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Note

Synthesis of L-*xylo* and L-*ribo* analogues of prumycin*

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In order to investigate the relationship between configuration of the amino sugar moiety and biological activity, two diastereomers of prumycin having the L-*xylo* and L-*ribo* configurations, 4-(D-alanyl)amino-2-amino-2,4-dideoxy-L-xylose (**13**) and -L-ribose (**18**) have been synthesized by a method similar to that developed in our laboratory for the preparation of prumycin[2].

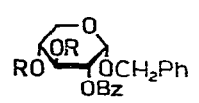
The L-*xylo* and L-*ribo* analogues of prumycin were synthesized via a common intermediate, benzyl 2,3-anhydro-4-azido-4-deoxy-β-L-lyxopyranoside (**5**). As previously reported[2], compound **5** was formed in ~20% yield as a minor component, together with its L-*ribo* isomer, by alkaline treatment of benzyl 4-azido-4-deoxy-2,3-di-*O*-(methylsulfonyl)-β-L-arabinopyranoside (**4**). The epoxide **5** could not, however, be isolated pure, and so **5** was obtained from benzyl 2-*O*-benzoyl-α-D-xylopyranoside (**1**)[3] for the present work. Its 3,4-bis(methanesulfonate) (**2**) was treated with sodium azide in hexamethylphosphoric triamide for several h at 80–90° to give exclusively the corresponding 4-azide (**3**) in 90% yield, whose structure was ascertained by the small values for $J_{3,4}$, $J_{4,5e}$, and $J_{4,5a}$ (1.5, 1.5, and 1.8 Hz, respectively) in its n.m.r. spectrum. Treatment of **3** with potassium hydroxide in methanol–water gave **5** in good yield.

Ammonolysis of **5** in methanol at 90–100° gave a mixture of two ring-opened products in high yield. The 2-amino derivative (**6**) preponderated (~75%) and was isolated readily in >60% yield by fractional recrystallization from ethanol. The 3-amino isomer (**7**) could be obtained from the mother liquor by separation on a column of silica gel by using benzene–2-propanol as the eluant. The structures of **6** and **7** were determined by their n.m.r. spectra, especially by the $J_{2,3}$ and $J_{3,4}$ values (8.7 and 8.6 Hz for **6**, and 9.8 and 3.5 Hz for **7**, respectively). In the case of **6**, the structure was further supported by the fully analyzed n.m.r. spectrum of its *N*,*O*-diacetyl derivative (**8**).

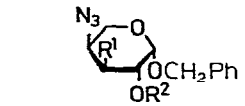
*Amino sugars, Part XXIX. For Part XXVIII, see ref. 1.

Compound **6** was converted into its *N*-benzyloxycarbonyl derivative (**9**) in excellent yield by treatment with benzyl chloroformate in 1,4-dioxane–water. Selective reduction of the azido group in **9** with Raney nickel in ethanol gave the corresponding 4-amino derivative (**10**) in 88% yield; its structure was ascertained from the n.m.r. spectrum of its *N*,*O*-diacetyl derivative (**11**). The amine **10** was coupled with *N*-benzyloxycarbonyl-D-alanine *p*-nitrophenyl ester in *N*,*N*-dimethylformamide to give the 4-(*N*-benzyloxycarbonyl-D-alanyl)amino derivative (**12**) in 73% yield. The structure of **12** was ascertained by the presence of Amide I and Amide II absorptions (1640 and 1530 cm^{-1}, respectively) in the i.r. spectrum and also by its n.m.r. spectrum. Hydrogenolysis of **12** in methanol–water containing hydrochloric acid gave quantitatively the L-*xylo* analogue of prumycin as its dihydrochloride (**13**).

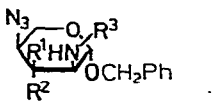
In subsequent experiments, the 3-(methanesulfonate) (**14**) of **9** was heated at 110° in 2-methoxyethanol containing 20% water in the presence of sodium acetate to give benzyl 4-azido-2-(benzyloxycarbonyl)amino-2,4-dideoxy-β-L-ribopyranoside (**15**) in good yield (60–70%). These reaction conditions appear to be the most convenient for inversion of configuration at C-3 in compound **9**, and detailed results will be presented elsewhere[4]. Compound **15** was then converted into the L-*ribo* analogue of prumycin (**18**) via **16** and **17** by a method similar to that used for the L-*xylo* isomer (**13**). The biological activities of the L-*xylo* and L-*ribo* isomers of prumycin are now under investigation.



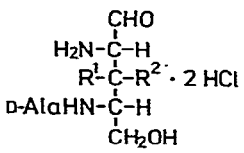
	R
1	H
2	Ms



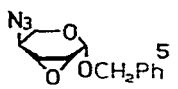
	R^1	R^2
3	OMs	Bz
4	OMs	Ms
7	NH_2	H

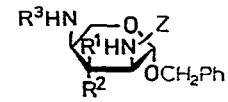


	R^1	R^2	R^3
6	H	OH	H
8	H	OAc	Ac
9	H	OH	Z
14	H	OMs	Z
15	OH	H	Z



	R^1	R^2
13	H	OH
18	OH	H





	R^1	R^2	R^3
10	H	OH	H
11	H	OAc	Ac
12	H	OH	*N*-Z-D-Ala
16	OH	H	H
17	OH	H	*N*-Z-D-Ala

Z = CO_2CH_2Ph, Ala = alanyl, Bz = benzoyl, Ms = methylsulfonyl, Ac = acetyl

EXPERIMENTAL

General methods. — Melting points were determined with a Mel-Temp apparatus and are not corrected. Optical rotations were measured in chloroform (C) or

methanol (M) at 23°, with a 0.5-dm tube and a Carl Zeiss LEP-A1 polarimeter. I.r. spectra were recorded with a Hitachi Model EPI-G2 grating spectrometer. N.m.r. spectra were recorded with a JNM PS-100 spectrometer for solutions in chloroform-*d* containing tetramethylsilane as an internal standard. Chemical shifts and coupling constants are given in δ and Hz, respectively, and i.r. frequencies in cm^{-1}. Evaporations were performed under diminished pressure. Unless otherwise stated, the products were recrystallized from ethanol.

Benzyl 4-azido-2-O-benzoyl-4-deoxy-3-O-(methylsulfonyl-β-L-arabinopyranoside (**3**). — A solution of benzyl 2-*O*-benzoyl-3,4-di-*O*-(methylsulfonyl)-α-D-xylopyranoside[5] (**2**, 20 g, 0.04 mol) and sodium azide (3.2 g, 0.05 mol) in hexamethylphosphoric triamide (35 mL) was heated for 7–8 h at 80–90°, and then poured into water. The aqueous layer was removed by decantation and the residual gum was dissolved in chloroform. The chloroform solution was washed with water, dried, and evaporated to give syrupy **3** (90% yield). The syrup was purified on a column of silica gel. $[\alpha]_D$ +197° (*c* 0.8, C); ν_{max}^{NaCl} 2120, 1730, 1365, 755, and 710; n.m.r.: 5.24 (d, $J_{1,2}$ 3.0, H-1), 5.41 (m, $J_{2,3}$ 10.2, H-2 and H-3), 4.26 (m, H-4), 4.04 (q, $J_{4,5e}$ 1.5, H-5e), 3.74 (q, $J_{4,5a}$ 1.8, H-5a), 4.48 and 4.72 (dd, CO_2CH_2Ph), and 3.00 (s, Ms). The $J_{2,3}$ value was obtained in the presence of a shift reagent, Eu $(fod)_3$.

Anal. Calc. for $C_{15}H_{21}N_3O_7S$: C, 46.50; H, 5.46; N, 10.84; S, 8.29. Found: C, 46.90; H, 5.77; N, 10.50; S, 8.00.

Benzyl 2,3-anhydro-4-azido-4-deoxy-β-L-lyxopyranoside (**5**). — To 4:1 methanol–water (250 mL) containing potassium hydroxide (6.9 g, 0.12 mol) was added **3** (20 g, 0.04 mol) with stirring. The solution was stirred for 4–5 h at room temperature, evaporated after the addition of water (50 mL), and the residue was extracted three times with benzene. Evaporation of the extract gave **5** in 92% yield, m.p. 39–40°, $[\alpha]_D$ +115° (*c* 0.4, C); ν_{max}^{KBr} 2110, 1070, 1035, and 720; n.m.r.: 5.10 (d, $J_{1,2}$ 2.0, H-1), 3.42 (m, H-2 and H-3), 3.62 (q, $J_{4,5}$ 1.3, H-5), 4.08 (q, $J_{4,5'}$ 2.4, H-5'), 4.61, and 4.83 (dd, OCH_2Ph).

Anal. Calc. for $C_{18}H_{21}N_3O_7$: C, 58.29; H, 5.30; N, 17.00. Found: C, 58.85; H, 5.37; N, 17.40.

Benzyl 2-amino-4-azido-2,4-dideoxy-β-L-xylopyranoside (**6**) *and benzyl 3-amino-4-azido-3,4-dideoxy-β-L-arabinopyranoside* (**7**). — Ammonolysis of **5** was performed in a sealed tube at 90–95° as described previously[1], although a longer reaction-time (5 days) was needed. Crystallization from ethanol gave pure **6** in 60% yield. The mother liquor was evaporated, and the residue further resolved on a column of silica gel to give additional crops of **6** (5–10%) and **7** (10–15%).

Compound **6** had m.p. 122–123°, $[\alpha]_D$ +23.6° (*c* 1.0, C); ν_{max}^{KBr} 3370, 3310, 2100, 745, and 700; n.m.r.: 4.18 (d, $J_{1,2}$ 7.5, H-1), 2.71 (t, $J_{2,3}$ 8.7, H-2), 3.34 (t, $J_{3,4}$ 8.6, H-3), 3.50 (dt, H-4), 3.19 (q, $J_{4,5a}$ 4.1, H-5a), 4.04 (t, $J_{4,5e}$ 10.0, H-5e), 4.55 and 4.90 (dd, OCH_2Ph), and 2.26 (NH_2 and OH).

Anal. Calc. for $C_{12}H_{16}N_4O_3$: C, 54.55; H, 6.10; N, 21.20. Found: C, 54.89; H, 6.07; N, 20.89.

Compound **7** had m.p. 99–100°, $[\alpha]_D$ +109° (*c* 0.9, C); ν_{max}^{KBr} 3320, 3270,

2130, 735, and 700; n.m.r.: 5.00 (d, $J_{1,2}$ 3.3, H-1), 3.10 and 3.56 (dq, $J_{2,3}$ 9.8, $J_{3,4}$ 3.5, H-2 and H-3), 3.82 (m, H-4), 3.78 (q, $J_{4,5a}$ 0.9, H-5a), 3.99 (q, $J_{4,5e}$ 2.0, H-5e).

Anal. Calc. for $C_{12}H_{16}N_4O_3$: C, 54.55; H, 6.10; N, 21.20. Found: C, 54.72; H, 6.23; N, 21.30.

*Benzyl 2-acetamido-3-O-acetyl-4-azido-2,4-dideoxy-β-*L*-xylopyranoside* (**8**). — Conventional acetylation of **6** gave **8** quantitatively; m.p. 157–158°, $[\alpha]_D$ +66.5° (*c* 0.8, C); ν_{max}^{KBr} 3280, 2110, 1753, 1655, 1548, 735, and 700; n.m.r.: 4.45 (d, $J_{1,2}$ 6.7, H-1), 4.05 (dt, $J_{2,3}$ 8.6, H-2), 4.90 (t, $J_{3,4}$ 8.6, H-3), 3.67 (dt, H-4), 3.27 (q, $J_{4,5a}$ 8.4, H-5a), 4.05 (q, $J_{4,5e}$ 4.3, H-5e), and 4.48 and 4.77 (dd, OCH_2Ph).

Anal. Calc. for $C_{16}H_{20}N_4O_5$: C, 55.16; H, 5.79; N, 16.08. Found: C, 55.19; H, 5.90; N, 16.38.

*Benzyl 4-azido-2-(benzyloxycarbonyl)amino-2,4-dideoxy-β-*L*-xylopyranoside* (**9**). — To a solution of **6** (8.2 g, 31 mmol) and sodium hydrogencarbonate (8.0 g, 95 mmol) in 50% aqueous 1,4-dioxane (300 mL) was added benzyl chloroformate in 5 or 6 portions with stirring in an ice–water bath. The solution was stirred overnight at room temperature. The precipitated mass was filtered off and recrystallized from ethanol to give **9** in 96% yield; m.p. 142–143°, $[\alpha]_D$ +54.3° (*c* 1.0, C); ν_{max}^{KBr} 3400, 3320, 2130, 1700, 1545, 735, and 698; n.m.r.: 4.56 (d, $J_{1,2}$ 4.5, H-1), 3.35 (q, $J_{4,5a}$ 6.5, H-5a), 4.08 (q, $J_{4,5e}$ 3.0, H-5e), 5.08 (s, CO_2CH_2Ph), and 4.53 and 4.82 (dd, OCH_2Ph).

Anal. Calc. for $C_{20}H_{22}N_4O_5$: C, 60.29; H, 5.57; N, 14.06. Found: C, 60.15; H, 5.58; N, 14.23.

*Benzyl 4-amino-2-(benzyloxycarbonyl)amino-2,4-dideoxy-β-*L*-xylopyranoside* (**10**). — To a solution of **9** (1.4 g, 3.5 mmol) in ethanol (100 mL) was added Raney nickel in small portions (~0.5 g each) and the mixture was shaken at room temperature until **9** disappeared (t.l.c.). The undissolved material was filtered off and the filtrate evaporated to give **10** in 88% yield; m.p. 158–159°, $[\alpha]_D$ +45.7° (*c* 0.8, pyridine); ν_{max}^{KBr} 3310, 1690, 1540, 735, and 695; n.m.r. (pyridine-d_5): 4.89 (d, $J_{1,2}$ 7.5, H-1), 5.26 (s, CO_2CH_2Ph), and 4.69 and 5.05 (dd, OCH_2Ph).

Anal. Calc. for $C_{20}H_{24}N_2O_5$: C, 64.50; H, 6.50; N, 7.52. Found: C, 64.80; H, 6.65; N, 7.37.

Conventional acetylation of **10** gave the *N,O*-diacetyl derivative **11**, m.p. 216–218°, $[\alpha]_D$ +85.6° (*c* 0.5, C); n.m.r.: 4.58 (d, $J_{1,2}$ 7.5, H-1), ~4.10 (m, H-2 and H-5e), 5.16 (q, H-3), 3.62 (q, $J_{3,4}$, $J_{4,NH}$ and $J_{4,5a}$ 8.9, $J_{4,5e}$ 1.0, H-4), 3.20 (t, H-5a), 5.05 (s, CO_2CH_2Ph), 4.51 and 4.82 (dd, OCH_2Ph), and 1.99 and 1.91 (NHAc and OAc).

Anal. Calc. for $C_{24}H_{28}N_2O_7$: C, 63.15; H, 6.18; N, 6.14. Found: C, 62.85; H, 6.03; N, 6.32.

*Benzyl 4-(N-benzyloxycarbonyl-*D*-alanyl)amino-2-(benzyloxycarbonyl)amino-2,4-dideoxy-β-*L*-xylopyranoside* (**12**). — Compound **10** (800 mg, 2.2 mmol) and *N*-benzyloxycarbonyl-D-alanine *p*-nitrophenyl ester (910 mg, 2.7 mmol) were dissolved in *N,N*-dimethylformamide (DMF, 30 mL), and kept overnight at room temperature. The DMF was evaporated at <2 mmHg and the residual mass was poured into ice–

water to crystallize. The crystals were filtered off, washed with ether, and recrystallized from DMF–ether to give **12** in 73% yield; m.p. 221–222°, $[\alpha]_D$ +31.8° (*c* 0.7, DMF); ν_{max}^{KBr} 3330, 1720, 1700, 1640, 1530, and 700; n.m.r. (in dimethyl sulfoxide-d_6: 4.35 (d, $J_{1,2}$ 7.5, H-1), 5.01 (s, CO_2CH_2Ph), 4.71 and 4.75 (dd, OCH_2Ph), and 1.20 (d, CH_3).

Anal. Calc. for $C_{31}H_{35}N_3O_8$: C, 64.46; H, 6.11; N, 7.28. Found: C, 64.41; H, 6.25; N, 6.96.

4-(D-Alanyl)amino-2-amino-2,4-dideoxy-L-xylose dihydrochloride (**13**). — A solution of **12** (200 mg, 0.35 mmol) in a 1 : 1 mixture of ethanol and 0.1M hydrochloric acid (20 mL) was hydrogenolyzed in the presence of 10% palladium-on-charcoal (120 mg). The catalyst was filtered off and the filtrate evaporated to a white residue, which crystallized from ethanol; yield 90 mg (90%), m.p. 185–190° (dec.), $[\alpha]_D$ −14° (*c* 0.6, M); ν_{max}^{KBr} 3200–3400 (broad), 1670, and 1555.

Anal. Calc. for $C_8H_{19}Cl_2N_3O_4$: C, 32.88; H, 6.55; N, 14.39. Found: C, 32.77; H, 6.25; N, 14.05.

Benzyl 4-azido-2-(benzyloxycarbonyl)amino-2,4-dideoxy-3-O-(methylsulfonyl)-β-L-xylopyranoside (**14**). — Conventional mesylation of **9** gave **14** in 88% yield; m.p. 125–127°, $[\alpha]_D$ +13.2° (*c* 1.0, C); ν_{max}^{KBr} 3320, 2120, 1700, 1350, 750, and 700; n.m.r.: 4.62 (d, $J_{1,2}$ 7.5, H-1), 3.50–3.80 (m, H-2, H-3 and H-4), 3.29 (q, $J_{4,5a}$ 9.3, H-5a), 4.11 (q, $J_{4,5e}$, 4.5, H-5e), 5.07 (s, CO_2CH_2Ph), 4.51 and 4.80 (dd, OCH_2Ph), and 2.96 (s, Ms).

Anal. Calc. for $C_{21}H_{24}N_4O_7S$: C, 52.92; H, 5.09; N, 11.76; S, 6.73. Found: C, 52.77; H, 5.06; N, 11.74; S, 6.88.

Benzyl 4-azido-2-(benzyloxycarbonyl)amino-2,4-dideoxy-β-L-ribopyranoside (**15**). — A solution of **14** (3.0 g, 7.0 mmol) and sodium acetate (6.0 g, 73 mmol) in 2-methoxyethanol containing 20% of water (50 mL) was heated for 2 days at 110–115°. The solvent was evaporated and the residue dissolved in chloroform. The chloroform solution was washed with water, dried, and evaporated to give syrupy **15** in 60–70% yield. It was purified on a column of silica gel with 50 : 1 benzene–methanol as eluant; $[\alpha]_D$ +83.2° (*c* 4.0, C); ν_{max}^{KBr} 3430, 3300, 2120, 1695, 1540, 750, and 700; n.m.r.: 4.80 (d, $J_{1,2}$, 2.4, H-1), 5.08 (s, CO_2CH_2Ph), and 5.69 (NH).

Anal. Calc. for $C_{20}H_{20}N_4O_5$: C, 60.29; H, 5.57; N, 14.06. Found: C, 60.06; H, 5.60; N, 14.16.

Benzyl 4-amino-2-(benzyloxycarbonyl)amino-2,4-dideoxy-β-L-ribopyranoside (**16**). — Selective reduction of the azido group in **15** was performed as described in the preparation of **10**; yield, 80%, m.p. 149–150°, $[\alpha]_D$ +75.6° (*c* 0.7, C); ν_{max}^{KBr} 3300, 1690, 1535, and 700.

Anal. Calc. for $C_{20}H_{24}N_2O_5$: C, 64.50; H, 6.50, N, 7.52. Found: C, 64.78; H, 6.68; N, 7.57.

Benzyl 4-(N-benzyloxycarbonyl-D-alanyl)amino-2-(benzyloxycarbonyl)amino-2,4-dideoxy-β-L-ribopyranoside (**17**). — Condensation of **16** with *N*-benzyloxycarbonyl-D-alanine *p*-nitrophenyl ester was effected as described in the preparation of **12**;

yield, 80%; m.p. 198–200°, $[\alpha]_D$ +45.6° (*c* 0.7, DMF); ν_{max}^{KBr} 3300, 1695, 1640, 1520, 755, and 695.

Anal. Calc. for $C_{31}H_{35}N_3O_8$: C, 64.46; H, 6.11; N, 7.28. Found: C, 64.66; H, 6.26; N, 6.96.

4-(D-Alanyl)amino-2-amino-2,4-dideoxy-L-ribose dihydrochloride (**18**). — Hydrogenolysis of **17** was performed as described in the preparation of **13**, to give **20** quantitatively as an amorphous powder from methanol–ether; m.p. 173–174° (dec.), $[\alpha]_D$ −62.6° (*c* 1.3, M); ν_{max}^{KBr} 3200–3400 (broad), 1665, and 1555.

Anal. Calc. for $C_8H_{19}Cl_2N_3O_4$: C, 32.88; H, 6.55; N, 14.39. Found: C, 33.05; H, 6.32; N, 14.00.

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