Tetrahedron Letters,Vol.25,No.37,pp 4133-4136,1984 0040-4039/84 $3.00 + .00
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ACYCLIC STEREOCONTROLLED SYNTHESIS OF (-)-DETOXININE

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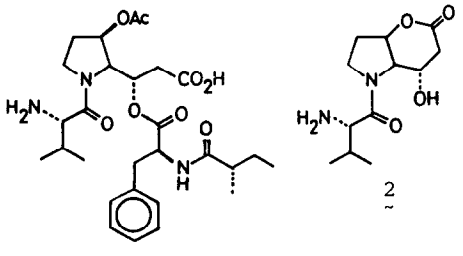
Summary: Allylic oxidation of (2S)-N-t-butoxycarbonyl-2-amino-4-pentenoic acid methyl ester afforded, stereoselectively, a (2S,3R)-2-amino-3-hydroxyl derivative, which was converted to the unusual amino acid (-)-detoxinine via a chelation controlled aldol condensation followed by a pyrrolidine ring formation.

Unusual amino acids which are highly functionalized in their side chains or rings are frequently found as constituents of biologically important peptides. There is significant interest in both the organic chemistry and biological aspects of these compounds.[2,3] Detoxinine (3), an amino acid constituent of detoxin D_1 (1)[4], which shows a potent antagonistic activity for the toxicity against living cells of blasticidin S, has been isolated as N-valyl derivatives, and the structure has been elucidated by the synthesis of N-valyl-detoxinolactone (2) from D-glucose by Kakinuma, Ōtake et al.[5] We wish to describe here the synthesis of optically active 3 in a stereocontrolled manner from (2S)-2-amino-4-pentenoic acid (L-allylglycine) (4).

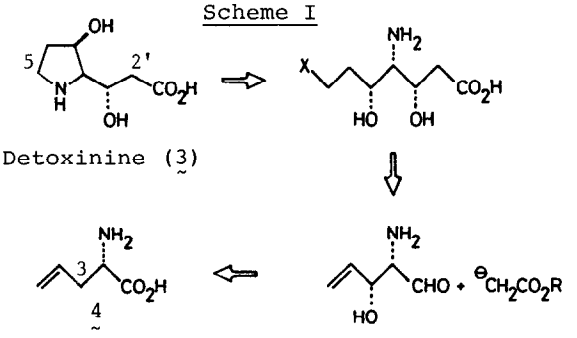
Since the structure 2 affords a relatively symmetrical carbon chain when the C5-N bond is cleaved, we planned a synthesis as shown in Scheme I. The synthesis requires the following key steps: (i) the threo-selective introduction of a hydroxyl group at C3 of allylglycine; (ii) stereoselective condensation of a two carbon unit with a β-hydroxy-α-aminoaldehyde; and (iii) pyrrolidine ring formation. The allylic oxidation of (2S)-N-t-butoxycarbonyl-2-amino-4-pentenoic acid methyl ester (5)[6] was examined first, as the stereoselective introduction of a hydroxyl group induced by a homoallylic chiral center into an allylic position has not yet been observed, except in cyclic systems.[7]

Scheme I



Detoxin D_1 (1)

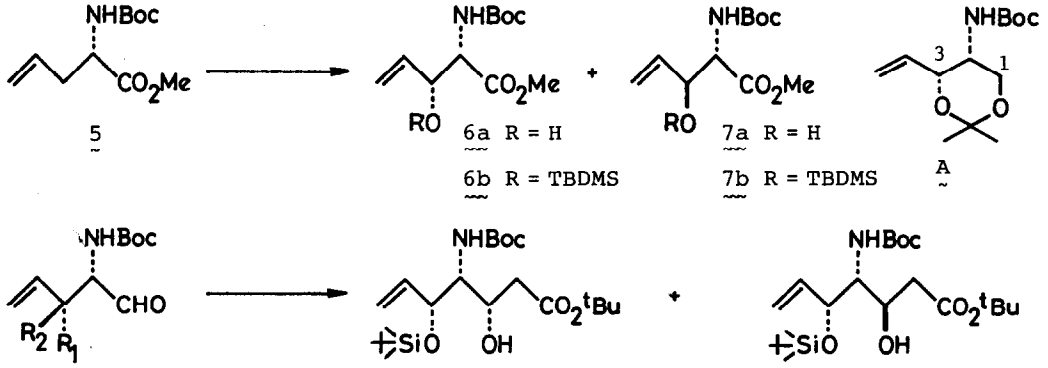
2



Detoxinine (3)

After several unsuccessful trials, we employed Sharpless' conditions[8] (SeO_2/t-BuOOH/CH_2ClCH_2Cl, 70°C, 3 h) which provided a 3.8 : 1 mixture of alcohols 6a and 7a in 55% yield.[9,10] These were separated after protection of the hydroxyl group with t-butyldimethylsilyl (TBDMS) group (TBDMSCl/imidazole/DMF) to the silyl ether 6b, 70% yield; oil; $[\alpha]_D$ +25.1°(c 1.0, $CHCl_3$), and 7b, 18%; oil; $[\alpha]_D$ +22.7°(c 1.0, $CHCl_3$). The major isomer 6b was assigned as the (2S,3R) configuration by converting into the acetonide A, (i) $LiAlH_4/Et_2O$; (ii) p-TsOH/MeOH; (iii) p-TsOH/2,2-dimethoxypropane, whose NMR revealed the same coupling pattern between C1-C2 and C2-C3 ($J_{1\alpha-2}=J_{1\beta-2}=J_{2-3}=2.0$ Hz) as those derived from L-threonine.[11]

We next tried to condense an acetic acid moiety with an β-hydroxy-α-amino-aldehyde. Although condensation of an α-amino aldehyde with the lithium enolate of ethyl acetate was known to give non-stereoselective aldol products,[12] we expected that the β-substituent of the present system might effect the selectivity. Thus, the methyl ester 6b was converted into the aldehyde 8a: (i) $LiAlH_4/Et_2O$; (ii) pyridinium dichromate/CH_2Cl_2; 64% yield in two steps; oil; $[\alpha]_D$ +57.2°(c 1.3, $CHCl_3$). Condensation of 8a with lithium t-butyl acetate (LDA/t-$BuOCOCH_3$) in Et_2O at -93°C yielded a 6.5 : 1 mixture of 9 and 10 in 96% yield: 9; oil; $[\alpha]_D$ -1.57°(c 3.5, $CHCl_3$). The configuration of the major isomer 9 was confirmed to be the desired stereochemistry by its conversion into the acetonide 11: (i) p-TsOH/MeOH, 100% yield; (ii) p-TsOH/2,2-dimethoxypropane, 76% yield; mp 102-103°C; $[\alpha]_D$ +17.8°(c 0.8, $CHCl_3$). Decoupling and NOE experiments by 360MHz ^1H NMR indicated compound 11 was (3S,4R,5R) as shown in B.[13,14] The selectivity of this reaction was obviously dependent upon the configuration of the β-substituent, and decreased to a 3 : 1 ratio when the erythro aldehyde 8b was employed under the same reaction conditions. In addition, condensation of 8c afforded a 1 : 1 diastereomixture. Therefore, we considered that the present reaction proceeded via C, in which both chelation and the bulky (3R)-substituent play an important role in this selectivity.

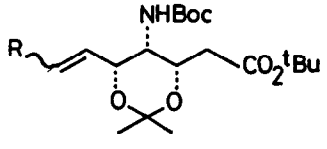


For the pyrrolidine ring formation, it was necessary to convert the vinyl group of acetonide 11 into a hydroxymethylene group. Since the hydroboration-oxidation method as an one-step procedure was not successful, the vinyl group was converted to the methoxyvinyl ether 12: (i) O_3/MeOH, -78°C, dimethylsulfide; (ii) $Ph_3P(Cl)CH_2OCH_3$/t-AmONa/benzene; 81% yield; oil. Treatment of 12 with $Hg(OAc)_2$ (THF/H_2O=9/1),[16] subsequent addition of aqueous KI, and reduction with $NaBH_4$/EtOH provided the alcohol 13, 73% yield; mp 120-121°C; $[\alpha]_D$ +10.8°(c 1.0, $CHCl_3$), accompanied with unexpected $\Delta^{4(5)}$-pyrrolidine 14, 20% yield; oil; $[\alpha]_D$ -241.1°(c 0.9, $CHCl_3$). The formation of 14 was observed after aqueous KI treatment, and could be explained as the initial cyclization of pyrrolidine ring D followed by elimination.[17] Hydrogenation (H_2/5% Pd-C/AcOEt) of 14 afforded the desired 16: 90% yield; mp 90-91°C; $[\alpha]_D$ -100.0°(c 1.8, $CHCl_3$); MS, m/z 371 (M^+). The alcohol 13 was also successfully converted into 16 by treatment with Ph_3P/NBS followed by NaH/THF in 63% yield.

The protecting groups were removed in the following sequences: (i) (±)-camphor-10-sulfonic acid (CSA)/MeOH; (ii) CSA/CH_2Cl_2; and (iii) CF_3CO_2H/CH_2Cl_2. Treatment of the resultant trifluoroacetate with Dowex 50W x 4 (H^+ form), and elution with 1N NH_3 yielded (-)-detoxinine (3) as white crystals: mp 225-228°C (decomp); $[\alpha]_D$ -4.8°(c 0.5, H_2O); MS, m/z 175 (M^+); 81% yield from 16.[18]

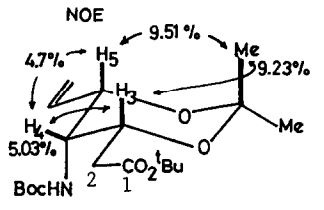
Other approaches to the total synthesis of detoxin D_1 (1) by employing an intermediate of this synthesis are in progress.

ACKNOWLEDGEMENT: We thank Professors N.Ōtake, H.Seto (University of Tokyo), and K.Kakinuma (Tokyo Institute of Technology) for valuable informations of 1-3.

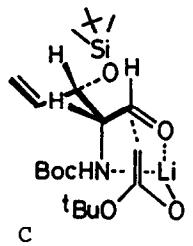


11 R = H

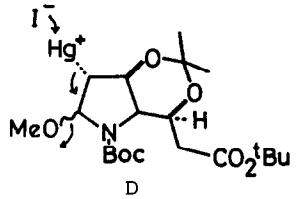
12 R = OMe



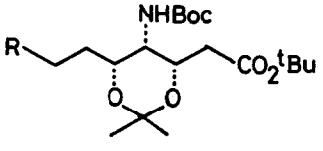
B $J_{3-4}=J_{4-5}=1.8Hz$



C

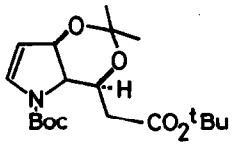


D



13 R = OH

15 R = Br



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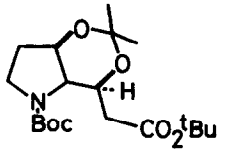

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2. For example, see: "Amino Acids, Peptides, and Proteins", The Chemical Society: London, 1968-1981; Vol. 1-14.
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5. (a) K.Kakinuma, N.Ōtake, and H.Yonehara, ibid., 167 (1980). (b) Recently, the synthesis of (±)-3 from 3-hydroxyproline in a non-stereoselective manner has been reported. J.Häusler, Liebigs Ann.Chem., 982 (1983).
6. Prepared from L-allylglycine (commercially available from Sigma Co. Ltd.) in 86% yield: (i) Boc-On/Et_3N; (ii) CH_2N_2; oil; $[\alpha]_D$ +19.3°(c 1.5, $CHCl_3$).
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9. Usually, 35-40% of starting material was recovered and recycled. It should be noted that the selectivity of this reaction decreased to a 2 : 1 ratio when a benzyloxymethyl group instead of methoxycarbonyl group of 5 was employed and no selectivity was observed in the case of 2,2-dimethyl-5-hexene-3-ol. Further studies of this reaction are in progress.
10. No racemization during this stage was ascertained by the recovery of starting material which showed the same $[\alpha]_D$ value with those of 5.[6] Further proof has been obtained by the synthesis of (2R,3R)-N-t-Boc-2-amino-4-pentene-1,3-diol diMTPA ester, which was a single diastereomer by ^1H NMR.
11. Partial ^1H NMR ($CDCl_3$) data of A: δ3.57 (m, 2-H), 3.76 (dd, J=2.0, 12.0 Hz, 1H of 1-CH_2), 4.08 (dd, J =2.0, 12.0 Hz, 1H of 1-CH_2), 4.50 (dd, J=2.0, 4.4 Hz, 3-H). Y.Ohfune and N. Kurokawa, Tetrahedron Lett., 1587 (1984).
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13. 360MHz ^1H NMR ($CDCl_3$) data of 11: δ1.40 (s, t-BuO), 1.42 (s, t-BuO and Me), 1.47 (s, Me), 2.37 (dd, J=6.5, 16.0 Hz, 1H of 2-CH_2), 2.44 (dd, J=6.0, 16.0 Hz, 1H of 2-CH_2), 3.62 (td, J=1.8, 10.5 Hz, 4-H), 4.41 (dt, J=1.8, 6.0 Hz, 3-H), 4.50 (m, 5-H), 4.99 (d, J=10.5 Hz, NH), 5.20 (m, 1H of 7-CH_2), 5.33 (m, 1H of 7-CH_2), 5.77 (ddd, J=5.0, 10.5, 17.0 Hz, 6-H).[14]
14. The peaks were fully assigned by an extensive decoupling technique. NOE values were shown in the figure.
15. Satisfactory spectroscopic data (^1H NMR, IR, MS) as well as elementary analytical data were obtained for all new compounds.
16. K.C.Nicolau, R.I.Magolda, and D.A.Claremon, J.Am.Chem.Soc., 102, 1404 (1980).
17. Another examples of this method for the synthesis of unsaturated heterocyclic ring will be described elswhere.
18. Identical spectroscopic data were obtained with those reported.[5b] 360MHz ^1H NMR (D_2O) data of synthetic 3: δ2.12 (dddd, J=1.5, 2.9, 7.2, 13.7 Hz, 1H of 4-CH_2), 2.24 (ddt, J=4.0, 10.1, 13.7 Hz, 1H of 4-CH_2), 2.43 (dd, J=7.9, 15.8 Hz, 1H of 2'-CH_2), 2.63 (dd, J=4.3, 15.8Hz, 1H of 2'-CH_2), 3.38-3.56 (m, 2-H and 5-CH_2), 4.32 (ddd, J=4.3, 7.9, 9.0 Hz, 1'-H), 4.50 (dt, J=1.5, 4.0 Hz, 3-H).

(Received in Japan 29 May 1984)