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Carbohydrates as chiral auxiliaries: Synthesis of 2-hydroxy-β-D-glucopyranosides

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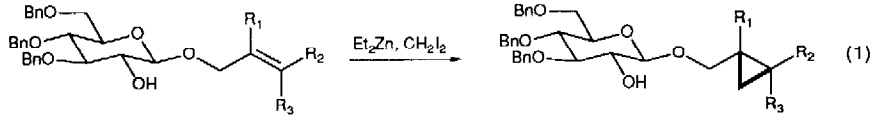
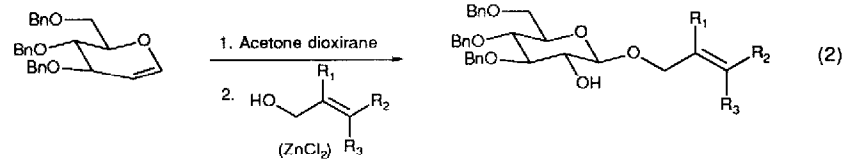
Abstract. A new 2-step, 1-pot procedure for the stereoselective glycosylation of allylic alcohols with 1,2-di-*O*-benzoyl-β-D-glucopyranosides to produce 2-hydroxy-β-D-glucopyranosides has been developed. The required precursor for the glycosylation was readily obtained from tri-*O*-benzyl-D-glucal in 2 steps (91% overall).

We recently reported that 2-hydroxy-3,4,6-tri-*O*-benzyl-β-D-glucopyranose was an extremely efficient new chiral auxiliary for the stereoselective cyclopropanation reaction of substituted allylic alcohols (eq 1).[2] The numerous potential applications of this chiral auxiliary in a number of stereoselective reactions led us to develop new and general routes for its incorporation on several allylic alcohols.

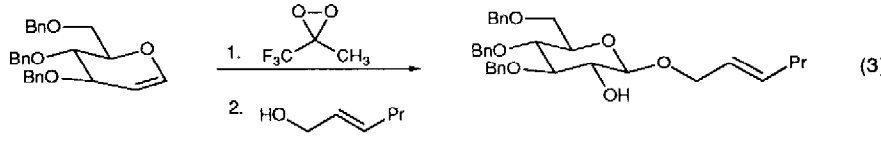


Yields: >97%
Diastereoselectivities: >50:1

A unique feature of this glycoside is that the C-2 hydroxy group has to be differentially protected from the other hydroxy groups so it can be revealed in the step prior to the cyclopropanation reaction. One method that directly produces 2-hydroxy-β-D-glucopyranosides was developed by Danishefsky[3] (eq 2). Stereoselective epoxidation of tri-*O*-benzyl-D-glucal with dimethyldioxirane followed by solvolysis with an alcohol afforded the corresponding 2-hydroxy-β-D-glucopyranosides in good yields. Similarly, we found that when allylic alcohols were used as nucleophiles, yields ranged from 65 to 90%, depending on the number of equivalents of the alcohol present in the reaction. Zinc chloride was added as a Lewis acid to facilitate epoxide opening when the reaction was run with a stoichiometric amount of the allylic alcohol.[3] Even though this method was extremely direct, scaling up was problematic due mainly to the very low concentration of the dimethyldioxirane solution (up to 0.08M) obtained from acetone and oxone.[4]



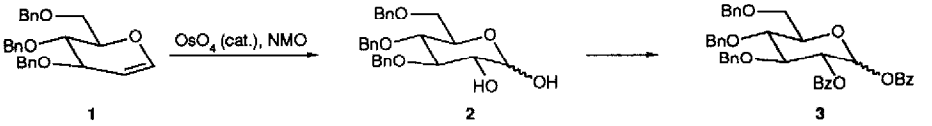
One alternative which circumvented this problem was to use methyl(trifluoromethyl)dioxirane, since this reagent can be obtained in higher concentration (0.6 to 0.9 M) from trifluoroacetone and oxone.[5] The reaction proceeded as with dimethyldioxirane and the diastereofacial selectivity of the epoxidation reaction was also similar.[6] Although this reaction was fully applicable to allylic alcohols it suffered from the relatively high cost of trifluoroacetone, the tedious large scale preparation and low stability of the reagent.



A third alternative would require using 1,2-di-*O*-benzoyl-3,4,6-tri-*O*-benzyl-β-D-glucopyranose (3β)[7] as the glycosylation precursor. It is well-established that glucopyranosides bearing a substituent capable of neighboring-group participation at C-2, undergo stereospecific glycosylation upon treatment with a variety of Lewis acids.[8] Subsequent base-catalyzed cleavage of the *O*-2 benzoyl would provide direct access to the desired compounds.

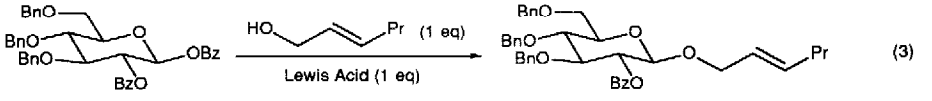
To be a useful and practical chiral auxiliary for the cyclopropanation reaction, the precursor **3** had to be available in a small number of steps from commercially available starting material. A very efficient approach was developed as illustrated in Scheme 1. Readily available tri-*O*-benzyl-D-glucal was treated with catalytic osmium tetroxide in the presence of N-methylmorpholine-N-oxide to produce stereoselectively diol **2** (98%) as a mixture of anomers.[9] Conversion of the diol to a dibenzoate was the critical step in the development of the new glycosylation precursor. Treatment of diol **2** with benzoyl chloride in pyridine at room temperature led to a 1:1 anomeric mixture of dibenzoate **3**. It was clear that in the subsequent Lewis acid mediated glycosylation, the α anomer (3α) was not reactive enough and extensive decomposition of the allylic alcohol occured instead of glycosylation.[10] The β anomer, however, was a suitable precursor and therefore had to be synthesized stereoselectively.[11] Formation of the dialkoxide from diol **2** (BuLi, C_6H_6, 2 eq, 5 °C) followed by warming to 80 °C prior to the addition of benzoyl chloride afforded the desired anomer **3β** in a relatively good yield (85%, β:α >18:1).[12,13] Subsequently, it was found that a much simpler procedure could produce the desired compound in a higher yield. When benzoyl chloride was added to a solution of diols **2** in refluxing pyridine, dibenzoate **3β** was isolated in 93% yield (β:α >18:1) as a stable white solid. The glycosylation precursor was therefore obtained in 2 steps (91% overall yield) from commercially available starting material.

Scheme 1



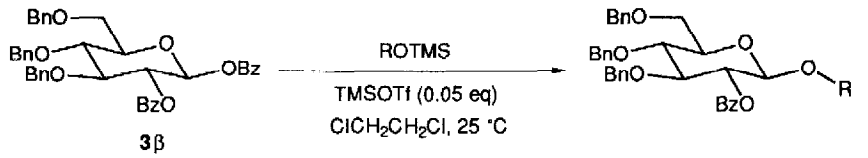
Conditions	β:α (Yields)
Pyridine, PhCOCl, 25 °C	1:1 (>95%)
Pyridine, PhCOCl, 115 °C	>18:1 (93%)
BuLi (2 eq), PhCOCl, 80 °C	>18:1 (85%)

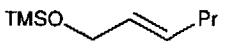
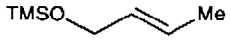
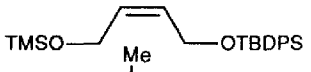
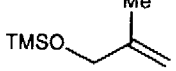
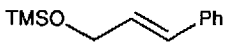
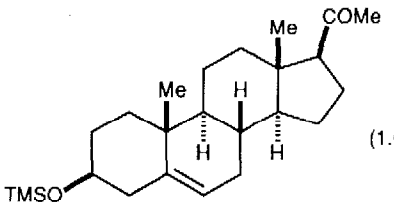
Several Lewis acids were initially surveyed for the subsequent glycosylation reaction (BBr_3, $SnCl_4$, $BF_3{\cdot}OEt_2$, TMSOTf) (eq 3).[14] TMSOTf (1 eq) was found to be the most promising reagent but the glycosylation yield was still too low (*ca.* 60%) to be acceptable.[15] Several relevant observations were made at this point. First of all, allylic alcohols decomposed rapidly upon treatment with TMSOTf in the absence of the dibenzoate. Secondly, the β-dibenzoate anomerized to the unreactive α anomer under the reaction conditions both in the presence or in the absence of the allylic alcohol. Finally, increasing the number of equivalents of the allylic alcohol resulted in a decrease in the yield of glycosylated material.



In order to minimize the amount of anomerization and alcohol decomposition in the presence of a large amount of TMSOTf, the TMS ether of the alcohol was chosen as the nucleophile instead of the free alcohol. This modification allowed us to use only a catalytic amount (0.05 eq) of TMSOTf to promote the glycosylation and prevented any triflic acid formation. After considerable optimization, it was found that if the reaction was carried out with a slight excess of dibenzoate **3β** (1.5 eq.), the yield of glycosylated material was significantly increased (Table 1).[16] Trisubstituted olefins and cinnamyl alcohol could not be successfully installed on the glycoside. In these cases, decomposition of the alcohol was significantly faster than glycosylation. Importantly, however, an excess of dibenzoate **3β** was not necessary when saturated aliphatic alcohols were used as nucleophiles and the corresponding β-glucopyranosides were isolated in high yields.

Table 1. Optimization of the glycosylation conditions.



ROTMS (# equivalents)	# equivalents (3β)	YIELD (%)[a]
	(1.0)	1.1	49%
	(1.0)	1.5	83%
	(1.0)	2.0	83%
	(2.0)	1.0	55-70%[b]
	(10.0)	1.0	<10%
	(1.0)	1.5	82% (1 h)
	(1.0)	1.5	88% (1.5 h)
	(1.0)	1.5	87% (2 h)
	(1.0)	1.5	50% (30 min)[c]
	(1.0)	1.5	39% (30 min)[c]
	(1.0)	1.5	<5% (<5 min)[c]
	(1.0)	1.1	83%
	(1.0)	1.5	92% (1 h)
	(1.0)	1.5	74% (3.5 h)

[a]Yield of pure, chromatographically isolated β-glucopyranosides. In all cases, the α anomer could not be detected by tlc analysis. [b]Yields were not reproducible and varied from 55-70%. [c]Tlc analysis showed complete disappearance of the starting TMS ether after that time.

Cleavage of the 2-benzoyl group could be achieved under standard conditions to produce the desired cyclopropanation precursors.

Acknowledgment. This research was supported by the Natural Sciences and Engineering Research Council (NSERC) of Canada, F.C.A.R. (Québec), Bio-Méga, Inc., and the Université Laval. A NSERC postgraduate fellowship to J.F.M. is gratefully acknowledged. B.C. thanks La Fondation de l'Université Laval for financial support. We also thank Drs. Pierre Lavallée and Bruno Simoneau for helpful suggestions.

References and Notes

1. NSERC (Canada) University Research Fellow, 1989-1994; Bio-Méga Young Investigator, 1991-1993.
2. Charette, A. B.; Côté, B.; Marcoux, J.-F. Accepted for publication, *J. Am. Chem. Soc.* **1991**, *113*, xxxx.
3. Halcomb, R. L.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1989**, *111*, 6661-6665.
4. For the preparation of dimethyldioxirane solutions see: Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847-2853.
5. For the preparation of methyl(trifluoromethyl)dioxirane, see: Mello, R.; Fiorentino, M.; Fusco, C.; Curci, R. *J. Am. Chem. Soc.* **1989**, *111*, 6749-6757.
6. Only the β-D-glucopyranoside derivative was detected by tlc and 200 MHz ^{1}H NMR.
7. For an alternative but longer synthesis of the D-galacto analog, see: Vernay, H. F.; Rachaman, E. S.; Eby, R.; Schuerch, C. *Carbohydr. Res.* **1980**, *78*, 267-273.
8. For a recent review on neighboring group participation in glycosylation reactions see: R. R. Schmidt *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 212-235.
9. For an alternative synthesis of **2** see: Schmidt, R. R.; Klotz, W. *Synlett* **1991**, 168-170. Schmidt, R. R.; Effenberger, G. *Carbohydr. Res.* **1987**, *171*, 59.
10. It is well-known that stereoselective glycosylation with Lewis acid is only possible with a neighboring, participating group at C-2 having a trans configuration relative to the anomeric leaving group: Paulsen, H.; Paal, M. *Carbohydr. Res.* **1984**, *135*, 53.
11. For an alternative strategy for the synthesis of *trans*-1,2-di-*O*-acetyl glycoses see: Pozsgay, V.; Jenning, H. J. *Synthesis* **1990**, 724-726 and references cited therein.
12. For a review on the control of the anomeric stereochemistry under basic conditions see ref. 8.
13. All new compounds gave satisfactory ^{1}H NMR (400 MHz), ^{13}C NMR (100 or 50 MHz), MS and elemental analyses.
14. For the use of BF_3-etherate in glycosylation reactions see: Lemieux, R. U.; Shyluk, W. P. *Can. J. Chem.* **1953**, *31*, 528. Ogawa, T.; Matsui *Carbohydr. Res.* **1976**, *51*, C13-C18. $SnCl_4$: Hanessian, S.; Banoub, J. *Carbohydr. Res.* **1977**, *59*, 261-267. TMSOTf: Ogawa, T.; Beppu, K.; Nakabayashi, S. *Carbohydr. Res.* **1981**, *93*, C6-C9. Paulsen, H. *Angew. Chem. Int. Ed. Engl.* **1982**, *215*, 155-273. Paulsen, H.; Paal, M. *Carbohydr. Res.* **1984**, *135*, 53-69.
15. For recent examples on the use of stoichiometric TMSOTf in a β-selective glycosylation reactions, see: Trumtel, M.; Veyrières, A.; Sinaÿ, P. *Tetrahedron Lett.* **1989**, *30*, 2529.
16. Typical procedure for the *in situ* silyl ether protection, glycosylation and debenzoylation sequence: To a solution of *trans*-2-hexen-1-ol (170 μL of 1.41M solution in dichloroethane, 0.24 mmol) in 1.2 mL of anhydrous dichloroethane was added 300 μL of a stock solution of triethylamine in dichloroethane (1.20 M, 0.360 mmol). The solution was cooled to -20 °C and 270 μL of a stock solution of trimethylsilyl triflate in dichloroethane (1.03 M, 0.278 mmol) was added dropwise. The clear solution was warmed to room temperature and a solution of 238.7 mg (0.36 mmol) of β-dibenzoate **3** in 1.2 mL of dichloroethane was added in one portion. A slight excess of TMSOTf (0.05 eq) relative to Et_3N was then added (110 μL of a 1.03 M solution in dichloroethane, 0.113 mmol). The mixture was then stirred at room temperature until tlc analysis showed complete consumption of the starting alcohol (1.3 h). The subsequent debenzoylation was then accomplished by the addition of 1.0 mL of a NaOMe/MeOH solution (1M). The mixture was stirred overnight at room temperature and few drops of acetic acid were added to neutralize the reaction. The solution was concentrated under reduced pressure and the residue was dissolved in 50 mL of ethyl acetate. The organic layer was washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash chromatography using 15% ethyl acetate:petroleum ether as eluent to afford 118 mg of the desired material (83%) as a white solid. Selected data: mp 59-60 °C; R_f 0.28 (15% ethyl acetate:hexanes); $[\alpha]_D$ -3.6° (*c* 1.24, $CHCl_3$); ^{1}H NMR (partial) (400 MHz, $CDCl_3$) δ 5.78-5.71 (m, 1H, $CH_2CH{=}CHC_3H_7$), 5.64-5.56 (m, 1H, $CH_2CH{=}CHC_3H_7$), 4.36 (dd, J = 11.7, 5.8 Hz, 1H, $CH_2C_5H_9$), 4.32 (d, J = 7.2 Hz, 1H, OCHO), 4.09 (dd, J = 11.8, 7.0 Hz, 1H, $CH_2C_5H_9$), 3.76 (dd, J =10.8, 2.0 Hz, 1H, CH_2OBn), 3.71 (dd, J = 10.7, 4.6 Hz, 1H, CH_2OBn), 3.63-3.56 (m, 3H, CHOH, CHOBn), 3.50-3.47 (m, 1H, $CHCH_2OBn$), 2.40 (d, J = 1.6 Hz, 1H, CHOH), 2.04 (dt, J = 7.1, 7.0 Hz, 2H, $CH_2C_2H_5$), 1.46-1.37 (m, 2H, CH_2CH_3), 0.92 (t, J = 7.3 Hz, 3H, CH_3). The reaction was also run in CH_2Cl_2 on a 5-g scale and proceeded equally well.

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