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Cleavage of the Imino Bonds of Validoxylamine A Derivatives with N-Bromosuccinimide

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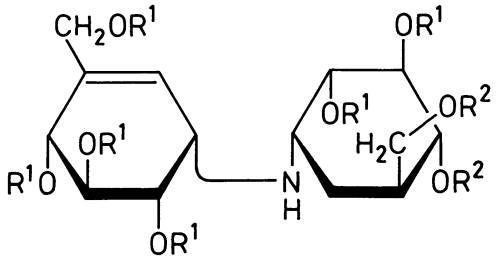
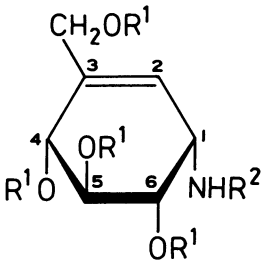
Reaction of validoxylamine A derivatives with N-bromosuccinimide in aqueous N,N-dimethylformamide resulted in a cleavage of the imino bonds to give rise to synthetically useful protected derivatives of (+)-validamine and valienamine, and the cyclohexanone and -hexenone derivatives.

During the course of synthetic studies on validamycins[1-3] and pseudo-oligosaccharidic alpha-amylase inhibitors,[4,5] we needed optically active synthons useful for construction of such pseudo-oligosaccharides linked by way of imino bonds.

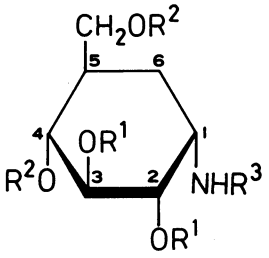
Hydrogenolysis of validoxylamine A (1) produced[6] (+)-validamine (8). Although it has been reported that valienamine (5) is obtained by microbial degradation[7] of validamycin A or 1 with Pseudomonas denitrificans, a chemical degradation to give 5 has never been carried out successfully so far. We report herein a cleavage of the C-N bond of 1 with N-bromosuccinimide (NBS) in aqueous N,N-dimethylformamide (DMF), conceivably via N-bromination, giving rise to 5 and 8, and hydroxy(hydroxymethyl)cyclohexanone and/or -cyclohexenone. The amines were characterized by converting into the N-acetyl derivatives, which were separable by chromatography on silica gel. The structures of the new compounds were established on the basis of ^{1}H NMR spectroscopy. The present procedure has been applicable for chemical degradation of the several protected derivatives (2 – 4) of 1, providing the appropriately protected synthons directly.



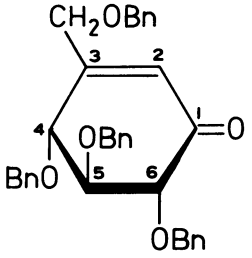
	R^1	R^2
1	H	H
2	Ac	Ac
3	Bn	Bn
4	Bn	=CHPh



	R^1	R^2
5	H	H
6	Ac	Ac
7	Bn	Ac



	R^1	R^2	R^3
8	H	H	H
9	Ac	Ac	Ac
10	Bn	Bn	Ac
11	Bn	=CHPh	Ac



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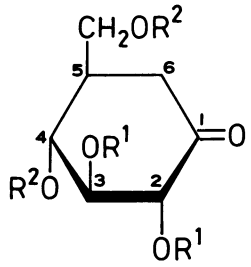
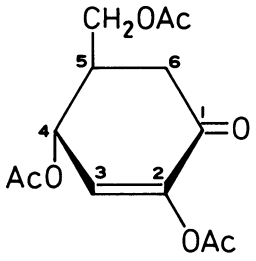


	R^1	R^2
13	Ac	Ac
14	Bn	Bn
15	Bn	=CHPh



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Treatment of validoxylamine A octaacetate[1] (2) with 3 molar equivalent of NBS in aqueous 80% DMF at ambient temperature for 2 d afforded, after chromatography on silica gel, a 45% yield of (4R,5R)-2,4-diacetoxy-5-acetoxymethylcyclohex-2-en-1-one[8] (16), $[\alpha]_D^{23}$ +96° (c 1.3, chloroform); ^{1}H NMR ($CDCl_3$) δ = 6.47 (1 H, d, J = 2.9 Hz, H-3); IR ($CHCl_3$) 1700 cm^{-1} (C=O), which was probably obtained by β-elimination of the initially formed tetraacetate (13) in situ or during separation on silica gel. The slower-moving components were acetylated with acetic anhydride in pyridine at ambient temperature to give penta-N,O-acetyl-(+)-valienamine[9] (6, 14%). On the other hand, validoxylamine A (1) readily reacted with 1.5 molar equivalent of NBS in water (or aqueous DMF) for 4 h. The reaction mixture was passed through a column of Amberlite CG-50 (NH_4^+) resin and the effluent was concentrated and the residue was acetylated to give a 23% yield of 16. Then the basic compounds were recovered by elution of the column with aqueous ammonia and were acetylated to afford 6 (9.2%) and penta-N,O-acetyl-(+)-validamine[10] (9, 17%).

In order to prepare the protected derivatives of 5, 8, and trihydroxy-(hydroxymethyl)cyclohexanone, the per-O-benzyl ether (3), $[\alpha]_D^{22}$ +63° (c 1.0, chloroform), and the hexa-O-benzyl-4,7-O-benzylidene derivative[1] (4) were subjected to the similar conditions. On treatment with 3 molar equivalent of NBS in aqueous 80% DMF at ambient temperature for 3 d, compound 3 afforded the cyclohexenone (12, 11%), $[\alpha]_D^{22}$ -12° (c 0.36, chloroform); ^{1}H NMR ($CDCl_3$) δ = 4.07 (1 H, d, J = 9.8 Hz, H-6), 6.21 (1 H, s, H-2); IR ($CHCl_3$) 1680 cm^{-1} (C=O), and the cyclohexanone (14, 47%), $[\alpha]_D^{23}$ +50° (c 0.57, chloroform); ^{1}H NMR ($CDCl_3$) δ = 4.13 (1 H, d, J = 9.5 Hz, H-2); IR ($CHCl_3$) 1730 cm^{-1} (C=O). The basic components were acetylated to give the valienamine derivative[2] (7, 26%) and the validamine derivative (10, 14%), $[\alpha]_D^{23}$ +22° (c 2.9, chloroform). Under moderate conditions (1.5 molar equivalent of NBS, 17 h), compound 4 gave 12 (16%) and the cyclohexanone derivative (15, 40%), $[\alpha]_D^{19}$ +14° (c 1.0, chloroform); ^{1}H NMR ($CDCl_3$) δ = 4.09 (1 H, d, J = 9.2 Hz, H-2); IR ($CHCl_3$) 1730 cm^{-1} (C=O). Acetylation of the amines afforded 7 (36%) and the validamine derivative (11, 18%), $[\alpha]_D^{22}$ +5° (c 0.4, chloroform). When similar reaction of 4 was conducted in aqueous acetonitrile instead of aqueous DMF, the reaction completed within 1.5 h to give nearly same ratio and yields of the products (7, 11, 12, and 15). On the other hand, in aqueous dimethylsulfoxide, 4 afforded selectively 7 (23%) and 15 (23%), but a half of 4 was recovered

unchanged. Further addition of NBS at this stage gave finally **7** (29%), **11** (17%), **12** (7%), and **15** (17%).

Per-O-benzylated derivatives of **5** and **8** derived from **3**, and the 4,7-O-benzylidene derivatives of **8** and 2,3,4-trihydroxy-5-hydroxymethyl-1-cyclohexanone readily obtainable from **4** may be versatile synthons for synthesis of pseudo-mono and oligosaccharides of biological interest.

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8) The physical data of new compounds **12-16** will be described in detail in a full paper.

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