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THE STEREOSELECTIVE SYNTHESIS OF L-TAGATOSE —— AN APPLICATION OF Zn(II) MEDIATED HIGHLY STEREOSELECTIVE ADDITION OF 2-FURYLLITHIUM TO POLYOXYGENATED ALDEHYDE ——[1)]

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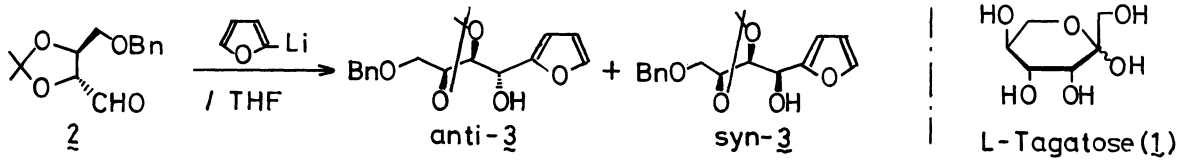
In the presence of $ZnBr_2$, the addition of 2-furyllithium to 4-O-benzyl-2,3-O-isopropylidene-L-threose proceeded in a highly stereoselective manner to afford the *anti*-adduct, which was further converted to L-tagatose.

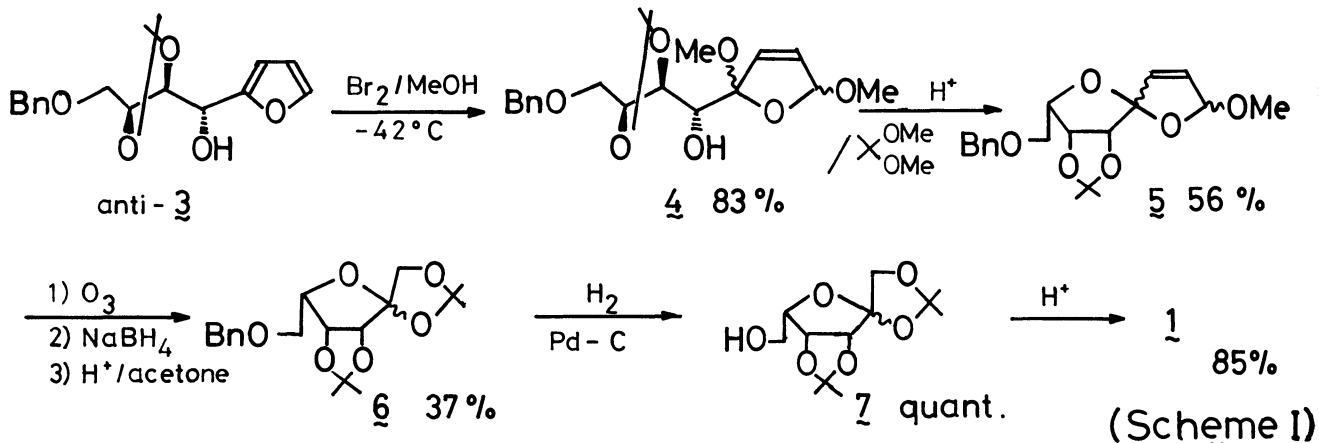
In the previous paper,[2)] we reported the highly stereoselective addition of 2-furyllithium to 2,3-O-isopropylidene glyceraldehyde in the presence of zinc(II) halides, where the adduct was converted to D-ribulose in three steps. The observed high stereoselectivity is reasonably explained by the enhancement of the Felkin's selectivity[3)] by virtue of the chelation effect of Zn(II).

In this communication, we wish to describe a convenient route to the synthesis of L-tagatose (1),[4)] the antipode of the naturally occurring ketose of physiological and immunological interests,[5)] based on the aforementioned highly stereoselective addition. When 2-furyllithium in THF was treated at -78°C with 4-O-benzyl-



2,3-O-isopropylidene-L-threose (2), a new building block for the sugar synthesis,[6)] the corresponding adducts 3 were obtained in 97% yield in a virtually non-stereoselective manner (*anti:syn* = 63:37).[7)] On the other hand, in the presence of an equimolar amount of $ZnBr_2$,[8)] the addition proceeded in a highly stereoselective manner to afford almost pure *anti*-3[9)] (*anti:syn* = 98:2)[7)] in 97% yield.

Next, the synthesis of L-tagatose starting from the *anti*-adduct was investigated (Scheme I). The adduct 3 was treated with Br_2 (1 equiv.) in MeOH at -42°C to give the dihydrofuran derivative 4,[10)] which in turn was converted to the bicyclic compound 5[10)] by the treatment with a catalytic amount of H_2SO_4 in 2,2-dimethoxypropane at room temperature. The spiro-ketal 5 was then ozonized (MeOH, -78°C), reductively worked up with $NaBH_4$, and acetalized (acetone, H_2SO_4) to give the diacetonide 6.[11)] The acetonide 6 was quantitatively debenzylated (1 atm H_2, 10% Pd-C, r.t., 12 hr) to give 1,2;3,4-di-O-isopropylidene-L-tagatose (7) as white crystal, which was identical with an authentic specimen of the D-series in all respects except for the sign of the optical rotation.[12)] The diacetonide 7, thus



(Scheme I)

obtained was further converted to 1 under the same condition reported for D-7[4] in 85% yield.[13] Thus, L-tagatose, the antipode of the naturally occurring ketose, was successfully synthesized from the adduct 3 in five steps.

References

1) Dedicated to Professor Takeo Sakan on the occasion of his 70th birthday.

2) K. Suzuki, Y. Yuki, and T. Mukaiyama, Chem. Lett., 1981, 1529.

3) M. Chérest, H. Felkin, and N. Prudent, Tetrahedron Lett., 1968, 2199.

4) T. Reichstein and W. Bosshard, Helv. Chim. Acta, 17, 753 (1934); P.A.J. Gorin, J.K.N. Jones, and W.W. Reid, Can. J. Chem., 38, 2290 (1960); and references cited therein.

5) J.J. Furth, J. Hurwitz, and M. Anders, J. Biol. Chem., 237, 2611 (1962); G.F. Springer and P. Williamson, Biochem. J., 85, 282 (1962); R.A. Anderson, Jr., C. Oswald, S. Leto, and J.D.L. Zaneveld, Biol. Reprod., 22, 1079 (1980).

6) T. Mukaiyama, K. Suzuki, and T. Yamada, Chem. Lett., 1982, 929.

7) The diastereomer ratio was determined by the HPLC analysis —Merck SI60 (hexane-AcOEt).

8) The reaction was carried out at 0°C. Concerning the detailed experimental procedure, see ref. 2).

9) NMR and IR data for the *anti* and *syn* adducts are presented: *Anti*-adduct NMR ($CDCl_3$) δ=1.3 (s, 6H), 3.1-4.5 (m, 5H), 4.35 (s, 2H), 4.7 (d, J=3 Hz, 1H), 6.2 (s, 2H), and 7.1-7.3 (m, 6H). IR (neat) 3430, 860, 740, and 700 cm^{-1}. *Syn*-adduct NMR ($CDCl_3$) δ=1.35 (s, 3H), 1.40 (s, 3H), 3.0 (broad, 1H), 3.1-3.6 (m, 2H), 4.0-4.3 (m, 2H), 4.5 (s, 2H), 4.5-4.9 (m, 1H), 6.3 (s, 2H), and 7.1-7.4 (m, 6H). IR (neat) 3430, 1080, 865, 740, and 700 cm^{-1}.

10) The compound exhibited satisfactory spectral properties.

11) NMR (CCl_4) δ=1.2 (s, 3H), 1.3 (s, 6H), 1.4 (s, 3H), 3.4-3.8 (m, 2H), 3.8-4.1 (m, 1H), 3.85 (d, J=6Hz, 1H), 4.15 (d, J=6Hz, 1H), 4.35 (d, J=3 Hz, 1H), 4.45 (s, 2H), 4.65 (dd, J_1=3 Hz, J_2=3.5 Hz, 1H), and 7.1-7.3 (m, 5H); IR (neat) 2980, 2930, 1390, 1370, 855, 735, and 695 cm^{-1}; Found: m/e 350.1720. Calcd for $C_{19}H_{26}O_6$: M, 350.1727.

12) M.p. 64-65°C (pentane); $[\alpha]_D^{24}$ -62° (c 1.1, $CHCl_3$); IR (CH_2Cl_2) 3600, 2930, 1370, 1210, 1070 and 860 cm^{-1}; ^1HNMR (CCl_4) δ=1.25 (s, 3H), 1.35 (s, 3H), 1.4 (s, 6H), 2.1 (broad, 1H), 3.5-4.1 (m, 3H), 3.9 (d, J=6 Hz, 1H), 4.15 (d, J=6 Hz, 1H), 4.5 (d, J=4 Hz, 1H), and 4.75 (dd, J_1=4 Hz, J_2=2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ=24.71, 25.95, 26.44, 69.22, 78.97, 80.48, 85.42, 111.69, 111.80, and 112.88; MS (70 eV), Found: m/e 245.1008. Calcd for $C_{11}H_{17}O_6$: M-CH_3^+ 245.1023.
An authentic sample of D-7 was prepared from commercial D-tagatose according to the method stated in ref. 4), where the optical rotation of D-7 was reported to be $[\alpha]_D$ +64° (c 0.80, $CHCl_3$).

13) M.p. 130-131°C (EtOH) ; $[\alpha]_D^{22}$ +3.1° (c 0.75, H_2O) (constant value).

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