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THE STEREOSELECTIVE SYNTHESIS OF D-RIBULOSE

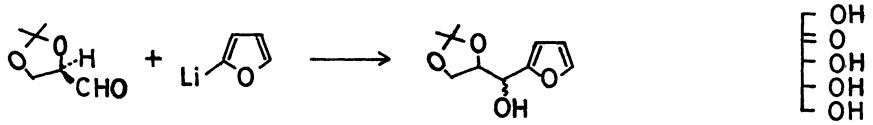
Keisuke SUZUKI, Yoichi YUKI, and Teruaki MUKAIYAMA

Department of Chemistry, Faculty of Science,
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

In the presence of zinc halide, 2-furyllithium reacts with 2,3-O-isopropylidene-D-glyceraldehyde in a highly stereoselective manner to give the chiral and stereo-defined alcohol, 2,2-dimethyl-4-(2-furyl)hydroxymethyl-1,3-dioxolane, which is further elaborated to afford D-ribulose in three steps.

The synthesis of sugars has held considerable attention in organic synthesis in recent years, and we have also shown the possibility of the synthesis of this class of compounds by highly stereoselective carbon-carbon bond forming reactions.[1)]

Now, we wish to describe a new and convenient method for the synthesis of D-*erythro*-2-pentulose(D-ribulose) (1), a rare sugar found as an intermediate of D-glucose metabolism, *via* the furyl alcohol 2 prepared by the stereoselective addition of 2-furyllithium (3) to 2,3-O-isopropylidene-D-glyceraldehyde (4).

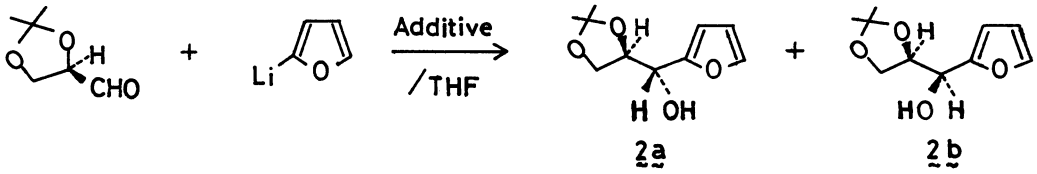


4 3 2 1

Furyl alcohols have been successfully employed by O. Achmatowicz *et al.* as key building blocks of the synthesis of sugars.[2)] Their method of furyl alcohols synthesis consists of two processes, preparation of furyl ketones followed by the metal hydride reduction, and there still remain two certain drawbacks; namely, 1) the necessity of resolution to obtain the alcohols in optically active forms, and 2) the lack of stereoselectivity in the reduction of furyl ketones. Thus, it is desirable to establish a convenient and straightforward method for the preparation of the optically active and stereo-defined furyl alcohols without resort to resolution.

In the first place, the stereoselectivity of the addition of 2-furyllithium to 2,3-O-isopropylidene glyceraldehyde was extensively studied, and it was found that the coexistence of metal salt causes a significant effect on the stereoselectivity. Preliminarily, when 2-furyllithium was allowed to react with 2,3-O-isopropylidene glyceraldehyde (4) in THF at -78°C, a mixture of the corresponding furyl alcohols (2a, 2b) was obtained in 68% yield where the *syn*-alcohol 2b[3)] predominated (entry 1). On the other hand, when carried out in the presence of metal salt, the present reaction was found to proceed stereoselectively to afford the *anti*-alcohol 2a, predominantly, as shown in the Table. Especially, in the presence of ZnI_2 almost pure 2a was obtained even at the temperature of 0°C.

Table Effect of the metal salt on the stereoselectivity



2a 2b

Entry	Additive	Temperature	Yield(%)	2a/2b[a]
1	None	-78°C	68	40/60
2	$MgBr_2$	0°C	49	50/50
3	$SnCl_4$	0°C	58	95/5[b]
4	$ZnCl_2$	-78°C	10	>95/<5
5	$ZnCl_2$	0°C	60	90/10
6	$ZnBr_2$	0°C	75	95/5
7	ZnI_2	0°C	57	>95/<5

a) The ratio was determined by the ^1H NMR integration study of the corresponding acetates[7] (methine proton) in CCl_4 in the presence of $Eu(FOD)_3$ as a shift reagent.

b) The reaction was carried out in toluene solvent.

Typical experimental procedure is as follows: To a THF solution of 2-furyllithium prepared by conventional manner[4] was added well dried zinc bromide (450 mg, 2 m mol) at 0°C and the resulting solution was stirred for 10 min. Then, to this solution was added 2,3-O-isopropylidene-D-glyceraldehyde[5] (260 mg, 2 mmol) in THF (3 ml) and the reaction mixture was kept standing at 0°C overnight. The reaction was stopped by the addition of a 4% $NaHCO_3$ solution and the subsequent extractive workup and the purification by silica-gel thin layer chromatography afforded 2,2-dimethyl-4-(2-furyl)hydroxymethyl-1,3-dioxolane (297 mg, 75%).[6]

As mentioned above, the enhancement of the *anti*-selectivity by metal salts could be explained by assuming the fixed conformation of the aldehyde 4 by the coordination of the zinc atom with the carbonyl oxygen and the 3-oxygen of the dioxolane ring as illustrated below.[8] Nucleophilic attack of the anionic species may occur from the less hindered side, i.e. the left side of the Figure I, to result in the selective formation of the *anti*-alcohol 2a.

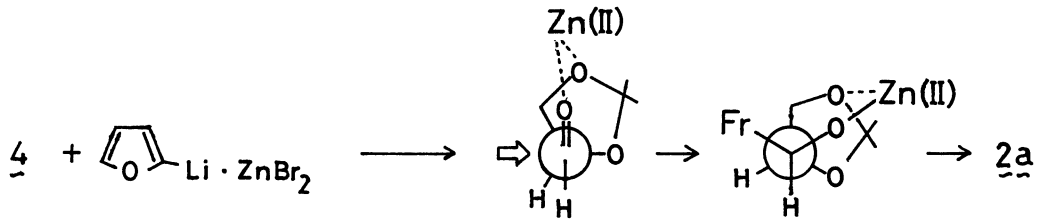
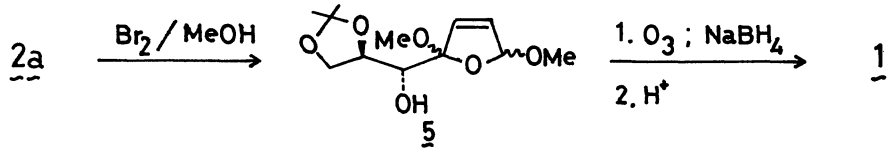


Fig. I

Apart from the mechanism of this highly stereoselective reaction, the furyl alcohol 2a thus obtained is a useful intermediate in the synthesis of sugars. Thus, we turned our attention to the synthesis of D-*erythro*-2-pentulose(D-ribulose), starting from the alcohol 2a. Initially, the alcohol 2a was treated with bromine in methanol at -42°C[9] to give the dihydrofuran derivative 5[10] in 80% yield.



Next, 5 was treated with O_3 in CH_2Cl_2-MeOH (-15°C, 8 hr), and then reductively worked up by the treatment with $NaBH_4$ (0°C, overnight). Finally, the crude oil obtained by the foregoing reaction was hydrolyzed with 2N HCl/THF (r.t. 5 hr) to give crude D-*erythro*-2-pentulose 1, which was purified by silica-gel column chromatography (AcOEt-n-BuOH-MeOH-H_2O, 80:15:15:10).[11] The structure of the product 1 was confirmed by its o-nitrophenylhydrazone derivative,[12a] ORD measurement,[12b] and comparison of the ^{13}C NMR spectrum with that of an authentic sample.[12c] Chemical synthesis of ribulose reported to date is based on i) base catalyzed isomerization of aldose[13a] or ii) one carbon extension of a 4-carbon sugar.[13b] Compared with these methods, the present method presents a very facile preparation of the ketose 1 without time-consuming separating operations.

It is noted that the present procedure enables a very convenient synthesis of D-*erythro*-2-pentulose *via* the chiral and stereo-defined furyl alcohol, prepared by the zinc halide mediated stereoselective addition reaction of 2-furyllithium to 2,3-O-isopropylidene-D-glyceraldehyde.

Extensive investigation is also underway on the scope of this highly stereoselective reaction by the use of the chelation effect of metal salts.

References

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b) T. Harada and T. Mukaiyama, Chem. Lett., 1981, 1109.
2) O. Achmatowicz, Organic Synthesis Today and Tomorrow, pp. 307-318, B. M. Trost and C. R. Hutchinson Edn. Pergamon (1981). And references cited therein.
3) *Syn* and *anti* are based on Masamune's nomenclature: S. Masamune, Sk. A. Ali, D. L. Snitman, and D. S. Garvey, Angew. Chem. Int. Ed. Engl., 19, 557 (1980).
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5) E. Baer and H. O. L. Fischer, J. Biol. Chem., 128, 463 (1939).
6) NMR (δ, CCl_4); 1.30 (s, 3H), 1.37 (s, 3H), 2.3 (br, 1H), 3.83 (d, J=2 Hz, 1H), 3.39 (s, 1H), 4.00-4.40 (m, 1H), 4.65 (d, J=4 Hz, 2H), 6.30 (m, 2H), 7.25 (m,1H).
IR (cm^{-1}, neat); 3420, 2980, 2930, 2880, 1600, 1385, 1375, 1250, 1220, 1150, 1070, 1015, 850, 745.
b.p. 105-110°C/1.5 mm Hg (bath temp.)

7) The physical data for the acetate of the *anti*-alcohol 2a is shown below.
NMR (δ, CCl_4); 1.29 (s, 3H), 1.33 (s, 3H), 2.00 (s, 3H), 3.83-4.13 (m, 2H), 4.38 (dd, J_1=5.5 Hz, J_2=12 Hz, 1H), 5.85 (d, J=5.5 Hz, methine proton), 6.25 (m, 2H), 7.40 (d, J=1 Hz).
IR (cm^{-1}, neat); 2970, 2920, 2875, 1735, 1365, 1220, 1150, 1075, 1055, 1010.
The methine proton of the acetate of the *syn*-alcohol 2b showed a doublet centered at 5.78 ppm (J=8 Hz).

8) From a molecular model inspection, the interaction between the zinc atom and the 1-oxygen of the dioxolane ring is considered to be unfavorable.

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10) NMR (δ, $CDCl_3$); 1.37 (s, 3H), 1.42 (s, 3H), 2.7 (br, 1H), 3.15, 3.18, 3.22 (three s, 3H), 3.47, 3.49 (two s, 3H), 3.65-4.10 (m, 3H), 4.10-4.50 (m, 1H), 5.48, 5.75 (two s, 1H), 5.95-6.20 (m, 2H).
IR (cm^{-1}, neat); 3470, 3000, 2950, 2845, 1380, 1220, 1060, 1025, 985.
b.p. 160-170°C/1.5 mm Hg (bath temp.)

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c) ^{13}C NMR (δ^*, D_2O, acetone as an internal standard); 105.7, 102.6, 75.9, 75.5, 72.6, 71.6, 70.9, 70.6, 70.3, 66.6, 62.9, 62.7, 61.4.
*Based on the value of the acetone-methyl as 30.4 ppm.

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b) D. L. MacDonald, J. D. Crum, and R. Barker, J. Am. Chem. Soc., 80, 3379 (1958).
c) A completely different approach was reported recently. P. M. Collins, P. Gupta, and A. S. Travis, J. Chem. Soc., Perkin 1, 1980, 277.

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