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A SYNTHESIS OF DL-PENTA-*N*,*O*-ACETYLVALIOLAMINE

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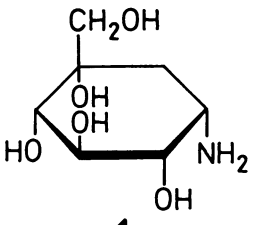
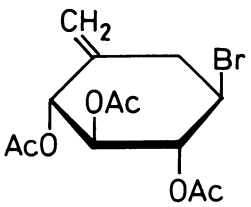
Valiolamine, (2*S*)-(1,2,4,5/3)-5-amino-1-*C*-hydroxymethyl-1,2,3,-4-cyclohexanetetrol, an α-glucosidase inhibitor isolated from *Streptomyces hygroscopicus* subsp. *limoneus*, has been synthesized as the racemic penta-*N*,*O*-acetyl derivative starting from DL-1,2,3-tri-*O*-acetyl-(1,3/2,4)-4-bromo-6-methylene-1,2,3-cyclohexanetriol.

Valiolamine (1) is a branched-chain aminocyclitol which was isolated from the fermentation broth of *Streptomyces hygroscopicus* subsp. *limoneus* and it has been shown to be a more potent α-glucosidase inhibitor than valienamine and validamine isolable together with 1.[1] The structure was deduced to be (2*S*)-(1,2,4,5/3)-5-amino-1-*C*-hydroxymethyl-1,2,3,4-cyclohexanetetrol on the basis of spectroscopic studies,[1] and it has finally been established by the stereoselective conversion of valienamine or validamine into 1.[2]

As a part of the study on the elucidation of structure-activity relationship of branched-chain aminocyclitols,[3] we now describe a synthesis of the racemic form of 1 from readily available DL-1,2,3-tri-*O*-acetyl-(1,3/2,4)-4-bromo-6-methylene-1,2,3-cyclohexanetriol (2).[4]



1



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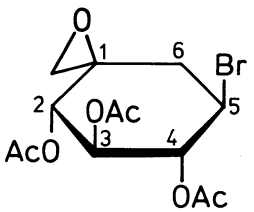

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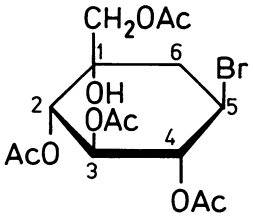

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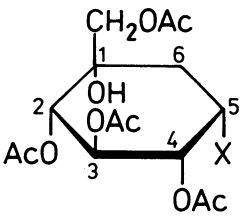

5 X = N_3

6 X = NHAc

The formulas except for 1 depict only one of the respective enantiomers.

Oxidation of 2 with *m*-chloroperbenzoic acid in the presence of sodium hydrogencarbonate in dichloromethane at room temperature for 9 d gave selectively a single epoxide (3), mp 146.5-147 °C, in 89% yield.[5] Hydrolysis of 3 with aqueous acetone containing concd sulfuric acid, followed by acetylation with acetic anhydride in pyridine at room temperature, gave the tetraacetyl derivative (4) of the branched-chain cyclitol bromide in 42% yield,[6,7] together with the 1,7-*O*-isopropylidene acetal tetraacetate (12%). Treatment of 4 with a large excess of sodium azide in *N*,*N*-dimethylformamide at 90 °C for 3 d gave mainly 54% yield of the azido compound (5), mp 122.5-124.5 °C, together with the elimination product.[8] The ^{1}H NMR spectrum ($CDCl_3$, 90 MHz) of 5 showed a narrow quartet (J = 3.5 Hz, δ 4.21) due to the equatorial proton attached to the 5-carbon atom bearing the azido group, supporting the proposed structure. Under these conditions, a direct S_N2 substitution reaction seems to be favorable. Catalytic hydrogenation of 5 in ethanol containing acetic anhydride in the presence of Raney nickel afforded 92% yield of crystalline penta-*N*,*O*-acetylvaliolamine (6), mp 151-153 °C: ^{1}H NMR data ($CDCl_3$, 90 MHz) δ = 2.00 (3H, s), 2.01 (3H, s), 2.07 (3H, s), and 2.10 (6H, s) (NAc and 4 OAc), 3.63 (1H, m, OH), 3.81 (1H, d) and 4.08 (1H, d) (J_{gem} 11.7 Hz, CH_2OAc), 4.79 (1H, m, H-5), 4.95 (1H, dd, $J_{3,4}$ = 9.8 Hz, $J_{4,5}$ = 4.5 Hz, H-4), 5.07 (1H, d, $J_{2,3}$ = 9.8 Hz, H-2), 5.55 (1H, t, H-3), 7.13 (1H, br d, $J_{5,NH}$ = 9 Hz, NH). These data were superimposable on those reported for the optically active 6.[1]

References

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2) S. Horii, H. Fukase, and Y. Kameda, *Carbohydr. Res.*, 140, 185 (1985).
3) S. Ogawa, T. Hattori, T. Toyokuni, and T. Suami, *Bull. Chem. Soc. Jpn.*, 56, 2077 (1983).
4) S. Ogawa, T. Toyokuni, M. Omata, N. Chida, and T. Suami, *Bull. Chem. Soc. Jpn.*, 53, 455 (1980).
5) Attack of the peroxy acid may be controlled by the steric factors.
6) The spiro anhydro ring was considered to be selectively cleaved by the assistance of the C-2 acetoxyl group at C-1.
7) Alternatively, a direct hydroxylation of 2 by oxidation with osmium tetraoxide and hydrogen peroxide, followed by acetylation, produced selectively the tetraacetate derivative different from 4.
8) Under these reaction conditions, dehydrobromination occurs as a side reaction (between C-5 and C-6). The elimination product was obtained exclusively when dimethyl sulfoxide was used as the reaction solvent. On the other hand, a neighboring group participation reaction via a formation of a cyclic 4,5-acetoxonium ion is likely to be involved in aqueous 2-methoxyethanol.

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