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SYNTHESIS OF OPTICALLY ACTIVE 4-AMINO-2-(HYDROXYMETHYL)TETRAHYDROFURAN-4-CARBOXYLIC ACIDS

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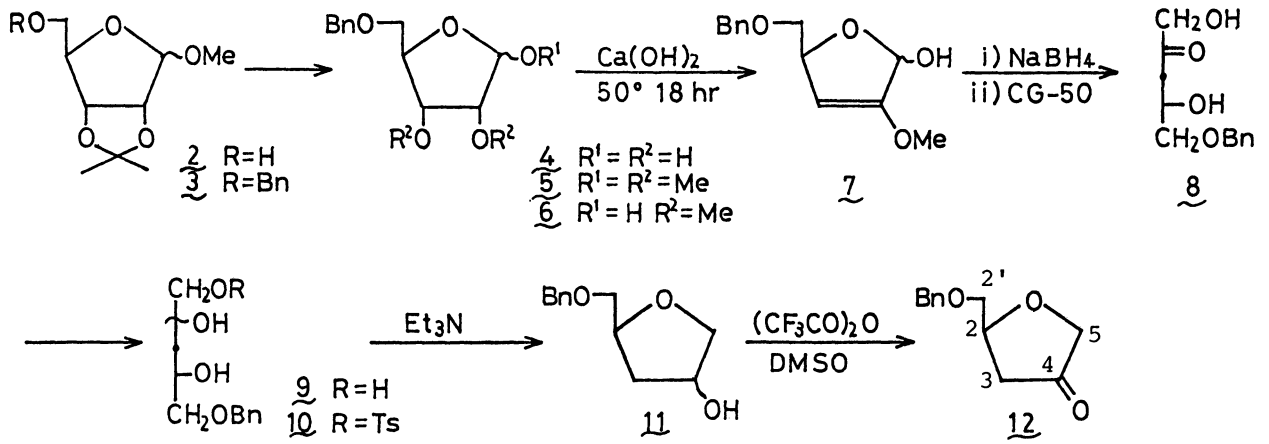
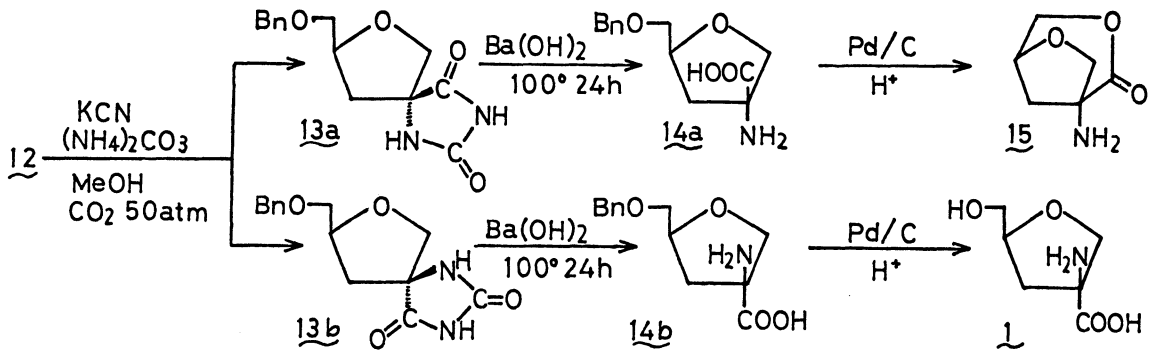
It was proved that optically active 4-amino-2-(hydroxymethyl)tetrahydrofuran-4-carboxylic acid (1) isolated from acid hydrolysate of diabetic urine has (2S,4S) configuration by synthesis of (2S)-diastereomers from D-ribose.

Compound (1) [mp 251-255°C, $[\alpha]_D$ +38.15° (*c* 0.5, H_2O)] was first isolated in 1974 by Mizuhara and coworkers from the acid hydrolysate of diabetic urine,[1a] and its plane structure was determined by spectral analyses.[1b] In the present paper we report the determination of its absolute configuration by chemical synthesis. Because it was found that (1) was also produced from D-hexoses and urea under the same hydrolytic conditions, (2S)-diastereomers of (1) were synthesized from D-ribose.

Methyl 2,3-O-isopropylidene-α,β-D-ribofuranoside (2)[2] was successively benzylated (3), hydrolyzed with acid (4), methylated (5), hydrolyzed again with acid (6), and then subjected to β-elimination reaction with $Ca(OH)_2$[3] to give the corresponding 2-enofuranose (7) as a syrup in 28% total yield from (2). Reduction of C-1 position of (7) with $NaBH_4$, followed by hydrolysis of enol ether function with cationic exchanger CG-50 gave the corresponding 2-ketopentose (8) [Syrup, $[\alpha]_D$ -9° (*c* 1.03, MeOH)] in 45% yield, which was again reduced with $NaBH_4$ to give a mixture of 2-epimeric pentitols (9). Selective tosylation of (9) in pyridine with 1.4 equimolar TsCl at -15°C gave 1-O-tosylate (10), a part of which successively changed into the corresponding tetrahydrofuran derivative (11) even at room temperature. The cyclization was prompted by addition of few drops of triethylamine to give an epimeric mixture [11a: $[\alpha]_D$ +114° (*c* 0.83, $CHCl_3$), 11b: $[\alpha]_D$





+36°(*c* 0.78, $CHCl_3$)] as a syrup in 42% yield. Oxidation of a mixture of (11a) and (11b) with dimethylsulfoxide-trifluoroacetic anhydride gave (2S)-(benzyloxymethyl)tetrahydrofuran-4-on [12: $[\alpha]_D$ +119°(*c* 0.94, $CHCl_3$), IR(cm^{-1}); 1760, NMR ($CDCl_3$, δ); 2.46(H_3 and $H_{3'}$;d), 3.56($H_{2'a}$;q, $J_{2,2'a}$=4.5, $J_{2'a,2'b}$=11 Hz), 3.72($H_{2'b}$;q, $J_{2,2'b}$=3.5 Hz), 3.84 and 4.10(H_5 and $H_{5'}$;ABq, J=16.5 Hz), and 4.50(H_2;m, $J_{2,3}$=$J_{2,3'}$=7.0 Hz)] in 86% yield.

Compound (12) was treated with potassium cyanide and ammonium carbonate in methanol at 50°C under 50 atm pressure of carbon dioxide[4] to afford the desired two epimers of hydantoin derivatives [13a: a yellowish crystal, mp 132-133°C, $[\alpha]_D$ +50°(*c* 0.80, CH_3OH), IR; 1780 and 1740, NMR(acetone-d_6); 2.08($H_{3'}$;dd, $J_{2,3'}$=6.0, $J_{3,3'}$=13.5 Hz), 2.56(H_3;dd, $J_{2,3}$=8.0 Hz), 3.88 and 3.98(H_5 and $H_{5'}$;ABq, J=8.5 Hz), and 4.30(H_2;m) and 13b: a yellowish crystal, mp 126-127°C, $[\alpha]_D$ +127°(*c* 0.44, CH_3OH), IR; 1780 and 1740, NMR(acetone-d_6); 2.12($H_{3'}$;dd, $J_{2,3'}$=7.5, $J_{3,3'}$=13.0 Hz), 2.26(H_3;dd, $J_{2,3}$=8.5 Hz), 3.78 and 4.04(H_5 and $H_{5'}$;ABq, J=8.5), and 4.30(H_2;m)] in 53% yield in a ratio of 3.5:1.

Hydrolysis of (13a) and (13b) in $Ba(OH)_2$ solution under reflux for 24 h gave the corresponding amino acid derivatives (14a and 14b), and successive hydrogenolysis of benzyl group in the presence of Pd/C gave the six-membered lactone (15) (hard syrup, IR; 1740) and (1) [mp 252-258°C, $[\alpha]_D$ +61.0°(*c* 0.3, H_2O), NMR(D_2O); 2.82 ($H_{3'}$;d, $J_{2,3}$=7.5 Hz), 4.18($H_{2'a}$ and $H_{2'b}$;d, $J_{2,2'a}$=$J_{2,2'b}$=5.0 Hz), 4.46 and 4.66(H_5 and $H_{5'}$;ABq, J=10 Hz), 4.82(H_2;m, $J_{2,3'}$=7.5 Hz), and 5.2(DOH;s)], respectively. The configuration of (15) was proved to be (2S,4R) by the lactone formation. All spectral data and the behavior in amino acid analysis of (1) having (2S,4S) configuration were identical with those of the natural product isolated by Mizuhara et al. The difference observed in their optical rotations may be due to the contamination of impurities in natural one.

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