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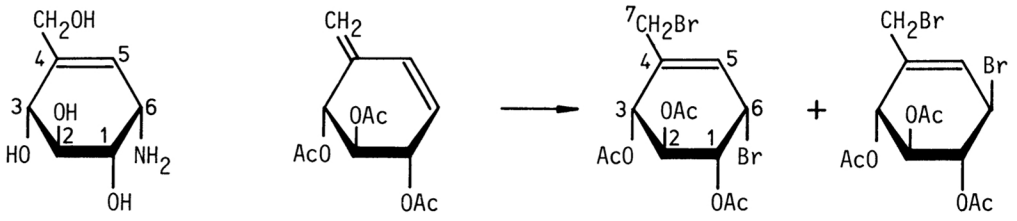
SYNTHESIS OF PENTA-N,O-ACETYL-DL-VALIENAMINE AND ITS RELATED BRANCHED-CHAIN UNSATURATED AMINOCYCLITOLS AND CYCLITOLS

Seiichiro OGAWA, Tatsushi TOYOKUNI, and Tetsuo SUAMI
Department of Applied Chemistry, Faculty of Engineering,
Keio University, Hiyoshi, Yokohama 223

Penta-N,O-acetyl-DL-valienamine, and its related branched-chain unsaturated aminocyclitols and cyclitols were synthesized from the dibromides derived from tri-O-acetyl-DL-(1,3/2)-4-methylene-5-cyclohexene-1,2,3-triol.

Microbial degradation of validamycin A with a cell suspension of Pseudomonas denitrificans gave validamine[1] and unsaturated aminocyclitol, valienamine (1).[2] The structure of 1 was assigned to 1D-(1,3,6/2)-6-amino-4-hydroxymethyl-4-cyclohexene-1,2,3-triol on the basis of ^{1}H NMR spectroscopy.

In continuation to the previous paper,[3] we wish to report herein a first synthesis of penta-N,O-acetyl-DL-valienamine (19a) and its related branched-chain unsaturated aminocyclitols and cyclitols, starting from common intermediates.

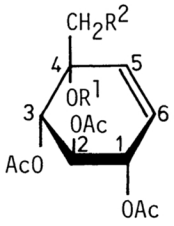


1 2 3 4

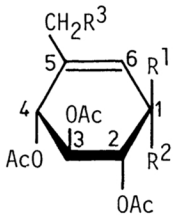
Treatment of the readily available tri-O-acetyl-DL-(1,3/2)-4-methylene-5-cyclohexene-1,2,3-triol (2)[4] with a molar equiv. of bromine in carbon tetrachloride at -15°C gave a mixture of 1,4-addition products (3 and 4) in 89% yield.[5] Fractionation of the mixture on a silica-gel column with 2-butanone–toluene as an eluent gave the dibromides 3 (syrup, 18%) and 4 (mp 108.5–109.5°C, 40%), along with a trace of a tetrabromide, mp 147–148°C.[6] In the ^{1}H NMR spectrum of 3, a signal due to olefinic proton (H-5) appeared as a doublet (J = 5.5 Hz) at δ 6.19, indicating that the C-6 bromine atom was situated in a pseudo-axial position in the favored half-chair conformation.[7] While, the spectrum of 4 contained a broad singlet for H-5 proton at δ 6.13. Therefore, the structures of 3 and 4 were assigned to DL-(1,3,6/2)- and DL-(1,3/2,6)-6-bromo-4-bromomethyl-4-cyclohexene-1,2,3-triol triacetates, respectively. When the same bromination was carried out at room temperature, a preferential formation of 3 (48%), along with 4 (17%), was

observed. On the other hand, the bromination of 2 in acetic acid at room temperature gave 3 (10%) and 4 (43%). The products ratio seems to depend on a reaction temperature and a polarity of the solvent used. Both 3 and 4 were found to be interconvertible under the conditions of bromination.

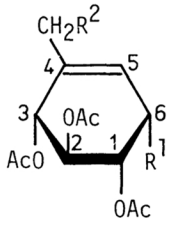
The dibromides 3 and 4 were expected to be potential intermediates for the present synthetic study. Introduction of amino and/or hydroxyl functions into the desired positions of cyclohexene ring and branched methylene group was conducted by taking advantage of the difference of reactivity of two bromine atoms at C-6 and C-7.



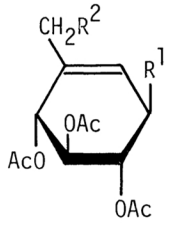
	R^1	R^2
5	H	Br
6	Ac	OMe



	R^1	R^2	R^3
7	H	OH	Br
8	H	OH	OAc
9	H	OAc	Br
10	H	OAc	OAc
11	OAc	H	Br
12	OAc	H	OAc
13	H	OAc	N_3
14	H	OAc	NHAc



a



b

	R^1	R^2
15	Br	OAc
16	N_3	N_3
17	NHAc	NHAc
18	N_3	OAc
19	NHAc	OAc

Treatment of 3 with a molar equiv. of silver acetate (AcOAg) in 90% aqueous acetic acid at room temperature for 24 h gave the bromo triacetate (5, syrup, 52%). The reaction is likely to involve allylic rearrangement (S_N2') with an assistance of the C-3 acetoxyl group. Attempt to remove the remaining bromine atom by further treatment with an excess of AcOAg failed. However, reaction of 5 with sodium methoxide in methanol proceeded smoothly via a spiro epoxide to give a crystalline methyl ether, which was characterized as the tetraacetate (6, mp 130–130.5°C, 66%): ^{1}H NMR δ=2.02 (3H, s), 2.04 (3H, s), and 2.09 (6H, s) (OAc), 3.29 (3H, s, OMe), 3.25 (1H, d) and 3.78 (1H, d) (J = 5 Hz, CH_2OMe), 5.17–5.61 (3H, m, H-1, H-2, and H-3), 5.76 (1H, dd, J = 2 and 10 Hz, H-6), 6.33 (1H, dd, J = 1 and 10 Hz, H-5).

Under the similar conditions (wet AcOH, room temperature, 2 h), 4 reacted with a molar equiv. of AcOAg to give the bromo triacetate (7, 73%) and tetraacetate (8, 13%). The 1,6-cyclic intermediary acetoxonium ion may be first formed by a neighboring-group participation of the C-1 acetoxyl group and then opened by attack of water to give 7, which is converted into 8 by further substitution by an acetate ion. Compound 8 was readily obtainable from 4 in 56% yield using 4 molar equiv. of AcOAg (wet AcOH, 90°C, 1 h). Acetylation (Ac_2O, pyridine) of 7 and 8 gave the corresponding bromo tetraacetate (9) and pentaacetate (10), respectively.

On the other hand, treatment of 4 with 3 molar equiv. of AcOAg in anhydrous conditions [AcOH-Ac_2O (1 : 1), 90°C, 3 h] gave the pentaacetate (12, syrup, 99%) different from 10, which was shown by TLC to arise from further substitution of an initially formed 11. The reaction involves the formation of the 1,6-cyclic acetoxonium ion and successive back side attack of an acetate ion at C-6. The olefinic protons of 10 and 12 appeared as a doublet of doublets (J = 2 and 6 Hz, δ 6.94) and a broad singlet (δ 5.82), respectively, being consistent with the proposed structures.

The C-7 bromo group of 7 was readily substituted by an azido group (2 molar equiv. of sodium azide, DMF, room temperature, 1 h), followed by acetylation, to give the azide (13, 80%) as a homogeneous syrup: ^{1}H NMR (90 MHz, $CDCl_3$) δ=2.02 (3H, s), 2.05 (3H, s), and 2.11 (6H, s) (OAc), 3.81 (2H, s, CH_2N_3), 5.15 (1H, dd, J = 4 and 10.5 Hz, H-2), 5.29–5.75 (2H, m, H-3 and H-4), 6.00 (1H, dd, J = 1.5 and 6 Hz, H-6). Reduction of 13 with hydrogen sulfide in pyridine–water (2 : 1) (room temperature, 1.5 h),[8] followed by acetylation, gave the acetamide (14, mp 148.5–149.5°C, 87%).

Reaction of 3 or 4 with a molar equiv. of sodium acetate (AcONa, room temperature, 24 h) afforded a mixture of the bromo tetraacetate (15a) and (15b) in 65–73% yield.[9] In this case, the primary bromo group was preferentially substituted by an acetate ion, which was verified by the down-field shift (0.6–0.7 ppm) of the methylene signals. The product ratio was shown by ^{1}H NMR spectroscopy to be about same, starting either from 3 or 4. On treatment of the mixture with an excess of AcONa (4 molar equiv.), a 1.7 : 1 mixture of 10 and 12 was obtained.

Treatment of 3 with 4 molar equiv. of sodium azide (DMF, room temperature, 1 h) gave via direct S_N2 displacement reaction by an azide ion a sole crystalline diazide (16b, mp 82–83°C, 88%) with an inversion of the configuration at C-6. The diazide (16a) was obtained as a homogeneous syrup from 4 in essentially quantitative yield. Both diazides are stable under the conditions in the presence of an excess of sodium azide. The ^{1}H NMR spectrum (90 MHz, $CDCl_3$) of 16a revealed the olefinic proton as a broad doublet (J = 7.5 Hz) at δ 5.94, suggesting the pseudo-axial conformation of the azido group. Reduction of 16a and 16b either with sodium borohydride (2-propanol, 90°C, 1 h) or more conveniently with hydrogen sulfide, followed by acetylation, gave the corresponding 6-epimeric diacetamides (17a, mp 253–255°C, 43%) and (17b, mp 229.5–230.5°C, 90%), respectively.

Finally, attempt to prepare a peracetyl derivative (19a) of valienamine from 4 was carried out. Compound 4 was first converted into a mixture of 15a and 15b by treatment with a molar equiv. of potassium acetate (DMF, 18-crown-6, 25°C, 2.5 h). Without isolation of the products, an excess of sodium azide was added to the reaction mixture. After one hour, formation of two major components was detected by TLC. The mixture was separated by chromatography on silica gel with 2-butanone–toluene as an eluent to give two azides (18a, syrup, 26%) and (18b, mp 68–68.5°C, 43%): ^{1}H NMR (90 MHz, $CDCl_3$) for 18a, δ=2.03 (3H, s), 2.05 (6H, s), and 2.12 (3H, s) (OAc), 4.41 (1H, dd, J = 4.5 and 7.5 Hz, H-6), 4.40 (1H, d) and 4.70 (1H, d) (J = 13 Hz, CH_2OAc), 5.15 (1H, dd, J = 4.5 and 10 Hz, H-1), 5.49 (1H, dd, J = 7 and 10 Hz, H-2), 5.68 (1H, broad d, J = 7 Hz, H-3), 5.96 (1H, broad d, J = 7.5 Hz, H-5); and for 18b, δ=2.01 (3H, s), 2.03 (3H, s), 2.05 (3H, s), and 2.08 (3H, s) (OAc), 4.21 (1H, m, H-6), 4.38 (1H, d) and 4.70 (1H, d) (CH_2OAc), 5.14–5.43 (2H, m, H-1

and H-2), 5.70 (2H, broad s, H-3 and H-5). Reduction of 18a with hydrogen sulfide [pyridine–water (2 : 1), room temperature, 1 h], followed by acetylation, afforded 19a (mp 180–181°C) in 70% yield. This compound was identified with an authentic optically active sample,[10] except for optical activity, by comparison with the ^{1}H NMR spectra in $CDCl_3$ and in dimethyl-d_6 sulfoxide: ^{1}H NMR (100 MHz, DMSO-d_6) δ= 1.86 (3H, s), 1.93 (3H, s), and 2.20 (9H, s) (NAc and four OAc), 4.42 (1H, d) and 4.67 (1H, d) (J = 14 Hz, CH_2OAc), 4.81 (1H, td, J = 4.5 and 9 Hz, H-6), 5.03 (1H, dd, J = 4.5 and 9.5 Hz, H-1), 5.36 (1H, dd, J = 7 and 9.5 Hz, H-2), 5.58 (1H, d, J = 7 Hz, H-3), 5.87 (1H, broad d, J = 4.5 Hz, H-5), 8.15 (1H, d, J = 9 Hz, NHAc). Compound 18b was reduced similarly, followed by acetylation, to give the 6-epimer (19b, mp 120–121°C) in 69% yield. The structure was confirmed by the ^{1}H NMR spectrum (90 MHz, $CDCl_3$): δ=1.94 (3H, s), 2.00 (3H, s), and 2.03 (9H, s) (NAc and four OAc), 4.35 (1H, d) and 4.68 (1H, d) (J = 13 Hz, CH_2OAc), 4.84 (1H, broad dd, J = 7.5 and 8.5 Hz, H-6), 5.10 (1H, dd, J = 8.5 and 10.5 Hz, H-1), 5.37 (1H, dd, J = 8 and 10.5 Hz, H-2), 5.74 (2H, broad s, H-3 and H-5), 6.06 (1H, broad d, J = 7.5 Hz, NHAc).

References and Notes

1) See S. Ogawa, Y. Shibata, N. Chida, and T. Suami, Chem. Lett., 1980, 135, and the references are cited therein.
2) Y. Kameda and S. Horii, J. Chem. Soc., Chem. Commun., 1972, 746.
3) S. Ogawa, N. Chida, and T. Suami, Chem. Lett., 1980, 139.
4) S. Ogawa, T. Toyokuni, M. Omata, N. Chida, and T. Suami, Bull. Chem. Soc. Jpn., 53, 455 (1980).
5) All the compounds reported in this paper are racemic. The formulas depict only one of the respective racemates. The nomenclature and numbering of cyclitols follow IUPAC and IUB tentative rules for cyclitol nomenclature [J. Biol. Chem., 243, 5809 (1968)]. Melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected. Unless otherwise stated, ^{1}H NMR spectra were measured on a Varian EM-360A (60 MHz) spectrometer in $CDCl_3$ with reference to tetramethylsilane as an internal standard. The 90 MHz and 100 MHz spectra were taken on a Varian EM-390 and Varian XL-100 spectrometers, respectively. All the new compounds gave satisfactory analytical data.
6) The tetrabromide was selectively obtained, in 91% yield, by treatment of 2 with an excess of bromine in carbon tetrachloride at 0°C.
7) R. J. Abraham, H. Gottschalck, H. Paulsen, and W. A. Thomas, J. Chem. Soc., 1965, 6268; A. A. Chalmers and R. H. Hall, J. Chem. Soc., Perkin Trans. 2, 1974, 728.
8) T. Adachi, Y. Yamada, and I. Inoue, Synthesis, 1977, 45.
9) Attempt to separate 15a from 15b were unsuccessful, because of their close similarity of chromatographic behavior.
10) The ^{1}H NMR spectrum (100 MHz, DMSO-d_6) of 19a was superimposable on that of an authentic optically active sample, which had been reported to show mp 93°C. The comparison of the spectra was kindly carried out by Dr. S. Horii.

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