n-Pentenyl Glycosides as Mediators in the Asymmetric Synthesis of Monosubstituted Chiral Nonracemic Tetrahydrofurans and γ-Lactones[1]

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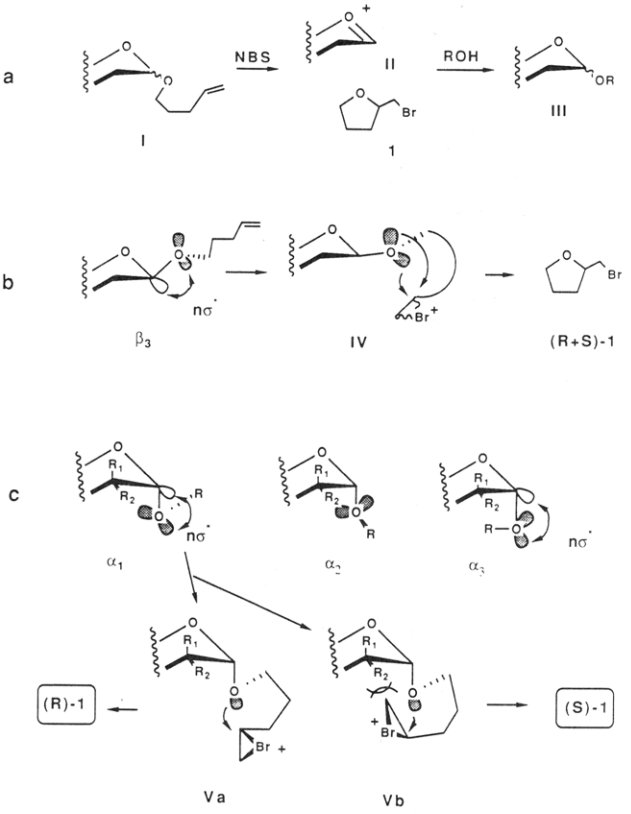
Summary: *n*-Pentenyl glycosides can be oxidatively hydrolyzed by treatment with *N*-bromosuccinimide, previous work having been focused on the usefulness of the resulting glycosyl moiety. In this paper, attention is focused on asymmetric induction in the 2-(bromomethyl)furan that is liberated. The enantiomeric excess depends strongly on the orientations at the anomeric centers and at C2, as well as on the protecting group on the C2 oxygen. α-Anomers display higher asymmetric induction, and rationalization of this observation is based on the assumption that the molecule reacts from the favored ground-state orientation, wherein the exo anomeric effect is displayed. The usefulness of this route to optically active furans has been probed by a synthesis of an insect pheromone from the *Bledius* species.

Since their discovery two years ago,[4] *n*-pentenyl-glycosides [NPGs] I have proven themselves to be remarkable substrates for reactions occurring at the anomeric center. Thus far our attention has been focused exclusively on the processes occurring via the glycosyl oxocarbonium ion II such as glycosidation[5] and hydrolysis,[4,6] and the results thus far have been most encouraging. Notably, the ability to "arm" or "disarm" NPGs by a C2 ester or a C2 ether, respectively,[5a] or to modulate their reactivity via the inorganic source of iodonium ion,[7] offer an unprecedented degree of finesse in glycoside coupling reactions, and this has been demonstrated in a recent synthesis of a complex pentasaccharide.[5b] However, as indicated in Scheme I, formation of II is accompanied by extrusion of a (halomethyl)furan 1. In view of their widespread occurrence among natural products,[8] tetrahydrofurans continue to be synthetic targets of opportunity, and this has encouraged us to focus our attention on 1.[9] In this paper we disclose some of our results.

Our first experiments were carried out on the α- and β-anomers of **2** which were found to give the *R* and *S* enantiomers of **1**[10] with 80 and 20% enantiomeric excesses,[13] respectively (Table I, entries i and ii). Our working hypothesis for rationalizing these results began with two assumptions: (1) that each anomer reacted from its stable ground state as reflected by the exo-anomeric effect,[14] and (2) that the transition state was early and therefore resembled the ground state. Thus, for **2**β the

Scheme I



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(10) Racemic (bromomethyl)furan 1 was prepared by reaction of *n*-pentenyl alcohol with NBS in the same conditions as stated in Table I, and its spectrum in the presence of $Eu(pvs)_3$ (tris[(3-heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III) derivative) as ^1H NMR chiral shift reagent[11] used as reference in the determination of the enantiomeric excess for the different halomethylfurans 1. Absolute configurations of the (halomethyl)furans were determined by the sign of their optical rotation compared with the ones described for the (+)-(*R*)- and (−)-(*S*)-tetrahydrofurfuryl bromides.[12]

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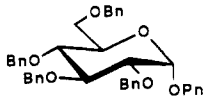
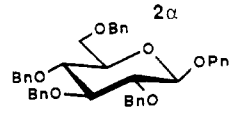
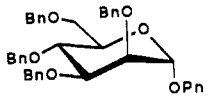
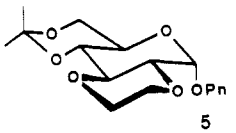
Table I. Formation of 2-(Bromomethyl)tetrahydrofuran 1 from *n*-Pentenyl Glycosides[a]

entry	substrate	reaction time, h	major enantiomer of 1	enantiomeric excess, %
i	 2α	3	*R*	80
ii	 2β	3	*S*	20
iii	 3	6	*R*	20
iv	 4	4	*R*	85
v	 5	4	*R*	80
vi	 6	48	*R*	70

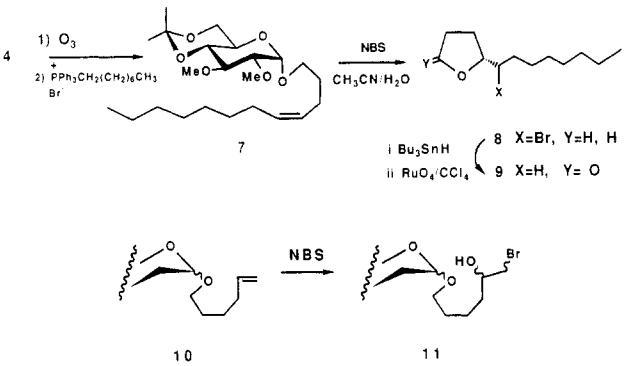
[a] Experimental conditions: as in ref 4. The methylfuran 1 was eluted by using petroleum ether–ethyl ether (14:1) as the solvent system.

elegant studies of Lemieux and co-workers have established conclusively that the predominant ground state rotamer is β_3 (Scheme Ib) which enjoys an n-σ^* stabilization as proposed by Altona.[15] Little facial selectivity in the formation of the diastereomeric bromonium ions, IV, nor in the nucleophilic attack thereon by the diastereotopic lone pairs was expected. Thus the degree of asymmetric induction was not expected to be very high, and the modest enantiomeric excess of (*S*)-1 (20%) (Table I, entry ii) is therefore rationalized.

The high enantiomeric excess observed for 2α (Table I, entry i) was more encouraging and therefore warranted greater scrutiny. For the three rotamers shown in Scheme Ic, α_1 and α_3 both enjoy exo-anomeric effects.[16] However, the latter is sterically disfavored because the alkyl substituent, R, is beneath the pyranoside ring. Rotamer α_2 is disfavored because it has no n-σ^* interaction. Therefore α_1 gains favor and is indeed observed to be the stable ground state.[14-16]

As with β_3 (Scheme Ib) differentiation in the facial selectivity of the olefinic double bond is not expected to be high, and reversible bromination[9a,b] to give the diastereomers Va and Vb is expected to occur. However by contrast, only one lone pair of α_1 is poised for nucleophilic attack, because the other lies beneath the pyranoside ring. Attack on Va vs Vb leads to the *R* and *S* enantiomers of 1, respectively. The observation of *R* selectivity (Table I, entry i) implies a preference for reaction via Va, and this is understandable in view of the indicated nonbonded interaction that destabilizes Vb.

Scheme II



On this reasoning, inversion of configuration at C2 should be correlated with lower enantiomeric excess but *retained R* selectivity. Indeed with the mannoside **3** (entry iii) *R* selectivity fell to 20% enantiomeric excess. However, with the *gluco* derivatives **4** and **5** (entries iv and v), high selectivity was restored. There is, however, a need for caution as indicated by the results in entry vi. We suggest that the *tert*-butyldimethylsilyl group is so large that the preference between α_1 and α_2 is no longer as great.[17] Notably the best stereoselectivity was observed with the di-*O*-methyl derivative **4**.

In order to test the synthetic potential of NPGs we have pursued a synthesis of (*S*)-(−)-γ-*n*-dodecanolactone, **9**, whose enantiomer is isolated from the pyrigidial glands of *Bledius mandibularis* and *Bledius spectabilis* from the Atlantic Coasts of USA and France, respectively.[18] Ozonolysis of the pentenyl glycoside **4** followed by Wittig coupling afforded the modified pentenyl glycoside **7** in 90% overall yield. Oxidative hydrolysis of this compound with NBS/CH_3CN/H_2O gave the bromo derivative **8** in 45% isolated yield. Radical debromination followed by oxidation to the lactone using Smith's methodology[19] afforded pheromone **9** in 30% yield and 75% enantiomeric excess.[20]

The data reported in this paper indicate that for the purposes of asymmetric induction, α-D-*gluco* derivatives appear to be the best substrates. Some light has also been shed, indirectly, on the mechanism of hydrolysis. Thus α anomers react mainly through α_1 type rotamers even where steric interactions are severe. The selectivity is driven kinetically by this 5-*exo-tet* transition state[21] depicted in Va, and the extent of this induction may be gauged by the observation that with the corresponding *n*-hexenyl glycoside **10**, the product of reaction is exclusively the bromohydrin **11**.

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