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A FORMAL TOTAL SYNTHESIS OF VALIDAMYCIN A

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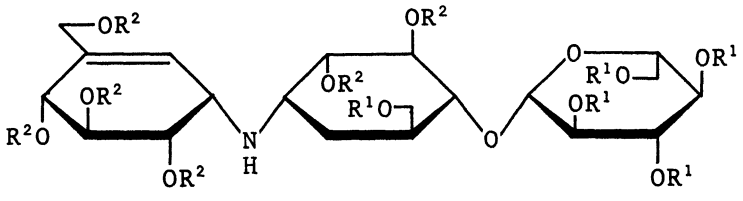
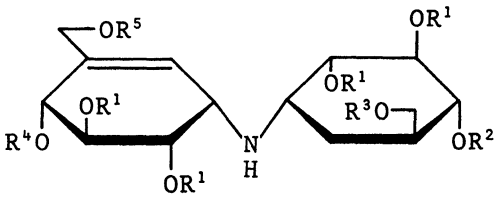
Validamycin A has been prepared by a glycosidation of the partly blocked validoxylamine A, followed by deprotection. Since a racemic form of validoxylamine A has been totally synthesized, the synthesis of validamycin A is achieved by the present study.

In connection with the preceding communication,[1] we wish to describe the first synthesis of validamycin A (1)[2] starting from validoxylamine A (5)[3] derived by degradation of the validamycins.[4] Since the total synthesis of DL-validoxylamine A had been accomplished by us,[5] we studied a partial blocking of 5 and a condensation reaction of the blocked derivatives thus obtained with a sugar halide.

Treatment of 5 with α,α-dimethoxytoluene (1.3 molar equiv) in anhydrous N,N-dimethylformamide (DMF) in the presence of p-toluenesulfonic acid (60 °C, 6 h) produced one major (Rf 0.40) and one minor components (Rf 0.83), detectable by TLC in chloroform–methanol (3:1, v/v). Without further purification, the mixture of products was treated with acetic anhydride in pyridine at room temperature overnight. Fractionation of the products on a silica-gel column with 2-butanone–toluene (1:6, v/v) as an eluent afforded the di-O-benzylidene derivative 6, mp 275–277 °C, $[\alpha]_D^{18}$ +105 ° (c 1.0, $CHCl_3$), and the O-benzylidene derivative 7, mp 173–174 °C, $[\alpha]_D^{18}$ +104 ° (c 1.0, $CHCl_3$), in 5.1 and 42% isolated yields, respectively. The elemental analyses and ^1H NMR spectra were consistent with the postulated



	R^1	R^2
1	H	H
2	Ac	Bn
3	Bn	Bn
4	Ac	Ac



	R^1	R^2	R^3	R^4	R^5
5	H	H	H	H	H
6	Ac	PhCH		PhCH	
7	Ac	PhCH		Ac	Ac
8	Bn	PhCH		Bn	Bn
9	Bn	H	H	Bn	Bn
10	Bn	H	Ac	Bn	Bn

structures. Thus, the ^{1}H NMR spectrum of 6 exhibits two singlets for the benzylic protons at δ = 5.46 and 5.60, the former of which can be attributed to that of the benzylidene group attached to the cyclohexane part. While, the spectrum of 7 shows only one singlet for the benzylic proton at δ = 5.47, and the AB quartet (J = 13 Hz) at δ = 4.35 and 4.67, ascribable to the allylic acetoxymethyl protons of the cyclohexene portion.

O-Deacetylation of 7 with methanolic sodium methoxide in methanol (room temperature, 5 h), followed by treatment with excess benzyl bromide in DMF in the presence of sodium hydride (room temperature, 45 h), yielded, after purification on a silica-gel column eluting with 2-butanone–toluene (1:10, v/v), the hexabenzyl ether 8, oil, $[\alpha]_D^{17}$ +46 ° (c 1.03, $CHCl_3$), in 59% yield. Then, O-debenzylidenation of 8 with 80% aqueous acetic acid (60 °C, overnight), followed by chromatography on silica gel, gave the dihydroxy compound 9, oil, $[\alpha]_D^{18}$ +48.5 ° (c 3.7, $CHCl_3$), in 59% yield. Selective acetylation of the primary hydroxyl group was effected by treatment with acetyl chloride (1.3 molar equiv) and imidazole in chloroform[6] to give the acetate 10, oil, $[\alpha]_D^{18}$ +59 ° (c 0.9, $CHCl_3$), in 59% yield.

Condensation of 10 with excess 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl chloride was carried out under the forcing conditions (silver triflate, 1,1,3,3-tetramethylurea, dichloromethane, room temperature, 4.5 h). The product was purified by chromatography on silica gel with 2-butanone–toluene (1:8, v/v) to give a single β-glucoside 2, oil, Rf 0.33, $[\alpha]_D^{18}$ +42 ° (c 1.7, $CHCl_3$), in 74.5% yield. O-Deacetylation of 2 with methanolic sodium methoxide, followed by benzylation in the usual way, gave the perbenzyl ether 3, oil, $[\alpha]_D^{19}$ +46 ° (c 0.69, $CHCl_3$), in 23% yield,[7] which was shown to be identical in all respects with the compound derived from 1. Removal of the O-benzyl protecting groups of 3 was successfully carried out with sodium in liquid ammonia (-70 °C, 2 h), followed by the conventional acetylation, to yield the peracetyl validamycin A (4) in 19% yield,[7] which was identified with an authentic sample[8] obtained from 1 on the basis of ^{1}H NMR spectroscopy and TLC [Rf 0.39 in ethanol–toluene (1:8, v/v) and Rf 0.28 in 2-butanone–toluene (2:3, v/v)]. Compound 4 was readily convertible into 1 by treatment with sodium methoxide in methanol. Accordingly, formal total synthesis of 1 has been completed and the structure of 1 has also been confirmed by the present synthesis.

References

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