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β-Glycosidation of Sterically Hindered Alcohols

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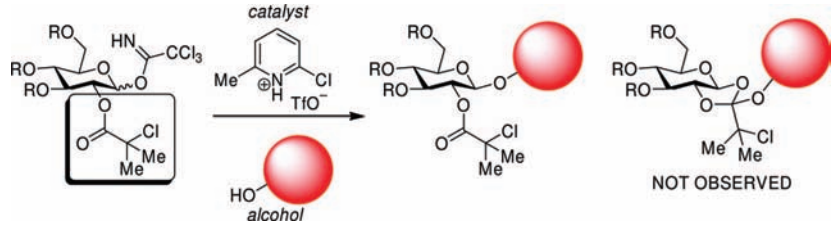
ABSTRACT

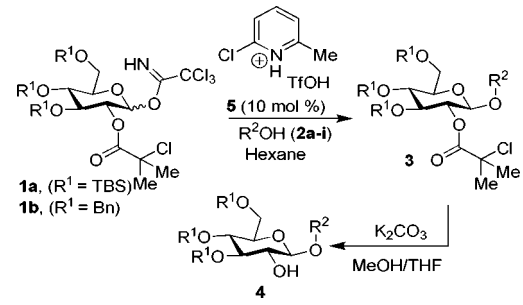


The 2-chloro-2-methylpropanoic ester serves as a steering group in the Schmidt glycosidation reaction. Rapid and efficient glycosidation of a range of sterically hindered alcohols takes place under mild, acidic conditions to afford the glycoside products in high yield and β-selectivity and without formation of orthoester side products. The 2-chloro-2-methylpropanoic ester is readily cleaved under mild, basic conditions.

β-Glycosidation of sterically hindered alcohols remains a significant challenge for the synthesis of oligosacharides and glycoside natural products.[1] Formation of β- over α-glycosides is commonly ensured by the incorporation of a C2 substituent capable of lending anchimeric assistance in the glycoside donor. However, in the coupling of sterically hindered alcohols, orthoesters are often formed as major products.[2] Sterically hindered steering groups, such as pivalyl[3] or isobutyryl[4] esters, may repress orthoester formation, yet their removal requires harsh conditions incompatible with base-sensitive substrates.

Herein, we report a protocol that enables the use of 2-chloro-2-methylpropanoic (CMP) ester as a steering group in β-glycosylation reactions of a host of sterically hindered alcohols without the observation of orthoester formation (Scheme 1).

Scheme 1. Glycosidation of Alcohols **2** with Donors **1**a and Subsequent Saponification



[a] The synthesis of donors **1a** and **1b** is detailed in the Supporting Information.

In the context of the synthesis of amphotericin B (AmB) analogues, we had documented the β-glycosidation of a protected AmB aglycon with an activated, masked mycosamine equivalent (Scheme 2).[5] Careful optimization studies in this case established the use of a CMP ester as a

(1) *Frontiers in Modern Carbohydrate Chemistry*; Demchenko, A. V., Ed.; ACS Symposium Series 960; Oxford University Press: Oxford, 2007.
(2) (a) Fürstner, A.; Jeanjean, F.; Razon, P.; Wirtz, C.; Mynott, R. *Chem.—Eur. J.* **2003**, *9*, 320. (b) Gung, B. W.; Fox, R. M. *Tetrahedron* **2004**, *60*, 9405. (c) Nicolaou, K. C.; Daines, R. A.; Ogawa, Y.; Chakraborty, T. K. *J. Am. Chem. Soc.* **1988**, *110*, 4696. (d) Kuszmann, J.; Medgyes, G.; Boros, S. *Carbohydr. Res.* **2004**, *339*, 2407. (e) Plante, O. J.; Palmacci, E. R.; Andrade, R. B.; Seeberger, P. H. *J. Am. Chem. Soc.* **2001**, *123*, 9545.
(3) Harreus, A.; Kunz, H. *Liebigs Ann. Chem.* **1986**, 717.
(4) Desmares, G.; Lefebvre, D.; Renevret, G.; Le Drian, C. *Helv. Chim. Acta* **2001**, *84*, 880.

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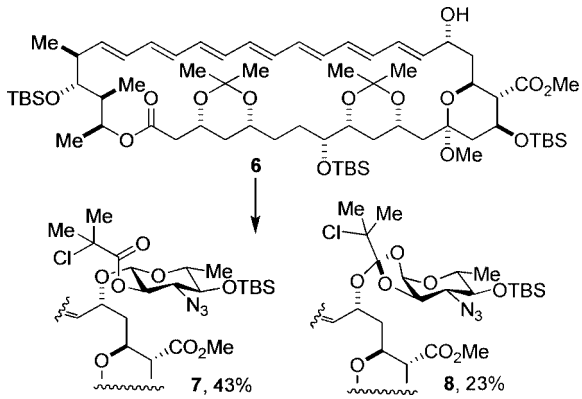
Scheme 2. Glycosidation of Protected Amphoteronolide[5a]



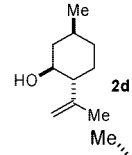
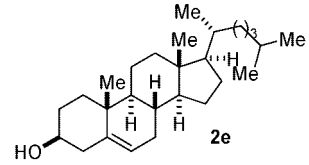
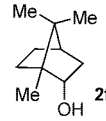
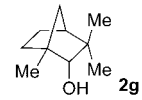
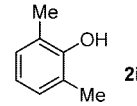
steering group at C2 able to provide selective β-glycosidation and somewhat reduce formation of the orthoester biproduct. Under optimal conditions for this substrate, protected AmB derivative **7** was obtained in 43% yield while the corresponding orthoester **8** was isolated in 23% yield. Importantly, this required the use of excess (3 equiv) mycosamine donor. As a consequence of this study in natural products chemistry, we became interested in investigating whether the glycosidation protocol was generally applicable to a broader range of hindered alcohols because their glycosidation is generally known to lead to unwanted orthoester biproducts.

The conditions we have identified involve the use of sterically hindered Brønsted acid **5** as a catalyst in the formation of product in high yield (Scheme 1).[5a] The use of hexane as the solvent is important.[2c] The trichloroacetamide formed during the reaction is poorly soluble in this solvent and precipitates out. This facilitates the isolation of the glycoside product **3** and minimizes the formation of glycosidated trichloroacetamide byproduct.

As shown in Table 1, this protocol can be employed with a range of sterically hindered alcohols **2a**−**i**, leading to the formation of β-glycosides without observation of orthoesters biproducts. Primary and secondary cyclic alcohols, as well as *tert*-butyl alcohol, are glycosidated in high yield. In each case, the reaction is complete within 30 min. In contrast to our work with AmB, the coupling can be conducted with merely 1−1.5 equiv of the alcohol.

The glycosidation of cholesterol (**2e**) is noteworthy, as this reaction is known to proceed with concomitant formation of significant amounts of orthoester (up to 55%).[3] In contrast, glycosidation of cholesterol using 1 equiv of **1b** provides the desired product in 67% yield. Higher yields have been achieved in the β-glycosidation of cholesterol **2e** but only using strongly acidic conditions under which any formed orthoester would rearrange to the glycoside product. For example, the glycosidation of **2e** using tetra-*O*-acetyl glycosyl

Table 1. Scope of the Glycosidation Reaction (See Scheme 1)[a]

donor	R^2	**3** % (β:α)	**4** % (β:α)
1a	BnOH (**2a**)	91 (4:1)	100 (4:1)
1a	$C_6H_{11}OH$ (**2b**)	80 (6:1)	97 (6:1)
1b	*t*-BuOH (**2c**)	95[b]	88[c]
1a	 **2d**	72	99
1b	 **2e**	67[d]	93
1b	 **2f**	68[e]	88
1b	 **2g**	72[e]	90
1a	PhOH (**2h**)	80 (4:1)	90 (4:1)
1b	 **2i**	62[e] (2.:1)	27(α) 47(β)

[a] All reactions were carried out using 1.5 equiv of alcohol unless otherwise noted. [b] Yield of unpurified product. [c] Yield of purified product, over two steps. [d] Using 1 equiv of **2e**. [e] Using 1.2 equiv of the alcohol.

trichloroacetimidate and the sulfonic acid based Amberlyst-15 resin proceeded in 83% yield,[6] and the reaction of tetra-*O*-benzoylgalactosyl trichloroacetimidate with **2e** using the strong Lewis acid tetramethylsilyl triflate proceeded in 75% yield.[7] In contrast to the protocol presented here, such conditions may be incompatible with acid-sensitive donors including **1a**.

Impressively, the bridged bicyclic, neopentylic secondary alcohol borneol (**2f**) and the doubly neopentylic alcohol fenchol (**2g**) are glycosidated by **1b** in 68 and 72% yield, respectively. No orthoester could be detected in the reaction in either of these cases. In stark contrast, reaction of borneol or fenchol (1 equiv) with tetra-*O*-pivaloylglucosyl bromide (2 equiv) under Koenigs−Knorr conditions (AgOTf, 2,6-di-*tert*butyl-4-methylpyridine) afforded the desired glycoside in 33−48% yield together with 27−47% orthoester.[4] The glycosidation of phenols is also possible, but yield and

(5) (a) Szpilman, A. M.; Manthorpe, J. M.; Carreira, E. M. *Angew.Chem., Int. Ed.* **2008**, *47*, 4339. (b) Szpilman, A. M.; Cereghetti, D. M.; Wurtz, N. R.; Manthorpe, J. M.; Carreira, E. M. *Angew.Chem., Int. Ed.* **2008**, *47*, 4335. (c) Manthorpe, J. M.; Szpilman, A. M.; Carreira, E. M. *Synthesis* **2005**, 3380.

(6) Tian, Q.; Zhang, S.; Yu, Q.; He, M.-B.; Yang, J.-S. *Tetrahedron* **2007**, *63*, 2142.

(7) Mbadugha, B. N. A.; Menger, F. M. *Org. Lett.* **2003**, *5*, 4041.

β-selectivity erode with increasing steric hindrance (compare **2h** with **2i**). Interestingly, glycosidation of less sterically hindered alcohols shows a similar trend. Thus, the glycosidation of benzyl alcohol (**2a**) by **1a** proceeds with 4:1 β-selectivity in 91% yield while the more hindered cyclohexyl alcohol (**2b**) is glycosidated in 80% yield and 6:1 β-selectivity.[6] In contrast, the more hindered alcohol **2d** is glycosidated by **1a** with exclusive formation of the β epimer in 72% yield.

Subsequent to coupling, the auxiliary CMP ester is readily hydrolyzed under mild basic conditions. Thus, saponification was complete within 14 h at room temperature to afford alcohols **4** in high yield (74−100%).

The glycosidation of *tert*-butyl alcohol is known to be capricious and often proceeds in low yields.[8] In contrast, the product is formed in high yield in the reaction of **1b** with 1.5 equiv of *tert*-butyl alcohol and 10 mol % of the mild acid **5**. The glycoside need not be purified prior to auxiliary removal. Simply decanting the reaction solution from the precipitated trichloroacetamide followed by aqueous workup leads to the isolation of glycoside **3c** of sufficient purity for submission to hydrolysis. Accordingly, reaction of this material with potassium carbonate (2 equiv) for 14 h and subsequent chromatographic purification leads to the desired alcohol **4c** in 88% yield over two steps.

In conclusion, in view of the unique properties of the CMP ester disclosed herein as well as the protocol described for coupling, it should be considered the ancillary group of choice for β-glycosidation of sterically hindered alcohols. It is especially attractive for applications in total synthesis of acid- and base-sensitive natural products.

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Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Glycosidation of *tert*-butyl alcohol proceeds in 20−85% yield under a variety of conditions. See, e.g.: (a) Lacombe, J. M.; Rakotomanomana, N.; Pavia, A. A. *Carbohydr. Res.* **1988**, *181*, 246. (b) Roen, A.; Padron, J. I.; Mayato, C.; Vazquez, J. T. *J. Org. Chem.* **2008**, *73*, 3351.