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AN ALTERNATIVE SYNTHESIS OF (1*R*,2*S*,3*R*,4*R*)-2,3-DIHYDROXY-4-HYDROXYMETHYL-1-CYCLOPENTANAMINE, A SYNTHETIC INTERMEDIATE OF (-)-ARISTEROMYCIN

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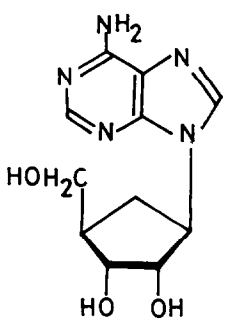
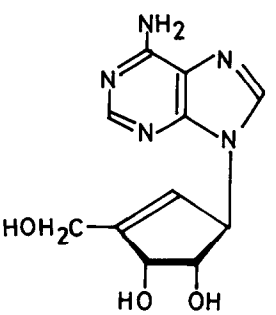
Summary : The title compound, an enantiomerically pure carbocyclic portion of the antibiotic (-)-aristeromycin, has been synthesized from D-erythrose. The synthesis involves a transformation of the known carbocyclic analogue of β-L-arabinofuranose to the α-D-ribo form by silica gel promoted epimerization at the branched carbon.

Aristeromycin (1)[1] and neplanocin A (2)[2] are representatives of the carbocyclic nucleoside antibiotics, which call much attention recently by their chemotherapeutic concerns.[3] In addition to their significant physiological interests such as an antitumor activity, the novelty of their structures has prompted much efforts on the synthesis of them and their stereocongeners. In regard to the synthetic approaches directed toward these antibiotics in an enantiomerically pure form, the highly oxygenated cyclopentane derivatives were prepared by 1) a chemicoenzymatic approach,[4] 2) an asymmetric Diels-Alder cycloaddition strategy,[5] or 3) optical resolution of the intermediate.[6] Meanwhile, a synthesis of (-)-neplanocin A 2 was achieved by employing D-(+)-ribonic acid δ-lactone as an enantiomerically pure starting material.[7] In the course of our continuous interests on the access to the enantiomerically pure carbocycles from carbohydrates,[8] we wish to describe herein a novel synthesis of the carbocyclic portion (3) of (-)-aristeromycin 1 starting from D-erythrose.[9]

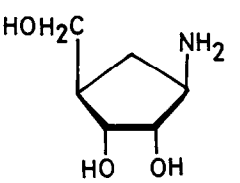
In previous papers,[10] we demonstrated an efficient route to a suitably protected pseudo-β-L-arabinofuranose (4).[11] This synthesis of 4 was achieved from D-erythrose involving a highly stereoselective hydroboration process, and the overall yield in the 13-steps reaction sequence was 12% yield. O-Deacetylation of 4 (MeONa/MeOH) followed by selective protection



Aristeromycin
1

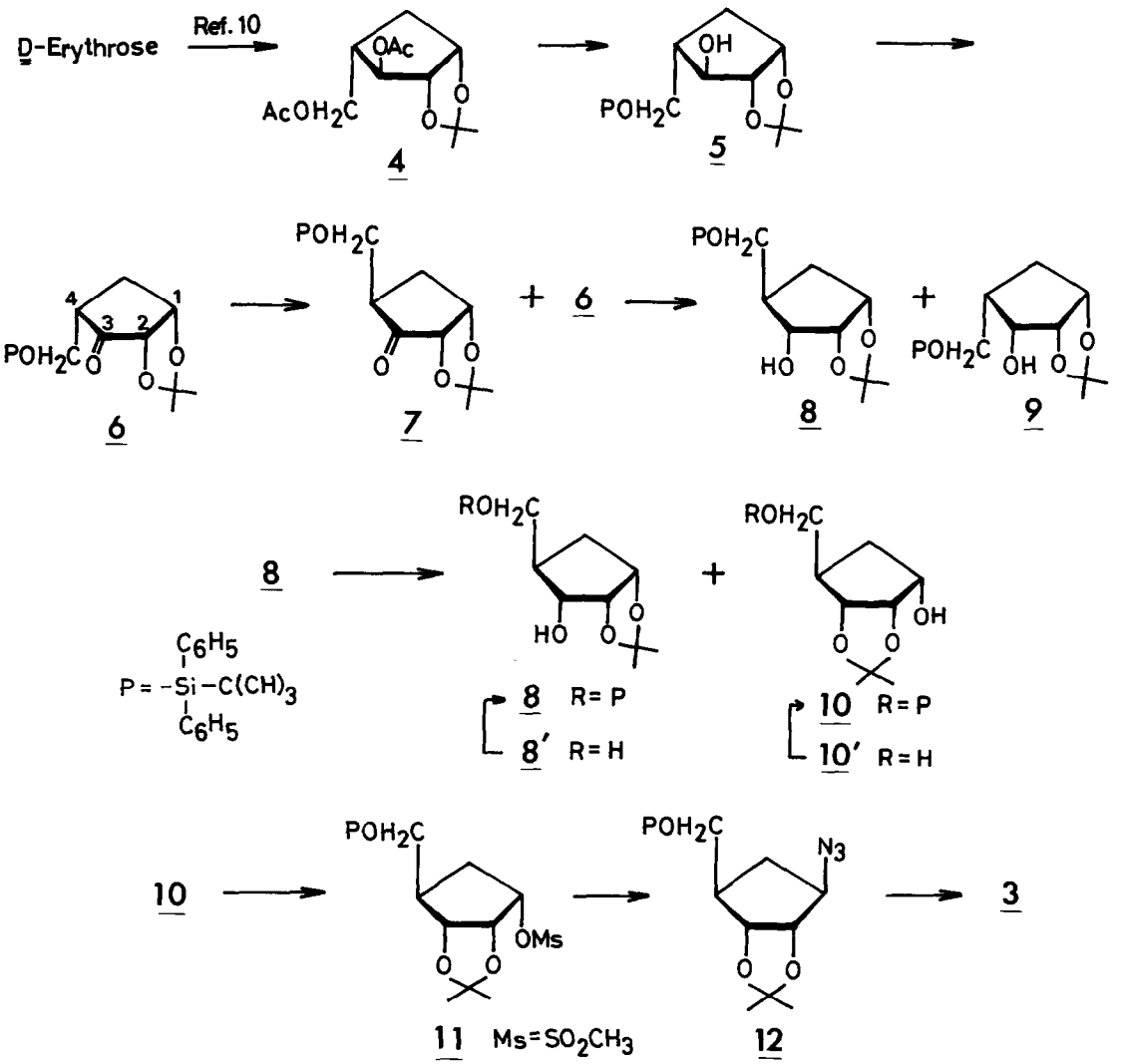


Neplanocin A
2



3

of the primary hydroxyl group as a silyl ether [t-Bu(Ph)$_2$SiCl/imidazole/DMF] provided (5)[12] in 91% yield. Pyridinium chlorochromate (PCC) oxidation of 5 (molecular sieves/CH_2Cl_2) gave (1S,2S,4S)-4-(t-butyldiphenylsilyloxymethyl)-1,2-isopropylidenedioxy-3-cyclopentanone (6).[12] The crucial stage of the present work was to find out an optimal reaction condition, for an epimerization of the branched carbon in 6, under which no other undesired reactions such as β-elimination accompanied. For achievement of this, several basic or acidic conditions were examined.[13] After accumulating a number of unsatisfied results, we could find out that silica gel worked effectively as a promoter for the epimerization without leading undesired reactions.[14] Although several examples of silica gel promoted organic synthesis are known, the present result should be specified as another use of silica gel in organic synthesis.[15] A mixture of the epimerized (7) and unreacted 6 was directly dealt with sodium borohydride. The resulting cyclopentane-triols were cleanly separated by chromatography on silica gel to



provide a derivative of pseudo-α-D-ribofuranose (8)[12] and that of pseudo-β-L-lyxofuranose (9)[12,16] in 58% (from 5) and 21% yield, respectively. The described silica gel promoted epimerization method is mild and simple to operate, and should be adaptable to the similar polyfunctionalized cyclic models.

By the sequential reactions, 1) acid hydrolysis for removal of the O-isopropylidene group (AcOH:H_2O:MeOH=20:4:1, r.t.), 2) re-O-isopropylidenation (2,2-dimethoxypropane/CSA/DMF), 3)selective O-silylation of the accompanied (8') and (10')[17], the 1,2-O-isopropylidene derivative 8 was converted into the 2,3-O-isopropylidene derivative (10)[12] in 25% yield (64% of 8 was recovered). We could not find out an appropriate condition for selective formation of 10, however, the recovered 8 was reusable. Mesylation of the compound 10 (MsCl/pyr., 10 to 11[12] in 95%), and a replacement of the mesyloxy group by an azide anion (NaN_3/DMF/120-140 °C) furnished the cyclopentylazide (12)[12] in 90% yield. The conversion of 12 into the desired 3 was achieved in 92% overall yield as follows: 1) O-desilylation (n-Bu_4NF/THF), 2) O-deisopropylidenation (80% AcOH/60 °C), and 3) hydrogenation (H_2/Raney Ni/MeOH). The ^1H NMR (400 MHz) spectrum of the synthetic 3 [$[\alpha]_D^{23}$ -10.7° (*c* 0.44, H_2O), lit.[6] $[\alpha]_D^{25}$ -10.3° (*c* 0.3, H_2O)] was fully in accordance with the reported one[6] and the structure of 3 was confirmed. The transformation of 3 to (-)-aristeromycin 1 in a 3-steps reaction has been described in the literature.[4] Therefore, our synthesis of the key intermediate 3 represents a formal total synthesis of (-)-aristeromycin.

References and Notes

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9) Racemic 3 was also prepared by Shealy and Clayton[1] and by Cermak and Vince: R. C. Cermak and R. Vince, Tetrahedron Lett., 22, 2331 (1981).

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11) The compounds described in the present work are considered to be carbocyclic analogues of carbohydrates, which are frequently designated as the "pseudo-sugars". Those carbocyclic compounds are named as derivatives of pseudo-aldopentofuranoses throughout this communication for the sake of convenience.

12) All new compounds were fully characterized by the IR and ^{1}H NMR spectra, and gave satisfactory elemental analyses and/or high resolution mass spectra. $[\alpha]_D$ (in $CHCl_3$) and ^{1}H NMR (in $CDCl_3$) of the selected compounds are as follows. 8: $[\alpha]_D^{26}$+23.9° (*c* 1.01), 9: $[\alpha]_D^{27}$+10.6° (*c* 1.08), 10: $[\alpha]_D^{22}$-16.8° (*c* 1.13); ^{1}H NMR δ 1.07 (9H), 1.33, 1.48 (3H x 2) 1.66-2.00 (2H), 2.00-2.47 (2H), 3.55 (2H, dd, J=5.5 and 2.5 Hz), 4.00-4.57 (3H), 7.20-7.73 (10H), 11: $[\alpha]_D^{21}$ -22.6° (*c* 1.01), 12: $[\alpha]_D^{21}$-31.9° (*c* 1.19); ^{1}H NMR δ 1.07(9H), 1.23, 1.43 (3H x 2), 1.53-1.57 (3H), 3.63 (2H, d, J=7 Hz), 3.95 (1H, dt, J=8 and 3 Hz), 4.28 (1H, dd, J=7 and 3 Hz), 4.55 (1H, dd, J=7 and 2 Hz), 7.20-7.80 (10H).

13) By treatment of 6 with TsOH (1.1 mol eq., pH 4) in CH_2Cl_2 at 0 °C for 6 h, an approximately 1 : 1 mixture of 6 and the O-deisopropylidene derivative was obtained. The structure of the latter was confirmed by O-isopropylidenation, which regenerated 6 as a sole product. By treatment of 6 with 0.1 mol eq. of DBU in benzene at r.t. for 17 h, a mixture of 7 (trace) and the presumably β-eliminated products was obtained (^{1}H NMR δ 5.4-5.6, 6.1-6.3 for vinyl protons; IR ν_{max} 1700, 1635 cm^{-1}). The products transformed to a more complex mixture through column of silica gel. Therefore, we could not purify them and could not estabilsh the structures.

14) The typical procedure of the epimerization was as follows : To a solution of 6 (454 mg) in dry CH_2Cl_2 (7 ml) was added silica gel [Katayama Chemicals, Silicagel 60(K070), 8 g]. After standing on at r.t. for 2.5 h, CH_2Cl_2 (10 ml) was added. The silica gel was removed by filtration and washed with a small amount of CH_2Cl_2. The combined filtrate and washing were concentrated in vacuo to afford a mixture of 6 and 7 as an oil, which was directly reduced with $NaBH_4$ (2.0 mol eq.) in a MeOH (14 ml) solution. For the epimerization of 6, TLC-Kieselgel 60 GF_{254} (Merck) also worked effectively as a promotor, and gave the similar result.

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16) The regeneration of 6 from 9 was achieved in a quantitative yield by PCC oxidation. On the other hand, the compound 9 was obtained in 80% yield by stereoselective $NaBH_4$ reduction of 6. In this case, the β-L-arabino isomer 5 was not detected.

17) Under the O-deisopropylidenation conditions, an approximately 10% of the further desilylated product, from which compounds 8' and 10' were obtained after O-isopropylidenation, was observed in the reaction mixture.

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