Synthetic Studies on Antibiotic Validamycins. Part 11.[1] Synthesis of Validamycin A†

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The antibiotic validamycin A (**1a**) has been synthesized for the first time (as its undeca-*O*-acetate) by glycosylation of the partially protected derivative (**8**) of the aglycone, validoxylamine A (**2a**), with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl chloride (**11**), followed by deprotection, thereby establishing the structure previously assigned. The totally *O*-acetylated derivative (**1b**) of 7-deoxyvalidamycin A has been synthesized in a similar fashion.

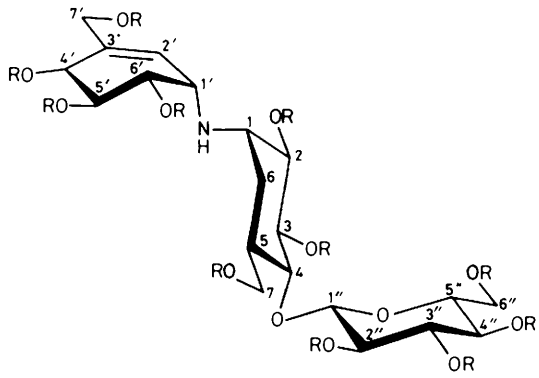
Validamycin A (**1a**) is a main component of the antibiotic validamycin complex which is widely used to control sheath blight of rice. It was isolated from the fermentation broth of *Streptomyces hygroscopicus* var. *limoneus* by Iwasa *et al.*[2] in 1970. The validamycins A, C, D, E, and F are D-glucopyranosides possessing validoxylamine A (**2a**) as their common aglycone. The structure where the β-D-glucopyranosyl residue is attached to the 3-O position of the amine (**2a**) was initially proposed for validamycin A by Horii and Kameda[3] in 1972 on the basis of degradative studies. However, the original structure was later revised to (**1a**) by the unequivocal synthesis of β-D-glucopyranosylvalidamine,[4] the key compound for elucidation of the position at which D-glucopyranose substitutes the amine (**2a**).

In the preceding paper[1] of this series, a total synthesis of the racemic form of the amine (**2a**) was reported. In this paper, we describe the preparation of several synthetically useful, protected derivatives from the optically active amine (**2a**),[5] and this amine's glycosylation reactions with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl chloride (**11**) leading to the first synthesis of validamycin A (**1a**) and its 7-deoxy analogue. In addition, the 400 MHz n.m.r. spectrum of the totally *O*-acetylated derivative (**1b**) of validamycin A was almost completely interpreted by a decoupling experiment, thereby establishing the previously assigned structure (**1a**) for validamycin A.

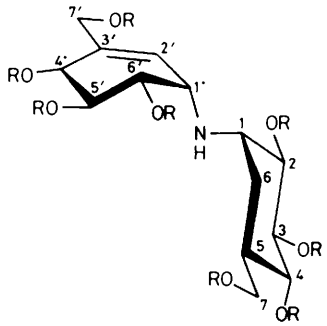
Treatment of the amine (**2a**)‡ with 1.3 mol equiv. of α,α-dimethoxytoluene in dry *NN*-dimethylformamide (DMF) in the presence of 1.2 mol equiv. of toluene-*p*-sulphonic acid (PTSA) at 60 °C gave one major and one minor product together with unchanged (**2a**). The mixture was then acetylated with acetic anhydride in pyridine and the product was separated on a silica gel column to afford the crystalline 4,7:4′,7′-di-*O*-benzylidene acetal (**3**) and 4,7-*O*-benzylidene acetal (**4**) in 5 and 42% yield, respectively. The structures of the acetals (**3**) and (**4**) were confirmed by elemental analyses and ^{1}H n.m.r. spectroscopy. Thus, the ^{1}H n.m.r. spectrum of the acetal (**3**) revealed two singlets for the benzylic protons at δ 5.46 and 5.60. In contrast, the spectrum of the acetal (**4**) showed a singlet for the corresponding proton at δ 5.47, and an AB quartet (δ 4.35 and 4.67) due to the allylic acetoxymethyl protons of the cyclohexene moiety.

O-Deacetylation of the acetal (**4**) with methanolic sodium methoxide, followed by treatment with α-bromotoluene and sodium hydride in DMF, gave the hexabenzyl ether (**5**) in 59% yield. Compounds (**4**) and (**5**) were *O*-debenzylidenated with aqueous acetic acid to give the dihydroxy compounds (**6**) and (**7**), respectively, in 64 and 59% yield. Selective protection of the C-7 hydroxy group of compound (**7**) was effected by treatment with acetyl chloride and imidazole in chloroform[6] to give the acetate (**8**) in 56% yield. The elemental analysis and ^{1}H n.m.r. spectral data of the product were consistent with the proposed structure.

Since it was reported that it was difficult to deprotect the partially benzylated validamycin A without the glucopyranosyl residue being cleaved,[7] we carried out a condensation reaction of the diol (**6**) with the halide (**11**). The condensation in dry benzene in the presence of mercury(II) cyanide and anhydrous calcium sulphate at reflux temperature for 8 days gave a mixture



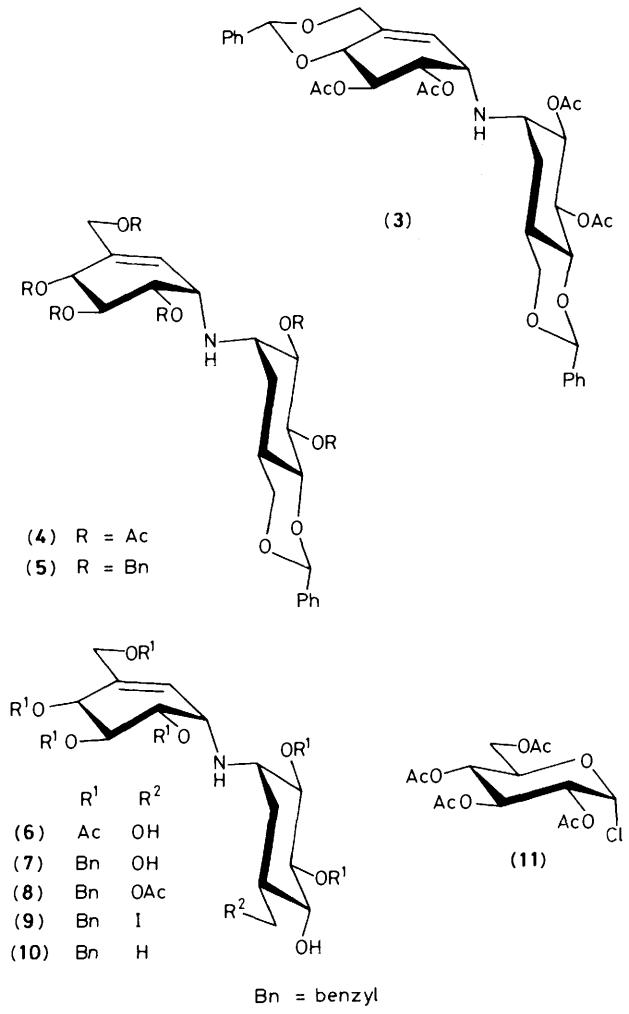
(**1a**) R = H (Validamycin A)
(**1b**) R = Ac

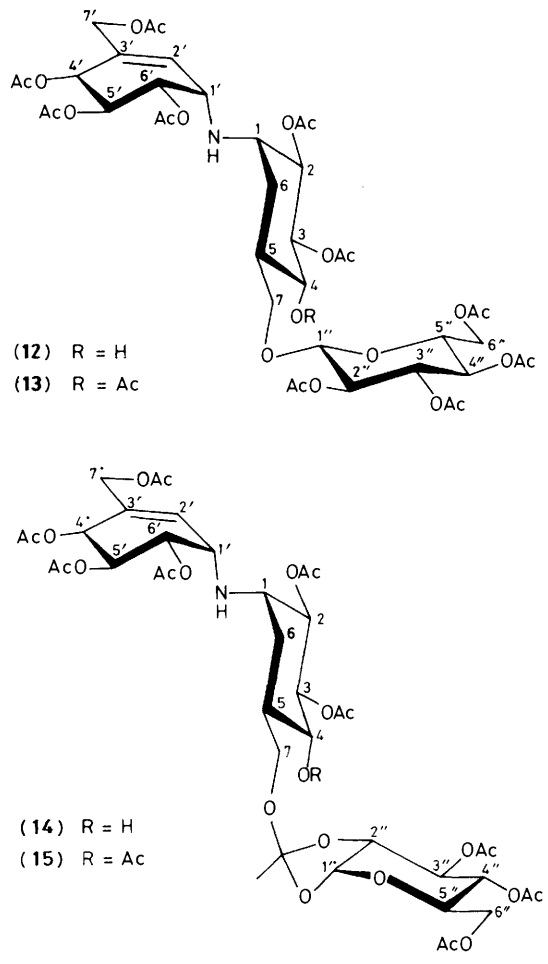


(**2a**) R = H (Validoxylamine A)
(**2b**) R = Ac

† A preliminary account of this work has been presented: S. Ogawa, T. Ogawa, T. Nose, T. Toyokuni, Y. Iwasawa, and T. Suami, *Chem. Lett.*, 1983, 921.

‡ Validoxylamine A (**2a**) was prepared from crude validamycin.[5]





of the products, which was separated by chromatography on silica gel to afford the 7-*O*(β-D-glucopyranoside) deca-acetate (**12**) (9%) and the orthoester nona-acetate (**14**) (35%). Acetylation gave the respective totally *O*-acetylated derivatives (**13**) and (**15**) in quantitative yield. The 400 MHz n.m.r. spectra supported their proposed structures (Table). These results indicated that the *O*-acetyl protecting groups considerably hindered the glycosylation reaction even at the C-7 primary hydroxy group in this case.[8] Therefore, further study using the diol (**6**) was abandoned.

A modified Koenigs–Knorr reaction[9] of the hydroxy compound (**8**) with the halide (**11**) was then conducted in dry dichloromethane in the presence of silver trifluoromethanesulphonate and 1,1,3,3-tetramethylurea at room temperature for 4.5 h. The product was purified on a silica gel column to give a single condensate (**16**) in 74% yield. *O*-Deacetylation of compound (**16**) with sodium methoxide, followed by conventional benzylation, afforded the totally *O*-benzylated compound (**17**). This compound was identical with an authentic sample[7] derived from validamycin A (**1a**) by direct benzylation. Removal of the benzyl groups of the benzyl ether (**16**) or (**17**) could be achieved by treatment with sodium in liquid ammonia at −70 °C. Formation of a sole product was observed in both cases, and it was shown to be identical with the antibiotic (**1a**) by t.l.c. The product was further characterised by conversion into the undeca-acetate (**1b**), identical with an authentic sample.[10] The yield of compound (**1b**) from compound (**16**) was 67%. The structure of validamycin A was firmly established by the present synthesis, and further supported by the 400 MHz n.m.r. spectral data listed in the Table.

Similarly, 7-deoxyvalidamycin A has been synthesized in the following way. Treatment of compound (**7**) with *N*-iodosuccinimide (NIS) and triphenylphosphine in DMF gave a 48% yield of the iodide (**9**), which was then dehalogenated with lithium aluminium hydride in tetrahydrofuran (THF) to give the protected 7-deoxyvalidoxylamine A (**10**) in 76% yield. The structure of the latter compound was supported by the ^{1}H n.m.r. spectrum, in which a doublet (*J* 6 Hz) due to the C-5 methyl group appeared at δ 0.93. Condensation of the protected amine (**10**) with the halide (**11**) gave a 70% yield of the β-D-glucopyranoside (**18**), which was then *O*-debenzylated in the usual way and acetylated to give 7-deoxyvalidamycin A deca-acetate (**19**) in 53% yield. The structure of compound (**19**) was assigned by ^{1}H n.m.r. spectroscopy.

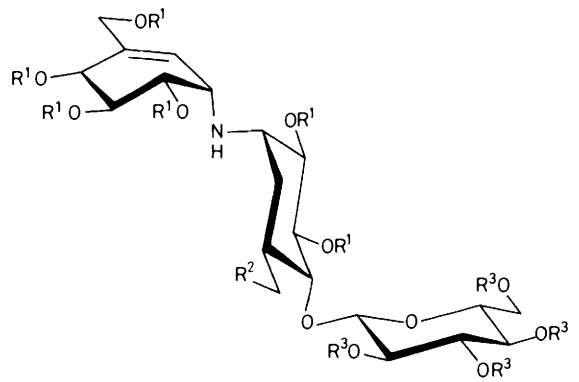
Experimental

M.p.s were determined on a Mitamura Riken micro hot-stage and are uncorrected. N.m.r. spectra were measured in deuteriochloroform solution with a Varian EM-390 (90 MHz) or JEOL FX-400 (400 MHz) instrument. Optical rotations were measured with a Jasco DIP-4 instrument. Mass spectra were recorded with a Hitachi M-80 instrument at 70 eV. T.l.c. was performed on precoated silica gel 60 F-254 (E. Merck, Darmstadt; 0.25 mm thickness). The silica gel used for column chromatography was Wakogel C-300 (Wako Co., Osaka, Japan; 300 Mesh).

Table. ^{1}H N.m.r. spectral data[a] (400 MHz; $CDCl_3$) for compounds (**1b**), (**2b**), (**13**), and (**15**)

	Chemical shifts (δ)					Coupling constants (Hz)			
Proton	(**1b**)	(**2b**)[b]	(**13**)	(**15**)	*J*	(**1b**)	(**2b**)	(**13**)	(**15**)
1	3.26(br q)	3.38(br q)	3.35(br q)	3.35(br q)	1,2	3.55	3.8	3.8	3.65
2	4.86(dd)	4.95(dd)	4.88(dd)	4.91(dd)	2,3	9.8	9.9	10.15	9.95
3	5.33(t)	5.39(t)	5.38(t)	5.37(t)	3,4	9.8	9.9	10.15	9.95
4	3.57(t)	4.95(t)	4.88(t)	4.95(dd)	4,5	9.8	9.9	10.15	11.0
5	2.29(br t)	2.42(br d)	2.33(br t)	2.32(br t)	5,6*ax*	13.4	14.8	14.1	14.3
6*ax*	1.37(td)	1.52(ddd)	1.55(ddd)	1.54(d)	5,6*eq*	3.6	3.3	3.5	
6*eq*	1.81(dt)	1.85(dt)	1.81(dt)	1.80(br dt)	5,7a	2.0	3.3	3.5	
7a	4.03(dd)	3.89(dd)	3.34(dd)	3.32(dd)	5,7b	6.2	4.6	2.95	4.6
7b	4.37(dd)	4.13(dd)	3.78(dd)	3.41(dd)	1,6*ax*		2.2	2.4	
1′	3.62(br t)	3.55(t)	3.54(t)	3.55(t)	1,6*eq*	3.6	3.3	3.5	4.15
2′	5.95(d)	5.99(d)	5.98(d)	5.98(d)	6*ax*,6*eq*	13.4	14.8	14.1	14.3
4′	5.48(d)	5.49(d)	5.48(d)	5.48(d)	7a,7b	12.55	11.5	9.55	9.05
5′	5.39(dd)	5.41(dd)	5.39(dd)	5.39(dd)	1′,2′	4.45	4.75	4.3	4.5
6′	4.96(dd)	4.99(dd)	5.01(dd)	4.97(dd)	4′,5′	6.0	6.1	5.75	6.8
7′a	4.37(d)	4.39(d)	4.39(d)	4.39(d)	5′,6′	9.35	9.65	9.4	9.55
7′b	4.65(d)	4.65(d)	4.65(d)	4.65(d)	1′,6′	4.45	4.75	4.3	4.5
1″	4.52(d)		4.40(d)	5.72(d)	7′a,7′b	13.2	13.0	13.0	13.2
2″	4.93(dd)		4.96(dd)	4.98(dd)	1″,2″	7.9		7.9	5.0
3″	5.14(t)		5.21(t)	5.14(t)	2″,3″	9.45		9.45	2.7
4″	5.07(t)		5.05(t)	4.89(dd)	3″,4″	9.45		9.45	2.7
5″	3.64(dq)		3.66(dq)	3.92(dq)	4″,5″	9.45		9.45	9.75
6″a	4.12(dd)		4.11(dd)	4.20(dd)	5″,6″a	4.05		2.4	2.95
6″b	4.29(dd)		4.26(dd)	4.22(dd)	5″,6″b	2.55		4.75	3.4
NH	1.78(br s)		1.67(m)	1.71(d)[c]	6″a,6″b	11.25		12.3	13.55
CH_3				1.66(s)					
$COCH_3$	2.10, 2.07, 2.06(2), 2.05, 2.045, 2.04, 2.03, 2.00, 1.99, 1.97	2.09, 2.07, 2.065, 2.06, 2.055(2), 2.03, 1.99	2.10, 2.09(2),[d] 2.07, 2.06(2), 2.055, 2.03, 2.02, 2.00, 1.98	2.12, 2.09, 2.08, 2.075, 2.07, 2.065, 2.06(2), 2.056, 2.054					

[a] Values given for coupling constants are of first-order spectra. [b] Deuteriated. [c] Coupling constant is 4.4 Hz. [d] Values in parentheses show number of acetoxy groups.



	R^1	R^2	R^3
(**16**)	Bn	OAc	Ac
(**17**)	Bn	OBn	Bn
(**18**)	Bn	H	Ac
(**19**)	Ac	H	Ac

Benzylidenation of (1S)-(1,2,4/3,5)-2,3,4-*Trihydroxy*-5-*hydroxymethyl*-N-[(1S)-(1,4,6/5)-4,5,6-*trihydroxy*-3-*hydroxymethylcylohex*-2-*enyl*]*cyclohexylamine* (*Validoxylamine A*) (**2a**).—A mixture of the amine (**2a**) (1.90 g, 5.67 mmol), α,α-dimethoxytoluene (1.12 ml, 7.37 mmol), and PTSA (1.3 g, 6.8 mmol) in dry DMF (50 ml) was stirred at 60 °C under reduced pressure (15—20 mmHg) for 6 h, at which time t.l.c. indicated the formation of two new components (R_F 0.83 and 0.40) in chloroform–methanol (3:1, v/v). After treatment with an excess of sodium hydrogen carbonate, the reaction mixture was concentrated and the residue was treated with acetic anhydride (35 ml) and pyridine (35 ml) at room temperature overnight. T.l.c. indicated the formation of three components (R_F 0.37, 0.32, and 0.22) in butan-2-one–toluene (1:5, v/v). The mixture was concentrated and the residue was chromatographed on a silica gel column (110 g) with butan-2-one–toluene (1:6, v/v) as eluant. The first fraction gave 4,7:4′,7′-*di*-O-*benzylidenevalidoxylamine A tetra*-O-*acetate* (**3**) (196 mg, 5.1%) as prisms, m.p. 275—277 °C (from EtOH) (Found: C, 63.8; H, 6.1; N, 1.9. $C_{36}H_{41}NO_{12}$ requires C, 63.6; H, 6.1; N, 2.1%); $[\alpha]_D^{18}$ + 105° (*c* 1.0 in $CHCl_3$); δ_H (90 MHz; $CDCl_3$) (*inter alia*) 1.98, 2.04, and 2.06 (total 12 H, 3 s, 4 $COCH_3$), 5.46 and 5.60 (each 1 H, s, *H*CPh), and 7.23—7.53 (10 H, m, 2 Ph).

The second fraction gave 4,7-O-*benzylidenevalidoxylamine A hexa*-O-*acetate* (**4**) (1.25 g, 42%) as plates, m.p. 173—174 °C (from EtOH) (Found: C, 58.6; H, 6.1; N, 2.1. $C_{33}H_{41}NO_{14}$ requires C, 58.7; H, 6.1; N, 2.1%); $[\alpha]_D^{18}$ + 104° (*c* 1.0 in $CHCl_3$); δ_H (90 MHz; $CDCl_3$) (*inter alia*) 2.03, 2.04, 2.05, 2.06, and 2.08 (total 18 H, 5 s, 6 $COCH_3$), 4.35 and 4.67 (each 1 H, d,

J_{gem} 13 Hz, together 7'-H_2), 5.47 (1 H, s, *H*CPh), 6.00 (1 H, br d, *J* 5 Hz, 2'-H), and 7.27—7.60 (5 H, m, Ph).

The third fraction gave validoxylamine A octa-*O*-acetate (**2b**) (457 mg, 12%) as a glass, $[\alpha]_D^{18}$ + 109° (*c* 1.22 in $CHCl_3$). The ^{1}H n.m.r. spectrum was superposable on that of an authentic sample.[2]

4,7-O-*Benzylidenevalidoxylamine A Hexabenzyl Ether* (**5**).—To a solution of the acetal (**4**) (566 mg, 0.84 mmol) in methanol (5 ml) was added 1M-methanolic sodium methoxide (0.8 ml), and the mixture was stirred at room temperature for 50 min. The reaction mixture was concentrated and the residue was dissolved in DMF (25 ml), and a mixture of sodium hydride (590 mg, 14.6 mmol) in DMF (5 ml) was added dropwise to the stirred solution during 70 min. α-Bromotoluene (1.72 ml, 14.6 mmol) was then added and the mixture was stirred at room temperature for 23 h. The reaction mixture was concentrated and the residue was taken up in ethyl acetate (100 ml). The solution was washed with water, dried, and concentrated to give a syrup, which was purified on a silica gel column (50 g) with butan-2-one–toluene (1:10, v/v) as eluant. The main fraction gave the *benzyl ether* (**5**) (474 mg, 59%) as a syrup (Found: C, 78.6; H, 6.8; N, 1.7. $C_{63}H_{65}NO_8$ requires C, 78.5; H, 6.8; N, 1.45%); $[\alpha]_D^{17}$ + 46° (*c* 1.03 in $CHCl_3$); δ_H (90 MHz; $CDCl_3$) (*inter alia*) 4.40—4.70 (12 H, m, 6 CH_2Ph), 4.80 (1 H, d, *J* 10.5 Hz, 4'-H), 5.54 (1 H, s, *H*CPh), 5.90 (1 H, br d, *J* 4.5 Hz, 2'-H), and 7.13—7.63 (35 H, m, 7 Ph).

2,3,4',5',6',7'-*Hexa*-O-*acetylvalidoxylamine A* (**6**).—A solution of the acetal (**4**) (579 mg, 0.857 mmol) in a mixture of ethanol (6 ml) and 80% aqueous acetic acid (10 ml) was stirred at 60 °C for 18 h. The reaction mixture was concentrated, and the residue was chromatographed on a silica gel column (20 g) with chloroform–methanol (25:1, v/v) as eluant. The main fraction gave the *hexa-acetate* (**6**) (321 mg, 64%) as a glass (Found: C, 51.4; H, 6.0; N, 2.3. $C_{26}H_{37}NO_{14}\cdot H_2O$ requires C, 51.6; H, 6.5; N, 2.3%); $[\alpha]_D^{17}$ + 119° (*c* 1.03 in $CHCl_3$); δ_H (90 MHz; $CDCl_3$) (*inter alia*) 2.02, 2.03, and 2.05 (total 18 H, s, 6 $COCH_3$), 3.26 (1 H, m, 1-H), 4.33 and 4.63 (each 1 H, d, J_{gem} 13.5 Hz, together CH_2OCOCH$_3$), and 5.98 (1 H, br d, *J* 5 Hz, 2'-H).

2,3,4',5',6',7'-*Hexa*-O-*benzylvalidoxylamine A* (**7**).—A mixture of the benzyl ether (**5**) (495 mg, 0.172 mmol) and 80% aqueous acetic acid (10 ml) was stirred at 60 °C for 20 h. The reaction mixture was concentrated and the residue was chromatographed on silica gel (15 g) with butan-2-one–toluene (1:3, v/v) as eluant. The main fraction gave the *hexabenzyl ether* (**7**) (264 mg, 59%) as a syrup (Found: C, 76.6; H, 7.0; N, 1.6. $C_{56}H_{61}NO_8$ requires C, 76.8; H, 7.0; N, 1.6%); $[\alpha]_D^{18}$ + 48.5° (*c* 3.73 in $CHCl_3$); δ_H (90 MHz; $CDCl_3$) (*inter alia*) 2.60—2.90 (2 H, m, OH, disappears upon deuteriation), 4.40—4.70 (12 H, m, 6 C_2HPh), 4.91 (1 H, d, *J* 11.5 Hz, 4'-H), 5.83 (1 H, br d, *J* 4.5 Hz, 2'-H), and 7.08—7.40 (30 H, m, 6 Ph).

7-O-*Acetyl*-2,3,4',5',6',7'-*hexa*-O-*benzylvalidoxylamine A* (**8**).—To a solution of imidazole (48 mg, 0.71 mmol) in chloroform (7 ml) was added dropwise acetyl chloride (25 μl, 0.35 mmol). The hexabenzyl ether (**7**) (238 mg, 0.27 mmol) was added to the filtered solution, and the mixture was heated at reflux for 40 h. The reaction mixture was diluted with chloroform (20 ml) and the solution was washed with water, dried, and concentrated. The residue was purified on a silica gel column (10 g), with butan-2-one–toluene (1:3, v/v) as eluant, to give the *acetate* (**8**) (139 mg, 55.7%) as a syrup (Found: C, 75.55; H, 6.9; N, 1.8. $C_{58}H_{63}NO_9$ requires 75.9; H, 6.9; N, 1.5%); $[\alpha]_D^{18}$ + 58.7° (*c* 0.90 in $CHCl_3$); δ_H (90 MHz; $CDCl_3$) (*inter alia*) 1.93 (3 H, s, $COCH_3$), 2.43—2.55 (1 H, m, OH, disappears upon deuteriation), 4.42—4.75 (12 H, m, 6 CH_2Ph), 4.95 (1 H, d, *J* 11.5 Hz, 4'-H), 5.90 (1 H, br d, *J* 3.5 Hz, 2'-H), and 7.24—7.40 (30 H, m, 6 Ph).

Condensation of the Diol (**6**) *with* 2,3,4,6-*Tetra*-O-*acetyl*-α-D-*glucopyranosyl Chloride* (**11**).—A mixture of the diol (**6**) (321 mg, 0.546 mmol), mercury(II) cyanide (1.16 g, 4.37 mmol), and dry benzene (60 ml) was refluxed for 2 h, and then a portion (27 ml) of benzene was distilled off. To the cooled suspension was added the halide (**11**) (1.60 g, 4.37 mmol) and anhydrous calcium sulphate (0.5 g), and the mixture was stirred at 90—95 °C for 180 h. After having been cooled and treated with excess of sodium hydrogen carbonate, the mixture was filtered through a Kaolin bed and concentrated. The residue was taken up in ethyl acetate (300 ml), and the solution was washed successively with saturated aqueous sodium hydrogen carbonate and water, and dried. Removal of the solvent gave a syrup (1.78 g) which was chromatographed on silica gel (60 g) with butan-2-one–toluene (2:3, v/v) as eluant. The first fraction [R_F 0.69 in butan-2-one–toluene (2:3, v/v)] gave the unchanged halide (**11**) (1.42 g). The second fraction (R_F 0.22) gave α-D-glucopyranose 3,4,6-triacetate 1,2-{(1*R*)-1,3/2,4,5-3,4-diacetoxy-2-hydroxy-5-[(1*S*)-1,4,6/5-4,5,6-triacetoxy-3-acetoxymethyl-cyclohex-2-enylamino]cyclohexyl methyl orthoacetate} (**14**) (175 mg, 35%) as a syrup; $[\alpha]_D^{17}$ + 80.6° (*c* 3.12 in $CHCl_3$); δ_H* (90 MHz; $CDCl_3$) (*inter alia*) 1.71 (3 H, s, orthoester Me), 2.09 (9 H, m) and 2.11 (3 H, s) (4 $COCH_3$), 2.69 (1 H, br d, *J* 6 Hz, OH), 3.33 (1 H, m, 1'-H), 4.36 and 4.69 (each 1 H, J_{gem} 13 Hz, together CH_2OCOCH$_3$), 5.73 (1 H, d, *J* 3 Hz, 3-H), and 6.01 (1 H, br d, *J* 4.5 Hz, 2'-H).

The third fraction (R_F 0.17) gave 2,3,4',5',6',7'-hexa-*O*-acetyl-7-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)validoxylamine A (**12**) (45 mg, 9%) as a syrup; $[\alpha]_D^{18}$ + 68.2° (*c* 1.29 in $CHCl_3$); δ_H (90 MHz; $CDCl_3$) (*inter alia*) 1.99, 2.01, and 2.06 (30 H, 3 s, 10 $COCH_3$), 4.36 and 4.67 (each 1 H, d, J_{gem} 13 Hz, together CH_2OCOCH$_3$), and 6.01 (1 H, d, *J* 4.5 Hz, 2'-H).

Compound (**14**) (51 mg) was treated with acetic anhydride (1 ml) and pyridine (1 ml) at room temperature for 5 h. The reaction mixture was concentrated and the product was purified by passage through a short column of alumina, with chloroform as eluant, to give the deca-acetate (**15**) (51 mg, 96%) as a syrup; $[\alpha]_D^{18}$ + 102° (*c* 1.28 in $CHCl_3$); δ_H (400 MHz; $CDCl_3$) see Table; *m/z* 959 (M^+) ($C_{42}H_{57}NO_{24}$ requires *M*, 959).

Compound (**12**) (21 mg) was similarly acetylated to give the undeca-acetate (**13**) (20 mg, 93%) as a syrup; $[\alpha]_D^{18}$ + 74.4° (*c* 0.91 in $CHCl_3$); δ_H (400 MHz; $CDCl_3$) see Table; *m/z* 959 (M^+) ($C_{42}H_{57}NO_{24}$ requires *M*, 959).

Condensation of the Hydroxy Compound (**8**) *with the Halide* (**11**).—To a stirred solution of compound (**8**) (139 mg, 0.15 mmol) in dry dichloromethane (2 ml) were added silver trifluoromethanesulphonate (86 mg, 0.30 mmol) and 1,1,3,3-tetramethylurea (54 μl, 0.45 mmol) under nitrogen, and then the halide (**11**) (123 mg, 0.34 mmol) was added to the mixture. After the mixture had been stirred at room temperature for 3 h, an additional quantity of halide (**11**) (62 mg, 0.15 mmol) was added and the mixture was stirred for a further 90 min. The reaction mixture was diluted with dichloromethane (10 ml), neutralised with triethylamine, and filtered through Kaolin. The filtrate was concentrated and the residue was chromatographed on a silica gel column (15 g) with butan-2-one–toluene (1:8, v/v) as eluant. The main fraction gave 7,2'',3'',4'',6''-*penta*-O-*acetyl*-2,3,4',5',-6',7'-*hexa*-O-*benzylvalidamycin A* (**16**) (140 mg, 74.2%) as a syrup (Found: C, 69.25; H, 6.6; N, 1.3. $C_{72}H_{81}NO_{18}$ requires C,

* The n.m.r. numbering scheme for compound (**14**) is that shown in the structure; the unprimed locants do not correspond to the systematic name given.

69.3; H, 6.5; N, 1.1%); $[\alpha]_D^{18}$ + 42.4° (*c* 1.73 in $CHCl_3$); δ_H (90 MHz; $CDCl_3$) (*inter alia*) 1.93, 1.95, 1.97, and 2.00 (15 H, 4 s, 5 $COCH_3$), 5.90 (1 H, br d, *J* 4.5 Hz, 2'-H), and 7.24—7.42 (30 H, m, 6 Ph).

Validamycin A Undecabenzyl Ether (**17**).—To a solution of validamycin A (**1a**) (200 mg, 0.40 mmol) in dry DMF (6 ml) was added a solution of sodium hydride (340 mg) in dry DMF (4 ml), and the mixture was stirred at room temperature for 1 h. α-Bromotoluene (1.01 ml, 8.5 mmol) was then added dropwise to the ice-cooled mixture, which was then stirred at room temperature for 23 h. After addition of methanol, the reaction mixture was concentrated and the residue was taken up in ethyl acetate (60 ml). The solution was washed with water, dried, and concentrated. The product was purified on a silica gel column (30 g), with butan-2-one–toluene (1:20, v/v) as eluant, to give the undecabenzyl ether (**17**) (346 mg, 62%) as a syrup (Found: C, 78.4; H, 7.1; N, 1.0. $C_{97}H_{101}NO_{13}$ requires C, 78.25; H, 6.8; N, 0.9%); $[\alpha]_D^{18}$ + 44.2° (*c* 1.85 in $CHCl_3$);* δ_H (90 MHz; $CDCl_3$) (*inter alia*) 5.92 (1 H, br d, *J* 4.5 Hz, 2'-H) and 7.10—7.40 (55 H, m, 11 Ph).

Compound (**17**) was also derived from compound (**16**) as follows. Compound (**16**) (43.7 mg) was treated with 1M-methanolic sodium methoxide (0.1 ml) in methanol at room temperature for 30 min. The reaction mixture was concentrated and the residual product was benzylated as described above to give the undecabenzyl ether (**17**) (13.4 mg, 23%) as a syrup; $[\alpha]_D^{18}$ + 45.8° (*c* 0.69 in $CHCl_3$); the ^1H n.m.r. spectrum was superposable on that of the compound obtained from validamycin A (**1a**).

Validamycin A Undeca-acetate (**1b**).—(a) O-*Debenzylation of the undecabenzyl ether* (**17**). To liquid ammonia (40 ml) containing sodium (130 mg, 5.65 mg-atom) at −70 °C was added a solution of the benzyl ether (**17**) (81.2 mg, 0.06 mmol) in dry THF (3 ml), and the mixture was stirred at the same temperature for 20 min. Then an additional amount of sodium (70 mg, 3 mg-atom) was added every hour for 4 h, and then, after addition of excess of ammonium chloride, the mixture was kept at room temperature for 4.5 h. The reaction mixture was filtered and the filtrate was concentrated. T.l.c. indicated the formation of a single compound identical with validamycin A (**1a**) [R_F 0.32 in butan-1-ol–ethanol–water (3:2:2, v/v)]. The product was acetylated in the usual way and purified on a silica gel column with butan-2-one–toluene (2:3, v/v) as eluant to give the undeca-acetate (**1b**) (26.6 mg, 50.8%) as a syrup; $[\alpha]_D^{19}$ + 56.3° (*c* 1.0 in $CHCl_3$).† The n.m.r. spectrum (90 MHz; $CDCl_3$) was superposable on that of an authentic sample[10] derived from validamycin A (**1a**).

(b) *Debenzylation of compound* (**16**). Compound (**16**) (73.3 mg) was *O*-debenzylated with sodium in liquid ammonia, and the product was acetylated as described above to give the undeca-acetate (**1b**) (37.7 mg, 67%) as a syrup; $[\alpha]_D^{15}$ + 61.1° (*c* 1.04 in $CHCl_3$). The ^1H n.m.r. spectrum was superposable on that of an authentic sample.[10]

2,3,4',5',6',7'-*Hexa*-O-*benzyl*-7-*deoxy*-7-*iodovalidoxylamine A* (**9**).—To a solution of the diol (**7**) (392 mg, 0.45 mmol) and NIS (201 mg, 0.89 mmol) in dry DMF (20 ml) was added triphenylphosphine (2.33 g), and the mixture was stirred at 50 °C for 14 h. The mixture was diluted with ethyl acetate (140 ml) and the solution was washed with water, dried, and concentrated. The residue was purified on a silica gel column (24 g), with ethyl acetate–hexane (1:6, v/v) as eluant, to give the *iodide* (**9**) (212 mg, 48%) as a syrup (Found: C, 68.5; H, 6.3; I, 12.55; N, 1.3. $C_{56}H_{60}INO_7$ requires C, 68.2; H, 6.1; I, 12.9; N, 1.4%); $[\alpha]_D^{25}$ + 37.4° (*c* 0.90 in $CHCl_3$); δ_H (90 MHz; $CDCl_3$) (*inter alia*) 1.70 (1 H, m, OH, disappears upon deuteriation), 4.40—4.74 (12 H, m, 6 CH_2Ph), 4.95 (1 H, d, *J* 11.5 Hz, 4'-H), 5.87 (1 H, br d, *J* 3.5 Hz, 2'-H), and 7.30 (30 H, s, 6 Ph).

2,3,4',5',6',7'-*Hexa*-O-*benzyl*-7-*deoxyvalidoxylamine A* (**10**).—To a suspension of lithium aluminium hydride (8.9 mg, 0.23 mmol) in dry THF (2 ml) was added a solution of the iodide (**9**) (137 mg, 0.16 mmol) in THF (2 ml), and the mixture was stirred at room temperature for 30 min. A mixture of ethyl acetate and methanol was added to the cooled mixture and it was concentrated to a syrup, which was chromatographed on a silica gel column (4 g), with ethyl acetate–hexane (1:5, v/v) as eluant, to give the *hexabenzyl ether* (**10**) (90 mg, 75.6%) as a syrup (Found: C, 78.1; H, 7.2; N, 1.7. $C_{56}H_{61}NO_7$ requires C, 78.2; H, 7.2; N, 1.6%); $[\alpha]_D^{21}$ + 53.2° (*c* 1.04 in $CHCl_3$); δ_H (90 MHz; $CDCl_3$) (*inter alia*) 0.93 (3 H, d, *J* 6 Hz, 7-H_3), 2.33 (1 H, m, OH, disappears upon deuteriation), 4.33—4.70 (12 H, m, 6 CH_2Ph), 4.96 (1 H, d, *J* 12 Hz, 4'-H), 5.88 (1 H, br d, *J* 4 Hz, 2'-H), and 7.36 (30 H, s, 6 Ph).

Condensation of the Hexabenzyl Ether (**10**) *with the Halide* (**11**).—To a suspension of compound (**10**) (80.3 mg, 0.090 mmol), silver trifluoromethanesulphonate (48 mg, 0.19 mmol), 1,1,3,3-tetramethylurea (34 μl, 0.28 mmol), and dichloromethane (2 ml) was added a solution of the halide (**11**) (69 mg, 0.19 mmol) in dichloromethane (1 ml), and the mixture was stirred at room temperature for 24 h. The reaction mixture was then processed, as in the preparation of compound (**16**), to give a syrup, which was chromatographed on a silica gel column (11 g), with ethyl acetate–hexane (1:2, v/v) as eluant, to give 2'',3'',4'',6''-*tetra*-O-*acetyl*-2,3,4',5',6',7'-*hexa*-O-*benzyl*-7-*deoxyvalidamycin A* (**18**) (78 mg, 70%) as a syrup (Found: C, 70.4; H, 6.7; N, 1.1. $C_{70}H_{79}NO_{16}$ requires C, 70.6; H, 6.7; N, 1.2%); $[\alpha]_D^{21}$ + 45.5° (*c* 1.80 in $CHCl_3$); δ_H (90 MHz; $CDCl_3$) (*inter alia*) 0.98 (3 H, d, *J* 7 Hz, 7-H_3), 1.94 and 1.97 (each 6 H, s, together 4 $COCH_3$), 4.40—4.74 (12 H, m, 6 CH_2Ph), 5.90 (1 H, br d, *J* 4.5 Hz, 2'-H), and 7.33 (30 H, 6 Ph).

7-*Deoxyvalidamycin A Deca-acetate* (**19**).—To liquid ammonia (40 ml) containing sodium (90 mg, 3.91 mg-atom) at −70 °C was added dropwise a solution of compound (**18**) (68 mg, 0.060 mmol) in dry THF (3 ml). The reaction mixture was processed as described in the preparation of compound (**1b**). The product was shown to be homogeneous by t.l.c. It was acetylated in the usual way and the product was purified on a silica gel column, with butan-2-one–toluene (1:3, v/v) as eluant, to give the *deca-acetate* (**19**) (28 mg, 55%) as a syrup (Found: C, 53.5; H, 6.2; N, 1.7. $C_{40}H_{55}NO_{22}$ requires C, 53.5; H, 6.15; N, 1.55%); $[\alpha]_D^{16}$ + 59° (*c* 0.76 in $CHCl_3$); δ_H (90 MHz; $CDCl_3$) (*inter alia*) 1.02 (3 H, d, *J* 6 Hz, 7-H_3), 1.97—2.04 (30 H, m, 10 $COCH_3$), 3.14 (1 H, br m, 1-H), 3.52 (1 H, m, 1'-H), and 5.93 (1 H, br d, *J* 4.5 Hz, 2'-H).

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* The specific rotation of compound (**17**) was not reported in ref. 7.
† The specific rotation of compound (**1b**) was not reported in ref. 10.

References

1 Part 10, S. Ogawa, T. Ogawa, Y. Iwasawa, T. Toyokuni, N. Chida, and T. Suami, *J. Org. Chem.*, 1984, **49**, 2594.
2 T. Iwasa, H. Yamamoto, and M. Shibata, *J. Antibiot.*, 1970, **23**, 595.
3 S. Horii and Y. Kameda, *J. Chem. Soc., Chem. Commun.*, 1972, 747.
4 S. Ogawa, N. Chida, and T. Suami, *Chem. Lett.*, 1980, 139; S. Ogawa, N. Chida, H. Ito, and T. Suami, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 499.
5 S. Horii, T. Iwasa, and Y. Kameda, *J. Antibiot.*, 1971, **24**, 57.
6 J. Vernon, S. Roseman, and Y. C. Lee, *Carbohydr. Res.*, 1980, **82**, 59.
7 A. Hasegawa, T. Kobayashi, H. Hibino, and M. Kiso, *Agric. Biol. Chem.*, 1980, **44**, 143.
8 P. Sinay, *Pure Appl. Chem.*, 1978, **50**, 1437.
9 S. Hanessian and J. Banoub, in 'Synthetic Methods for Carbohydrates,' ed. H. S. Khadem, American Chemical Society, Washington, D. C., 1976, p. 36.
10 T. Iwasa, Y. Kameda, M. Asai, S. Horii, and K. Mizuno, *J. Antibiot.*, 1971, **24**, 119.

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