Synthetic Studies on Antibiotic Validamycins. Part 13.[1,2] Total Synthesis of (+)-Validamycins A and E, and Related Compounds

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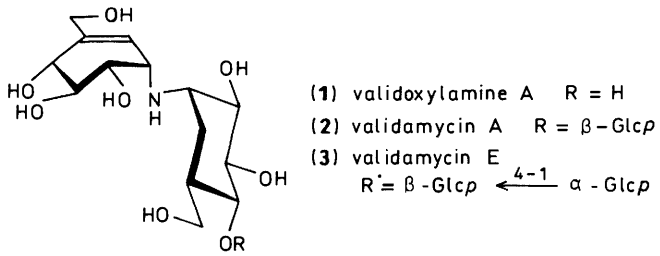
(+)-Validoxylamine A (**1**) has been completely synthesized by deoxygenation of the validoxylamine B derivative (**6**) through formation of the aziridine, nucleophilic displacement with toluenethiol, reduction with Raney nickel, and deprotection. The validoxylamine A derivative (**10**) obtained was convertible, by glycosylation followed by deprotection, into validamycins A (**2**), E (**3**), and their analogues, which constitutes a total synthesis thereof.

The antibiotic validamycin complex[3] shows growth inhibition activity against *Pellicularia sasakii* (sheath blight disease of rice plants). Since validamycin A was first isolated as the major and most active compound from the fermentation broth of *Streptomyces hygroscopicus* var. *limoneus* by Iwasa *et al.*[4] in 1970, other minor validamycins B, C, D, E, F, and G,[5] and validoxylamines A, B, and G[5] have been isolated and characterised successfully. Structurally, validamycins A and E contain validoxylamine A as a common constituent, and



validamycin E[3] is known to show strong activity comparable to validamycin A. Here we describe the detail of the first total synthesis of (+)-validoxylamine A, and (+)-validamycins A and E.

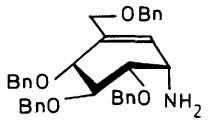
Our common synthetic strategy for construction of the pseudo-di and tri-saccharide structures linked by way of an imino group is a facile coupling of the amino and epoxy derivatives of pseudo-sugars. Since validoxylamine A is only different from validoxylamine B in lacking a 6-hydroxy group, so we envisaged a transformation of the diaxial-opening compound (**6**) into validoxylamine A derivative (**10**) by removal of the hydroxy group of (**6**). First, radical deoxygenation of the dithiocarbonate derivative of (**6**) by use of tributyltin hydride[6] was attempted, but failed. The next approach, sulphonylation of compound (**6**) resulted, unexpectedly, in exclusive formation of the aziridine (**8**). However, this aziridine was rather reactive, and deoxygenation was finally achieved by opening of the aziridine ring with toluene-*p*-thiol followed by reduction with Raney nickel-T4 to give the validoxylamine A derivative (**10**). Glycosylation of the alcohol (**13**) derived from (**10**) afforded validamycins A and E, and related compounds of biological interest.

The optically resolved Diels-Alder *endo* adduct[7] of furan and acrylic acid has been used as a starting material, from which the key intermediate, the protected derivative[2] (**4**) of valienamine and the epoxide[2] (**5**) have been derived in 12 and 9 steps of reaction, respectively, following essentially the procedure employed in a synthesis of the related racemic compounds.[8,9] Coupling of the epoxide (**5**) with the amine (**4**) was carried out in propan-2-ol in a sealed tube at 120 °C for 110 h to afford two products (**6**) and (**7**) in 75 and 15% yields, respectively. Since our purpose was to transform compound (**6**) into the aglycone (**13**) *via* (**10**), we attempted to replace the hydroxy group with the readily removable chloro or iodo atoms under various conditions. In both cases the aziridine (**8**) was formed as the major constituent together with a complex mixture of products. Compound (**6**) was then treated with sodium hydride and di-imidazolyl sulphone[10] in dry *N*,*N*-dimethylformamide (DMF) at 50 °C to yield (**8**) (89%), the structure of which was established on the basis of its ^{1}H n.m.r. spectrum (400 MHz, $CDCl_3$). Compound (**8**) was highly reactive, and the aziridine ring was found to be easily cleaved by nucleophilic attack with acetic acid. Thus, treatment of (**8**) with toluene-*p*-thiol in propan-2-ol at 80 °C gave a single sulphide (**9**) (91%), the n.m.r. spectrum of which contained a doublet of doublets (*J* 2.9 and 3.4 Hz) at δ 3.31, indicating the introduction of the *p*-tolylthio group at C-6. The structure of (**9**) was fully established by treatment of the compound with sodium in liquid ammonia followed by acetylation to convert it into the (+)-validoxylamine A octa-acetate (**11**) (56%). Treatment of compound (**9**) with deactivated Raney nickel T-4 gave the desired, protected validoxylamine A (**10**) in good yield. Debenzylidenation of (**10**) in aqueous 80% acetic acid gave the diol (**12**) (86%). The primary hydroxy group of (**12**) was selectively acetylated with imidazole and acetyl chloride[11] in chloroform to afford the mono-acetate (**13**) (61%).

Condensation of the aglycone (**13**) with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl chloride† (**14**) in dry dichloromethane in the presence of silver trifluoromethanesulphonate (AgOTf) and 1,1,3,3-tetramethylurea (TMU) at room temperature for 10 h afforded the β-glucoside (**15**) (84%). On the other hand, the reaction of (**13**) with 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucopyranose[12] (**17**) (α,β-anomeric mixture) was conducted in the presence of trimethylsilyl trifluoromethanesulphonate[13] (TMSOTf) in dry dichloromethane at room temperature for 5 h to give the α-glucoside (**18**) (52%). Furthermore, condensation of the aglycone (**13**) with the readily available halides (**20**), (**23**), and (**26**)‡ obtained from the disaccharides D-maltose, D-cellobiose, and D-lactose were attempted similarly in the presence of AgOTf and TMU.

† The chloride (**14**) was prepared from D-glucose according to the standard procedure.

‡ The bromides (**20**), (**23**), and (**26**) were prepared from the corresponding free disaccharides according to the standard procedures.



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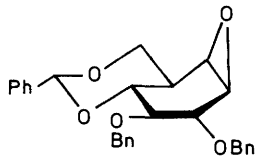

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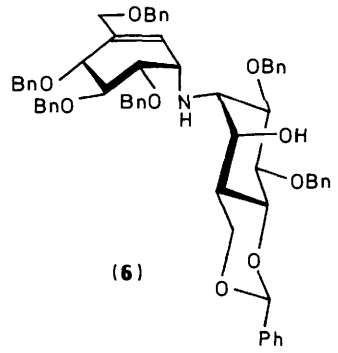

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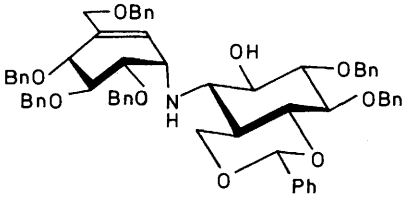

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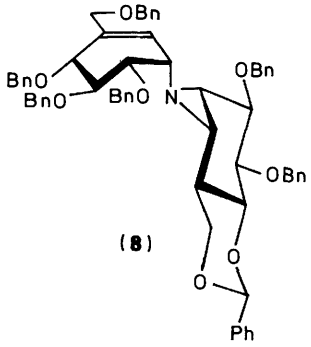

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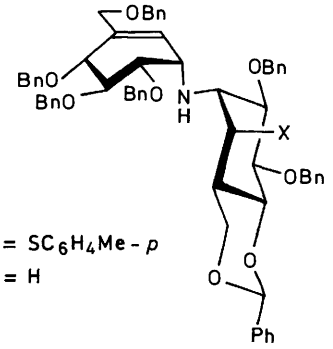
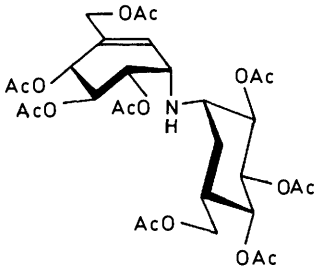


(9) X = SC_6H_4Me-*p*
(10) X = H

Bn = $PhCH_2$



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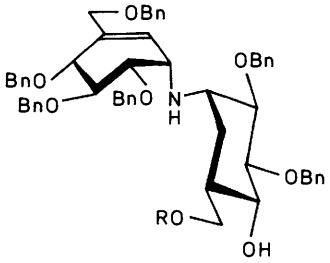


(12) R = H
(13) R = Ac

Table 1. Condensation of the aglycone (**13**) with various sugars

Sugar	Reagent	Solvent	Temp.	Time (h)	Product	Yield (%)
(**14**)	AgOTf[a]	CH_2Cl_2	R.t.	10	(**15**)	84
(**17**)	TMSOTf[b]	CH_2Cl_2	R.t.	5	(**18**)	52
(**20**)	AgOTf	$(CH_2Cl)_2$	Reflux	15	(**21**)	33
(**23**)	AgOTf	$(CH_2Cl)_2$	Reflux	2.5	(**24**)	70
(**26**)	AgOTf	$(CH_2Cl)_2$	Reflux	1.5	(**27**)	81

[a] Silver trifluoromethanesulphonate. [b] Trimethylsilyl trifluoromethanesulphonate.

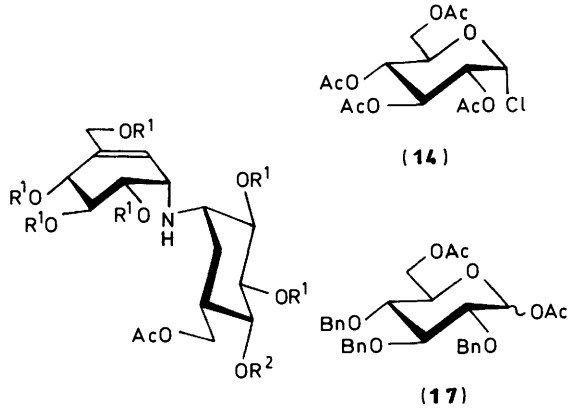
However, the reaction would not proceed under the conditions employed in the case of (**13**) and (**14**). Finally, the more forcing conditions (in 1,2-dichloroethane at reflux temperature) were shown to be necessary for coupling of (**13**) with the disaccharide halides, to yield the desired condensates in appropriate yields (Table 1).

The condensates (**15**), (**18**), (**21**), (**24**), and (**27**) were deprotected with sodium in liquid ammonia at −78 °C followed by acetylation to give the total acetates (**16**), (**19**), (**22**), (**25**), and (**28**), the structures of which were confirmed by the ^1H n.m.r. spectra (Table 2). ^1H N.m.r. data and optical rotations of the acetates (**11**), (**16**), and (**22**) were identical with those reported for authentic samples.

Experimental

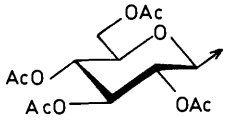
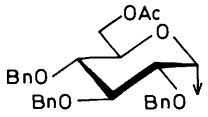
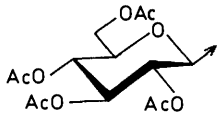
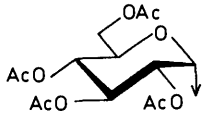
M.p.s were determined on a MEL-TEMP capillary melting point apparatus and are uncorrected. N.m.r. spectra were measured in deuteriochloroform solution with a Varian EM-390 (90 MHz) or JEOL FX-400 (400 MHz) instrument. Optical rotations were measured with a Jasco DIP-4 instrument. T.l.c. was performed on Silica gel 60 F-254 (E. Merck, Darmstadt). The silica gel used for column chromatography was Wakogel C-300 (Wako Co., Osaka, Japan; 300 Mesh).

2,3,4′,5′,6′,7′-*Hexa*-O-*benzyl*-4,5-O-*benzylidenevalidoxylamine B* (**6**) and (1S,3S,6S,7R,8S,9S,10R)-9,10-*Dibenzyloxy*-7-



(14)

(17)

	R^1	R^2
(15)	Bn	
(18)	Bn	
(16)	Ac	
(19)	Ac	

[(1S)-(1,4,6/5)-4,5,6-*tribenzyloxy*-3-*benzyloxymethylcyclohex*-2-*enylamino*]-8-*hydroxy*-3-*phenyl*-2,4-*dioxabicyclo*[4.4.0]-*decane* (**7**).—A mixture of the amine (**4**) (0.23 g, 0.43 mmol) and the epoxide (**5**) (0.21 g, 0.47 mmol) in propan-2-ol (2 ml) was heated in a sealed tube at 120 °C for 110 h. The mixture was concentrated and the residue was purified on a silica gel column (25 g), with butan-2-one–toluene (1:15, v/v) as eluant, to give, first, the amine (**7**) (61 mg, 15%) as a syrup (Found: C, 76.95; H, 6.6; N, 1.4. $C_{53}H_{65}NO_9$ requires C, 77.2; H, 6.7; N, 1.4%); $[\alpha]_D^{23}$ +13° (*c* 1.5 in $CHCl_3$); δ_H (90 MHz, $CDCl_3$) (*inter alia*) 2.30—2.54 (1 H, m, 6-H), 5.38 (1 H, s, 3-H), 5.92 (1 H, d, *J* 4.5 Hz, 2′-H), and 7.13—7.70 (35 H, m, 7 Ph).

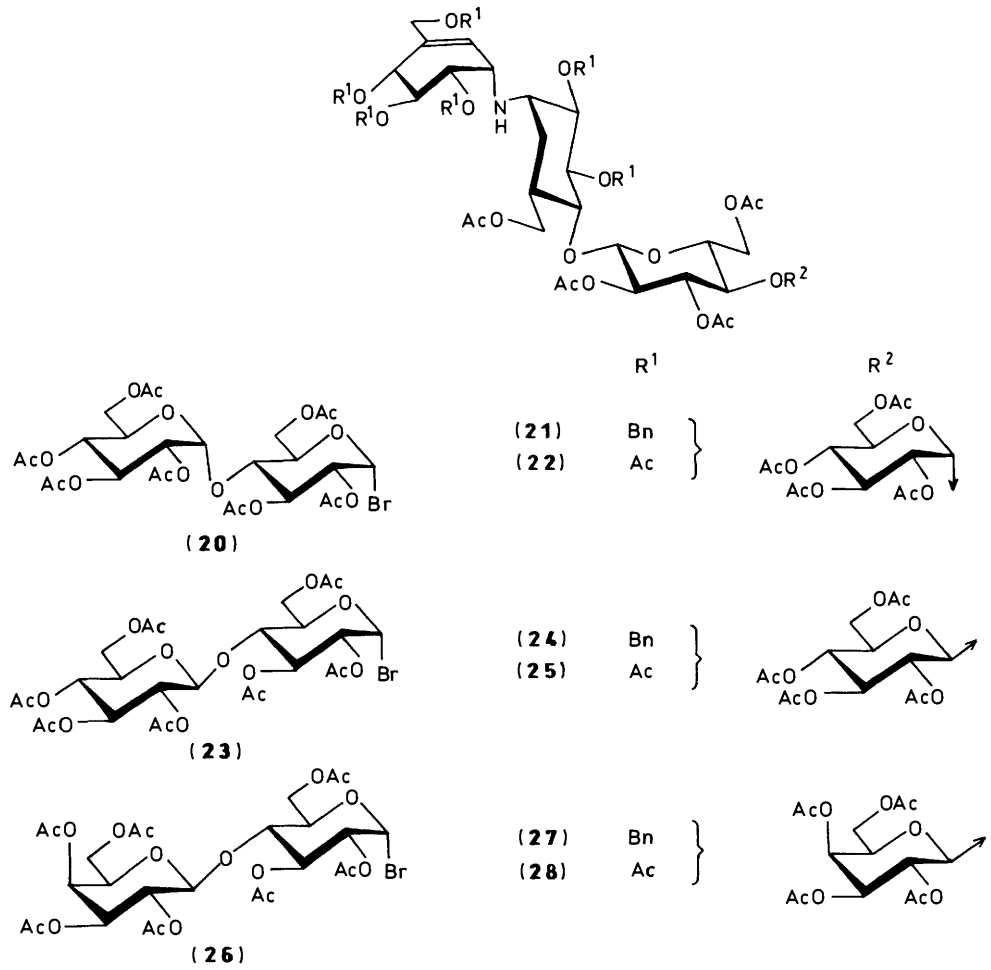
The second fraction gave the amine (**6**) (0.31 g, 75%) as a syrup (Found: C, 76.9; H, 6.8; N, 1.4. $C_{53}H_{65}NO_9$ requires C, 77.2; H, 6.7; N, 1.4%); $[\alpha]_D^{23}$ +46° (*c* 2.5 in $CHCl_3$); δ_H (90 MHz, $CDCl_3$) (*inter alia*) 1.70 (1 H, br s, OH), 2.35—2.57 (1 H, m, 5-H), 3.01—3.18 (1 H, m, 1-H), 3.20—3.38 (1 H, m, 1′-H), 5.54 (**1** H, s, CHPh), 5.84 (1 H, d, *J* 4.5 Hz, 2′-H), and 7.17—7.73 (35 H, m, 7 Ph).

(1S,2R,5R,7R,8S,10S)-8,9-*Dibenzyloxy*-11-[(1S)-(1,4,6/5)-4,5,6-*tribenzyloxy*-3-*benzyloxymethylcyclohex*-2-*enyl*]-5-*phenyl*-4,6-*dioxa*-11-*azatricyclo*[8.1.0.0.^{2,7}]*undecane* (**8**).—To a solution of the alcohol (**6**) (309 mg, 0.315 mmol) in DMF (8 ml) was added sodium hydride (38 mg, 0.945 mmol), and the mixture was stirred at 50 °C for 40 min. Di-imidazolyl sulphone (245 mg, 1.26 mmol) was then added to it and the mixture was stirred at the same temperature for 50 min. The mixture was diluted with EtOAc (50 ml), washed with water, dried, and concentrated. The residue was chromatographed on a silica gel column (10 g), with EtOAc–hexane (1:5, v/v) as eluant, to give the aziridine (**8**) (269 mg, 89%) as a syrup (Found: C, 78.5; H, 6.6; N, 1.9. $C_{63}H_{63}NO_8$ requires C, 78.6; H, 6.6; N, 1.5%); $[\alpha]_D^{28}$ +115° (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) (*inter alia*) 1.42 (1 H, dd, *J* 5.9 and 1.5 Hz, 1-H), 1.93 (1 H, dd, *J* 5.9 and 3.9 Hz, 10-H), 2.14—2.22 (1 H, m, 2-H), 2.22 (1 H, dd, *J* 4.9 and 4.2 Hz, 1′-H), 3.32 (1 H, t, *J* 10.5 Hz, 7-H), 3.50 (1 H, t, J_{gem} 11.3 Hz, 3-H_{ax}), 3.59 (1 H, dd, *J* 9.8 and 4.2 Hz, 6′-H), 3.60 (1 H, dd, *J* 10.5 and 8.1 Hz, 8-H), 3.79 (1 H, br d, J_{gem} 13.2 Hz, 7′a-H), 3.81 (1 H, dd, *J* 8.1 and 3.9 Hz, 9-H), 3.87 (1 H, dd, J_{gem} 11.3 Hz, *J* 4.6 Hz, 3-H_{eq}), 4.10 (1 H, br d, J_{gem} 13.2 Hz, 7′b-H), 4.36 (1 H, br d, *J* 6.8 Hz, 4′-H), 5.47 (1 H, s, 5-H), and 5.82 (1 H, dd, *J* 4.9 and 1.0 Hz, 2′-H).

2,3,4′,5′,6′,7′-*Hexa*-O-*benzyl*-4,7-O-*benzylidene*-6-p-*toluene-sulphenylvalidoxylamine* A(**9**).—The aziridine (**8**) (134 mg, 0.14 mmol) and toluene-*p*-thiol (87 mg, 0.70 mmol) in propan-2-ol (1 ml) was stirred at 80 °C for 4 h. The reaction mixture was concentrated and chromatographed on a silica gel column (3 g), with EtOAc–hexane (1:9—1:5, v/v) as eluant, to give the sulphide (**9**) (137 mg, 91%) as a syrup (Found: C, 77.4; H, 6.6; N, 1.4. $C_{70}H_{71}NO_8S$ requires C, 77.4; H, 6.6; N, 1.3%); $[\alpha]_D^{26}$ +41° (*c* 1.0 in $CHCl_3$), δ_H (400 MHz, $CDCl_3$) (*inter alia*) 2.29 (3 H, s, CH_3), 2.90—3.07 (**1** H, m, 5-H), 2.95—3.05 (1 H, m, 1′-H), 3.26 (1 H, dd, *J* 3.9 and 2.9 Hz, 1-H), 3.31 (1 H, t, *J* 3.4 and 2.9 Hz, 6-H), 3.46 (1 H, dd, *J* 8.3 and 4.4 Hz, 6′-H), 3.74 (1 H, br d, J_{gem} 12.0 Hz, 7′a-H), 3.83 (1 H, dd, J_{gem} 11.0 Hz, *J* 4.4 Hz, 7-H_{eq}), 3.85 (1 H, t, *J* 9.4 Hz, 3-H), 3.98 (1 H, dd, *J* 8.3 and 5.7 Hz, 5′-H), 4.00 (1 H, t, *J* 9.4 Hz, 4-H), 4.05 (1 H, br d, *J* 5.7 Hz, 4′-H), 4.08 (1 H, dd, *J* 9.4 and 3.9 Hz, 2-H), 4.15 (1 H, t, J_{gem} 11.0 Hz, 7-H_{ax}), 4.18 (1 H, d, J_{gem} 12.0 Hz, 7′b-H), and 5.64 (1 H, br d, *J* 4.4 Hz, 2′-H).

2,3,4′,5′,6′,7′-*Hexa*-O-*benzyl*-4,7-O-*benzylidenevalidoxyl-amine A* (**10**).—To the sulphide (**9**) (128 mg, 0.12 mmol) in 1,4-dioxane–ethanol (4 ml/4 ml) was added Raney nickel T-4, and stirred at 60 °C for 6 h. The catalyst was filtered off, and the filtrate was concentrated. The syrupy residue was chromatographed on a silica gel column (5 g), with EtOAc–hexane (1:5, v/v) as eluant, to give validoxylamine A derivative (**10**) (85 mg, 75%) as a syrup (Found: C, 78.6; H, 6.8; N, 1.7. $C_{53}H_{65}NO_8$ requires C, 78.5; H, 6.8; N, 1.45%); $[\alpha]_D^{17}$ +46° (*c* 1.0 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, CHPh), 5.90 (1 H, br d, *J* 4.5 Hz, 2′-H), and 7.13—7.63 (35 H, m, 7 Ph).

Validoxylamine A *Octa*-O-*acetate* (**11**).—To liquid ammonia (30 ml) containing sodium (0.33 g, 14 mmol) was added a solution of compound (**9**) (153 mg, 0.14 mmol) in THF (5 ml) at −78 °C, and the mixture was stirred at the same temperature for 6 h. After addition of excess of ammonium chloride, the mixture was kept at room temperature and then concentrated. T.l.c. indicated the formation of a single compound identical to validoxylamine A (**1**) in propanol–acetic acid–water (3:1:1, v/v). The amine was acetylated with acetic anhydride in pyridine at room temperature overnight, and the product was purified on a silica gel column (3 g), with butan-2-one–toluene (1:3, v/v) as eluant, to give the octa-acetate (**11**) (53 mg, 56%) as a syrup (Found: C, 53.55; H, 6.0; N, 2.0. $C_{30}H_{41}NO_{16}$ requires C, 53.65; H, 6.15; N, 2.1%); $[\alpha]_D^{20}$ +107° (*c* 1.6 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) (*inter alia*) 1.52 (1 H, td, *J* 14.2 and 2.2 Hz, 6-H_{ax}), 1.84 (1 H, dt, *J* 14.2 and 4.2 Hz, 6-H_{eq}), 2.00 (3 H, s, $COCH_3$), 2.03 (3



H, s, $COCH_3$), 2.06 (9 H, s, 3 $COCH_3$), 2.07 (3 H, s, $COCH_3$), 2.075 (3 H, s, $COCH_3$), 2.09 (3 H, s, $COCH_3$), 2.38—2.49 (1 H, m, 5-H), 3.38 (1 H, br q, *J* 4.4, 4.2, and 2.2 Hz, 1-H), 3.55 (1 H, br t, *J* 3.9 Hz, 1′-H), 3.89 (1 H, dd, J_{gem} 11.4, *J* 3.2 Hz, 7a-H), 4.13 (1 H, dd, J_{gem} 11.4 and 4.6 Hz, 7b-H), 4.39 (1 H, br d, J_{gem} 13.2 Hz, 7′a-H), 4.65 (1 H, br d, J_{gem} 13.2 Hz, 7′b-H), 4.94 (1 H, dd, *J* 9.5 and 3.9 Hz, 6′-H), 4.97 (1 H, t, *J* 9.8 Hz, 4-H), 4.98 (1 H, dd, *J* 9.8 and 4.4 Hz, 2-H), 5.39 (1 H, t, *J* 9.8 Hz, 3-H), 5.41 (1 H, dd, *J* 9.5 and 6.1 Hz, 5′-H), 5.49 (1 H, br d, *J* 6.1 Hz, 4′-H), and 5.99 (1 H, br d, *J* 3.9 Hz, 2′-H).

2,3,4′,5′,6′,7′-*Hexa*-O-*benzylvalidoxylamine A* (**12**).—A solution of compound (**10**) (678 mg, 0.70 mmol) in aqueous 80% acetic acid (30 ml) was stirred at 50 °C for 9 h. The mixture was concentrated and coevaporated with ethanol. The residue was purified on a silica gel column (20 g), with butan-2-one–toluene (2:7, v/v) as eluant, to give the diol (**12**) (528 mg, 86%) 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° (*c* 3.7 in $CHCl_3$); δ_H (90 MHz, $CDCl_3$) (*inter alia*) 2.60—2.90 (2 H, m, 2 OH), 4.40—4.70 (12 H, m, 6 CH_2Ph), 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* (**13**).—To a solution of imidazole (164 mg, 2.4 mmol) in $CHCl_3$ (10 ml) was added acetyl chloride (0.086 ml, 1.2 mmol) dropwise at 0 °C. The insoluble material was filtered off and washed with $CHCl_3$ (1 ml). To a solution of the diol (**12**) (528 mg, 0.60 mmol) in $CHCl_3$ (5 ml) was added the imidazole solution, and the mixture was refluxed for 48 h. The reaction mixture was diluted with $CHCl_3$ (50 ml), washed with water, dried, and concentrated. The residue was chromatographed on a silica gel column (20 g), with butan-2-one–toluene (1:9, v/v) as eluant, to give the monoacetate (**13**) (336 mg, 61%) as a syrup (Found: 75.55; H, 6.9; N, 1.8. $C_{58}H_{63}NO_9$ requires C, 75.9; H, 6.9; N, 1.5%); $[\alpha]_D^{18}$ +58° (*c* 0.9 in $CHCl_3$); δ_H (90 MHz, $CDCl_3$) (*inter alia*) 1.94 (3 H, s, $COCH_3$), 2.43—2.55 (1 H, br s, OH), 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, d, br d, *J* 3.5 Hz, 2′-H), and 7.24—7.40 (30 H, m, 6 Ph).

Condensation of the Alcohol (**13**) *with the Halide* (**14**).—To a solution of the aglycone (**13**) (100 mg, 0.11 mmol) in dry dichloromethane (3 ml) was added silver trifluoromethanesulphonate (67 mg, 0.26 mmol) and 1,1,3,3-tetramethylurea (0.046 ml, 0.39 mmol) in the dark, and then a solution of the halide (**14**) (160 mg, 0.44 mmol) in dry dichloromethane (2 ml) was added to the mixture. The reaction mixture was stirred at room temperature for 10 h, neutralised with 10% Et_3N in $CHCl_3$ and the insoluble material was filtered off. The filtrate was concentrated and the residue was chromatographed on a silica gel column (10 g), with butan-2-one–toluene (1:7, v/v) as eluant, to give the β-condensate (**15**) (115 mg, 84%) as a syrup (Found: C, 69.25; H, 6.6; N, 1.3. $C_{72}H_{81}NO_{18}$ requires C, 69.3; H, 6.6; N, 1.1%); $[\alpha]_D^{18}$ +42° (*c* 1.7 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, 6Ph).

Validamycin A Undeca-O-*acetate* (**16**).—Compound (**15**) (115 mg, 0.092 mmol) was deprotected as described in the

Table 2. ^{1}H N.m.r. spectral data (400 MHz, $CDCl_3$) for compounds (**16**), (**19**), (**22**), (**25**), and (**28**)

	Chemical shifts δ (p.p.m.)					Coupling constants (Hz)					
Proton	(**16**)	(**19**)	(**22**)	(**25**)	(**28**)	*J*	(**16**)	(**19**)	(**22**)	(**25**)	(**28**)
1	3.27(dd)	3.28(br q)	3.27(q)[a]	3.26(q)[a]	3.26(q)[a]	1,2	3.6	3.9	3.4	3.9	3.9
2	4.87(dd)	4.86(dd)	4.86(dd)	4.85(dd)	4.85(dd)	2,3	9.8	10.2	10.2	10.2	10.3
3	5.35(t)	5.41(t)[a]	5.35(dd)	5.38(t)[a]	5.33(t)[a]	3,4	9.8	8.8	9.3	9.3	8.8
4	3.58(t)	3.81(dd)	3.59(dd)	3.56(dd)	3.56(dd)	4,5	9.8	9.8	10.7	10.8	10.3
5	2.25—2.34(m)	2.36—2.48 (m)	2.23—2.35(m)	2.25—2.38(m)	2.26—2.36(m)	$5,6_{ax}$	13.4	12.5	12.2	12.2	12.5
6_{ax}	1.38(td)[a]	1.46(td)[a]	1.38(td)[a]	1.37(td)[a]	1.37(td)[a]	$5,6_{eq}$	3.6	3.4	3.3	3.4	3.4
6_{eq}	1.80(dt)	1.82(dt)	1.79(dt)	1.78(dt)	1.78(dt)	5,7a	2.0	2.6	4.9	4.4	4.4
7a	4.04(dd)	4.03(dd)	4.12(dd)	4.12(dd)	4.10(dd)	5,7b	6.2	4.4	2.0	2.7	3.4
7b	4.40(dd)	4.34(dd)	4.31(dd)	4.30(dd)	4.30(dd)	$6_{ax},6_{eq}$	13.4	14.0	14.2	14.2	14.7
1′	3.57(t)	3.59(br t)	3.52—3.60(m)	3.53—3.60(m)	3.57(t)[a]	7a,7b	12.6	11.6	11.2	11.2	11.2
2′	5.96(br d)	5.99(br d)	5.96(d)	5.96(d)	5.96(d)	$1,6_{ax}$		2.2	2.2	2.2	2.2
4′	5.50(br d)	5.53(br d)	5.49(br d)	5.49(br d)	5.49(br d)	$1,6_{eq}$	3.6	3.4	3.3	3.4	3.4
5′	5.40(dd)	5.43(dd)	5.39(dd)	5.39(dd)	5.39(dd)	1′,2′	4.5	4.4	4.4	3.9	3.9
6′	4.95(dd)	5.01(dd)	4.97(dd)	4.97(dd)	4.97(dd)	4′,5′	6.0	5.9	5.9	6.4	5.9
7′a	4.39(br d)	4.40(br d)	4.39(br d)	4.39(br d)	4.39(br d)	5′,6′	9.4	9.3	9.5	9.3	9.3
7′b	4.66(br d)	4.67(br d)	4.66(br d)	4.66(br d)	4.66(br d)	1′,6′	4.5	4.4	4.6	4.9	4.9
1″	4.52(d)	5.43(d)	4.57(d)	4.50(d)	4.51(d)	7′a,7′b	13.2	13.2	13.2	13.2	13.2
2″	4.97(dd)	4.99(dd)	4.78(t)[a]	4.87(dd)	4.85(dd)	1″,2″	7.9	3.9	7.8	7.8	7.8
3″	5.15(t)	5.08(t)	5.18(t)	5.13(t)	5.15(t)	2″,3″	9.5	9.8	8.8	9.3	8.8
4″	5.09(t)	5.07(t)	4.01(dd)	3.79(t)[a]	3.81(t)	3″,4″	9.5	9.8	8.8	9.3	8.8
5″	3.65(ddd)	3.72(ddd)	3.67(ddd)	3.64(ddd)	3.59(ddd)	4″,5″	9.5	9.8	9.3	9.8	9.3
6″a	4.14(dd)	4.23(dd)	4.27(dd)	4.12(dd)	4.12(dd)	5″,6″a	4.1	4.1	3.9	4.0	4.4
6″b	4.31(dd)	4.33(dd)	4.34(dd)	4.36(dd)	4.36(dd)	5″,6″b	2.6	2.8	2.9	2.9	2.0
1‴			5.38(d)	4.49(d)	4.45(d)	6″a,6″b	11.3	11.7	12.3	12.2	12.2
2‴			4.86(dd)	4.91(dd)	4.94(dd)	1‴,2‴			3.9	8.3	7.8
3‴			5.34(dd)	5.33(dd)	5.35(dd)	2‴,3‴			10.3	10.3	10.3
4‴			5.06(t)	5.06(t)	4.95(t)	3‴,4‴			9.9	9.3	3.4
5‴			3.85—3.95(m)	3.53—3.60(m)	3.52—3.60(m)	4‴,5‴			9.9	9.3	3.4
6‴a			4.03(dd)	4.04(dd)	4.08(dd)	5‴,6‴a			2.0	2.0	2.0
6‴b			4.23(dd)	4.24(dd)	4.30(dd)	5‴,6‴b			3.4	3.1	3.5
						6‴a,6‴b			12.2	12.2	12.2
$COCH_3$	2.115 2.08	2.12 2.10	2.16 2.14	2.14 2.115	2.15 2.13						
	2.071 2.071	2.08 2.08	2.10 2.07	2.09 2.069	2.12 2.067						
	2.068 2.06	2.073 2.067	2.07 2.06	2.065 2.059	2.067 2.067						
	2.06 2.05	2.063 2.05	2.06 2.05	2.059 2.048	2.058 2.058						
	2.010 2.007	2.03 2.00	2.05 2.04	2.046 2.040	2.058 2.050						
	1.99	1.99	2.03 2.00	2.01 2.00	2.050 2.03						
			1.99 1.99	1.98 1.97	1.97 1.96						

[a] Splitting pattern in appearance.

preparation of (**11**) from (**9**) to give validamycin A (**2**), which was identified with an authentic sample on t.l.c. in propanol–acetic acid–water (R_F 0.28, 3:1:1, v/v). This compound was then treated with acetic anhydride in pyridine to give the undeca-acetate (**16**) (53 mg, 60%) as a syrup (Found: C, 52.1; H, 5.9; N, 1.45. $C_{42}H_{57}NO_{24}$ requires C, 52.55; H, 6.0; N, 1.5%); $[\alpha]_D^{15}$ +61° (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) data shown in Table 2.

2,3,7,4′,5′,6′,7′-*Hepta*-O-*acetyl*-4-O-(2,3,4,6-*tetra*-O-*acetyl*-α-D-*glucopyranosyl*)*validoxylamine A* (**19**).—To a suspension of the aglycone (**13**) (226 mg, 0.25 mmol), the acetate (**17**) (311 mg, 0.58 mmol) and molecular sieve 4A (225 mg) in dry dichloromethane (5 ml) was added trimethylsilyl trifluoromethanesulphonate (0.12 ml, 0.62 mmol), and the mixture was stirred at room temperature for 5 h. It was then neutralised with 10% Et_3N in $CHCl_3$, filtered, and concentrated. The resulting syrup was chromatographed on a silica gel column (60 g), with butan-2-one–toluene (1:20, v/v) as eluant, to give the condensate (**18**) (178 mg, 52%) as a syrup, , $[\alpha]_D^{20}$ +16° (*c* 1.6 in $CHCl_3$); δ_H (90 MHz, $CDCl_3$) (*inter alia*) 2.00 and 2.03 (6 H, 2 s, 2 $COCH_3$), 6.07 (1 H, br d, *J* 4.5 Hz, 2′-H), and 7.37—7.75 (45 H, m, 9 Ph).

Compound (**18**) (178 mg, 0.13 mmol) was deprotected as described in the preparation of (**11**) from (**9**) and reacetylated in the usual way to give the validamycin A derivative (**19**) (15 mg, 12%) as a syrup (Found: C, 52.1; H, 5.9; N, 1.4. $C_{42}H_{57}NO_{24}$ requires C, 52.5; H, 6.0; N, 1.5%); $[\alpha]_D^{24}$ +99° (*c* 0.8 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) data shown in Table 2.

7,2″,3″,6″,2‴,3‴,4‴,6‴-*Octa*-O-*acetyl*-2,3,4′,5′,6′,7′-*hexa*-O-*benzylvalidamycin E* (**21**).—To a mixture of the aglycone (**13**) (138 mg, 0.15 mmol), silver trifluoromethanesulphonate (77 mg, 0.30 mmol), and 1,1,3,3-tetramethylurea (0.063 ml, 0.52 mmol) in dry 1,2-dichloroethane (4 ml) was added a solution of acetobromomaltose (**20**) (368 mg, 0.53 mmol) in dry 1,2-dichloroethane (4 ml) dropwise at room temperature; the mixture was then refluxed with stirring overnight in the dark. It was then neutralised with 10% Et_3N in $CHCl_3$ and insoluble material was filtered off. The filtrate was concentrated and the residue was chromatographed on a silica gel column (65 g), with butan-2-one–toluene (1:5, v/v) as eluant, to give the condensate (**21**) (77 mg, 33%) as a syrup, $[\alpha]_D^{18}$ +71° (*c* 2.5 in $CHCl_3$); δ_H (90 MHz, $CDCl_3$) (*inter alia*) 2.02, 2.05, 2.10, and 2.12 (24 H, 4 s, 8 $COCH_3$), 6.05 (1 H, br d, *J* 4.5 Hz, 2′-H), and 7.42—7.64 (30 H, m, 6 Ph).

Validamycin E Tetradeca-O-*acetate* (**22**).—Compound (**21**) (72 mg, 0.047 mmol) was deprotected as described in the preparation of (**11**) from (**9**) and acetylated in the usual way to give tetradeca-acetate (**22**) (16 mg, 28%) as a syrup (Found: C, 51.7; H, 5.7; N, 1.2. $C_{54}H_{73}NO_{32}$ requires C, 52.0; H, 5.9; N, 1.1%); $[\alpha]_D^{24}$ +78.5° (*c* 0.8 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) data shown in Table 2.

7,2″,3″,6″-*Tetra*-O-*acetyl*-4″-O-(2,3,4,6-*tetra*-O-*acetyl*-β-D-*glucopyranosyl*)-2,3,4′,5′,6′,7′-*hexa*-O-*benzylvalidamycin A* (**24**).—Condensation of the aglycone (**13**) (148 mg, 0.16 mmol) with acetobromocellobiose (**23**) (394 mg, 0.56 mmol) was conducted in a similar way to that described in the preparation of (**21**) from (**13**) at reflux temperature for 2.5 h to give the condensate (**24**) (174 mg, 70%) as a syrup (Found: C, 64.6; H, 6.4; N, 0.9. $C_{84}H_{97}NO_{26}\cdot H_2O$ requires C, 64.9; H, 6.4; N, 0.9%); $[\alpha]_D^{25}$ +23° (*c* 1.7 in $CHCl_3$); δ_H (90 MHz, $CDCl_3$) (*inter alia*) 1.96, 2.00, 2.03, and 2.11 (24 H, 4 s, 8 $COCH_3$), 6.06 (1 H, m, 2′-H), and 7.33—7.67 (30 H, m, 6 Ph).

2,3,7,4′,5′,6′,7′,2″,3″,6″-*Deca*-O-*acetyl*-4″-O-(2,3,4,6-*tetra*-O-*acetyl*-β-D-*glucopyranosyl*)*validamycin* A (**25**).—Compound (**24**) (143 mg, 0.093 mmol) was deprotected as described in the preparation of (**11**) from (**9**) and acetylated in the usual way to give tetradeca-acetate (**25**) (25 mg, 21%) as a syrup (Found: C, 52.1; H, 5.8; N, 1.1. $C_{54}H_{73}NO_{32}$ requires C, 52.0; H, 5.9; N, 1.1%); $[\alpha]_D^{23}$ +33° (*c* 0.9 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) data shown in Table 2.

7,2″,3″,6″-*Tetra*-O-*acetyl*-4″-O-(2,3,4,6-*tetra*-O-*acetyl*-β-D-*galactopyranosyl*)-2,3,4′,5′,6′,7′-*hexa*-O-*benzylvalidamycin* A (**27**).—Condensation of the aglycone (**13**) (180 mg, 0.20 mmol) with acetobromolactose (**26**) (480 mg, 0.69 mmol) was conducted in a similar way as described in the preparation of (**21**) from (**13**) at reflux temperature for 1.5 h to give the condensate (**27**) (244 mg, 81%) as a syrup (Found: C, 64.8; H, 6.3; N, 0.9. $C_{84}H_{97}NO_{26}\cdot H_2O$ requires C, 64.9; H, 6.3; N, 0.9%); $[\alpha]_D^{23}$ +29° (*c* 1.55 in $CHCl_3$); δ_H (90 MHz, $CDCl_3$) (*inter alia*) 2.03, 2.08, 2.12, and 2.22 (24 H, 4 s, 8 $COCH_3$), 6.09 (1 H, br d, *J* 4.5 Hz, 2′-H), and 7.36—7.70 (30 H, m, 6 Ph).

2,3,7,4′,5′,6′,7′,2″,3″,6″-*Deca*-O-*acetyl*-4″-O-(2,3,4,6-*tetra*-O-*acetyl*-β-D-*galactopyranosyl*)*validamycin* A (**28**).—Compound (**27**) (207 mg, 0.13 mmol) was deprotected as described in the preparation of (**11**) from (**9**) and acetylated in the usual way to give the tetradeca-acetate (**28**) (32 mg, 19%) as a syrup (Found: C, 51.5; H, 6.1; N, 1.1. $C_{54}H_{73}N_{32}$ requires C, 52.0; H, 5.9; N, 1.1%); $[\alpha]_D^{23}$ +61° (*c* 1.5 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) data shown in Table 2.

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