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A TOTAL SYNTHESIS OF 6"-EPIVALIDAMYCIN A AND ITS DIASTEREOMER

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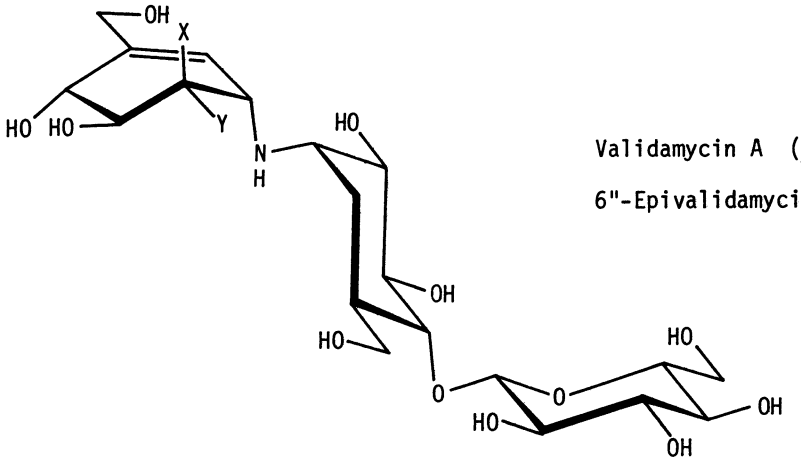
A total synthesis of the 6"-epimer of validamycin A and its diastereomer has been accomplished by a coupling reaction of the racemic peracyl 5,6-dihydroxy-1-hydroxymethyl-1,3-cyclohexadiene monoepoxide, the precursor of the unsaturated branched-chain cyclitol portion, with the protected β-D-glucopyranosylvalidamine, followed by acid hydrolysis and O-deacylation.

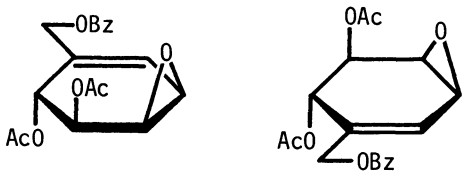
Validamycin A (1) is a main component of the validamycin complex, which is produced by *Streptomyces hygroscopicus* var. *limoneus*[1] and is now widely used to control a sheath blight desease of rice plants. As part of the studies directed toward total synthesis of 1[2] and related substances, we describe here a first total synthesis of 6"-epivalidamycin A (2) by a coupling reaction of the racemic peracyl dihydroxy(hydroxymethyl)-1,3-cyclohexadiene monoepoxide[3] with the blocked β-D-glucopyranosylvalidamine,[4,5] followed by deprotection. As had been expected from the previous results of the synthesis of DL-6'-epivalidoxylamine A,[6] the coupling reaction proceeded regioselectively to produce a single diastereomeric pair of the products, which could be successfully separated by a silica-gel column chromatography. Although it is rather difficult to determine the absolute structures of both diastereomers, a tentative assignment is proposed on the basis of ^{1}H NMR spectroscopy and optical rotation.



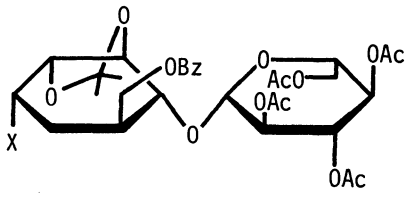
Validamycin A (1): X = H, Y = OH

6"-Epivalidamycin A (2): X = OH, Y = H

Scheme 1.



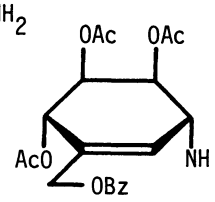
3 (racemate)



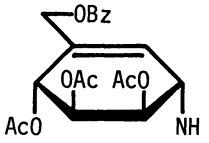
4 : X = N_3

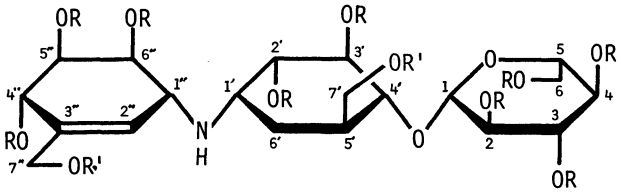
5 : X = NH_2

6a : X =



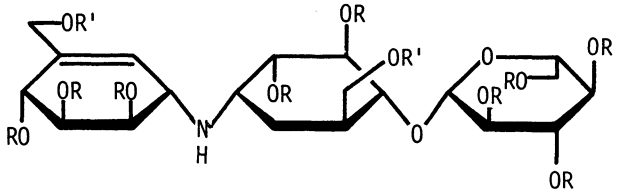
6b : X =





7a : R = Ac, R' = Bz

8a : R = R' = H



7b : R = Ac, R' = Bz

8b : R = R' = H

Scheme 2.

We have chosen DL-3,4-di-O-acetyl-1,2-anhydro-(1,2,3/4)-5-benzoyloxymethyl-5-cyclohexene-1,2,3,4-tetrol (3)[3] as the protected 1,3-cyclohexadiene monoepoxide. Compound 3 was readily prepared by peroxy acid-oxidation of DL-trans-5,6-diacetoxy-1-benzoyloxymethyl-1,3-cyclohexadiene. The blocked β-D-glucopyranosylvalidamine (5) was provided, in quantitative yield, by reduction of 1L-1-O-(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-2,3-O-isopropylidene-(1,3,4/2,6)-4-azido-6-benzoyloxymethyl-1,2,3-cyclohexanetriol (4)[5] with hydrogen sulfide in aqueous pyridine. The crude amine 5 was directly used in the coupling reaction.

Condensation of slight excess 3 (0.31 mmol) and 5 (0.24 mmol) was carried out in 2-propanol at 60 °C for 3 d. To complete the reaction, an additional amount of 3 (0.13 mmol) was added to the reaction mixture, and it was heated at 60 °C for further 4 d. At this time, TLC (silica gel) indicated the formation of two major components (Rf 0.60 and 0.49) in ethyl acetate–hexane (3:2, v/v). The products were successfully fractionated by a silica-gel column eluting with the same solvent system. Treatment of the compounds, thus separated, with acetic anhydride in pyridine at room temperature afforded the blocked pseudotrisaccharides 6a, oil, $[\alpha]_D^{17}$

+25 ° (c 0.98, $CHCl_3$), and 6b, oil, $[\alpha]_D^{17}$ +12 ° (c 1.03, $CHCl_3$), in 40 and 42% isolated yields (based on 5 used), respectively. Compounds 6a and 6b showed almost identical mobilities on TLC in several solvent systems applied, but their ^1H NMR spectra (200 MHz, chloroform-d) were clearly distinguishable from each other. The spectra indicate the presence of seven acetoxyl, two benzoxyl, and one isopropylidene groups. In the region of the signals ascribable to the ring protons, the signals of H-2", H-4", H-5", and H-6" of 6a appear as a doublet (J = 3.6 Hz), a doublet (J = 6.2 Hz), a doublet of doublets (J = 2.6 and 6.2 Hz), and a doublet of doublets (J = 2.6 and 5.8 Hz) at δ = 6.03, 5.68, 5.35, and 5.10, respectively.[7] These spectral data would be consistent with the proposed structure, where the cyclohexene ring adopts the half-chair conformation, somewhat distorted, with the C-1" imino group being oriented pseudoaxial disposition.[6,8] The ^1H NMR spectrum of 6b is very similar to that of 6a except for small differences in the chemical shifts of the signals due to the ring protons of cyclohexene portion. Thus, the signals of H-4" and H-5" of 6b appear slightly higher-field at δ = 5.59 and 5.28, respectively, as compared with those of 6a. These differences may be explained by a proximity of the C-4" and C-5" protons to the oxygen atoms of the 2',3'-isopropylidene group in the prefered conformation of 6a. The similar effects have been observed in the cases of the diastereomeric pair of related pseudodisaccharides.[9]

O-Deisopropylidenation of 6a and 6b with 70% aqueous acetic acid (room temperature, 2 d), followed by the conventional acetylation, gave the peracyl pseudotrisaccharides 7a, oil, $[\alpha]_D^{18}$ +31 ° (c 1.04, $CHCl_3$), and 7b, oil, $[\alpha]_D^{19}$ +25 ° (c 0.96, $CHCl_3$), in 51 and 60% yields, respectively. Their ^1H NMR spectra were in accord with the structures proposed.[10] In the spectrum of 7a, the signals of the C-5" and C-6" protons seem deshielded by 0.20 and 0.10 ppm, respectively, relative to those of 7b. It may be attributable to a proximity of the C-5" and C-6" protons to the 2'- and 3'-acetoxyl groups in the favored conformation of 7a. O-Deacylation of 7a and 7b was effected by treatment with methanolic sodium methoxide in methanol at room temperature overnight to afford, in quantitative yields, the pseudotrisaccharides 8a, oil, $[\alpha]_D^{19}$ +62 ° (c 0.25, H_2O), and 8b, oil, $[\alpha]_D^{19}$ +25 ° (c 0.19, H_2O). Compounds 8a and 8b showed, on TLC (silica gel), Rf 0.32 and 0.34 in 1-propanol–water–acetic acid (4:1:1, v/v) (cf. validamycin A:[11] Rf 0.27), and Rf 0.25 and 0.26 in 1-butanol–pyridine–water–acetic acid (6:4:3:1, v/v) (cf. validamycin A:[11] Rf 0.27), respectively.

If Lemieux's rules for optical rotation of cyclohexanepolyols[12] are applicable for estimation of those of cyclohexenepolyols, the 6-epimer of L-valienamine (the branched-chain cyclohexene part of 8b) will give a negative contribution to the rotation of pseudotrisaccharide that contains it. In addition, the chromatographic behaviors (Rf values on TLC) of 6a,b as well as 8a,b correspond to those observed for DL-validoxylamine B and its diastereomer.[13] Accordingly, compound 8b was tentatively assigned as 6"-epivalidamycin A and compound 8a as its diastereomer (Scheme 2), in conjunction with the consideration of the aforementioned ^1H NMR spectral data.

Biological and biochemical studies of 8a and 8b are now on the way.

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7) ^{1}H NMR spectra were taken on a JEOL FX-200 (200 MHz) spectrometer in chloroform-d with reference to tetramethylsilane as an internal standard. All the signals reported here were assigned by decoupling experiments, and the chemical shifts (δ) and coupling constants (Hz) were measured by a first-order method. Data for compound 6a: δ = 1.43 (6H, s, isopropylidene), 1.92 (3H, s), 1.99, 2.01 (9H, s), 2.06, and 2.08 (9H, s) (OAc), 3.77 (1H, t, J = 9.4 Hz, H-4'), 4.75 (1H, d, J = 8.8 Hz, H-1), 4.78 (2H, br s, C$\underline{H}_2$OBz), and 5.00 (1H, t, J = 8.8 Hz, H-2), Data for compound 6b: δ = 1.42 (3H, s) and 1.44 (3H, s) (isopropylidene), 1.90 (3H, s), 1.99, 2.01 (6H, s), 2.04, 2.05, and 2.07 (12H, s) (OAc), 3.42 (1H, dd, J = 3 and 9.2 Hz, H-2'), 3.77 (1H, t, J = 9.2 Hz, H-4'), 4.19 (1H, t, J = 9.2 Hz, H-3'), 4.03 (1H, dd, J = 2.4 and 12.4 Hz) and 4.34 (1H, dd, J = 3.2 and 12.4 Hz) (C$\underline{H}_2$OAc), 4.78 (2H, br s, C$\underline{H}_2$OBz), 5.00 (1H, t, J = 8.8 Hz, H-2), 5.28 (1H, dd, J = 2.4 and 5.2 Hz, H-5"), 5.59 (1H, d, J = 5.2 Hz, H-4"), and 6.07 (1H, d, J = 3.2 Hz, H-2").
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10) ^{1}H NMR (200 MHz, chloroform-d) data for compound 7a: δ = 1.97, 1.98, 2.02, 2.05, 2.07, and 2.10 (27H, s, OAc), 3.22 (1H, t, J = 4 Hz, H-1"), 3.73 (1H, dd, J = 9.2 and 10.4 Hz, H-4'), 3.98 (1H, dd, J = 2.2 and 12.6 Hz) and 4.36 (1H, dd, J = 3.8 and 12.6 Hz) (C$\underline{H}_2$OAc), 4.56 (1H, d, J = 7.6 Hz, H-1), 4.79 (2H, br s, C=CC$\underline{H}_2$OBz), 5.14 (1H, dd, J = 2.4 and 4 Hz, H-6"), 5.35 (1H, dd, J = 9.2 and 10 Hz, H-3'), 5.38 (1H, dd, J = 2.4 and 6.6 Hz, H-5"), 5.76 (1H, d, J = 6.6 Hz, H-4"), and 5.90 (1H, d, J = 4 Hz, H-2"). Data for compound 7b: δ = 1.97, 1.98, 2.02, 2.05, 2.07, and 2.10 (27H, s, OAc), 4.00 (1H, dd, J = 2.2 and 12.4 Hz) and 4.35 (1H, dd, J = 4 and 12.4 Hz) (C$\underline{H}_2$OAc), 4.57 (1H, d, J = 7.4 Hz, H-1), 4.82 (2H, br s, C=CC$\underline{H}_2$OBz), 5.05 (1H, m, H-6"), 5.17 (1H, dd, J = 2 and 6.4 Hz, H-5"), 5.44 (1H, t, J = 9.4 Hz, H-3'), 5.71 (1H, d, J = 6.4 Hz, H-4"), and 5.97 (1H, d, J = 3.8 Hz, H-2").
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