Synthesis of 2-deoxy and 2,6-dideoxy glycosides under neutral conditions in $LiClO_4/Et_2O$ mixtures

Heidrun Schene and Herbert Waldmann*

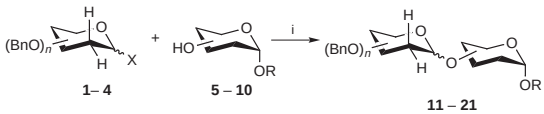
Universität Karlsruhe, Institut für Organische Chemie, Richard-Willstätter-Allee 2, D-76128 Karlsruhe, Germany. E-mail: waldmann@ochhades.chemie.uni-karlsruhe.de

Received (in Cambridge, UK) 5th October 1998, Accepted 6th November 1998

Glycosides of 2-deoxy and 2,6-dideoxy carbohydrates were built up in high yields and with high stereoselectivity in 0.1 M $LiClO_4/Et_2O$ mixtures; the glycosidations proceed under neutral conditions and without need for an additional promoter such as a strong Lewis acid, a heavy metal salt or an alkylating reagent.

2-Deoxy and 2,6-dideoxy glycosides are important substructures of antitumor drugs, antibiotics active against Gram-positive bacteria and drugs used in the treatment of cardiac insufficiency. Owing to this biological relevance the development of methods for the efficient and stereoselective construction of deoxyglycosidic linkages is of great relevance to organic synthesis, medicinal and bioorganic chemistry.[1] In comparison to the synthesis of other glycosides this problem is particularly challenging, since 2-deoxy glycosides are more acid-labile. Furthermore no stereodirecting neighboring group adjacent to the anomeric center is available that may direct the steric course of the glycosidation reaction. To circumvent these problems for deoxy glycoside synthesis, mostly electrophile-mediated addition of acceptor alcohols to the double bond of glycals followed by reductive removal of the C-2 substituents introduced into this position is employed.[2] Alternatively, glycosyl donors with 2-substituents acting as a neighboring group[3] or 1,2-anhydropyranoses[4] are used followed by reductive removal of the 2-substituent. Clearly, the application of direct methods for the efficient construction of 2-deoxy and 2,6-dideoxy glycosides is highly desirable.[5] These transformations should proceed under very mild and preferably neutral conditions without the use of strong Lewis acids or other promoters such as toxic and expensive heavy metal salts. We now report that trichloroacetimidates and fluorides of 2-deoxy and 2,6-dideoxy carbohydrates are activated under neutral conditions in solutions of $LiClO_4$ in Et_2O to give the correspondig deoxyglycosides with pronounced stereoselectivity and in high yields (Scheme 1).[6]

If benzyl-protected 2-deoxyglucosyl trichloroacetatimidate **1**[7] was treated with 6-O-deprotected benzylated glucoside **5a** in Glycosides of 2-deoxy and 2,6-dideoxy carbohydrates were built up in high yields and with high stereoselectivity in 0.1 M $LiClO_4/Et_2O$ mixtures; the glycosidations proceed under neutral conditions and without need for an additional promoter such as a strong Lewis acid, a heavy metal salt or an alkylating reagent.solutions of metal perchlorates in different solvents, the desired disaccharide **11** was formed smoothly. A brief survey of the reaction conditions (solvent, metal perchlorate, other metal salts, concentration of the salt) revealed that the best results were recorded in 0.1 M $LiClO_4$ in Et_2O. Under these conditions the desired glycoside was formed in 89% yield with a slight preference for the α-anomer (Table 1, entry 1). At lower or higher perchlorate concentration (0.03–0.5 M), in CH_2Cl_2, toluene or MeCN and in the presence of $Ba(ClO_4)_2$, $Zn(ClO_4)_2$ or $Mg(ClO_4)_2$, the yield was lower and the α/β selectivity remained almost unchanged. $LiClO_4$ could be replaced by $Li(NTf)_2$,[8] $LiBF_4$ or $LiPF_6$; however in the presence of these salts the results were not improved. Also the β-imidate corresponding to **1** gave inferior yields and the α/β selectivity remained unchanged. Therefore, all further reactions were conducted with the α-anomer **1** in 0.1 M $LiClO_4/Et_2O$ solutions.



Scheme 1 *Reagents and conditions*: i, 0.1 M $LiClO_4$, 4 Å molecular sieves, solvent, room temp.

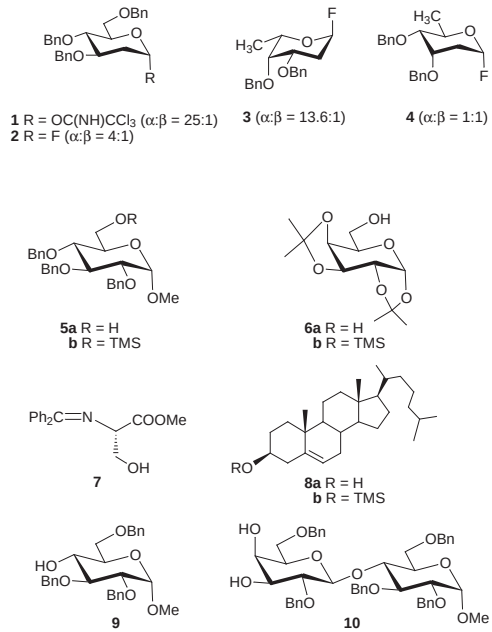


Table 1 Results of the glycosylation reactions in $LiClO_4/Et_2O$ mixtures employing 2-deoxy and 2,6-dideoxyglycosyl donors **1–4** and glycosyl acceptors **5–10** to give glycosides **11–21**

Entry	Glycosyl donor	Glycosyl acceptor	Product	Yield (%)[a]	Anomeric ratio (α : β)[b]
1	**1**	**5a**	**11**	89	1.5 : 1
2	**1**	**6a**	**12**	91[c]	2 : 1
3	**1**	**7**	**13**	57[d]	2.4 : 1
4	**1**	**8a**	**14**	78	1 : 1
5	**1**	**9**	**15**	37	only α
6	**2**	**5a**	**11**	65	13.4 : 1
7	**2**	**6a**	**12**	49	6 : 1
8	**2**	**8**	**14**	31	11.3 : 1
9	**3**	**5b**	**16**	49	8.1 : 1
10	**3**	**6b**	**17**	75	12.7 : 1
11	**3**	**8b**	**18**	66	only α
12	**3**	**10**	**19**	33	only α
13	**4**	**5b**	**20**	52	1 : 1.3
14	**4**	**6b**	**21**	61	9.5 : 1

[a] All glycosides were chromatographically purified and identified by ^1H NMR spectroscopy (250, 400 or 500 MHz). [b] Determined by integration of the relevant signals in the ^1H NMR spectra of the anomeric mixtures after chromatographic purification. [c] 0.15 M $LiClO_4$. [d] In CH_2Cl_2.

Under these gentle conditions glycosyl donor **1** reacts with galactose derivative **6a**, serine imine **7** and cholesterol **8a** to give the desired glycosides **12–14** in high yields, while glucosyl disaccharide **15** is obtained with lower yield (Table 1, entries 1–5). Thus 2-deoxyglycosyl imidate **1** is efficiently activated in the absence of a strong Lewis acid. The rate-accelerating effect of this reaction medium may be attributed to the ability of $LiClO_4/Et_2O$ solutions to stabilize polar or ionic transition states or intermediates like glycosyl cations.[6,9]

Although with imidate **1** the desired glycosides were formed in high yields the stereoselectivity remained low (Table 1, entries 1–4, see, however, entry 5). Therefore other glycosyl donors were investigated. Whereas use of the diethyl phosphite analogous to **1** did not improve this situation, 2-deoxyglycosyl fluoride **2** led to significantly higher anomer ratios. Glycosyl donor **2** is also activated in 1 M $LiClO_4$ in Et_2O under very mild conditions and reacts with selectively deprotected glucose **5a**, galactose **6a** and cholesterol **8a** to give glycosides **11**, **12** and **14** in useful yields. However, in these cases the α-anomers are formed with ratios ranging from 6:1 to 13.4:1 (Table 1, entries 6–8). Thus, by means of this method 2-deoxyglycosides can be constructed under very gentle conditions and with pronounced stereoselectivity.

In order to extend the scope of this very mild method, glycosylation of 2,6-dideoxy carbohydrates was investigated. Since in the case of 2-deoxyglucose the glycosyl fluoride had shown the most advantageous results, deoxy-L-fucosyl fluoride **3** and D-digitoxosyl fluoride **4** were prepared[7] and subjected to the glycosidation reactions.† As glycosyl acceptors silyl ethers **5b**, **6b** and **8b** were employed to facilitate the reactions by formation of the very stable Si–F bond. Lactose derivative **10** was used to investigate if regioselectivity can be achieved. Upon treatment of benzyl-protected 2-deoxyfucosyl fluoride with glucose derivative **5b**, galactosyl acceptor **6b**, cholesteryl silyl ether **8b** and lactose derivative **10** in 0.1 M $LiClO_4$ in Et_2O, glycosides **16–19** were smoothly formed in moderate to high yields. In all cases the anomer ratio was gratifyingly high (Table 1, entries 9–12). Whereas the glucose and the galactose disaccharides were obtained with α/β ratios of 8.1 to 12.7, cholesteryl glycoside **18**‡ and trisaccharide **19** were formed with complete α-selectivity. Furthermore, the glycosylation of lactose acceptor **10** proceeded with complete regioselectivity to deliver exclusively the 4′-deoxyfucosyl trisaccharide. Thus, under these reaction conditions glycosides of 2-deoxy-L-fucose can be prepared with high selectivity and the method is applicable to the construction of oligosaccharides.

D-Digitoxosyl fluoride **4** reacted with glucosyl and galactosyl silyl ethers **5b** and **6b** under the mild conditions provided by the $LiClO_4/Et_2O$ systems to give the corresponding disaccharides **20** and **21** in satisfying yields (Table 1, entries 13 and 14). Whereas with glucose acceptor **5b** the anomers were formed in nearly a 1:1 ratio, for galactose disaccharide **21** a high α/β ratio was once more recorded.

In conclusion the results detailed above demonstrate that in 0.1 M $LiClO_4/Et_2O$ mixtures glycosides of 2-deoxy and 2,6-dideoxy carbohydrates are formed in useful yields and with high stereoselectivity. The glycosidation reactions proceed under neutral conditions and without need for an additional promoter usually applied in glycoside synthesis, *i.e.* a strong Lewis acid, a heavy metal salt or an alkylating reagent.

This research was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

Notes and references

† *General procedure* for the glycosydations with the fluorides **2**, **3** and **4** as donors. Pulverized, freshly activated molecular sieves (4 Å) (70 mg), $LiClO_4$ or $Ba(ClO_4)_2$ (0.2 mmol) and acceptor (0.2 mmol) were stirred in Et_2O, CH_2Cl_2 or MeCN (1 ml) for 30 min under argon. To this suspension was added a solution of the donor (0.1 mmol) in the same solvent (1 ml). In the case of acceptors without a TMS group, CsF (0.1 mmol) was used as an acid scavenger. After stirring for 3 d (2 d with the donors **3** and **4**) at room temperature, the reaction mixture was diluted with CH_2Cl_2 (50 ml), filtered and washed with water. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by flash chromatography.

‡ *Selected data* for **18**: This compound was purified by flash chromatography with EtOAc–hexane (1% NEt_3) 1:8→1:4→1:2. White solid; mp 109 °C; R_f: 0.66 (EtOAc–hexane 1/2); $[\alpha]_D$ −72.2 (*c* 1.0, $CHCl_3$); δ_H(500 MHz, $CDCl_3$) 0.67 (s, 3H), 0.85–1.57 (m, 33H), 1.15 (d, $J_{5,6}$ 6.5, 3H, 6-CH_3), 1.76–1.84 (m, 3H), 1.93–2.01 (m, 3H, 2′-H, 2H Chol), 2.17–2.21 (m, 2H, 2-H), 2.32 (dd, *J* 3.0, 13.2, 1H), 3.41–3.44 (m, 1H), 3.61 (s, 1H, 4-H), 3.87 (q, $J_{5,6}$ 6.6, 1H, 5-H), 3.94–3.96 (m, 1H, 3-H), 4.59–4.64 (m, 2H, OCH_2Ph), 4.69, 4.96 (2d, J_{gem} 11.8, 2H, OCH_2Ph), 5.11 (d, $J_{1,2}$ 3.3, 1H, 1-H), 5.32 (d, *J* 4.8, 1H), 7.24–7.39 (m, 10H, Ph*H*).

1 J. Thiem and W. Klaffke, *Top. Curr. Chem*., 1990, **154**, 285; K. Toshima and K. Tatsuta, *Chem. Rev*., 1993, **93**, 1503.

2 For recent references see: J. Thiem and W. Klaffke, *J. Org. Chem*., 1989, **54**, 2006; S. Sabesan and S. Neira, *J. Org. Chem*., 1991, **56**, 5468; K. Suzuki, G. A. Sulikowski, R. W. Friesen and S. J. Danishefsky, *J. Am. Chem. Soc*., 1990, **112**, 8895; H. Mereyala, V. R. Kulkarni, D. Ravi, G. V. M. Sharma, B. Venkateswara Rao and G. B. Reddy, *Tetrahedron Lett*., 1992, **48**, 545; K. Toshima, S. Mukaiyma, Y. Nozaki, H. Inokuchi, M. Nakata and K Tatsuta, *J. Am. Chem. Soc*., 1994, **116**, 9042;

3 For recent references see: J. Thiem, M. Gerken and K. Bock, *Liebigs Ann. Chem*., 1983, 462; Y. Ito and T. Ogawa, *Tetrahedron Lett*., 1990, **46**, 89; K. Toshima, Y. Nozaki and K. Tatsuta, *Tetrahedron Lett*., 1991, **32**, 6887; R. Preuss and R. R. Schmidt, *Synthesis*, 1988, 694; S. Hashimoto, Y. Yanagiya, T. Honda and S. Ikegami, *Chem. Lett*., 1992, 1511.

4 J. Gervay and S. Danishefsky, *J. Org. Chem*., 1991, **56**, 5448.

5 Recent references: application of the Koenigs–Knorr reaction in the direct synthesis of 2-deoxy glycosides employing the insoluble silver silicate: (*a*) J. Thiem and S. Köpper, *Tetrahedron*, 1990, **46**, 133; (*b*) R. W. Binkley, *J. Carbohydr. Chem*., 1990,**9**, 507; application of glycosyl phosphoramidites and phosphites for the direct synthesis of 2-deoxy glycosides: (*c*) H. Li, M. Chem and K. Zhao, *Tetrahedron Lett*., 1997, **38**, 6143; (*d*) S. Hashimoto, A. Sano, H. Sakamoto, M. Nakajima, Y Yanagiya and S. Ikegami, *Synlett*, 1995, 1271; application of glycosyl sulfoxides for the direct synthesis of 2-deoxy glycosides: (*e*) S.-H. Kim, D. Augeri, D. Yang and D. Kahne, *J. Am. Chem. Soc*., 1994, **116**, 1766; application of gylcosyl fluorides for the direct synthesis of 2-deoxy glycosides: (*f*) J. Junnmann, I. Lundt and J. Thiem, *Liebigs Ann. Chem*., 1991, 759.

6 H. Waldmann, G. Böhm, U. Schmid and H. Röttele, *Angew. Chem*., 1994, **106**, 2024; *Angew. Chem., Int. Ed. Engl*., 1994, **33**, 1944; G. Böhm and H. Waldmann, *Tetrahedron Lett*., 1995, **36**, 3843; G. Böhm and H. Waldmann, *Liebigs. Ann. Chem*., 1996, 613 and 621; U. Schmid and H. Waldmann, *Chem. Eur. J*., 1998, **4**, 494; H. Schene and H. Waldmann, *Eur. J. Org. Chem*., 1998, 1227.

7 α-Configured glucosyl trichloroacetimidate **1** was synthesized by treatment of 3,4,6-tri-*O*-benzyl-2-deoxyglucose with NaH and Cl_3CCN in CH_2Cl_2 according to the general procedure described by R. R. Schmidt, J. Michel and M. Roos, *Liebigs Ann. Chem*., 1984, 1343. The corresponding β-anomer was obtained by employing K_2CO_3 as base. In both cases the yield was quantitative. Glycosyl fluorides **2–4** were obtained in quantitative yield by treatment of the corresponding 1-*O*-deprotected benzylated carbohydrates with diethylamino sulfur trifluoride (DAST) in CH_2Cl_2 according to the general procedure (W. Rosenbrook, Jr., D. A. Riley and P. A. Lartey, *Tetrahedron Lett*., 1985, **26**, 3).

8 S. T. Handy, P. A. Grieco, C. Mineur and L. Ghosez, *Synlett* 1995, 565; R. Tamion, C. Mineur and L. Ghosez, *Tetrahedron Lett*., 1995, **36**, 8977.

9 P. A. Grieco, *Aldrichim. Acta*, 1991, **24**, 59; H. Waldmann, *Angew. Chem*., 1991, **103**, 1335; *Angew. Chem., Int. Ed. Engl*., 1991, **30**, 1306; U. Schmid and H. Waldmann, in *Organic Synthesis Highlights III*, ed. J. Mulzer and H. Waldmann, Wiley-VCH, Weinheim, 1997, pp. 205–210

Communication 8/07734G