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The Use of α-D-glucopyranosides as Surrogates for the β-L-glucopyranosides in the Stereoselective Cyclopropanation Reaction.

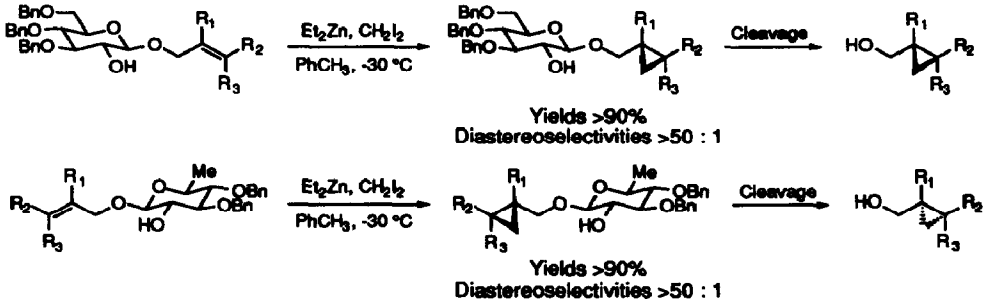
André B. Charette*[1], Nathalie Turcotte, and Jean-François Marcoux

Département de chimie, Université de Montréal
Montréal, Québec CANADA H3C 3J7

Abstract: Treatment of substituted allyl α-D-glucopyranosides with Et_2Zn/CH_2I_2 in *t*-butyl methyl ether produced the corresponding cyclopropane derivatives in >90% yields with diastereoselectivities ranging from 11:1 to 17:1.

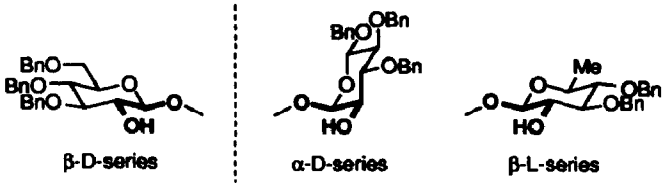
We recently reported that 3,4,6-tri-*O*-benzyl-D-glucose could be used as an efficient and practical chiral auxiliary for the cyclopropanation of a variety of substituted allylic alcohols (Scheme 1).[2] The other enantiomer of substituted cyclopropylmethanol moieties were shown to be equally accessible from the corresponding 6-deoxy-β-D-glucopyranosides. The relatively long synthesis of this auxiliary from a rather expensive starting material (L-Rhamnose) led us to investigate more practical methods for generating the opposite enantiomer.

Scheme 1

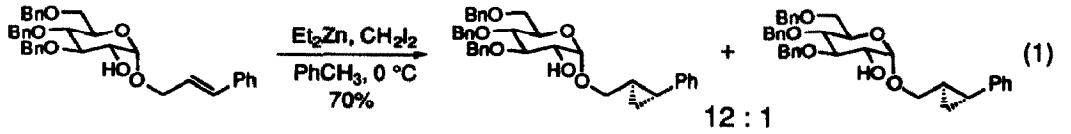


The study of the key structural requirements of the auxiliary derived from the β-D-glycoside led us to postulate that the corresponding α-anomer should behave as its pseudo mirror image (Figure 1).[3]

Figure 1



In the previous report, we showed that indeed, the α-anomer could produce the opposite enantiomer of the cyclopropane with excellent diastereoselectivity and modest yield (eq 1).

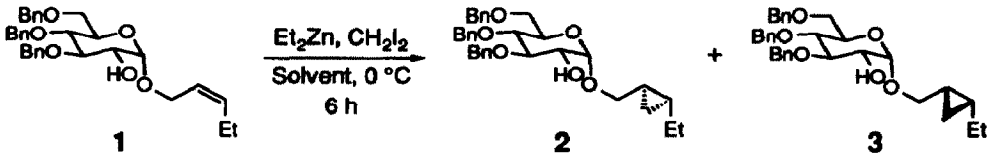


(1)

In this paper we report that this method is applicable to a number of substituted allylic ethers and that the diastereoselectivities and yields can be improved under specific conditions.

As in the β-series, the presence of a free hydroxy group at *C*-2 is essential for obtaining high diastereoselectivities. The effect of the solvent was first to be investigated and is shown in Table 1. The glycoside **1** derived from *cis*-2-penten-1-ol[4] was chosen for the optimization study since the starting material and both diastereomers are readily separated by HPLC.[5]

Table 1. Effect of solvent in the cyclopropanation of glycoside 1.[a]



1 **2** **3**

Entry	Solvent	Yield	Ratio (2:3)
1	1,2-Dichloroethane	99%	8.5 : 1
2	Dichloromethane	98%	9.2 : 1
3	Toluene	89%	12.1 : 1
4	Hexane	78%	6.1 : 1
5	Diethyl ether	32%[b]	13.9 : 1
6	Diethyl ether (22h)	91%	13.6 : 1
7	Diethyl ether (22 h)[c]	46%[b]	4.4 : 1
8	THF (22 h)	6%[b]	13.9 : 1
9	DME	<5%[b]	---
10	*t*-Butyl methyl ether	97% (91%)[d]	13.2 : 1
11	*t*-Butyl methyl ether[c]	45%[b]	4.8 : 1

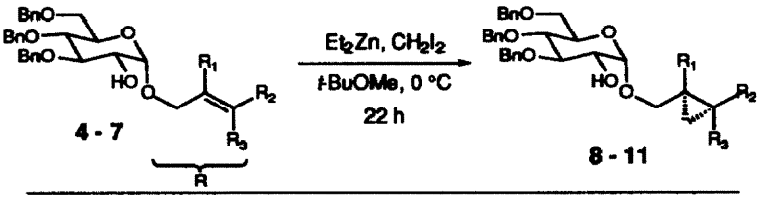
[a] Unless otherwise stated, all the reaction were carried out using 10 equiv. of Et_2Zn and CH_2I_2 and stirred at 0 °C for 6 h. [b] Unreacted starting material accounts for the rest of the mass balance. [c] $ClCH_2I$ was used instead of CH_2I_2. [d] Isolated yield of diastereomerically pure compound.

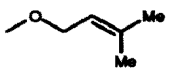
In sharp contrast with the β-series, very low yields of the cyclopropane products were obtained if the reactions were carried out below 0 °C. Chlorinated and non-basic solvents generally produced high yields of the cyclopropane derivatives, but the diastereoselectivities obtained were slightly lower than in basic solvents (Entry 1-4). The basicity of the solvent plays a crucial role for obtaining high yields of the cyclopropylmethyl glycosides. Highly coordinating solvents such as DME or THF almost completely suppressed the reactivity of the bis(iodomethyl)zinc[6] by complexation (entry 8,9). These observations are consistent with the postulate that the uncomplexed reagent is much more reactive than the ether-complexed reagent. For that reason, diethyl ether

and *t*-butyl methyl ether were found to be the solvents of choice for this reaction, althought the latter is usually preferred due to its lower coordinating ability. After only 6 h at 0 °C, high yields (97%) are obtained in this solvent (vs 32% in diethyl ether). The use of the more reactive bis(chloromethyl)zinc reagent[7] led to a decrease in the diastereoselectivities.

As in the β-series, this methodology is quite general since excellent yields and diastereoselectivities were obtained when a number of substituted allylic ethers were submitted to the optimal reaction conditions (Table 2). In all the cases the auxiliary can be cleaved by a ring contraction method that was previously reported.[8]

Table 2. Cyclopropanation of substituted allyl α-D-glycosides.[9]



Compound	R	Yield (%)	ds[b]
4		93[a]	16.5 : 1
5		83	12.3 : 1
6		95	11.0 : 1
7		93[a]	15.0 : 1

[a]Isolated yields of diastereomerically pure compounds. [b]The diastereoselectivities were determined by ^{1}H and/or ^{13}C NMR by comparison with an authentic 1:1 mixture.

In conclusion, these results greatly enhance the synthetic utility of this methodology since both enantiomers of substituted cyclopropylmethanol compounds can be efficiently prepared from a single chiral auxiliary simply by controlling the stereochemistry of the glycosylation reaction.[10]

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3. Charette, A. B.; Marcoux, J.-F. Manuscript in Preparation.
4. For a general synthesis of the α-anomers see: Charette, A. B.; Turcotte, N.; Côté, B. *J. Carbohydr. Chem.* **1993**, xxxx.

5. Column: Partisil-5. Flow rate: 1.0 mL/min. Retention times: **1**: 9.60 min; **2**: 10.55 min; **3**: 9.10 min (25% ethyl acetate-hexane).
6. For a solid-state and a NMR study of the reagent see: Denmark, S. E.; Edwards, J. P.; Wilson, S. R. *J. Am. Chem. Soc.* **1992**, *114*, 2592-2602.
7. For an excellent discussion of the difference in reactivity between bis(iodomethyl)zinc and bis(chloromethyl)zinc see: Denmark, S. E.; Edwards, J. P. *J. Org. Chem.* **1991**, *56*, 6974-6981.
8. Charette, A. B.; Côté, B. *J. Org. Chem.* **1993**, *58*, 933-936.
9. Typical experimental procedure: To a solution of 46.3 mg (0.088 mmol) of glycoside **1** in 1.25 mL of *t*-butyl methyl ether at rt was added 90 μL (0.88 mmol) of diethyl zinc. The clear reaction mixture was stirred at rt for 10 min, cooled to 0 °C, and 980 μL (0.88 mmol) of a 0.9 M solution of CH_2I_2 in *t*-BuOMe was added over 10 min. The reaction mixture was stirred at 0 °C for 22 h and then poored into a sep. funnel containing ether and 10% aqueous HCl. The layers were separated and the organic layer was washed with sat. aq. $NaHCO_3$, sat. aq. NaCl, dried over $MgSO_4$, and concentrated under reduced pressure the afford a 13.3:1 mixture of diastereomers (HPLC). Flash chromatography using 20% ethyl acetate:hexane afforded 42 mg (92%) of the desired cyclopropane **2**: mp 45-48 °C (ether/hexane); R_f 0,25 (20% ethyl acetate:hexane); $[\alpha]_D$ +100,5° (*c* 2,33, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7,41-7,12 (m, 15H, C_6H_5), 4,97 (d, 1H, J = 11 Hz, OCH_2Ph), 4,96 (d, 1H, J = 3 Hz, $CHOC_6H_{11}$), 4,83 (d, 2H, J = 12 Hz, OCH_2Ph), 4,62 (d, 1H, J = 12 Hz, OCH_2Ph), 4,49 (d, 2H, J = 11 Hz, OCH_2Ph), 3,82-3,49 (m, 8H, $CHCH_2OBn$, CHOBn, CHOH, $OCH_2C_5H_9$), 2,17 (d, 1H, J = 9 Hz, CHOH), 1,45-1,35 (m, 1H, CH_2CH_3), 1,35-1,10 (m, 1H, CH_2CH_3), 1,10-1,03 (m, 1H, OCH_2CH), 0,99 (t, 3H, J = 7 Hz, CH_3), 0,90-0,80 (m, 1H, CHC_2H_5), 0,80-0,60 (m, 1H, $CHCH_2CH$), -0,16 (q, 1H, J = 5 Hz, $CHCH_2CH$); RMN-^{13}C (50 MHz, $CDCl_3$) δ 138,7; 138,2; 137,9; 128,2; 127,7; 127,5; 127,4; 98,2; 83,6; 77,3; 75,2; 74,8; 73,4; 73,0; 70,5; 68,7; 68,5; 21,7; 17,8; 14,9; 14,3; 9,5. Anal. Calcd for $C_{33}H_{40}O_6$: C 74.41%; H 7.57%. Found: C 74.22%; H 7.68%.
10. For other chiral auxiliaries in asymmetric Simmons-Smith see the following. Chiral acetals: (a) Mori, A.; Arai, I.; Yamamoto, H. *Tetrahedron* **1986**, *42*, 6447-6458. (b) Mash, E. A.; Hemperly, S. B.; Nelson, K. A.; Heidt, P. C.; Van Deusen, S. *J. Org. Chem.* **1990**, *55*, 2045-2055. Mash, E. A.; Hemperly, S. B. *J. Org. Chem.* **1990**, *55*, 2055-2060. (c) Mash, E. A.; Nelson, K. A. *Tetrahedron* **1987**, *43*, 679-692. (d) Arai, I.; Mori, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 8254-8256. (e) Mash, E. A.; Nelson, K. A. *J. Am. Chem. Soc.* **1985**, *107*, 8256-8258. Chiral diols: (f) Sugimura, T.; Yoshikawa, M.; Futagawa, T.; Tai, A. *Tetrahedron* **1990**, *46*, 5955-5966. (g) Sugimura, T.; Futagawa, T.; Yoshikawa, M.; Tai, A. *Tetrahedron Lett.* **1989**, *30*, 3807-3810. (h) Sugimura, T.; Futagawa, T.; Tai, A. *Tetrahedron Lett.* **1988**, *29*, 5775-5778. Chiral acyl iron complexes: (i) Ambler, P. W.; Davies, S. G. *Tetrahedron Lett.* **1988**, *29*, 6979-6982. (j) Ambler, P. W.; Davies, S. G. *Tetrahedron Lett.* **1988**, *29*, 6983-6984. Chiral boronic esters: (k) Imai, T.; Mineta, H.; Nishida, S. *J. Org. Chem.* **1990**, *55*, 4986-4988.

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