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SYNTHESES OF VALIDAMINE, EPI-VALIDAMINE, AND VALIENAMINE, THREE OPTICALLY ACTIVE PSEUDO-AMINO-SUGARS, FROM D-GLUCOSE

Masayuki Yoshikawa, Bae Cheon Cha, Yoshihiko Okaichi, Yoshihiko Takinami, Yoshihiro Yokokawa, and Isao Kitagawa*

Faculty of Pharmaceutical Sciences, Osaka University, 1-6, Yamada-oka, Suita, Osaka 565, Japan

Using as a key reaction a Michael-type addition reaction to nitro-olefins or a substitution reaction for an acetoxyl residue at the β-position of the nitro group in pseudo-nitro-sugar, three optically active pseudo-amino-sugars: validamine, epi-validamine, and valienamine, were synthesized from D-glucose.

KEYWORDS —— pseudo-amino-sugar optically active; validamine; epi-validamine; valienamine; pseudo-amino-sugar synthesis; Michael-type addition; pseudo-nitro-sugar

Validamine (6),[1] epi-validamine (11),[2] and valienamine (16)[2] have been known as the component pseudo-amino-sugars of antibiotic validamycins and pseudo-oligosaccharidic α-glucosidase inhibitors (adiposins, trestatins, acarbose, etc.).[3] Afterwards, these pseudo-amino-sugars (6, 16) themselves were isolated from the fermentation broth of Streptomyces hygroscopicus subsp. limoneus and have been shown to have several interesting biological properties such as potent α-glucosidase inhibitory activity and antibiotic activity against Bacillus species.[4,5] These facts have stimulated many synthesis studies of validamine (6), valienamine (16), and their analogs.[3,6]

Recently, we have developed a versatile method for converting carbohydrate to optically active pseudo-hexopyranose. In this method a stereoselective deacetoxylation reaction with $NaBH_4$ and a cyclitol formation from nitrofuranose with KF in the presence of 18-crown-6 were used as key reactions.[7] Furthermore, by utilizing nitrofuranoses which were common reaction intermediates in these pseudo-hexopyranose syntheses, a method has been developed for synthesizing optically active pseudo-pentofuranose and several new pseudo-pentofuranoses were synthesized.[8] As an extension of these studies on synthesizing pseudo-sugar, we have found a new method for synthesizing optically active pseudo-amino-sugar. This paper deals with some successful examples of synthesizing optically active validamine (6), epi-validamine (11), and valienamine (16).[9]

Treatment of a nitrofuranose derivative (1)[7] with KF in DMF in the presence of 18-crown-6 (23°C, 3 h) and subsequent acetylation of the product with Ac_2O in the presence of p-TsOH·H_2O (23°C, 3 h), yielded a nitro-olefin (2, 80 %),[10a] colorless oil, $[\alpha]_D^{22}$ +42.6° ($CHCl_3$), $C_{25}H_{25}NO_9$.[11] The nitro-olefin (2) was then subjected to a Michael-type addition reaction to synthesize amino-nitrocyclitols.

When 2 was treated with 28 % aq. NH_4OH in 95 % EtOH at room temperature (23°C) for 2 h and the product was acetylated with Ac_2O and p-TsOH·H_2O, a 1β-acetamide (3, 81 %),[10b] colorless oil, $[\alpha]_D^{22}$ +7.0° ($CHCl_3$), $C_{27}H_{30}N_2O_{10}$, was obtained. But when 2 was treated with liq. NH_3 in THF at -78°C for 2 h and the product was acetylated with Ac_2O and p-TsOH·H_2O, 1α-acetamides (4, a mixture of 6α-nitro and 6β-nitro epimers) were formed, colorless oil, IR ($CHCl_3$): 1719, 1675, 1552, 1363 cm^{-1}, EI-MS (m/z): 542 (M^+). Elimination of the nitro group in 4 with n-Bu_3SnH in benzene in the presence of α,α'-azobis-iso-butyronitrile (AIBN) (80°C, 3 h), furnished 5 (56 %),[10c] colorless oil, $[\alpha]_D^{20}$ +16.7° ($CHCl_3$), $C_{27}H_{31}NO_8$. After removal of the acetyl groups and the benzoyl group in 5 with 1 % NaOH-MeOH, the product was subjected to debenzylation (Na, liq. NH_3, -78°C, 30 min) and subsequent acetylation with Ac_2O in pyridine to provide pentaacetylvalidamine (6a, 88 %), which was found to be identical with the authentic sample by mixed mp determination and by $[\alpha]_D$, TLC, IR ($CHCl_3$), and ^1H NMR (500 MHz, $CDCl_3$) comparisons. Finally, de-O-acetylation of 6a with 10 % NaOMe-MeOH (25°C, 3 h) followed by de-N-acetylation with 80 % aq. NH_2NH_2 in a sealed tube (100°C, 72 h) furnished validamine (6, 90 %), identical with the authentic sample [TLC, IR (KBr), $[\alpha]_D$].

On the other hand, cyclitol formation of the other nitrofuranose derivative (7)[7] with KF and 18-crown-6 in DMF and subsequent acetylation of the resulting cyclitol as described above for 1, provided an isomeric nitro-olefin (8, 80 %),[10d] colorless oil, $[\alpha]_D^{22}$ -27.2° ($CHCl_3$), $C_{25}H_{25}NO_9$. Treatment of 8 with liq. NH_3 at -78°C yielded 1α-acetamides (9, a mixture of 6α-nitro and 6β-nitro epimers), colorless oil, IR ($CHCl_3$): 2931, 1741, 1691, 1560, 1371 cm^{-1}, EI-MS (m/z): 542 (M^+). Elimination of the nitro group in 9 with n-Bu_3SnH and AIBN gave 10 (56 %),[10e] colorless oil, $[\alpha]_D^{20}$ -7.5° ($CHCl_3$), $C_{27}H_{31}NO_8$. Deacylation of 10 with 1 % NaOH-MeOH followed by debenzylation with Na-liq. NH_3 and de-N-acetylation with 80 % aq. NH_2NH_2, furnished epi-validamine (11, 83 %).[12]

Next, we applied a substitution reaction for an acetoxyl group at the β-position of a nitro group to a synthesis of valienamine (16). Treatment of a pseudo-nitro-sugar (12)[7] with liq. NH_3 in THF (-78°C, 2 h) and subsequent acetylation of the product yielded 13 (60 %, a mixture of 6α-nitro and 6β-nitro epimers), a white powder, IR ($CHCl_3$): 3434, 1737, 1685, 1555, 1365 cm^{-1}, EI-MS (m/z): 558 (M^+). Elimination of the nitro group in 13 with n-Bu_3SnH provided 14 (60 %),[10f] colorless oil, $[\alpha]_D^{22}$ +11.4° ($CHCl_3$), $C_{27}H_{31}NO_9$. Dehydration of 14 with $SOCl_2$ in pyridine (2°C, 15 min) gave selectively 15 (89 %),[10g] colorless oil, $[\alpha]_D^{22}$ -16.5° ($CHCl_3$), $C_{27}H_{29}NO_8$.

After removal of all protecting groups in 15, the product was acetylated to furnish pentaacetylvalienamine (16a, 91 %), which was found to be identical with the authentic sample by mixed mp determination, and by $[\alpha]_D$, IR ($CHCl_3$), and ^1H NMR (500 MHz, $CDCl_3$) comparisons. Deacetylation of 16a with 80 % aq. NH_2NH_2 (in a sealed tube as above) yielded valienamine (16, 92 %), identical with the authentic sample [TLC, IR (KBr), $[\alpha]_D$].

We are currently working on further application of this method to the syntheses of other types of pseudo-amino-sugars.

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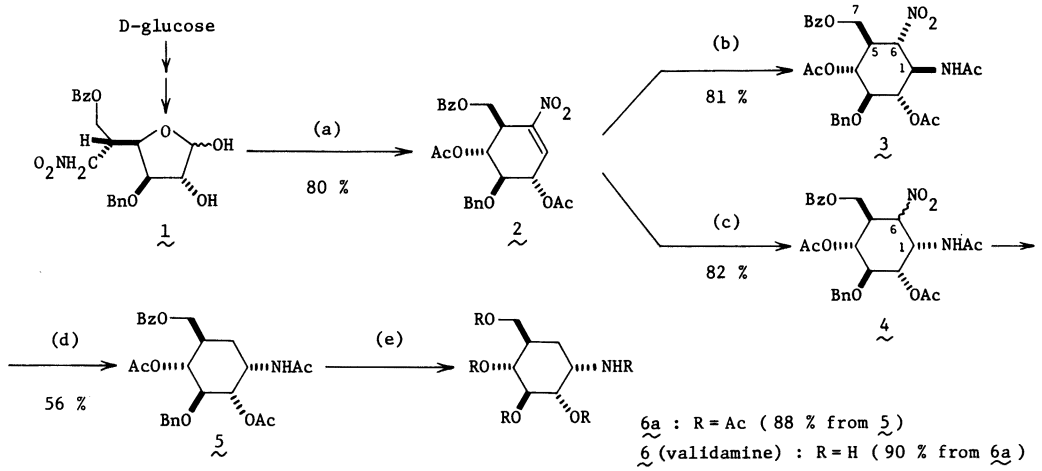

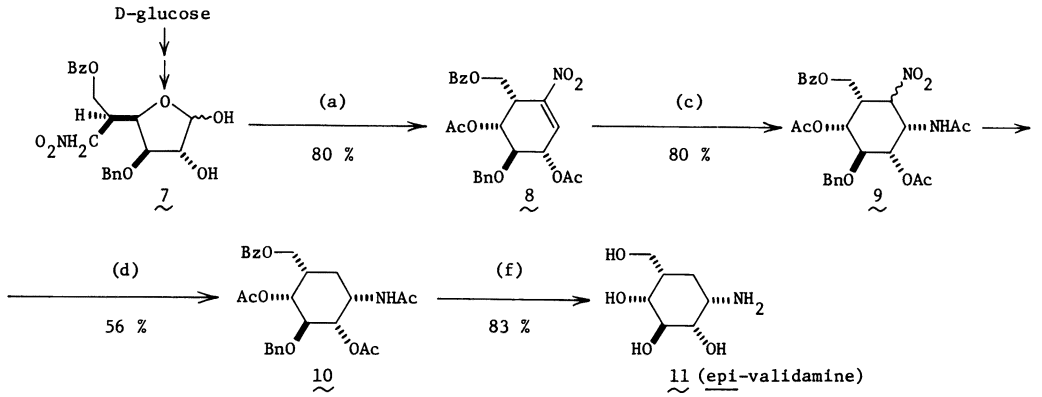

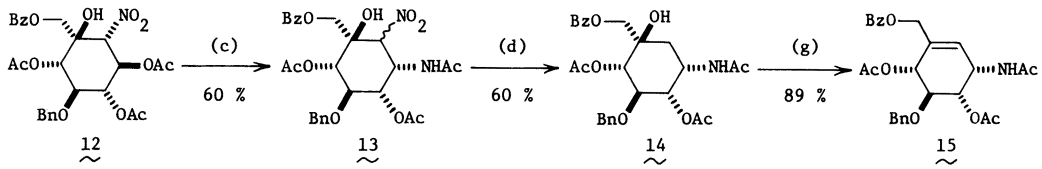

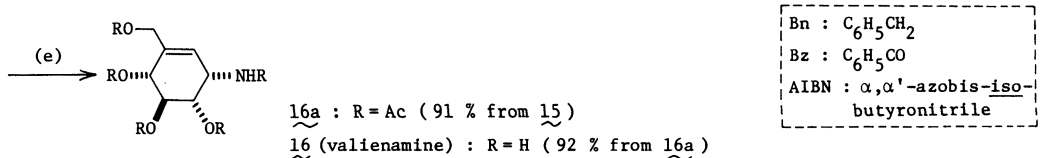

Bn : $C_6H_5CH_2$
Bz : C_6H_5CO
AIBN : α,α'-azobis-iso-butyronitrile

(a) KF / 18-crown-6 / DMF; Ac_2O / p-TsOH·H_2O (b) 28 % aq. NH_4OH / 95 % EtOH (23°C); Ac_2O / p-TsOH·H_2O (c) liq. NH_3 / THF (-78°C); Ac_2O / p-TsOH·H_2O (d) n-Bu_3SnH / AIBN / benzene (e) 1) 1 % NaOH-MeOH; Na / liq. NH_3; Ac_2O / pyridine; 2) 10 % NaOMe-MeOH; 80 % aq. NH_2NH_2 (f) 1 % NaOH-MeOH; Na / liq. NH_3; 80 % aq. NH_2NH_2 (g) $SOCl_2$ / pyridine

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6) a) R.R.Schmidt and A.Köhn, Angew. Chem. Int. Ed. Engl., 26, 482 (1987);
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9) M.Yoshikawa, B.C.Cha, Y.Okaichi, Y.Takinami, Y.Yokokawa, and I.Kitagawa, presented at the 108th Annual Meeting of the Pharmaceutical Society of Japan, Hiroshima, April, 1988, Abstract Papers p.45.
10) All new compounds were fully characterized by IR, ^{1}H NMR, and mass spectra:
   a) 2 : IR ($CHCl_3$): 1733, 1558, 1368 cm^{-1}, ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.04, 2.07 (3H each, both s, OAc X2), 7.20 (1H, d, J = 3.5 Hz, 1-H), EI-MS (m/z): 483 (M^+);
   b) 3 : IR ($CHCl_3$): 1722, 1706, 1562, 1355 cm^{-1}, ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.09, 1.97, 1.98 (3H each, all s, OAc X2, NHAc), 2.79 (1H, dddd, J = 2.5, 4.0, 9.3, 9.5 Hz, 5α-H), 3.81 (1H, dd, J = 9.4, 9.5 Hz, 3α-H), 4.18 (1H, dd, J = 2.5, 12.5 Hz), 4.32 (1H, dd, J = 4.0, 12.5 Hz) (7-H_2), 4.63, 4.67 (1H each, both d, J = 11.5 Hz, φ-CH_2-), 4.75 (1H, dd, J = 9.0, 9.3 Hz, 6β-H), 4.76 (1H, ddd, J = 7.0, 8.8, 9.0 Hz, 1α-H), 5.09 (1H, dd, J = 8.8, 9.5 Hz, 2β-H), 5.25 (1H, dd, J = 9.4, 9.5 Hz, 4β-H), 6.08 (1H, d, J = 7.0 Hz, N-H), 7.21-8.01 (10H, aromatic protons), EI-MS (m/z): 542 (M^+);
   c) 5 : IR ($CHCl_3$): 1741, 1682 cm^{-1}, ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.74 (1H, ddd, J = 3.3, 11.9, 15.0 Hz, 6β-H), 1.95, 2.02, 2.05 (3H each, all s, OAc X2, NHAc), 2.14 (1H, ddd, J = 4.3, 5.8, 15.0 Hz, 6α-H), 2.21 (1H, m, 5α-H), 3.72 (1H, dd, J = 8.8, 9.1 Hz, 3α-H), 4.22 (1H, dd, J = 5.2, 11.3 Hz), 4.35 (1H, dd, J = 4.2, 11.3 Hz) (7-H_2), 4.58 (1H, dddd, J = 3.3, 4.2, 4.3, 7.3 Hz, 1β-H), 4.62, 4.70 (1H each, both d, J = 11.5, 11.9 Hz, φ-CH_2-), 5.00 (1H, dd, J = 4.2, 9.1 Hz, 2β-H), 5.11 (1H, dd, J = 8.5, 8.8 Hz, 4β-H), 5.48 (1H, d, J = 7.3 Hz, N-H), 7.24-8.03 (10H, aromatic protons), EI-MS (m/z): 497 (M^+);
   d) 8 : IR ($CHCl_3$): 1726, 1531, 1372 cm^{-1}, ^{1}H NMR (90 MHz, $CDCl_3$): δ 2.04, 2.07 (3H each, both s, OAc X2), 7.19 (1H, d, J = 3.8 Hz, 1-H), EI-MS (m/z): 483 (M^+);
   e) 10: IR ($CHCl_3$): 1733, 1672 cm^{-1}, ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.80 (1H, ddd, J = 3.6, 3.9, 11.9 Hz, 6β-H), 1.93 (1H, ddd, J = 11.9, 11.9, 11.9 Hz, 6α-H), 1.98, 2.02, 2.09 (3H each, all s, OAc X2, NHAc), 2.64 (1H, m, 5β-H), 3.93 (1H, dd, J = 2.7, 3.0 Hz, 3α-H), 4.21 (1H, dd, J = 7.9, 10.6 Hz), 4.26 (1H, dd, J = 7.0, 10.6 Hz) (7-H_2), 4.55 (1H, dddd, J = 2.8, 3.9, 8.8, 11.9 Hz, 1β-H), 4.65, 4.72 (1H each, both d, J = 11.6, 11.9 Hz, φ-CH_2-), 5.06 (1H, dd, J = 2.8, 3.0 Hz, 2β-H), 5.15 (1H, dd, J = 2.7, 2.7 Hz, 4β-H), 5.57 (1H, d, J = 8.8 Hz, N-H), 7.33-8.04 (10H, aromatic protons), EI-MS (m/z): 497 (M^+);
   f) 14: IR ($CHCl_3$): 3438, 1735, 1673 cm^{-1}, ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.97, 1.99, 2.00 (3H each, all s, OAc X2, NHAc), 2.04-2.19 (2H, m, 6-H_2), 4.01 (1H, dd, J = 10.0, 10.0 Hz, 3α-H), 4.02, 4.32 (1H each, both d, J = 11.6 Hz, 7-H_2), 4.59, 4.77 (1H each, both d, J = 11.6 Hz, φ-CH_2-), 4.74 (1H, m, 1β-H), 4.94 (1H, dd, J = 4.2, 10.0 Hz, 2β-H), 5.18 (1H, d, J = 10.0 Hz, 4β-H), 7.00 (1H, d, J = 8.6 Hz, N-H), 7.24-8.04 (10H, aromatic protons), EI-MS (m/z): 513 (M^+);
   g) 15 : IR ($CHCl_3$): 1731, 1678 cm^{-1}, ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.97, 2.03, 2.05 (3H each, all s, OAc X2, NHAc), 4.05 (1H, dd, J = 3.3, 6.1 Hz, 3α-H), 4.74 (2H, s, 7-H_2), 4.76, 4.79 (1H each, both d, J = 13.1, 13.3 Hz, φ-CH_2-), 5.05 (1H, dd, J = 4.3, 6.1 Hz, 2β-H), 5.15 (1H, ddd, J = 2.4, 4.3, 9.4 Hz, 1β-H), 5.43 (1H, d, J = 3.3 Hz, 4β-H), 5.71 (1H, d, J = 9.4 Hz, N-H), 5.90 (1H, d, J = 2.4 Hz, 6-H), 7.27-8.06 (10H, aromatic protons), EI-MS (m/z): 495 (M^+).
11) The molecular composition of the compound given with the chemical formula was determined either by elemental analysis or by high resolution mass spectrometry.
12) mp 211-212°C, $[\alpha]_D^{22}$ +4.5° (H_2O), ^{1}H NMR (500 MHz, D_2O): δ 1.78 (1H, ddd, J = 10.1, 11.3, 11.3 Hz, 6α-H), 2.11 (1H, ddd, J = 3.4, 3.6, 11.3 Hz, 6β-H), 2.12 (1H, m, 5-H), 3.63 (1H, dd, J = 6.4, 11.0 Hz), 3.71 (1H, dd, J = 7.0, 11.0 Hz) (7-H_2), 3.65 (1H, ddd, J = 2.7, 3.4, 11.3 Hz, 1β-H), 3.97 (1H, dd, J = 2.4, 3.3 Hz, 4β-H), 4.04 (1H, dd, J = 2.7, 3.6 Hz, 2β-H), 4.12 (1H, dd, J = 3.3, 3.6 Hz, 3α-H).

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