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Note

Total synthesis of (+)-validamycin H*

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Validamycin H (**1**), a new component of the antibiotic validamycin[2] isolated from the fermentation broth of *Streptomyces hygroscopicus* subsp. *limoneus* by Asano *et al.*[3], shows slightly weaker growth inhibitory activity[2] against *Rhizoctonia solani* (sheath blight disease of rice plants) than validamycin A. Validamycin H is one of the four pseudo-tetrasaccharide validamycins[3] and consists of validoxylamine A β-linked to gentiobiose. We now report the first total synthesis of **1** by coupling of the aglycon **3** and the glycosyl donor **4**, followed by deblocking.

The synthesis of 7-*O*-acetyl-2,3,4′,5′,6′,7′-hexa-*O*-benzylvalidoxylamine A (**3**) has been described[4] and 2,3,4,2′,3′,4′,6′-hepta-*O*-acetyl-α-gentiobiosyl bromide (**4**) was prepared from gentiobiose hepta-acetate by conventional treatment with 30% hydrobromic acid in acetic acid.

Condensation of **3** and **4** in the presence of silver trifluoromethanesulfonate and 1,1,3,3-tetramethylurea in boiling dichloromethane gave, after chromatography, **5**, the ^{1}H-n.m.r. spectrum of which contained signals for anomeric protons at δ 4.64 ($J_{1'',2''}$ 7.8 Hz, H-1″) and 4.44 ($J_{1''',2'''}$ 9.2 Hz, H-1‴) indicative of the β linkage.

The protecting groups of **5** were removed by treatment with sodium in liquid ammonia at −78° to give **1**, which was isolated as the tetradeca-acetate **2** obtained by treatment of **1** with acetic anhydride and pyridine.

The above synthesis provides an easy route to validamycin H (**1**).

EXPERIMENTAL

General methods. — Optical rotations were measured with a Jasco DIP-370 digital polarimeter. ^{1}H-N.m.r. spectra were recorded for solutions in $CDCl_3$ (internal Me_4Si) with a Jeol GSX-270 (270 MHz) instrument. T.l.c. was performed on Silica Gel 60 GF (Merck) with detection by charring with H_2SO_4. Column chromatography was conducted on Wakogel C-300 (300 mesh). Organic solutions were dried over anhydrous $MgSO_4$, and the solvents were evaporated at <40° under diminished pressure.

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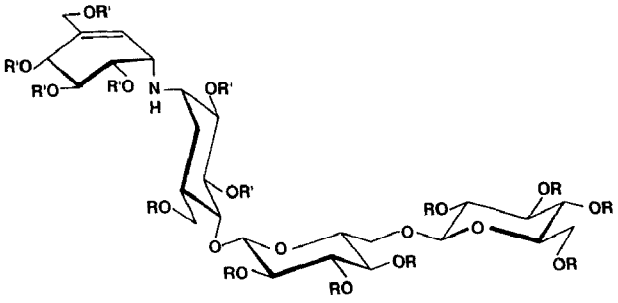
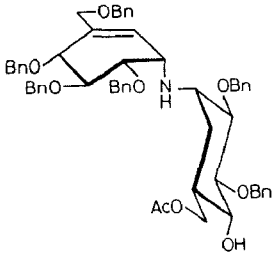


1 R = R' = H (Validamycin H)
2 R = R' = Ac
5 R = Ac, R' = Bn



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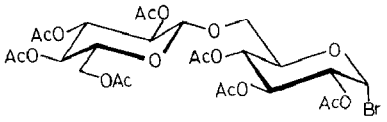

4

7,2″,3″,4″,2‴,3‴,4‴,6‴-Octa-O-acetyl-2,3,4′,5′,6′,7′-hexa-O-benzylvalidamycin H (**5**). — To a solution of 7-*O*-acetyl-2,3,4′,5′,6′,7′-hexa-*O*-benzylvalidoxylamine A (**3**; 356 mg, 0.388 mmol) in dry dichloromethane (10 mL) was added silver trifluoromethanesulfonate (AgOTf; 199 mg, 0.775 mmol) and 1,1,3,3-tetramethylurea (0.14 mL, 1.17 mmol) at room temperature under argon and in the dark, followed by 2,3,4,2′,3′,4′,6′-hepta-*O*-acetyl-α-gentiobiosyl bromide (**4**; 678 mg, 0.912 mmol). The mixture was stirred for 4 h at the room temperature, and then stirred and boiled under reflux. More AgOTf (100 mg, 0.389 mmol) and **4** (319 mg, 0.456 mmol) were added at intervals of 8 and 24 h. After a further 15 h, the mixture was neutralised with 5% Et_3N in CH_2Cl_2 and filtered, and the solvent was evaporated. Column chromatography (1:6 butan-2-one–toluene and rechromatography with 1:3 butan-2-one–hexane) of the syrupy residue gave 4,7-di-*O*-acetyl-2,3,4′,5′,6′,7′-hexa-*O*-benzylvalidoxylamine A (43 mg, 11.5%), **3** (51 mg, 14%), and **5** (293 mg, 49%), $[\alpha]_D^{24}$ +40° (*c* 1.2, chloroform). ^{1}H-N.m.r. data: δ 7.42–7.13 (m, 30 H, 6 Ph), 5.94 (br d, 1 H, $J_{1',2'}$ 3.8 Hz, H-2′), 5.20 (t, 1 H, $J_{2'',3''} = J_{3'',4''}$ = 9.2 Hz, H-3″), 5.17 (t, 1 H, $J_{2'',3''} = J_{3'',4''}$ = 9.2 Hz, H-3″), 4.64 (d, 1 H, $J_{1'',2''}$ 7.8 Hz, H-1″), 4.44 (d, 1 H, $J_{1''',2'''}$ 9.2 Hz, H-1‴), 4.33 (dd, 1 H, $J_{5'''a,6'''a}$ 3.4, $J_{6''',6'''}$ 10.8 Hz, H-6‴a), 4.24 (br d, 1 H, $J_{7',7'}$ 11.4 Hz, H-7′a), 2.61–2.45 (m, 1 H, H-5), 2.10, 2.04, 2.03, 2.02, 1.97, and 1.91 (6 s, 24 H, 6 OAc), 1.12 (bt, 1 H, $J_{5,6a} = J_{6,6}$ = 14 Hz, H-6a).

Anal. Calc. for $C_{84}H_{97}NO_{26}$: C, 65.65; H, 6.36; N, 0.91. Found: C, 65.62; H, 6.33; N, 0.95.

Validamycin H tetradeca-acetate (**2**). — Liquid ammonia (30 mL) was reacted with sodium (440 mg, 19 matom), a solution of **5** (293 mg, 0.191 mmol) in tetrahydrofuran at −78° was added, and the mixture was stirred for 6 h at −78°. Excess of ammonium chloride was added, and the mixture was kept at room temperature for 3 h, then concentrated. T.l.c. revealed a product with a mobility identical to that of validamycin H (R_F 0.18; 1-propanol–acetic acid–water, 3:1:1). The crude product was treated conventionally with acetic anhydride and pyridine at room temperature overnight. Column chromatography (butan-2-one–toluene, 1:2) of the product gave **2** (79 mg, 33%), isolated as a syrup, $[\alpha]_D^{18}$ +56° (*c* 0.8, chloroform). ^{1}H-N.m.r. data: δ 5.96 (dd, 1 H, $J_{1',2'}$ 1.4, $J_{2',3'}$ 4.7 Hz, H-2'), 5.50 (br d, 1 H, $J_{4',5'}$ 5.9 Hz, H-4'), 5.41 (dd, 1 H, $J_{5',6'}$ 9.2 Hz, H-5'), 5.32 (dd, 1 H, $J_{2,3}$ 9.9, $J_{3,4}$ 9.2 Hz, H-3), 5.21 (apparent t, 1 H, $J_{2'',3''}$ 9.5, $J_{3'',4''}$ 9.2 Hz, H-3''), 5.13 (t, 1 H, $J_{2''',3'''} = J_{3''',4'''} = 9.5$ Hz, H-3'''), 5.05 (apparent t, 1 H, $J_{4'',5''}$ 9.9 Hz, H-4''), 4.97 (dd, 1 H, $J_{1''',2'''}$ 7.7 Hz, H-2'''), 4.93 (dd, 1 H, $J_{4''',5'''}$ 10.6 Hz, H-4'''), 4.892 (dd, 1 H, $J_{1,2}$ 4 Hz, H-2), 4.887 (dd, 1 H, $J_{1'',2''}$ 7.7 Hz, H-2''), 4.66 (br d, 1 H, $J_{7',7'}$ 13.2 Hz, H-7'a), 4.60 (d, 1 H, H-1''), 4.48 (d, 1 H, H-1'''), 4.38 (br d, 1 H, H-7'b), 4.32 (dd, 1 H, $J_{5,7a}$ 2.9, $J_{7,7}$ 10.6 Hz, H-7a), 4.24 (dd, 1 H, $J_{5''',6'''}$ 4.8, $J_{6''',6'''}$ 12.1 Hz, H-6'''a), 4.11 (dd, 1 H, $J_{5''',6'''}$ 2.2 Hz, H-6'''b), 4.10 (dd, 1 H, $J_{5,7b}$ 4.4 Hz, H-7b), 3.94 (br d, 1 H, $J_{6'',6''}$ 8.8 Hz, H-6''a), 3.71 (ddd, 1 H, $J_{5'',6''a}$ 2.6, $J_{5'',6''b}$ 4.8 Hz, H-5''), 3.63–3.50 (m, 4 H, H-4,1',6''b,5'''), 3.28 (br q, 1 H, $J_{1,6ax} = J_{1,6eq} = \sim 3$ Hz, H-1), 2.37–2.21 (m, 1 H, H-5), 2.12, 2.088, 2.086, 2.072, 2.069, 2.06, 2.053, 2.049, 2.03, 2.02, 2.01, and 1.98 (12 s, 42 H, 14 OAc), 1.82 (br d, 1 H, $J_{6,6}$ 15 Hz, H-6*eq*), and 1.39 (apparent br t, 1 H, $J_{5,6ax}$ 12.5 Hz, H-6*ax*).

Anal. Calc. for $C_{54}H_{73}NO_{32}$: C, 51.96; H, 5.90; N, 1.12. Found: C, 51.80; H, 5.78; N, 1.15.

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