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THE STEREOSELECTIVE SYNTHESIS OF D- AND L-RIBOSE

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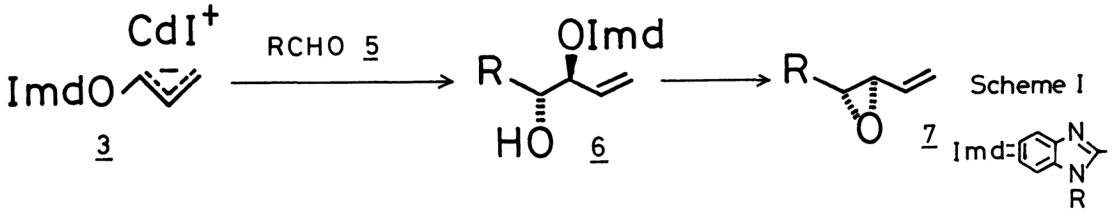
The allylcadmium compound, prepared in situ from 2-allyloxybenzimidazole, reacts with 2,3-O-isopropylidene-D and L-glyceraldehyde in highly regio- and stereoselective manner to give the corresponding enantiomeric adducts. The adducts are futher transformed to D- and L-ribose, respectively, by a four-steps process.

Sugars are one of the most common organic compounds in nature, and have been a challenging target for synthetic organic chemists. However, the effective method[1] for the synthesis of sugars involving highly stereoselective carbon-carbon bond formation has been rather a few, and the investigation of the process is earnestly desired.

Now, we wish to report a new and efficient method for the synthesis of D- and L-ribose(D-1 and L-1), an important component of nucleic acids, coenzymes etc., via vinyloxiranes(2) prepared by the stereoselective addition of allylcadmium compound(3) to 2,3-O-isopropylidene-D and L-glyceraldehyde(D-4 and L-4).

2,3-O-Isopropylideneglyceraldehyde(4) is frequently employed in the synthesis of a variety of optically active organic compounds,[2),3)] because 1) either D-4[4)] or L-4[5)] is obtained in optically pure form; 2) under appropriate reaction conditions, nucleophiles stereoselectively[2)] add to a carbonyl group to form adducts with anti-configuration[6)] about two vicinal asymmetric centers.

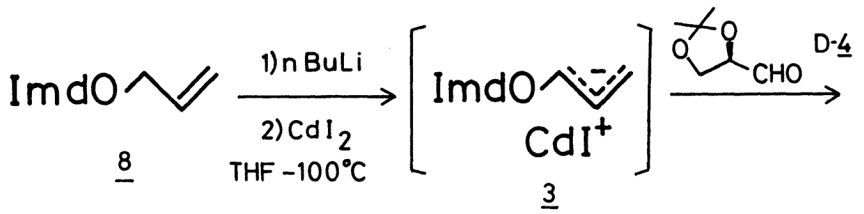
In the previous communication, we reported[7)] that allylcadmium compounds(3) react regio- and stereoselectively with a variety of aldehydes(5) to form adducts(6) in good yields, and that 6 are smoothly transformed to trans-vinyloxiranes(7) as shown in Scheme I.

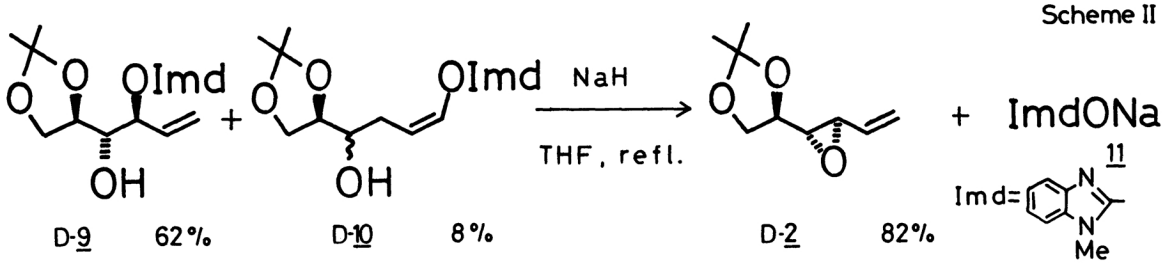


Scheme I

Thus, the preparation of vinyloxiranes(D-2) by the reaction of D-4 with 3 was tried first. Organocadmium compound (3) was prepared from 1-methyl-2-propenyloxybenzimidazole(8) by the treatment with n-butyllithium followed by cadmium iodide at -100°C in tetrahydrofuran(THF),[7)] and was allowed to react with D-4. The reaction proceeded selectively at the α-carbon of benzimidazolyloxy group of 3 to afford 5,6-dideoxy-1,2-O-isopropylidene-4-O-(1-methylbenzimidazol-2-yl)-

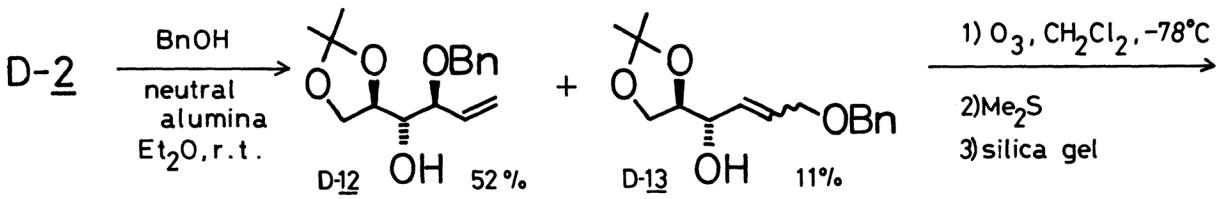
D-ribo-5-hexenitol(D-9,62%),[8] and only a small of γ-adduct(D-10,8%) was detected as a by-product. The α-adduct(D-9) was then treated with sodium hydride in refluxing THF and was transformed to 3,4-anhydro-5,6-dideoxy-1,2-O-isopropylidene-D-arabino-5-hexenitol(D-2,[9] in 82% yield with the loss of 1-methyl-2-benzimidazolone(11). Though D-2 contained three asymmetric carbon centers in the molecule, it was confirmed by ^{13}C-NMR, ^{1}H-NMR and GLC that the product thus obtained consisted of a single isomer (Scheme II).

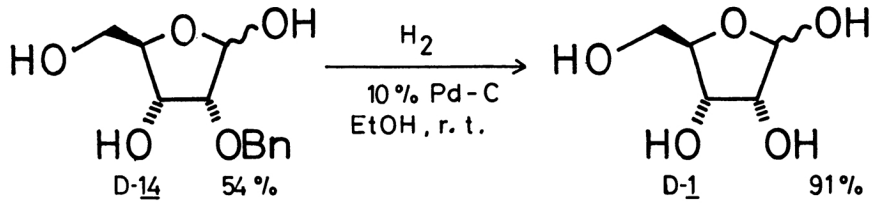




Scheme II

The oxirane(D-2), a quite useful synthetic intermediate, was then transformed to D-ribose(D-1) according to the following procedure. The cleavage of the oxirane ring was performed with benzylalcohol in ether at room temperature utilizing neutral alumina(Merck) as an activator.[22] The reaction proceeded predominantly at 4-carbon of D-2 to afford 4-O-benzyl-5,6-dideoxy-1,2-O-isopropylidene-D-ribo-5-hexenitol(D-12,52%;[10] as the major product along with the minor product(D-13,11%) resulted from the reaction of benzylalcohol at 6-carbon. The alcohol(D-12) was then treated with ozone at -78°C in methylene chloride, and the ozonide was reduced with dimethyl sulfide.[11] The resulted product was purified by chromatography on silica gel, which effected hydrolysis of the ketal group, and crystalline 2-O-benzyl-D-ribose(D-14,54%)[12] was obtained. The debenzylation was carried out in ethanol under a hydrogen atmosphere utilizing 10%Pd-C as a catalyst. The ^{13}C-NMR spectra of the crude product(91%) agreed with that of D-ribose. The structure was further confirmed by converting the product to D-ribose anilide(D-15).[13] Based on these results, the absolute configuration of each of the intermediate was determined as D-2,9,12,14 (Scheme II).

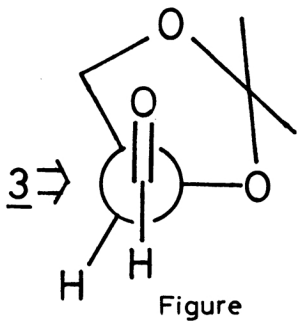




Scheme III

Bn = $PhCH_2$

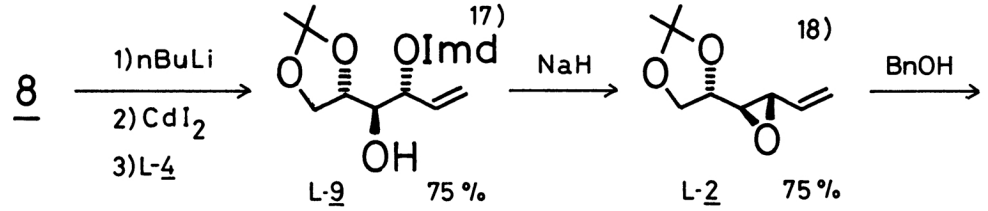
The stereoselectivity in the formation of D-9 with 2R,3R-configuration(anti) may be explained according to the Felkin's model.[14] It is presumed that the nucleophile(3) adds to a carbonyl group from the less hindered site of the conformation shown in the Figure. It should be also mentioned that the effect of cadmium salt is crucial in the generation of D-9 with 3R,4S-configuration(anti) and that use of other metal salts (eg. Li,Zn,Mg) gave unsatisfactory results.



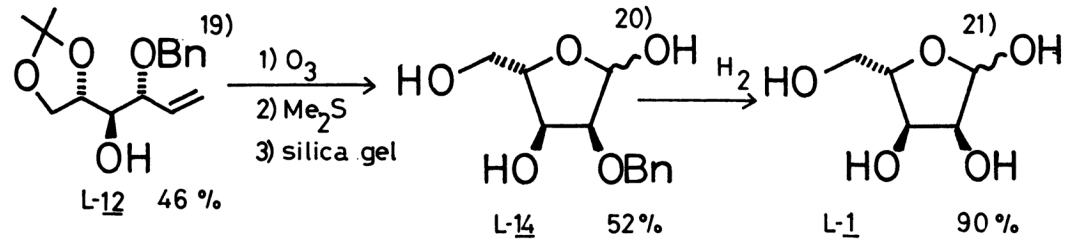
Figure

Among many reports for the synthesis of D-ribose[15] (D-1), the present method is characterized by the utilization of the unique stereoselective carbon-carbon bond formation reaction. Also 2-O-benzyl-D-ribose, in which only the hydroxyl group at 2-position is protected, is an interesting intermediate in sugar chemistry.

The achievement of the synthesis of D-ribose(D-1) starting from D-4 led to the idea that L-ribose(L-1), a rare sugar, can be synthesized from 2,3-O-isopropylidene-L-glyceraldehyde(L-4). Thus we performed the stereoselective synthesis of L-ribose(1-1) according to the same procedure except that the starting material was L-4 (Scheme IV).



Scheme IV



L-Ribose(L-1) is quite rare in nature, and the only practical method for the preparation[16] was the transformation of L-arabinose(16). However, according to this method, a mixture of L-1 and 16 was formed, so that the isomers had to be separated. On the other hand, our procedure synthesizing L-1 stereoselectively might be a useful synthetic method.

It is noted that the allylcadmium compound(3) adds to 2,3-O-

isopropylidene-D and L-glyceraldehyde(D-4 and L-4) stereoselectively, and the corresponding two enantiomeric adducts, useful synthetic intermediates, opened a new and efficient route to the synthesis of D- and L-ribose(D-1 and L-1).

Acknowledgement: We thank Mr. Jun-ichi Kato for his assistance in the synthesis of L-ribose.

References and Notes

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8) Mp. 123°C(n-hexane recryst.). $[\alpha]_D^{22}$=-58°(c 1.0,$CHCl_3$). NMR($CDCl_3$) δ 1.32(3H, s), 1.42(3H,s), 3.43(3H,s), 3.99(5H,s), 5.1-5.6(3H,m), 5.0-6.5(1H,m), 6.9-7.2 (3H,m), 7.2-7.4(1H,m). IR(KBr) 3000-3600 cm^{-1}. Found: C, 63.87; H, 6.78; N, 8.86%. Calcd for $C_{17}H_{22}N_2O_4$: C, 64.13; H, 6.97; N, 8.80%.
9) Bp 70°C/0.5 mmHg(bath temp.). $[\alpha]_D^{26}$=+14°(c 4.0, $CHCl_3$). ^{1}H-NMR($CDCl_3$) δ 1.39 (3H,s), 1.43(3H,s), 2.96(1H,dd,J=2,4 Hz), 3.2-3.4(1H,m), 3.8-4.2(3H,m), 5.2-5.7(3H,m). ^{13}C-NMR($CDCl_3$) δ 25.2, 26.5, 57.3, 59.8, 66.8, 75.7, 109.8, 119.9, 134.4. IR(neat) 840 cm^{-1}. Found: C, 63.42; H, 8.58%. Calcd for $C_9H_{14}O_3$: C; 63.51; H, 8.29%.
10) Bp 200°C/0.1 mmHg(bath temp.). $[\alpha]_D^{23}$=+43°(c 1.0, $CHCl_3$). NMR($CDCl_3$) δ 1.28 (3H,s), 1.33(3H,s), 2.72(1H,s), 3.6-4.3(5H,m), 4.26(1H,d,J=12Hz), 4.89(1H,d,J= 12Hz), 5.0-6.0(3H,m), 7.18(5H,s). IR(neat) 3450 cm^{-1}. Found: C, 69.02; H, 8.10. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.99%.
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12) Mp 91°C.(C_6H_6-$CHCl_3$ recryst.). $[\alpha]_D^{24}$=-31→-18°(c 1.0, EtOH). NMR($CDCl_3$) δ 3.3-4.0(8H,m), 4.6-4.8(2H,m), 5.05(1H,d,J=6Hz), 7.2-7.5(5H,m). IR(KBr) 3400 cm^{-1}. Found: C, 59.62; H, 6.85%. Calcd for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71%.
13) Mp 119°C $[\alpha]_D^{22}$=+59°(c 1.0, pyridine). Cf. G. A. Howard, G. W. Kenner, B. Lythgoe, and A. R. Todd, J. Chem. Soc., 1946, 855.
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16) W. C. Austin and F. L. Humoller, J. Am. Chem. Soc., 56, 1152 (1934).
17) Mp 121°C (n-hexane recryst.) $[\alpha]_D^{22}$=+59°(c 1.0, $CHCl_3$).
18) Bp 70°C/0.5 mmHg(bath temp.). $[\alpha]_D^{24}$=-13°(c 1.0, $CHCl_3$).
19) Bp 170°C/0.5 mmHg(bath temp.). $[\alpha]_D^{24}$=-45°(c 1.0, $CHCl_3$).
20) Mp 92.5°C(C_6H_6-$CHCl_3$ recryst.). $[\alpha]_D^{24}$=+17°(c 1.0, EtOH, equil.).
21) Anilide; Mp 119°C. $[\alpha]_D^{24}$=-57°(c 0.9, pyridine).
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