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# A Convenient Route for the Synthesis of 2-C-Substituted 2-Deoxyhexoses

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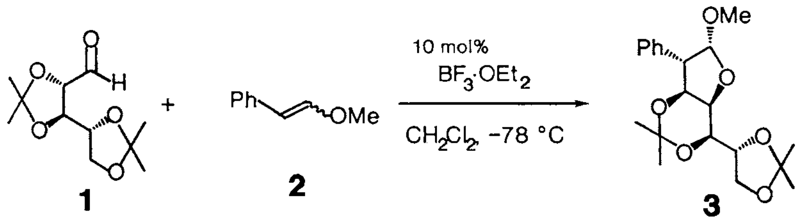
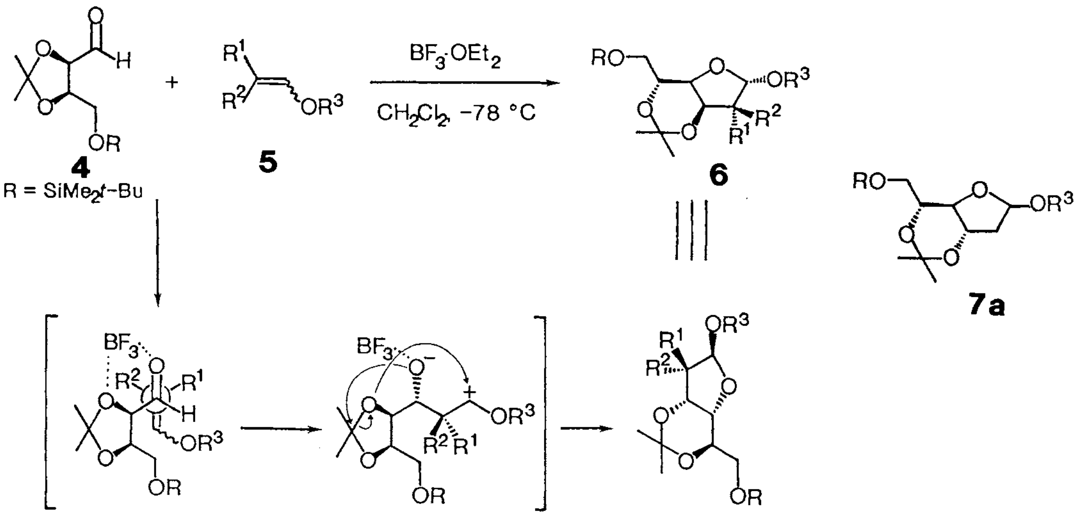
A facile method has been developed for the synthesis of 2-C-substituted 2-deoxy-D-glucoses and 2-C-disubstituted 2-deoxy-D-arabino-hexoses using the $BF_3$-catalyzed cyclization between 1-alkenyl ethers and 2,3-O-isopropylidene derivative of aldehydo-D-erythrose.

2-C-Substituted 2-deoxy sugars have been of interest not only as a potentially bio-active substance but also as a chiral synthon for the synthesis of naturally occurring products;[1)] therefore synthetic efforts have been focused on the development of convenient procedures for their preparation. The common approaches for synthesizing the class of compounds can be classified into two broad categories: (1) modification of intact sugars by replacing the 2-hydroxy function with the desired substituent,[2)] (2) construction of the carbon skeletons by homologation of chiral aldehydes using allylation,[3)] aldol or Reformatosky reaction[4)] etc. In the latter strategy a method for the stereocontrolled formation of the new chiral centers, C-2 and C-3, is required.

Recently, we have found that methyl 2-deoxy-2-C-phenyl-β-D-gluco-heptofuranoside derivative **3** is formed in a stereoselective manner by treatment of 2,3;4,5-di-O-isopropylidene-aldehydo-D-arabinose(**1**) and methyl styryl ether (**2**) with a catalytic amount of boron trifluoride etherate (Eq. 1).[5)] Since a variety of β-functionarized vinyl ethers are readily accessible, it occurred us that this reaction could provide a direct approach for the stereoselective synthesis of 2-C-substituted 2-deoxy sugars. In this letter, we wish to report a new route to 2-C-substituted 2-deoxyhexoses using the $BF_3$-catalyzed ring formation between 1-alkenyl ethers and 2,3-O-isopropylidene-aldehydo-D-erythrose derivative, outlined in Scheme 1.



(1)



Scheme 1.

The results are summarized in Table 1. The reaction of vinyl ether **5a** proceeded smoothly in the presence of 5 mol% of $BF_3 \cdot OEt_2$ at -78 °C to give 2-deoxy-D-arabino-hexofuranoside **6a**[6] in 64% yield along with a 27% yield of 2-deoxy-D-ribo-hexofuranoside **7a** after the separation by silica gel chromatography. In contrast, the reactions of β-substituted vinyl ethers **5b-e** under the same reaction conditions as above turned out to be incomplete even when the reaction time was prolonged or the temperature was raised. However, this problem was overcome by the use of 0.3 equivalent or, more practically, equimolar amount of $BF_3 \cdot OEt_2$. Even under the stoichiometric conditions the reaction of **5d** was quite sluggish at -78 °C, because the electron withdrawing substituent at β-position probably decreases the nucleophilicity (Run 6). Allenyl ether **5f** can be also employed in this reaction to give 2-methylene-hexofuranoside derivative **6f** in a moderate yield (Run 9).

It should be pointed out that the reactions of β-substituted vinyl ethers proceeded with highly diastereofacial selectivity and simple diastereoselectivity (syn/anti) to provide essentially only one of the four possible diastereomers (in disregard of the anomeric carbon) via the transition state as depicted in Scheme 1, which is similar to that previously discussed in the formation of **3**.[5,7]

The newly introduced stereocenters at C-1, C-2, and C-3 were established by the $^1H$ NMR analysis[8] and n.O.e. experiments. For example, n.O.e. measurements on **6b** revealed clear enhancements both between H-1 and H-2 and between H-3 and H-4, but no n.O.e. between H-2 and H-3, indicating α-gluco configuration. This analysis was also successful in establishing the stereochemistries of **6c-f**.

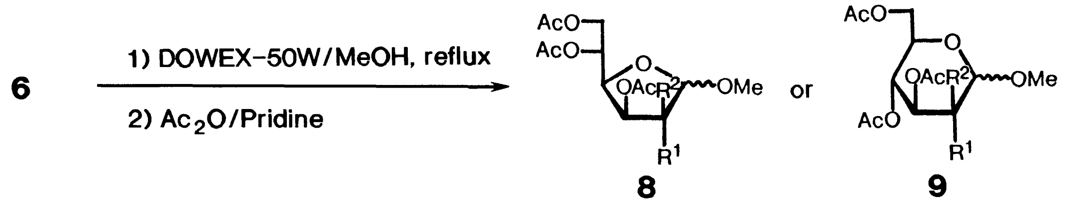
2-Deoxyhexofuranosides obtained above were treated with ion-exchange resin (DOWEX-50W $H^+$-form) in absolute methanol under reflux, followed by

Table 1. Reaction of Various 1-Alkenyl Ethers with Aldehyde **4**[a)]

| Run | 1-Alkenyl Ethers | [ $R^1$ | $R^2$ | $R^3$ | : E/Z] | Equiv. of $BF_3 \cdot OEt_2$ | Time | Product[b)] | Yield/%[c)] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **5a** | H | H | Et | - | 0.05 | 10 min | **6a** | 64[d)] |
| 2 | **5b** | Ph | H | Me | Z | 0.3 | 2.5 h | **6b** | 72 |
| 3 | **5b** | | | | | 1.0 | 30 min | **6b** | 77 |
| 4 | **5c** | Br | H | Et | E | 0.3 | 3 h | **6c** | 73 |
| 5 | **5c** | | | | | 1.0 | 1 h | **6c** | 82 |
| 6[e)] | **5d** | $EtO_2C$ | H | Et | 3/1 | 1.0 | 4.5 h | **6d**[f)] | 62[g)] |
| 7 | **5e** | Me | Me | Et | - | 0.3 | 1 h | **6e** | 77 |
| 8 | **5e** | | | | | 1.0 | 30 min | **6e** | 87 |
| 9[h)] | **5f** | $CH_2=$ | | Me | - | 0.1 | 1 h | **6f** | 55 |

a) Unless otherwise noted, the reaction was carried out using 1.2 equiv. of **5** to **4** at -78 °C in $CH_2Cl_2$ under Ar. b) All products gave $^1H$ and $^{13}C$ NMR and IR spectra consistent with their assigned structures.
c) Isolated yield by chromatography on silica gel. d) Diastereoisomer **7a** was obtained in 27% yield. e) The reaction was carried out using 2.2 equiv. of **5d** at -78 to 40 °C. f) The product was obtained as an anomeric mixture (α/β=2/1). g) Combined yield of α- and β-anomers.
h) Two equiv. of **5f** was used.

acetic anhydride in pyridine to provide the corresponding methyl furanosides **8** or pyranosides **9**, depending on the nature of the C-2 substituents, as shown in Table 2. Compound **6f** decomposed under the acidic conditions to lead to the formation of an unidentified elimination product.



(2)

Table 2. Conversion of **6** to methyl furanosides or pyranosides

| Run | Compound **6** | Time/h | Product | Yield/%[a)] |
|---|---|---|---|---|
| 1 | **6a** | 4 | **9a** | 70 |
| 2 | **6b** | 11 | **9b** | 89 |
| 3 | **6c** | 8 | **8c** | 73 |
| 4 | **6d** | 7 | **8d** | 77 |
| 5 | **6e** | 9 | **9e** | 81 |

a) Isolated yield by chromatography on silica gel, not optimized.

In conclusion, we have developed a simple procedure for the synthesis of 2-C-substituted 2-deoxyhexoses using the $BF_3$-catalyzed cyclization between 1-alkenyl ethers and 2,3-O-isopropylidene derivative of D-erythrose. Especially high stereoselectivities were found to be obtained from the reaction of vinylic ethers bearing substituents at the β-position. The products obtained from this study will serve as chiral synthons for the synthesis of various natural products.

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## References

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3) For example, allylation to chiral aldehydes using allylboronates has been extensively studied by Roush: See W. R. Roush, L. K. Hoong, M. A. J. Palmer, J. A. Straub, and A. D. Palkowitz, J. Org, Chem., 55, 4117 (1990); W. R. Roush, X. Lin, and J. A. Straub, ibid., 56, 1649 (1991) and references cited therein.
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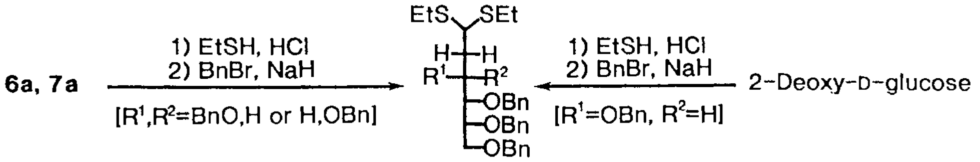
6) The stereochemical assignment at C-3 was confirmed by the transformation of **6a** and **7a** into the corresponding dithioacetals. The spectral data of the dithioacetal resulting from **6a** was identical with those of an authentic sample derived from commercial 2-deoxy-D-glucose (2-deoxy-D-*arabino*-hexose), but not those of the dithioacetal resulting from **7a**.



**(3)**

7) Generally, $BF_3$ is considered to be incapable of chelation. However, the observed stereochemistry of the major components **6** is consistent with that of chelation controlled *syn* products. Further details of the reaction pathway is now under investigation.
8) The values of the coupling constants, $J_{1,2}$, $J_{2,3}$, and $J_{3,4}$ of **6b-d** closely agreed with those of α-D-xylofuranose derivatives reported in the following paper; B. L. Kam, J.-L. Barascut, and J.-L. Imbach, Carbohydr. Res., 69, 135 (1979).

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