Carbohydrate Research, 60 (1978) 75–84

A SYNTHESIS OF PRUMYCIN*

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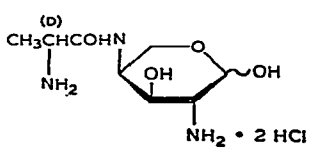
(Received December 14th, 1976; accepted for publication in revised form, April 5th, 1977)

ABSTRACT

Prumycin, 4-D-(alanylamino)-2-amino-2,4-dideoxy-L-arabinose, was synthesized from D-xylose by nine-step conversion via a key intermediate, benzyl 2,3-anhydro-4-azido-4-deoxy-β-L-ribopyranoside. An isomer of prumycin, 4-D-alanylamino-3-amino-3,4-dideoxy-L-xylose, was also synthesized from the same intermediate.

INTRODUCTION

To study the relationship between configuration of the aminosugar moiety in aminosugar-containing antibiotics and biological activity, we were interested in prumycin (**1**), a new antifungal antibiotic, which was found in 1971 by Hata *et al.* to have a remarkable biological activity[2,3]. Its structure was determined to be 4-D-(alanylamino)-2-amino-2,4-dideoxy-L-arabinose by Ohmura *et al.*[4] and ascertained also by a chemical synthesis[5], in which methyl 2-azido-2-deoxy-α-D-allopyranoside was converted into **1** in eleven steps, including the inversion of the reduced and unreduced terminal of the sugar chain. We have recently communicated a facile synthesis of **1** from D-xylose[6], and now present details of the synthesis, together with synthesis of one of the isomers (**12**) having the L-*xylo* configuration.



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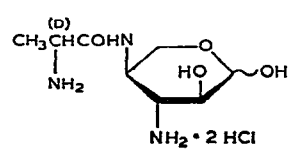

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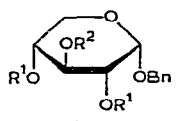
RESULTS AND DISCUSSION

Two amino groups were introduced stepwise at C-4 and C-2 of D-xylose by selective azidolysis of the corresponding sulfonates, and by ammonolysis of a key intermediate, benzyl 2,3-anhydro-4-azido-4-deoxy-β-L-ribopyranoside (**4**), respec-

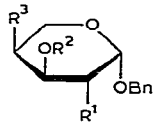
*Aminosugars XXVII. For Part XXVI, see ref. 1.

tively. At first, compound **4** was prepared in the manner reported by Jones *et al.*[7] for the corresponding methyl glycoside. The methylsulfonyloxy group at C-4 in benzyl 2,3,4-tri-*O*-methylsulfonyl-α-D-xylopyranoside (**2**) was substituted selectively by use of sodium azide in *N*,*N*-dimethylformamide. In the n.m.r. spectrum of the resulting 4-azido derivative (**3**), the $J_{3,4}$, $J_{4,5_a}$, and $J_{4,5_e}$ values are smaller than those of **2**, as shown in Table I, indicating that inversion had occurred at C-4. Compound **3** reacted with potassium hydroxide in methanol–water to give a mixture of 2,3-epoxides having L-*ribo* and L-*lyxo* configurations (**4** and **5**), respectively. Although the same treatment of the corresponding methyl glycoside gave exclusively the L-*ribo* epoxide[7], in this instance, compound **5** was also formed in relatively high yield (about 30% of the epoxide mixture isolated). The difference in the selectivity in the formation of epoxides seems to be due to the effect of the aglycon on the rate of hydrolysis of the methylsulfonyl groups at C-2 and C-3. The separation of these two epoxides was very difficult, and only **4** could be obtained pure, and then only in poor yield, by crystallization from methanol at about −30°.

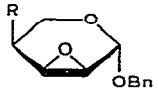
Selective preparation of **4** was also achieved by treating benzyl 3-*O*-acetyl-4-azido-4-deoxy-2-*O*-p-tolylsulfonyl-β-L-arabinopyranoside (**7**) with sodium methoxide; compound **7** was derived in good yield from the 2,4-di-*O*-*p*-tolylsulfonyl derivative[8] (**6**) by selective azidolysis. The total yield (50%) of **4** from benzyl α-D-xylopyranoside was better than in the foregoing one (15%). The structure of **4** was determined from the $J_{1,2}$ (<0.5 Hz) and $J_{3,4}$ (3.8 Hz) couplings, indicating *cis* and *trans* relation-



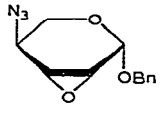
2 $R^1 = R^2 =$ Ms
6 $R^1 =$ Ts, $R^2 =$ Ac



3 $R^1 =$ OMs, $R^2 =$ Ms, $R^3 = N_3$
7 $R^1 =$ OTs, $R^2 =$ Ac, $R^3 = N_3$
14 $R^1 = N_3$, $R^2 = H$, $R^3 = N_3$
16 $R^1 = NH_2$, $R^2 = H$, $R^3 = N_3$
18 $R^1 =$ NHAc, $R^2 =$ Ac, $R^3 = N_3$
19 $R^1 =$ NH-t-BOC, $R^2 = H$, $R^3 = N_3$
20 $R^1 =$ NH-t-BOC, $R^2 = H$, $R^3 =$ NHCOR′a



4 R = N_3
8 R = NH_2
9 R = NHCOR′



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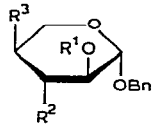

10 $R^1 = H$, $R^2 = N_3$, $R^3 =$ NHCOR′
11 $R^1 =$ Ac, $R^2 = N_3$, $R^3 =$ NHCOR′
13 $R^1 = H$, $R^2 = N_3$, $R^3 = N_3$
15 $R^1 = H$, $R^2 = NH_2$, $R^3 = N_3$
17 $R^1 =$ Ac, $R^2 =$ NHAc, $R^3 = N_3$

R′: a = CHCH$_3$(D) (NHCO$_2$Bn), b = Bz, c = t-BOC, d = Ac

t-BOC = $Me_3COC(=O)$—

TABLE I

N.M.R. CHEMICAL SHIFTS (δ) AND COUPLING CONSTANTS (Hz) (100 MHz, $CDCl_3$)

Compound	*H-1*	*H-2*	*H-3*	*H-4*	*H-5a*[a]	*H-5e*[b]	*$PhCH_2O$*	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5a}$	$J_{4,5e}$	$J_{5a,5e}$	*Other signals*
2	5.13	4.56	5.08	4.66	3.79	4.01	4.53, 4.75	3.8	10.0	10.0	10.0	6.0	11.0	2.88, 3.11, 3.14(Ms)
3	5.15	4.81	5.12	4.27	3.69	3.98	4.51, 4.73	2.1	6.3	2.3	1.0	1.0	7.5	2.97, 3.13(Ms)
4	4.99	3.14		←3.3–3.6→		3.89	4.49, 4.74	<0.5	3.8	3.8[b]	3.0[b]	3.8 (4.5[b])	12.3[b]	
6	4.89	4.42	5.44	–4.57(1H), 3.77(2H)[c]			4,40, 4.67	3.5	9.5	9.5	—[d]	—[d]	—[d]	1.68(Ac), 2.47(CH_3 of Ts)
7	5.00	4.80	5.32	4.05	3.60	3.92	4.43, 4.68	3.5	10.2	3.9	1.8	1.7	12.4	1.90(Ac), 2.44(CH_3 of Ts)
8	4.89	3.13	3.34	3.07	3.79	3.14	4.47, 4.73	<0.5	3.8	5.2	4.3	2.5	11.8	1.94(NH_2)
9a	4.94	3.11	3.41	4.30	3.85	3.24	4.47, 4.73	<0.5	3.8	5.4	3.6	<0.5	12.2	5.66(NH, 7.5[e]), 6.89(NH, 7.5)
9b	5.02	3.20	3.56	4.54	3.97	3.44	4.53, 4.78	<0.5	3.7	5.8	3.0	<0.5	12.3	6.86(NH, 9.5)
9c	4.93	3.11	3.44	3.94	3.83	3.29	4.49, 4.83	<0.5	3.8	5.9	3.8	<0.5	11.6	5.25(NH, 7.5)
9d	4.99	3.15	3.47	4.32	3.88	3.31	4.53, 4.76	<0.5	4.3	5.3	3.6	<0.5	12.1	6.29(NH, 8.0), 2.00(Ac)
11a	4.42	4.86	3.59	3.85	←~3.35→		4.48, 4.77	5.8	8.0	8.0	—[d]	—[d]	—[d]	5.67(NH, 7.4), 6.95(NH), 2.00(Ac), 1.33(CH_3 of Ala)
15	4.29	~3.25	2.66	~3.35	~3.25	5.03	4.55, 4.88	6.9	8.9	8.9	10.5[b]	4.5[b]	10.5[b]	1.35(NH_2)
17	4.57	4.44	3.54	3.11	3.38	3.89	4.50, 4.75	4.5	6.6	6.7	12.0	3.8	12.0	5.90(NH, 8.6), 1.59, 2.01(Ac)
18	4.89	4.60	5.21	3.91	3.69	3.93	4.44, 4.69	3.3	10.5	3.6	12.4	1.0	12.4	5.60(NH), 1.88, 2.08(Ac)

[a]H-5a and H-5e designate the axially and equatorially oriented protons on C-5, respectively, in the $^4C_1$(L) or $^0H_5$(L) conformation. [b]Obtained by using $Pr(FOD)_3$ as shift reagent. [c]These protons show a typical AB_2 pattern. [d]Could not be obtained from the spectrum. [e]Coupling constants in Hz.

ships[9-11], respectively, of the corresponding, vicinal, proton pairs. The $J_{3,4}$ value could be determined in the presence of a shift reagent, as shown in Table I. On the other hand, the values for $J_{1,2}$ (1.8 Hz) and $J_{3,4}$ (<0.5 Hz) of **5**, which was also selectively prepared through another route[12], show an inverse relationship of these two pairs of vicinal protons in comparison with **4**.

Synthetically, it is convenient to introduce the amino group at C-2 after introduction of the D-alanyl group at the N-4, although cleavage of 2,3-anhydro-ribopyranosides normally occurs at C-3, giving *xylo* derivatives[13]. Selective hydrogenation of **4** in the presence of platinum oxide gave the corresponding 4-amino derivative (**8**) in quantitative yield, and this was converted into *N*-acyl derivatives (**9a–c**) in good yields. As expected, **9a–c** gave exclusively the 3-azido derivatives (**10a–c**) in 85–90% yields by azidolysis in 2-methoxyethanol. These results were also consistent with the fact that **9a–d** exist almost exclusively in the $^0H_5$ (L), conformation, which is deduced from the relatively large values for $J_{3,4}$ of **9a–d** (5.2–5.9 Hz, see Table I)[10]. This conformation is unfavorable[13] for attack of nucleophiles at C-2. The structures of **10a–c** were ascertained by the values for $J_{1,2}$ (5.8–7.5 Hz) and $J_{2,3}$ (7.9–9.3 Hz) for these compounds and for their 2-*O*-acetyl derivatives (**11a–c**). Compound **10a** was hydrogenolyzed in dilute hydrochloric acid–ethanol to give 4-D-(alanylamino)-3-amino-3,4-dideoxy-L-xylose dihydrochloride (**12**) in quantitative yield.

The next experiments involved direct azidolysis and ammonolysis of **4**. In both instances, two isomers were obtained, with preponderant formation of the 3-azido (**13**) or 2-amino (**16**) derivatives. In the first instance, **13** was isolated crystalline in 60% yield, and its structure was inferred from the value of $J_{1,2}$ (6.6 Hz). Ammonolysis of **4** gave a preponderance of the 2-amino derivative, so that the ratio of 3-amino (**15**) to 2-amino derivative (**16**) was lower (2:3) than that in the case of azidolysis (3:1. Considering the dipole–dipole interactions in the transition states, these results may be attributed to the difference of ionic character of the two nucleophiles. The abnormal substitution at C-2 of **4**, in comparison with exclusive substitution at C-3 of **9a–c**, seems to be due not only to the electrostatic effect of the azido group at C-4, but also to the different conformational equilibria. Whereas **9a–d** exist exclusively in the $^0H_5$(L) conformation already described, nearly one half of **4** adopts the $^5H_0$(L) conformation, which favors the initiation of substitution at C-2. The conformational equilibrium of **4** was estimated from the $J_{3,4}$ value (3.8 Hz), assuming those for the $^0H_5$ and $^5H_0$(L) conformations to be 5.9 (maximum value of those for **9a–d**) and[10] 1.7 Hz, respectively*. although the conformational equilibrium must be expected to change slightly in the presence of the shift reagent.

The amines **15** and **16** were separated on a column of silica gel with benzene–

*The conformational equilibrium deduced for **4** seems to be supported also by the $J_{4,5e}$ coupling-constant. The latter accords with an equatorial proton at C-5 in the $^0H_5$ (L) conformation (see Table I), and such a proton is expected to have a larger chemical-shift than an axial one. Although only one such case[9] is known to us, and even then the assignment involves some ambiguity, it is very significant that the $J_{3,4}$ and $J_{4,5e}$ values both lead to the same estimated ratio of two half-chair conformers.

2-propanol or benzene–pyridine as the solvent system. The structures of **15** and **16** were deduced from their n.m.r. spectra and from the spectra of their *N,O*-diacetyl derivatives (**17** and **18**). The coupling constants of **15** and **17** shown in Table I clearly indicate the *xylo* configuration, but the conformation of **17** seems to deviate from $^1C_4$ (L), judging from the slightly smaller coupling-constants in comparison with those of **15**. The coupling constants of **18** are typical for the *arabino* configuration, as shown already for **3**. These configurational assignments were also supported by the chemical shifts of H-2 and H-3 in **17** and **18**, considering the larger deshielding effect of the acetoxyl group relative to the acetamido group, and the lower chemical-shift of an equatorial ring proton compared with an axial one[14]. The slower moving, 2-amino derivative (**16**) was converted into the *N-tert*-butoxycarbonyl derivative (**19**) in 65% yield by treatment with *tert*-butyl azidoformate. As already reported[6], compound **19** could be obtained from the mixture of **15** and **16** in fairly good yield. After reduction of the azido group, **19** was then condensed with *N*-benzyloxycarbonyl-D-alanine by the use of *N,N'*-dicyclohexylcarbodiimide to give **20** in 65% yield. The protecting groups of the coupled product (**20**) were removed by successive treatment with formic acid and then hydrogenolysis in dilute hydrochloric acid–methanol–water, to give prumycin as its dihydrochloride (**1**) in high yield. Physical data, chromatographic behavior, and spectroscopic data were identical with values for the natural[2] compound and of the compound synthesized by Kuzuhara and Emoto[5].

EXPERIMENTAL

General methods. — Melting points were determined with a Mel-Temp melting point apparatus and not corrected. Optical rotations were measured in chloroform at *c* 1.0, unless otherwise stated, using a 0.5-dm tube with a Carl Zeiss LEP-Al polarimeter. I.r. spectra were recorded with a Hitachi Model EPI-G2 grating spectrometer. N.m.r. spectra were recorded with JNM-4H-100 and JNM PS-100 spectrometer in chloroform-*d* containing tetramethylsilane as the internal reference. Chemical shifts and coupling constants are recorded in δ and Hz units, and i.r. frequencies in cm^{-1}. Evaporations were conducted under diminished pressure. The products were recrystallized from ethanol unless otherwise stated.

*Benzyl 2,3,4-tri-*O*-methylsulfonyl-α-*D*-xylopyranoside* (**2**). — To a cold solution of benzyl α-D-xylopyranoside (50 g, 0.21 mol) in pyridine (400 ml) was added methanesulfonyl chloride (103 g, 0.90 mol) dropwise with stirring. Stirring was continued overnight in an ice–water bath and then for several h at room temperature. The solution was poured into ice–water with vigorous stirring and the resulting syrup was kept for a few h to crystallize. The crystals were filtered off and recrystallized from chloroform–ethanol to yield 86 g (90%) of **2**, m.p. 134–136°, $[\alpha]_D^{23}$ +99.6°; ν_{max}^{KBr} 1370 and 1180.

Anal. Calc. for $C_{15}H_{22}O_{11}S_3$: C, 37.96; H, 4.67; S, 20.27. Found: C, 38.13; H, 4.59; S, 20.09.

*Benzyl 4-azido-4-deoxy-2,3-di-*O*-methylsulfonyl-β-L-arabinopyranoside* (**3**). —

A mixed solution of **2** (50 g, 0.10 mol), sodium azide (8.2 g, 0.13 mol), and urea (1.5 g) in *N,N*-dimethylformamide containing 10% of water (550 ml) was heated at 110–120° in an oil bath for 18–20 h, and was then evaporated to dryness. The residue was extracted with chloroform, and the extract was washed with water, dried with anhydrous sodium sulfate, and evaporated to give syrupy **3**; yield 42 g (95%). This syrup was purified by column chromatography on silica gel with 200:1 benzene–methanol as an eluant; $[\alpha]_D^{23}$ +146°; ν_{max}^{NaCl} 2260, 1370, and 1185.

Anal. Calc. for $C_{14}H_{19}N_3O_8S_2$: C, 39.90; H, 4.54; N, 9.97; S, 15.52. Found: C, 40.09; H, 4.45; N, 9.94; S, 15.18.

*Benzyl 2,3-anhydro-4-azido-4-deoxy-β-*L*-ribopyranoside* (**4**). — A. *From* **3**. A suspension of **3** (12 g, 29 mmol) and potassium hydroxide (10 g, 180 mmol) in aqueous methanol (80%, 200 ml) was refluxed for 2 h in a water bath. The solution was cooled and extracted three times with benzene after evaporation of the methanol. The dried extracts were evaporated to a syrup, which was purified on a column of silica gel with benzene as an eluant. The fraction first eluted was a mixture of the epoxides (**4** and **5**), from which only **4** crystallized upon cooling the methanolic solution of the mixture at −30°; yield, 1.3 g (18%), m.p. 51–52°, $[\alpha]_D^{23}$ +17.0°; ν_{max}^{KBr} 2200, 755, and 750. The yield of the epoxide mixture was about 60%.

Anal. Calc. for $C_{12}H_{13}N_3O_3$: C, 58.29; H, 5.30; N, 17.00. Found: C, 58.22; H, 5.29; N, 17.30.

B. *From benzyl 3-O-acetyl-4-azido-4-deoxy-2-*O*-p-tolylsulfonyl-β-*L*-arabinopyranoside* (**7**). To M sodium methoxide in methanol (18 ml) was added **7** (1.6 g, 3.8 mmol) at room temperature. After 1 h, water (20 ml) was added to the solution, and methanol was evaporated off. The further isolation was performed as just described, but column purification was not necessary; yield 0.81 g (87%), m.p. 50–51°.

*Benzyl 3-*O*-acetyl-2,4-di-*O*-*p*-tolylsulfonyl-α-*D*-xylopyranoside* (**6**). — Benzyl 2,4-di-*O*-p-tolylsulfonyl-α-D-xylopyranoside[7] was acetylated conventionally with acetic anhydride in dry pyridine to give **6**; yield 90%, m.p. 104–107°, $[\alpha]_D^{23}$ +73.9°; ν_{max}^{KBr} 1760, 1600, 1375, 1230, and 1185.

Anal. Calc. for $C_{28}H_{30}O_{10}S_2$: C, 56.93; H, 5.12; S, 10.86. Found: C, 56.85; H, 5.14; S, 10.59.

*Benzyl 3-*O*-acetyl-4-azido-4-deoxy-2-*O*-p-tolylsulfonyl-β-*L*-arabinopyranoside* (**7**). — Azidolysis of **6** was performed by the same procedure as for **3** to give **7**; yield 95%, m.p. 74–76°, $[\alpha]_D^{23}$ +124°; ν_{max}^{KBr} 2150, 1755, 1595, 1375, 1230, and 1185.

Anal. Calc. for $C_{19}H_{21}N_3O_6S$: C, 54.40; H, 5.05; N, 10.01; S, 7.64. Found: C, 54.35; H, 5.03; N, 9.65; S, 6.85.

*Benzyl 4-amino-2,3-anhydro-4-deoxy-β-*L*-ribopyranoside* (**8**). — Compound **4** (4 g) was hydrogenolyzed in methanol (60 ml) in the presence of platinum oxide (100 mg) for a few h. After removal of the catalyst by filtration the filtrate was evaporated to give a clear syrup in quantitative yield. The syrup was purified on a column of silica gel by using 19:1 benzene–methanol as eluant; $[\alpha]_D^{23}$ +66.6° (*c* 1.4, methanol).

Anal. Calc. for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.92; H, 6.95; N, 6.23.

*Benzyl 2,3-anhydro-4-(*N*-benzyloxycarbonyl-*D*-alanyl)amino-4-deoxy-β-*L*-ribopyranoside* (**9a**). — To a solution of **8** (1.2 g, 5.5 mmol) and *N*-benzyloxycarbonyl-D-alanine (2.0 g, 6.6 mmol) in pyridine (25 ml) was added *N,N'*-dicyclohexylcarbodiimide (1.7 g, 8.2 mmol) at 0°. The solution was stirred for 24 h at room temperature. The separated *N,N'*-dicyclohexylurea was filtered off and the filtrate was poured into ice–water. A white precipitate was filtered and dissolved in chloroform. The chloroform solution was washed successively with saturated sodium hydrogencarbonate, M sulfuric acid, and water, and then dried. Evaporation of the filtrate gave a white crystalline residue that was recrystallized to give **9a**; yield 1.7 g (65%), m.p. 155–157°, $[\alpha]_D^{23}$ +42.0°; ν_{max}^{KBr} 3290, 1695, 1645, 1540, and 695.

Anal. Calc. for $C_{23}H_{26}N_2O_6$: C, 64.77; H, 6.15; N, 6.57. Found: C, 64.78; H, 6.24; N, 6.68.

*Benzyl 2,3-anhydro-4-benzamido-4-deoxy-β-*L*-ribopyranoside* (**9b**). — Compound **8** was benzoylated conventionally with benzoyl chloride in dry pyridine to give **9b** in 85% yield, m.p. 145–146°, $[\alpha]_D^{23}$ +131°; ν_{max}^{KBr} 3300, 1630, 1530, and 695.

Anal. Calc. for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.21; H, 5.88; N, 4.28.

*Benzyl 2,3-anhydro-4-(*tert*-butoxycarbonyl)amino-4-deoxy-β-*L*-ribopyranoside* (**9c**). — A solution of **8** (1.6 g, 7.2 mmol), *tert*-butylazidoformate (1.2 g, 8.0 mmol), and triethylamine (2.2 g, 2.2 mmol) in dry 1,4-dioxane (20 ml) was heated overnight (about 20 h) at 60–70°. The solution was evaporated to dryness and the residue subjected directly to column chromatography on silica gel with benzene or benzene–methanol (200:1) as the eluant. Evaporation of the eluate gave a clear syrup that crystallized from ethanol to yield **9c**; 1.0 g (43%), m.p. 115–116°, $[\alpha]_D^{23}$ +56.3°; ν_{max}^{KBr} 3440, 1695, 1485, and 705.

Anal. Calc. for $C_{17}H_{23}NO_5$: C, 63.53; H, 7.21; N, 4.36. Found: C, 63.73; H, 7.24; N, 4.28.

*Benzyl 4-acetamido-2,3-anhydro-4-deoxy-β-*L*-ribopyranoside* (**9d**). — Compound **8** was acetylated as before with acetic anhydride in dry pyridine to give **9d** in 90% yield, m.p. 155–157°, $[\alpha]_D^{23}$ +91.3°; ν_{max}^{KBr} 3310, 1635, 1540, and 700.

Anal. Calc. for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.29; H, 6.47; N, 5.11.

General method for azidolysis of 2,3-anhydro sugars. — Azidolysis of **9a**, **9b**, and **9c** were performed under the same conditions, as described here. A suspension of the 2,3-anhydro derivative (1 mmol), sodium azide (4 mmol), and ammonium chloride (2 mmol) in 2-methoxyethanol–water (14:1, 14 ml) was heated for 7–8 h at 110°. The solution was evaporated directly and the residue extracted with chloroform. The extract was washed with water, dried, and evaporated to give a syrupy or crystalline residue, which was crystallized or recrystallized from ethanol. Compounds **9a**, **9b**, and **9c** gave exclusively the 3-azido derivative (**10a**, **10b**, and **10c**) in 85–90% yield.

Compound **10a** had m.p. 166–167°, $[\alpha]_D^{23}$ +74.0°; ν_{max}^{KBr} 3300, 2100, 1685, 1665, 1525, and 695; n.m.r.: 1.35 (d, 2H, $J_{CH_3,H\alpha}$ 7.0, CH_3), 4.19 (quintet, Hα in Ala), 4.37 (d, $J_{1,2}$ 6.3, H-1).

Anal. Calc. for $C_{23}H_{27}N_5O_6$: C, 58.84; H, 5.80; N, 14.92. Found: C, 58.78; H, 5.80; N, 14.75.

Compound **10b** had m.p. 176–177°, $[\alpha]_D^{23}$ +97.5°; ν_{max}^{KBr} 3270, 2080, 1628, 1520, and 690; n.m.r.: 4.38 (d, $J_{1,2}$ 7.2, H-1).

Anal. Calc. for $C_{19}H_{20}N_4O_4$: C, 61.94; H, 5.47; N, 15.21. Found: C, 62.05; H, 5.49; N, 15.29.

Compound **10c** had m.p. 122–123°, $[\alpha]_D^{23}$ +61.1°; ν_{max}^{KBr} 3335, 2095, 1678, 1520, and 695; n.m.r.: 4.26 (d, $J_{1,2}$ 7.8, H-1).

Anal. Calc. for $C_{17}H_{24}N_4O_5$: C, 56.03; H, 6.64; N, 15.38. Found: C, 55.78; H, 6.63; N, 15.37.

O-*Acetylation of* **10a**, **10b**, *and* **10c**. — Each compound was acetylated conventionally with acetic anhydride in pyridine to give **11a**, **11b**, or **11c** in 90–95% yields.

Compound **11a** had m.p. 174–175°, $[\alpha]_D^{23}$ +93.5°; ν_{max}^{KBr} 3310, 3280, 2110, 1753, 1685, 1658, 1530, and 700.

Anal. Calc. for $C_{25}H_{29}N_5O_7$: C, 58.70; H, 5.71; N, 13.69. Found: C, 58.68; H, 5.69; N, 13.54.

Compound **11b** had m.p. 212–213°, $[\alpha]_D^{23}$ +155°; ν_{max}^{KBr} 3280, 2090, 1750, 1635, 1530, and 710; n.m.r.: 4.80 (d, $J_{1,2}$ 7.5, H-1), 5.41 (dd, $J_{2,3}$ 9.3, H-2).

Anal. Calc. for $C_{21}H_{22}N_4O_5$: C, 61.45; H, 5.40; N, 13.65. Found: C, 61.40; H, 5.42; N, 13.62.

Compound **11c** had m.p. 127°, $[\alpha]_D^{23}$ +86.8°: ν_{max}^{KBr} 3350, 2100, 1750, 1685, 1528, and 710; n.m.r.: 4.46 (d, $J_{1,2}$ 6.1, H-1), 4.86 (d, $J_{2,3}$ 7.9, H-2).

Anal. Calc. for $C_{19}H_{26}N_4O_6$: C, 56.14; H, 6.45; N, 13.79. Found: C, 55.94; H, 6.41; N, 13.74.

*4-(*D*-Alanylamino)-3-amino-3,4-dideoxy-β-*L*-xylose dihydrochloride* (**12**). — A suspension of **10** (1.0 g, 2.1 mmol) in 1:1 of ethanol–0.2M hydrochloric acid (50 ml) was hydrogenolyzed in the presence of 10% palladium-on-charcoal (0.7 g) for 15 h. The catalyst was filtered off and the filtrate was evaporated to a syrup that was crystallized from ethanol; yield 0.53 g (85%); m.p. 170–173° (dec.), $[\alpha]_D^{23}$ −9.3° (*c* 8.9, methanol); ν_{max}^{KBr} 3200–3400 (broad), 1680, and 1555.

Anal. Calc. for $C_8H_{21}Cl_2N_3O_5$ (as monohydrate): C, 30.97; H, 6.82; N, 13.55. Found: C, 30.70; H, 6.40; N, 13.27.

*Benzyl 3,4-diazido-3,4-dideoxy-β-*L*-xylopyranoside* (**13**). — Azidolysis of **4** was performed as described for **10** to yield a mixture of 3-azido (**13**) and 2-azido (**14**) derivatives in 3:1 ratio; only the former was obtained as pure crystals, in 60% yield, after separation on a column of silica gel.

Compound **13** had m.p. 89–91°, $[\alpha]_D^{23}$ −21.3°; ν_{max}^{KBr} 3460, 2120, 760, and 710; n.m.r.: 4.29 (d, $J_{1,2}$ 6.6, H-1), 4.02 (m, H-4).

Anal. Calc. for $C_{12}H_{14}N_6O_3$: C, 49.65; H, 4.86; N, 28.95. Found: C, 49.69; H, 4.85; N, 28.83.

*Benzyl 3-amino-4-azido-3,4-dideoxy-β-*L*-xylopyranoside* (**15**) *and benzyl 2-amino-4-azido-2,4-dideoxy-β-*L*-arabinopyranoside* (**16**). — A solution of **4** (2.5 g, 10 mmol) in methanol (80 ml) was saturated with dry ammonia at 0° and heated in a sealed tube for 30 h at 90–100°. After cooling, the mixture was evaporated to give a crystalline mixture of **15** and **16** in quantitative yield. The ratio of **15** to **16** was determined densitometrically to be 2:3. These two isomers were separated out on a column of silica gel eluted with 49:1 benzene–2-propanol or 49:1 benzene–pyridine. Although the faster-eluted component (**15**) was obtained pure, the second component (**16**) could not be separated completely from the first one. Using about 20 times the amount of silica gel, compounds **15** and **16** could be obtained pure or almost pure in yields of 20 and 10%, respectively. About 60% was a mixture of both compounds. Preparative t.l.c. gave pure **16**. For the next step, the second component-rich fraction (about 30–40% of the mixture) was used without further purification.

Compound **15** had m.p. 117°, $[\alpha]_D^{23}$ +85.8° (*c* 1.1, methanol); ν_{max}^{KBr} 3360, 3300, 2090, 730, and 690.

Anal. Calc. for $C_{12}H_{16}N_4O_3$: C, 54.55; H, 6.10; N, 21.20. Found: C, 54.34; H, 6.05; N, 21.83.

Compound **16** had m.p. 126–131°, $[\alpha]_D^{23}$ +186° (*c* 0.6, methanol); ν_{max}^{KBr} 3360, 2290, 2100, 730, and 695; n.m.r. 4.90 (d, $J_{1,2}$ ~1.5, H-1).

Anal. Calc. for $C_{12}H_{16}N_4O_3$: C, 54.55; H, 6.10; N, 21.20. Found: C, 54.75; H, 6.07; N, 21.00.

N,O-*Diacetylation of* **15** *and* **16**. — Each compound was acetylated conventionally with acetic anhydride in dry pyridine to give **17** or **18** in 85–90% yield. Compound **17** had m.p. 164–167°, $[\alpha]_D^{23}$ +104° (*c* 0.3, chloroform); ν_{max}^{KBr} 3275, 2110, 1738, 1658, 1550, 735, and 695.

Anal. Calc. for $C_{16}H_{20}N_4O_5$: C, 55.16; H, 5.79; N, 16.08. Found: C, 55.27; H, 5.82; N, 15.93.

Compound **18** had m.p. 119–120°, $[\alpha]_D^{23}$ +149°; ν_{max}^{KBr} 3285, 2090, 1730, 1655, 1540, and 730.

Anal. Calc. for $C_{16}H_{20}N_4O_5$: C, 55.16; H, 5.79; N, 16.08. Found: C, 54.92; H, 5.73; N, 16.02.

*Benzyl 4-azido-2-(*tert*-butoxycarbonyl)amino-2,4-dideoxy-β-*L*-arabinopyranoside* (**19**) — Compound **16** was converted into **19** in the same procedure as described for **9c**; yield 75%, m.p. 161–162°, $[\alpha]_D^{23}$ +137° (*c* 0.6, chloroform); ν_{max}^{KBr} 3355, 2100, 1685, 1525, and 728; n.m.r.: 4.91 (d, $J_{1,2}$ 3.0, H-1), 1.49 (s, 9H, CH_3).

Anal. Calc. for $C_{17}H_{24}N_4O_5$: C, 56.03; H, 6.64; N, 15.38. Found: C, 56.11; H, 6.59; N, 15.51.

*Benzyl 4-(*N*-benzyloxycarbonyl-*D*-alanyl)amino-2-(*tert*-butoxycarbonyl)amino-2,4-dideoxy-β-*L*-arabinopyranoside* (**20**). — Hydrogenolysis of **19** as described for **8** gave quantitatively the corresponding 4-amino derivative, which was converted into **20** in the same procedure as described for **9a**; yield 65%, m.p. 160–161°, $[\alpha]_D^{23}$ +115°

(*c* 0.5, chloroform); ν_{max}^{KBr} 3435, 3240, 3220, 1718, 1700, 1665, 1500, 745, and 705; n.m.r.: 4.94 (d, $J_{1,2}$ 3.5, H-1), 3.42 (d, H-5e), 3.54 (d, H-5a), 4.74 and 4.47 (dd, CH_2 of $PhCH_2$), 4.24 (quintet, CH of Ala), 1.36 (s, 9H, CH_3), 1.28 (d, 3H, CH_3), 5.50 and 7.10 (NH).

Anal. Calc. for $C_{28}H_{37}N_3O_8$: C, 61.86; H, 6.86; N, 7.73. Found: C, 62.10; H, 6.83; N, 7.93.

4-(D-Alanylamino)-2-amino-2,4-dideoxy-L-arabinose dihydrochloride (**1**). — Compound **20** (0.80 g, 1.5 mmol) was treated with 98% formic acid (10 ml) for several h at room temperature. The solution was evaporated to a syrup, which gave **1** by hydrogenolysis as described for **12**; yield, 0.33 g (80%), m.p. 195–198° (dec.), $[\alpha]_D^{23}$ +90° (*c* 0.5, methanol); lit.[4]: m.p. ~195° (dec.), $[\alpha]_D^{23}$ +115° (*c* 0.5, methanol); and[5] m.p. 196–200° (dec.), $[\alpha]_D^{17}$ +93° (*c* 0.7, methanol); ν_{max}^{KBr} 3400–2800 (broad), 1680, 1600, 1560, and 1495.

Anal. Calc. for $C_8H_{19}Cl_2N_3O_4$: C, 32.88; H, 6.55; N, 14.39. Found: C, 32.52; H, 6.26; N, 14.10.

REFERENCES

1 J. YOSHIMURA, H. ANDO, T. SATO, S. TSUCHIDA, AND H. HASHIMOTO, *Bull. Chem. Soc. Jpn.*, 49 (1976) 2511–2514.
2 T. HATA, S. OHMURA, M. KATAGIRI, K. ATSUMI, J. AWAYA, S. HIGASHIKAWA, K. YASUI, H. TERADA, AND S. KUYAMA, *J. Antibiot.*, 24 (1971) 900–901.
3 S. OHMURA, M. KATAGIRI, J. AWAYA, K. ATSUMI, R. OIWA, T. HATA, S. HIGASHIKAWA, K. YASUI, H. TERADA, AND S. KUYAMA, *Agr. Biol. Chem.*, 37 (1973) 2805–2812.
4 S. OHMURA, M. KATAGIRI, K. ATSUMI, T. HATA, A. A. JAKUBOWSKI, E. B. SPRINGS, AND M. TISHLER, *J. Chem. Soc. Perkin Trans. 1*, (1974) 1627–1631.
5 H. KUZUHARA AND S. EMOTO, *Tetrahedron Lett.*, (1975) 1853–1856.
6 J. YOSHIMURA, H. HASHIMOTO, AND T. NISHIDE, *Chem. Lett.*, (1976) 201–202.
7 A. J. DICK AND J. K. N. JONES, *Can. J. Chem.*, 43 (1965) 977–982; 44 (1966) 79–87.
8 R. C. CHALK AND D. H. BALL, *Carbohydr. Res.*, 28 (1973) 313–325.
9 J. G. BUCHANAN, R. FLETCHER, K. PARRY, AND W. A. THOMAS, *J. Chem. Soc., B*, (1969) 377–385.
10 S. A. S. AL JANABI, J. G. BUCHANAN, AND A. R. EDGAR, *Carbohydr. Res.*, 35 (1974) 151–164.
11 O. ACHMATOWICZ, JR. AND B. SZECHNER, *Carbohydr. Res.*, 50 (1976) 23–33.
12 H. HASHIMOTO, F. CHIBA, AND J. YOSHIMURA, unpublished results.
13 N. R. WILLIAMS, *Adv. Carbohydr. Chem. Biochem.*, 25 (1970) 109–179.
14 L. D. HALL, *Adv. Carbohydr. Chem.*, 19 (1964) 51–93.