Tetrahedron Letters, Vol 33, No 25, pp. 3595-3598, 1992
Printed in Great Britain

0040-4039/92 $5.00 + 00
Pergamon Press Ltd

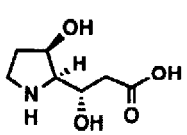
Total Synthesis of (–)-Detoxin D_1

Wen-Ren Li, So-Yeop Han, and Madeleine M. Joullié*

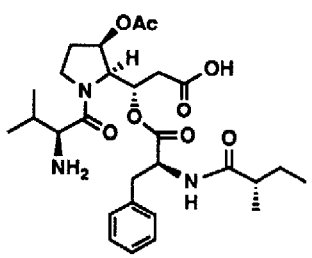
Department of Chemistry, University of Pennsylvania
Philadelphia, PA 19104-6323

Abstract: *An efficient stereocontrolled total synthesis of (–)-detoxin D_1, the most active component of the detoxin complex, is described.*

Many interesting and structurally diverse amino acids are components of biologically active natural products. The detoxin complex, the first isolated natural product displaying detoxification as its biological activity, is produced by the organism *Streptomyces caespitosus* var. *detoxicus* 7072 GC_1 and other strains of streptomyces.[1, 2] This complex shows a potent antagonistic activity to the cytotoxicity of the antibiotic blasticidin S,[3, 4] a fungicide used in the treatment of rice blast disease, and also exhibits antimicrobial activity against some microorganisms. The parent component of the complex is a β-hydroxy-γ-amino acid, (–)-detoxinine. Five research groups have reported syntheses of detoxinine[5-10] and detoxins B_1 and B_3.[11] Häusler synthesized (–)-detoxin D_1, the most active component of the detoxin complex, by extending his synthesis of racemic detoxinine.[12] Detoxin D_1 is a novel depsipeptide consisting of detoxinine, L-valine, L-phenylalanine, and (+)-S-2-methylbutyric acid as the structural components. The synthetic challenges of detoxin D_1 and its unique biological activity led us to investigate a stereospecific approach to this depsipeptide.



detoxinine
1

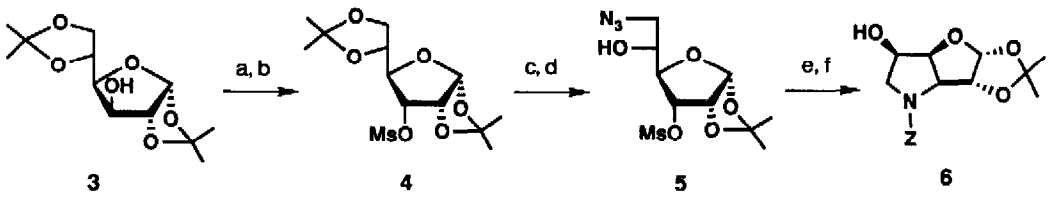


detoxin D_1
2

Carbohydrates are important synthetic precursors to enantiomerically pure molecules because of their ready availability, well defined stereochemistry, and highly functionalized nature. As shown in **Scheme 1**, we constructed the pyrrolidinol ring by a modification of methodology previously developed by our group for the synthesis of 1,4-dideoxy-1,4-imino-D-lyxitol hydrochloride.[13] The synthesis began with diacetone D-glucose (**3**) which was isomerized at the C-3 position to give 1,2:5,6-di-O-isopropylidene-α-D-allofuranose in 82% yield. This α-D-allofuranose was then converted to the corresponding mesylate **4** in 95% yield using methanesulfonyl chloride and pyridine. Subsequent mild acid hydrolysis with dilute aqueous sulfuric acid selectively removed the 5,6-O-isopropylidene group to afford the diol in 74% yield. The primary alcohol was converted into the corresponding bromide with carbon tetrabromide and triphenylphosphine in THF Displacement of the bromide with sodium azide afforded compound **5**. The azide function could also be

introduced selectively at C-6 in one step using lithium azide, carbon tetrabromide and triphenylphosphine. The azide **5** was reduced to an amine using Raney Ni, followed by cyclization and protection of the resulting secondary amino group with benzyl chloroformate to afford alcohol **6** in 78% yield. Treatment of **6** with iodine, imidazole, and triphenylphosphine in toluene gave the corresponding iodide with inversion of configuration in 90% yield. Subsequent free radical reduction of the iodide with tributyltin hydride was initiated with azobis(isobutyronitrile) (AIBN), in refluxing benzene, and proceeded to completion to afford compound **7** in 97% yield.

Scheme 1

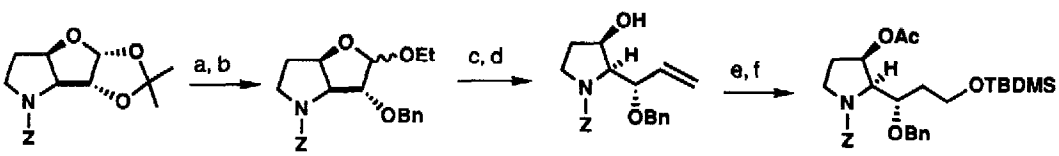


3 4 5 6 7

[a] 1. PCC, molecular sieves, CH_2Cl_2; 2. $NaBH_4$, EtOH, 82%; [b] MsCl, Pyr., 95%; [c] $H_2SO_{4(aq)}$, 74%; [d] 1. Ph_3P, CBr_4, THF; 2. NaN_3, DMF, 76%; or Ph_3P, CBr_4, LiN_3, DMF, 70%; [e] 1. Raney Ni, H_2; 2. NaOAc, EtOH, reflux; [f] benzyl chloroformate, H_2O, acetone, Na_2CO_3, 78%; [g] I_2, imidazole, Ph_3P, toluene, 90%; [h] *n*-Bu_3SnH, benzene, AIBN, 97%.

The synthesis of the key compound (**10**) from the protected amine **7** required a one carbon chain extension. The successful formation of the fully protected pyrrolidinol **10** is shown in **Scheme 2**. Treatment of **7** with ethanol in the presence of 15% HCl/Et_2O at room temperature gave the corresponding ethyl glycoside, which was treated with benzyl bromide and potassium hydride to afford the benzyl ether (**8**) in 84% yield from **7**. Hydrolysis of **8** with aqueous TFA gave the corresponding lactol in 90% yield. Several attempts to generate the methyl enol ether from the resulting lactol using the Wittig reaction,[14] and Peterson olefination[15, 16] were unsuccessful. Therefore, we decided to prepare the terminal olefin **9**, instead. Thus, the lactol was treated with methylenetriphenylphosphorane to afford compound **9** in 71% yield.[17] Since detoxin D_1 (**2**) contains a free carboxylic acid, our first approach was to bring up a precursor which could be easily oxidized to an acid. After acetylation of the secondary alcohol **9**, direct conversion of the terminal olefin into the corresponding aldehyde was attempted using Brown's method.[18, 19] Unfortunately, this protocol gave disappointing results, forcing us to develop an alternate strategy. Treatment of compound **9** with disiamylborane, followed by oxidation using 30% hydrogen peroxide and 2 N aqueous NaOH, led to the diol

Scheme 2



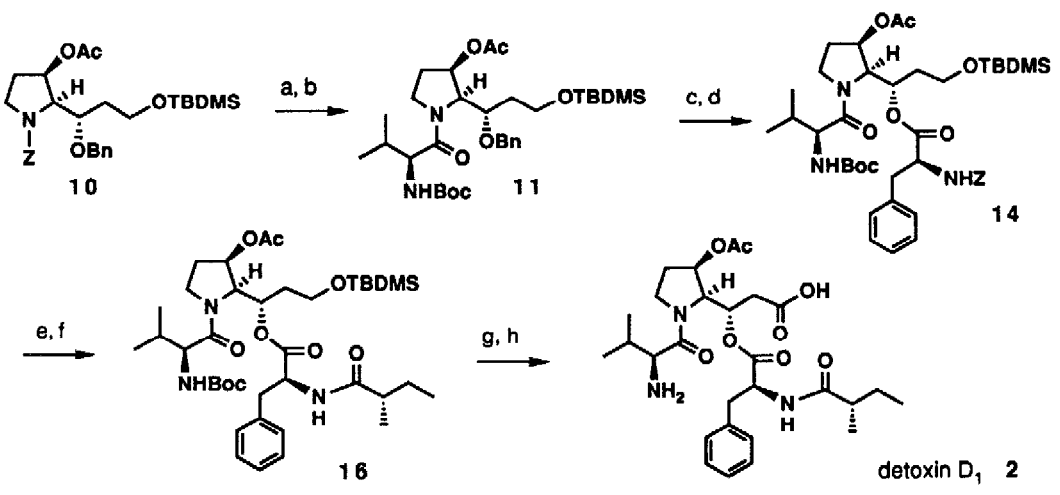
7 8 9 10

[a] EtOH, 15% HCl/Et_2O, 94%; [b] BnBr, KH, DMF, 89%; [c] TFA, H_2O, 90%; [d] $Ph_3P{=}CH_2$, THF, 71%; [e] disiamylborane, then H_2O_2, NaOH, 83%; [f] TBDMSCl, Et_3N, DMAP, CH_2Cl_2, then Ac_2O, Et_3N, 91%.

in 83% yield. The resulting diol was then converted to acetate **10** by selective *tert*-butyldimethylsilylation and acetylation in one pot reaction (91% yield).[20]

The completion of the synthesis is detailed in Scheme 3. The benzoxycarbonyl protecting group of compound **10** was selectively removed by catalytic hydrogenolysis using Raney Ni as the catalyst under an atmosphere of hydrogen (40 psi). Coupling of the resulting secondary amine with Boc-valine (**12**) was then accomplished with *N,N'*-bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl). A preactivation protocol developed by Anteunis gave the best yield.[21] Boc-Valine (**12**) was treated with BOP-Cl at -15 °C, and after 20 min, the secondary amine was added to afford the coupled product **11** in 90% yield from compound **10**. Hydrogenolysis of the benzyl ether of **11** in ethanol in the presence of palladium black gave the corresponding alcohol. With the alcohol in hand, a convergent approach for the synthesis of the protected precursor of detoxin D_1 (**2**) was examined. Attempts to couple the secondary alcohol with (S)-2-methylbutyryl-L-phenylalanine using different activation methods gave low yields of the desired depsipeptide, and led to an unexpected product derived from the intramolecular cyclization of the activated ester. At this point, sequential coupling procedures were used to synthesize the protected precursor of detoxin D_1 (**16**). Treatment of the alcohol with Z-phenylalanine (**13**), in the presence of dicyclohexylcarbodiimide (DCC), a catalytic amount of 4-dimethylaminopyridine (DMAP), and 10-camphorsulfonic acid (CSA), in methylene chloride, afforded the depsipeptide **14** in 88% yield. Removal of the benzoxycarbonyl protecting group by catalytic hydrogenolysis, and subsequent treatment with (S)-2-methylbutyric acid (**15**) in the presence of 1*H*-1,2,3-benzotriazol-1-yloxytris-(dimethylamino)phosphonium hexafluorophosphate (BOP) reagent and *N,N*-diisopropylethylamine (DIEA), afforded the depsipeptide **16** in 70% yield.[22] Deprotection of the *tert*-butyldimethylsilyl protecting group was then accomplished in 99% yield by using HOAc : THF : H_2O (3 : 1 : 1). To synthesize detoxin D_1 (**2**), the primary alcohol in depsipeptide **16** was oxidized to the corresponding carboxylic acid, which was immediately treated with TFA to remove the Boc group and afford detoxin D_1 (**2**) in 70% yield Synthetic detoxin D_1 was identified by comparison of its physical data with that reported by Hausler.[12, 23]

Scheme 3



[a] Raney Ni, H_2, EtOAc, MeOH; [b] Boc-valine (**12**), BOP-Cl, Et_3N, CH_2Cl_2, 90%; [c] H_2, palladium black, EtOH, [d] Z-phenylalanine (**13**), DCC, DMAP, 10-camphorsulfonic acid (CSA), CH_2Cl_2, 88%; [e] Pd/C, H_2, EtOAc, MeOH; [f] (S)-2-methylbutyric acid (**15**), BOP, DIEA, CH_2Cl_2, 70%; [g] HOAc, THF, H_2O, 99%; [h] 1. TFAA, DMSO, Et_3N, CH_2Cl_2, then 1 M $KMnO_4$, 5% $NaHPO_4$; 2. TFA, CH_2Cl_2, then ion exchange

This approach represents the first stereospecific total synthesis of detoxin D_1. All three asymmetric centers in the detoxinine portion of the molecule were obtained from D-glucose. The advantages of the reported strategy are: (1) the oxidation of the primary hydroxyl group to a carboxylic acid is carried out in the last stage of the synthesis to avoid elimination of the β-hydroxyl group, which has plagued other investigators. This approach also facilitates the subsequent esterification. (2) The synthesis does not involve separation of diastereomers and affords a better overall yield than previous syntheses.

Acknowledgments. Support from NSF (CHE 89-13869 A04 and undergraduate supplement program) is gratefully acknowledged. We are indebted to Dr J. Häusler (Institut fur Organische Chemie der Universität Wien) for copies of the NMR spectra of (–)-detoxin D_1. We thank Dr. G. Furst and Mr. J. Dykins of the University of Pennsylvania Spectroscopic Facilities for their assistance. We also thank undergraduate participants Mr. Rafik Samuel and Mr. Henry Willis for their technical assistance in the preparation of intermediates.

REFERENCES AND NOTES

1 Yonehara, H.; Seto, H.; Aizawa, S.; Hidaka, T.; Shimazu, A.; Otake, N. *J. Antibiot.* **1968**, *21*, 369.
2. Otake, N.; Kakinuma, K.; Yonehara, H. *J. Antibiot* **1968**, *21*, 371.
3. Yonehara, H.; Takeuchi, S.; Otake, N.; Endo, T.; Sakagami, Y.; Sumiki, Y. *J. Antibiot* **1963**, *16A*, 195.
4. Takeuchi, S.; Hirayama, K.; Ueda, K.; Sakai, H.; Yonehara, H. *J Antibiot.* **1958**, *11A*, 1.
5. Hausler, J. *Liebigs Ann Chem* **1983**, 982.
6. Ohfune, Y.; Nishio, H. *Tetrahedron Lett.* **1984**, *25*, 4133.
7. Ewing, W. R.; Joullié, M. M. *Heterocycles* **1988**, *27*, 2843.
8. Ewing, W. R.; Harris, B D.; Bhat, K. L ; Joullié, M. M. *Tetrahedron* **1986**, *42*, 2421.
9. Kogen, H.; Kadokawa, H.; Kurabayashi, M. *J. Chem. Soc., Chem. Commun.* **1990**, 1240.
10. Takahata, H.; Banba, Y.; Tajima, M.; Momose, T. *J. Org. Chem.* **1991**, *56*, 240.
11. Harris, B. D.; Bhat, K. L.; Joullié, M. M. *Heterocycles* **1986**, *24*, 1045.
12. Häusler, J. *Liebigs Ann. Chem.* **1986**, 114.
13. Han, S.-Y.; Liddel, P. A.; Joullié, M. M. *Synth. Commun.* **1988**, *18*, 275.
14. Nicolaou, K. C.; Magolda, R. L.; Claremon, D. A. *J. Am. Chem Soc.* **1980**, *102*, 1404.
15 Danishefsky, S.; Chackalamannil, S.; Harrison, P., Silvestri, M.; Cole, P. *J. Am. Chem. Soc* **1985**, *107*, 2474.
16. Magnus, P.; Roy, G. *J. Chem Soc., Chem. Commun.* **1979**, 822.
17. Nishimura, Y.; Kondo, S.; Umezawa, H. *J. Org. Chem* **1985**, *50*, 5210.
18 Brown, H. C.; Gundu Rao, C.; Kulkarni, S. U. *Synthesis* **1980**, 151.
19. Gundu Rao, C.; Kulkarni, S. U.; Brown, H. C *J. Organomet. Chem* **1979**, *172*, C20.
20. Chaudhary, S. K.; Hernandez, O. *Tetrahedron Lett* **1979**, *20*, 99.
21. van der Auwera, C.; van Damme, S.; Anteunis, M. J O. *Int. J. Peptide Protein Res.* **1987**, *29*, 464.
22. Castro, B.; Dormoy, J. R.; Evin, G.; Selve, C. *Tetrahedron Lett.* **1975**, *14*, 1219
23. All yields refer to isolated, chromatographically pure materials that were fully characterized by IR, NMR, MS, and HRMS data. The full physical data of the compounds and the synthesis of other members of the detoxin complex will be reported elsewhere.

(Received in USA 26 March 1992)