CHEMISTRY LETTERS, pp. 139-142, 1980.

SYNTHESIS OF 1-O-β-D-GLUCOPYRANOSYL-1L-(1,3,4/2,6)-4-AMINO-6-HYDROXYMETHYL-1,2,3-CYCLOHEXANETRIOL. ON THE STRUCTURE OF THE ANTIBIOTIC, VALIDAMYCIN A

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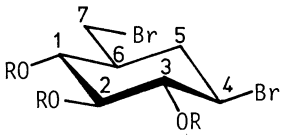
1-O-β-D-Glucopyranosyl-1L-(1,3,4/2,6)-4-amino-6-hydroxymethyl-1,2,3-cyclohexanetriol (12) was synthesized and found to be identical with β-D-glucopyranosyl-validamine derived from validamycin A. The position at which validamine moiety was substituted with D-glucopyranose was revised to C-1 on the basis of the present synthesis.

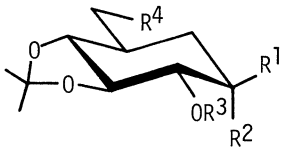
In the previous paper,[1] we described the unambiguous synthesis of β-D-glucopyranosylvalidamine[2] and found that it was not identical with an authentic sample derived from validamycin A.[3] These results suggested that, contrary to the previous structural assignment by Horii and Kameda,[2] 1L-(1,3,4/2,6)-4-amino-6-hydroxymethyl-1,2,3-cyclohexanetriol [(+)-validamine][4] moiety might be substituted with D-glucopyranose at C-1 or C-3 rather than at C-2 in the antibiotic. Therefore, in order to elucidate the position of the β-glucosidic linkage, attempts were first made to prepare the 1-O-β-D-glucopyranoside (12) by condensation of a protected precursor of validamine with acetobromoglucose. In the present communication, we wish to report a successful synthesis of 12, identical to an authentic sample, and to discuss on the revised structure of validamycin A.

7-O-Benzoyl-2,3-O-isopropylidene-DL-(1,3,4/2,6)-4-azido-6-hydroxymethyl-1,2,3-cyclohexanetriol (4c) was chosen as a protected precursor of the aglycone moiety and was prepared starting from readily available tri-O-acetyl-DL-(1,3/2,4,6)-4-bromo-6-bromomethyl-1,2,3-cyclohexanetriol (1)[5] in the following way (Scheme I).

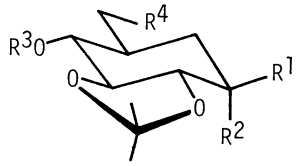
Treatment of 1 with boiling aqueous ethanol containing 5% hydrobromic acid gave the trihydroxy compound (2), mp 153.5–154°C, in 95% yield.[6] Acetonation of



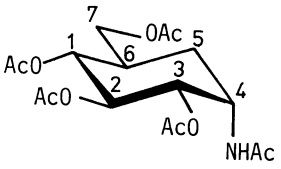
1 R = Ac
2 R = H



3a-d



4a-e



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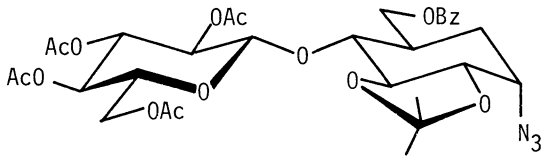
a $R^1 = R^4 = Br$, $R^2 = R^3 = H$
b $R^1 = Br$, $R^2 = R^3 = H$, $R^4 = OBz$
c $R^1 = R^3 = H$, $R^2 = N_3$, $R^4 = OBz$
d $R^1 = H$, $R^2 = N_3$, $R^3 = Ac$, $R^4 = OBz$
e $R^1 = H$, $R^2 = N_3$, $R^3 = Me$, $R^4 = OBz$

Scheme I.
Synthesis of Precursor of Aglycone Moiety (All the formulas depict one of the respective racemates)



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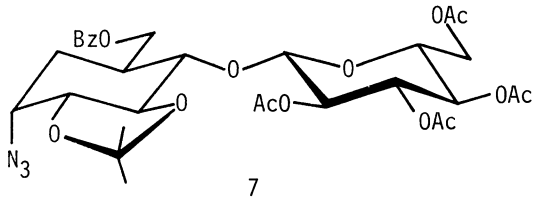

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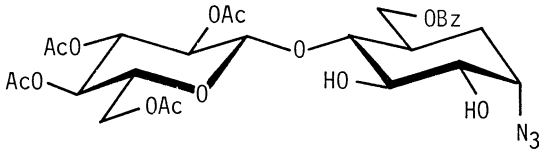

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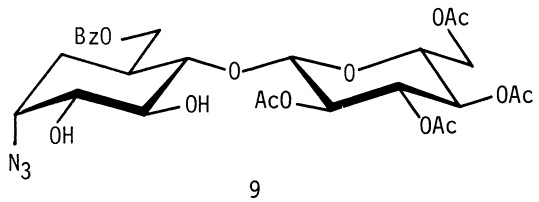

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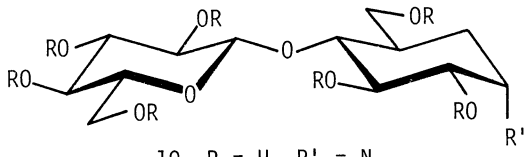
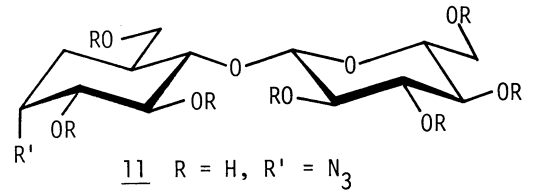


10 R = H, R' = N_3
12 R = H, R' = NH_3Cl
14 R = Ac, R' = NHAc



11 R = H, R' = N_3
13 R = H, R' = NH_3Cl
15 R = Ac, R' = NHAc

Scheme II. Synthesis of 1-O-β-D-Glucopyranosyl-1L-(1,3,4/2,6)-4-amino-6-hydroxymethyl-1,2,3-cyclohexanetriol Hydrochloride (12) and Its Diastereomer (13)

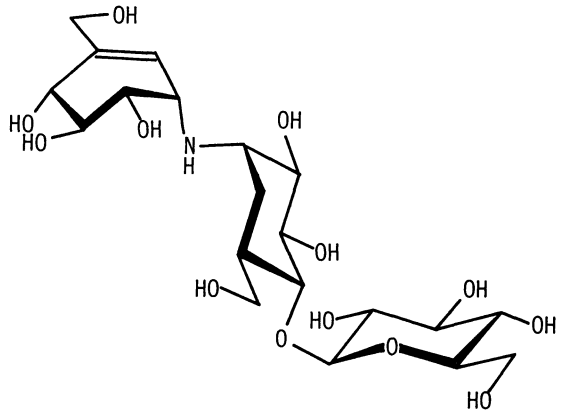
2 with 2,2-dimethoxypropane in N,N-dimethylformamide (DMF) in the presence of p-toluenesulfonic acid at 60°C for 2 h gave a mixture of the 1,2-O- (3a) and 2,3-O-isopropylidene derivatives (4a) in 86% yield. Without further separation, direct treatment with sodium benzoate in aqueous DMF (at 70°C, 6 h) resulted in preferential displacement of the 7-bromine atom with benzoyloxy group giving a mixture of products (3b) and (4b). By fractionation on a silica gel column, and later by fractional crystallization, they were separated into 3b (8%), mp 125–127°C, and 4b (35%), mp 130–132°C. Treatment of 3b and 4b with sodium azide under the conditions favorable for direct S_N2 reaction with an azide

ion (in dimethyl sulfoxide at 120°C, 18 h) gave the azides (3c), mp 118.5–120°C, and (4c), mp 105–108°C, in 46 and 70% yields, respectively. The structures were established by the ^{1}H NMR spectra of their acetyl derivatives (3d) and (4d), and the O-methyl derivative (4e). Thus, 3d and 4d showed a one-proton doublet of doublets (δ 5.05, J = 4 and 10.5 Hz) and one-proton triplet (δ 5.19, J = 9 Hz), respectively, attributable to a proton attached to the carbon atom bearing the acetoxyl group. In 4e, the triplet (J = 9 Hz) appeared at δ 3.32. Furthermore, both 3c and 4c could be converted into penta-N,O-acetyl-validamine (5) by the following sequence: O-deisopropylidenation, O-deacylation, catalytic reduction, and acetylation. Therefore, 4c was expected as a suitable compound for the synthesis of the desired β-D-glucopyranoside (12) (Scheme II).

Condensation of 4c with 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide was conducted in dry benzene in the presence of mercuric(II) cyanide and anhydrous calcium sulfate at 70°C for 50 h. Under these reaction conditions, only β-D-glucopyranosides were considered to be obtainable. The mixture of products was roughly fractionated by chromatography on silica gel to give a syrupy mixture of condensates (6) and (7), showing a single spot on TLC in several solvent systems. Without further purification, it was directly O-deisopropylidenated by treatment with Amberlite IR-120B (H^+) in ethanol at ambient temperature overnight. The dihydroxy compounds (8) and (9) thus formed were clearly separated by a silica gel column with 2-butanone–toluene (2 : 5, v/v) as an eluent to give 8, mp 182–183.5°C, $[\alpha]_D^{24}$ +27°, and 9, mp 158–161°C, $[\alpha]_D^{23}$ -16°, in 12 and 10% yields, respectively. Considering from the optical rotation, 8 was expected to be the β-D-glucopyranoside which contained the precursor of (+)-validamine as the aglycone moiety. O-Deacylation of 8 with methanolic sodium methoxide in methanol gave the hydroxy azide (10) as a homogeneous syrup, which was successively hydrogenated with 5% palladium on carbon in ethanol containing an excess of hydrochloric acid to give the amine hydrochloride (12), $[\alpha]_D^{23}$ +22° (H_2O), as a homogeneous syrup in 94% overall yield. This compound was shown to be identical with an authentic sample of β-D-glucopyranosylvalidamine hydrochloride derived from validamycin A[3] by comparison of chromatographic behavior (TLC on cellulose and silica gel) in several solvent systems. It was further characterized by converting into the octa-N,O-acetyl derivative (14),[7,8] $[\alpha]_D^{23}$ +16° (lit.[2] $[\alpha]_D$ +17.6°), whose IR ($CHCl_3$) and ^{1}H NMR spectra were superimposable on those of an authentic sample.

On the other hand, the amine hydrochloride (13) obtained similarly from 9 via the hydroxy azide (11) showed very similar spectral properties to those of 10, however, they were clearly differentiated from each other by TLC. Its octa-N,O-acetyl derivative (15) has $[\alpha]_D^{23}$ -49°.

On the basis of the present synthesis, the structure of "β-D-glucopyranosyl-validamine" should be revised to 1-O-β-D-glucopyranosyl-1L-(1,3,4/2,6)-4-amino-6-hydroxymethyl-1,2,3-cyclohexanetriol, and, accordingly, the gross structure of validamycin A was convincingly formulated as shown in Scheme III.



Scheme III. The Revised Structure of Validamycin A

References and Notes

1) For the preceding paper, see: S. Ogawa, Y. Shibata, N. Chida, and T. Suami, Chem. Lett., 1980,
2) S. Horii and Y. Kameda, J. Chem. Soc., Chem. Commun., 1972, 747.
3) S. Horii, T. Iwasa, and Y. Kameda, J. Antibiot., 24, 57 (1971).
4) (+)-Validamine was designated as 1S-(1,2,4/3,5)-1-amino-5-hydroxymethyl-2,3,4-cyclohexanetriol in the original paper [K. Kamiya, Y. Wada, S. Horii, and M. Nishikawa, J. Antibiot., 24, 317 (1971)].
5) S. Ogawa, K. Nakamoto, Y. Tanno, N. Chida, and T. Suami, Bull. Chem. Soc. Jpn., 52, 1174 (1979), and references are cited in.
6) All the new compounds whose melting points and/or optical rotations were reported gave satisfactory analytical data. Unless otherwise stated, optical rotations were measured in chloroform (c = ca. 1).
7) Compound 14 isolated as an amorphous solid melted at 114–118°C (lit.[2] mp 117–119°C) and the melt, on continuous heating, crystallized to give needles, which melted again sharply at 187–189°C. The same melting and crystallization behavior was observed for an authentic sample.
8) An authentic sample was kindly supplied by Dr. Satoshi Horii.

(Received October 30, 1979)