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SYNTHESIS OF PRUMYCIN AND RELATED COMPOUNDS*

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ABSTRACT

Prumycin (**1**) and related compounds have been synthesized from benzyl 2-(benzyloxycarbonyl)amino-2-deoxy-5,6-*O*-isopropylidene-β-D-glucofuranoside (**4**). Benzoylation of **4**, followed by deisopropylidenation, gave benzyl 3-*O*-benzoyl-2-(benzyloxycarbonyl)amino-2-deoxy-β-D-glucofuranoside (**6**), which was converted, *via* oxidative cleavage at C-5–C-6 and subsequent reduction, into the related benzyl β-D-xylofuranoside derivative (**7**). Benzylation of 3-*O*-benzoyl-2-(benzyloxycarbonyl)-amino-2-deoxy-D-xylopyranose (**8**), derived from **7** by hydrolysis, afforded the corresponding derivatives (**9**, **11**) of β- and α-D-xylopyranoside, and compound **7** as a minor product. Treatment of benzyl 3-*O*-benzoyl-2-(benzyloxycarbonyl)amino-2-deoxy-4-*O*-mesyl-β-D-xylopyranoside (**10**), formed by mesylation of **9**, with sodium azide in *N*,*N*-dimethylformamide gave benzyl 4-azido-3-*O*-benzoyl-2-(benzyloxycarbonyl)amino-2,4-dideoxy-α-L-arabinopyranoside (**13**), which was debenzoylated to compound **14**. Selective reduction of the azide group in **14**, and condensation of the 4-amine with *N*-[*N*-(benzyloxycarbonyl)-D-alaninoyloxy]succinimide, gave the corresponding derivative (**15**) of **1**. Reductive removal of the protecting groups of **15** afforded **1**. Prumycin analogs were also synthesized from compound **14**. Evidence in support of the structures assigned to the new derivatives is presented.

INTRODUCTION

2,4-Diamino sugars have been isolated from such antibiotics as Kasugamycin[1], Prumycin[2], and Minosaminomycin[3], and from other natural sources[4–6].

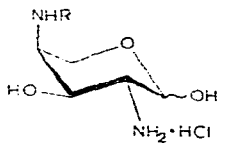
Prumycin, isolated by Hata *et al.*[7] in 1971, is a new antibiotic exhibiting a selective, inhibitory effect against phytopathogenic fungi such as *Sclerotinia sclerotiorum*. The structure was finally elucidated to be 4-(D-alanylamino)-2-amino-2,4-dideoxy-L-arabinopyranose by Ōmura *et al.*[2] in 1974. Recently, Kuzuhara *et al.*[8] and Yoshimura *et al.*[9] independently confirmed the structure by chemical synthesis.

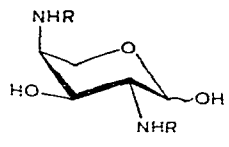
In previous papers[10–12], we have shown that various *N*-substituted 2-amino-2-deoxy-D-aldohexoses react with 2,2-dialkoxypropane–*N*,*N*-dimethylformamide–*p*-

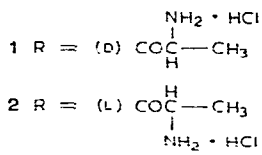
*For a preliminary communication on part of this work, see *Carbohydr. Res.*, 51 (1976) C10–C12.

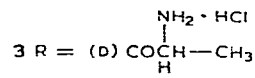
toluenesulfonic acid at room temperature to give 4,6-*O*-isopropylidene derivatives, and at 80–90° to give mainly 5,6-*O*-isopropylidenehexofuranoses. The potential utility of this reagent for syntheses in the amino sugar field was emphasized.

We have now extended these studies to provide a facile, stereoselective synthesis of Prumycin (**1**) and related compounds (**2** and **3**).





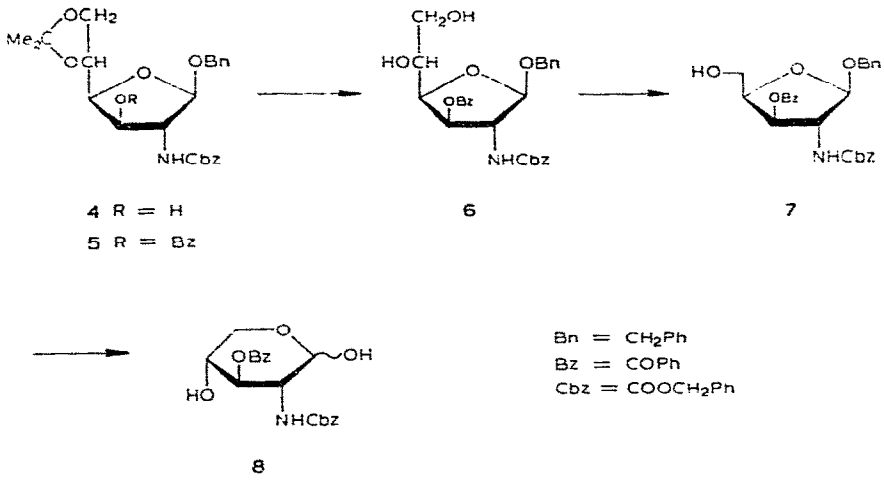




RESULTS AND DISCUSSION

Treatment[1,2] of 2-(benzyloxycarbonyl)amino-2-deoxy-D-glucose with the 2,2-dibenzyloxypropane reagent for 1 h at 85° gave benzyl 2-(benzyloxycarbonyl)amino-2-deoxy-5,6-*O*-isopropylidene-*β*-D-glucofuranoside (**4**) (40%). When the reagent mixture was employed for 10 min at 120° for preparative work, compound **4** was obtained in 55% yield. Benzoylation of **4** gave the 3-benzoate **5**, from which the isopropylidene group could be cleaved by mild, acid hydrolysis to give benzyl 3-*O*-benzoyl-2-(benzyloxycarbonyl)amino-2-deoxy-*β*-D-glucofuranoside (**6**) in good yield. Oxidative cleavage between C-5 and C-6 of compound **6** with sodium metaperiodate gave a syrupy aldehyde, which was converted by reduction with sodium borohydride for 10 min at 0° into benzyl 3-*O*-benzoyl-2-(benzyloxycarbonyl)amino-2-deoxy-*β*-D-xylofuranoside (**7**) in 95% yield. Hydrolytic removal of the benzyl group of **7** with 20:1 acetic acid–2M hydrochloric acid at 55° afforded 3-*O*-benzoyl-2-(benzyloxycarbonyl)amino-2-deoxy-D-xylopyranose (**8**).

Treatment of **8** with benzyl alcohol in the presence of Amberlite IR-120 (H^+) resin at 85° gave a mixture from which benzyl 3-*O*-benzoyl-2-(benzyloxycarbonyl)-amino-2-deoxy-*β*-D-xylopyranoside (**9**, 45%) and the corresponding *α*-D-xylopyranoside (**11**, 36%), together with compound **7** as a minor product, were isolated. Compounds **9** and **11** were respectively mesylated with methanesulfonyl chloride in pyridine at 0° to produce the 4-*O*-mesyl derivatives (**10**, **12**) in quantitative yield. The structures of **9** and **11** were determined from their n.m.r. data and those of the corresponding 4-*O*-mesyl derivatives (**10**, **12**) (see Table I). Benzyl 3-*O*-benzoyl-2-(benzyloxycarbonyl)amino-2-deoxy-4-*O*-mesyl-*β*-D-xylopyranoside (**10**) was treated with an excess of sodium azide in *N*,*N*-dimethylformamide for 10 h at 120° to afford benzyl 4-azido-3-*O*-benzoyl-2-(benzyloxycarbonyl)amino-2,4-dideoxy-*α*-L-arabino-



pyranoside (**13**) in 91% yield. The n.m.r. spectrum of **13** was well resolved, and the values of the coupling constants (see Table I) indicated that this compound had the *arabino* configuration. As the mesyl and the benzoyl groups in **10** are *trans* to each other, the formation of small amounts of *xylo* azide and 3-azido compounds resulting from neighboring-group participation may be expected. However, no such compounds were isolated, probably because they were formed in only very small amounts. Saponification of **13** with sodium methoxide in methanol afforded benzyl 4-azido-2-(benzyloxycarbonyl)amino-α-L-arabinopyranoside (**14**) quantitatively.

Selective reduction of the azide group in compound **14** (in 1:1 1,4-dioxane–triethylamine) with hydrogen in the presence of 10% Pd/C catalyst gave the desired benzyl 4-amino-2-(benzyloxycarbonyl)amino-2,4-dideoxy-α-L-arabinopyranoside, which was used for the next reaction without purification. The amino compound was treated with an equivalent amount of *N*-[*N*-(benzyloxycarbonyl)-D-alaninoyloxy]-succinimide in 1,4-dioxane at room temperature, affording benzyl 4-[*N*-(benzyloxycarbonyl)-D-alanylamino]-2-(benzyloxycarbonyl)amino-2,4-dideoxy-α-L-arabinopyranoside [benzyl *N*,*N*′-bis(benzyloxycarbonyl)-α-Prumycinide] (**15**) in 83% yield on the basis of compound **14**. When treated with *N*-[*N*-(benzyloxycarbonyl)-L-alaninoyloxy]succinimide according to the same procedure, the amino compound yielded benzyl 4-[*N*-(benzyloxycarbonyl)-L-alanylamino]-2-(benzyloxycarbonyl)amino-2,4-dideoxy-α-L-arabinopyranoside (**16**) in 88% yield. By the same treatment of the benzyl diaminodideoxy-L-arabinopyranoside derived from compound **14**, with the D-alanine derivative, benzyl 2,4-di-(*N*-benzyloxycarbonyl-D-alanylamino)-2,4-dideoxy-α-L-arabinopyranoside (**17**) was obtained in good yield.

In the n.m.r. spectra (see Table II) of compounds **15**, **16**, and **17** in chloroform-*d*, the coupling constants are 2.0, 1.5, and 2.0 Hz, respectively. However, in a more polar solvent (dimethyl sulfoxide-d_6), those of compounds **15** and **17** are 5.0 and 4.6 Hz, respectively. It appears that, in dimethyl sulfoxide solution, both chair conformations

TABLE I

CHEMICAL SHIFTS (τ VALUES) AND COUPLING CONSTANTS OF RING PROTONS[a], AND OPTICAL ROTATIONS OF COMPOUNDS **9**, **10**, **11**, **12**, AND **13**

Compound	*Chemical shifts*						*Coupling constants*						$[\alpha]_D$ (*degrees*)
	H-1	*H-2*	*H-3*	*H-4*	*H-5a*	*H-5e*	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5a}$	$J_{4,5e}$	$J_{5a,5e}$	
9	5.27d	5.98m	4.88t	6.12m	6.51dd	6.53dd	4.2	6.2	6.2	5.9	3.8	12.0	−3.3
10	5.25d	5.98m	4.66t	5.25m	6.31dd	5.69dd	5.0	6.0	6.0	6.2	4.0	12.4	−35.5
11	5.08d	5.90m	4.82dd	6.05m	6.22t	6.15dd	3.7	10.0	8.0	10.2	4.0	10.2	+179
12	5.06d	5.86m	4.45t	5.13m	6.05t	5.97dd	3.8	10.0	10.0	10.2	4.2	10.2	+103
13	5.35d	5.90m	4.55dd	6.0m	6.36dd	5.92d	6.0	8.2	3.0	2.0	~0	10.5	−25.5

[a]N.m.r. spectra were measured at 90 MHz for solutions in $CDCl_3$. Multiplicity of resonances: d, doublet; dd, doublet of doublets; m, multiplet; t, triplet. Assignments of all the ring protons were determined by the decoupling technique.

of the compounds are present in substantial proportions in equilibrium, but that, in chloroform, there is a shift in the conformational equilibrium to favor the $^1C_4(L)$ conformation. It is known that the solvent-dependence of the conformational population of polysubstituted, pyranoid ring-systems is affected by the anomeric

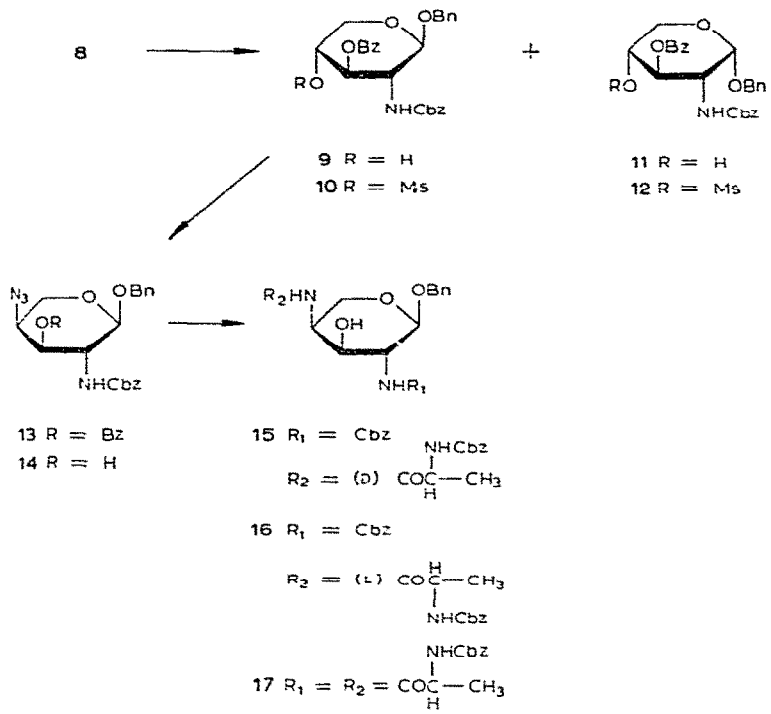
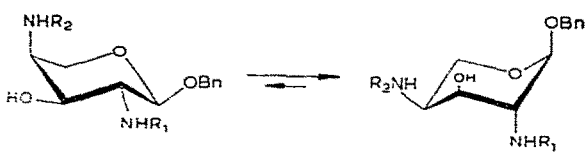


TABLE II

N.M.R. DATA FOR COMPOUNDS **15**, **16**, AND **17** IN $CDCl_3$ AND Me_2SO-d_6



Compound	*Solvent*	*Anomeric proton*	
		Chemical shift (τ)	*Coupling constant*, $J_{1,2}$ (*Hz*)
15	$CDCl_3$	5.27	2.0
15	Me_2SO-d_6	5.57	5.0
16	$CDCl_3$	5.30	1.5
17	$CDCl_3$	5.34	2.0
17	Me_2SO-d_6	5.57	4.6

effect[13,14], 1,3-diaxial interaction[15,16], vicinal–gauche interaction, and intramolecular hydrogen-bonding[17]. The main cause for compounds **15** to **17** to adopt the $^1C_4$(L) conformation in chloroform must be the anomeric effect, which favors the axial orientation for the benzyloxyl group. It is also important to add the effect of intramolecular hydrogen-bonding between the *O*-benzyl group at O-1 and the hydrogen atom of OH-3 in axial orientation in stabilizing the $^1C_4$(L) conformation in chloroform. The *gauche* interaction between the C-1 and C-2 substituents, and the nonbonded interaction between the bulky, axial substituent at C-4 and the ring-oxygen atom to destabilize the $^4C_1$(L) conformation must also be important.

The protecting groups of compound **15** were removed by hydrogenolysis with 10% Pd/C catalyst in aqueous methanol in the presence of acetic acid. After evaporation of the methanol, the amount of 0.1M hydrochloric acid calculated to be equivalent to the base was added to the residual solution, and the mixture was evaporated *in vacuo* at 30° to give Prumycin dihydrochloride (**1**) in almost quantitative yield.

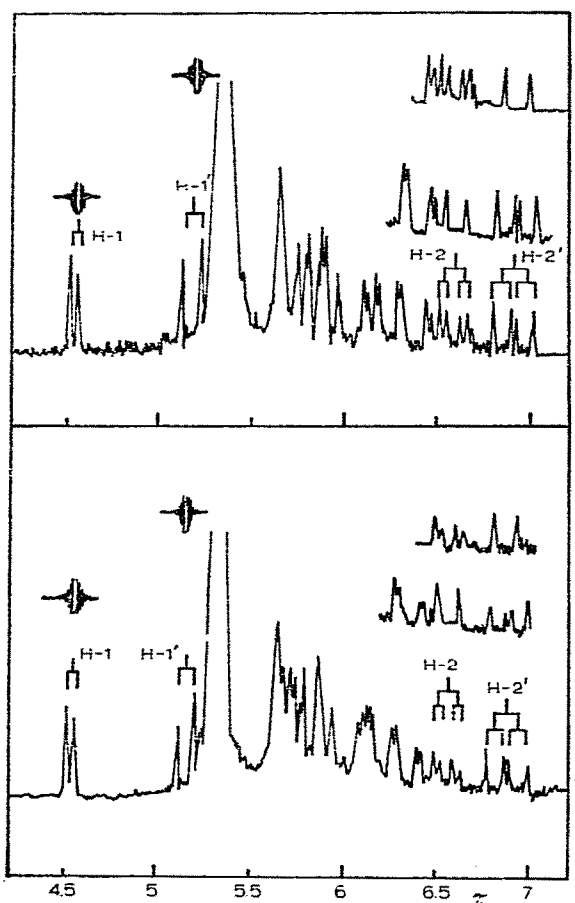


Fig. 1. Partial n.m.r. spectra of Prumycin dihydrochloride (**1**) and the analog (**2**) at 90 MHz in D_2O.

The i.r. and n.m.r. spectra, and R_F values in t.l.c. were identical with those of an authentic sample of Prumycin dihydrochloride. By the same procedure, the related compounds **2** and **3** were synthesized from **16** and **17**, respectively. The n.m.r. spectrum (see Fig. 1) of the Prumycin analog (**2**) is similar to that of Prumycin (**1**), and the values of the coupling constants indicate that both of the compounds have the $^4C_1$(L) conformation.

EXPERIMENTAL

General. — Melting points were determined on a Yanagimoto micro melting-point apparatus and are uncorrected. Specific rotations were determined with a Yanagimoto OR-50 polarimeter. N.m.r. spectra were recorded at 90 MHz for solution in chloroform-*d*, unless otherwise noted. I.r. spectra were recorded with a Jasco IRA-1 spectrophotometer. Preparative chromatography was performed on 300-mesh silica gel (Wako Co.) with the solvent systems specified. *N,N*-Dimethylformamide was distilled, and dried over Drierite (W. A. Hammond Drierite Co.). Evaporations were conducted *in vacuo*.

*Benzyl 2-(benzyloxycarbonyl)amino-2-deoxy-5,6-O-isopropylidene-β-*D*-glucofuranoside* (**4**). — A solution of 2-(benzyloxycarbonyl)amino-2-deoxy-D-glucose (100 g) in dry *N,N*-dimethylformamide (400 ml) at 120° was stirred whilst 2,2-dibenzyloxypropane[18] (400 ml) and *p*-toluenesulfonic acid (5 g) were added. The mixture was stirred for 10 min at 120°, cooled, and deacidified with Amberlite IRA-410 ion-exchange resin. The mixture was filtered, and the filtrate evaporated, and the syrupy residue was eluted from a column of silica gel (1,000 g) with benzene, and then with 70:1 benzene–methanol. The latter eluted the title compound (**4**; 77.8 g, 55%). Recrystallization from ethanol–ether gave needles, m.p. 89.5° (lit.[12] syrup), $[\alpha]_D^{25}$ −44° (*c* 0.3, chloroform) (lit.[12] $[\alpha]_D^{23}$ −35°); n.m.r. data: τ 2.68 (Ph), 5.0 (1 H, s, H-1), and 8.60 and 8.68 (2 s, Me_2C).

Anal. Calc. for $C_{24}H_{29}NO_7$: C, 65.00; H, 6.59; N, 3.16. Found: C, 64.95; H, 6.63; N, 3.19.

*Benzyl 3-O-benzoyl-2-(benzyloxycarbonyl)amino-2-deoxy-5,6-O-isopropylidene-β-*D*-glucofuranoside* (**5**). — To a solution of **4** (23.5 g) in pyridine (60 ml) was added benzoyl chloride (10 g) at 0°. The mixture was kept for 5 h at 0°, and extracted with benzene. The extract was successively washed with 2M hydrochloric acid, M sodium carbonate, and water, dried (sodium sulfate), and evaporated. The product, purified by chromatography on a column of silica gel with 10:1 benzene–methanol, was obtained as a syrup: wt. 27.2 g (93%), $[\alpha]_D^{25}$ −69° (*c* 1.0, chloroform); ν_{max}^{film} 3270 (NH), 1715 (ester), 1690 and 1500 (amide), 840 (Me_2C), and 725, 700, and 690 cm^{-1} (phenyl); n.m.r. data: τ 1.92–2.53 (5 H, COPh), 2.62 (10 H, 2 Ph), 4.33 (1 H, dd, $J_{2,3}$ 6.0 Hz, $J_{3,4}$ 2.2 Hz, H-3), 4.51 (1 H, d, $J_{2,NH}$ 8.0 Hz, NH), 4.80 (1 H, d, $J_{1,2}$ 1.5 Hz, H-1), 4.83 (2 H, s, CO_2CH_2Ph), and 8.59 and 8.79 (2 s, Me_2C).

Anal. Calc. for $C_{31}H_{33}NO_8$: C, 67.99; H, 6.07; N, 2.56. Found: C, 68.20; H, 6.22; N, 2.56.

Benzyl 3-O-benzoyl-2-(benzyloxycarbonyl)amino-2-deoxy-β-D-glucofuranoside (**6**). — A solution of **5** (5 g) in 70% aqueous acetic acid (50 ml) was heated for 5 h at 40–45°, and then evaporated at 40°. The residue crystallized from ether, and recrystallization from ethanol–ether gave **6** as needles (4.3 g, 93%), m.p. 131°, $[\alpha]_D^{25}$ −15° (*c* 0.3, chloroform); ν_{max}^{Nujol} 3430 (OH), 3280 (NH), 1730 (ester), 1730 and 1540 (amide), and 730, 710, and 700 cm^{-1} (phenyl).

Anal. Calc. for $C_{28}H_{29}NO_8$: C, 66.26; H, 5.76; N, 2.76. Found: C, 66.31; H, 5.77; N, 2.82.

Benzyl 3-O-benzoyl-2-(benzyloxycarbonyl)amino-2-deoxy-β-D-xylofuranoside (**7**). — To a stirred solution of **6** (6 g) in methanol (180 ml) was added 0.4M aqueous sodium metaperiodate solution (36 ml) at 0°, and the mixture was kept for 50 min at 0°. In order to decompose the excess of the reagent, ethylene glycol was added to the mixture, and the precipitate was removed by filtration. The filtrate was evaporated to a syrup, which was extracted with benzene. The extract was washed with water, dried (sodium sulfate), and evaporated to a syrup which was used in the next reaction without further purification. A solution of the syrup in methanol (150 ml) was stirred at 0° while sodium borohydride (300 mg) was added. The mixture was gently stirred for 10 min at 0°. Acetic acid (1 ml) was added to the mixture, and it was evaporated at 20° to a syrup which was extracted with benzene. The extract was successively washed with 2M hydrochloric acid, M sodium carbonate, and water, dried (sodium sulfate), and evaporated, to afford a crystalline product; this was recrystallized from methanol to give needles (5.4 g, 95%); m.p. 117–118°, $[\alpha]_D^{25}$ −33° (*c* 0.4, methanol); ν_{max}^{Nujol} 3400 (OH), 3320 (NH), 1740 (ester), 1680 and 1530 (amide), and 690 and 700 cm^{-1} (phenyl); n.m.r. data: τ 1.96–2.60 (5 H, COPh), 2.69 (10 H, 2 Ph), 4.66 (1 H, dd, $J_{2,3}$ 6.5 Hz, $J_{3,4}$ 3.3 Hz, H-3), 4.67 (1 H, d, $J_{2,NH}$ 8.0 Hz, NH), 4.85 (1 H, d, $J_{1,2}$ 1.5 Hz, H-1), and 4.90 (2 H, s, CO_2CH_2Ph).

Anal. Calc. for $C_{27}H_{27}NO_7$: C, 67.91; H, 5.70; N, 2.93. Found: C, 67.89; H, 5.73; N, 3.10.

3-O-Benzoyl-2-(benzyloxycarbonyl)amino-2-deoxy-D-xylopyranose (**8**). — To a solution of **7** (10 g) in acetic acid (60 ml) was added 2M hydrochloric acid (3 ml). The mixture was heated for 1 h at 55°, and again 2M hydrochloric acid (1 ml) was added. The reaction was continued for another 2 h at 55°; starting material was then no longer detectable by t.l.c. The mixture was evaporated below 55° to give a syrup which was crystallized from chloroform–ether. Recrystallization from chloroform afforded **8** (4.1 g, 50%) as needles, m.p. 168°, $[\alpha]_D^{21}$ +52.5° (*c* 0.5, equil., methanol); ν_{max}^{Nujol} 3500 (OH), 3380 (NH), 1700 (ester), 1690 and 1510 (amide), and 700 and 690 cm^{-1} (phenyl).

Anal. Calc. for $C_{20}H_{21}NO_7$: C, 62.01; H, 5.46; N, 3.62. Found: C, 62.23; H, 5.51; N, 3.62.

Benzyl 3-O-benzoyl-2-(benzyloxycarbonyl)amino-2-deoxy-β-D-xylopyranoside (**9**) and *benzyl 3-O-benzoyl-2-(benzyloxycarbonyl)amino-2-deoxy-α-D-xylopyranoside* (**11**). — To a solution of **8** (15 g) in benzyl alcohol (160 ml) was added Amberlite IR-120(H^+) resin (20 g), and the mixture was stirred for 44 h at 85°. The resin was

filtered off, and the filtrate evaporated to a syrup which was chromatographed on a column of silica gel (200 g) with benzene, and then 200:1 benzene–methanol. With the latter eluant, compound **11** issued as the faster-moving component, and was obtained as needles (6.6 g, 36%), m.p. 153–154°, $[\alpha]_D^{25}$ +179° (*c* 0.3, chloroform); ν_{max}^{Nujol} 3500–3350 (OH, NH), 1720 (ester), 1700 and 1500 (amide), and 740, 720, and 690 cm^{-1} (phenyl); n.m.r. data: τ 1.90–2.62 (5 H, COPh), 2.69 and 2.85 (1 H, 2 s, 2 Ph), and 5.06 (2 H, s, CO_2CH_2Ph). Other n.m.r. data are given in Table I.

Anal. Calc. for $C_{27}H_{27}NO_7$: C, 67.91; H, 5.70; N, 2.93. Found: C, 67.86; H, 5.51; N, 2.99.

Compound **9** appeared as the slower-moving component: wt. 8.3 g (45%), m.p. 142–143°, $[\alpha]_D^{25}$ −3.3° (*c* 0.3, chloroform); ν_{max}^{Nujol} 3400–3300 (OH, NH), 1700 (ester), 1680 and 1500 (amide), and 745, 720, and 690 cm^{-1} (phenyl); n.m.r. data: τ 2.02–2.65 (5 H, COPh), 2.71 and 2.78 (10 H, 2 s, 2 Ph), and 4.96 (2 H, s, CO_2CH_2Ph). Other n.m.r. data are given in Table I.

Anal. Calc. for $C_{27}H_{27}NO_7$: C, 67.91; H, 5.70; N, 2.93. Found: C, 67.88; H, 5.71; N, 2.95.

Further elution of the column yielded 1.4 g of **7** and the starting material **8** (360 mg).

Benzyl 3-O-benzoyl-2-(benzyloxycarbonyl)amino-2-deoxy-4-O-mesyl-β-D-xylopyranoside (**10**). — To an ice-cooled solution of **9** (3.9 g) in pyridine (20 ml) was added methanesulfonyl chloride (1.2 g), and the mixture was kept for 4 h at 0°. The mixture was evaporated, the residue extracted with chloroform, and the extract successively washed with 2M hydrochloric acid, M sodium carbonate, and water, dried (sodium sulfate), and evaporated to give a crystalline product. Recrystallization from ethanol afforded **10** (4.2 g, 93%) as needles, m.p. 149°, $[\alpha]_D^{25}$ −37° (*c* 0.3, chloroform); ν_{max}^{Nujol} 3320 (NH), 1730 (ester), 1700 and 1530 (amide), 1180 (SO_2), and 730, 700, and 690 cm^{-1} (phenyl); n.m.r. data: τ 1.98–2.68 (5 H, COPh), 2.71 and 2.76 (10 H, 2 Ph), 4.97 (2 H, s, CO_2CH_2Ph), and 3.70 (3 H, Me). Other n.m.r. data are given in Table I.

Anal. Calc. for $C_{28}H_{29}NO_9S$: C, 60.53; H, 5.26; N, 2.52. Found: C, 60.58; H, 5.34; N, 2.52.

Benzyl 3-O-benzoyl-2-(benzyloxycarbonyl)amino-2-deoxy-4-O-mesyl-α-D-xylopyranoside (**12**). — To an ice-cooled solution of **11** (500 mg) in pyridine (7 ml) was added methanesulfonyl chloride (200 mg). The mixture was kept for 4 h at 0°, and evaporated to a syrup which was extracted with chloroform. The extract was successively washed with 2M hydrochloric acid, M sodium carbonate, and water, dried (sodium sulfate), and evaporated to a crystalline mass (560 mg, 96%) that migrated as a single spot in t.l.c. Recrystallization from ethanol gave needles, m.p. 115–116°, $[\alpha]_D^{25}$ +103° (*c* 0.3, chloroform); ν_{max}^{Nujol} 3280 (NH), 1720 (ester), 1680 and 1510 (amide), 1170 (SO_2), and 730, 710, and 690 cm^{-1} (phenyl); n.m.r. data: τ 1.90–2.60 (5 H, COPh), 2.69 and 2.87 (10 H, 2 Ph), 5.12 (2 H, s, CO_2CH_2Ph), and 3.18 (3 H, s, Me). Other n.m.r. data are given in Table I.

Anal. Calc. for $C_{28}H_{29}NO_9S$: C, 60.53; H, 5.26; N, 2.52. Found: C, 60.51; H, 5.19; N, 2.49.

Benzyl 4-azido-3-O-benzoyl-2-(benzyloxycarbonyl)amino-2,4-dideoxy-α-L-arabinopyranoside (**13**). — To a solution of **10** (950 mg) in dry *N,N*-dimethylformamide (10 ml) was added sodium azide (950 mg), and the mixture was heated with stirring for 10 h at 120°. It was then cooled, the salts were filtered off, and the filtrate was evaporated to a syrup which was extracted with benzene. The extract was successively washed with 2M hydrochloric acid, M sodium carbonate, and water, dried (sodium sulfate), and evaporated to a syrup which was purified on a column of silica gel (20 g) with chloroform. Compound **13** was obtained as needles, 780 mg (91%), m.p. 114°, $[\alpha]_D^{25}$ −25.5° (*c* 0.3, chloroform); ν_{max}^{Nujol} 3320 (NH), 2090 (N_3), 1730 (ester), 1700 and 1520 (amide), and 730, 700, and 690 cm^{-1} (phenyl); n.m.r. data: τ 1.91–2.64 (5 H, COPh), 2.73 and 2.78 (10 H, 2 Ph), 4.96 (2 H, s, CO_2CH_2Ph), and 5.08 (1 H, d, $J_{2,NH}$ 9.0 Hz, NH). Other n.m.r. data are given in Table 1.

Anal. Calc. for $C_{27}H_{26}N_4O_6$: C, 64.53; H, 5.22; N, 11.15. Found: C, 64.51; H, 5.33; N, 11.08.

Benzyl 4-azido-2-(benzyloxycarbonyl)amino-2,4-dideoxy-α-L-arabinopyranoside (**14**). — To a solution of **13** (1.7 g) in methanol (120 ml) was added sodium metal (50 mg), and the mixture was kept for 10 min at room temperature, and then treated with Amberlite IR-120 ion-exchange resin. The solution was evaporated to give a crystalline mass. Recrystallization from ethanol afforded the title compound **14**, wt 1.3 g (96%), m.p. 185°, $[\alpha]_D^{25}$ −110° (*c* 0.4, methanol); ν_{max}^{Nujol} 3300 (OH, NH), 2110 (N_3), 1690 and 1540 (amide), and 720 and 690 cm^{-1} (phenyl); n.m.r. data: τ 2.64 (10 H, 2 Ph), 4.90 (2 H, s, CO_2CH_2Ph), 5.08 (1 H, d, $J_{2,NH}$ 8.0 Hz, NH), and 5.41 (1 H, d, $J_{1,2}$ 4.5 Hz, H-1).

Anal. Calc. for $C_{20}H_{22}N_4O_5$: C, 60.29; H, 5.57; N, 14.06. Found: C, 60.30; H, 5.57; N, 14.01.

N,N'-Bis(benzyloxycarbonyl)-α-Prumycinide (**15**). — The azido compound **14** (100 mg) was dissolved in 1,4-dioxane (12 ml) and triethylamine (12 ml), 10% Pd/C catalyst (10 mg) was added, and hydrogen was bubbled through the mixture, with stirring, for 35 min at room temperature. The catalyst was removed by filtration, and the filtrate was evaporated to give a crystalline mass which was used for the next reaction without purification. To a solution of the amino compound in dry 1,4-dioxane (95 ml) was added *N*-[*N*-(benzyloxycarbonyl)-D-alaninoyloxy]succinimide (100 mg), and the mixture was stirred at room temperature while the progress of the reaction was monitored by t.l.c.; after 1 h, the starting material was no longer detectable. The mixture was treated with Amberlite IR-410 (OH^-) ion-exchange resin, and evaporated to a syrup, which was extracted with chloroform. The extract was washed with water, dried, and evaporated to a syrup. The product was chromatographed on a column of silica gel (10 g) with 100:1 chloroform–methanol, to give 120 mg (83%) of compound **15**; after recrystallization from ether, this was obtained as needles, m.p. 124–125°, $[\alpha]_D^{25}$ −44° (*c* 0.4, methanol); ν_{max}^{Nujol} 3420–3320 (OH, NH), 1700, 1660, and 1525 (amide), and 730–690 cm^{-1} (phenyl); n.m.r. data: τ 2.71 (15 H,

3 Ph), 3.38, 4.38, and 4.50 (3 H, 3 NH), 4.93 (4 H, s, 2 CO_2CH_2Ph), 5.27 (1 H, d, $J_{1,2}$ 2.0 Hz, H-1), and 8.71 (3 H, d, $J_{Me,H}$ 6.0 Hz, Me).

Anal. Calc. for $C_{31}H_{35}N_3O_8$: C, 64.46; H, 6.11; N, 7.28. Found: C, 64.50; H, 6.11; N, 7.32.

Benzyl 4-(N-benzyloxycarbonyl-L-alanylamino)-2-(benzoylxycarbonyl)amino-2,4-dideoxy-α-L-arabinopyranoside (**16**). — Selective reduction of compound **14** (400 mg) in 1,4-dioxane (48 ml) and triethylamine (48 ml) with hydrogen in the presence of 10% Pd/C catalyst (40 mg), and subsequent coupling with *N*-[*N*-(benzyloxycarbonyl)-L-alaninoyloxy]succinimide (600 mg) in 1,4-dioxane (30 ml), by the same procedure as just described, afforded the title compound; wt. 510 mg (88%), m.p. 89–90°, $[\alpha]_D^{25}$ −63.5° (*c* 0.3, chloroform); ν_{max}^{Nujol} 3400–3240 (OH, NH), 1680, 1640, and 1500 (amide), and 730 and 690 cm^{-1} (phenyl); n.m.r. data: τ 2.62 and 2.64 (10 H, 2 Ph), 3.42, 3.94, and 4.25 (3 H, 3 NH), 4.93 and 4.96 (4 H, 2 s, 2 CO_2CH_2Ph), 5.30 (1 H, d, $J_{1,2}$ 1.5 Hz, H-1), and 8.76 (3 H, d, $J_{Me,H}$ 7.0 Hz, Me).

Anal. Calc. for $C_{31}H_{35}N_3O_8$: C, 64.46; H, 6.11; N, 7.28. Found: C, 64.51; H, 5.98; N, 7.30.

Benzyl 2,4-di-(N-benzyloxycarbonyl-D-alanylamino)-2,4-dideoxy-α-L-arabinopyranoside (**17**). — Compound **14** (200 mg) was dissolved in ethanol (30 ml); 10% Pd/C catalyst (200 mg) was added, and hydrogen was bubbled through for 1 h while the solution was stirred at room temperature. After removal of the catalyst by filtration, the filtrate was evaporated to a crystalline mass which was used for the next reaction. The amino compound obtained was coupled with *N*-[*N*-(benzyloxycarbonyl)-D-alaninoyloxy]succinimide (200 mg) as already described, to give compound **17**; wt. 295 mg (91%), m.p. 194–195°, $[\alpha]_D^{25}$ −33° (*c* 0.4, methanol); ν_{max}^{Nujol} 3400–3270 (OH, NH), 1695, 1665, and 1530 (amide), and 730 and 690 cm^{-1} (phenyl); n.m.r. data: τ 2.65 (15 H, 3 Ph), 4.91 (4 H, s, 2 CO_2CH_2Ph), 5.34 (1 H, d, $J_{1,2}$ 2.0 Hz, H-1), 8.64, and 8.66 (6 H, 2 d, $J_{Me,H}$ 7.5 Hz, 2 Me).

Anal. Calc. for $C_{34}H_{40}N_4O_9$: C, 62.95; H, 6.22; N, 8.64. Found: C, 63.25; H, 6.21; N, 8.50.

Prumycin dihydrochloride (**1**). — Compound **15** (300 mg) was dissolved in methanol (70 ml) and water (7 ml), 10% Pd/C catalyst (300 mg) was added, and hydrogen was bubbled through while the mixture was stirred for 30 min at room temperature. The catalyst was removed by filtration and washed with water (10 ml). After evaporation of the methanol below 30°, 10% Pd/C (200 mg), acetic acid (0.5 ml), and water (15 ml) were added to the residual solution. Hydrogen was again bubbled through the mixture, with stirring for 1.5 h at room temperature, the course of the reaction being monitored by t.l.c. The catalyst was filtered off, and 0.1M hydrochloric acid (10.35 ml) was added. The solution was evaporated below 30°, to give an amorphous mass of **1** (150 mg, 93%), $[\alpha]_D^{25}$ +95° (*c* 0.5, equil., methanol); lit.[8] $[\alpha]_D^{20}$ −98° (*c* 0.7, methanol). The i.r. and n.m.r. spectra, and the R_F values of the thin-layer chromatograms were all identical with those of an authentic sample.

The crystalline β anomer was isolated from methanol, m.p. 195–199° (dec.) [lit.[2] m.p. 198–200° (dec.)]; n.m.r. data (D_2O): τ 4.56 (d, $J_{1,2}$ 3.8 Hz, H-1), 5.18 (d,

$J_{1',2'}$ 9.5 Hz, H-1'), 6.59 (dd, $J_{1,2}$ 3.8 Hz, $J_{2,3}$ 10.0 Hz, H-2), 6.91 (dd, $J_{1',2'}$ 9.5 Hz, $J_{2',3'}$ 11.0 Hz, H-2'), and 8.49 (3 H, d, $J_{Me,H}$ 7.2 Hz, Me).

Anal. Calc. for $C_8H_{17}N_3O_4 \cdot 2\ HCl \cdot H_2O$: C, 30.95; H, 6.95; N, 13.55. Found: C, 30.81; H, 7.15; N, 13.28.

4-(L-Alanylamino)-2-amino-2,4-dideoxy-L-arabinopyranose dihydrochloride (**2**). — By the same procedure described in the previous section, all of the protecting groups of compound **16** (300 mg) were removed. The dihydrochloride of the anomeric mixture was obtained; colorless, amorphous; wt. 160 mg (quantitative yield), $[\alpha]_D^{25}$ −44° (*c* 1.6, equil.; methanol); n.m.r. data (D_2O): τ 4.56 (d, $J_{1,2}$ 3.8 Hz, H-1), 5.18 (d, $J_{1',2'}$ 9.5 Hz, H-1'), 6.59 (dd, $J_{1,2}$ 3.8 Hz, $J_{2,3}$ 10.0 Hz, H-2), 6.90 (dd, $J_{1',2'}$ 9.5 Hz, $J_{2',3'}$ 11.0 Hz, H-2'), and 8.49 (3 H, d, $J_{Me,H}$ 7.2 Hz, Me).

Anal. Calc. for $C_8H_{17}N_3O_4 \cdot 2\ HCl \cdot H_2O$: C, 30.95; H, 6.95; N, 13.55. Found: C, 30.70; H, 7.24; N, 13.35.

2,4-Bis(D-alanylamino)-2,4-dideoxy-L-arabinopyranose dihydrochloride (**3**). — To a solution of **17** (300 mg) in methanol (60 ml), water (4 ml), and acetic acid (1 ml) was added 10% Pd/C catalyst (300 mg), and hydrogen was bubbled through for 2 h while the solution was stirred at room temperature. The catalyst was removed by filtration, and the filtrate was evaporated below 30° to give a syrup which was dissolved in water (15 ml); 0.1M hydrochloric acid (9 ml) was added to the solution, and the mixture was again hydrogenated with 10% Pd/C (150 mg), with stirring, for 2 h at room temperature. The solution was evaporated below 35° to a crystalline product which was recrystallized from ethanol, affording the title compound **3** (150 mg, 92%), m.p. 190–200° (dec.), $[\alpha]_D^{25}$ +33° (*c* 0.4, equil., methanol); n.m.r. data (D_2O): τ 4.76 (d, $J_{1,2}$ 3.0 Hz, H-1), 5.17 (d, $J_{1',2'}$ 10.0 Hz, H-1'), and 8.47 and 8.49 (6 H, 2 d, $J_{Me,H}$ 7.5 Hz, 2 Me).

Anal. Calc. for $C_{11}H_{22}N_4O_5 \cdot 2\ HCl$: C, 36.62; H, 6.66; N, 15.53. Found: C, 36.30; H, 6.95; N, 15.22.

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