CHEMISTRY LETTERS, pp. 279-282, 1982.

SYNTHESIS OF DL-VALIDOXYLAMINE B

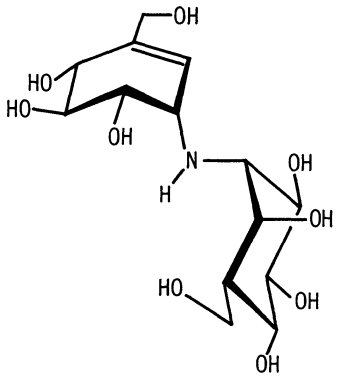
Seiichiro OGAWA*, Tatsushi TOYOKUNI, Yoshikazu IWASAWA,
Yasuo ABE, and Tetsuo SUAMI
Department of Applied Chemistry, Faculty of Science and Technology,
Keio University, Hiyoshi, Yokohama 223

DL-Validoxylamine B was first synthesized by the reaction of DL-4,7:5,6-di-O-isopropylidene-(1,4,6/5)-4,5,6-trihydroxy-3-hydroxymethyl-2-cyclohexenylamine with DL-3,4-di-O-acetyl-1,2-anhydro-5,7-O-benzylidene-(1,2,4,6/3,5)-6-hydroxymethyl-1,2,3,4,5-cyclohexanepentol, followed by removal of the protecting groups.

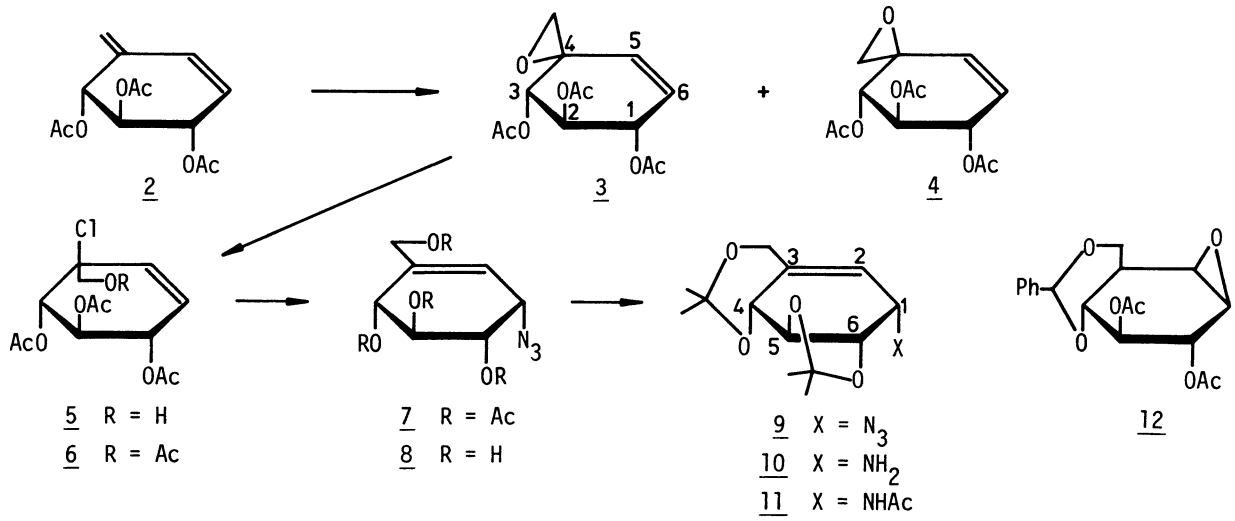
Validoxylamine B, [(1S)-(1,4,6/5)-4,5,6-trihydroxy-3-hydroxymethyl-2-cyclohexenyl][(1S)-(1,2,4/3,5,6)-2,3,4,6-tetrahydroxy-5-(hydroxymethyl)cyclohexyl]-amine (1), which was first obtained by acid hydrolysis of antibiotic validamycin B,[1] was isolated from the fermentation broth of Streptomyces hygroscopicus var. limoneus.[2] In this communication, we wish to describe the first total synthesis of the racemic form of 1.

We have undertaken the reaction of the blocked valienamine with an epoxycyclohexane derivative that was the precursor of the branched-chain cyclitol moiety, for this synthesis.

Di-O-isopropylidene derivative (10) of DL-valienamine was prepared by the following new reaction sequence.[3] Oxidation of the conjugated diene (2)[4] with a molar equiv. of m-chloroperbenzoic acid (CH_2Cl_2, $NaHCO_3$, 1 h) gave, after fractionation over a silica gel column (1:5 2-butanone–toluene), two spiro epoxides (3, mp 108.5–109.5°C, 45%) and (4, mp 124.5–125.5°C, 29%). The structures were tentatively assigned on the basis of the reactivity[5] and ^1H NMR spectroscopy: ^1H NMR ($CDCl_3$) for 3, δ 2.02 (3H, s) and 2.06 (6H, s) (OAc), 2.88 (2H, s, H-7 and H-7'), 5.29–5.60 (4H, m, H-1, H-2, H-3, and H-6), 5.96 (1H, dd, J = 2.3 and 10.5 Hz, H-5); and for 4, δ 2.01 (6H, s) and 2.05 (3H, s) (OAc), 2.73 (1H, d) and 3.18 (1H, d)

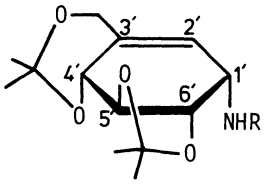


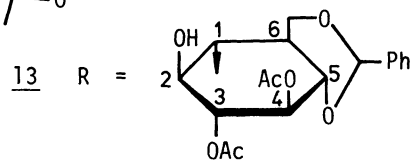
Validoxylamine B



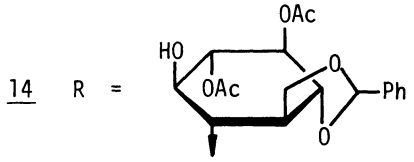
(AB quartet J = 5.3 Hz, H-7 and H-7'), 5.32–5.55 (3H, m, H-1, H-2, and H-6), 5.60 (1H, m, H-3), 5.84 (1H, dd, J = 1.5 and 10.5 Hz, H-5). Treatment of 3 with a molar equiv. of hydrochloric acid (THF, 0–5°C, 50 min) gave the chlorohydrin (5, mp 125–126.5°C, 100%), which was subsequently converted into the tetraacetate (6, mp 90–91°C, 100%) by the usual way (Ac_2O, H_2SO_4): ^{1}H NMR ($CDCl_3$) δ 1.98 (3H, s), 2.01 (3H, s), 2.08 (3H, s), and 2.11 (3H, s) (OAc), 4.32 (2H, s, H-7 and H-7'), 5.37–5.62 (3H, broad s, H-1, H-2, and H-3), 5.62 (1H, d) and 5.78 (1H, d) (J = 10 Hz, H-5 and H-6). Azidolysis of 6 with sodium azide (2 moles, DMF, 60°C, 15 h) gave stereoselectively via an S_N2' mechanism (apofacial) DL-tetra-O-acetyl-(1,3, 6/2)-6-azido-4-hydroxymethyl-4-cyclohexene-1,2,3-triol (7)[6] as an oil in 93% yield. De-O-acetylation of 7 with methanolic sodium methoxide (MeOH, 0–5°C, overnight) gave the hydroxy azide (8, oil, 100%), which was successively treated with an excess of 2,2-dimethoxypropane (TsOH, DMF, room temperature, 2 d) to give the di-O-isopropylidene derivative (9, mp 116.5–117.5°C, 60%). Compound 9 was reduced with hydrogen sulfide in 1:1 pyridine–water at room temperature to give the amine (10) in 95% yield, which was further converted to the crystalline N-acetyl derivative (11, mp 241–242°C): ^{1}H NMR ($CDCl_3$) δ 1.42 (3H, s), 1.46 (6H, s), and 1.57 (3H, s) (isopropylidene), 2.01 (3H, s, NAc), 3.55–3.72 (2H, m, H-5 and H-6), 4.10 (1H, d, J = 15 Hz, H-7), 4.32–4.59 (2H, m, H-4 and H-7'), 4.67–4.91 (1H, m, H-1), 5.65 (1H, d, J = 4.8 Hz, H-2).

Condensation of 10 with an equimolar amount of the epoxycyclohexane (12)[7] was carried out in 2-propanol in a sealed tube at 120°C. After the reaction mixture had been heated for 84 h, the products were roughly separated over a silica gel column (1:10 ethanol–toluene) to give a mixture of four condensation products [two minor components (13) and (14): Rf 0.39 and 0.35, and two major components (15) and (16): Rf 0.33 and 0.30] in 46% yield, together with 11 (5%) and recovered 12 (31%). Only 13 and 16 were partly isolated in a pure state: ^{1}H NMR ($CDCl_3$) for 13, δ 1.47 (3H, s), 1.50 (3H, s), 1.53 (3H, s), and 1.59 (3H, s) (isopropylidene), 2.06 (3H, s) and 2.11 (3H, s) (OAc), 5.02 (1H, t, J = 9.3 Hz) and 5.14 (1H, dd, J = 9.3 and 9.8 Hz) (two CHOAc), 5.45 (1H, s, benzylic), 5.40–5.59 (1H, m, H-2') 7.25–7.65 (5H, m, phenyl); and for 16, δ 1.48 (12H, broad s, isopropylidene),

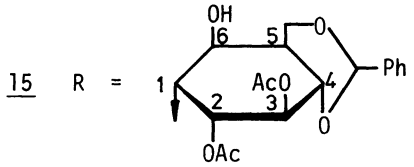




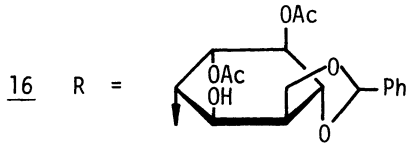
13 R =



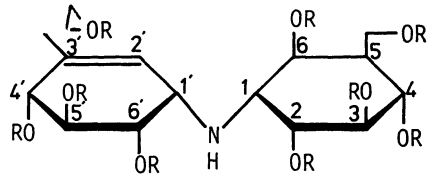
14 R =



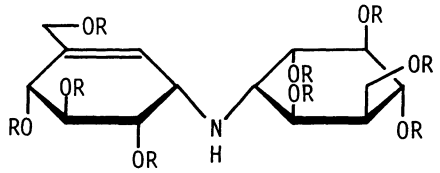
15 R =



16 R =



17 R = Ac
19 R = H



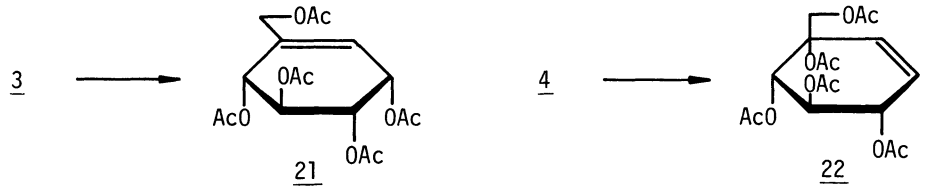
18 R = Ac
20 R = H

2.03 (3H, s) and 2.11 (3H, s) (OAc), 3.17–3.53 (2H, m, H-1 and H-1'), 5.25–5.65 (4H, m, H-2', benzylic, and two CHOAc), 7.12–7.65 (5H, m, phenyl).[8] Removal of the blocking groups of the mixture of condensates with 80% aqueous acetic acid (60°C, 10 h) followed by acetylation (Ac_2O, pyridine) gave, after fractionation over a silica gel column (1:3 2-butanone–toluene), a crystalline mixture of the nona-O-acetates (17) and (18) in 35% yield based on 12 consumed. Fractional crystallization from ethanol gave first 17 as prisms (mp 144–146.5°C, 12%) and then from methanol 18 as thin needles (mp 175–176°C, 12%): ^{1}H NMR ($CDCl_3$) for 17, δ 1.95–2.24 (27H, m, OAc), 3.36 (1H, t, J = 3.8 Hz, H-1), 3.62 (1H, t, J = 4.5 Hz, H-1'), 3.93 (1H, dd, J = 4.6 and 11.7 Hz) and 4.14 (1H, dd, J = 8.4 and 11.7 Hz) (CH_2OAc), 4.39 (1H, d) and 4.68 (1H, d) (J = 13 Hz, C=CCH_2OAc), 5.93 (1H, d, J = 4.9 Hz, H-2'); and for 18, δ 1.95–2.16 (27H, m, OAc), 3.29 (1H, t, J = 3.6 Hz, H-1), 3.56 (1H, t, J = 4.8 Hz, H-1'), 3.97 (1H, dd, J = 4.5 and 11.3 Hz) and 4.19 (1H, dd, J = 9.2 and 11.3 Hz) (CH_2OAc), 4.36 (1H, d) and 4.68 (1H, d) (J = 13.6 Hz, C=CCH_2OAc), 5.98 (1H, d, J = 5.4 Hz, H-2').[9] Compound 16 was convertible into 18 by the same way. Hydrolysis of 18 with 4M hydrochloric acid (90°C, 50 min) followed by treatment with Amberlite IRA-400 (OH^-) gave the free base (20), which showed a single spot at Rf 0.34 on TLC in 4:1:1 1-propanol–water–acetic acid (cf. validoxylamine A: Rf 0.26). The ^{1}H NMR spectrum of 20 in deuterium oxide was identical with that of an authentic sample of validoxylamine B.[10] Similarly, 17 was converted to the free base (19, Rf 0.27 in the same solvent system). The olefinic

protons of 19 and 20 appeared as doublets at δ 5.88 (J = 3.9 Hz) and 6.18 (J = 5.1 Hz), respectively. Compound 19 was assigned as the racemic diastereomer of validoxylamine B.

References

1) S. Horii, T. Iwasa, and Y. Kameda, J. Antibiot., 24, 57 (1971).
2) S. Horii, Y. Kameda, and K. Kawahara, J. Antibiot., 25, 48 (1971).
3) All the compounds described in this paper are racemic. For convenience, the formulas depict only one of the respective enantiomers. Melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected. ^{1}H NMR spectra were measured on a Varian EM-390 (90 MHz) spectrometer in chloroform-d or deuterium oxide with reference to tetramethylsilane or 4,4-dimethyl-4-silapentane-1-sulfonate, respectively, as an internal standard. TLC was performed on precoated silica gel 60 f-254 plaques (Merck, Darmstadt). All the new compounds gave satisfactory analytical data.
4) S. Ogawa, T. Toyokuni, M. Omata, N. Chida, and T. Suami, Bull. Chem. Soc. Jpn., 53, 455 (1980).
5) Acid catalyzed cleavage of the oxirane ring (TsOH, CH_2Cl_2) of 3 followed by acetylation gave the branched-chain unsaturated cyclitol (21).[6] This conversion may involve the intramolecular attack of the C-1 acetoxyl group at C-6 via an S_N1' mechanism giving rise to the intermediate cyclic acetoxonium ion between C-1 and C-6, which was then opened by a trace of water present. On the other hand, under the same reaction conditions, 4 gave the new cyclitol peracetate (22, oil), resulting from a neighboring assistance of the C-3 acetoxyl group at C-4: ^{1}H NMR ($CDCl_3$) δ 2.00 (3H, s), 2.02 (3H, s), 2.05 (3H, s), and 2.07 (6H, s) (OAc), 4.15 (1H, d) and 4.51 (1H, d) (J = 11.3 Hz, CH_2OAc), 5.23 (1H, broad d, J = ca. 10.5 Hz, H-3), 5.32–5.64 (2H, m, H-1 and H-2), 5.73 (1H, dd, J = 1.8 and 9.8 Hz, H-6), 6.33 (1H, dd, J = 1.0 and 9.8 Hz, H-5).



6) S. Ogawa, T. Toyokuni, and T. Suami, Chem. Lett., 1980, 713.
7) S. Ogawa, N. Chida, and T. Suami, Chem. Lett., 1980, 1559.
8) In the spectrum of 13, appearance of two widely splitted signals due to the protons on carbon atoms bearing acetoxyl groups indicates the axial–axial–axial conformations for H-2, H-3, and H-4. Therefore, 13 was assigned as the condensate formed by the diequatorial opening of the epoxide ring. The structures of 13 and 14 shown in the Scheme may be reversed.
9) The signals due to the protons on C-1 and C-1' were assigned after deuteration.
10) The ^{1}H NMR spectrum of 1 was kindly presented by Dr. Satoshi Horii.

(Received December 10, 1981)