BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, VOL. 51 (3), 951—952 (1978)

Synthesis of 4-(D-Alanylamino)-2-amino-2,4-dideoxy-D-xylose*

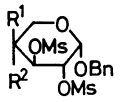
Hassan Akhtar KHAN,** Hironobu HASHIMOTO, and Juji YOSHIMURA

Laboratory for Chemistry of Natural Products, Faculty of Science, Tokyo Institute of Technology, Nagatsuta-machi, Midori-ku, Yokohama, 227

(Received September 22, 1977)

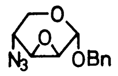
Synopsis. A prumycin diastereomer having D-configuration, 4-(D-alanylamino)-2-amino-2,4-dideoxy-D-xylose, was first synthesized from L-arabinose *via* benzyl 2,3-anhydro-4-azido-α-D-lyxopyranoside.

Prumycin, 4-(D-alanylamino)-2-amino-2,4-dideoxy-L-arabinose, is an antifungal antibiotic[2] and was synthesized independently by three Japanese groups.[3,4,5] In the course of study for the relationship between structures and biological activities, we have also synthesized prumycin and its diastereomers having L-configuration except L-lyxo one.[1] In the present paper, we would like to report the first synthesis of a prumycin diastereomer in D-series using the method developed by us for the synthesis of prumycin.[4] L-Arabinose was used as starting material instead of D-xylose, which was used for the synthesis of L-stereoisomers. 2,3,4-Tri-*O*-mesylate(**1**) of benzyl β-L-arabinopyranoside was subjected to azidolysis to give the corresponding 4-azido derivative(**2**) in excellent yield. Treatment of **2** with sodium methoxide in methanol gave a mixture of benzyl 2,3-anhydro-4-azido-α-D-lyxo(**3**) and -α-D-ribo-pyranoside (**4**), which were separated easily on a silica gel column. The yields of these epoxides depend on the reaction conditions, especially on the concentration of the bases and on the reaction times. As the rates of formation and ring opening reaction of **3** are apparently slower than those of **4**, higher base concentration and longer reaction time facilitate the predominant formation of **3**. In the optimal conditions the both epoxides were formed in 60% yield. By treatment of **2** with 0.7 M sodium methoxide in methanol under reflux for 6—7 h **3** and **4** were obtained in 20 and 15% yields, respectively. The structures of these epoxides were ascertained by the $J_{1,2}$ and $J_{3,4}$ values in their NMR spectra.[6]

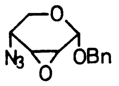


1 R^1=OMs, R^2=H

2 R^1=H, R^2=N_3



3



4

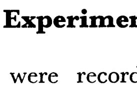
Ammonolysis of **3** gave benzyl 2-amino-4-azido-α-D-xylopyranoside(**5**) predominantly, which was obtained in 65% yield after chromatographic separation from its ring opening isomer(**6**). The structures of these products were determined by their NMR data, especially by the coupling constants of ring protons as shown in the Experimental. Then, **5** was treated with *t*-butyl azidoformate to give the *N*-*t*-butoxycarbonylated derivative(**7**). The azido group of **7** was hydrogenated selectively in the presence of platinum oxide and condensed with *N*-benzyloxycarbonyl-D-alanine *p*-nitrophenyl ester successively as reported for the synthesis of prumycin. The condensation product(**9**) was converted into 4-(D-alanylamino)-2-amino-2,4-dideoxy-D-xylose hydrochloride(**10**) in good yield by treatment with formic acid, followed by hydrogenolysis under acidic conditions in the presence of palladium-carbon. The biological activities of **10** will be presented elsewhere.

5 R^1=N_3, R^2=H

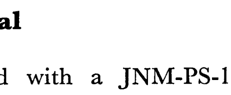
7 R^1=N_3, R^2=*t*-BOC

8 R^1=NH_2, R^2=*t*-BOC

9 R^1=*N*-Cbz-D-Ala, R^2=*t*-BOC



6



10

Experimental

^{1}H NMR spectra were recorded with a JNM-PS-100 spectrometer at 100 MHz in deuteriochloroform containting tetramethylsilane as an internal standard. IR spectra were taken with a Hitachi Model EPI-GS grating spectrometer. Optical rotations were measured in chloroform(C) or methanol (M) in a 0.5 dm tube with a Carl Zeiss LEP-AL polarimeter. Chemical shifts and coupling constants were recorded in δ and Hz units, and IR frequencies in cm^{-1}.

*Benzyl 2,3,4-Tri-O-mesyl-β-L-arabinopyranoside (**1**).* Benzyl β-L-arabinopyranoside[7] (50 g) was mesylated with mesyl chloride (100 g) in pyridine(400 ml) in the usual manner. Yield 75—80%. mp 100—102 °C, $[\alpha]_D$ +71.2° (*c* 1.0, C); NMR: 5.21 (d, H_1, $J_{1,2}$=3.8), 4.90 (dd, H_2, $J_{2,3}$=11.0), 5.12 (dd, H_3, $J_{3,4}$=3.3), 2.92 and 3.15 (s, 3 and 6H, OMs); IR(KBr): 1180 and 1360 (SO_2). Found: C, 38.21; H, 4.63; S, 19.91%. Calcd for $C_{15}H_{22}O_{11}S_3$: C, 37.96; H, 4.67; S, 20.27%.

*Benzyl 4-Azido-4-deoxy-2,3-di-O-mesyl-α-D-xylopyranoside (**2**).* A solution of **1**(50 g), sodium azide(8 g) and urea(1.5 g) in *N,N*-dimethylformamide(370 ml) containing water(40 ml) was heated at 110 °C for 24 h. The reaction mixture was evaporated, and the residue was extracted with chloroform. The extract was washed with water, dried with anhydrous sodium sulfate, and evaporated to give a syrup in 81% yield. The syrup was purified on a silica gel column (Wako gel C-200); $[\alpha]_D$ +123.5° (*c* 0.85, C); NMR: 5.15 (d, H_1, $J_{1,2}$=3.6), 4.91 (dd, H_2, $J_{2,3}$=9.5), 4.59 (dd, H_3, $J_{3,4}$=6.0), 2.95 and 3.13 (s, 3H each, OMs); IR(NaCl): 2110 (N_3), 1180 and 1360 (SO_2). Found: C, 40.16; H, 4.73; N, 9.69; S, 15.42%. Calcd for $C_{14}H_{19}N_3O_8S_2$: C, 39.90; H, 4.54; N, 9.97; S, 15.22%.

*Benzyl 2,3-Anhydro-4-azido-4-deoxy-α-D-lyxopyranoside (**3**) and -ribopyranoside (**4**).* A 4—5% solution of **2** in methanol containing *ca.* 6 equimolar sodium was refluxed for 6—7 h, until the most of **2** has disappeared. Methanol was evapo-

---

* Aminosugars XXX. For part XXIX, see Ref. 1.

** UNESCO fellow 1975—1976.

rated and the residue was dissolved in benzene. The benzene layer was washed with water, dried, and evaporated to give a syrup, which was fractionated on a silica gel column by elution with benzene to obtain at first an oily **3** and secondly **4**, in 20% and 15% yields, respectively. **3**: $[\alpha]_D$ +101.4° (*c* 1.2, M); NMR: 4.96 (s, H_1, $J_{1,2}$=0.5), 3.13 and 3.30 (dd, H_2 and H_3, $J_{2,3}$=3.3, $J_{3,4}$=0.5); IR(NaCl): 2100 (N_3). Found: C, 58.79; H, 5.26; N, 17.01%. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 17.00%. **4**: $[\alpha]_D$ +181° (*c* 1.0, M); NMR: 4.94 (d, H_1, $J_{1.2}$=2.7); IR (NaCl): 2100 (N_3). Found: C, 58.61; H, 5.21; N, 16.82%. Calcd for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 17.00%.

*Benzyl 2-Amino-4-azido-2,4-dideoxy-α-D-xylopyranoside (**5**) and Benzyl 3-Amino-4-azido-3,4-dideoxy-α-D-arabinopyranoside (**6**).* A methanol solution of **3**(3.5 g) was saturated with ammonia at 0 °C, and then heated in a sealed glass tube at 90 °C for 24 h. After complete evaporation of the solvent, the crystalline product obtained(3.5 g) was fractionated on a silica gel column by elution with benzene containing 5% 2-pronanol (v/v). The faster-eluting component was **5** (2.2 g, 61%) followed by the isomeric 3-amino derivative (**6**: 0.8 g, 23%). **5**: Mp 95—96 °C, $[\alpha]_D$ +184.6° (*c* 1.0, M); NMR: 4.78 (d, H_1, $J_{1,2}$=3.5), 2.69 (dd, H_2, $J_{2,3}$=9.3) and $J_{3,4}$ was found to be 9.4 Hz with the aid of $Eu(FOD)_3$. IR(KBr): 2100 (N_3), 3300 and 3350 (NH_2 and OH). Found: C, 54.40; H, 6.24; H, 21.39%. Calcd for $C_{12}H_{16}N_4O_3$: C, 54.54; H, 6.06; N, 21.21%. **6**: Mp 110—111° C, $[\alpha]_D$ −45.1° (*c* 1.0, M); NMR: 4.23 (d, H_1, $J_{1,2}$=6.9), 3.35 (dd, H_2, $J_{2,3}$=9.2), 2.81 (dd, H_3, $J_{3,4}$=3.9), 3.66 (m, H_4), 3.50 and 4.00 (dd each, H_5 and $H_{5'}$, $J_{4,5}$ and $J_{4,5'}$: 1.2 and 2.4); IR(KBr): 2100 (N_3), 2280 and 2320 (NH_2 and OH). Found: C, 54.92; H, 6.15; N, 21.51%. Calcd for $C_{12}H_{16}N_4O_3$: C, 54.54; H, 6.10; N, 21.21%.

*Benzyl 4-Azido-2-(*t*-butoxycarbonylamino)-2,4-dideoxy-α-D-xylopyranoside (**7**).* A solution of **5** (1.5 g), *t*-butyl azidoformate (2 g) and triethylamine(1.8 g) in dioxane (15 ml) was heated at 60—70 °C for 3—4 h. The crude product obtained was passed through a column of silica gel by elution with benzene. The first fraction was collected to give **7** (1.8 g), which was recrystallized from methanol. Mp 119—120 °C, $[\alpha]_D$ +191° (*c* 0.7, M); NMR; 4.87 (d, H_1, $J_{1,2}$=1.8) and 1.46 (s, 9H, *t*-Bu); IR(KBr): 2100 (N_3) and 1685 (urethane). Found; C, 55.78; H, 6.66; N, 15.59%. Calcd for $C_{17}H_{24}N_4O_5$: C, 56.08; H, 6.64; N, 15.38%.

*Benzyl 4-Amino-2-(*t*-butoxycarbonylamino)-2,4-dideoxy-α-D-xylopyranoside (**8**).* Hydrogenation of **7** (1.7 g) in methanol was carried out in the presence of platinum oxide to give **8** (1.3 g); mp 172—175 °C, $[\alpha]_D$ +157° (*c* 1.1, M); NMR (DMSO-d_6): 4.90 (d, H_1, $J_{1,2}$=3.0) and 1.46 (s, 9H, *t*-Bu); IR (KBr): 1685 (urethane) and 3370 (NH_2 and OH). Found: C, 59.81; H, 7.67; N, 8.66%. Calcd for $C_{17}H_{26}N_2O_5$: C, 60.34; H, 7.74; N, 8.28%.

*Benzyl 4-(*N*-Benzyloxycarbonyl-D-alanylamino)-2-(*t*-butoxycarbonylamino)-2,4-dideoxy-α-D-xylopyranoside (**9**).* The compound **8** was coupled with *N*-benzyloxycarbonyl-D-alanine *p*-nitrophenyl ester in *N,N*-dimethylformamide in the usual manner to give **9** in 60% yield. Mp 145—147 °C, $[\alpha]_D$ +2.3° (*c* 1.0, M), IR(KBr): 1710 and 1690 (urethane), *1650 and 1520 (amide) and 3320 (NH and OH). Found*: C, 61.92; H, 6.50; N, 7.51%. Calcd for $C_{28}H_{37}N_3O_8$: C, 61.87; H, 6.81; N, 7.73%.

*4-(D-Alanylamino)-2-amino-2,4-dideoxy-D-xylose Dihydrochloride (**10**).* Compound **9** was treated with 98% formic acid for removal of *t*-butoxycarbonyl group and then hydrogenated with palladium-charcoal (10%) in 0.1 N in 50% aqueous ethanol to give **10** in 80% yield, mp 170—175 °C (dec), $[\alpha]_D$ +76.3° (*c* 1.0, M). Found: C, 32.50; H, 6.40; N, 14.09%. Calcd for $C_8H_{19}Cl_2N_3O_4$: C, 32.88; H, 6.55; N, 14.39%.

We thank Mr. Matsumoto for measuring the NMR spectra, and the members of our organic analysis laboratory for microanalysis.

References

1) H. Hashimoto, F. Chiba, K. Araki, and J. Yoshimura, *Carbohydr. Res.* (submitted).

2) T. Hata, S. Omura, M. Katagiri, K. Atsumi, J. Awaya, S. Higashikawa, K. Yasui, H. Terada, and S. Kuyama, *J. Antibiot.*, **24**, 900 (1971).

3) H. Kuzuhara and S. Emoto, *Tetrahedron Lett.* **1975**, 1853.

4) J. Yoshimura, H. Hashimoto, and T. Nishide, *Chem. Lett.*, **1976**, 201.

5) A. Hasegawa, N. Aritake, and M. Kiso, *Carbohydr. Res.*, **52**, 137 (1976).

6) O. Achmatowicz, Jr. and B. Szechner, *Carbohydr. Res.*, **50**, 23 (1976).

7) L. E. Ballou, *J. Am. Chem. Soc.*, **79**, 165 (1957).