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# Total Synthesis of (+)-Validoxylamine A

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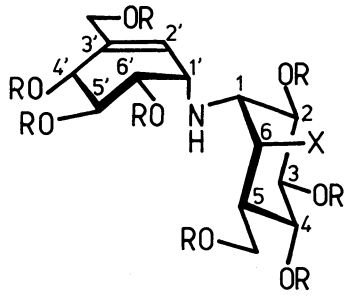
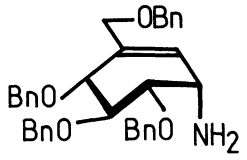
(+)-Validoxylamine A was synthesized by selective deoxygenation of (+)-validoxylamine B derivative, which was obtained by the coupling of the partially protected (+)-valienamine and (1R,2S,5R,7R,8R,9R,10R)-8,9-dibenzyloxy-5-phenyl-4,6,11-trioxatricyclo[8.1.0.$0^{2,7}$]undecane. The present synthesis constitutes a formal total synthesis of antibiotic validamycin A.

(+)-Validoxylamine A[1] (**1**) is a common component of antibiotic validamycin A, C, D, E, and F, and also isolated from the fermentation broth of *Streptomyces hygroscopicus* var. *limoneus*. The racemic modification of **1** has already been synthesized[2] by introduction of unsaturation into the appropriate pseudo-disaccharide. Recently, we have reported a total synthesis of (+)-validoxylamine B (**3**) and (+)-validamycin B starting from the condensate of the amine (**4**) and the epoxide (**5**).[3] Compound **1** only differs from **3** in lacking the hydroxyl group on C-6. The present paper describes a ready conversion of the protected derivative of **3** into **1**, which constitutes a formal total synthesis of validamycin A and would therefore provide a generally applicable route for synthesis of validamycins and related pseudo-oligosaccharides.

Condensation of **4** and **5** in 2-propanol at 120 °C afforded the protected (+)-validoxylamine B derivative (**6**, 75%), together with the positional isomer (15%).[3] Direct deoxygenation of the 6-hydroxyl group of **6** by reduction of its dithiocarbonate [**7**, 97%, $[\alpha]_D^{25}$ +28° ($CHCl_3$)] with tributyltinhydride failed. Attempts to replace the hydroxyl group with chloro or iodo atom under various conditions resulted in formation of a complex mixture of products being mainly composed of the aziridine. Therefore, **6** was treated with sodium hydride and sulfuryl diimidazole in *N*,*N*-dimethylformamide to transform selectively into the aziridine [**8**, 89%, $[\alpha]_D^{28}$ +115° ($CHCl_3$)]. Cleavage of the aziridine ring with *p*-toluenethiol in 2-propanol proceeded selectively to afford a sole product [**9**, 91%, $[\alpha]_D^{26}$ +41° ($CHCl_3$)], the structure of which was established on the basis of $^1$H NMR spectrum (400 MHz, $CDCl_3$). Thus, the signal due to H-6 appeared as a narrow doublet of doublets ($J$ = 2.9 and 3.4 Hz) at $\delta$ 2.29, indicative of the presence of the axial *p*-toluenethio function at C-6. Desulfurization of **9** was effected by treatment with inactivated Raney nickel T-4 catalyst in ethanol-dioxane to give the protected derivative [**10**, 75%, $[\alpha]_D^{17}$ +46° ($CHCl_3$)], which was converted by reduction with sodium in liquid ammonia at -78 °C to **1**, identical to an authentic sample[1] on TLC. This compound was further characterized as the octa-*O*-acetate



1 R = X = H
2 R = Ac, X = H
3 R = H, X = OH



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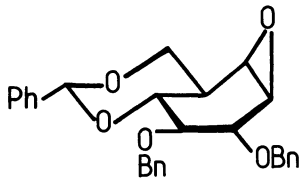

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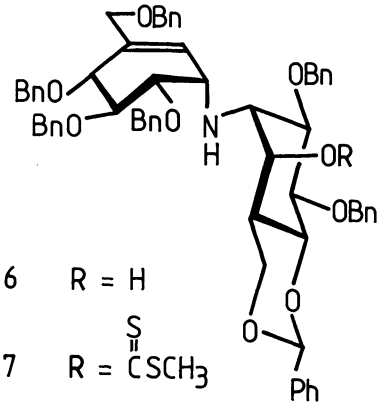
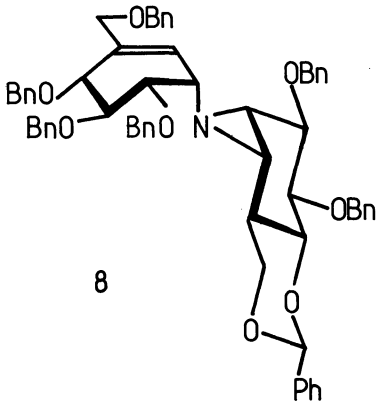


6 R = H
7 R = C(=S)SCH3



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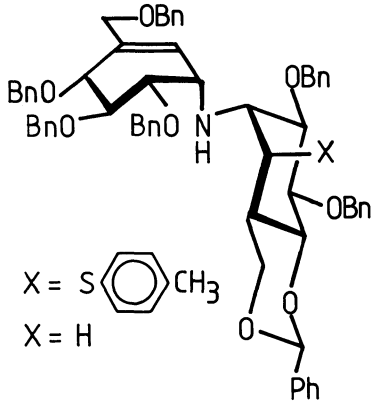

9 X = S-C6H4-CH3
10 X = H

[2, 56%, $[\alpha]_D^{20}$ +107° ($CHCl_3$)], identical to an authentic sample,[4] $[\alpha]_D^{18}$ +109° ($CHCl_3$), in all respects. The previous synthesis of validamycin A was carried out by glycosidation of the aglycone that was prepared in two steps of reaction from **10** derived from natural **1**. Accordingly, the present synthesis constitutes a formal total synthesis of validamycin A.

References

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