Activation of Glycosyl Phosphites under Neutral Conditions in Solutions of Metal Perchlorates in Organic Solvents

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Glycosyl phosphites **1–3** derived from glucose are activated under neutral conditions and without the addition of any further promoter in 1 M solutions of $LiClO_4$, $Mg(ClO_4)_2$ or $Ba(ClO_4)_2$ in ether, CH_2Cl_2, or CH_3CN and react under these conditions with the alcohols **5–9** to give the glycosides **10–14**. The best results are obtained in the presence of $Ba(ClO_4)_2$. In CH_2Cl_2 and ether the α-anomers predominate, in CH_3CN the β-isomers are formed in excess. Whereas the methyl phosphite **1** and the benzyl phosphite **3** deliver the desired glycosides in yields of 35–66%, the ethyl phosphite **2** is a more reactive glycosyl donor, giving the glycosides **10**, **11** and **13** in 62–95% yield.

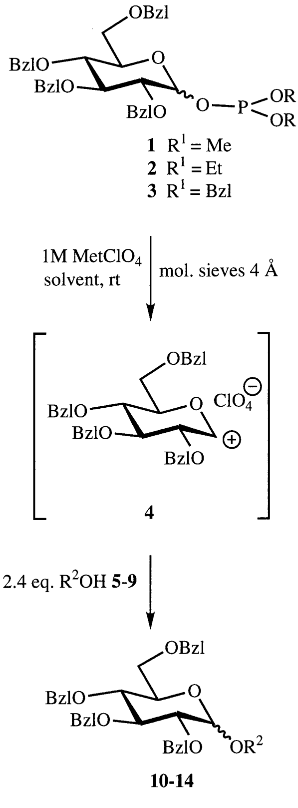
Introduction

Glycoconjugates play important roles in numerous biological processes,[1] and due to this relevance the development of new methods for the synthesis of tailor-made glycosides is of great interest to synthetic[2] and medicinal chemistry.[3]

Since numerous biologically relevant polyfunctional glycoconjugates contain many reactive functionalities as well as acid- and base labile structures it is highly desirable to develop synthetic methods by which glycosidic bonds can be built up under mild, preferably neutral conditions and without the need to use additional promoters like alkylating reagents or strong Lewis acids. We have recently reported[4] that these criteria are met by using concentrated solutions of $LiClO_4$ in organic reaction media.[5] In these solvent systems glycosyl halides, -trichloroacetimidates and -phosphates are activated under neutral conditions and participate as glycosyl donors in glycosylation reactions with different glycosyl acceptors. Recently, the repertoire of these established classes of glycosyl donors was enriched by glycosyl phosphites.[6] These carbohydrate derivatives are activated by treatment with strong Lewis acids and have, in particular, found interesting applications in the construction of *N*-acetylneuraminyl glycosides.

In this paper we report that glycosyl phosphites can be activated under neutral conditions in concentrated solutions of metal perchlorates in organic solvents.

Scheme 1

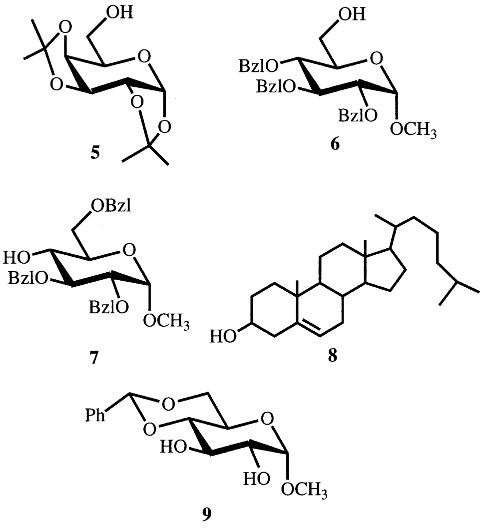


Results and Discussion

In order to study if glycosyl phosphites can be employed as glycosyl donors in metal perchlorate solutions without any further promoter, the benzyl protected glucosyl phosphites **1**[7], **2**[8] and **3**[9] were treated with the alcohols **5−9** (Scheme 2) in 3 M, 1 M and 0.5 M solutions of $LiClO_4$, $Mg(ClO_4)_2$ or $Ba(ClO_4)_2$ in different solvents (Scheme 1).

In initial experiments the reaction conditions were optimized for the dimethyl phosphite **1**, the respective results are given in Table 1. In general, the best results were obtained in 1 M solutions of the metal perchlorates. For

Scheme 2



$LiClO_4$ in diethyl ether or dichloromethane the yields and the stereoselectivity of the glycoside formation are comparable (Table 1, entries 1, 3, 5 and 6). In these solvent systems the α-anomers are formed predominantly but the stereoselectivity is not very pronounced. If acetonitrile is used instead, the β-anomers are generated in excess (Table 1, entries 4 and 9).

This reversal of the stereoselectivity is due to participation of the solvent in the glycosylation reaction, resulting in the formation of nitrilium/nitrile adducts which shield the α-face of the anomeric center.[10] If $Mg(ClO_4)_2$ or $Ba(ClO_4)_2$ are employed instead of $LiClO_4$ the α-glycosides are formed in excess, too (Table 1, entries 2, 7, 8, 10−17 and 19). With respect to the yield, $Mg(ClO_4)_2$ does not provide an advantage over $LiClO_4$, however, in the presence of $Ba(ClO_4)_2$ significantly more product is formed and the desired glycosides **10**−**14** are obtained in yields of 27−64% (Table 1, entries 2, 8, 10, 11, 12, 14, 15, 17 and 19). This may be rationalized by the fact that Ba^{2+} is a much larger and softer Lewis acid than Li^+. Consequently it coordinates better with the soft and relatively weak Lewis base provided by the phosphorus atom of the phosphite, thereby activating it.

Increasing the $Ba(ClO_4)_2$ concentration from 1 M to 3 M leads to a decrease in the yield of the desired product (Table 1, compare entry 8 with entry 10), lowering the concentration from 1 M to 0.5 M, however, does not give inferior results (Table 1, compare entry 8 with entry 11 and entry 14 with entry 15). In the 3 M solution an undesired side reaction occurs which is not relevant at lower salt concentrations. As was already observed for the benzyl protected glycosyl halides analogous to **1**, in concentrated solutions of metal perchlorates 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose is formed in yields up to 51%. In the glycosylations of the less reactive glycosyl acceptors **7** and **9** this byproduct is also formed in 5−10% yield. In **9** two secondary hydroxyl groups are available for glycoside bond formation. If $LiClO_4$ is employed, only the 3-OH group reacts to give **14a** (Table 1, entry 20), with $Ba(ClO_4)_2$ a small amount of the 2-glycoside **14b** is formed, too (Table 1, entry 19).

In order to determine if the nature of the alcohols present in the phosphite leaving group does influence the result of the glycosylation reactions, e.g. by enhancing the leaving group ability, the diethyl phosphite **2** and the dibenzyl phosphite **3** were employed as glycosyl donors (Table 2 and Table 3).

In the reactions of **2** and **3** with the primary carbohydrate derived alcohols **5** and **6** and the secondary steroid alcohol **8** the general trends delineated above for the influence of the type of the metal perchlorate and its concentration, the solvent and the stereoselectivity basically are the same (see

Table 1. Results of the glycosylations with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl dimethyl phosphite **1**

Entry	Promoter	Glycosyl acceptor	Solvent	Glycoside	Yield [%]	Anomeric ratio (α:β)
1	$LiClO_4$	**5**	Et_2O	**10**	38	1.5:1
2	$Ba(ClO_4)_2$	**5**	Et_2O	**10**	47	3.5:1
3	$LiClO_4$	**5**	CH_2Cl_2	**10**	40	1:1
4	$LiClO_4$	**5**	CH_3CN	**10**	24	1:3.3
5	$LiClO_4$	**6**	Et_2O	**11**	38	1.4:1
6	$LiClO_4$	**6**	CH_2Cl_2	**11**	38	1.5:1
7	$Mg(ClO_4)_2$	**6**	CH_2Cl_2	**11**	20	1.7:1
8	$Ba(ClO_4)_2$[a]	**6**	CH_2Cl_2	**11**	50	1.6:1
9	$LiClO_4$	**6**	CH_3CN	**11**	32	1:2.6
10	$Ba(ClO_4)_2$[b]	**6**	CH_2Cl_2	**11**	32	1.7:1
11	$Ba(ClO_4)_2$[c]	**6**	CH_2Cl_2	**11**	64	1.5:1
12	$Ba(ClO_4)_2$	**7**	Et_2O	**12**	27	5:1
13	$Mg(ClO_4)_2$	**7**	CH_2Cl_2	**12**	30	1.4:1
14	$Ba(ClO_4)_2$	**7**	CH_2Cl_2	**12**	36	1.7:1
15	$Ba(ClO_4)_2$[c]	**7**	CH_2Cl_2	**12**	32	3:1
16	$Mg(ClO_4)_2$	**8**	Et_2O	**13**	46	2.4:1
17	$Ba(ClO_4)_2$	**8**	Et_2O	**13**	35	3.6:1
18	$Ba(ClO_4)_2$	**8**	CH_2Cl_2	**13**	59	1:1
19	$Ba(ClO_4)_2$	**9**	Et_2O	**14a/14b**	29/6	2:1/only α
20	$LiClO_4$	**9**	Et_2O	**14a/14b**	30/-	2.5:1/−

[a] Without molecular sieves. − [b] 3 M promoter. − [c] 0.5 M promoter.

Table 2. Results of the glycosylations with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl diethyl phosphite **2**

Entry	Promoter	Glycosyl acceptor	Solvent	Glycoside	Yield [%]	Anomeric ratio (α:β)
1	$LiClO_4$	**5**	Et_2O	**10**	41	1.7:1
2	$Ba(ClO_4)_2$	**5**	Et_2O	**10**	62	2.5:1
3	$LiClO_4$	**5**	CH_3CN	**10**	62	1:3.3
4	$Ba(ClO_4)_2$[a]	**6**	CH_2Cl_2	**11**	77	1.7:1
5	$Mg(ClO_4)_2$	**8**	Et_2O	**13**	30	4:1
6	$Ba(ClO_4)_2$	**8**	Et_2O	**13**	95	3:1

[a] 0.5 M promoter.

Table 3. Results of the glycosylations with 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl dibenzyl phosphite **3**

Entry	Promoter	Glycosyl acceptor	Solvent	Glycoside	Yield [%]	Anomeric ratio (α:β)
1	$LiClO_4$	**5**	Et_2O	**10**	54	1.8:1
2	$Ba(ClO_4)_2$	**5**	Et_2O	**10**	41	1.9:1
3	$LiClO_4$	**5**	CH_3CN	**10**	51	1:3
4	$Ba(ClO_4)_2$[a]	**6**	CH_2Cl_2	**11**	49	1.5:1
5	$Ba(ClO_4)_2$	**6**	Et_2O	**11**	50	5.2:1
6	$Ba(ClO_4)_2$	**8**	Et_2O	**13**	66	2:1

[a] 0.5 M promoter.

Table 2 and Table 3). However, whereas for the dibenzyl phosphite **3** the yields were comparable to those recorded for the dimethyl phosphite **1**, the diethyl phosphite **2** in $Ba(ClO_4)_2$ solutions delivered the desired glycosides with significantly improved results. Thus, with this glycosyl donor the galactosyl glycoside **10** was obtained in 62% yield, the glucosyl glycoside **11** was formed in 77% yield and for the cholesteryl glycoside **13** a yield of 95% was recorded (Table 2, entries 2, 4 and 6). Obviously, under these conditions the diethyl phosphite **2** is a much better glycosyl donor than the dimethyl phosphite **1** and the dibenzyl phosphite **3**.

The results recorded for the use of metal perchlorates (in particular $Ba(ClO_4)_2$) in organic solvents as reaction media for the activation of glycosyl phosphites compare favorably with those from other methods currently in use for glycoside synthesis employing glycosyl phosphites as glycosyl donors. For instance, cholesteryl glucoside **13** was obtained in 89% yield by $ZnCl_2$ promoted glycosylation using dimethyl phosphite **1**,[7] whereas upon activation of diethyl phosphite **2** in $Ba(ClO_4)_2$/ether the glycoside **13** was formed in 95% yield (Table 2, entry 6). Also, formation of Glc-(1→6)-Glc saccharides by activation of dibenzyl phosphite **3** with TMSOTf, Tf_2O or TfOH proceeded with 62−72%[9] whereas the use of diethyl phosphite **2** in $Ba(ClO_4)_2/CH_2Cl_2$ gave the glucosyl disaccharide **11** in 77% yield (Table 2, entry 4). Although better results can often be obtained with dimethyl phosphites,[7][9] this requires the use of expensive and toxic heavy metal salts like $AgClO_4$ or strong Lewis acids like $BF_3 \cdot Et_2O$ as promoters which may cause severe problems if acid-sensitive oligosaccharides are built up. This disadvantage is clearly overcome by using metal perchlorate/solvent mixtures as reaction media.

In conclusion we have demonstrated that glycosyl phosphites can be activated as glycosyl donors under neutral conditions in 1 M solutions of metal perchlorates in different organic solvents. Under optimized conditions the desired glycosides may be obtained in preparatively very useful yields.

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Experimental Section

General: Melting points (uncorrected): Büchi 530 melting point apparatus. − ^1H and ^{13}C NMR: Bruker DRX 500; internal standard tetramethylsilane (TMS). − MS: A.E.I. (Kratos), matrix: 3-nitrobenzyl alcohol. − Optical rotations: Perkin-Elmer polarimeter 241. − Elemental analyses: Elementar CHN-Rapid Analyzer. − TLC: Macherey-Nagel silica gel 60 F_{254}. − Flash chromatography: silica gel (Baker, 40−60 μm). − $LiClO_4$ was obtained from Acros (Jansen) as a >99% pure solid. $Mg(ClO_4)_2$ was obtained from Fluka as a >92% pure solid and $Ba(ClO_4)_2$ from Aldrich as a 99% pure solid. Prior to use they were dried extensively in vacuo (0.1 Torr; 24 h) at 150°C.

General Procedure for the Glycosylations: To a mixture of the glycosyl donors **1**−**3** (0.25 mmol), the glycosyl acceptor (0.5 mmol), the metal perchlorate (5 mmol) and 0.25 g of powdered molecular sieves (4 Å) was added 5 ml of the respective organic solvent under an argon atmosphere (Solubility of the metal perchlorates: $Mg(ClO_4)_2$ used in concentrations of 1 M/l was soluble in all three solvents. 1 M/l $LiClO_4$ was soluble in Et_2O but not in CH_2Cl_2. In CH_3CN 0.9 M/l $LiClO_4$ were dissolved. $Ba(ClO_4)_2$ in the concentration of 1 M/l was soluble in CH_3CN but not in Et_2O and CH_2Cl_2. After stirring for 3−5 d, the reaction mixture was diluted with 50 ml of the solvent, filtered and washed with 50 ml of water. The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography by using *n*-hexane/ethyl acetate mixtures as eluents.

By this procedure the following compounds were prepared (for yields and anomeric ratios see Tables 1−3).

6-O-(2,3,4,6-Tetra-O-benzyl-α/β-D-glucopyranosyl)-1,2:3,4-di-O-isopropylidene-α-D-galactopyranoside[11] (**10**)

Methyl 6-O-(2,3,4,6-Tetra-O-benzyl-α/β-D-glucopyranosyl)-(1→6)-2,3,4-tri-O-benzyl-α-D-glucopyranoside[9] (**11**)

Methyl 4-O-(2,3,4,6-Tetra-O-benzyl-α/β-D-glucopyranosyl)-(1→4)-2,3,6-tri-O-benzyl-α-D-glucopyranoside[7] (**12**)

Cholesteryl 2,3,4,6-Tetra-O-benzyl-α/β-D-glucopyranoside[7] (**13**)

Methyl 3-O-(2,3,4,6-Tetra-O-benzyl-α/β-D-glucopyranosyl)(1→3)-4,5-di-O-benzylidene-α-D-glucopyranoside (**14a**): R_f = 0.19 (n-hexane/ethyl acetate, 2:1). − $[\alpha]_D^{20}$ = +92.4 (c = 0.6, $CHCl_3$ for the α anomer). − 500 MHz ^{1}H NMR ($CDCl_3$) (α): δ = 7.10−6.91 (m, 25 H, Ph-*H*), 5.49 (s, 1 H, C*H*-Ph), 5.40 (d, $J_{1b,2b}$ = 3.9 Hz, 1 H, 1b-H), 5.00 (d, J = 10.9 Hz, 1 H, OCH_2-Ph) 4.83−4.78 (m, 3 H, 2 OCH_2-Ph, 1a-H), 4.59−4.45 (m, 4 H, 4 OCH_2-Ph), 4.32 (d, J = 12.4 Hz, 1 H, OCH_2-Ph), 4.28 (dd, $J_{6a',5a}$ = 4.7 Hz, $J_{6a,6a'}$ = 10.3 Hz, 1 H, 6a′-H), 4.16 (t, $J_{2a,3a}$ = $J_{3a,4a}$ = 9.4 Hz, 1 H, 3a-H), 4.00 (t, $J_{2b,3b}$ = $J_{3b,4b}$ = 9.3 Hz, 1 H, 3b-H), 3.85 (dt, $J_{5a,6a'}$ = 4.6 Hz, $J_{5a,6a}$ = $J_{5a,4a}$ = 9.9 Hz, 1 H, 5a-H), 3.79−3.42 (m, 8 H, 2a, 4a, 6a, 2b, 4b, 5b, 6b,b′-H), 3.40 (s, 3 H, OCH_3), 2.52 (d, $J_{2a,OH}$ = 10.7 Hz, 1 H, 2a-OH). (β anomer): 5.52 (s, 1 H, C*H*-Ph), 3.42 (s, 3 H, OCH_3). − 125 MHz ^{13}C NMR ($CDCl_3$): δ = 138.93−137.2 (C-*ipso*), 129.45−126.34 (25 C, Ph), (α anomer) 102.21 (*C*H-Ph), 100.35 (C-1a), 96.49 (C-1b), 81.77, 81.70, 78.75, 77.87, 75.86, 71.19, 69.94, 62.46 (C-2a, 3a, 4a, 5a, 2b, 3b, 4b, 5b), 75.69, 74.98, 73.63, 71.07 (4 CH$_2$Ph), 69.15 (C-6a, 6b), 55.51 (CH$_3$); (β anomer) 103.25 (*C*H-Ph), 101.49 (C-1b), 99.84 (C-1a), 82.2, 85.18, 80.81, 79.11, 78.01, 75.13, 72.68, 62.96 (C-2a, 3a, 4a, 5a, 2b, 3b, 4b, 5b), 75.6, 75.37, 73.7 (4 · CH$_2$Ph), 69.0, 68.85 (C-6a, 6b), 55.39 (CH$_3$). − $C_{48}H_{52}O_{11}$ (804.9): calcd. C 71.62, H 6.51; found C 71.81, H 6.64.

Methyl 2-O-(2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl)-(1→2)-4,5-di-O-benzylidene-α-D-glucopyranoside (**14b**): R_f = 0.33 (n-hexane/ethyl acetate, 2:1). − $[\alpha]_D^{20}$ = +160.8 (c = 0.1, $CHCl_3$). − 500 MHz ^{1}H NMR ($CDCl_3$): δ = 7.5−7.1 (m, 25 H, Ph-*H*), 5.52 (s, 1H,C*H*-Ph), 4.97 (d, J = 10.9 Hz, 1 H, OCH_2-Ph), 4.93 (d, $J_{1a,2a}$ = 3.7 Hz, 1 H, 1a-H), 4.84 (d, $J_{1b,2b}$ = 4.3 Hz, 1 H, 1b-H), 4.84−4.43 (m, 7 H, OCH_2-Ph), 4.28 (dd, $J_{6a',5a}$ = 4.8 Hz, $J_{6a,6a'}$ = 10.1 Hz, 1 H, 6a′-H), 4.13 (t, $J_{3a,2a}$ = $J_{3a,4a}$ = $J_{3b,2b}$ = $J_{3b,4b}$ = 9.2 Hz, 2 H, 3a, 3b-H), 4.04 (t, $J_{4b,5b}$ = $J_{5b,6b}$ = 9.3 Hz, 1 H, 5b-H), 3.85 (dt, $J_{5a,6a'}$ = 4.8 Hz, $J_{5a,4a}$ = $J_{5a,6a}$ = 10.1 Hz, 1 H, 5a-H), 3.75−3.61 (m, 4 H, 6b, 6b′, 6a, 4a-H), 3.61−3.58 (m, 2 H, 2a, 2b-H), 3.64 (t, $J_{3a,4a}$ = $J_{4a,5a}$ = 9.4 Hz, 1 H, 4a-H), 3.42 (s, 3 H, OCH_3), 2.87 (br. s, 1 H, 3a-OH). − 125 MHz ^{13}C NMR ($CDCl_3$): δ = 138.76−137.16 (C-*ipso*), 129.15−126.39 (25 C, Ph), 102.03 (*C*H-Ph), 98.26 (C-1a), 96.48 (C-1b), 81.65 (C-5b), 81.3 (C-4a), 79.58, 77.22 (C-2a, 2b), 77.64 (C-4b), 70.63, 69.31 (C-3a, 3b), 62.07 (C-5a) 75.64, 75.12, 73.47, 73.17 (4 · CH$_2$Ph), 69.06, 68.37 (C-6a, 6b), 55.35 (CH$_3$). − $C_{48}H_{52}O_{11}$ (804.9): calcd. C 71.62, H 6.51; found C 71.74, H 6.63.

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[1] R. A. Dwek, *Chem. Rev.* **1996**, *96*, 683−720. − A. Varki, *Glycobiology* **1993**, *3*, 97−130. − L. A. Lasky, *Science* **1992**, *258*, 964−969. − T. Feizi, *Nature* **1985**, *314*, 53−57.

[2] Reviews on glycoside synthesis: H. Paulsen, *Angew. Chem.* **1982**, *94*, 184−201; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 155−172. − R. R. Schmidt, *Angew. Chem.* **1986**, *98*, 213−236; *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 212−235. − K. Toshima, K. Tatsuta, *Chem. Rev.* **1993**, *93*, 1503−1531. − C.-H. Wong, R. L. Halcomb, Y. Ichikawa, T. Kajimoto, *Angew. Chem.* **1995**, *107*, 453−474 and 569−593; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 412−433 and 521−545.

[3] Review on the relevance of oligosaccharides to medicinal chemistry: J. H. Musser, *Ann. Rep. Med. Chem.* **1992**, *27*, 301.

[4] H. Waldmann, G. Böhm, U. Schmid, H. Röttele, *Angew. Chem.* **1994**, *106*, 2024−2025; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1944−1946. − G. Böhm, H. Waldmann, *Tetrahedron Lett.* **1995**, *36*, 3843−3846. − G. Böhm, H. Waldmann, *Liebigs Ann.* **1996**, 613−619 and 621−625. − U. Schmid, H. Waldmann, *Tetrahedron Lett.* **1996, 37**, 3837−3840. − U. Schmid, H. Waldmann, *Liebigs Ann.* **1997**, 2573−2577. − U. Schmid, H. Waldmann, *Chem. Eur. J.* **1997**, *4*, 490−497.

[5] Recent review: A. Flohr, H. Waldmann, *J. Prakt. Chem.* **1995**, *337*, 609−611.

[6] T. J. Martin, R. R. Schmidt, *Tetrahedron Lett.* **1992**, *33*, 6123−6126. − T. Müller, R. Schneider, R. R. Schmidt, *ibid.* **1994**, *35*, 4763−4766. − M. M. Sim, H. Kondo, C.-H. Wong, *J. Am. Chem. Soc.* **1993**, *115*, 2260−2267. − Y. Watanabe, C. Nakamoto, S. Ozaki, *Synlett* **1993**, 115−116. − T. Müller, G. Hummel, R. R. Schmidt, *Liebigs Ann. Chem.* **1994**, 325−329. − S. Hashimoto, K. Umeo, N. Watanabe, M. Nakajima, S. Ikegami, *Tetrahedron Lett.* **1995**, *36*, 2251−2254.

[7] Y. Watanabe, C. Nakamoto, T. Yamamoto, S. Ozaki, *Tetrahedron* **1994**, *50*, 6523−6536.

[8] S. Hashimoto, K. Umeo, A. Sano, N. Watanabe, M. Nakajima, S. Ikegami, *Tetrahedron Lett.* **1995**, *36*, 2251−2254.

[9] H. Kondo, S. Aoki, Y. Ichikawa, R. L. Halcomb, H. Ritzen, C.-H. Wong, *J. Org. Chem.* **1994**, *59*, 864−877.

[10] R. R. Schmidt, M. Behrendt, A. Toepfer, *Synlett* **1990**, 694−696. − Y. D. Vankar, P. S. Vankar, M. Behrendt, R. R. Schmidt, *Tetrahedron* **1991**, *47*, 9985−9992. − T. J. Martin, R. Brescello, A. Toepfer, R. R. Schmidt, *Glycoconjugate J.* **1993**, *10*, 16−25.

[11] H.-W. Liu, K. Nakanishi, *J. Am. Chem. Soc.* **1982**, *104*, 1178−1185.

[97412]