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SYNTHESIS OF DL-VALIDOXYLAMINE A

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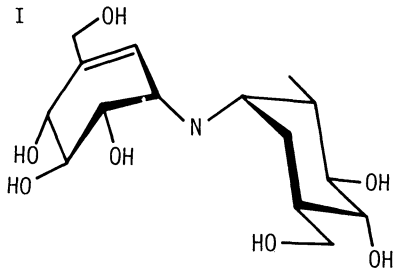
The first total synthesis of DL-validoxylamine A, one of the components of the antibiotic validamycin complex, is described.

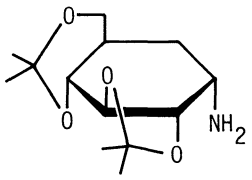
Validoxylamine A, [(1S)-(1,4,6/5)-4,5,6-trihydroxy-3-hydroxymethyl-2-cyclohexenyl][(1S)-(1,2,4/3,5)-2,3,4-trihydroxy-5-(hydroxymethyl)cyclohexyl]-amine (1), was isolated from the fermentation broth of Streptomyces hygroscopicus var. limoneus.[1] In continuation of the preceding communication,[2] we wish to describe herein the first total synthesis of the racemic form of 1. The present synthetic sequence can also be adapted to the synthesis of several α-glucosidase inhibitors, the oligosaccharides containing the valienamine portion in their molecules.[3]

We have undertaken the reaction of DL-2,3:4,7-di-O-isopropylidene-(1,2,4/3,5)-2,3,4-trihydroxy-5-(hydroxymethyl)cyclohexylamine (2)[4,5] with DL-3,4-di-O-acetyl-1,2-anhydro-5,7-O-benzylidene-(1,2,4,6/3,5)-1,2,3,4,5-cyclohexanepentol (3)[6] to construct the pseudo-disaccharide, in which two kinds of polyhydroxy(hydroxymethyl)-cyclohexane are combined by way of an imino linkage.

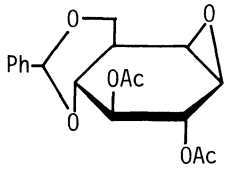
Scheme I



Validoxylamine A (1)



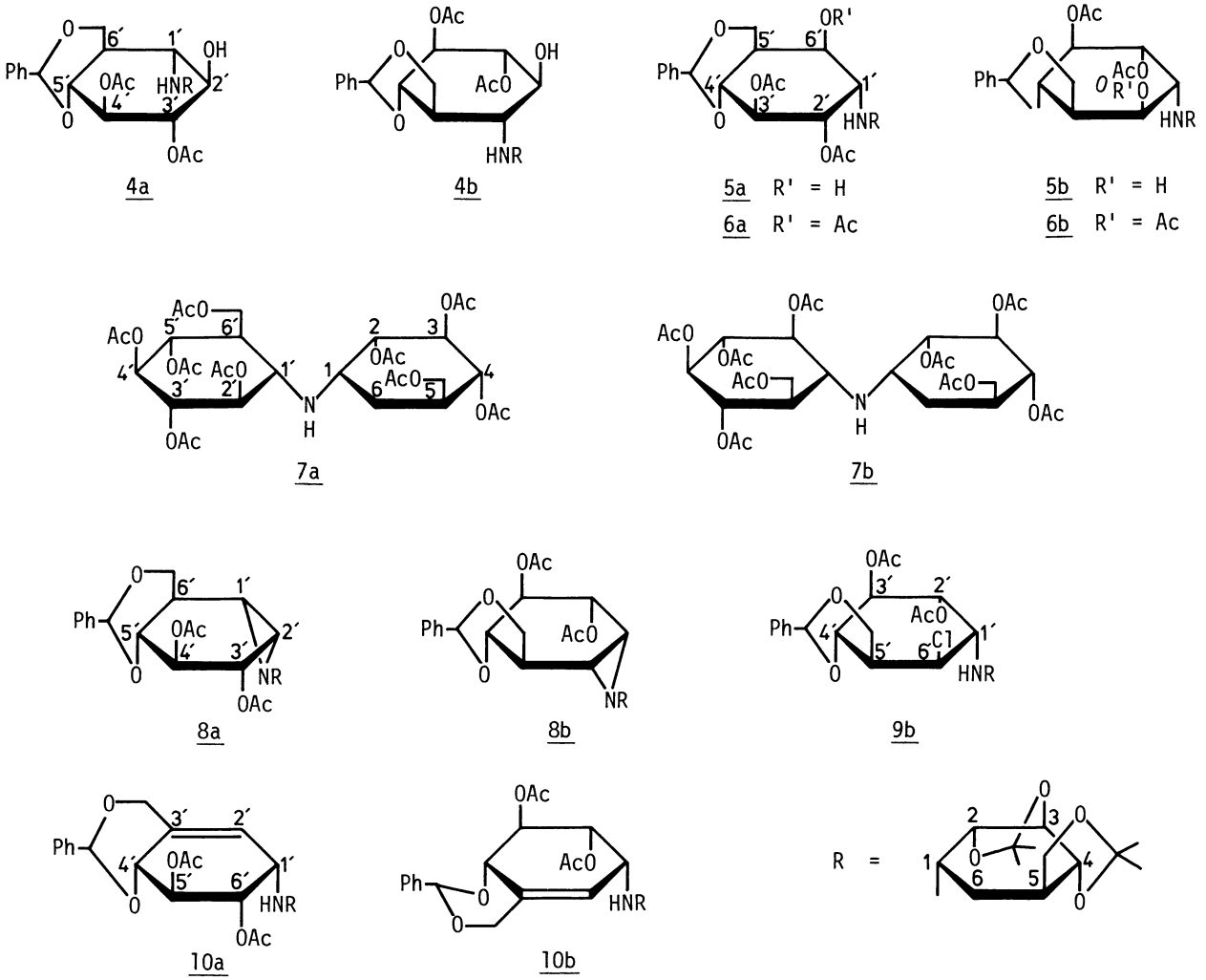
2



3

The reaction of 2 with a molar equiv. of 3 was carried out in 2-propanol by heating in a sealed tube at 120°C for 9 days.[6] The products were fractionated by a silica gel column chromatography using 2:9 2-butanone–toluene as an eluent to afford diastereomeric mixtures of 4a and 4b (mp 234–237°C, Rf 0.40,[7] 10%), and of 5a and 5b (mp 255–257°C, Rf 0.35, 44%). Treatment of the former mixture with 80% aqueous acetic acid (90°C, overnight) followed by acetylation (Ac_2O, pyridine, room temperature, overnight) gave the corresponding nona-O-acetates, which were separated by chromatography on silica gel (1:3 2-butanone–toluene) to afford two diastereomers (7a, mp 213–214°C, Rf 0.16, 43%) and (7b, mp 208–208.5°C, Rf 0.13, 36%): ^{1}H NMR for 7a, δ 1.96, 1.98, 1.99, 2.01, and 2.05 (27H, OAc), 2.63–3.03 (1H, m, H-1'), 3.59 (1H, br. q, J = 3 Hz, H-1), 3.77 (1H, dd) and 4.10 (1H, dd) (J = 3

Scheme II



and 12 Hz, CH_2OAc), 4.24 (1H, dd) and 4.41 (1H, dd) (J = 3.5 and 12 Hz, CH_2OAc), 4.91 (1H, dd, J = 4.5 and 10 Hz, H-2), 4.95 (1H, dd, J = ∿10 Hz, H-4), 5.33 (1H, t, J = 10 Hz, H-3), and for 7b, δ 1.93, 1.95, 1.99, 2.03, 2.04, and 2.05 (27H, OAc), 2.88 (1H, br. q, J = 10 Hz, H-1'), 3.35 (1H, br. q, J = 3 Hz, H-1), 3.87 (1H, dd) and 4.08 (1H, dd) (J = 3.5 and 12 Hz, CH_2OAc), 4.10 (1H, dd) and 4.44 (1H, dd) (J = 3 and 12 Hz, CH_2OAc), 4.91 (1H, dd, J = 3 and 10 Hz, H-2), 4.93 (1H, t, J = 10 Hz, H-4), 5.32 (1H, t, J = 10 Hz, H-3). The ^{1}H NMR spectral and analytical data were in accord with the proposed structures shown in Scheme II.[8]

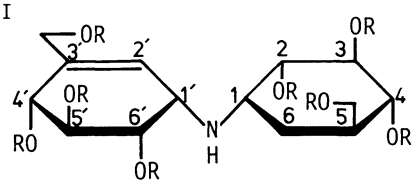
Acetylation of the latter diastereomeric mixture (5a, 5b) gave, after separation by a silica gel column chromatography (1:6 2-butanone–toluene), two tri-O-acetates (6b, oil, Rf 0.37,[9] 14%) and (6a, oil, Rf 0.32, 13%): ^{1}H NMR for 6a, δ 1.40 (3H, s), 1.43 (3H, s), and 1.47 (6H, s) (isopropylidene), 2.00 (3H, s), 2.02 (3H, s), and 2.08 (3H, s) (OAc), 5.02 (1H, t, J = 3 Hz, H-6'), 5.09 (1H, dd, J = 4.5 and 10.5 Hz, H-2'), 5.34 (1H, s, benzylic), 5.34 (1H, dd, J = 8.3 and 10.5 Hz, H-3'), and for 6b, δ 1.43 (9H, s) and 1.47 (3H, s) (isopropylidene), 2.00 (3H, s), 2.02 (3H, s), and 2.09 (3H, s) (OAc), 3.38 (1H, dd, J = 4 and 9 Hz, H-2), 4.79 (1H, t, J = 3 Hz, H-6'), 5.10 (1H, dd, J = 4.5 and 10.5 Hz, H-2'), 5.38 (1H, s, benzylic), 5.38 (1H, dd, J = 9 and 10.5 Hz, H-3'). The structures were assigned

tentatively on the basis of ^{1}H NMR spectroscopy. In the spectrum of 6a, the signal due to H-6' shifted down field by 0.23 ppm, as compared with that of 6b, which may be attributed to the deshielding effect of the oxygen atom of the 2,3-O-isopropylidene group situated very near to H-6'.

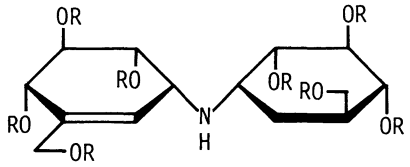
The reaction products of the mixture of 5a and 5b with methanesulfonyl chloride (four molar equiv., pyridine, 0–3°C, overnight) were separated by chromatography (silica gel, 2:9 2-butanone–toluene) to give the chloride (9b, mp 185–187°C, Rf 0.45, 13%) and the aziridine (8a, mp 207–221°C,[10] Rf 0.36, 21%), and a fraction (Rf 0.40) of a complex mixture consisting of unidentified compounds. The structures of 8a and 9b were assigned tentatively on the basis of the analytical data, postulated reaction mechanism, and ^{1}H NMR spectral data:[11] ^{1}H NMR for 8a, δ 1.42 (3H, s) and 1.49 (9H, s) (isopropylidene), 2.01 (3H, s) and 2.09 (3H, s) (OAc), 2.00–2.50 (4H, m, H-1', H-2', H-5, and H-6'), 5.44 (1H, s, benzylic), and for 9b, δ 1.45 (9H, s) and 1.49 (3H, s) (isopropylidene), 2.03 (3H, s) and 2.06 (3H, s) (OAc), 2.60–3.05 (1H, m, H-1), 3.25 (1H, m, H-1'), 4.01 (1H, t, J = 3 Hz, H-6'), 5.51 (1H, s, benzylic). The intermediate 6'-methanesulfonate of 5a seems to be readily attacked by the adjacent nitrogen atom to produce 8a, whereas, that of 5b is substituted by a chloride ion with retention of the configuration at C-6' via an aziridinium ion or an S_N1 like mechanism. The selectivity of the reaction depending on the diastereomers may be ascribed to the steric effect.

On the other hand, treatment of the diastereomeric mixture of 5a and 5b with three molar equiv. of sulfonyl chloride in pyridine at -15°C (2 h) and then at 3°C (overnight) gave 8a (9.2%) and 9b (34%), together with the olefinic compound (10a, oil, Rf 0.41, 24%) that was shown by the ^{1}H NMR spectrum to be contaminated with some unidentified compounds. In the case of the intermediate 6'-chlorosulfate of 5a, elimination reaction is likely to occur between C-5' and C-6' to give 10a. The difference in the reaction course seems to depend on the nature of the leaving groups.

Scheme III



11a R = Ac
12a R = H



11b R = Ac
12b R = H

Without further purification, the crude 10a was treated with 80% aqueous acetic acid and successively acetylated to afford, after chromatography, one major compound (11a, oil, 49%) and a small proportion of unidentified compounds. The ^{1}H NMR spectrum of 11a was superimposable on that of an authentic sample of the octa-O-acetyl derivative of 1.[12] Hydrolysis of 11a with 4M hydrochloric acid (90°C, 4 h) followed by treatment with Amberlite IRA-400 (OH^-) gave the free base (12a), which showed a single spot at Rf 0.37 on TLC in 4:1:1 1-propanol–acetic acid–water, being indistinguishable from 1.

Dehydrochlorination of 9b with 1,8-diazabicyclo[5.4.0]undec-5-ene (toluene, reflux, 3 h) proceeded smoothly to give rise to the olefin (10b, mp 211–212°C, Rf

0.44, 56%) as the major product, together with the aziridine (8b, mp 142–143°C, Rf 0.37, 30%):[13] ^{1}H NMR for 10b, δ 1.42 (9H, s) and 1.49 (3H, s) (isopropylidene), 2.07 (6H, s, OAc), 5.08 (1H, dd, J = 5 and 9 Hz, H-6'), 5.55 (1H, dd, J = 6.5 and 9 Hz, H-5'), 5.63 (1H, s, benzylic), 5.69 (1H, d, J = 5 Hz, H-2'). Compound 10b was converted into the corresponding octa-O-acetate (11b) and the free base (12b) in the similar way. The ^{1}H NMR spectra of 10b and 11b indicated that they were the diastereomers of 10a and 11a, respectively. The olefinic protons of 11a and 11b appeared as doublets at δ 5.96 (J = 5 Hz) and 5.85 (J = 5 Hz). The free bases 12a and 12b showed the similar mobilities on TLC in several solvent systems, but the octa-O-acetates were clearly differentiated from each other: 11a (Rf 0.36) and 11b (Rf 0.39) in 1:10 ethanol–toluene, and 11a (Rf 0.39) and 11b (Rf 0.41) in 2:3 2-butanone–toluene.[14]

In summary, the first total synthesis of DL-validoxylamine A and its diastereomer has been achieved. We are now studying to improve the reaction sequence in order to use its strategy for the total synthesis of validamycin A and its analogs.

References

1) S. Horii, Y. Kameda, and K. Kawahara, J. Antibiot., 25, 48 (1972).
2) S. Ogawa, T. Toyokuni, Y. Iwasawa, Y. Abe, and T. Suami, Chem. Lett., 1982, 279.
3) E. Truscheit, W. Frommer, B. Junge, L. Müller, D. D. Schmidt, and W. Wingender, Angew. Chem. Int. Ed. Engl., 20, 744 (1981).
4) All the compounds described in this paper are racemic. For convenience, each formula depicted shows only one of the respective enantiomers. Melting points were determined on a Mitamura Riken micro hot stage and are uncorrected. ^{1}H NMR spectra were measured on a Varian EM-390 (90 MHz) spectrometer in chloroform-d with reference to tetramethylsilane as an internal standard. All the new compounds gave satisfactory analytical data.
5) S. Ogawa, T. Toyokuni, and T. Suami, Chem. Lett., 1981, 947.
6) S. Ogawa, N. Chida, and T. Suami, Chem. Lett., 1980, 1559.
7) Unless otherwise noted, TLC was performed on silica gel (Wakogel B-5F) with 1:10 ethanol–toluene as developing solvent.
8) Much difference was observed between the spectra of 7a and 7b, but it was rather difficult to assign the correct structure to each diastereomer. The structures shown in Scheme II may be reversed.
9) The solvent system was 1:3 2-butanone–toltuene.
10) Compound 8a has a transition point at 180°C. The crystals (plates) change into needles, which melt completely at 221°C.
11) The assigned structures were proved by the following reaction sequence.
12) An authentic sample of 1 and the ^{1}H NMR spectrum of its octa-O-acetyl derivative were kindly provided by Dr. Satoshi Horii (Takeda Chemical Ind. Ltd.).
13) Formation of 8b under these conditions probably suggested that the chlorination reaction of 5b would not involve the intermediate 8b.
14) Although the structures of 5a and 5b were fully confirmed, neither of them has been isolated in a pure state. Therefore, correlation between 5a and 6a, as well as 5b and 6b, has not yet been established.

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