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A NEW SYNTHESIS OF PRUMYCIN

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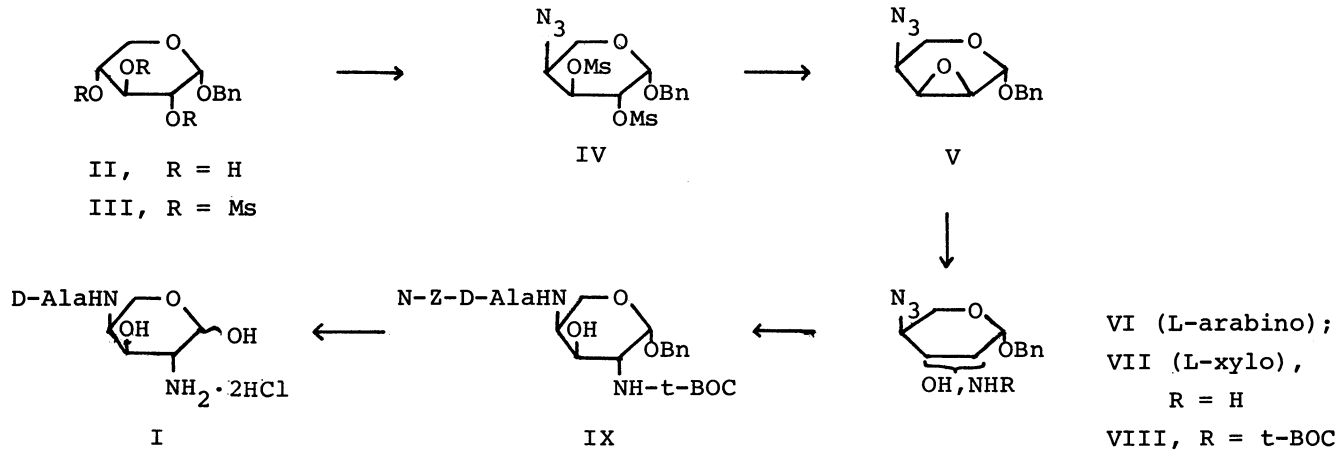
Prumycin (4-D-alanylamino-2-amino-2,4-dideoxy-L-arabinose) was synthesized from D-xylose through nine-step conversions.

Prumycin, a new antifungal antibiotic isolated by Hata et al.,[1] was elucidated to be 4-D-alanylamino-2-amino-2,4-dideoxy-L-arabinose by Omura et al.[2] Recently, Kuzuhara and Emoto[3] confirmed this structure by chemical synthesis from methyl 2-azido-2-deoxy-α-D-allopyranoside via eleven-step conversions. We wish to describe a facile synthesis of prumycin dihydrochloride (I) from D-xylose.

Benzyl α-D-xylopyranoside (II) was mesylated by a usual method to give 2,3,4-tri-O-mesyl derivative (III) [mp 133-134°C; $[\alpha]_D^{23}$ +99.6°(c 1.0, $CHCl_3$); NMR δ($CDCl_3$): 4.66(H_4, sextet, $J_{3,4}=J_{4,5}=10$, $J_{4,5}=6$ Hz)] in 85 % yield. By the selective substitution of III with sodium azide as reported for the corresponding methyl glycoside,[4] benzyl 4-azido-4-deoxy-2,3-di-O-mesyl-β-L-arabinopyranoside (IV) [sirup; $[\alpha]_D^{23}$ +146° (c 1.0, $CHCl_3$); IR cm^{-1}: 2130(N_3), 1370, 1185(SO_2); NMR δ($CDCl_3$): 4.29(H_4; m, $J_{3,4}=J_{4,5}=3.5$, $J_{4,5'}=2.5$ Hz)] was obtained in 95 % yield. Compound IV in methanol-water was refluxed with potassium hydroxide to give benzyl 2,3-anhydro-4-azido-4-deoxy-β-L-ribopyranoside (V) [mp 47-48°C; $[\alpha]_D^{23}$ +17.0° (c 1.0, $CHCl_3$); IR cm^{-1}: 2100(N_3); NMR δ($CDCl_3$): 3.14(H_2; d, $J_{1,2}=0$, $J_{2,3}=3.8$ Hz), 3.89(H_5; q, $J_{4,5}=3.8$ Hz)] in 40 % yield, together with the corresponding β-L-lyxopyranoside as a minor product. The structure of V was further ascertained by the NMR spectrum of benzyl 2,3-anhydro-4-acetamido-4-deoxy-β-L-ribopyranoside ($J_{3,4}=5.3$, $J_{4,5}=0$ Hz), which was derived form V by the selective hydrogenation with platinum oxide and then N-acetylation.

Treatment of V with methanolic ammonia at 80-90°C gave a crystalline mixture of two epoxide-ring opening products, i.e. benzyl 2-amino-4-azido-2,4-dideoxy-β-L-arabino- (VI) and 3-amino-4-azido-2,4-dideoxy-β-L-xylopyranoside (VIII) in a good yield, which could be separated as N,O-diacetates and each structure was predicted by NMR spectrum of the methine proton attached to the carbon having acetoxyl group ($J_{2,3}=11$, $J_{3,4}=4$ Hz



for the former and $J_{1,2}$=8, $J_{2,3}$=10 Hz for the latter). This mixture was succesively N-t-butyloxycarbonylated with t-butyl azidoformate and triethylamine in dioxane, hydrogenolyzed with platinum oxide in methanol and coupled with N-benzyloxycarbonyl-D-alanine by DCC method to give a mixture, from which benzyl 4-(D-alanylamino)-2-(t-butyloxycarbonylamino)-2,4-dideoxy-β-L-arabinopyranoside(IX) [mp 160-161°C;IR cm^{-1}: 3410, 3320, 3200(OH,NH), 1730, 1720, 1690(NHCOO), 1650(NHCO), 1540, 1520, 1505(NH)] was separated in ca. 35 % yield (based on V) by tlc on silica gel [benzene-pyridine (9:1)].

Compound IX was treated with 98 % formic acid and hydrogenated with palladium-charcoal to afford prumycin dihydrochloride (I) in 80 % yield [mp 195-198°C (decomp.); $[\alpha]_D^{23}$ +90° (c 0.5, CH_3OH);IR cm^{-1}:3400-2800(OH, NH, NH_3^+), 1680(NHCO), 1600, 1495(NH_3^+), 1560(NH);lit., mp ca. 195°C (decomp.);$[\alpha]_D^{23}$ +115° (c 0.5, CH_3OH)(natural prumycin[2]); mp 196-200°C (decomp.);$[\alpha]_D^{17}$ +93° (c 0.70, CH_3OH)(synthesized prumycin[3])]. The IR spectrum and chromatographic behavior of I were identical with those of natural prumycin.

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