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TOTAL SYNTHESIS AND ABSOLUTE CONFIGURATION OF (+)-(1,2,3/4,5)-2,3,4,5-TETRAHYDROXY-1-CYCLOHEXANEMETHANOL

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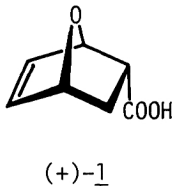
The title branched-chain cyclitol has been synthesized from chiral 7 *endo*-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid, the absolute configuration of which was established on the basis of X-ray analysis of crystalline bromolactone derived from it. From this result the C-1 configuration of the cyclitol is determined to be *R*.

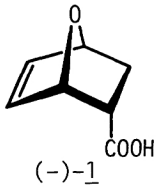
During the course of the studies on pseudo-sugars,[1] carbocyclic analogs of hexopyranose, it became necessary to prepare optically active compounds for biochemical and biological tests. Since we had been utilizing a Diels-Alder adduct of furan with acrylic acid, DL-7 *endo*-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid (1)[2] as a common starting material for construction of all pseudo-sugars so far synthesized in our laboratory, it seemed most desirable to provide optically active 1 for this purpose.

Attempts to resolve racemic 1 were then made extensively, and (*R*)-(+)- and (*S*)-(-)-α-methylbenzylamines were demonstrated to be very effective resolving agents to offer (-)-1 and (+)-1, respectively. In the present communication, we wish to describe an optical resolution of racemic 1 and a total synthesis of optically active pseudo-sugars including (+)-(1,2,3/4,5)-2,3,4,5-tetrahydroxy-1-cyclohexanemethanol (+)-6, (+)-pseudo-α-galactose, which was isolated as an antibiotic from the fermentation broth of *Streptomyces* sp. MA-4145.[3]

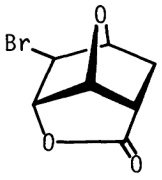
Treatment of racemic 1 with a molar equiv. of (*R*)-(+)-α-methylbenzylamine in



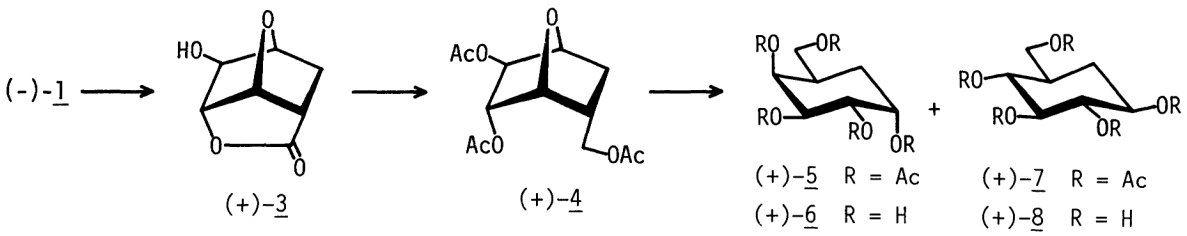
(+)-1
$[\alpha]_D^{22}$ +110.7° (EtOH)



(-)-1
$[\alpha]_D^{22}$ -111.8° (EtOH)



(+)-2



(+)-5 R = Ac
(+)-6 R = H

(+)-7 R = Ac
(+)-8 R = H

ethanol yielded a crystalline mixture of (*R*)-(+)-amine salts with (+)-1 and (-)-1. Fractional crystallization from ethanol gave optically pure (*R*)-(+)-amine salt with (-)-1 (mp 137.5-138.5 °C, $[\alpha]_D^{27}$ -66.4° (*c* 1.1, MeOH)) in 30% yield. Similarly, by use of (*S*)-(-)-amine, pure (*S*)-(-)-amine salt with (+)-1 was obtained (mp 137.5-138.5 °C, $[\alpha]_D^{27}$ +66.7° (*c* 1.0, MeOH)). The free acids were recovered from the corresponding salts, respectively, by treatment of its aqueous solution with Dowex 50W X2 resin: (+)-1, needles from ethyl acetate-ligroin, mp 97-98.5 °C, $[\alpha]_D^{22}$ +110.7° (*c* 1.0, EtOH); (-)-1, mp 97-98.5 °C, $[\alpha]_D^{22}$ -111.8° (*c* 1.0, EtOH). Compound (-)-1 was converted, in the usual way,[4] into crystalline bromolactone (+)-2 (mp 117.5-118.5 °C, $[\alpha]_D^{25}$ +92.0° (*c* 1.0, $CHCl_3$)), whose absolute configuration was established on the basis of X-ray analysis as exhibited in Scheme.[5] Therefore, the stereochemistry of (-)-1, as well as that of (+)-1, could be determined.

The optically active pseudo-sugars were synthesized starting from (-)-1[6] following the procedure previously employed for synthesis of their racemate.[7] Compound (-)-1 was treated with 90% formic acid and 35% hydrogen peroxide at 70 °C gave the triacetate (+)-4 in quantitative yield. Without purification, (+)-4 was directly subjected to acetolysis with a mixture of acetic acid-acetic anhydride-concd sulfuric acid (18:10:1, v/v) at 80 °C for 20 h. A mixture of peracetyl derivatives of 2,3,4,5-tetrahydroxy-1-cyclohexanemethanol thus formed was fractionated by using a silica-gel column with 2:9 acetone-hexane as an eluant, affording (+)-5 (mp 143-144 °C, $[\alpha]_D^{20}$ +43.2° (*c* 1.1, $CHCl_3$)) and (+)-7 (mp 115-116 °C, $[\alpha]_D^{20}$ +13.8° (*c* 1.0, $CHCl_3$)) in 27 and 34% yields, respectively.[8] *O*-Deacetylation of (+)-5 with methanolic sodium methoxide gave the free pseudo-sugar (+)-6 (mp 161.5-162.5 °C, $[\alpha]_D^{23}$ +66.3° (*c* 1.5, H_2O), lit.[3] mp 164 °C, $[\alpha]_D$ +61.5 ±4° (H_2O)), which was identified with an authentic sample[3] by comparing the IR (KBr) spectra. Similarly, (+)-7 was converted into (+)-8 (oil, $[\alpha]_D^{20}$ +13.0° (*c* 2.1, H_2O)).

The present synthesis has established the C-1 configuration of (+)-(1,2,3/4,5)-2,3,4,5-tetrahydroxy-1-cyclohexanemethanol to be *R*. A synthesis of biologically interesting pseudo-sugars and aminosugars from (+)-1 and (-)-1 is on the way.

References

1) S. Ogawa, T. Hattori, T. Toyokuni, and T. Suami, *Bull. Chem. Soc. Jpn.*, 56, 2077 (1983) and references cited therein.
2) T. Suami, S. Ogawa, K. Nakamoto, and I. Kasahara, *Carbohydr. Res.*, 58, 240 (1977).
3) T. W. Miller, B. H. Arison, and G. Albers-Schonberg, *Biotechnol. Bioeng.*, 15, 1075 (1973).
4) S. Ogawa, I. Kasahara, and T. Suami, *Bull. Chem. Soc. Jpn.*, 52, 118 (1979).
5) The X-ray analysis of (+)-2 was carried out by Prof. Yoshihiko Saito and Prof. Masatoki Ito (Department of Chemistry, Faculty of Science and Technology, Keio University), to whom our thanks are due. The details of the analytical data will be published elsewhere.
6) The reason we had first chosen (-)-1 as a starting compound was that its absolute configuration corresponded to those of D-series pseudo-sugars.
7) S. Ogawa, M. Ara, T. Kondoh, M. Saitoh, R. Masuda, T. Toyokuni, and T. Suami, *Bull. Chem. Soc. Jpn.*, 53, 1121 (1980).
8) The ^1H NMR spectra of (+)-5 and (+)-7 in chloroform-*d* were shown to be identical with those of the corresponding racemates,[7] respectively.

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