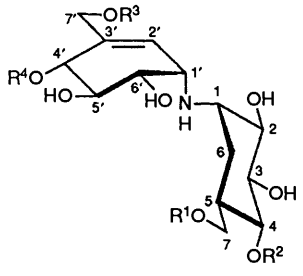
Synthetic Studies on Antibiotic Validamycins. Part 14.[1] Total Synthesis of (+)-Validamycins C, D and F

Yasunobu Miyamoto and Seiichiro Ogawa *
Department of Applied Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Yokohama, 223 Japan

(+)-Validamycins C and F were first completely synthesised by use of a common blocked derivative **5** of (+)-validoxylamine A. The diols **6** and **7**, obtained by acid hydrolysis of **5**, were appropriately protected to give the aglycones **17**, **25** and **30**, which were condensed with glycosyl donor **11** or **19** to afford the condensates **20** and **26**, being convertible, by deprotection and acetylation, to the totally *O*-acetylated derivates **21** and **33** of validamycins C and F, respectively. In addition, (+)-validamycin D was first synthesised by α-glycosylation of the protected derivative **37** of validoxylamine A.

The antibiotic validamycin complex[2] shows growth inhibitory activity against *Rhizoctonia solani* (sheath blight diseases of rice plant). Among its eight components, validamycins A–H;[2,3] validamycins C (**1**) and F (**3**) possess unique pseudo-tetrasaccharidic structures, and are positional isomers with the α-D-glucopyranosides, bonded to the valienamine moiety of validamycin A **4**. Validamycin D contains an α-D-glucopyranose residue at C-7 of validoxylamine A.[4] Thus validamycins A, C and F belong to the same category.



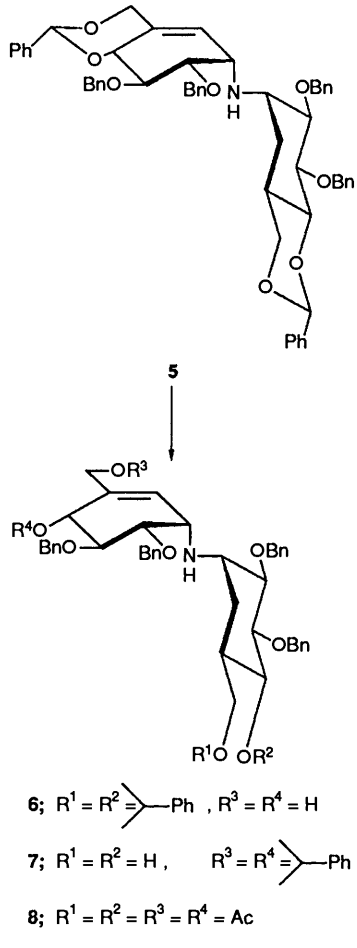
	R^1	R^2	R^3	R^4	
1;	H	β-Glc	α-Glc	H	(Validamycin C)
2;	α-Glc	H	H	H	(Validamycin D)
3;	H	β-Glc	H	α-Glc	(Validamycin F)
4;	H	β-Glc	H	H	(Validamycin A)

Although validamycins C and D show weak activity, validamycin F possesses strong activity almost comparable to validamycin A. Since these are minor components of the validamycin family, we thought it was very important to establish the synthetic route to these compounds, providing sufficient quantities for biochemical study. We now describe the detail of a first total synthesis of (+)-validamycins C, D and F.

We have already achieved the total synthesis of (+)-validoxylamine A,[1,5] therefore, it was advantageous for us to make use of validoxylamine A as a common starting compound, because it is a common constituent of validamycins C, D and F.

Validoxylamine A was easily converted into the 4,7; 4′,7′-di-*O*-benzylidene tetrabenzyl ether **5** in a two-step reaction. Treatment of **5** with AcOH–THF–H_2O (4:2:1) at 60 °C yielded 26% of the 4′,7′-diol **6**, 20% of the 4,7-diol **7**, 16% of the 4,7,4′,7′-tetrol isolated as the tetraacetate (Scheme 1), and 36% of **5** recovered unchanged, when the reaction was quenched before all **5** had reacted in order to suppress the formation of the undesired tetrol.

The diol **6** was transformed into the 7′-OH unsubstituted



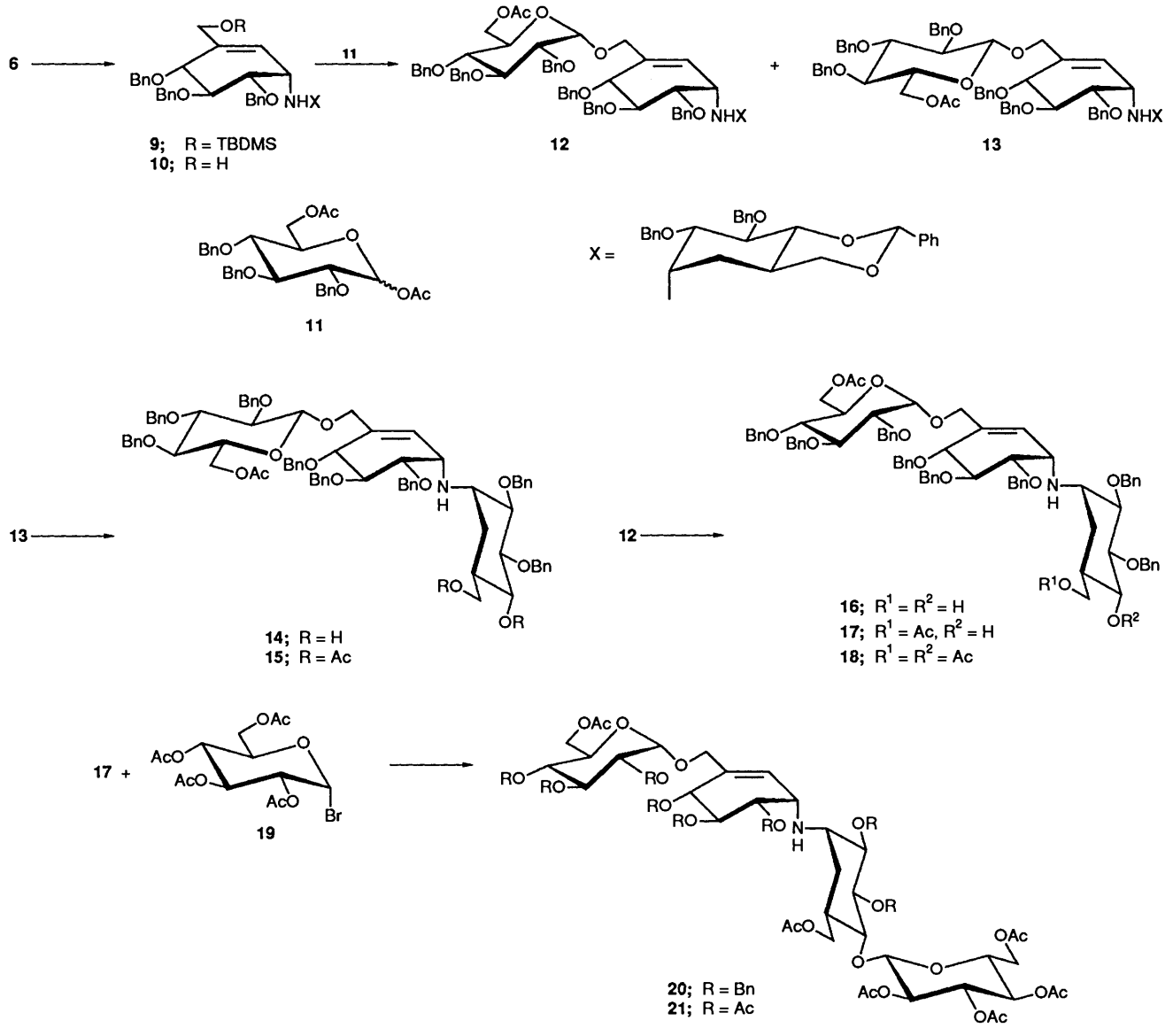
6; $R^1 = R^2 =$, $R^3 = R^4 = H$

7; $R^1 = R^2 = H$, $R^3 = R^4 =$

8; $R^1 = R^2 = R^3 = R^4 = Ac$

Scheme 1

derivative **10**[6] in three-steps in 54% overall yield. Glycosylation of the alcohol **10** with the glycosyl donor, 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucopyranose **11** in the presence of trimethylsilyl trifluoromethanesulphonate (TMSOTf)[7] produced 49% of the desired α-glucoside **12** and 26% of the β-glucoside **13**, whose ^1H NMR spectra revealed anomeric-proton signals at δ 4.83 (*J* 3.66 Hz) and δ 4.35 (*J* 7.69 Hz), respectively, indicative of the α- and β-glucosides. The compound **12** was *O*-debenzylidenated in aqueous 80% acetic acid to afford the 4,7-diol **16**. The primary hydroxy group was protected by treatment with imidazole and acetyl chloride[8] to give the



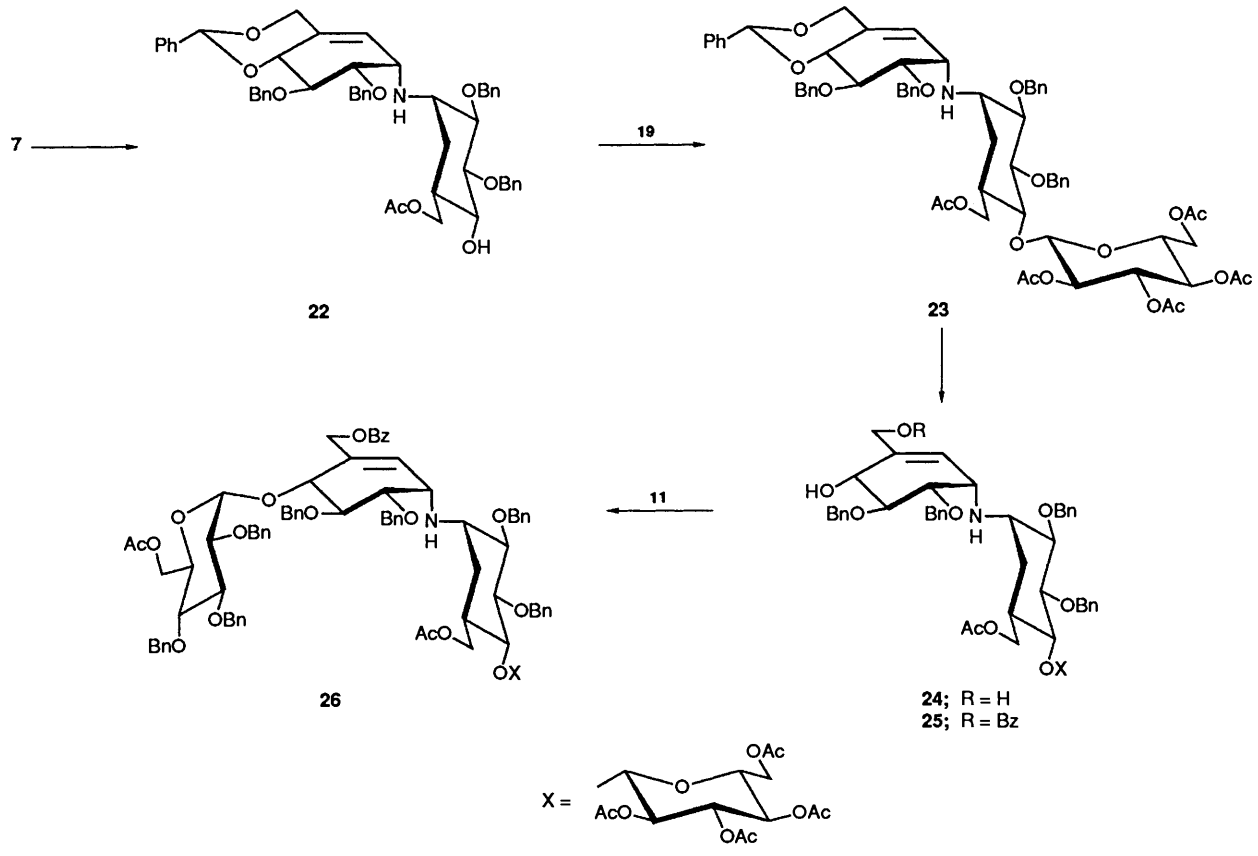
Scheme 2

7-acetate **17**. Condensation of **17** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide **19** in the presence of silver trifluoromethanesulphonate (AgOTf) and 1,1,3,3-tetramethylurea (TMU) for 9 h at room temperature yielded, after fractionation through a column of silica gel, the protected derivative **20** of validamycin C in 76% yield. Compound **20** was deprotected with sodium in liquid ammonia and isolated as its totally *O*-acetylated compound **21** (Scheme 2), the ^{1}H NMR data of which was identical with those reported[9] for an authentic validamycin C tetradecaacetate.

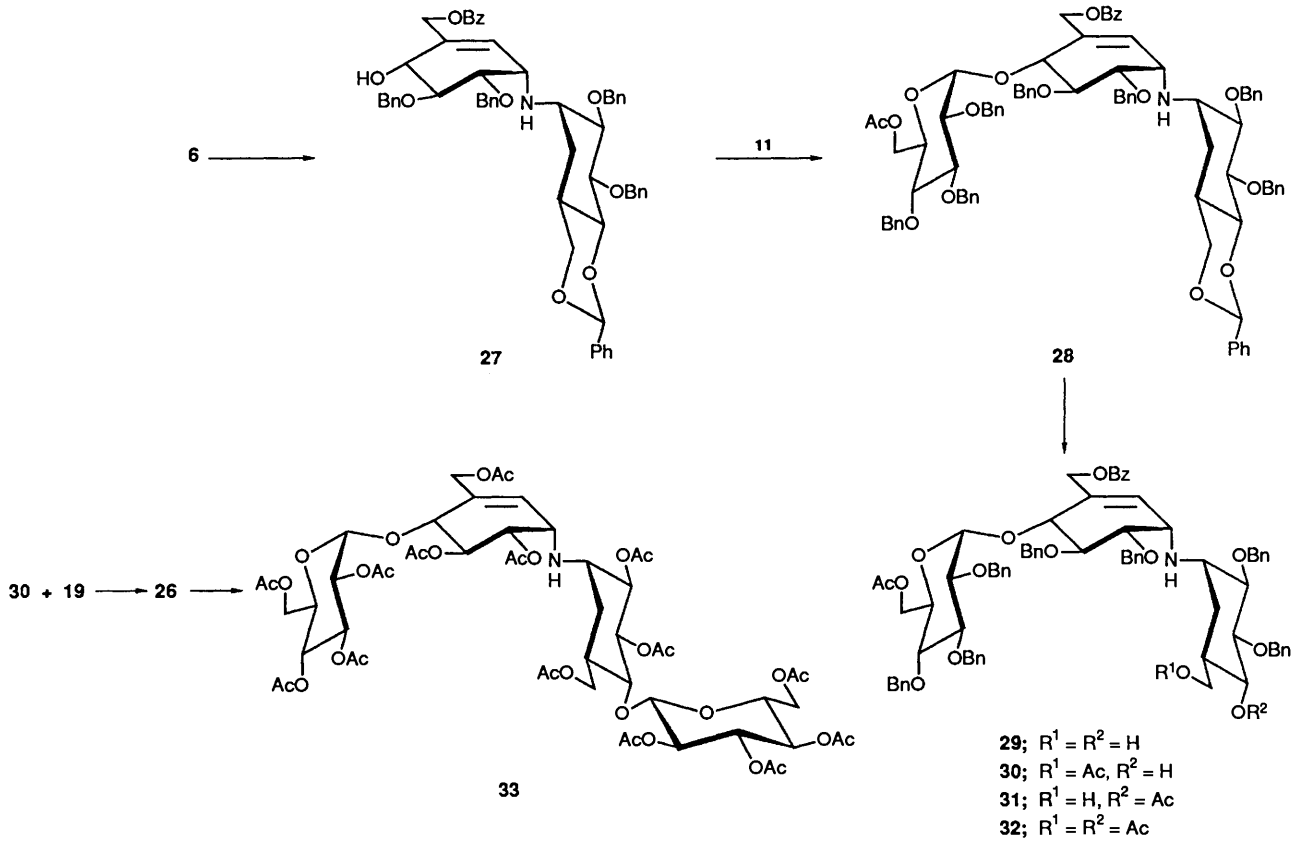
On the other hand, the primary hydroxy group of compound **7** was selectively acetylated in a similar manner to give the acetate **22**. Condensation of **22** with the bromide **19** in the presence of AgOTf and TMU for 23 h at room temperature afforded the β-glucoside **23** in 55% yield. Since both hydroxy groups of **24** were located at the allylic positions, they were highly reactive for the acetylation, and we adopted the benzoyl group as the protecting group for the primary hydroxy. Similar *O*-debenzylidenation followed by benzoylation of the primary hydroxy group with benzoyl chloride in pyridine gave the aglycone **25**. The secondary alcohol **25** was then glycosylated to give the α-glucoside **26** in 39% yield (Scheme 3). As isolation of **26** purely from the reaction mixture was very difficult, we employed the inverse order of glycosylation as shown in Scheme 4.

Treatment of the diol **6** with benzoyl chloride afforded 79% yield of the 7′-benzoate **27**, of which ^{1}H NMR spectrum showed signals due to the C-7′ methylene proton at δ 4.83 and 4.98 (J_{gem} 12.8 Hz). Condensation of **27** with the glycosyl donor **11** in the presence of TMSOTf gave 34% of the condensate **28**, with 36% of the aglycone **27** being recovered. In the ^{1}H NMR spectrum (270 MHz; $CDCl_3$) of **28**, the signals due to the anomeric proton appeared at δ 5.07 (3.3 Hz), indicative of the α-glucoside. *O*-Debenzylidenation and selective acetylation of the primary hydroxy group gave the monoacetate **31** in 63% yield. The aglycone **31** was condensed with **19** in the presence of AgOTf and TMU to produce derivative **26** of validamycin F in good yield. The physical data of this compound were identical with those of the compound derived from **25**. Compound **26** was deprotected with sodium in liquid ammonia, and the product was isolated as its tetradecaacetate **33**, whose ^{1}H NMR spectral data were also identical with those[9] of an authentic sample.

The structure of validamycin D, which had once been assigned as the α-anomer of validamycin A, was later revised to the 7-*O*-α-D-glucopyranoside of validoxylamine A. The diol **34**



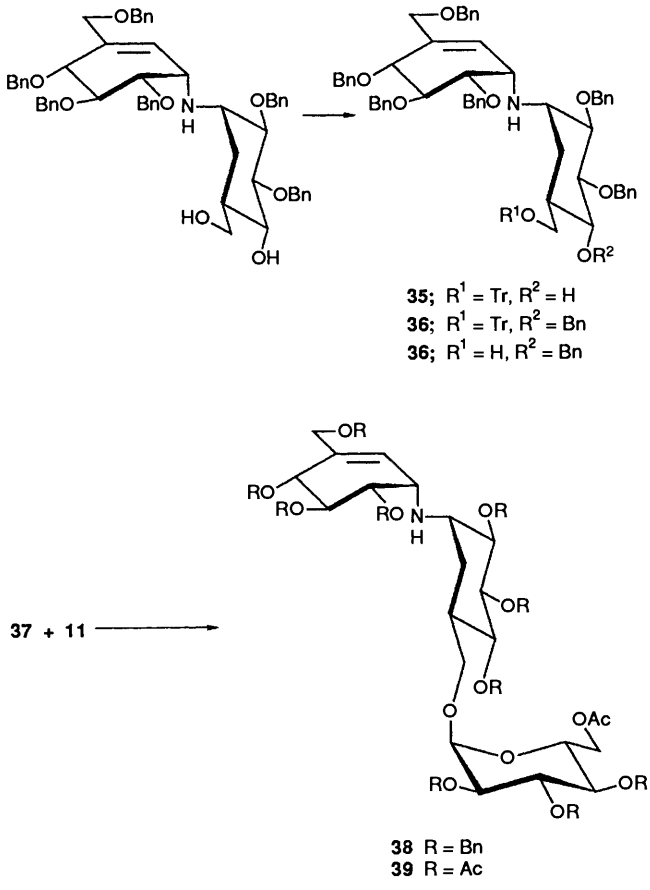
Scheme 3



Scheme 4

was conveniently utilized for a synthesis of validamycin D. On successive tritylation, benzylation, and detritylation, compound **34** was converted into the 7-OH unsubstituted derivative **37**, in 60% yield, α-glycosylation of which was carried out in the similar manner to afford the protected derivative **38** of validamycin D in 49% yield. The ^{1}H NMR of **38** showed a signal due to the anomeric proton at δ 4.73 (*J* 3.9 Hz), giving a good indication of the α-glucoside. Compound **38** was deprotected with sodium in liquid ammonia and then acetylated to give validamycin D undecaacetate **39** (Scheme 5), identical with an authentic sample.[9]

Thus, the first total synthesis of validamycins C, D and F have been achieved.



Scheme 5

Experimental

M.p.s were determined on a MEL-TEMP capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were measured in deuteriochloroform solution with a Varian EM-390 (90 MHz), JEOL JNM FX-270 f.t. (270 MHz) and JEOL JNM FX-400 f.t. (400 MHz) instrument and *J* values are given in Hz. Optical rotations were measured with a JASCO DIP-370 instrument and are given in 10^{-1} deg cm^2 g^{-1}. TLC was performed using Silica gel 60 F-254 (E. Merck, Darmstadt). The silica gel used for column chromatography was Wakogel C-300 (Wako Co., Osaka, Japan) or Silica gel 60 K070 (Katayama Co., Osaka, Japan).

2,3,5′,6′-*Tetra*-O-*benzyl*-4,7;4′,7′-*di*-O-*benzylidenevalidoxylamine A* **5**.—Validoxylamine A (10.00 g, 29.8 mmol) was suspended in *N*,*N*-dimethylformamide (DMF) (100 cm^3), and was added α,α-dimethoxytoluene (13.4 cm^3, 89.3 mmol) and toluene-*p*-sulphonic acid monohydrate (6.16 g, 35.8 mmol). The reaction mixture was stirred under reduced pressure at 60 °C for 7 h. The solution was neutralized with sodium hydrogen carbonate, filtered, and then concentrated to dryness. The syrupy residue was dried under reduced pressure and dissolved in DMF (100 cm^3). The solution was added 60% sodium hydride (7.16 g, 0.179 mol) at 0 °C and stirred for 1 h at the same temperature. Then benzyl bromide (21.3 cm^3, 0.179 mol) was added to the solution and stirred at room temperature for 2 h. An excess of methanol was added to the reaction solution and it was evaporated. The residue was diluted with ethyl acetate (500 cm^3), washed twice with water (300 cm^3), dried, and concentrated. The syrupy residue was purified on a silica gel column (300 g), with EtOAc–hexane (1:4, v/v) as eluent, to give *compound* **5** (16.65 g, 64%) as a syrup (Found: C, 76.8; H, 6.9; N, 2.0. $C_{56}H_{57}NO_8$ requires C, 77.1; H, 6.6; N, 1.6%); $[\alpha]_D^{23}$ +68.6 (*c* 2.65 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) (*inter alia*) 0.81 (1 H, br t*, *J* 13.4, *J* 12.4, 6ax-H), 1.71 (1 H, dt*, *J* 13.4, *J* 3.3, *J* 2.6, 6eq-H), 2.48–2.66 (1 H, m, 5-H), 3.27–3.33 (2 H, m, 1-H, 1′-H), 3.46 (1 H, t, *J* 10.6, 7ax-H), 3.45–3.53 (2 H, m, 2-H, 4-H), 3.55 (1 H, dd, *J* 9.5, *J* 4.4, 6′-H), 3.84 (1 H, dd, *J* 10.6, *J* 4.4, 7eq-H), 3.93 (1 H, t, *J* 9.2, 3-H), 4.10 (1 H, dd, *J* 9.5, *J* 6.2, 5′-H), 4.43 (1 H, br d, *J* 6.2, 4′-H), 4.38 (1 H, br d, *J* 13.5, 7′a-H), 4.46 (1 H, br d, *J* 13.5, 7′b-H), 4.70 and 4.82 (each 1 H, ABq, *J* 12.8, CH_2Ph), 4.66 (2 H, s, CH_2Ph), 4.77 and 4.88 (each 1 H, ABq, *J* 11.0, CH_2Ph), 4.89 (2 H, s, CH_2Ph), 5.54 (1 H, s, PhCH), 5.65 (1 H, br d, *J* 4.8, 2′-H), 5.69 (1 H, s, PhCH) and 7.20–7.59 (30 H, m, 6 Ph).

2,3,5′,6′-*Tetra*-O-*benzyl*-4,7- **6** *and* 4′,7′-O-*benzylidenevalidoxylamine A* **7**, and 4,7,4′,7′-*Tetra*-O-*acetyl*-2,3,5′,6′-*tetra*-O-*benzylvalidoxylamine A* **8**.—A solution of compound **5** (3.62 g, 4.15 mmol) in THF (10 cm^3) was added to aqueous 80% acetic acid (25 cm^3) and was stirred at 60 °C for 33.5 h. The solution was concentrated and azeotroped with ethanol and toluene to give a brown syrup, which was chromatographed on a silica gel column (180 g), with butan-2-one–toluene (1:3, v/v)→acetone–toluene (1:2, v/v) as eluent, to give, first, the *diol* **6** (860 mg, 26%) as a syrup (Found: C, 75.0; H, 6.8; N, 1.85. $C_{49}H_{53}NO_8$ requires C, 75.1; H, 6.8; N, 1.8%); $[\alpha]_D^{24}$ +60.8 (*c* 1.67 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) (*inter alia*) 0.90 (1 H, br t*, *J* 14.3, *J* 12.1, 6ax-H), 1.57 (1 H, br d, *J* 14.3, 6eq-H), 1.96 (1 H, br s, 4′-OH), 2.36–2.53 (1 H, m, 5-H), 2.95–3.22 (1 H, m, 7′-OH), 3.39–3.47 (2 H, m, 1-H, 1′-H), 3.58 (1 H, t*, *J* 11.0, *J* 10.6, 7ax-H), 3.50–3.59 (2 H, m, 2-H, 4-H), 3.98 (1 H, t, *J* 9.2, 3-H), 4.10 (1 H, dd, *J* 11.0, *J* 4.4, 7eq-H), 4.13–4.26 (2 H, m, 4′-H, 7′b-H), 4.59 and 4.65 (each 1 H, ABq, *J* 12.1, CH_2Ph), 4.61 and 4.66 (each 1 H, ABq, *J* 11.4, CH_2Ph), 4.69 and 4.74 (each 1 H, ABq, *J* 13.2, CH_2Ph), 4.79 and 4.90 (each 1 H, ABq, *J* 11.4, CH_2Ph), 5.59 (1 H, s, PhCH), 5.73 (1 H, br s, 2′-H) and 7.18–7.60 (25 H, m, 5 Ph).

The second fraction gave the *diol* **7** (641 mg, 20%), isolated as needles, m.p. 137–138 °C (from ethanol) (Found: C, 75.0; H, 6.7; N, 1.8. $C_{49}H_{53}NO_8$ requires C, 75.1; H, 6.8; N, 1.8%); $[\alpha]_D^{24}$ +73.4 (*c* 1.02 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) (*inter alia*) 0.96 (1 H, br t*, *J* 14.3, *J* 12.5, 6ax-H), 1.81 (1 H, dt, *J* 14.3, *J* 3.7, 6eq-H), 2.25–2.40 (1 H, m, 5-H), 2.47–2.58 (1 H, m, 7-OH), 2.79 (1 H, br s, 4-OH), 3.30–3.54 (6 H, m, 1-H, 4-H, 7ax-H, 7eq-H, 1′-H, 6′-H), 3.58 (1 H, dd, *J* 9.5, *J* 4.4, 2-H), 3.75 (1 H, t, *J* 9.2, 3-H), 4.10 (1 H, dd, *J* 9.2, *J* 6.2, 5′-H), 4.36–4.50 (3 H, m, 4′-H, 7′-H, 7′b-H), 4.54 and 4.63 (each 1 H, ABq, *J* 11.4, CH_2Ph), 4.63 and 4.99 (each 1 H, ABq, *J* 11.4, CH_2Ph), 4.69 and 4.81 (each 1 H, ABq, *J* 11.7, CH_2Ph), 4.89 (2 H, s, CH_2Ph), 5.66 (1 H, br d, *J* 4.8, 2′-H), 5.71 (1 H, s, PhCH) and 7.22–7.54 (25 H, m, 5 Ph).

The third fraction gave the tetrol (447 mg, 16%), which was acetylated in the usual way, after purification on a silica gel column, to afford the *tetraacetate* **8** (532 mg, 96%) as a syrup

* Apparent splitting pattern.

(Found: C, 69.7; H, 6.8; N, 1.7. $C_{50}H_{57}NO_{12}$ requires C, 69.5; H, 6.65; N, 1.6%); $[\alpha]_D^{26}$ +46.7 (*c* 0.93 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) (*inter alia*) 1.23 (1 H, br t*, *J* 14.2, *J* 12.4, 6ax-H), 1.78 (1 H, dt, *J* 14.2, *J* 3.6, 6eq-H), 1.96, 1.97, 2.03 and 2.07 (each 3 H, 4 s, 4 $COCH_3$), 2.24–2.39 (1 H, m, 5-H), 3.32 (1 H, br s, 1-H), 3.46 (1 H, br s, 1′-H), 3.54 (1 H, dd, *J* 9.5, *J* 4.3, 2-H), 3.76 (1 H, dd, *J* 11.5, *J* 3.6, 7a-H), 3.97 (1 H, dd, *J* 11.5, *J* 5.3, 7b-H), 4.43 (1 H, br d, *J* 12.8, 7′a-H), 4.68 (1 H, br d, *J* 12.8, 7′b-H), 4.92 (1 H, dd, *J* 11.5, *J* 9.4, 4-H), 5.37 (1 H, br s, 4′-H), 5.97 (1 H, br s, 2′-H) and 7.19–7.35 (20 H, m, 4 Ph).

2,3,4′,5′,6′-*Penta*-O-*benzyl*-4,7-O-*benzylidene*-7′-O-tert-*butyldimethylsilylvalidoxylamine A* **9**.—To a solution of the diol **6** (1.05 g, 1.34 mmol) in DMF (20 cm^3) was added *tert*-butylchlorodimethylsilane (304 mg, 2.02 mmol) and imidazole (183 mg, 2.69 mmol), and the mixture was stirred at room temperature for 5 h. The reaction solution was diluted with EtOAc (150 cm^3), washed with water, dried, concentrated and dried under reduced pressure. The syrupy residue was dissolved in DMF (10 cm^3) and 60% sodium hydride (67 mg, 1.68 mmol) was added at 0 °C, and the solution was stirred for 15 min. Then benzyl bromide (0.2 cm^3, 1.68 mmol) was added dropwise to it and the mixture was stirred for 2 h at the same temperature. Work-up and chromatography on a silica gel column (40 g), with EtOAc–hexane (1:8, v/v) as eluent, gave the *silyl ether* **9** (812 mg, 61%) as a syrup (Found: C, 75.2; H, 7.25; N, 1.5. $C_{62}H_{73}NO_8Si$ requires C, 75.35; H, 7.45; N, 1.4%); $[\alpha]_D^{26}$ +45.2 (*c* 2.50 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) (*inter alia*) 0.02 and 0.03 (each 3 H, 2 s, 2 $SiCH_3$), 0.83 (1 H, br t, *J* 13.9, 6ax-H), 0.89 (9 H, s, 3 CCH_3), 1.67 (1 H, dt, *J* 13.9, *J* 2.9, 6eq-H), 2.45–2.63 (1 H, m, 5-H), 3.34 (1 H, br t, *J* 4.0, 1′-H), 3.41 (1 H, br q*, *J* 3.9, *J* 3.2, *J* 2.9, 1-H), 3.44–3.54 (3 H, m, 2-H, 4-H, 7ax-H), 3.60 (1 H, dd, *J* 7.0, *J* 4.0, 6′-H), 3.88–4.03 (4 H, m, 3-H, 7eq-H, 5′-H, 7′a-H), 4.11–4.20 (2 H, m, 4′-H, 7′b-H), 4.53–4.90 (10 H, m, 5 CH_2Ph), 5.55 (1 H, s, PhCH), 5.90 (1 H, br d, *J* 4.3, 2′-H) and 7.18–7.55 (30 H, m, 6 Ph).

2,3,4′,5′,6′-*Penta*-O-*benzyl*-4,7-O-*benzylidenevalidoxylamine A* **10**.—A THF (30 cm^3) solution of **9** (812 mg, 0.82 mmol) was added to Bu_4NF–THF (1 mol dm^{-3}; 1 cm^3, 1 mmol) at 0 °C and it was stirred at the same temperature for 2.5 h. After addition of $NaHCO_3$, the mixture was concentrated, diluted with EtOAc (100 cm^3), washed with water, dried and evaporated. The residue was purified on a silica gel column (30 g), with butan-2-one–toluene (1:7, v/v) as eluent, to give the *alcohol* **10** (635 mg, 88%) as a syrup (Found: C, 76.6; H, 6.7; N, 1.5. $C_{56}H_{59}NO_8$ requires C, 76.95; H, 6.8; N, 1.6%); $[\alpha]_D^{26}$ +62.4 (*c* 1.05 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) (*inter alia*) 0.85 (1 H, br t*, *J* 13.9, *J* 12.5, 6ax-H), 1.58–1.80 (2 H, m, 6eq-H, OH), 2.41–2.61 (1 H, m, 5-H), 3.29–3.40 (2 H, m, 1-H, 1′-H), 3.47–3.56 (2 H, m, 2-H, 4-H), 3.51 (1 H, t*, *J* 10.3, *J* 9.2, 7ax-H), 3.62 (1 H, dd, *J* 6.3, *J* 4.0, 6′-H), 3.92–4.10 (6 H, m, 3-H, 7eq-H, 4′-H, 5′-H, 7′a-H, 7′b-H), 4.48–4.92 (10 H, m, 5 CH_2Ph), 5.57 (1 H, s, PhCH), 5.84 (1 H, br d, *J* 4.2, 2′-H) and 7.19–7.56 (30 H, m, 6 Ph).

7′-O-(6-O-*Acetyl*-2,3,4-*tri*-O-*benzyl*-α- **12** *and* β-D-*glucopyranosyl*)-2,3,4′,5′,6′-*penta*-O-*benzyl*-4,7-O-*benzylidenevalidoxylamine A* **13**.—To a solution of the alcohol **10** (617 mg, 0.71 mmol) and 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-D-glucopyranose **11** (453 mg, 0.85 mmol) in dichloromethane (20 cm^3) was added powdered molecular sieves 4 Å (500 mg) and trimethylsilyl trifluoromethanesulfonate (TMSOTf) (164 mm^3, 0.85 mmol), and then the mixture was stirred at room temperature for 30 min. The mixture was neutralized with 10% Et_3N–$CHCl_3$ and filtered. The filtrate was diluted with dichloromethane (50 cm^3), washed with water, dried and concentrated. The resulting syrup was chromatographed on a silica gel column (50 g), with EtOAc–hexane (1:3, v/v) as eluent, to give, first, the β-*glucoside* **13** (246 mg, 26%) as a syrup (Found: C, 75.4; H, 6.4; N, 1.05. $C_{85}H_{89}NO_{14}$ requires C, 75.7; H, 6.4; N, 1.0%); $[\alpha]_D^{25}$ +30.4 (*c* 0.86 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) (*inter alia*) 0.79 (1 H, br t*, *J* 14.2, *J* 12.5, 6ax-H), 1.99 (3 H, s, $COCH_3$), 2.38–2.58 (1 H, m, 5-H), 3.22–3.31 (2 H, m, 1-H, 1′-H), 4.07 (1 H, br d, *J* 3.7, 4′-H), 4.35 (1 H, d, *J* 7.7, 1″-H), 5.56 (1 H, s, PhCH), 5.96 (1 H, br d, *J* 4.5, 2′-H) and 7.13–7.60 (45 H, m, 9 Ph).

The second fraction gave the α-*glucoside* **12** (464 mg, 49%), isolated as a syrup (Found: C, 75.6; H, 6.6; N, 1.1. $C_{85}H_{89}NO_{14}$ requires C, 75.7; H, 6.65; N, 1.0%); $[\alpha]_D^{25}$ +62.2 (*c* 1.48 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) (*inter alia*) 0.83 (1 H, br t*, *J* 13.9, *J* 12.1, 6ax-H), 1.55–1.65 (1 H, m, 6eq-H), 1.98 (3 H, s, $COCH_3$), 2.40–2.58 (1 H, m, 5-H), 3.32–3.38 (2 H, m, 1-H, 1′-H), 4.17 (1 H, dd, *J* 12.1, *J* 2.2, 6″a-H), 4.25 (1 H, dd, *J* 12.1, *J* 4.0, 6″b-H), 4.41 (1 H, br d, *J* 12.5, 7′b-H), 4.83 (1 H, d, *J* 3.7, 1″-H), 5.56 (1 H, s, PhCH), 5.91 (1 H, br d, *J* 4.5, 2′-H) and 7.14–7.58 (45 H, m, 9 Ph).

7′-O-(6-O-*Acetyl*-2,3,4-*tri*-O-*benzyl*-β-D-*glucopyranosyl*)-2,3,4′,5′,6′-*penta*-O-*benzylvalidoxylamine A* **14**.—To a solution of the compound **13** (229 mg, 0.17 mmol) in THF (2 cm^3) was added aqueous 80% acetic acid (10 cm^3) and it was stirred at 50 °C for 88 h. The solution was concentrated and azeotroped with ethanol and toluene to afford a syrup, which was purified on a silica gel column (10 g), with butan-2-one–toluene (2:7, v/v) as eluent, to give the *diol* **14** (136 mg, 64%) as a syrup (Found: C, 74.1; H, 6.95; N, 1.2. $C_{78}H_{85}NO_{14}$ requires C, 74.3; H, 6.8; N, 1.1%); $[\alpha]_D^{25}$ +38.4 (*c* 2.40 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) (*inter alia*) 0.90 (1 H, br t, *J* 12.1, 6ax-H), 1.68 (1 H, br d, *J* 12.1, 6eq-H), 1.98 (3 H, s, $COCH_3$), 2.17–2.34 (1 H, m, 5-H), 2.67–2.86 (1 H, m, 7-OH), 2.80 (1 H, br s, 4-OH), 3.28–3.35 (2 H, m, 1-H, 1′-H), 3.93 (1 H, dd, *J* 6.6, *J* 4.0, 6′-H), 4.32 (1 H, br d, *J* 11.4, 7′b-H), 4.34 (1 H, d, *J* 7.7, 1″-H), 5.94 (1 H, br d, *J* 4.5, 2′-H) and 7.14–7.38 (40 H, m, 8 Ph).

4,7-*Di*-O-*acetyl*-7′-O-(6-O-*acetyl*-2,3,4-*tri*-O-*benzyl*-β-D-*glucopyranosyl*)-2,3,4′,5′,6′-*penta*-O-*benzylvalidoxylamine A* **15**.—The diol **14** (120 mg, 0.096 mmol) was acetylated in the usual way to give, after chromatography, the *diacetate* **15** (119 mg, 92%) as a syrup (Found: C, 73.2; H, 6.6; N, 1.0. $C_{82}H_{89}NO_{16}$ requires C, 73.25; H, 6.7; N, 1.0%); $[\alpha]_D^{26}$ +40.0 (*c* 2.62 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) (*inter alia*) 1.18 (1 H, br t, *J* 12.4, 6ax-H), 1.82 (1 H, br d, *J* 12.4, 6eq-H), 1.96 and 1.98 (each 3 H, 2 s, 2 $COCH_3$), 2.30–2.46 (1 H, m, 5-H), 3.26 (1 H, br s, 1-H), 3.34 (1 H, br s, 1′-H), 4.32 (1 H, br d, *J* 12.3, 7′b-H), 4.35 (1 H, d, *J* 8.1, 1″-H), 4.91 (1 H, t, *J* 8.5, 4-H), 5.94 (1 H, br d, *J* 4.0, 2′-H) and 7.13–7.40 (40 H, m, 8 Ph).

7′-O-(6-O-*Acetyl*-2,3,4-*tri*-O-*benzyl*-α-D-*glucopyranosyl*)-2,3,4′,5′,6′-*penta*-O-*benzylvalidoxylamine A* **16**.—Similar O-debenzylidenation (60 °C, 47 h) of compound **12** (434 mg, 0.32 mmol) yielded the *diol* **16** (222 mg, 55%) as a syrup (Found: C, 74.1; H, 6.7; N, 1.1. $C_{78}H_{85}NO_{14}$ requires C, 74.3; H, 6.8; N, 1.1%); $[\alpha]_D^{25}$ +65.3 (*c* 1.30 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) (*inter alia*) 0.94 (1 H, br t, *J* 12.1, 6ax-H), 1.97 (3 H, s, $COCH_3$), 2.17–2.35 (1 H, m, 5-H), 2.66–2.83 (2 H, m, 2 OH), 3.61 (1 H, dd, *J* 6.6, *J* 4.0, 6′-H), 3.77 (1 H, t, *J* 9.2, 3-H), 4.05 (1 H, t, *J* 9.2, 3″-H), 4.17 (1 H, dd, *J* 12.1, *J* 2.2, 6″a-H), 4.25 (1 H, dd, *J* 12.1, *J* 3.7, 6″b-H), 4.41 (1 H, br d, *J* 12.1, 7′b-H), 4.83 (1 H, d, *J* 3.3, 1″-H), 5.91 (1 H, br d, *J* 4.2, 2′-H) and 7.16–7.38 (40 H, m, 8 Ph).

7-O-*Acetyl*- **17** *and* 4,7-*Di*-O-*acetyl*-7′-O-(6-O-*acetyl*-2,3,4-*tri*-O-*benzyl*-α-D-*glucopyranosyl*)-2,3,4′,5′,6′-*penta*-O-*benzyl*-

* See footnote on p. 2124.

validoxylamine A **18**.—To an ice-cooled solution of imidazole (31 mg, 0.45 mmol) in chloroform (2 cm^3) was added acetyl chloride (16 mm^3, 0.23 mmol), and the resulting precipitates were filtered off. This solution was added to a solution of the diol **16** (219 mg, 0.17 mmol) in chloroform (3 cm^3) and then it was stirred under reflux for 141 h. The reaction solution was diluted with chloroform (30 cm^3), washed with water, dried and concentrated. The syrupy residue was purified on a silica gel column (10 g), with EtOAc–hexane (1:2, v/v) as eluent, to give, first, the *diacetate* **18** (51 mg, 22%) as a syrup (Found: C, 73.0; H, 6.7; N, 1.2. $C_{82}H_{89}NO_{16}$ requires C, 73.25; H, 6.7; N, 1.0%); $[\alpha]_D^{26}$ +69.7 (*c* 2.47 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) (*inter alia*) 1.21 (1 H, br t*, *J* 13.6, *J* 12.5, 6ax-H), 1.84 (1 H, br d, *J* 13.6, 6eq-H), 1.95, 1.98 and 2.04 (each 3 H, 3 s, 3 $COCH_3$), 2.31–2.46 (1 H, m, 5-H), 3.31 (1 H, br s, 1-H), 3.36 (1 H, br t, *J* 4.2, 1′-H), 3.66 (1 H, dd, *J* 11.4, *J* 3.3, 7a-H), 3.84 (1 H, t, *J* 9.2, 3-H), 3.97 (1 H, dd, *J* 11.4, *J* 4.8, 7b-H), 4.06 (1 H, t, *J* 9.2, 3″-H), 4.18 (1 H, dd, *J* 12.1, *J* 2.2, 6″a-H), 4.25 (1 H, dd, *J* 12.1, *J* 4.0, 6″b-H), 4.43 (1 H, br d, *J* 12.1, 7′b-H), 4.83 (1 H, d, *J* 3.9, 1″-H), 4.90 (1 H, t, *J* 10.9, 4-H), 5.91 (1 H, br d, *J* 4.2, 2′-H) and 7.16–7.37 (40 H, m, 8 Ph).

The second fraction gave the *monoacetate* **17** (133 mg, 59%), isolated as a syrup (Found: C, 73.2; H, 6.7; N, 1.2. $C_{80}H_{87}NO_{15}$·0.5H_2O requires C, 73.3; H, 6.8; N, 1.1%); $[\alpha]_D^{26}$ +66.9 (*c* 2.82 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) (*inter alia*) 1.13 (1 H, br t*, *J* 14.3, *J* 12.5, 6ax-H), 1.83 (1 H, br d, *J* 14.3, 6eq-H), 1.96 and 1.98 (each 3 H, 2 s, 2 $COCH_3$), 2.22–2.37 (1 H, m, 5-H), 2.53 (1 H, br s, OH), 3.76 (1 H, t, *J* 8.8, 3-H), 4.06 (1 H, t, *J* 9.2, 3″-H), 4.25 (1 H, dd, *J* 12.5, 4.0 Hz, 6″b-H), 4.42 (1 H, br d, *J* 12.5, 7′b-H), 4.83 (1 H, d, *J* 3.9, 1″-H), 5.90 (1 H, br d, *J* 4.1, 2′-H) and 7.15–7.36 (40 H, m, 8 Ph).

7,2″,3″,4″,6″,6‴-*Hexa*-O-*acetyl*-2,3,4′,5′,6′,2‴,3‴,4‴-*octa*-O-*benzylvalidamycin C* **20**.—To a stirred solution of the alcohol **17** (130 mg, 0.10 mmol) in dichloromethane (5 cm^3) was added in turn AgOTf (51 mg, 0.20 mmol), TMU (36 mm^3, 0.30 mmol) and 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide **19** (164 mg, 0.40 mmol), and then the mixture was stirred for 9 h in the dark at room temperature. The reaction mixture was neutralized with 10% Et_3N–$CHCl_3$ and evaporated. The resulting syrup was eluted from a silica gel column (15 g), with butan-2-one–toluene (1:6, v/v) as eluent, to give the *condensate* **20** (123 mg, 76%) as a colourless syrup (Found: C, 69.6; H, 5.9; N, 0.9. $C_{94}H_{105}NO_{24}$ requires C, 69.1; H, 6.5; N, 0.9%); $[\alpha]_D^{24}$ +57.5 (*c* 1.15 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) (*inter alia*) 1.04 (1 H, br t, *J* 12.5, 6ax-H), 1.85 (1 H, br d, *J* 12.5, 6eq-H), 1.94, 1.955, 1.970, 1.978, 1.981 and 2.01 (each 3 H, 6 s, 6 $COCH_3$), 2.35–2.50 (1 H, m, 5-H), 3.73 (1 H, dd, *J* 10.6, *J* 2.2, 6″a-H), 4.16 (1 H, br d, *J* 10.6, 7a-H), 4.23 (1 H, dd, *J* 10.6, *J* 3.7, 6‴b-H), 4.42 (1 H, dd, *J* 12.5, *J* 3.7, 6″b-H), 4.93 (1 H, t, *J* 11.0, 3″-H), 5.89 (1 H, br s, 2′-H) and 7.12–7.34 (40 H, m, 8 Ph).

Validamycin C Tetradecaacetate **21**.—Compound **20** (121 mg, 0.074 mmol) was deprotected with sodium (170 mg, 7.40 matom) in liquid ammonia (*ca.* 30 cm^3) at −78 °C over 5 h. After addition of excess amount of ammonium chloride, the reaction mixture was evaporated at room temperature. TLC indicated a formation of single validamycin C (R_f 0.19, propanol–acetic acid–water, 3:1:1, v/v). The residue was acetylated in the usual way to afford the *acetate* **21** (28 mg, 30.0%) as a syrup (Found: C, 52.1; H, 5.9; N, 1.3. $C_{54}H_{73}NO_{32}$ requires C, 52.0; H, 5.9; N, 1.1%); $[\alpha]_D^{25}$ +72.2 (*c* 0.97 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) (*inter alia*) 1.41 (1 H, br t, *J* 14.5, 6ax-H), 1.82 (1 H, br d, *J* 14.5, 6eq-H), 1.99, 2.00, 2.01, 2.03, 2.057, 2.063, 2.08, 2.09, 2.10 and 2.11 (42 H, 10 s, 14 $COCH_3$), 2.21–2.36 (1 H, m, 5-H), 3.28 (1 H, br q*, *J* 3.7, *J* 3.3, *J* 2.1, 1-H), 3.580 (1 H, br s, 1′-H), 3.583 (1 H, t*, *J* 10.2, *J* 9.3, 4-H), 3.57–3.68 (1 H, m, 5″-H), 3.88 (1 H, br d, *J* 12.8, 7′a-H), 3.97 (1 H, ddd, *J* 10.1, *J* 4.4, *J* 2.2, 5‴-H), 4.03 (1 H, dd, *J* 12.5, *J* 2.2, 6‴a-H), 4.09 (1 H, dd, *J* 12.5, *J* 2.2, 6‴a-H), 4.13 (1 H, dd, *J* 11.4, *J* 4.4, 7a-H), 4.18 (1 H, br d, *J* 12.8, 7′b-H), 4.27 (1 H, dd, *J* 12.5, *J* 4.4, 6‴b-H), 4.31 (1 H, dd, *J* 11.4, *J* 2.6, 7b-H), 4.39 (1 H, *J* 12.5, *J* 4.0, 6″b-H), 4.51 (1 H, d, *J* 8.1, 1″-H), 4.84 (1 H, dd, *J* 10.2, *J* 3.7, 2-H), 4.94 (1 H, t*, *J* 9.2, *J* 8.1, 2″-H), 4.97 (1 H, dd, *J* 8.6, *J* 4.4, 6′-H), 5.049 (1 H, t*, *J* 10.1, *J* 9.9, 4‴-H), 5.055 (1 H, d, *J* 3.7, 1‴-H), 5.07 (1 H, t, *J* 9.2, 4″-H), 5.15 (1 H, t, *J* 9.2, 3″-H), 5.33 (1 H, br d, *J* 5.5, 4′-H), 5.34 (1 H, t*, *J* 10.2, *J* 9.3, 3-H), 5.39 (1 H, dd, *J* 8.6, *J* 5.5, 5′-H), 5.45 (1 H, t*, *J* 10.3, *J* 9.9, 3‴-H) and 5.99 (1 H, br d, *J* 4.4, 2′-H).

Compound **21** was readily convertible into validamycin c **1** by *O*-deacetylation with methanolic sodium methoxide, followed by purification over a column of Dowex 50W–X2 (H^+) resin with water ⟶ aqueous ammonia as eluent.

7-O-*Acetyl*-2,3,5′,6′-*tetra*-O-*benzyl*-4′,7′-O-*benzylidenevalidoxylamine A* **22**.—The diol **7** (1.00 g, 1.28 mmol) was selectively acetylated in chloroform (10 cm^3) with the reagent prepared from imidazole (261 mg, 3.8 mmol) and acetyl chloride (136 mm^3, 1.9 mmol) under reflux for 90 h. The reaction mixture was processed as described in the preparation of **17** and **18**. The product was chromatographed on a silica gel column (50 g), with butan-2-one–toluene (1:9, v/v) as eluent, to give the *monoacetate* **22** (700 mg, 67%) as a syrup (Found: C, 74.1; H, 6.8; N, 1.7. $C_{51}H_{55}NO_9$ requires C, 74.2; H, 6.7; N, 1.7%); $[\alpha]_D^{23}$ +80.3 (*c* 1.67 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) (*inter alia*) 1.15 (1 H, br t*, *J* 14.3, *J* 12.1, 6ax-H), 1.91 (1 H, dt, *J* 14.3, *J* 3.7, 6eq-H), 1.98 (3 H, s, $COCH_3$), 2.30–2.45 (1 H, m, 5-H), 2.58 (1 H, d, *J* 2.6, OH), 3.28–3.37 (3 H, m, 1-H, 4-H, 1′-H), 3.47 (1 H, dd, *J* 9.2, *J* 3.7, 2-H), 3.56 (1 H, dd, *J* 9.5, *J* 4.4, 6′-H), 3.74 (1 H, t, *J* 9.2, 3-H), 3.86 (1 H, dd, *J* 11.0, *J* 3.3, 7a-H), 4.09 (1 H, dd, *J* 9.5, *J* 6.6, 5′-H), 4.20 (1 H, dd, *J* 11.0, *J* 4.8, 7b-H), 4.38–4.49 (3 H, m, 4′-H, 7′a-H, 7′b-H), 4.56 and 4.64 (each 1 H, ABq, *J* 11.4, CH_2Ph), 4.67 and 4.96 (each 1 H, ABq, *J* 11.4, CH_2Ph), 4.69 and 4.79 (each 1 H, ABq, *J* 12.1, CH_2Ph), 4.89 (2 H, s, CH_2Ph), 5.66 (1 H, br d, *J* 4.4, 2′-H), 5.71 (1 H, s, PhCH) and 7.19–7.53 (25 H, m, 5 Ph).

7,2″,3″,4″,6″-*Penta*-O-*acetyl*-2,3,5′,6′-*tetra*-O-*benzyl*-4′,7′-O-*benzylidenevalidamycin A* **23**.—To a solution of the alcohol **22** (513 mg, 0.62 mmol) in dichloromethane (10 cm^3) was added AgOTf (319 mg, 1.24 mmol), TMU (0.23 cm^3, 1.92 mmol), and the bromide **19** (1.02 g, 2.48 mmol), and the mixture was stirred at room temperature for 23 h in the dark. The reaction solution was neutralized with 10% Et_3N–$CHCl_3$, filtered, and evaporated. The residue was chromatographed on a silica gel column (50 g), with EtOAc–toluene (1:3, v/v) as eluent, to give the β-*glucoside* **23** (397 mg, 55%) as a syrup (Found: C, 67.45; H, 6.3; N, 1.2. $C_{65}H_{73}NO_{18}$ requires C, 67.5; H, 6.4; N, 1.2%); $[\alpha]_D^{25}$ +69.5 (*c* 1.01 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) (*inter alia*) 1.08 (1 H, br t*, *J* 14.0, *J* 12.5, 6ax-H), 1.95, 1.98, 1.99 and 2.00 (15 H, 4 s, 5 $COCH_3$), 2.43–2.58 (1 H, m, 5-H), 3.23–3.38 (3 H, m, 1-H, 1′-H, 5″-H), 3.44 (1 H, dd, *J* 9.2, *J* 4.0, 4-H), 3.52 (1 H, t*, *J* 10.6, *J* 9.2, 4-H), 3.75 (1 H, dd, *J* 12.5, *J* 2.2, 7a-H), 3.88 (1 H, t, *J* 9.2, 3-H), 3.98 (1 H, dd, *J* 11.4, *J* 5.5, 6″a-H), 4.13 (1 H, dd, *J* 11.4, *J* 3.2, 6″b-H), 5.62 (1 H, br d, *J* 4.4, 2′-H), 5.69 (1 H, s, PhCH) and 7.12–7.51 (25 H, m, 5 Ph).

7,2″,3″,4″,6″-*Penta*-O-*acetyl*-2,3,5′,6′-*tetra*-O-*benzylvalidamycin A* **24**.—To a solution of compound **23** (383 mg, 0.33 mmol) in THF (1 cm^3) was added aqueous 80% acetic acid (5 cm^3), and the mixture was stirred at 50 °C for 55 h. The mixture was concentrated and azeotroped with ethanol and toluene to give a syrup, which was chromatographed on a silica gel column (20 g), with butan-2-one–toluene (3:5, v/v) as eluent,

* See footnote on p. 2124.

to afford the *diol* **24** (215 mg, 61%) as a syrup (Found: C, 64.9; H, 6.3; N, 1.3. $C_{58}H_{69}NO_{18}$ requires C, 65.2; H, 6.5; N, 1.3%); $[\alpha]_D^{26}$ +52.2 (*c* 1.26 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) (*inter alia*) 1.07 (1 H, br t*, *J* 14.2, *J* 12.5, 6ax-H), 1.82 (1 H, br d, *J* 14.2, 6eq-H), 1.94, 1.96, 1.98 and 2.06 (15 H, 4 s, 5 $COCH_3$), 2.28–2.43 (1 H, m, 5-H), 3.48 (1 H, dd, *J* 9.2, *J* 3.6, 2-H), 3.56 (1 H, dd, *J* 10.9, *J* 9.2, 4-H), 3.75 (1 H, dd, *J* 12.8, *J* 2.7, 7a-H), 3.90 (1 H, t, *J* 9.2, 3-H), 4.25 (1 H, dd, *J* 11.2, *J* 3.6, 6″a-H), 4.83 (1 H, d, *J* 7.9, 1″-H), 5.01 (1 H, dd, *J* 9.7, *J* 7.9, 2″-H), 5.09 (1 H, t, *J* 9.7, 4″-H), 5.13 (1 H, t, *J* 9.7, 3″-H), 5.71 (1 H, br s, 2′-H) and 7.11–7.36 (20 H, m, 4 Ph).

*7,2″,3″,4″,6″-Penta-*O*-acetyl-7′-*O*-benzoyl-2,3,5′,6′-tetra-*O*-benzylvalidamycin A* **25**.—The diol **24** (212 mg, 0.20 mmol) was dissolved in pyridine (2 cm^3), to which benzoyl chloride (26 mm^3, 0.22 mmol) was added, the mixture was stirred at 0 °C for 1.5 h and then at room temperature for 7.5 h. After addition of excess methanol, the solution was concentrated and azeotroped with toluene. The resulting syrup was diluted with EtOAc (50 cm^3), washed with water, dried and concentrated. The syrupy residue was purified on a silica gel column (10 g), with butan-2-one–toluene (1:9, v/v) as eluent, to give the *benzoate* **25** (153 mg, 66%) as a syrup (Found: C, 66.6; H, 6.3; N, 1.2. $C_{65}H_{73}NO_{19}$ requires C, 66.6; H, 6.3; N, 1.2%); $[\alpha]_D^{24}$ +37.6 (*c* 1.26 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 1.06 (1 H, br t*, *J* 14.2, *J* 12.5, 6ax-H), 1.83 (1 H, br d, *J* 14.2, 6eq-H), 1.93, 1.96, 1.97, 1.99 and 2.06 (each 3 H, 5 s, 5 $COCH_3$), 2.23–2.42 (1 H, m, 5-H), 3.54 (1 H, dd, *J* 10.3, *J* 8.8, 4-H), 3.73 (1 H, dd, *J* 12.5, *J* 2.2, 7a-H), 3.80 (1 H, br t, *J* 4.4, 1′-H), 3.88 (1 H, t, *J* 8.8, 3-H), 4.24 (1 H, dd, *J* 11.0, *J* 3.3, 6″b-H), 4.82 (1 H, br d, *J* 12.5, 7′a-H), 4.83 (1 H, d, *J* 7.6, 1″-H), 4.97 (1 H, br d, *J* 12.5, 7′b-H), 5.83 (1 H, br s, 2′-H) and 7.10–8.11 (25 H, m, 5 Ph).

*7,2″,3″,4″,6″,6‴-Hexa-*O*-acetyl-7′-*O*-benzoyl-2,3,5′,6′,2‴,3‴,-4‴-hepta-*O*-benzylvalidamycin F* **26**.—α-Glucosylation of the alcohol **25** (147 mg, 0.13 mmol) with the glucosyl donor **11** (101 mg, 0.19 mmol) was carried out in the similar manner, as described in the preparation of **12** from **10**, to produce, after chromatography, the protected *derivative* **26** (80 mg, 39%) of validamycin F as a syrup, and unchanged **25** (59 mg, 40%) (Found: C, 68.3; H, 6.25; N, 0.9. $C_{94}H_{103}NO_{25}$ requires C, 68.6; H, 6.3; N, 0.85%); $[\alpha]_D^{21}$ +44.6 (*c* 1.34 in $CHCl_3$); δ_H(270 MHz, $CDCl_3$) (*inter alia*) 1.00 (1 H, br t*, *J* 13.2, *J* 12.8, 6ax-H), 1.76 (1 H, br d, *J* 13.2, 6eq-H), 1.93, 1.96, 1.97, 1.98 and 2.03 (18 H, 5 s, 6 $COCH_3$), 2.23–2.38 (1 H, m, 5-H), 3.95 (1 H, br s, 4′-H), 4.03 (1 H, dd, *J* 12.6, *J* 3.7, 6″a-H), 6.01 (1 H, br s, 2′-H) and 7.07–8.05 (40 H, m, 8 Ph).

*7′-*O*-Benzoyl-2,3,5′,6′-tetra-*O*-benzyl-4,7-*O*-benzylidenevalidoxylamine A* **27**.—The diol **7** (1.11 g, 1.42 mmol) in pyridine (20 cm^3) was added benzoyl chloride (0.18 cm^3, 1.55 mmol) and the solution was stirred at 0 °C for 4 h and at room temperature for 1.5 h. Work-up and chromatography afforded the *benzoate* **27** (991 mg, 79%) as a syrup (Found: C, 75.7; H, 6.3; N, 1.5. $C_{56}H_{57}NO_9$ requires C, 75.8; H, 6.5; N, 1.6%); $[\alpha]_D^{22}$ +35.7 (*c* 4.51 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) (*inter alia*) 0.90 (1 H, br t*, *J* 14.3, *J* 12.5, 6ax-H), 1.58 (1 H, br d, *J* 14.3, 6eq-H), 2.33–2.72 (2 H, m, 5-H, OH), 3.54 (1 H, t*, *J* 11.0, *J* 9.2, 4-H), 3.58 (1 H, t, *J* 11.4, 7ax-H), 3.82 (1 H, br t, *J* 4.0, 1′-H), 4.10 (1 H, dd, *J* 11.4, *J* 4.4, 7eq-H), 4.83 (1 H, br d, *J* 12.8, 7′a-H), 4.98 (1 H, br d, *J* 12.8, 7′b-H), 5.59 (1 H, s, PhCH), 5.87 (1 H, br s, 2′-H) and 7.16–8.06 (30 H, m, 6 Ph).

*4′-*O*-(6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α-*D*-glucopyranosyl)-7′-*O*-benzoyl-2,3,5′,6′-tetra-*O*-benzyl-4,7-*O*-benzylidenevalidoxylamine A* **28**.—The aglycone **27** (749 mg, 0.84 mmol) was condensed with the glucosyl donor **11** (541 mg, 1.01 mmol) in a similar way, as described in the preparation of **12** from **10**, to yield, after chromatography on a silica gel column, the *glucoside* **28** (387 mg, 34%) as a syrup, and unchanged **27** (267 mg, 36%) (Found: C, 74.6; H, 6.3; N, 1.0. $C_{85}H_{87}NO_{15}$ requires C, 74.9; H, 6.4; N, 1.0%); $[\alpha]_D^{22}$ +45.8 (*c* 1.66 in $CHCl_3$); δ_H 0.84 (1 H, br t*, *J* 13.9, *J* 12.5, 6ax-H), 1.53 (1 H, br d, *J* 13.9, 6eq-H), 1.97 (3 H, s, $COCH_3$), 2.32–2.48 (1 H, m, 5-H), 3.72 (1 H, br t, *J* 3.7, 1′-H), 4.86 (1 H, br d, *J* 12.8, 7′a-H), 5.07 (1 H, d, *J* 3.3, 1″-H), 5.10 (1 H, br d, *J* 12.8, 7′b-H), 5.56 (1 H, s, PhCH), 6.05 (1 H, br s, 2′-H) and 7.06–8.05 (45 H, m, 9 Ph).

*4′-*O*-(6-*O*-Acetyl-2,3,4-tri-*O*-benzyl-α-*D*-glucopyranosyl)-7′-*O*-benzoyl-2,3,5′,6′-tetra-*O*-benzylvalidoxylamine A* **29**.—Compound **28** (376 mg, 0.28 mmol) was debenzylidenated in the similar manner to give, after chromatography, the *diol* **29** (214 mg, 61%) as a syrup (Found: C, 73.4; H, 6.7; N, 1.1. $C_{78}H_{83}NO_{15}$ requires C, 73.5; H, 6.6; N, 1.1%); $[\alpha]_D^{21}$ +48.8 (*c* 0.85 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) (*inter alia*) 0.91 (1 H, br t*, 13.9, *J* 12.5, 6ax-H), 1.62 (1 H, br d, *J* 13.9, 6eq-H), 1.97 (3 H, s, $COCH_3$), 2.10–2.28 (1 H, m, 5-H), 2.70 (1 H, br s, 4-OH), 2.83–2.90 (1 H, m, 7-OH), 3.35 (1 H, br t*, *J* 10.3, *J* 9.5, 4-H), 3.74 (1 H, br t, *J* 4.0, 1′-H), 3.77 (1 H, t, *J* 9.5, 3-H), 3.95 (1 H, t, *J* 9.2, 3″-H), 4.86 (1 H, br d, *J* 12.8, 7′a-H), 5.02 (1 H, br d, *J* 12.8, 7′b-H), 5.05 (1 H, d, *J* 3.3, 1″-H), 6.04 (1 H, br s, 2′-H) and 7.10–8.05 (40 H, m, 8 Ph).

*7-*O*- **30**, 4-*O*- **31**, and 4,7-Di-*O*-acetyl-4′-*O*-(6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-*D*-glucopyranosyl)-7′-*O*-benzoyl-2,3,5′,6′-tetra-*O*-benzylvalidoxylamine A* **32**.—The diol **29** (280 mg, 0.22 mmol) was selectively acetylated in chloroform (6 cm^3) with the reagent prepared from imidazole (45 mg, 0.7 mmol) and acetyl chloride (23 mm^3, 0.3 mmol) for 60 h under reflux, and the mixture was processed as described for the preparation of **17** and **18**. The product was chromatographed on a silica gel column (10 g), with butan-2-one–toluene (1:10 ~ 1:3, v/v) as eluent to give, first, the *diacetate* **32** (45 mg, 15%) as a syrup (Found: C, 72.4; H, 6.1; N, 1.2. $C_{82}H_{87}NO_{17}$ requires C, 72.5; H, 6.45; N, 1.0%); $[\alpha]_D^{25}$ +44.2 (*c* 2.26 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) (*inter alia*) 1.19 (1 H, br t, *J* 14.3, 6ax-H), 1.74 (1 H, br d, *J* 14.3, 6eq-H), 1.92, 1.94 and 1.97 (each 3 H, 3 s, 3 $COCH_3$), 2.18–2.33 (1 H, m, 5-H), 3.36 (1 H, br s, 1-H), 3.69 (1 H, br t, *J* 4.0, 1′-H), 3.72 (1 H, dd, *J* 11.7, *J* 2.9, 6″a-H, 3.86 (1 H, t, *J* 9.5, 3-H), 3.98 (1 H, t, *J* 9.2, 3″-H), 4.83 (1 H, br d, *J* 12.8, 7′a-H), 5.02 (1 H, br d, *J* 12.8, 7′b-H), 5.07 (1 H, d, *J* 3.3, 1″-H), 6.03 (1 H, br s, 2′-H) and 7.10–8.08 (40 H, m, 8 Ph).

The second fraction gave the *monoacetate* **30** (181 mg, 63%), isolated as a syrup (Found: C, 72.95; H, 6.4; N, 1.1. $C_{80}H_{85}NO_{16}$ requires C, 73.0; H, 6.5; N, 1.1%); $[\alpha]_D^{18}$ +50.9 (*c* 1.12 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) (*inter alia*) 1.10 (1 H, br t*, *J* 14.3, *J* 12.5, 6ax-H), 1.74 (1 H, br d, *J* 14.3, 6eq-H), 1.93 and 1.97 (each 3 H, 2 s, 2 $COCH_3$), 2.08–2.23 (1 H, m, 5-H), 2.45 (1 H, d, *J* 4.2, OH), 3.29 (1 H, br t*, *J* 9.2, *J* 8.8, 4-H), 3.71 (1 H, br t, *J* 4.0, 1′-H), 3.77 (1 H, t*, *J* 9.2, *J* 8.8, 3-H), 3.96 (1 H, t, *J* 9.5, 3″-H), 4.02 (1 H, dd, *J* 11.7, *J* 3.7, 6″a-H), 4.87 (1 H, br d, *J* 12.5, 7′a-H), 5.02 (1 H, br d, *J* 12.5, 7′b-H), 5.07 (1 H, d, *J* 5.1, 1″-H), 6.04 (1 H, br s, 2′-H) and 7.10–8.09 (40 H, m, 8 Ph).

The third fraction gave the *monoacetate* **31** (19 mg, 7%), isolated as a syrup (Found: C, 72.4; H, 6.4; N, 1.1. $C_{80}H_{85}NO_{16}$·$0.5H_2O$ requires C, 72.5; H, 6.5; N, 1.1%); $[\alpha]_D^{26}$ +51.2 (*c* 0.96 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) (*inter alia*) 1.44 (1 H, br t*, *J* 14.7, *J* 12.5, 6ax-H), 1.63 (1 H, br d, *J* 14.7, 6eq-H), 1.97 and 2.01 (each 3 H, 2 s, 2 $COCH_3$), 2.43–2.52 (1 H, m, OH), 3.16–3.28 (1 H, m, 7a-H), 3.67 (1 H, br t, *J* 4.0, 1′-H), 3.94 (1 H, t, *J* 9.2, 3-H), 3.98 (1 H, t, *J* 8.8, 3″-H), 4.87 (1 H, br d, *J* 12.5, 7′a-H), 5.01 (1 H, br d, *J* 12.5, 7′b-H), 5.08 (1 H, d, *J* 3.7, 1″-H), 6.05 (1 H, br s, 2′-H) and 7.10–8.06 (40 H, m, 8 Ph).

* See footnote on p. 2124.

7,2″,3″,4″,6″,6‴-*Hexa*-O-*acetyl*-7′-O-*benzoyl*-2,3,5′,6′,2‴,-3‴,4‴-*hepta*-O-*benzylvalidamycin F* **26**.—Condensation of the aglycone **30** (181 mg, 0.14 mmol) with the bromide **19** (226 mg, 0.55 mmol) was carried out in a similar manner, as described in the preparation of **20**, to produce validamycin F derivative **26** (159 mg, 61%), whose physical data were identical to those of the product **26** prepared from **25**.

Validamycin F Tetradecaacetate **33**.—Compound **26** (210 mg, 0.13 mmol) was deprotected in the usual way to give validamycin F (TLC, R_f 0.19, propanol–acetic acid–water, 3:1:1, v/v), which was isolated as its totally O-*acetylated derivative* **33** (43 mg, 27%) as a syrup (Found: C, 52.1; H, 6.1; N, 1.1. $C_{54}H_{73}NO_{32}$ requires C, 52.0; 5.9; N, 1.1%); $[\alpha]_D^{25}$ +61.0 (*c* 2.02 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) (*inter alia*) 1.40 (1 H, br t*, *J* 14.0, *J* 12.5, 6ax-H), 1.73 (1 H, br d, *J* 12.5, 6eq-H), 1.99, 2.00, 2.01, 2.016, 2.022, 2.05, 2.06, 2.09, 2.11, 2.12 and 2.17 (42 H, 11 s, 14 $COCH_3$), 2.31–2.45 (1 H, m, 5-H), 3.36 (1 H, br q, 1-H), 3.47–3.53 (1 H, m, 1′-H), 3.55–3.68 (2 H, m, 4-H, 5″-H), 3.93 (1 H, br s, 4′-H), 4.04 (1 H, br d, *J* 12.5, 6″a-H), 4.05–4.15 (2 H, m, 7a-H, 5‴-H), 4.12 (1 H, br d, *J* 12.8, 6″a-H), 4.24 (1 H, dd, *J* 12.8, *J* 4.4, 6‴b-H), 4.34 (1 H, dd, *J* 11.0, *J* 2.9, 7b-H), 4.40 (1 H, dd, *J* 12.5, *J* 4.0, 6″b-H), 4.53 (1 H, d, *J* 7.7, 1″-H), 4.60 (2 H, br s, 7′a-H, 7′b-H), 4.90 (1 H, dd, *J* 11.0, *J* 4.0, 2-H), 4.94 (1 H, t*, *J* 9.2, *J* 7.7, 2″-H), 5.00 (1 H, t*, *J* 5.0, *J* 3.7, 6′-H), 5.03 (1 H, dd, *J* 10.6, *J* 3.7, 2‴-H), 5.09 (1 H, t, *J* 9.2, 4‴-H), 5.14 (1 H, dd, *J* 5.0, *J* 2.6, 5′-H), 5.15 (1 H, t*, *J* 9.6, *J* 9.2, 3″-H), 5.28 (1 H, d, *J* 3.7, 1‴-H), 5.37 (1 H, dd, *J* 10.6, *J* 9.2, 3‴-H), 5.40 (1 H, t*, *J* 11.0, *J* 9.2, 3-H) and 5.88 (1 H, br s, 2′-H).

Compound **33** was convertible into validamycin F **3** as described in the preparation of **1**.

2,3,4′,5′,6′,7′-*Hexa*-O-*benzyl*-7-O-*triphenylmethylvalidoxylamine A* **35**.—To a solution of the diol **34** (307 mg, 0.35 mmol) in pyridine (10 cm^3) was added chlorotriphenylmethane (147 mg, 0.53 mmol) and it was stirred at 50 °C for 21.5 h. After evaporation and azeotroping with toluene, the residue was diluted with EtOAc (100 cm^3), washed with water, dried and concentrated. The residue was chromatographed on a silica gel column (15 g), with EtOAC–hexane (1:8, v/v) as eluent, to give the *trityl ether* **35** (354 mg, 90%) as a syrup (Found: C, 80.2; H, 6.9; N, 1.3. $C_{75}H_{75}NO_8$ requires C, 80.5; H, 6.8; N, 1.25%); $[\alpha]_D^{20}$ +38.1 (*c* 2.11 in $CHCl_3$); δ_H(90 MHz; CDCl) (*inter alia*) 2.70 (1 H, br s, OH), 6.10 (1 H, br s, 2′-H) and 7.25–8.00 (45 H, m, 9 Ph).

2,3,4,4′,5′,6′,7′-*Hepta*-O-*benzyl*-7-O-*triphenylmethylvalidoxylamine A* **36**.—To a solution of the alcohol **35** (509 mg, 0.455 mmol) in DMF (7 cm^3) was added 60% NaH (36 mg, 0.91 mmol), and it was stirred for 50 min at 0 °C. Benzyl bromide (0.11 cm^3, 0.93 mmol) was then added to the suspension, which was stirred for 33 h at room temperature. Work-up and chromatography on a silica gel column (15 g), with EtOAc–hexane (1:8, v/v) as eluent, afforded *compound* **36** (441 mg, 80%) as a syrup (Found: C, 80.8; H, 6.8; N, 1.3. $C_{82}H_{81}NO_8 \cdot 0.5H_2O$ requires C, 80.9; H, 6.8; N, 1.15%); $[\alpha]_D^{22}$ +47.7 (*c* 1.12 in $CHCl_3$); δ_H(90 MHz; $CDCl_3$) (*inter alia*) 3.30 (1 H, br s, 1-H), 6.05 (1 H, br s, 2′-H) and 7.05–7.70 (50 H, m, 10 Ph).

2,3,4,4′,5′,6′,7′*Hepta*-O-*benzylvalidoxylamine A* **37**.—The trityl ether **36** (441 mg, 0.44 mmol) was treated with aqueous 80% acetic acid (15 cm^3) at 50 °C for 15 h. The usual work-up and chromatography gave the *alcohol* **37** (291 mg, 83%) as a syrup (Found: C, 78.0; H, 7.15; N, 1.4. $C_{63}H_{67}NO_8$ requires C, 78.3; H, 7.0; N, 1.45%); $[\alpha]_D^{22}$ +61.1 (*c* 1.34 in $CHCl_3$); δ_H(90 MHz; $CDCl_3$) (*inter alia*) 1.75 (1 H, br s, OH), 6.12 (1 H, br s, 2′-H) and 7.00–7.95 (35 H, m, 7 Ph).

6″-O-*Acetyl*-2,3,4,4′,5′,6′,7′,2″,3″,4″-*deca*-O-*benzylvalidamycin D* **38**.—α-Condensation of the aglycone **37** (203 mg, 0.21 mmol) with the sugar **11** (135 mg, 0.25 mmol) was conducted in the similar way, as described in the preparation of **12** from **10**, to afford the protected *derivative* **38** of validamycin D (149 mg, 49%) as a syrup (Found: C, 76.7; H, 6.8; N, 0.9. $C_{92}H_{97}NO_{14}$ requires C, 76.7; H, 6.8; N, 1.0%); $[\alpha]_D^{26}$ +76.9 (*c* 0.88 in $CHCl_3$); δ_H(400 MHz; $CDCl_3$) (*inter alia*) 1.42 (1 H, br t*, *J* 14.2, *J* 12.2, 6ax-H), 1.78 (1 H, br d, *J* 14.2, 6eq-H), 1.91 (3 H, s, $COCH_3$), 2.30–2.40 (1 H, m, 5-H), 3.04 (1 H, br d, *J* 7.8, 7a-H), 3.31 (1 H, br q, 1-H), 3.40 (1 H, br t, 1′-H), 3.42 (1 H, t, *J* 9.8, 4-H), 3.62 (1 H, dd, *J* 7.3, *J* 4.4, 6′-H), 3.69 (1 H, ddd, *J* 10.3, *J* 3.9, *J* 2.4, 5″-H), 3.98 (1 H, t, *J* 9.8, 3″-H), 4.07 (1 H, dd, *J* 12.2, *J* 3.9, 6″b-H), 4.25 (1 H, br d, *J* 11.7, 7′b-H), 4.73 (1 H, d, *J* 3.9, 1″-H), 5.94 (1 H, br d, *J* 2.9, 2′-H) and 7.05–7.51 (50 H, m, 10 Ph).

Validamycin D Undecaacetate **39**.—Compound **38** (131 mg, 0.091 mmol) was deprotected in the usual way to afford validamycin D (TLC, R_f 0.40, propanol–acetic acid–water, 3:1:1, v/v), and isolated as the totally O-*acetylated derivative* **39** (43 mg, 49%) as a syrup (Found: C, 52.05; H, 5.8; N, 1.4. $C_{42}H_{57}NO_{24} \cdot 0.5H_2O$ requires C, 52.1; H, 6.0; N, 1.45%); $[\alpha]_D^{25}$ +145.5 (*c* 1.76 in $CHCl_3$); δ_H(400 MHz; $CDCl_3$) (*inter alia*) 1.63 (1 H, td*, *J* 14.7, *J* 12.5, *J* 2.5, 6ax-H), 1.79 (1 H, dt, *J* 14.7, *J* 3.4, 6eq-H), 2.02, 2.046, 2.05, 2.06, 2.069, 2.073, 2.079, 2.087 and 2.091 (33 H, 9 s, 11 $COCH_3$), 2.31–2.42 (1 H, m, 5-H), 3.24 (1 H, dd, *J* 9.8, *J* 3.9, 7a-H), 3.40 (1 H, br q*, *J* 3.9, *J* 3.4, *J* 2.0, 1-H), 3.59 (1 H, br t, *J* 4.4, 1′-H), 3.73 (1 H, dd, *J* 9.8, *J* 3.9, 7b-H), 3.98–4.06 (1 H, m, 5″-H), 4.30 (1 H, dd, *J* 12.7, *J* 3.9, 6″b-H), 4.40 (1 H, br d, *J* 12.7, 7′a-H), 4.66 (1 H, br d, *J* 12.7, 7′b-H), 4.86 (1 H, dd, *J* 10.3, *J* 3.8, 2″-H), 4.96 (1 H, dd, *J* 10.3, *J* 3.9, 2-H), 5.00 (1 H, d, *J* 3.4, 1″-H), 5.05 (1 H, t, *J* 9.8, 4-H), 5.07 (1 H, t, *J* 9.8, 4″-H), 5.41 (1 H, t*, *J* 10.3, *J* 9.2, 3″-H), 5.43 (1 H, t*, *J* 10.3, *J* 9.8, 3-H), 5.49 (1 H, br d, *J* 5.9, 4′-H) and 5.99 (1 H, br d, *J* 4.4, 2′-H).

Compound **39** was convertible into validamycin D **2** as described in the preparation of **1**.

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* See footnote on p. 2124.