = 23.76$). Anal. calc. for $C_{26}H_{43}FO_9$ (518.6): C 60.22, H 8.36; found: C 60.49, H 8.32.

*2,3:5,6-Di-*O*-isopropylidene-α-*D*-mannofuranosyl Fluoride* (**3**). Diethyl azodicarboxylate (2 ml, 1.27 mol) dissolved in dry CH_2Cl_2 (8 ml) was added dropwise to a solution of Ph_3P (3.34 g, 1.27 mol) in CH_2Cl_2 (50 ml). To this mixture was added, at −78°, a solution of 2,3:5,6-di-*O*-isopropylidene-D-mannofuranose [13] (3.3 g, 1.27 mol) and Et_3OBF_4 (2.41 g, 1.27 mol) in CH_2Cl_2 (8 ml). After 4 h, precipitation of a solid was observed which, however, redissolved on warming to r.t. After addition of petroleum ether (100 ml), $Ph_3PO \cdot BF_3$ precipitated from the soln.: 2.57 g (57%), m.p. 231° [14]: m.p. 239°. After filtration, the filtrate was concentrated and **3** isolated by column chromatography on silica gel using petroleum ether/AcOEt 3:1 (*v/v*): 1.8 g (54%), m.p. *ca.* 20°, $[\alpha]_D^{23} = -7.5$ ($c = 1$, $CHCl_3$). ^{1}H-NMR (60 MHz): 5.83 (*d*, $J_{1,F} = 59.5$, H–C(1)); 1.46, 1.40 (2*s*, $2(CH_3)_2C$). ^{13}C-NMR (22.63 MHz): 113.22 (*d*, $J_{C(1),F} = 221.4$, C(1)); 112.75, 108.07 ($(CH_3)_2C$); 84.44 (*d*, $J_{C(2),F} = 41.7$, C(2)); 82.34, 78.28, 72.36 (C(3), C(4), C(5)); 66.26 (C(6)); 26.41, 25.41, 24.78, 24.09 ($(CH_3)_2C$). ^{19}F-NMR (84.67 MHz, fluorobenzene as standard): 1.44 (*dd*, $J_{1,F} = 59.5$, $J_{2,F} = 5.8$). MS (EI): 247 (100, $M^+ - CH_3$). Anal. calc. for $C_{12}H_{19}FO_5$ (262.28): C 54.93, H 7.30; found: C 54.95, H 7.42.

Glycosylation of Alcohols and Silyl Ethers Using Glycosyl Fluorides and BF_3. General Procedure. The glycosyl fluoride (**1**, **2**, or **3**; 3 mmol) and the silyl ether or the alcohol (**6**, **7**, or **8**; 3 mmol), the latter in combination with Et_3N (300 mg, 3 mmol), were dissolved in dry CH_2Cl_2 (50 ml). In the case of **1** and **3**, 2 drops of destilled $BF_3 \cdot Et_2O$ were added. In the case of the acyl-protected fluoride **2**, 1.8 ml (12.5 mmol BF_3) was required. After 10 (silyl ether) or 30 min (alcohol/Et_3N) at r.t., the mixture was washed sequentially with H_2O (50 ml), sat. $NaHCO_3$ soln. (50 ml) and H_2O (50 ml). The org. phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography using the appropriate eluent indicated below. Yields and $[\alpha]_D$ see *Table.*

*3β-Cholesteryl 2,3,4-Tri-*O*-benzyl-α-*D*-xylopyranosid* (**9a**). R_f 0.41 (petroleum ether/AcOEt 8:1), m.p. 132°. ^{13}C-NMR (22.63 MHz): 140.88, 121.71 (C(5), C(6) of cholesteryl); 94.67 (C(1)).

*3β-Cholesteryl 2,3,4-Tri-*O*-benzyl-β-*D*-xylopyranoside* (**9b**). R_f 0.45 (petroleum ether/AcOEt 8:1), m.p. 94°. ^{13}C-NMR (22.63 MHz): 140.56, 121.91 (C(5), C(6) of cholesteryl); 102.67 (C(1)).

*O^3-(2,3,4-Tri-*O*-benzyl-α/β-*D*-xylopyranosyl)-N^2-(benzyloxycarbonyl)-*L*-serine Allyl Ester* (**10a/10b**). Identified by comparison with authentic material prepared as described earlier [8]. R_f 0.68 (α), 0.64 (β) ($CHCl_3/Et_2O$ 9:1). ^{13}C-NMR (22.63 MHz, CD_3OD): 104.9 (C(1), β-D-anomer); 98.6 (C(1), α-D-anomer).

*Benzyl 2,3,4,6-Tetra-*O*-pivaloyl-β-*D*-glucopyranoside* (**11**). Identified by comparison with authentic material [9]. R_f 0.36 (petroleum ether/AcOEt 8:1), m.p. 124°. ^{13}C-NMR (22.63 MHz): 98.9 (C(1)).

*3β-Cholesteryl 2,3,4,6-Tetra-*O*-pivaloyl-β-*D*-glucopyranoside* (**12**). Identified by comparison with authentic material [9]. R_f 0.53 (petroleum ether/acetone 10:1), m.p. 197°. ^{13}C-NMR (22.63 MHz): 99.6 (C(1)).

O^3-*(2,3,4,6-Tetra-*O*-pivaloyl-β-*D*-glucopyranosyl)*-N^2-*(benzyloxycarbonyl)*-L-*serine Allyl Ester* (**13**). R_f 0.41 (petroleum ether/AcOEt 4:1). ^{1}H-NMR (200 MHz): 5.57 (*d*, J = 8.25, NH); 4,48 (*d*, $J_{1,2}$ = 7.9, H–C(1)). ^{13}C-NMR (22.63 MHz): 156.44 (C=O, urethane); 131.46 (CH=CH_2); 118.66 (CH=CH_2). Anal. calc. for $C_{39}H_{59}NO_{12}$ (777.9): C 61.76, H 7.64, N 1.81; found: C 62.13, H 7.60, N 2.06.

*Benzyl 2,3:5,6-Di-*O*-isopropylidene-α-*D*-mannofuranoside* (**14**). R_f 0.51 (petroleum ether/AcOEt 3:1), m.p. 53° ([15]: m.p. 53–54°, $[\alpha]_D^{23}$ = 78.3 (c = 1.18, acetone)). ^{1}H-NMR (90 MHz): 5.0 (*s*, H–C(1)).

*3β-Cholesteryl 2,3:5,6-Di-*O*-isopropylidene-α-*D*-mannofuranoside* (**15**). R_f 0.70 (petroleum ether/AcOEt 3:1), m.p. 118°. ^{1}H-NMR (90 MHz): 5.14 (*s*, H–C(1)). Anal. calc. for $C_{39}H_{63}O_6$ (627.9): C 74.60, H 10.11; found: C 74.56, H 9.98.

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