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
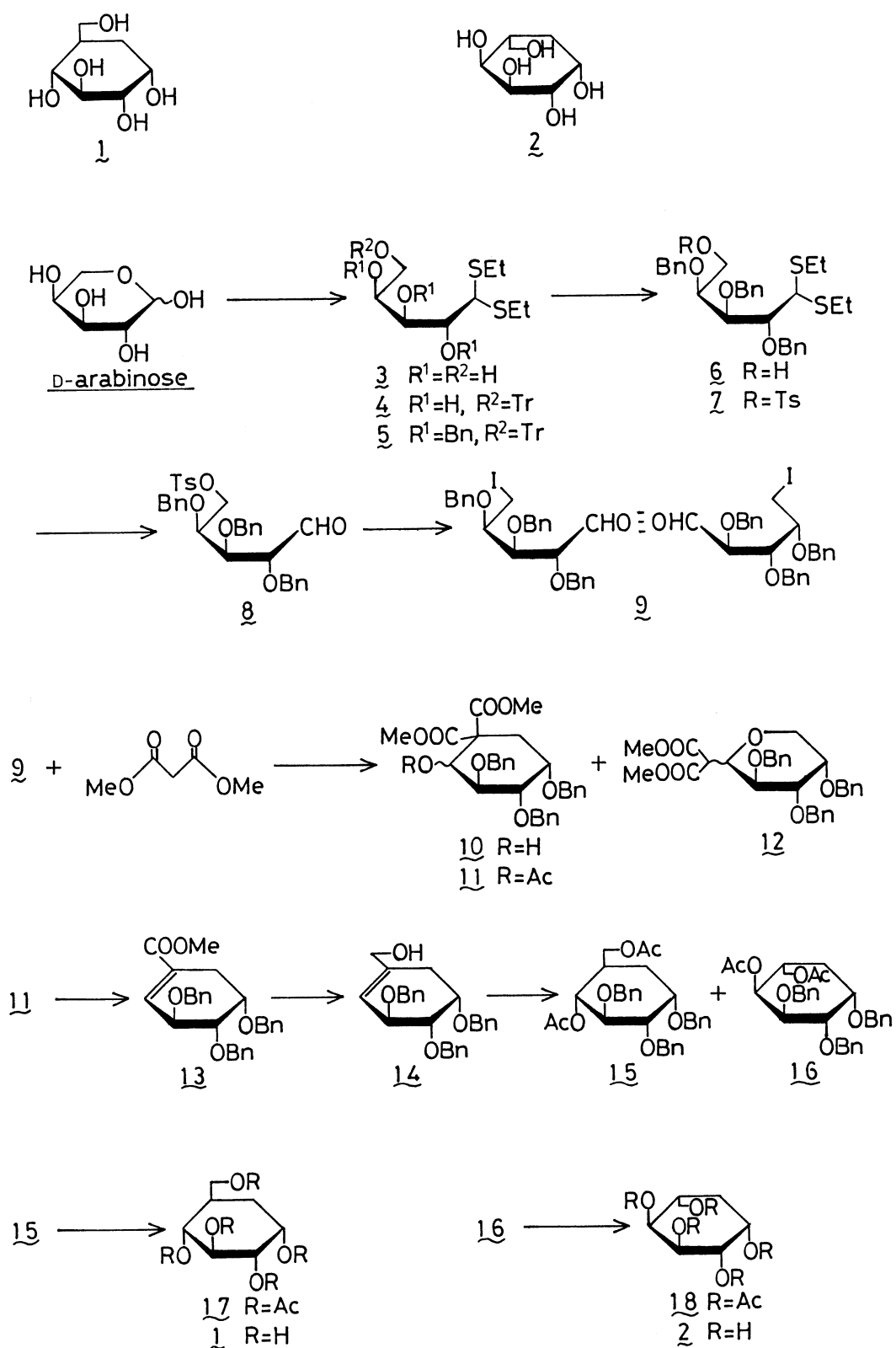
derivative ($\underline{12}$) were obtained in 43 and 33% yields, respectively. $\underline{11}$: $[\alpha]_D^{19}$+10.7°
($\underline{c}$ 1.12, $CHCl_3$); IR $\nu_{max}^{CHCl_3}$ 3100, 1755, 1745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.99 (3H, s,
$OCOCH_3$), 3.45 (3H, s, $COOCH_3$), 3.65 (3H, s, $COOCH_3$), 6.18-6.28 (1H, m, $CHOCOCH_3$),
$\underline{12}$: $[\alpha]_D^{19}$+7.7° ($\underline{c}$ 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, $CH(COOCH_3)_2$), 7.31
(15H, s, $3xOCH_2C_6H_5$). The structure of $\underline{11}$ 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 $\underline{10}$ (therefore $\underline{11}$) and $\underline{12}$ is explain-
able as follows: 1) At first the anion of malonate attacks the aldehyde in $\underline{9}$ 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 $\underline{10}$, 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 $\underline{12}$. From
this assumed mechanism, structure of $\underline{12}$ has been tentatively assigned to be (2R,
3S,4S,5S)-2-[bis(methoxycarbonyl)]methyl-3,4,5-tribenzyloxytetrahydropyran.
Compound $\underline{12}$ is a C-glycoside of β-$\underline{L}$-arabinopyranose which seems to be a versatile
synthon for chiral synthesis.

Thermal decarboxylation of $\underline{11}$ in aqueous dimethyl sulfoxide with NaCl (110-
170 °C) proceeded with simultaneous β-elimination of the acetoxyl group gave a
compound ($\underline{13}$) in 75% yield, $\underline{13}$: $[\alpha]_D^{17}$+64° ($\underline{c}$ 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, $3xOCH_2C_6H_5$). Treatment of $\underline{13}$ with $LiAlH_4$
at -15 °C afforded ($\underline{14}$), (3S,4S,5S)-3,4,5-tribenzyloxy-1-hydroxymethyl-1-cyclo-
hexene, in 83% yield, $\underline{14}$: $[\alpha]_D^{20}$+66° ($\underline{c}$ 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 $\underline{14}$ 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 ($\underline{15}$)
and ($\underline{16}$) in 34 and 35% yields, respectively. $\underline{15}$: mp 98-100 °C, $[\alpha]_D^{21}$+20° ($\underline{c}$ 1.25,
$CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.90, 1.99 (each 3H, each s, $2xOCOCH_3$), 3.40 (1H, dd, J=
10 and 3.5 Hz, H-1), $\underline{16}$: $[\alpha]_D^{20}$-24° ($\underline{c}$ 0.67, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.00, 2.02
(each 3H, each s, $2xOCOCH_3$), 5.10 (1H, dd, J=12 and 4.5 Hz, H-4). Compound $\underline{15}$,
(1S,2S,3S,4R,5R)-isomer, was formed by attack of diborane to $\underline{14}$ 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, $\underline{16}$. No stereoselectivity was observed
in this hydroboration reaction. Compounds $\underline{15}$ and $\underline{16}$ were treated with sodium-
liquid ammonia and acetylation of the products afforded (1S,2S,3S,4R,5R)-($\underline{17}$)
and (1S,2S,3S,4S,5S)-($\underline{18}$) 1,2,3,4-tetraacetoxy-5-acetoxymethylcyclohexane in 49
and 31% yields, respectively. $\underline{17}$: syrup; $[\alpha]_D^{22}$+37° ($\underline{c}$ 0.79, $CHCl_3$); ^1H NMR ($CDCl_3$)
δ 2.00 (6H, s, $2xOCOCH_3$), 2.04, 2.06 and 2.12 (each 3H, each s, $OCOCH_3$), $\underline{18}$: syrup;
$[\alpha]_D^{21}$+7° ($\underline{c}$ 0.75, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.00 (6H, s, $2xOCOCH_3$), 2.05, 2.10 and
2.14 (each 3H, each s, $CHCl_3$). ^1H NMR spectra of $\underline{17}$ and $\underline{18}$ were superimposable
with those of the racemates.[12,13] Deacetylation of $\underline{17}$ and $\underline{18}$ with sodium metho-

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

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