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SYNTHESIS OF DETOXININOLACTONE DERIVATIVES AND THE REVISED ABSOLUTE STEREOCHEMISTRY OF DETOXININE

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Summary: A stereospecific synthesis of acetyl-L-valyl-detoxininolactone has been performed and the absolute stereochemistry of detoxinine has been revised to (2S, 3R, 1'S)-2-(2'-carboxy-1'-hydroxyethyl)-3-hydroxypyrrolidine.

A recent publication[1] on the biosynthesis of a microbial amino acid, (3S, 4S)-4-amino-3-hydroxy-6-methylheptanoic acid (AHMHA) prompted us to reinvestigate the absolute configuration of detoxinine, an unusual β-hydroxy-γ-imino acid found in detoxin D_1[2], a selective antagonist of an antibiotic blasticidin S. Though the stereochemistry of detoxinine was previously assigned by the ^{1}H-NMR and ORD studies on N-deuteroacetyl-L-valyl-detoxininolactone 1,[3] obtained from detoxin D_1 by alkaline hydrolysis and cation exchange resin treatment, the absolute configuration of detoxinine would be reversed if detoxinine is biosynthesized from L-proline as AHMHA.

We undertook a synthetic approach to this problem and prepared two isomeric detoxininolactone derivatives with reversed configuration for comparison with 1 and conformational analysis.

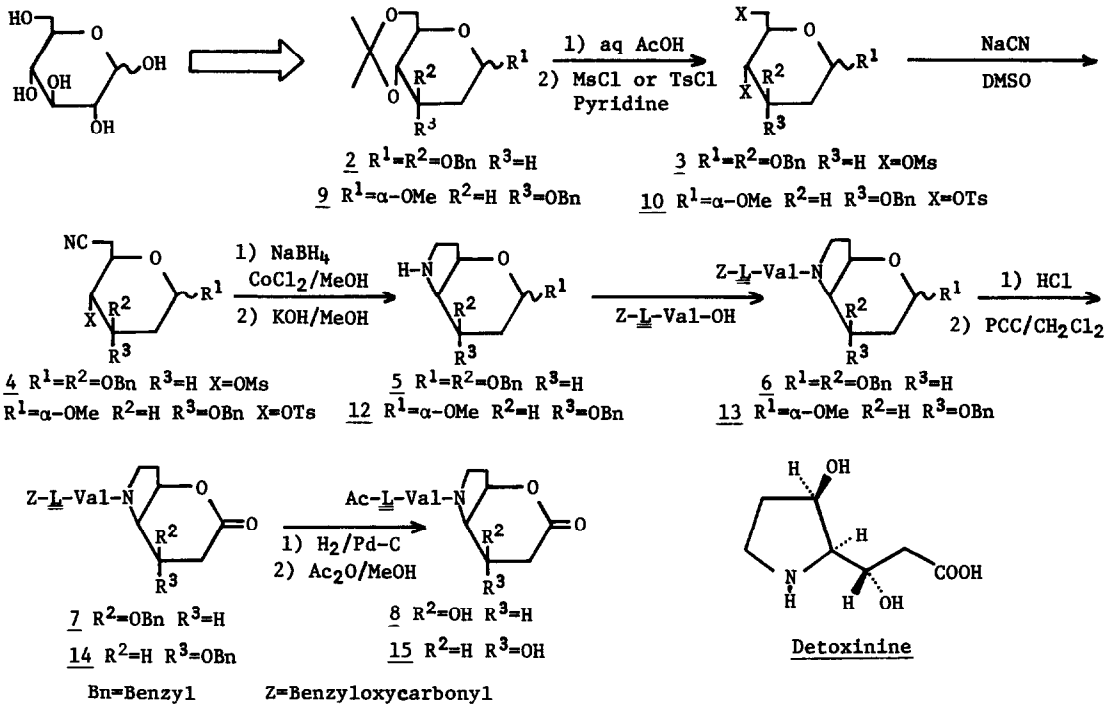
Chemistry involved was quite straightforward and the synthetic routes were described in the Figure.

The starting materials, benzyl 3-O-benzyl-2-deoxy-4,6-O-isopropylidene-α(and β)-D-arabino-hexopyranoside 2 and methyl 3-O-benzyl-2-deoxy-4,6-O-isopropylidene-α-D-ribo-hexopyranoside 3 were prepared from D-glucose by known procedures.[4),5)]

The crucial step was the formation of the pyrrolidine compounds 5 and 12, colored to yellow by ninhydrin, which was effected by $NaBH_4$ reduction of the cyanosulfonates 4 and 11, respectively, in the presence of $CoCl_2$, followed by alkaline treatment, though attempted similar reductive cyclization employing $LiAlH_4$ under various conditions was not successful.

The pyrrolidine compounds 5, 12 were then coupled with benzyloxycarbonyl-L-valine via an active ester (HONB) or by the DCC method. The resulted peptide glycoside 6, 13 were converted to the lactones 7, 14 by acid hydrolysis followed by oxidation with pyridinium chlorochromate. Finally, the protected lactones 7, 14 were hydrogenated and N-acetylated to give the desired lactone 8 and 15.

The first synthesized lactone 8, which contains reversed configurations of the detoxinine moiety to the previously described, showed the similar negative ORD maximum at 250 nm to that of 1 (243 nm), suggesting the identical ring configuration, however, the ^{1}H-NMR of 8 was quite different from that of 1.



2 R^1=R^2=OBn R^3=H
9 R^1=α-OMe R^2=H R^3=OBn
3 R^1=R^2=OBn R^3=H X=OMs
10 R^1=α-OMe R^2=H R^3=OBn X=OTs
4 R^1=R^2=OBn R^3=H X=OMs
11 R^1=α-OMe R^2=H R^3=OBn X=OTs
5 R^1=R^2=OBn R^3=H
12 R^1=α-OMe R^2=H R^3=OBn
6 R^1=R^2=OBn R^3=H
13 R^1=α-OMe R^2=H R^3=OBn
7 R^2=OBn R^3=H
14 R^2=H R^3=OBn
8 R^2=OH R^3=H
15 R^2=H R^3=OH

Bn=Benzyl Z=Benzyloxycarbonyl

On the other hand, the epimeric lactone 15, MS: m/e 298 (M^+), 240, 239, 213, 195, 163, 156, 142, 114, 86, 84 and 82; IR(neat): 3400, 1730 and 1640 cm^{-1}, was chromatographically identical with 1 under various TLC conditions and showed the identical negative ORD maximum at 243 nm. Furthermore, the ^{1}H-NMR spectrum: δ($CDCl_3$) 0.97 ppm (6H d, J=7 Hz), 2.03 (3H s), 2.05 (2H m), 2.60 (1H dd, J=12 & 15), 2.82 (1H dd, J=5 & 15), 3.66 (1H oct, J=6, 10 & 11), 3.84 (1H dt, J=5 & 12), 4.17 (1H t, J=5), 4.22 (1H br. t, J=9.5 & 11), 4.56 (1H dd, J=7 & 9), 4.98 (1H br. t, J=4 & 5), 5.24 (OH, br. s) and 6.34 (1H br. d, J=9, CONH), was superimposable with that of 1 except an additional singlet at 2.03 ppm due to the N-acetyl group.

As a result, the absolute stereochemistry of 1 must be revised and the structure of detoxinine was therefore determined to be (2S, 3R, 1'S)-2-(2'-carboxy-1'-hydroxyethyl)-3-hydroxypyrrolidine as shown in the figure.

Acknowledgements

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