Total Synthesis of (+)-Validamycin B

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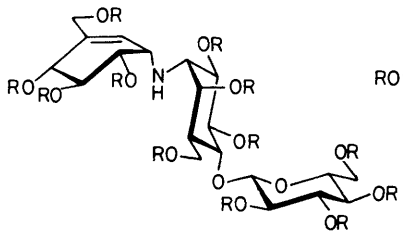
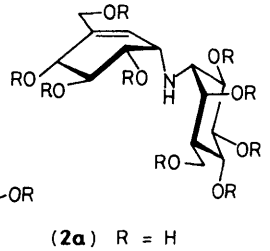
The first complete synthesis of the antibiotic validamycin B as its dodeca-*O*-acetate is reported; coupling of the epoxide (**6**) and the partially protected valienamine derivative (**14**), followed by deprotection, gives the product (**1b**) which was identified by ^{1}H n.m.r. spectroscopy.

Validamycin B is one of the components of the antibiotic validamycin complex,[1] and shows growth inhibition activity against *Pellicularia sasakii* (sheath blight disease of rice plants). Since validamycin A was first isolated as the major compound from the fermentation broth of *Streptomyces hygroscopicus* var. *limoneus* by Iwasa *et al.*[2] in 1970, other minor validamycins B, C, D, E, F, and G, and validoxylamines A, B, and G[3] have been isolated and characterised successfully. Validamycin A[4] and racemic validoxylamine A[5,6] and B[7] have been synthesised. We now describe the first total synthesis of (+)-validamycin B and (+)-validoxylamine B.



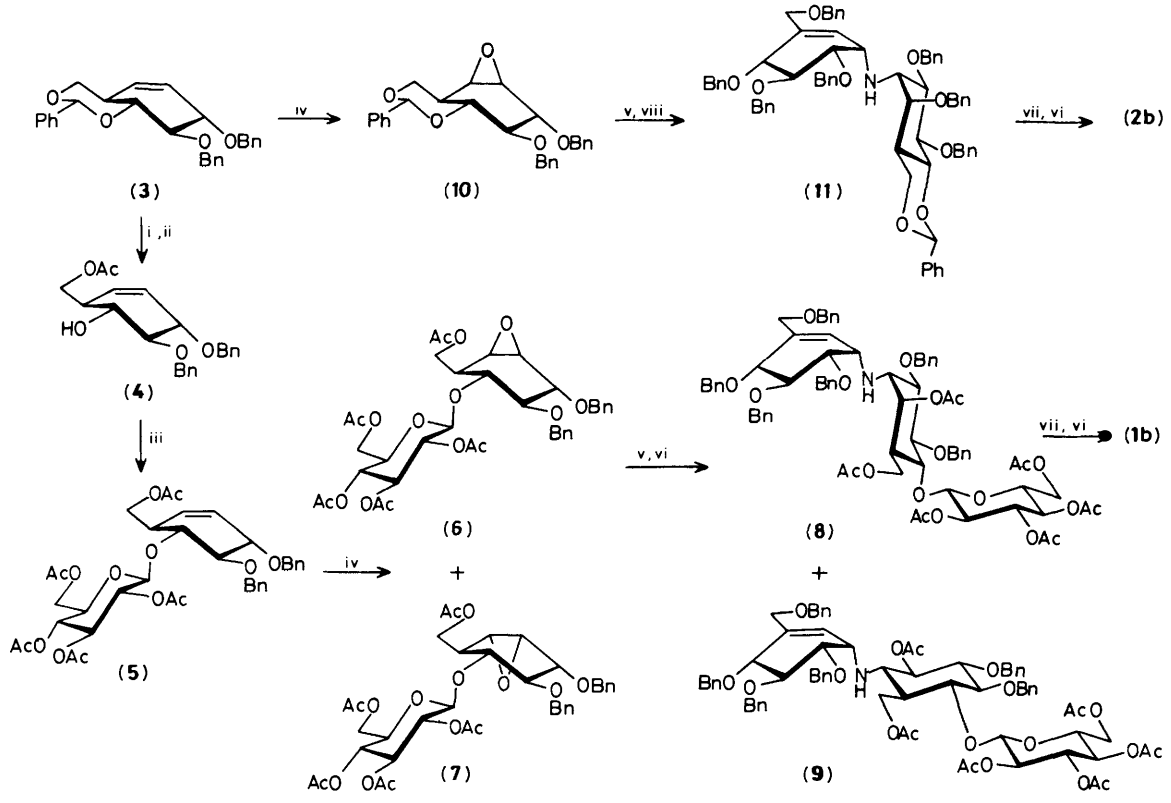
(**1a**) R = H (Validamycin B)
(**1b**) R = Ac



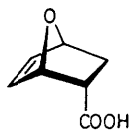
(**2a**) R = H (Validoxylamine B)
(**2b**) R = Ac

The optically resolved Diels–Alder *endo*-adduct[8] (**12**) of furan and acrylic acid was used as the starting material. The key intermediate alkene (**3**), $[\alpha]_D^{20}$ +34° ($CHCl_3$), and the partially protected derivative (**14**), $[\alpha]_D^{22}$ +4.2° ($CHCl_3$), of valienamine were derived from (**12**) in 8 and 12 reaction steps, respectively, following essentially the procedure employed in a synthesis of the related racemic compounds.[9] Thus, compounds (**3**) and (**14**) were prepared from the respective acetates by *O*-deacetylation with methanolic sodium methoxide, followed by the conventional benzylation.

Debenzylidenation of compound (**3**) and successive acetylation of the primary hydroxy group gave the aglycone (**4**). The modified Königs–Knorr condensation reaction of (**4**) with acetochloroglucose (**13**) was conducted in dry dichloromethane in the presence of silver trifluoromethanesulphonate (AgOTf) and 1,1,3,3-tetramethylurea (TMU) to afford the



Scheme 1. *Reagents and conditions*: i, 80% aqueous AcOH, 40 °C, 1 h; ii, AcCl, imidazole, $CHCl_3$, reflux, 44 h; iii, (**13**), AgOTf, TMU, CH_2Cl_2, reflux, 4 h; iv, 1M Na_2HPO_4, 1M NaH_2PO_4, *m*CPBA, CH_2ClCH_2Cl, 50 °C, 22 h; v, (**14**), propan-2-ol in sealed tube, 120 °C, 125 h; vi, Ac_2O, pyridine, room temp., overnight; vii, Na, liq. NH_3, −78 °C, 6 h; viii, BnBr, NaH, *N,N*-dimethyl formamide (DMF), 0 °C, 4 h.



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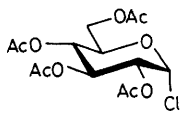
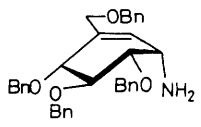


(13)



(14)

Bn = $PhCH_2$

β-glucoside [(**5**), m.p. 112—112.5 °C (from EtOH), $[\alpha]_D^{19}$ +85° ($CHCl_3$)] in 87% yield. Treatment of (**5**) with *m*-chloroperbenzoic acid (*m*CPBA) gave a 5 : 1 mixture of the epoxides [(**6**), 70%, $[\alpha]_D^{20}$ +51° ($CHCl_3$)] and [(**7**), 14%, m.p. 141—142 °C (from EtOH), $[\alpha]_D^{22}$ +18° ($CHCl_3$)]. The structure of (**6**) was evident from the ^1H n.m.r. spectrum. Coupling of (**6**) with (**14**) in propan-2-ol, in a sealed tube at 120 °C for 125 h, followed by acetylation, gave a 3 : 2 mixture of the condensates [(**8**), 47%] and [(**9**), 30%]. Cleavage of the epoxide ring was not as regioselective as has been observed in a reported synthesis of racemic validoxylamine B.[6,7] Birch reduction of (**8**) gave, after acetylation, (+)-validamycin B dodeca-*O*-acetate [(**1b**), $[\alpha]_D^{23}$ +39° ($CHCl_3$), lit.,[10] +42°] in 45% yield based on (**8**); the 400 MHz ^1H n.m.r. spectrum† and specific rotation were in good accord with those of an authentic sample.[3]

Similar coupling of the epoxide (**10**) obtained from (**3**) with (**14**), followed by successive deprotection and acetylation, afforded (+)-validoxylamine B nona-*O*-acetate (25%) [(**2b**), $[\alpha]_D^{20}$ +79° ($CHCl_3$), lit.,[10] +85°], identified by comparison (^1H n.m.r. spectroscopy and specific rotation) with an authentic sample.

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