CHEMISTRY LETTERS, pp. 929-932, 1982.

4-O-BENZYL-2,3-O-ISOPROPYLIDENE-L-THREOSE
—— A NEW AND USEFUL BUILDING BLOCK FOR THE SYNTHESES OF L-SUGARS ——

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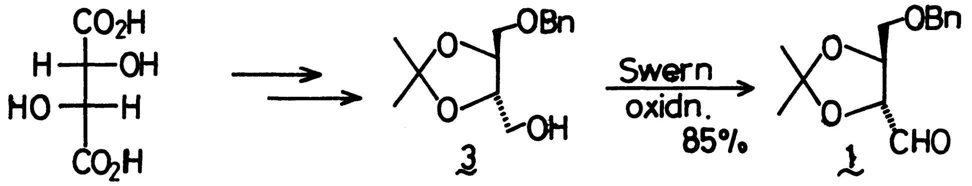
4-O-Benzyl-2,3-O-isopropylidene-L-threose (1), a new building block for the synthesis of carbohydrates was prepared. The stereoselective addition of various nucleophiles to 1 afforded useful intermediates toward L-sugar derivatives.

The natural occurrence of a number of L-sugars,$^{1)}$ some of which are the constituents of physiologically important substances, has stimulated much recent efforts toward the synthesis of this class of compounds. In many cases, it has been accomplished by the transformation from naturally abundant sugars of the D-series with lengthy and painstaking sequence of synthetic pathways. A more versatile approach is the synthesis starting from non-sugar precursors, however, most of such methods to date have been concerned with DL-mixture calling for a resolution step at any stage. We have already described some examples of the syntheses of carbohydrates based on the newly devised stereoselective C-C bond forming reactions employing D- or L-O-isopropylidene glyceraldehyde 2 as a key building block.$^{2)}$ These results indicate that the preparation of an appropriate building block obviously opens up a new entry into the syntheses of various sugars.

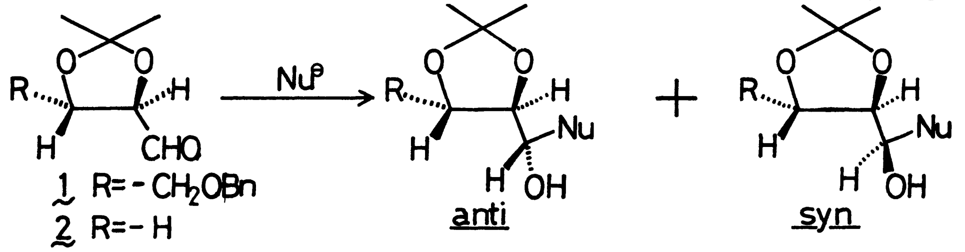
In this communication, we wish to describe the preparation of 4-O-benzyl-2,3-O-isopropylidene-L-threose (1), a new and potentially useful four-carbon building block for the syntheses of the L-sugars, and the stereochemical features of the addition of some nucleophiles to the aldehyde 1. As a starting material, L-tartaric acid was chosen, and was transformed to 2,3-O-isopropylidene-L-threitol in the conventional manner,$^{3)}$ which in turn was led to mono-benzylated alcohol 3 according to the method of Seebach *et al.*$^{4)}$ The alcohol 3 was then subjected to oxidation. Of several methods screened, the Swern oxidation$^{5)}$ cleanly afforded the new aldehyde 1$^{6)}$ as a colorless liquid which was readily purified by vacuum distillation. Different from glyceraldehyde acetonide 2, the aldehyde 1 is a fairly stable compound, which could be used in the reaction without substantial decrease of the yield even after storage at room temepurature for one week. It is apparent that this procedure enables the facile preparation of D-1, since



eqn. 1

D-tartaric acid is also available.

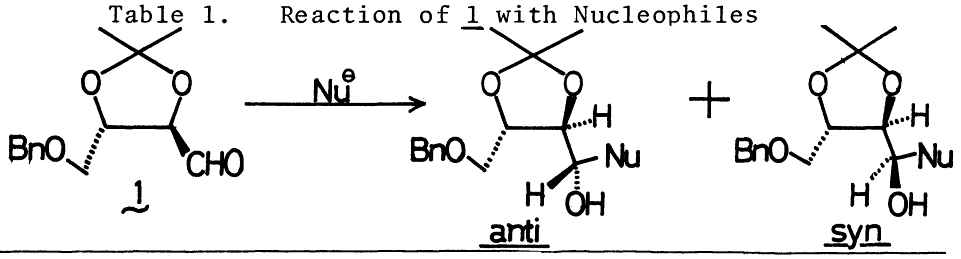
In the next place, the nucleophilic addition of "$-CH_2CHO$" equivalents to the aldehyde 1 was studied. It is well documented that the attack of the nucleophiles to the aldehyde 2 occurs *anti*-selective manner in most cases, which is explained by the Felkin's model (eqn. 2).[7)] Our main interest in the case of the aldehyde 1 was the effect of the chelation by means of the additional group ($-CH_2OBn$) on the stereochemical course of the reaction. The aldehyde 1 was treated with some nucleophiles listed in Table 1, and the diastereomer ratios of the products were determined by the HPLC and/or ^{1}H-NMR analysis.

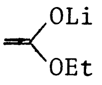
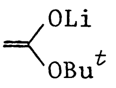
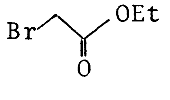
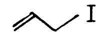


eqn. 2

The results show that the effective 1,2-asymmetric induction took place with any nucleophiles examined. Especially, in the reaction of lithio ethyl acetate carried out in THF at -100°C, the diastereomer selectivity over 90% was achieved (entry 2). Another noteworthy point is the efficiency of the organotin species in the reactions, new synthetic tools recently developed in our laboratory,[8)] where

Table 1. Reaction of 1 with Nucleophiles

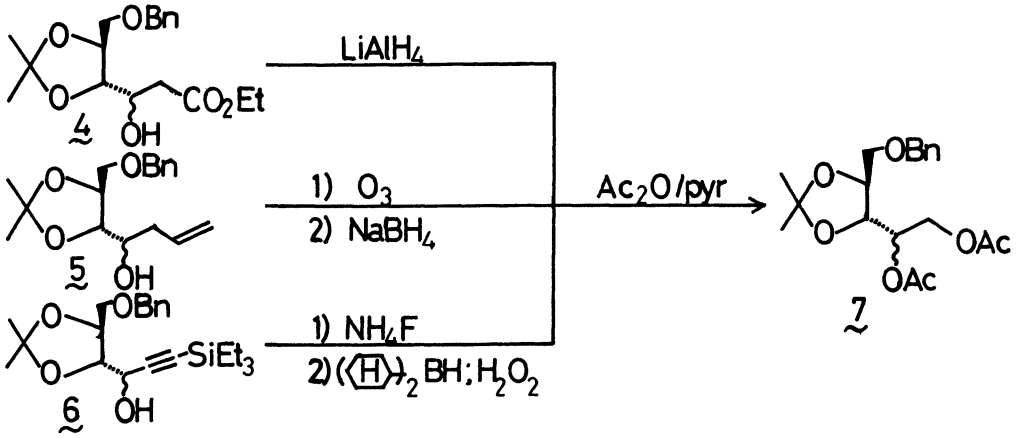


Entry	Nucleophile	Conditions	Product[a)]	Yield	*anti*/*syn*[b)]
1		THF, -78°C	4	72	83/17
2		THF, -100°C	4	81	90/10
3		THF, -78°C	4'	72	74/26
4	 + Sn	THF, r.t.	4	58	87/13
5	 + SnF_2	THF, 0°C	5	64	92/ 8[c)]
6	$LiC{\equiv}CSiEt_3$	DME, -78°C	6	44	80/20

a) Satisfactory NMR and IR spectra were obtained.[9)]
b) Determined by HPLC analysis (Merck LiChrosorb SI60, hexane-AcOEt).
c) The diastereomers were separated by silica gel preparative TLC (hexane-Et_2O).

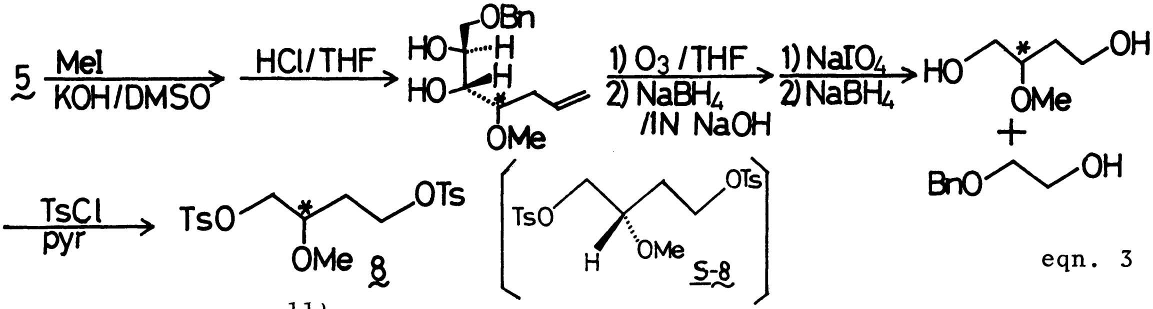
the corresponding products were obtained with high diastereoselectivity even at the temperature above 0°C (entry 4, 5).

Concerning the relative stereochemistry of the products, extensive correlation experiments were performed as shown in Scheme I. Thus, the adducts 4, 5 and 6 were converted to the diastereomer mixture of the di-acetate 7, each of which was subjected to HPLC analysis. It was revealed that the diastereomer ratio of 7 was in good accordance with that of the starting mixture 4, 5, or 6, respectively, and the predominant isomer of 7 was the same in the above three cases.



Scheme I

In addition, the chiral center of 5 in question was determined by the degradation study shown in the eqn. 3.



eqn. 3

The di-tosylate 8[11)] thus obtained was rich in the *S*-enantiomer judged from the optical rotation,[12)] and these data indicate that the preferred course of the addition of the nucleophiles to the aldehyde 1 was the *anti*-manner. And this stereochemical feature is again reasonably explained by the Felkin's model, and the additional substituent ($-CH_2OBn$), being apart from the reaction site, has little effect on the reaction path as shown in Fig. 1.

Extensive investigation concerning the synthesis of L-sugar derivatives employing the adducts thus obtained is now under way.

We wish to thank Mr. Akihiko Ikegawa for his help during this work.

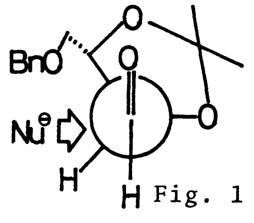


Fig. 1

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2) M. Yamaguchi and T. Mukaiyama, Chem. Lett., 1981, 1005; T. Harada and T. Mukaiyama, ibid., 1981, 1109; K. Suzuki, Y. Yuki, and T. Mukaiyama, ibid., 1981, 1529; T. Mukaiyama, T. Miwa, and T. Nakatsuka, ibid., 1982, 145; M. Murakami and T. Mukaiyama, ibid., 1982, 241.

3) P. W. Feit, J. Med. Chem., 7, 14 (1964).

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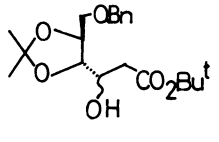
5) A. J. Mancuso, S.-L. Huang, and D. Swern, J. Org. Chem., 43, 2480 (1978).

6) bp 140-150°C/0.6 mmHg (bath temp.); NMR (δ, CDCl$_3$) 1.4 (s, 3H), 1.5 (s, 3H), 3.4-3.6 (m, 2H), 4.0-4.2 (m, 2H), 4.5 (s, 2H), 7.1 (s, 5H), 9.5 (s, 1H); IR (neat, cm^{-1}) 1725, 740, 700; $[\alpha]_D^{21}$ +16.8° (c 1.10, CHCl$_3$); Found: C, 66.86; H, 7.30%; M$^+$, 250.1219; Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25%; M, 250.1204.

7) M. Chérest, H. Felkin, and N. Prudent, Tetrahedron Lett., 1968, 2199; C. H. Heathcock, S. D. Young, J. P. Hagen, M. C. Pirrung, C. T. White, D. VanDerveer, J. Org. Chem., 45, 3846 (1980); S. Hagen, T. Anthonsen, and L. Kilaas, Tetrahedron, 35, 2583 (1980). An exceptional example, *syn*-addition, was reported: S. David, M.-C. Lépine, J. Chem. Soc., Perkin I, 1980, 1262.

8) T. Mukaiyama, T. Harada, and S. Shoda, Chem. Lett., 1980, 1507; T. Harada and T. Mukaiyama, ibid., 1982, 161.

9) Physical data of the adducts 4, 4', 5 and 6 are as follows.
4: NMR (δ, CDCl$_3$) 1.2 (t, J=7 Hz, 3H), 1.4 (s, 6H), 2.5-2.7 (m, 2H), 3.5-4.3 (m, 8H), 4.5 (s,2H), 7.2 (s, 5H); IR (neat, cm^{-1}) 1725, 750, 700.
4': NMR (δ, CDCl$_3$) 1.3 (s, 6H), 1.4 (s, 9H), 2.3-2.6 (m, 2H), 3.3-4.3 (m, 6H), 4.5 (s, 2H), 7.2 (s, 5H); IR (neat, cm^{-1}) 1725, 740, 700.
5: NMR (δ, CDCl$_3$) 1.4 (s, 6H), 2.0-2.5 (m, 2H), 2.7 (broad, 1H), 3.4-3.8 (m, 4H), 4.0-4.3 (m, 1H), 4.6 (s, 2H), 4.9-5.3 (m, 2H), 5.6-6.1 (m, 1H), 7.3 (s, 5H); IR (neat, cm^{-1}) 1635, 910, 730, 695.



4'

6: NMR (δ, CDCl$_3$) 0.3-1.3 (m, 15H), 1.4 (s, 6H), 2.5 (broad, 1H), 3.6 (d, J=4.5 Hz, 2H), 3.5-4.5 (m, 3H), 4.5 (s, 2H), 7.2 (s,5H); IR (neat, cm^{-1}) 3430, 2180, 740, 700.

10) NMR (δ, CDCl$_3$) 1.4 (s, 6H), 1.9-2.1 (m, 2H), 1.9 (s, 3H), 2.0 (s, 3H), 3.55 (d, J = 3 Hz, 2H), 3.7-4.2 (m, 6H), 4.55 (s, 2H), 4.9-5.3 (m, 1H), 7.3 (s, 5H); IR (neat, cm^{-1}) 1740.

11) NMR (δ, CDCl$_3$) 1.6-2.0 (m, 2H), 2.5 (s, 6H), 3.2 (s, 3H), 3.4-3.6 (m, 1H), 3.9-4.2 (m, 4H), 7.3 (d, J = 8 Hz, 4H), 7.8 (d, J = 8 Hz, 4H); IR (neat, cm^{-1}) 1350, 1190, 1175; $[\alpha]_D^{22}$ -11° (c 0.6, acetone).

12) The optical rotation of the optically pure (*S*)-8 is $[\alpha]_D^{25}$ -15.4 ± 0.8° (c 2.23, acetone); K. Brenneisen, Ch. Tamm, and T. Reichstein, Helv. Chim. Acta, 39, 1233 (1956).

(Received April 8, 1982)