An Efficient Stereocontrolled Synthesis of (−)-Detoxinine

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A highly stereoselective total synthesis of (−)-detoxinine (**2**) is achieved *via* diastereoselective epoxidation of allylic alcohol (**9**) and bromolactonization of *syn*-β-hydroxy-γ-amino acid (**12**).

The synthesis of unusual, highly functionalized amino acids, which are components of biologically important peptides, is of great interest in organic chemistry and biology.[1] In 1968, Ōtake and co-workers isolated detoxin complex, a group of metabolites that showed potent antagonistic activity to the cytotoxicity of blasticidin S.[2] The most active component among them has been characterized as depcipeptide, detoxin D_1 (**1**), which includes a new amino acid (−)-detoxinine (**2**) as the crucial subunit.[3] Ōtake and Kakinuma determined the structure of (−)-detoxinine (**2**) to be a β-hydroxy-γ-amino acid containing a 3-hydroxy-pyrrolidine unit having three contiguous stereocentres.[3,4] Three groups have reported syntheses of detoxinine (**2**).[5,6]† However, one approach[5a] involves a non-stereoselective route, while the other two routes[5b,c] have not provided highly stereoselective construction of both hydroxy groups in (−)-detoxinine (**2**).

In this paper, we describe a stereocontrolled synthesis of (−)-detoxinine (**2**). In a previous paper,[7] we reported an efficient synthesis of a *syn*-4-amino-2,3-epoxy alcohol, which is readily converted to a *syn*-β-hydroxy-γ-amino acid. Our synthetic strategy for (−)-detoxinine (**2**) utilizes *syn*-β-hydroxy-γ-amino acid (**12**), which can be synthesized from L-dehydroprolinal (**3**) *via* the *syn*-epoxide (**10**), to lactone (**14**) (Scheme 1).

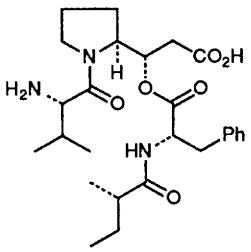
Owing to the instability of *N*-protected (**3**),‡ the masked equivalent (**6**) was used as an intermediate. Thus, (2*S*,4*S*)-*N*-Boc-4-iodoproline methyl ester (**4**), easily prepared from (2*S*,4*R*)-4-hydroxyproline,[8] was reduced to alcohol (**5**) in 92% yield (m.p. 73—74 °C, $[\alpha]_D^{25}$ −0.55°, MeOH). Swern oxidation of (**5**) provided the aldehyde (**6**), which was transformed using Still's method[9] to the α,β-unsaturated ester (**7**) with no epimerization, (*cis*-isomer >30 : 1), in 86% overall yield from (**5**) ($[\alpha]_D^{25}$ −34.7°, MeOH). Reduction of the ester (**7**) afforded allylic alcohol (**8**) in 78% yield (m.p. 111—112 °C, $[\alpha]_D^{25}$ −3.3°, MeOH), which was converted to diene alcohol (**9**) in 92% yield ($[\alpha]_D^{25}$ −81.0°, MeOH), *via* elimination of the selenoxide.[10] The *m*-chloroperbenzoic acid (MCPBA) epoxidation of the allylic alcohol (**9**) proceeded with high diastereoselectivity (94% yield as a 13 : 1 ratio of isomers) to give the desired isomer *syn*-(**10**) (m.p. 85—86 °C, $[\alpha]_D^{25}$ −132.6°, MeOH), which was easily separable by flash column chromatography or recrystallization (Scheme 2).§

Reduction of the epoxide *syn*-(**10**) provided the desired *syn*-amino alcohol (**11**) in 74% yield (m.p. 84.5—85.5 °C, $[\alpha]_D^{25}$ −210.9°, MeOH), which was converted to *syn*-β-hydroxy-γ-amino acid (**12**) in 84% yield ($[\alpha]_D^{25}$ −188.9°, MeOH) by a platinum-catalysed air oxidation.[11] The acid (**12**) was transformed into its sodium salt on treatment with aqueous sodium bicarbonate (1.1 equiv.), followed by freeze-drying. The resulting sodium salt was treated with bromine (1.1 equiv.), affording the bromolactone (**13**) in 95% yield (m.p. 104—105 °C, $[\alpha]_D^{25}$ −81.1°, EtOH), with no other isomers detectable by ^{1}H NMR and silica gel TLC. Treatment of (**13**) with tributyltin hydride provided the known lactone

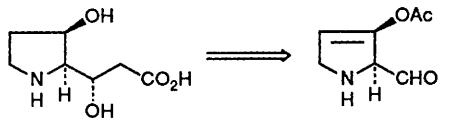
† Recently detoxin D_1 has been synthesized from racemic detoxinine (**2**).[6]

‡ The oxidation of L-*N*-Boc-dehydroprolinol {$(COCl)_2$/DMSO/Et_3N, py–SO_3/DMSO/Et_3N, *etc.*} provided L-*N*-Boc-dehydroprolinal with partial racemization in low yield.

§ All new compounds were characterized by ^{1}H NMR, IR, and high-resolution mass spectrometry and/or combustion analysis. *Anti*-(**10**): m.p. 72—73 °C, $[\alpha]_D^{25}$ −119.8° (MeOH); R_F values on Merck Kieselgel 60F_{254} (50% AcOEt in hexane), *syn*-(**10**): 0.26; *anti*-(**10**): 0.72; ^{1}H NMR (270 MHz, $CDCl_3$): *syn*-(**10**): 1.52 (9 H, s), 1.89 (1 H, s, D_2O exchangeable), 2.92—3.03 (1 H, m), 3.08—3.12 (1 H, m), 3.79—3.94 (2 H, m), 4.03—4.40 (2 H, m), 4.60 (1 H, m), 5.53—5.68 (1 H, m), 5.55—5.68 (1 H, m), 5.85—5.96 (1 H, m), 5.91 (1 H, br s); *anti*-(**10**): 1.47 (9 H, s), 1.61 (1 H, s, D_2O, exchangeable), 2.77 (1 H, dd, *J* 9.0, 3.5 Hz), 3.26 (1 H, dt, *J* 9.5, 3.7 Hz), 3.56 (1 H, dd, *J* 12.0, 9.5 Hz), 3.98—4.11 (1 H, m), 4.13—4.27 (2 H, m), 4.34—4.39 (1 H, m), 4.87 (1 H, br d, *J* 10.6 Hz), 5.86—5.94 (2 H, m).

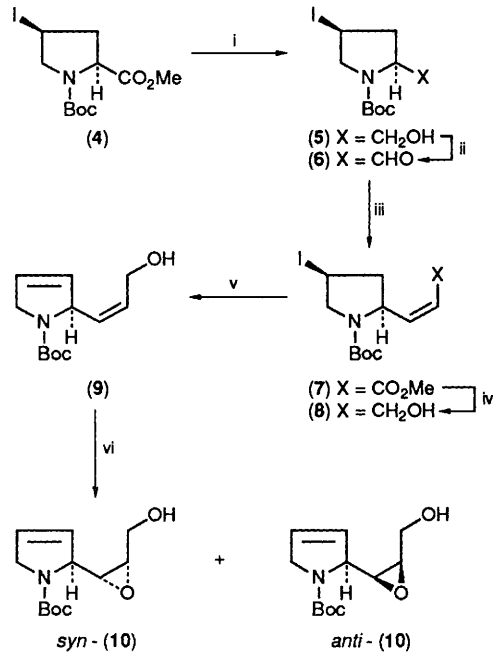


Detoxin D_1 (1)



(-) - Detoxinine (2) L- Dehydroprolinal (3)

Scheme 1

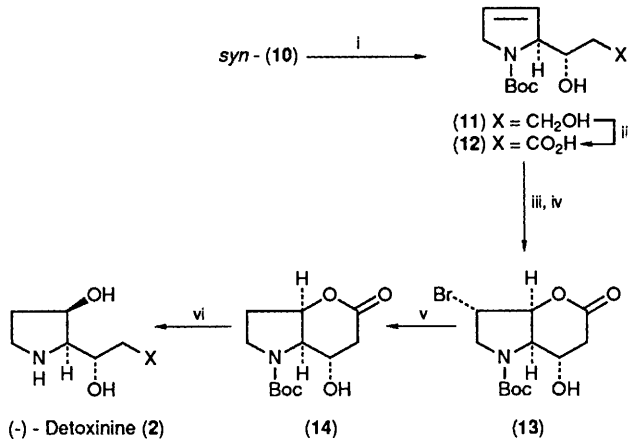


syn : anti = 13:1

Scheme 2. *Reagents and conditions*: i, $NaBH_4$–LiCl, EtOH–THF, 25 °C; ii, $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 to 0 °C; iii, $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, 18-crown-6, $(TMS)_2NK$, THF, −78 °C; iv, DIBAL, CH_2Cl_2, −78 °C; v, PhSeNa, EtOH, reflux, then H_2O_2, EtOH–THF, 25 °C; vi, MCPBA, CH_2Cl_2, −10 °C.

(**14**)¶ in 97% yield (m.p. 141—142 °C, $[\alpha]_D^{25}$ −31.7°, $CHCl_3$), which was converted to (−)-detoxinine (**2**) in 90% yield, {m.p. 225—227 °C (decomp.), $[\alpha]_D^{25}$ −4.7°, H_2O, lit.[5b]: m.p. 225—228 °C (decomp.), $[\alpha]_D^{25}$ −4.8° (H_2O)}, by treatment

¶ Joullié *et al.* have reported a lower optical rotation for lactone (**14**) ($[\alpha]_D^{25}$ −6.5°, $CHCl_3$) than that of our compound.[5c]



(-) - Detoxinine (2) (14) (13)

Scheme 3. *Reagents and conditions*: i, Red-Al®, THF, 0 °C; ii, Pt/O_2, $NaHCO_3$, H_2O, 25 °C; iii, $NaHCO_3$, H_2O; iv, Br_2, EtOH, −78 °C; v, $(Bu)_3SnH$, cat. AIBN, THF, reflux; vi, CF_3CO_2H, 0 °C; Dowex-50W ×2 (H^+ form), 1 M NH_4OH.

with trifluoroacetic acid followed by ion-exchange resin purification (Scheme 3). Our synthetic compound (**2**) proved to be (−)-detoxinine by comparison of its physical data with those of the authentic sample.[5b,5c]

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