Pergamon

Tetrahedron Letters 40 (1999) 581–584

TETRAHEDRON LETTERS

The Stereoselective Conversion of 2-Alkenyl Alcohols to (R)- or (S)-alkane-1, 2-diols Using D-Glucose as a Chiral Auxiliary

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Received 12 August 1998; revised 10 November 1998; accepted 14 November 1998

ABSTRACT: The stereoselective addition of the 2-hydroxyl group of glucose to the mercurated vinyl group of 2-alkenyl glycosides followed by hydride reduction and removal of the saccharide fragment was used to prepare enantiomerically pure 1,2-dihydroxy alkanes. Diols of (R) or (S) configuration can be synthesized from (α)-glycosides or the (β) form respectively. Demercuration with chloride ion led to the insertion of a halo group adjacent to the new chiral center thus allowing for the possibility of further functionalization.

The enantio-selective functionalization of alkenes is one of the more important reactions in synthetic organic chemistry and one for which much effort has already been expended. The oxidation of the vinyl group of allylic alcohols is a very important transformation and the use of transition metal complexes with chiral ligands is a very prominent way of achieving this end.[1,2] There is, however, always a need for general methods for enantioselectively oxidizing the vinyl group of 2-alkenyl alcohols especially when absolute control of stereochemistry is required. Here we describe the use of glucose as a chiral auxiliary to effect such transformations. Despite their availability and high intrinsic chirality, the structural complexity and highly redundant functionality of carbohydrates have hindered their use in such applications.[3] The use of carbohydrates as chiral auxiliaries to functionalize 2-alkenyl alcohols requires attachment of the substrate to be transformed to a strategically simple site on the sugar, such as the anomeric position, and an easy way of transforming and removing said substrate. There are some precedents for the use of carbohydrates in this fashion. For instance, the relatively high diastereoselective cyclopropanation of 2-alkenyl glycosides has been demonstrated.[4] However, the more widely used reactions, such as epoxidation,[5] dihydroxylation,[6] and dibromination,[7] which involve the addition of heteroatoms gave poor selectivities. The reason for the poor control is that the strong steric requirements that accompany fused ring formation are absent. These steric constraints promote high levels of diastereoselectivity that translates into high enantioselectivity once the auxiliary is removed.

In this study, we demonstrate the stereoselective functionalization of the vinyl group of 2-alkenyl alcohols by arranging for the nucleophilic addition of the 2-hydroxyl group of glucose to the activated double bond (**Figure 1**). A nucleophile (X), which can be later displaced, is used to activate the double bond. The glucose moiety is then removed to give optically pure (R)- or (S)-alkane-1, 2-diols depending on the anomeric configuration of the starting glycoside. A high degree of stereoselectivity is ensured because the bulky alkyl group in the intermediate bicyclic system is forced to be equatorial. Hence the α-glycoside should yield the (R)-diol and the β-glycoside should yield the (S) isomer. Unlike the case with other auxiliaries, it is not necessary to have both chiral forms of the auxiliary to prepare the two different enantiomers. Contamination of one glycoside by the other can be readily resolved by crystallization of the glycoside or by forming a crystalline derivative if the simple glycoside does not readily crystallize. Alternatively, one anomer can be removed by treatment with an appropriate glycosidase.

0040-4039/99/$ - see front matter
PII: S0040-4039(98)02472-1

Because α and β glycosides can be interconverted by anomerization with Lewis acids, only one form of the glycoside is really needed.

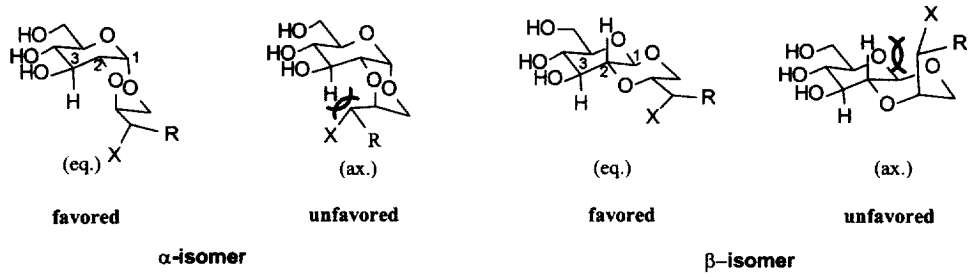
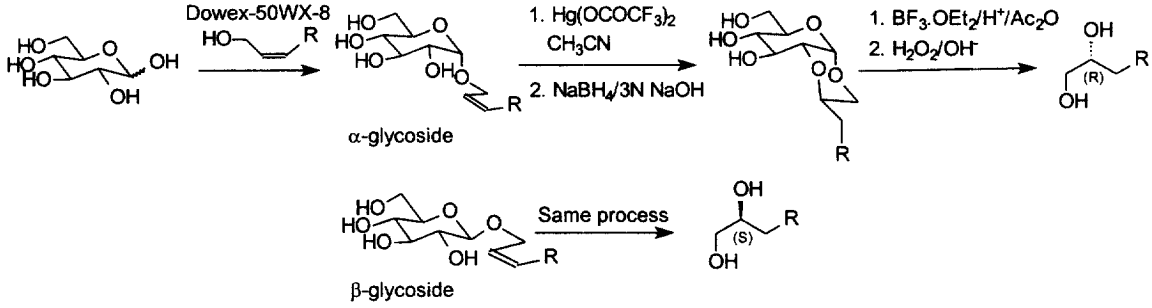


Figure 1. Products formed by activation of the double bond in a 2-alkenylglycoside by a nucleophile X followed by nucleophilic attack by the 2- hydroxyl group of the carbohydrate. Note the steric clashing in the axial isomers.

In the present scheme, the double bond is activated by mercuration and the alkoxy mercurated intermediate is reduced by borohydride. The diol is recovered by acetolysis followed by oxidative removal of the glucose anomeric carbon as formic acid using alkaline hydrogen peroxide (**Scheme 1**).[8]



Scheme 1

Activation with mercury II trifluoroacetate was very effective in facilitating the addition of the 2-hydroxyl group to the double bond. Reduction of the alkoxy mercurial formed from α-allyl glucoside (converted to its 4,6-benzylidene acetal to aid in crystallization) proceeded smoothly to give the desired product. NMR spectroscopy (both ^{1}H and ^{13}C) of the crude product showed the presence of predominantly one kind of methyl group (91:9). This indicated the formation of largely one diastereomer. The methyl group presumably occupied the equatorial position, which would give (R)-1,2-propanediol. Analysis of the diol by chiral column chromatography confirmed its absolute configuration to be (R) and the enantiomeric excess to be over 99% from the major isomer. The cyclization of the β-allylglycoside was not as stereospecific as that of the α-form and NMR spectra indicated that 25% of cyclized products was the one with the axial methyl group. The desired isomer could however be

separated by column chromatography (hexane/ethyl acetate, 5/8). The basis for the slight loss in specificity with the β-anomer is quite evident (**Figure 1**). Here the new ring system being formed is a *trans* trioxabicyclodecalin, in which the newly formed methyl ring substituent has only the typical 1,3-*syn* interactions. In the case of the α-glycoside, the ring system is a cis-fused one. Here there is a severe clash between the axial methyl group and the 3-proton of the glucose moiety. The *cis*-trioxabicyclodecalin system therefore is formed exclusively with the equatorial methyl group.

The generality of the method was demonstrated by converting cis-2-pentenol to the (R) and (S) 1, 2-diols. The cis-2-pentenyl-β-D-glucopyranoside (synthesized by Koenigs-Knorr reaction) could be transformed to the α-glycoside by anomerization with titanium tetrachloride. This is a useful point at which to exercise some steric control. The diastereoselectivity as well as the enantioselectivity for the final products were excellent for both α and β glycosides due to the bulkiness of the side chain which is forced to occupy the equatorial position exclusively (**Table 1**).

Table 1

Diols[a]	Diastereoselectivity of cyclization	Yield of desired diastereomer (%)[d]	ee (%)[e]
(R)-1,2-propanediol	91:9[b]	81	> 99
(S)-1,2-propanediol	75:25[b]	58	> 99
(S)-1,2-pentanediol	>99:1[c]	60	> 99
(R)-1,2-pentanediol	>99:1[c]	66	> 99

a: Determined by comparing to standard alkane-1,2-diol using chiral column chromatography; b: Determined by ^{1}H NMR of crude product; c: Determined by separation of crude product; d: Determined by the weight of purified cyclized product; e: Measured by chiral column chromatography of 1,2-dihydroxy-alkane after removal of the glucose moiety from the major diastereomer.

The easy formation of α- and β -glycosides of glucose by 2-alkenols, the facile and stereoselective cyclization of the 2-hydroxy group to the activated double bond, and a general method for recovering the functionalized aglycon make the strategy described above for functionalizing simple allylic alcohols an attractive one. The stereochemistry at the newly formed chiral center can be chosen simply by deciding which anomer to start with. The α- and β-anomers can be reached by different routes and can also be interconverted. This makes this method a good general one for the selective hydroxylation of all simple and many complex allylic alcohols. It is possible to cleave the intermediate mercurial with bromine instead of hydride to generate an α-bromo ether. This affords several possibilities since the bromo group could serve as the site for further functionalization reactions such as cyanation, amination and chain elongation. Attempts at this were successful as was evidenced by the presence of a characteristic signal at 29.8 ppm for a bromomethyl group in the carbon-13 spectra and signals at ~ 3.24 ppm in the proton spectra of the bicyclic system formed form the α-allyl glycoside. Further work on activating the double bond using other reagents to create two chiral centers in one step is in progress and will be reported in due course.

References and Notes:

1. Finn, M. G., Sharpless, K. B. *Comprehensive Organic Synthesis*, Pergamon Press, **1991**, *7*, 389-436
2. Finn, M. G., Sharpless, K. B. *Asymmetric Synthesis*, Academic Press, New York, **1985**, *5*, 247
3. Kunz, H.; Rück, K. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 336-358
4. Charette, A. B.; Cote, B.; Marcoux, J. –F. *J. Am. Chem. Soc.* **1991**, *113*, 8166-8167
5. Charette, A. B.; Cote, B. *Tetrahedron: Asymmetry* **1993**, *4*, 2283-2286
6. Gurjar, M. K.; Mainkar, A. S. *Tetrahedron: Asymmetry* **1992**, *3*, 21-24
7. Bellucci, G.; Chiappe, C., D'Andrea, F. *Tetrahedron: Asymmetry* **1995**, *6*, 221-230
8. In a typical reaction for preparing (R)-1,2-dihydroxypropane, α–allyl glycoside derivatized as the 4,6-O-benzylidene acetal (1.60 g, 5.2 mmol) in acetonitrile (200 mL) was treated with mercury trifluoroacetate (4.40 g, 10.4 mmol) in 100 mL CH_3CN (added dropwise). The mixture was stirred at room temperature for 6 hours after which 10 mL of 3M NaOH solution was added and stirring was continued for a further 10 minutes. Sodium borohydride (0.79 g, 20.8 mmol) dissolved in 10 mL of 3M NaOH solution was added and the mixture was stirred for 3 hour. The suspension was then filtered through Celite and the clear filtrate was concentrated under vacuum at 30 °C to remove acetonitrile. The white precipitate was recovered by filtration and purified by column chromatography (hexane/ethyl acetate, 5/8) to give 1.30 g of product **(2)** (Yield: 81.3%). (Crystallized spontaneously on standing), m.p.: 215-218°C; IR (KBr, cm^{-1}): 3414 (s), 3368 (s), 1088 (s), 750 (s); ^1H NMR (300 MHz, $CDCl_3$): δ 7.48 (m, 2H), 7.35 (m, 2H), 5.50 (s, 1H), 4.95 (d, J = 3.4 Hz, 1H), 4.47 (dd, J = 9.3 Hz, 1H), 4.30 (dd, J = 10.3, 5.2 Hz, 1H), 3.89-4.00 (m, 3H), 3.71 (dd, J = 9.4, 3.7 Hz, 1H), 3.67 (dd, J = 10.3 Hz, 1H), 3.49 (dd, J = 9.4 Hz, 1H), 3.46 (dd, J = 11.9, 10.7 Hz, 1H), 1.09 (d, J = 6.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.93, 129.29, 128.35, 126.29, 101.88, 94.69, 80.87, 75.37, 72.09, 68.75, 65.76, 64.08, 63.44, 16.07; HRMS Exact mass: calcd for $C_{16}H_{20}O_6$ $M^{+\bullet}$, 308.1260. Found 308.1262; $[\alpha]_D^{20}$ +21°C (*c* 2.08, $CHCl_3$). To recover the chiral diol, the benzylidene group of 1.30 g (4.2 mmol) product **2** was treated with 100 mL 1N HCl. at 70 °C for one hour. Benzaldehyde was removed by extraction with chloroform. The aqueous layer was concentrated, peracetylated (1:1 acetic anhydride, pyridine 70° C for 2 hours), concentrated and acetolyzed (acetic anhydride (3 mL), trifluoroacetic acid (2 mL) and boron trifluoride diethyletherate (1.5 mL) at room temperature for 5 hours). The diol was recovered by first diluting with 100 mL chloroform, washing with water (30 mL), and saturated sodium bicarbonate (2x20 mL), concentrating and heating with 1.1 g NaOH and 9.0 g H_2O_2 (30%) at 70°C for 10 hours. It was then desalted on Dowex MR-3 mixed bed ion exchange resin. After evaporation under reduced pressure, 0.30 g of (R)-1,2-dihydroxypropane (Yield: 95%) was recovered: IR ($CHCl_3$, cm^{-1}): 3409 (bs), 2975 (s), 1040 (s); ^1H NMR (300 MHz, $CDCl_3$) δ 3.89 (m, 1H), 3.61 (dd, J = 11.1, 3.1 Hz, 1H), 3.38 (dd, J = 11.2, 7.8 Hz, 1H), 1.14 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 68.28, 67.84, 18.66; ee > 99% by gas chromatography (Betadex cyclodextrin phase column , Supelco, Bellefonte, PA).