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STEREOSELECTIVE SYNTHESIS OF L-SUGARS OF BIOLOGICAL IMPORTANCE STARTING FROM 4-O-BENZYL-2,3-O-ISOPROPYLIDENE-L-THREOSE AS A CHIRAL BUILDING BLOCK

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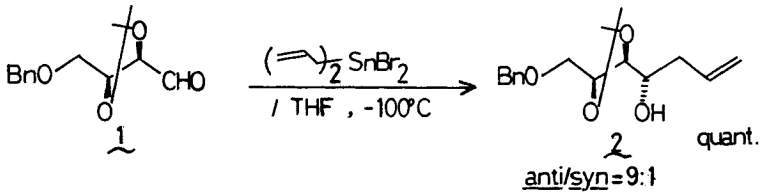
Biologically important L-sugars 2-deoxy-L-galactose, 3-amino-2,3-dideoxy-L-*xylo*-hexose, and L-diginose were successfully synthesized from the homoallyl alcohol, prepared by the stereoselective addition of allylic Sn(IV) reagent to 4-O-benzyl-2,3-O-isopropylidene-L-threose.

In the past decades, there have been isolated a number of biologically active carbohydrate derivatives such as anthracycline antibiotics, amino-sugar and other oligosaccharide antibiotics.[1] As the components of these substances, a wide variety of so-called "rare-sugars" has been reported to date, for example, daunosamine in daunomycin, diginose in digitoxose, cladinose in erythromycin, and so on. Because of the scarcity of their natural sources, and increasing interests on their biological activities, the chemical synthesis of this class of compounds is one of the current interests in synthetic organic chemistry. There are two main approaches towards these substances, that is, i) modification of the naturally abundant sugars, ii) synthesis from the small chiral precursors. In contrast to the former approach, which usually requires lengthy and troublesome synthetic transformations, the latter approach offers an attractive and convenient access to these substances provided with the suitable chiral precursor and reliable stereoselective reactions. Thus, much efforts have been made along the latter line.[2]

We have previously reported the preparation of a new four-carbon polyoxyaldehyde; 4-O-benzyl-2,3-O-isopropylidene-L-threose (1), and stereoselective addition of some nucleophiles to the aldehyde 1.[3),4)] The aldehyde 1 is a new and potentially useful building block for the carbohydrate synthesis, and could be transformed to a wide variety of sugars when coupled with the suitable nucleophiles.[5)]

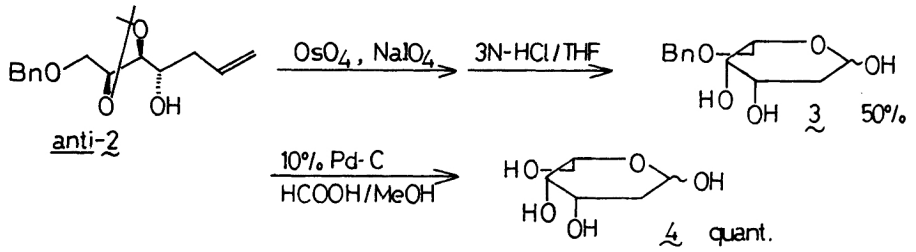
In this communication, we wish to describe the syntheses of three sugars of biological importance 2-deoxy-L-galactose, 3-amino-2,3-dideoxy-L-*xylo*-hexose, and L-diginose, starting from the aldehyde 1, respectively. First, the homoallyl alcohol 2 was prepared from the aldehyde 1 by the stereoselective addition of allylic Sn(IV) species generated *in situ* from allyl iodide and SnF_2,[3)] or by the action of preformed diallyl tin(IV) dibromide in THF at -100°C in virtually quantitative yield (Eq. 1).[6),7)]



(Eq.1)

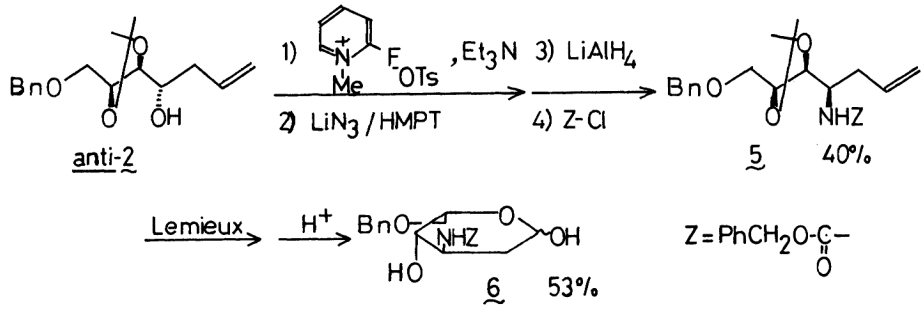
Since the *anti*-alcohol 2, thus prepared, is regarded as *selectively protected* 2-deoxy-L-hexose precursor, ready manipulation at its specific position is possible. To exemplify the above mentioned merit, the syntheses of the aforementioned three sugars were undertaken, and the synthetic sequences of each sugar are described below.

2-Deoxy-L-galactose (2-Deoxy-L-*lyxo*-hexose)



Oxidation of *anti*-2 under the Lemieux conditions[8] (cat. OsO_4, 2 eq. $NaIO_4$, THF-H_2O 1:1, 30 min), and the subsequent acid treatment (3N HCl-THF, rt, 3 hr) gave 6-O-benzyl-2-deoxy-L-*lyxo*-hexose (3)[9] in 50% yield. Then, deprotection of the benzyl group was effected by catalytic transfer hydrogenolysis[10] (10% Pd-C, HCOOH-MeOH 1:9, rt, 6 hr) to afford 2-deoxy-L-*lyxo*-hexose[11] ("2-deoxy-L-galactose" 4) in quantitative yield.

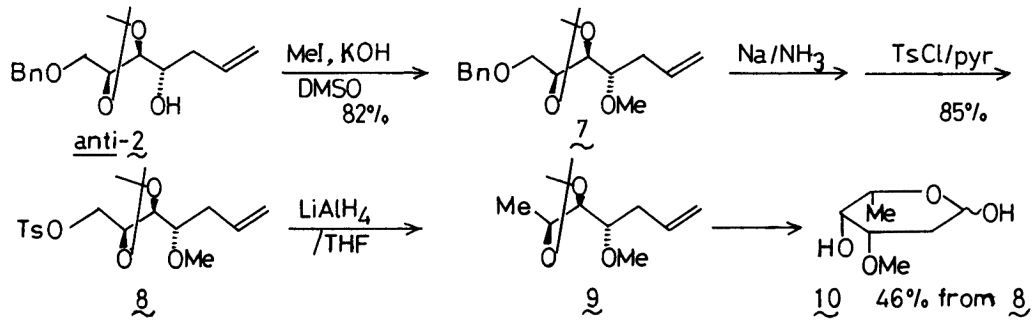
3-Amino-2,3-dideoxy-L-*xylo*-hexose



There has been an increasing interest on amino-sugars in connection with cancer chemotherapic agents, and extensive screening works on the analogs have been done to avoid the serious side-effects.[12] Here, it is demonstrated that the stereospecific amine synthesis reported from our laboratory[13] is effective

in the synthesis of daunosamine-related amino-sugar analog.[12] That is, the treatment of *anti*-2 with 1-methyl-2-fluoropyridinium tosylate and lithium azide, and subsequent reduction and protection gave the urethane 5 with a clean inversion of the chiral center.[14),15] Then, the same treatment as above gave protected 3-amino-2,3-dideoxy-L-*xylo*-hexose 6 (53%), which showed satisfactory analytical data.[16]

L-Diginose



The cardiac glycosides, such as digitoxin, digitalin, constitute one of the physiologically and clinically important groups of substances because of their specific effect on heart.[17] They are composed of steroidal aglycone and various 2,6-dideoxy sugars. As stated before, the selective protection pattern of the homoallylic alcohol 2 enables us to manipulate it in various ways. Thus, the synthesis of L-diginose, one of the cardiac sugar components, is readily accomplished by the following synthetic sequence. The *anti*-alcohol 2 was methylated with MeI-KOH in DMSO[18] to give the ether 7[19] in 82% yield. Deprotection of the benzyl group under the Birch conditions, followed by tosylation afforded the tosylate 8[20] in 85% yield. Reductive removal of the tosyloxy group of 8, followed by the same transformation as above gave L-diginose[21] in 46% yield.

Thus, three types of L-sugars of biological importance were readily synthesized from the four-carbon chiral aldehyde, 4-O-benzyl-2,3-O-isopropylidene-L-threose 1, derived from L-tartaric acid.

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11) a) This compound exhibited satisfactory physical properties indistinguishable from that of a commercially available 2-deoxy-D-galactose except for the sign of the optical rotation. Mp 118-120°C (MeOH); ^{1}H NMR (D_2O) δ=1.7-2.4 (m, 2H), 3.7-4.4 (m, 9H), 5.1-5.2 and 5.6-6.0 (m, 1H); ^{13}C NMR (D_2O, acetone as an internal standard) δ=32.1, 35.0, 41.5, 61.5, 61.8, 64.8, 66.9, 67.9, 70.8, 75.4, 91.6, 94.0. Based on the value of the acetone-methyl as 30.4 ppm; $[\alpha]_D^{20}$ -30.0° (c 1.55, MeOH) (constant value) (cf. W. G. Overend, F. Shafizadeh, and M. Stacy, J. Chem. Soc., 1950, 671, who give $[\alpha]_D^{22}$ +32.2° (c 0.58, MeOH) (constant value) for the antipode); Found: C, 43.39; H, 7.38%; M-H_2O^+, 146.0562; Calcd for $C_6H_{12}O_5$: C, 43.90; H, 7.37%, Calcd for $C_6H_{10}O_4$: M-H_2O, 146.0577.
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15) Mp 56-58°C; ^{1}H NMR ($CDCl_3$) δ=1.4 (s, 6H), 2.1-2.6 (m, 2H), 3.4-4.0 (m, 5H), 4.5 (s, 2H), 4.8-5.2 (m, 2H), 5.1 (s, 2H), 5.4-6.0 (m, 1H), 7.3 (s, 11H); IR (KBr) 1690, 1540, 1275, 700 cm^{-1}; $[\alpha]_D^{20}$ -11° (c 1.3, $CHCl_3$); Found: C, 70.63; H, 7.41; N, 3.25%; Calcd for $C_{25}H_{31}O_5N$: C, 70.56; H, 7.34; N, 3.29%.
16) Mp 95-97°C (hexane-AcOEt); ^{1}H NMR ($CDCl_3$) δ=1.0-1.7 (m, 2H), 2.0-2.4 (broad, 2H), 3.3-4.0 (m, 5H), 4.5 (s, 2H), 5.0 (s, 2H), 5.2-5.5 (m, 1H), 6.2-6.5 (m, 1H), 7.3 (s, 10H); IR (KBr) 3400, 1710, 1510, 1040, 915, 890, 700 cm^{-1}; $[\alpha]_D^{21}$ -6.5° (c 0.73, MeOH) (constant value); Found: C, 64.87; H, 6.41; N, 3.64%; Calcd for $C_{21}H_{25}O_6N$: C, 65.10; H, 6.50; N, 3.62%.
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19) ^{1}H NMR ($CDCl_3$) δ=1.4 (s, 6H), 2.2-2.5 (m, 2H), 3.1-3.9 (m, 4H), 3.3 (s, 3H), 4.0-4.3 (m, 1H), 5.6 (s, 2H), 4.9-5.2 (m, 2H), 5.5-6.1 (m, 1H), 7.3 (s, 5H); IR (neat) 1640, 1500, 1100, 910, 740, 700 cm^{-1}; $[\alpha]_D^{20}$ +7.2° (c 1.1, benzene).
20) ^{1}H NMR ($CDCl_3$) δ=1.30 (s, 3H), 1.35 (s, 3H), 1.9-2.4 (m, 2H), 2.4 (s, 3H), 3.3 (s, 3H), 3.5-3.8 (m, 1H), 3.9-4.4 (m, 4H), 4.8-5.2 (m, 2H), 5.5-6.1 (m, 1H), 7.3 (d, J=5Hz, 2H), 7.7 (d, J=5Hz, 2H); IR (neat) 1640, 1600, 1500, 1180, 1100, 990, 665 cm^{-1}; $[\alpha]_D^{20}$ -5.8° (c 1.0, benzene).
21) Bp 100°C (bath temp. 0.1 mmHg); ^{1}H NMR ($CDCl_3$) δ=1.1-1.3 (m, 3H), 1.7-2.3 (m, 2H), 3.4 (s, 3H), 3.3-4.2 (m, 5H), 4.6-4.8 and 5.3-5.7 (m, 1H); IR (neat) 3400, 1640, 1450, 1380, 1100, 1040, 1000 cm^{-1}; $[\alpha]_D^{19}$ -60° (c 0.7, H_2O) (constant value), (lit. $[\alpha]_D^{22}$ +60° ± 1° (H_2O) in ref. 22)); Found; M^+, 162.0888; Calcd for $C_7H_{14}O_4$: M, 162.0891.
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