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A NEW METHOD FOR THE SYNTHESIS OF α-L-THREOFURANOSIDES FROM ACYCLIC PRECURSOR

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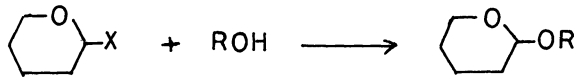
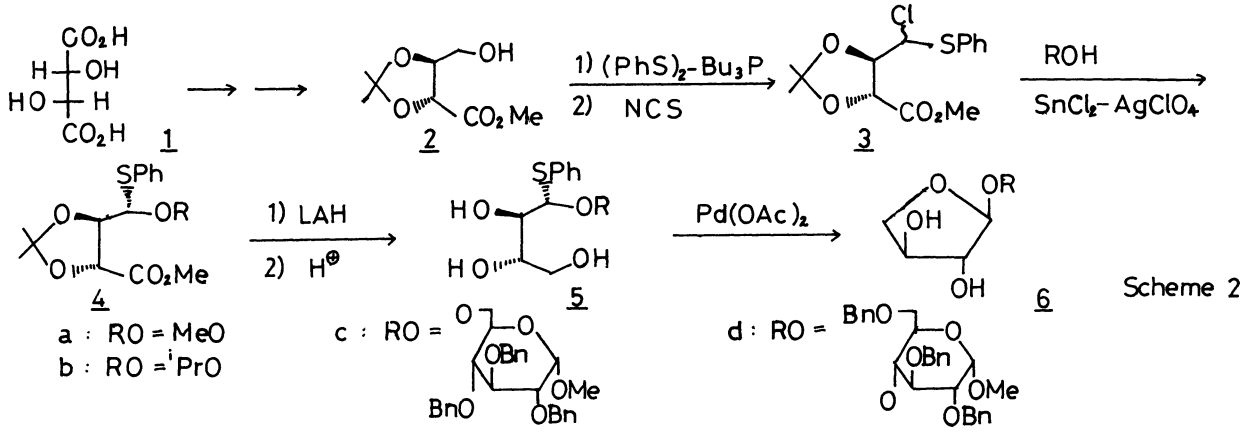
Stereoselective alkoxylation of acyclic precursor, (2S,3S)-2,3-O-isopropylidene-4-chloro-4-phenylthiobutyric acid methyl ester (3) in the presence of $SnCl_2$-$AgClO_4$, followed by $Pd(OAc)_2$ promoted cyclization gave α-L-threofuranosides in good yields.

In spite of the many researches concerning the glycoside forming reactions, an efficient glycosidation method is still strongly desired from the viewpoint of organic synthesis. Most of the methods for the stereoselective synthesis of these glycosides are based on the substitution reactions of cyclic precursors activated at anomeric center with various alcohols[1] as depicted in Scheme 1.



Scheme 1

Now, we wish to report a new method for the stereoselective synthesis of α-L-threofuranosides by the reaction of acyclic precursor, (2S,3S)-2,3-O-isopropylidene-4-chloro-4-phenylthiobutyric acid methyl ester (3) derived from L-tartaric acid, with alcohols, followed by cyclization as shown in Scheme 2.



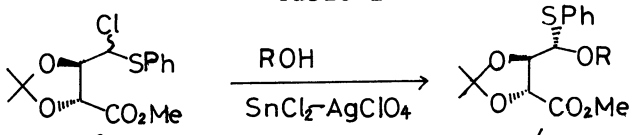
Scheme 2

Starting material 3 was prepared as follows: Alcohol 2 derived from L-tartaric acid[2] was converted to the corresponding sulfide on treatment with diphenyldisulfide and tributylphosphine in pyridine[3] (92%) and the sulfide was chlorinated

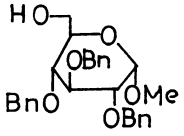
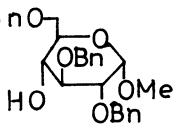
with N-chlorosuccinimide to give 3[4,5] in quantitative yield.

First, alkoxylation of 3 with alcohols promoted by Lewis acid was examined. Among a number of metal salts screened, the combination of $SnCl_2$-$AgClO_4$[6] gave the best results. Typical procedure for the synthesis of 4c is as follows: Under argon, to the slurry of $SnCl_2$ (0.60 mmol), $AgClO_4$ (0.60 mmol) and molecular sieves 3A in Et_2O was added the solution of 3 (0.5 mmol) and methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside (1.8 mmol) in Et_2O (8 ml) at 0°C and the reaction mixture was stirred for 2 h at 0°C. Then pH 7 buffer solution (7.5 ml) was added to the reaction mixture and the insoluble materials were filtered off. Then the filtrate was separated and the organic layer was washed with pH 7 buffer solution and brine successively, and dried over Na_2SO_4. After the evaporation of the solvent, the resulting residue was purified by silica-gel chromatography to give 4c (0.26 mmol, 56%, diastereomer ratio = >10 : 1). Other results are summarized in Table 1.

Table 1

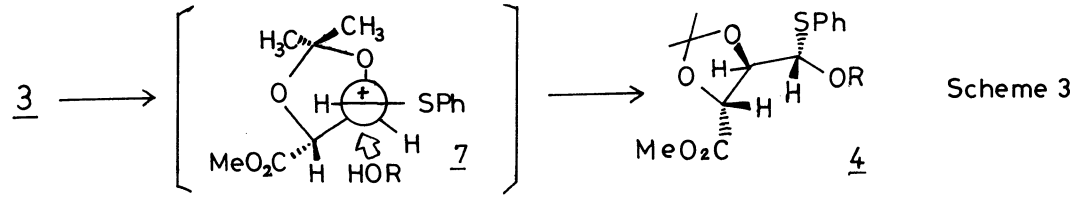


3 4

	ROH	Yield of 4[1]	Diastereomer ratio
a	MeOH	69	6:1 [2]
b	iPrOH	75	9:1 [2]
c		56	>10:1 [3]
d		40	>10:1 [3]

1) Yields were based on 3.
2) Diastereomer ratio was determined by ^{13}C-NMR.
3) Only one stereoisomer was detected by ^{13}C-NMR.

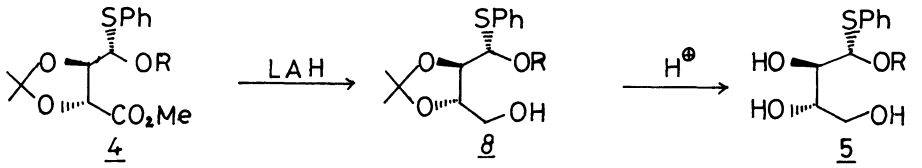
The present stereoselective reaction is assumed to proceed via S_N1 type reaction path. Nucleophile such as alcohol attacks the intermediate cationic species 7 from less hindered side as shown in Scheme 3.



Scheme 3

The ester 4 was reduced to alcohol 8 with $LiAlH_4$ in THF, then the acetonide moiety was hydrolyzed to afford 5. Yields and reaction conditions are summarized in Table 2.

Table 2



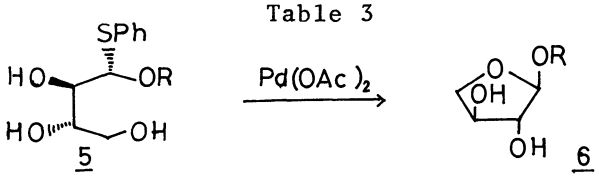
4 8 5

Ester	Yield of 8 (%)	Hydrolysis condition of 8	Yield of 5 (%)
4a	83	A	63
4b	94	B	56
4c	94	A	66
4d	91	A	74

1) The reduction was carried out with 1 ∿ 2 equimolar amount of $LiAlH_4$ in THF at 0°C for 1 h under argon.
2) Acid hydrolysis of acetonide moiety was carried out under the condition A or B. Condition A: 2 N HCl aq - MeOH (1 : 1.5) at r.t. for 6 ∿ 8 h. Condition B: 60% aqueous AcOH at 60°C for 2.5 h.

Next, cyclization of intermediate 5 to threofuranoside 6[7] in the presence of a variety of metal salts was examined and $Pd(OAc)_2$ or $HgCl_2$-HgO was found to be an efficient promoter. Of these metal salts, $Pd(OAc)_2$ gave better yields[8] of the threofuranosides though diastereomer ratios of the products were almost same in each case. Surprisingly, $CuCl_2$-CuO, having a strong affinity for sulfur, showed no activity for the cyclization of 5 to 6 though 4-cyclohexyloxy-4-phenylthiobutan-1-ol gave the cyclized product in good yield. It is supposed that 1,2,3-triol system like 5 forms a stable metal chelate with $CuCl_2$ and this chelate is hard to cyclize to form 6. Typical procedure for the cyclization of 5c to threofuranoside 6c is as follows: To the solution of 5c (0.14 mmol) in DME-H_2O (1 : 1, 10 ml) was added $Pd(OAc)_2$ (0.071 mmol) and the reaction mixture was stirred for 1.5 h at r.t. After insoluble materials were filtered off, the filtrate was evaporated in vacuo. The resulting residue was purified by silica-gel column chromatography to give 6c (0.095 mmol, 68%). Other results are summarized in Table 3.

Table 3



5 6

Triol	Yield of 6 (%)	Isomer ratio (α : β)
5a	93	6.6 : 1[1),2)]
5b	73	10.7 : 1[2)]
5c	68	>10 : 1[3)]
5d	74	>10 : 1[3)]

1) Two diastereomers of 6a were separated by column chromatography. α-Anomer was identified by specific rotation and ^{13}C-NMR.
2) Diastereomer ratio was determined by GC.
3) Only one isomer was detected by ^{13}C-NMR.

This cyclization is assumed to proceed via intramolecular S_N2 type substitution reaction, because the diastereomer ratio of 6 was almost the same as that of 5.

It is noted that the present procedure starting from acyclic precursor opens a new possibility of stereoselective glycoside synthesis and, by this method, D- or L-threofuranoside is conveniently prepared from D- or L-tartaric acid, respectively.

References

1) G. Röhle and G. Wulff, Angew. Chem.,Int. Ed. Engl., 13, 157 (1974), A. F. Bochkov and G. E. Zaikov, "Chemistry of the O-Glycosidic Bond", Pergamon Press, (1979).
2) J. A. Musich and H. Rapoport, J. Am. Chem. Soc., 100, 4865 (1978).
3) I. Nakagawa and T. Hata, Tetrahedron Lett., 1975, 1409.
4) Two diastereomers concerning C-4 position were present and the ratio was almost 1 : 1.
5) Satisfactory spectral and analytical data were obtained.
6) T. Mukaiyama, Y. Murai, and S. Shoda, Chem. Lett., 1981, 431. The combination of $SnCl_2$-$AgClO_4$ gave excellent results in the preparation of 1,2-cis glucosides from glucosyl fluoride and alcohols.
7) Specific rotation and ^{13}C-NMR data of the major anomer of 6a were as follows; $[\alpha]_D^{20}$ -93° (c 1.6, H_2O); lit.[9] methyl α-D-threofuranoside, $[\alpha]_D^{20}$ +97° (c 1.6, H_2O); ^{13}C-NMR ($CDCl_3$) δ = 108.5 ppm, (anomeric carbon), lit.[10] ^{13}C-NMR (D_2O, external TMS) δ = 109.4 ppm.
8) Yield of cyclized product 6c was 76% in the case of $HgCl_2$-HgO.
9) J. N. Baxter and A. S. Perlin, Can. J. Chem., 38, 2217 (1960).
10) R. G. S. Ritchie, N. Cry, K. Koush, H. J. Koch, and A. S. Perlin, Can. J. Chem., 53, 1424 (1975).
11) Spectral data of C-4 carbon of 4 and anomeric carbon of threose 6 are as follows: 4a; 92.5 (major), 91.6 (minor), 4b; 87.5 (major), 87.3 (minor), 4c; 98.0 4d; 90.3 ppm: 6a; 108.5 (major), 102.7 (minor), 6b; 105.2, 6c; 106.4, 6d; 108.1 ppm.

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