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Spontaneous Cyclization of Triflates Derived from δ–Benzyloxy Alcohols: Efficient and General Synthesis of *C*-Vinyl Furanosides

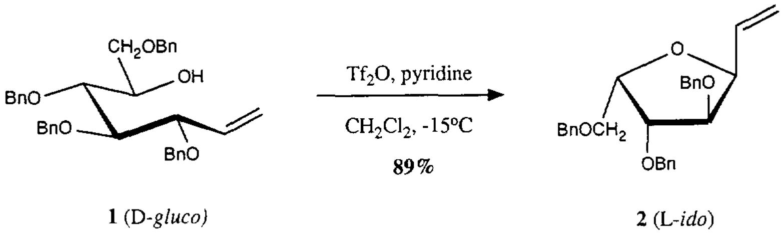
Olivier R. Martin,* Feng Yang, and Fang Xie

Department of Chemistry, State University of New York, Binghamton, NY 13902-6000

Summary: *On reaction with triflic anhydride, the hept-1-enitols resulting from the Wittig reaction of tetra-O-benzyl D-hexopyranoses with [$Ph_3P=CH_2$] lead, in one step, to 3,6-anhydro-hept-1-enitol derivatives ("C-vinyl furanosides") in high yield, by way of the participation of the benzyloxy group at C-3 with concomitant debenzylation.*

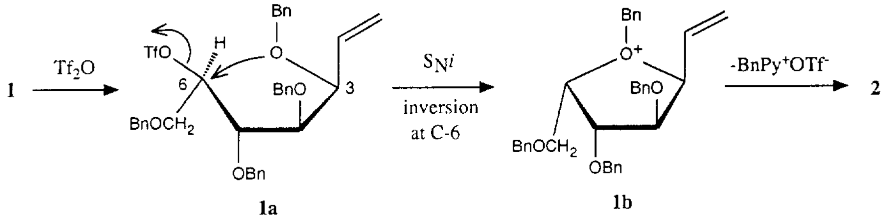
The ability of benzyloxy groups to participate in ring-forming reactions by intramolecular displacements with concomitant debenzylation has long been recognized.[1] Such process occurs readily when the reacting groups are in 1,4-relationship, thus leading to tetrahydrofuran derivatives.[1] However, as it has been observed frequently as an undesired or unexpected reaction,[2-4] or has led in many cases to mixtures of products,[5] the synthetic usefulness of this process remains limited. This is in contrast with the electrophile-mediated cyclization of γ–benzyloxy alkenes which constitutes a useful cycloetherification method.[6] In the course of our studies on the synthesis of aza-sugars by aminomercuration, we found that triflates derived from open-chain alcohols bearing a benzyloxy group in 1,4-relationship with respect to the alcohol function spontaneously cyclize to the corresponding cyclic ether. In this communication, we demonstrate with several examples that this process provides an efficient method for the preparation of substituted tetrahydrofurans ("*C*-vinyl furanosides").

With the goal of substituting the 6-OH group in D-*gluco* heptenitol **1**,[7] the preparation of the triflate derived from **1** was attempted. The reaction led, however, exclusively to the 3,6-anhydro-heptenitol **2**[9] (Scheme 1). The loss of a benzyl group and the characteristic chemical shifts of the ring carbon atoms of the furanoid system unambiguously established the constitution of **2**; its L-*ido* configuration was deduced from the comparison of its spectral data with those of other epimers (see below). The formation of **2** is clearly the result of a novel example of benzyloxy group participation: sulfonylation of **1** undoubtedly occurred to give



Scheme 1

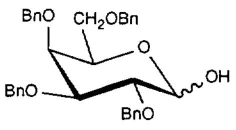
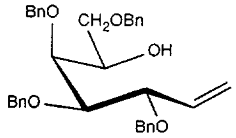
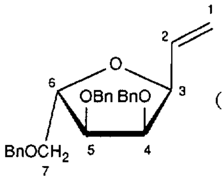
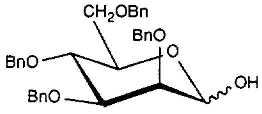
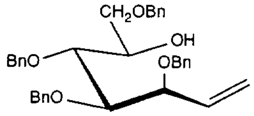
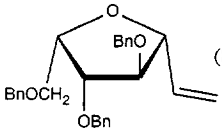
triflate **1a** (Scheme 2) which underwent spontaneous internal displacement, with inversion at C-6, by the favorably placed alkoxy group at C-3. Dealkylation of the resulting benzyloxonium ion (**1b**), by transfer of the benzyl group to a nucleophile present in the medium, most probably pyridine, then led to **2**.



Scheme 2

This unexpected result prompted us to examine the ring-forming process with other heptenitols. Thus, the D-*galacto* and D-*manno* heptenitols **4** and **7**[10] were prepared from the corresponding tetra-*O*-benzyl-D-hexopyranoses **3** and **6**, under essentially the same conditions as **1** (using BuLi to generate the Wittig reagent). While the Wittig reaction leading to **4** was nearly as high-yielding as that[8] leading to **1**, we were not able to improve the yield reported for the preparation of **7**.[6c,10] Treatment of **4** and **7** with triflic anhydride gave the 3,6-anhydro-L-*altro* and L-*gulo*-hept-1-enitol derivatives **5** and **8**, respectively, in excellent yield and as single products (Table 1). Furthermore, in spite of the strong tendency of these heptenitols to undergo internal displacements, the configuration at C-6 of both **1** and **4** could be inverted effectively under Mitsunobu conditions (Table 2):[11] the reaction of **1** (D-*gluco*) and **4** (D-*galacto*) with benzoic acid and *p*-nitrobenzoic acid,[12] respectively, in the presence of triphenylphosphine and diethyl azodicarboxylate, gave the corresponding inverted benzoates which were immediately debenzoylated to provide L-*ido* and L-*altro*

Table 1

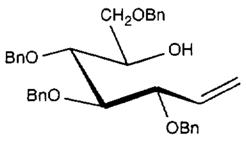
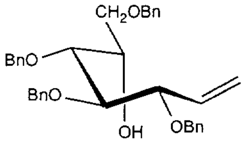
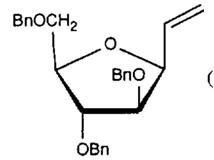
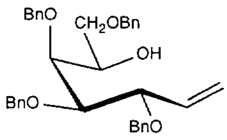
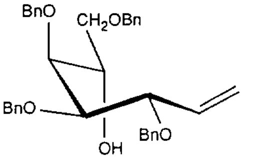
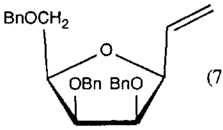
A	$\xrightarrow{[Ph_3P=CH_2]^a}$ B		$\xrightarrow{Tf_2O^b}$ C	
 3	 4 (D-*galacto*)	(84%)	 5 (L-*altro*)	(90%)
 6	 7 (D-*manno*)	(33%)	 8 (L-*gulo*)	(80%)

[a] Conditions: $Ph_3P^+CH_3Br^-$/BuLi (3–5 equiv.), toluene, 25°C, 12–18h.

[b] Conditions: Tf_2O (2–3 equiv.), pyridine (4–6 equiv.), CH_2Cl_2, -15 –0°C, 1–6h.

heptenitols **9** and **11**, respectively. On reaction with triflic anhydride, both **9** and **11** afforded the corresponding 3,6-anhydro-D-*gluco*- and D-*galacto*-hept-1-enitols in good yields. The latter case is particularly remarkable since all substituents in the final furanoid ring are *cis*!

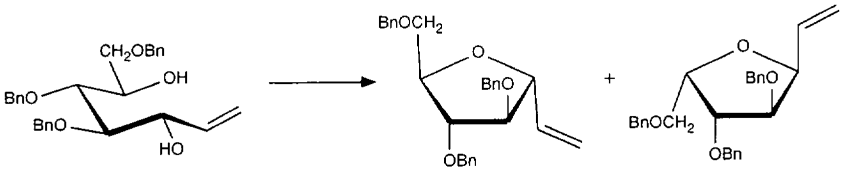
Table 2

B	$\xrightarrow[\text{2. MeOH/MeO}^-]{\text{1. Mitsunobu}^a}$ D		$\xrightarrow{\text{Tf}_2\text{O}^b}$ E	
 **1**	 **9** (L-*ido*)	(61%)	 **10** (D-*gluco*)	(83%)
 **4**	 **11** (L-*altro*)	(65%)	 **12** (D-*galacto*)	(72%)

[a]Conditions: PhCOOH (from **1**) or $pO_2NC_6H_4COOH$ (from **4**) /Ph_3P/DEAD, ether, 25°C, 6h

[b]See Table 1.

The reaction of diol **13**, readily available from 2,3,5-tri-*O*-benzyl-D-arabinofuranose,[13] provided further support for the proposed mechanism of the ring-forming process: the treatment of **13** with triflic anhydride (1.1 equiv.) gave a mixture of two similar products in nearly equal amounts. While this mixture could not be resolved by chromatography, the NMR spectra of the mixture clearly revealed that one of the components was the same product as that obtained from **1**, namely L-*ido* epimer **2**. The second product was the new D-*manno* epimer **14**, in which all substituents of the furanoid ring are in *trans* relationship. Compound **2** and **14** arose from the mono-*O*-sulfonyl derivatives of **13** at O-6 and O-3, respectively, by way of a simple internal displacement in this case, with inversion at C-6 or C-3. Interestingly, diol **13** led to **14** as the major product under Mitsunobu conditions, presumably as the result of the greater reactivity of the allylic C–O bond in the reactive intermediate.



13 → **14** (D-*manno*) + **2** (L-*ido*)

Conditions:		14		2	
	Tf_2O-pyridine	1	:	1	(95%)
	Ph_3P-DEAD	2	:	1	(85%)

Scheme 3

As with other types of *C*-furanosyl compounds,[14] the chemical shifts of the ring carbon atoms[15] provided the most useful probes of the configuration of the new products: starting with the all-*trans* system **14** (average ring-carbon chemical shift: 84.44 ppm) and ending with the all-*cis* system **12** (average ring-carbon chemical shift: 79.57 ppm), an examination of the chemical shift changes promoted by single epimerizations (characteristic upfield shifts of 2–5 ppm) led to the configurations shown.

In conclusion, heptenitols resulting from the Wittig reaction of tetra-*O*-benzyl-D-hexopyranoses with $Ph_3P=CH_2$ can be converted, in one step and in high yield, into *C*-vinyl furanosides, by taking advantage of the participation of the benzyloxy group at C-3. The *C*-furanosyl compounds thus obtained constitute very useful synthetic intermediates, for example for the preparation of *C*-nucleosides.

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7. Compound **1** was prepared in 92% yield from 2,3,4,6-tetra-*O*-benzyl-D-glucose (see ref. 8). The best yields were obtained using phenyllithium (instead of butyllithium) to generate the Wittig reagent.
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