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SYNTHESIS OF OPTICALLY ACTIVE PSEUDO-α-D-GLUCOSE AND PSEUDO-β-L-ALTROSE

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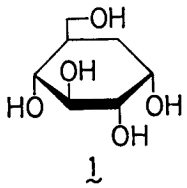
Optically active two pseudo-sugars, pseudo-α-D-glucose and pseudo-β-L-altrose have been synthesized by cyclization of 2,3,4-tri-O-benzyl-5-deoxy-5-iodo-L-arabinose with dimethyl malonate in the presence of sodium hydride as a key reaction.

In recent years, special interests have been focused on natural product syntheses utilizing carbohydrate as a chiral starting material (the chiron approach).[1] One of the topics in this field is a transformation of synthons derived from carbohydrates to carbocyclic compounds which include physiologically important substances, especially prostaglandins and their synthetic precursors.[2-4] Besides, Kiely and coworkers have extensively investigated a conversion of delta-dicarbonyl sugars into branched unsaturated six-membered compounds and branched aminocyclitols.[5] Up to date, a numbers of pseudo-sugars and the related compounds were known as components of antibiotics such as validamycins and emzyme inhibitors such as adiposins and so on.[6] Recently, optically active pseudo-β-D-glucose,[7] pseudo-α-D-galactose[7,8] and pseudo-β-D-mannose[8] have been synthesized. On the course of syntheses of biologically interesting natural products employing carbohydrates as starting materials,[9] we wish to report in the present letter a synthesis of pseudo-α-D-glucose (1) and pseudo-β-L-altrose (2) from L-arabinose.

L-Arabinose was converted into the diethyl dithioacetal derivative (3) according to a reported procedure.[10] Selective tritylation of the primary hydroxyl group of 3 with trityl chloride in the presence of 4-dimethylaminopyridine gave the 5-O-trityl derivative (4) in 85% yield. Benzylation of 4 with benzyl bromide in the presence of sodium hydride gave the tri-O-benzyl derivative (5) which was hydrolyzed with p-toluenesulfonic acid to afford 2,3,4-tri-O-benzyl-L-arabinose diethyl dithioacetal (6) in 79% yield. Tosylation of 6 with p-toluenesulfonyl chloride (6 to 7), dethioacetalization with mercury (II) chloride and calcium carbonate (7 to 8) and a displacement of the tosyloxy group by an iodo group with sodium iodide yielded 2,3,4-tri-O-benzyl-5-deoxy-5-iodo-L-arabinose (9) in 54% yield.[11] The crusial cyclization of 9 with a dianion of dimethyl malonate generated by sodium hydride in DMF was performed at 0 °C, and the products (10 and 12) were acetylated in a conventional manner. By separation of the products on silicagel column, the desired cyclohexane derivative (11) and the tetrahydropyran



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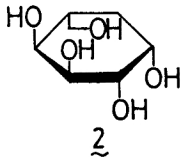

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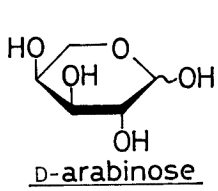
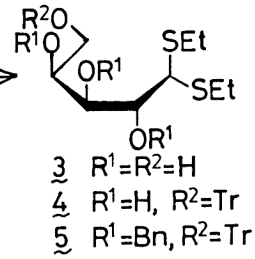
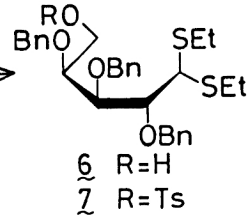


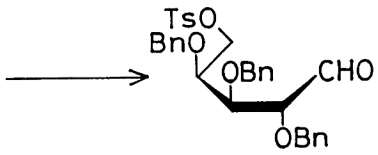
D-arabinose



3 $R^1=R^2=H$
4 $R^1=H$, $R^2=Tr$
5 $R^1=Bn$, $R^2=Tr$



6 R=H
7 R=Ts



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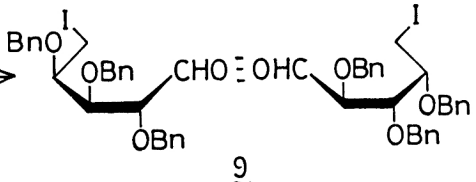

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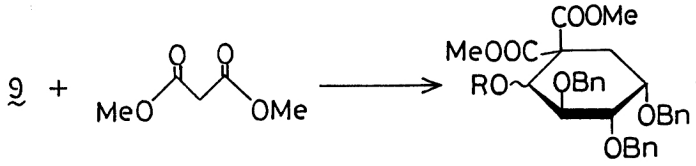
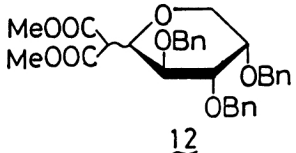


10 R=H
11 R=Ac



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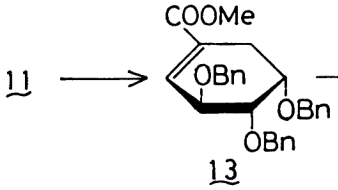

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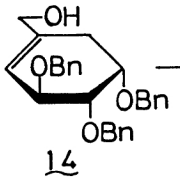

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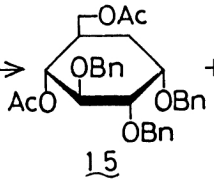

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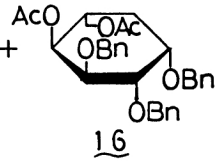

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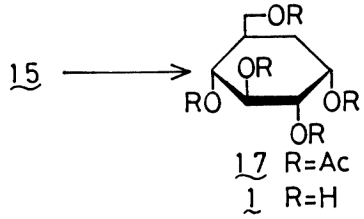
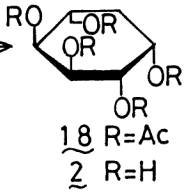


17 R=Ac
1 R=H



18 R=Ac
2 R=H

derivative (12) were obtained in 43 and 33% yields, respectively. 11: $[\alpha]_D^{19}$+10.7° (c 1.12, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 3100, 1755, 1745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.99 (3H, s, $OCOCH_3$), 3.45 (3H, s, $COOCH_3$), 3.65 (3H, s, $COOCH_3$), 6.18-6.28 (1H, m, C<u>H</u>$OCOCH_3$), 12: $[\alpha]_D^{19}$+7.7° (c 0.65, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 1755, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.54 (3H, s, $COOCH_3$), 3.69 (3H, s, $COOCH_3$), 5.02 (1H, d, J=12 Hz, C<u>H</u>$(COOCH_3)_2$), 7.31 (15H, s, 3xOCH_2C_6<u>H_5</u>). The structure of 11 has been determined to be (2R,3S,4S, 5S)-dimethyl 2-acetoxy-3,4,5-tribenzyloxy-1,1-cyclohexanedicarboxylate by the ^1H NMR spectrum which shows a singlet at δ 1.99 attributable to an equatorial acetoxy methyl protons (that is 2R). Formation of 10 (therefore 11) and 12 is explainable as follows: 1) At first the anion of malonate attacks the aldehyde in 9 to furnish the aldol adduct possessing (2R)-hydroxyl group exclusively, 2) the second anion formed at the malonyl methine carbon of the adduct attacks the terminal methylene carbon with removal of the iodo group to lead the formation of 10, 3) the oxygen anion generated from (2R)-hydroxyl group of the aldol adduct attacks the terminal methylene carbon with removal of the iodo group to give 12. From this assumed mechanism, structure of 12 has been tentatively assigned to be (2R, 3S,4S,5S)-2-[bis(methoxycarbonyl)]methyl-3,4,5-tribenzyloxytetrahydropyran. Compound 12 is a C-glycoside of β-L-arabinopyranose which seems to be a versatile synthon for chiral synthesis.

Thermal decarboxylation of 11 in aqueous dimethyl sulfoxide with NaCl (110-170 °C) proceeded with simultaneous β-elimination of the acetoxyl group gave a compound (13) in 75% yield, 13: $[\alpha]_D^{17}$+64° (c 0.85, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 1720 and 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.51-2.70 (2H, H-6 and 6'), 3.72 (3H, s, $COOCH_3$), 6.80-6.94 (1H, m, H-2), 7.35 (15H, s, 3xOCH_2C_6<u>H_5</u>). Treatment of 13 with $LiAlH_4$ at -15 °C afforded (14), (3S,4S,5S)-3,4,5-tribenzyloxy-1-hydroxymethyl-1-cyclohexene, in 83% yield, 14: $[\alpha]_D^{20}$+66° (c 0.76, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 3450, 1680, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.52-5.77 (1H, m, H-2). Hydroboration of 14 with diborane, oxidation (35% H_2O_2 in 3M NaOH), acetylation, and chromatography on silicagel column afforded two 4-acetoxy-5-acetoxymethyl-1,2,3-tribenzyloxycyclohexane (15) and (16) in 34 and 35% yields, respectively. 15: mp 98-100 °C, $[\alpha]_D^{21}$+20° (c 1.25, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.90, 1.99 (each 3H, each s, 2x$OCOCH_3$), 3.40 (1H, dd, J= 10 and 3.5 Hz, H-1), 16: $[\alpha]_D^{20}$-24° (c 0.67, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.00, 2.02 (each 3H, each s, 2x$OCOCH_3$), 5.10 (1H, dd, J=12 and 4.5 Hz, H-4). Compound 15, (1S,2S,3S,4R,5R)-isomer, was formed by attack of diborane to 14 from the opposite side to the 3-benzyloxy group, and the attack from the same side of the benzyloxy group afforded (1S,2S,3S,4S,5S)-isomer, 16. No stereoselectivity was observed in this hydroboration reaction. Compounds 15 and 16 were treated with sodium-liquid ammonia and acetylation of the products afforded (1S,2S,3S,4R,5R)-(17) and (1S,2S,3S,4S,5S)-(18) 1,2,3,4-tetraacetoxy-5-acetoxymethylcyclohexane in 49 and 31% yields, respectively. 17: syrup; $[\alpha]_D^{22}$+37° (c 0.79, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.00 (6H, s, 2x$OCOCH_3$), 2.04, 2.06 and 2.12 (each 3H, each s, $OCOCH_3$), 18: syrup; $[\alpha]_D^{21}$+7° (c 0.75, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.00 (6H, s, 2x$OCOCH_3$), 2.05, 2.10 and 2.14 (each 3H, each s, $CHCl_3$). ^1H NMR spectra of 17 and 18 were superimposable with those of the racemates.[12,13] Deacetylation of 17 and 18 with sodium metho-

xide in methanol furnished (1S,2S,3S,4R,5R)- (pseudo-α-D-glucose, 1) and (1S,2S, 3S,4S,5S)- (pseudo-β-L-altrose, 2) 1,2,3,4-tetrahydroxy-5-hydroxymethylcyclohexane in 65 and 86% yields, respectively. 1: $[\alpha]_D^{25}+30^o$ (c 1.00, MeOH), 2: $[\alpha]_D^{24}$ -49.5^o (c 1.03, MeOH).

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11) Compounds 7 and 8 were somewhat unstable on silicagel, so the yiled of 9 from 6 was reduced to 22% when 7 and 8 were purified on silicagel columns, 7: $[\alpha]_D^{18}-2^o$ (c 0.59, $CHCl_3$), 8: $[\alpha]_D^{16}+6^o$ (c 0.67, $CHCl_3$), 9: $[\alpha]_D^{20}+9^o$ (c 1.22, $CHCl_3$).
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