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Preparation of Ether-linked 2-Acetamido-2-deoxy β-Glycolipids via Zinc Chloride Promoted Coupling of Ac_4GlcNAc-Cl with Lipid Hydroxy Groups

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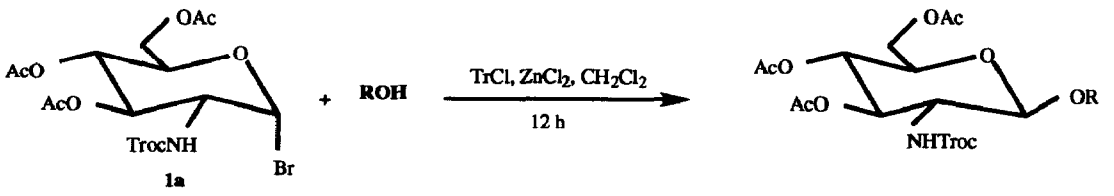
Abstract: Stereoselective glycosidation of lipid hydroxy groups has been achieved using 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glycosyl chloride as the glycosyl donor in CH_2Cl_2. In the presence of $ZnCl_2$ (1 equiv.) and various "promoters" (1 equiv.) such as Ph_3CCl, 18-crown-6/KCl, *n*-Bu_4NBr, or Me_3SiCl, β-glycolipid conjugates are formed as the initial products, but they undergo anomerization on prolonged reaction times. The promoters may enhance the solubility of $ZnCl_2$ in CH_2Cl_2.

As part of our program on the study of biologically active ether-linked glycolipids,[1] we sought to prepare ether glycolipids having a 2-acetamido-2-deoxy group. 2-Acetamido-2-deoxyglycolipid conjugates are of interest as potentially new biologically active compounds. Zinc chloride has been used previously to promote glycosidation reactions with a high β/α ratio.[2] Szabò and Polt reported that $ZnCl_2$ activated the coupling of a GlcNHTroc donor with a serine or threonine ester derivative, forming 1-*O*-acyl-β-glycopyranose.[3] α-Glycosidation of 1-*O*-acyl-β-glucopyranoses with alcohol was reported to be catalyzed by trityl cation.[4] Recently, Higashi *et al.*[5] reported that an equimolar mixture of trityl chloride (TrCl) and $ZnCl_2$ promoted the coupling reaction between 2-trichloroethoxycarbonylamino(NHTroc)-2-deoxy-3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl bromide (**1a**) and an alcohol, giving the β anomer selectively (Eq. 1).

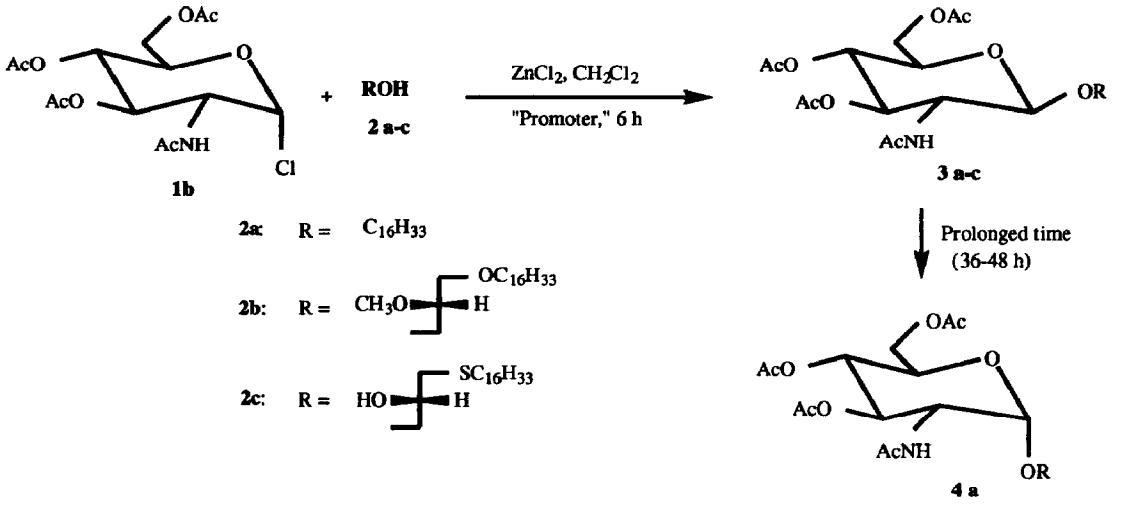
Equation 1



In efforts to avoid use of 2-deoxy-2NHTroc-protected α-glucosyl bromide [which requires three steps to prepare starting from 2-deoxyglucosamine (step 1: glucosamine to 2-NH-Troc-glucosamine; step 2: Ac_2O;

step 3: TMSBr)], we tried to couple the bromo analog of 2-acetamido sugar **1b** to 1-*O*-hexadecyl-2-*O*-methyl-*sn*-glycerol (**2b**) by using an equimolar mixture of $ZnCl_2$ and TrCl. It was observed that the 2-acetamido-1-bromo sugar was highly unstable under the reaction conditions used, eliminating HBr and forming a stable oxazolidine intermediate. However, we found that 2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-α-D-gluco-pyranosyl chloride (Ac_4GlcNAc-Cl) (**1b**) was more stable than the bromo sugar and could be made in one step from 2-acetamido-2-deoxyglucosamine.[6] Although **1b** is generally not used as a glycosyl donor because of oxazolidine formation, we report here that Ac_4GlcNAc-Cl (**1b**) is a useful starting material for the preparation of 2-acetamido-containing glycolipids. In this report we describe the coupling of lipid hydroxy groups (**2**) to **1b** in the presence of various "promoters" to give initially β-glycolipid **3**, which is isomerized on prolonged reaction times to the α anomer.

Scheme 1



The reaction of 1-*O*-hexadecyl-2-*O*-methyl-*sn*-glycerol (**2b**) with **1b** in the presence of TrCl as the promoter and $ZnCl_2$ gave β-glycolipid **3b** selectively in 70% yield after stirring for 6 h at room temperature (Scheme 1).[7] Unsaturated alcohols such as phytol and geraniol failed to undergo glycosidation, as did secondary alcohols such as cholesterol and 1-*O*-hexadecyl-3-*O*-methyl-*sn*-glycerol. The glycosidation of 1-thiohexadecyl-*sn*-glycerol (**2c**) took place in 6 h specifically at the primary hydroxyl group, giving **3c** in 50% yield, together with 20% of the starting glycerol **2c**, indicating that it is not necessary to protect the secondary hydroxyl group of the glycerol moiety. Scheme 1 is noteworthy for the lack of need to use any protecting group strategy at the 2 position, which is advantageous since the 2-acetamido conjugate **3** was desired for application in growth inhibition studies.

Table 1. Glycolipid **3a/4a** obtained by reaction of **1b** with hexadecyl alcohol in the presence of $ZnCl_2$ and promoter at 25 °C

Entry	Promoter[a]	Time (h)	Anomer formed	Yield (%)[b]	Time (h)	Anomer formed	Yield (%)[c]
1	TrCl	6	β	82	36	α	70
2	Ph_3CPF_6				36	α	22
3	HCl				48	α	46
4	KCl, 18-crown-6	6	β	75	36	α	65
5	Bu_4NBr	6	β	65	36	α	45
6	TMSCl	6	β	55	36	α	45

[a]In the absence of any co-promoter (i.e., 1 equiv. of $ZnCl_2$ alone), the glycosidation reaction was sluggish; after a reaction period of 3-4 days, only α anomer was obtained. [b] Isolated yields of the β anomers are shown. [c]Isolated yields of the α anomers are shown. Traces of β anomer were present based on TLC analysis (ethyl acetate/hexanes 2:1; R_f α anomer 0.60; R_f β anomer 0.54).

Since the role of TrCl as a co-promoter in the β-glycosidation reaction was not clear to us, we examined whether glycosidation of **2a** occurred without TrCl (Table 1). The reactions of **1b** and **2a** with triphenylcarbenium hexafluorophosphate and $ZnCl_2$ (entry 2) or with $ZnCl_2$ and HCl gas (entry 3) were very sluggish because of the low solubility of $ZnCl_2$ in methylene chloride. These coupling reactions required longer time and afforded the α anomer as the major product. We also used other promoters such as 18-crown-6 and KCl, Bu_4NBr, and TMSCl (1 equiv. of each). The reactions of **1b** and **2a** with these promoters gave β-glycolipids in good yields (entries 4-6) after 6 h. We also observed that shorter reaction time gives the β-anomer specifically, indicating that the reaction is under kinetic control irrespective of the promoter. Thus, the results shown in Table 1 indicate that *TrCl is not required* to obtain β-glycosidation of **2a**.

In a further efforts to examine the role of TrCl in the $ZnCl_2$-catalyzed glycosidation reaction, we prepared *n*-hexadecyl trityl ether. No reaction was observed when ROTr was stirred for more than 2 days in CH_2Cl_2 with **1b** in the presence of $ZnCl_2$, indicating that the lipid alcohol is not undergoing derivatization during the $ZnCl_2$/TrCl-promoted glycosidation reaction. A working hypothesis is that TrCl and the other promoters shown in Table 1 enhance the solubility of $ZnCl_2$ in CH_2Cl_2.

To examine whether a thermodynamic equilibrium between β and α glycolipid **3** can occur, we treated the isolated β anomer and the isolated α anomer separately with TrCl and $ZnCl_2$ in CH_2Cl_2. We observed that about 50% of the β anomer **3a** was epimerized to α glycoside in 48 h at room temperature; however, there was no change in the stereochemistry of the α anomer. This result suggests that the α anomer is more stable than the β anomer. Anomerization of β to α of *O*-acylated derivatives of glycosides in the presence of Lewis

acids are known to occur.[9]

In summary, we report here a simple and efficient method for the preparation of 2-acetamido-2-deoxy glycolipids in good yields by the reaction of primary lipid hydroxy groups with 2-acetamido-2-deoxy-3,4,6-tri-*O*-acetyl-α-D-gluocopyranosyl chloride, various promoters, and $ZnCl_2$ to afford β glycoside initially followed by isomerization to the α glycoside. The synthetic method presented here is applicable to the preparation of the other glycolipid conjugates.

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References

1. Guivisdalsky, P. N.; Bittman, R.; Smith, Z.; Blank, M. L.; Snyder, F.; Howard, S.; Salari, H. *J. Med. Chem.* **1990,** *33,* 2614-2621.
2. Kallin, E.; Lönn, H.; Norberg, T. *J. Carbohydr. Chem.* **1990,** *9,* 721-733.
3. Szabò, L.; Polt, R. *Carbohydr. Res.* **1993,** in press.
4. Mukaiyama, T.; Kobayashi, S.; Shoda, S. *Chem. Lett.* **1984,** 907-910.
5. Higashi, K.; Nakayama, K.; Soga, T.; Shioya, E.; Uoto, K.; Kusama, T. *Chem. Pharm. Bull.* **1990,** *38,* 3280-3282.
6. Horton, D. *Org. Synth.*; Wiley: New York; Collective Vol. V, **1973,** pp 1-5.
7. In a typical procedure for the β-glycosidation, to a suspension of $ZnCl_2$ (1 equiv.) and promoter (1 equiv.) in dry CH_2Cl_2 were added Ac_4GlcNAc-Cl (**1b**, 2 equiv.) and hydroxy lipid acceptor (**2a-c**, 1 equiv.). The reaction mixture was stirred at room temperature, and the progress of the reaction was monitored by TLC (developed in ethyl acetate). After 6 h, the reaction mixture was diluted with ethyl acetate, washed with 5% aqueous sodium bicarbonate solution and with water, dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography, giving the desired β-glycolipids in 55-82% yield.[8]
8. All compounds gave satisfactory analytical and spectroscopic data. The analytical and spectroscopic data of **3b**: R_f 0.54 (ethyl acetate); $[\alpha]_D^{25}$ -1.31° (*c* 5.6, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.80 (t, 3H, *J* = 6.0 Hz, CH_3), 1.25 (br. m, 26H, $(CH_2)_{13}CH_3$), 1.45 (m, 2H, OCH_2CH_2), 1.87, 1.95, and 2.01 (s, 12H, OAc, and NAc), 3.32-3.41 (m, 8H, with a singlet at δ 3.36, $CH_2OCH_2C_{15}H_{31}$, CH_3OCH), 3.63 (m, 3H, *H*-5 and OCH_2), 3.81 (m, 1H, *H*-2), 4.02 (dd, 1H, *H*-6a), 4.08 (dd, 1H, *J* = 4.57 Hz, 12.22 Hz, *H*-6b), 4.60 (d, 1H, *J* = 8.34 Hz, *H*-1), 5.05 (t, 1H, *J* = 9.50 Hz, *H*-4), 5.17 (t, 1H, *J* = 9.83 Hz, *H*-3), 5.84 (d, 1H, *J* = 8.51 Hz, NH).
9. Lemieux, R. U. *Adv. Carb. Chem. Biochem.* **1954,** *9,* 1-57.

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