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TETRAHEDRON: *ASYMMETRY*

A stereocontrolled synthesis of (−)-detoxinine from L-ascorbic acid

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Abstract

A stereoselective synthesis of (−)-detoxinine, the core unit of the detoxifying agent detoxin D_1, is presented. The approach, characterized by the use of an inexpensive starting material and by the easy and stereoselective preparation of the key 4,5-disubstituted oxazolidin-2-one **11**, proves to be a suitable alternative to the known procedures.

1. Introduction

The detoxin complex is a collection of twelve depsipeptides, isolated from *Streptomyces caespitosus* var. detoxicus 7072 GC1, which displays a unique detoxifying effect against the nucleoside antibiotic blasticidin S.[1,2] Coadministration of blasticidin S and the detoxin complex reduces the cytotoxicity of the antibiotic without affecting the activity in the treatment of rice blast disease.[3] Moreover, in vivo studies showed that its administration decreased eye irritation caused by the antibiotic together with a remarkable decrease of conjunctivitis in rats.[3] Detoxin D_1 **1** was identified as the most active component of the complex.[4]

Ten of the twelve components of the detoxin complex possess the uncommon amino acid (−)-detoxinine **2** as the core scaffold. Albeit (−)-detoxinine itself did not show any particular biological activity, we hypothesized that its incorporation into oligopeptides could promote new and interesting biological responses, as for detoxin D_1.

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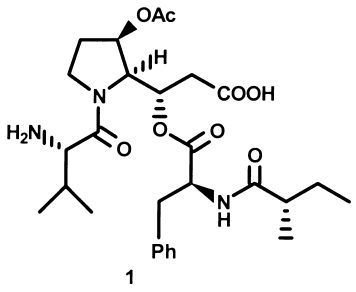
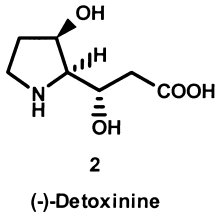


1

Detoxin D_1



2

(-)-Detoxinine

Besides the obvious interest in highly functionalized amino acids, the synthesis of (−)-detoxinine has also been undertaken for the application of new synthetic methods which have previously been reported for both enantiomers[5] and for the racemic form.[6] Most of the syntheses were based on an acetate aldol addition as the key bond-forming event either with a protected 3-hydroxy pyrrolidine or before pyrrolidine ring formation. Recently, an asymmetric tandem inter [4+2]/intra [3+2] nitroalkene cycloaddition[7] was employed to introduce all the functional groups.

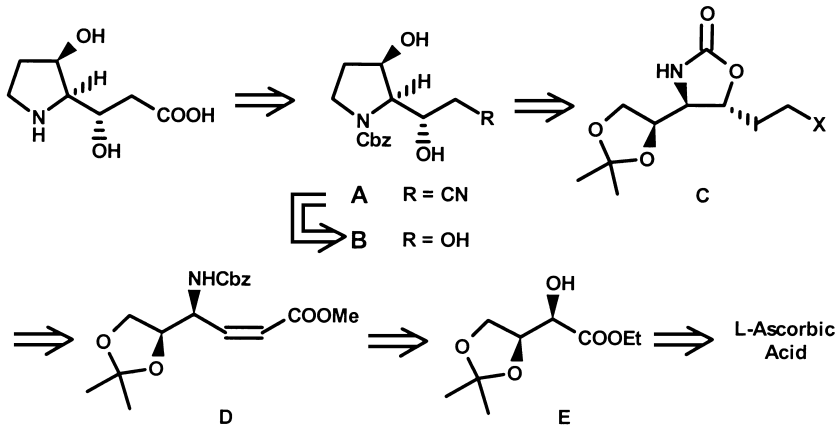
In previous reports[8] we highlighted the stereoselective formation of 4,5-disubstituted oxazolidin-2-ones, via a highly stereoselective iodocyclocarbamation of an electron poor *N*-Cbz *Z*-allylamine, and their use in the synthesis of natural products. These reports have described inter alia the stereoselective syntheses of (2*R*,3*S*)-3-hydroxy ornithine,[8b] proclavaminic acid[8c] and threo-γ-hydroxy-L-β-lysine lactone,[8d] as well as a general method for the asymmetric synthesis of threonine analogues,[8e] using L-serine as starting material. This paper deals with a stereocontrolled synthesis of (−)-detoxinine and represents a further extension of the use of chiral 4,5-disubstituted oxazolidin-2-ones as valuable intermediates.

2. Results and discussion

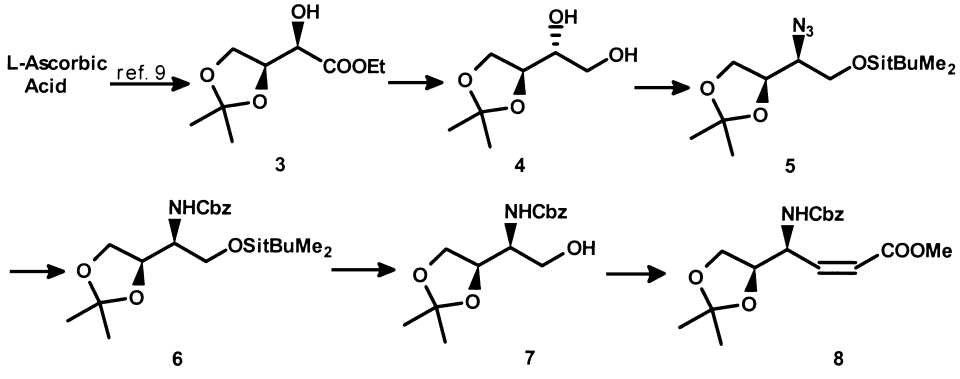
A retrosynthetic approach to (−)-detoxinine revealed that the natural product could be obtained from the nitrile A (Scheme 1), which in turn was expected to arise from the differentially protected 3-hydroxy pyrrolidine B, by the elaboration of the 1,2-dihydroxy function. On the other hand, hydroxy-pyrrolidine itself may derive from the alkaline hydrolysis of the 4,5-disubstituted 2-oxazolidinone C, bearing a suitable leaving group (X in Scheme 1) in the C-5 side chain. The key step for the set-up of all stereogenic centers and the functional groups is the stereoselective iodo-cyclocarbamation reaction of the electron poor allyl amine D. The last intermediate was foreseen to originate from the differentially protected α-hydroxy ester E, which can be obtained from L-ascorbic acid.[9]

Thus the α-hydroxy ester[9] **3** was treated with PhCOOH/Ph_3P/DIAD, following a slightly modified procedure of Abushanab et al.[9] to give the corresponding diester (83% yield) with inversion of configuration at C-2. The latter was reduced ($LiAlH_4$, 1 M in THF) to afford the diol **4** in 92% yield (Scheme 2). The last compound was easily converted into the azide **5**, by regioselective protection of the primary hydroxy function with *t*-butyldimethylsilylchloride/imidazole in THF at −5°C, followed by activation of the secondary alcohol as the mesylate and nucleophilic displacement with NaN_3. The azide **5** was obtained in 76% yield from **4** and reduced with H_2 in the presence of catalytic 10% Pd/C, followed by treatment with *N*-benzyl-oxycarbonyloxy succinimide, to give the *N*-Cbz compound **6** (97% yield).

Exposure of **6** to tetrabutylammonium fluoride (TBAF) in THF afforded, in quantitative yield, the *N*-Cbz aminoalcohol **7**.



Scheme 1.



Scheme 2.

The synthetic plane foresaw the conversion of **7** into the *Z*-α,β-unsaturated ester **8**: the fully protected aminoalcohol **7** was thus oxidized under Swern condition to the corresponding α-amino aldehyde and immediately subjected to a modified Horner–Wadsworth–Emmons[10] reaction with different phosphonates, with the aim to obtain mainly the *Z*-isomer (Scheme 2). The results of these experiments are reported in Table 1.

Wittig reaction with methoxycarbonyl methylidene triphenylphosphorane in MeOH at 0°C (entry 1) gave the corresponding α,β-unsaturated ester in a fair yield, but with poor *Z*/*E* selectivity. Reaction with methyl diphenylphosphono acetate (entries 2–3), following the procedure of Ando,[11] gave mainly the *Z*-isomer under all tested conditions, although with moderate yields. The most selective conditions (entry 4) were achieved using the Still reagents[12] which afforded the *Z*-isomer in good yield (93%) and selectivity (*Z*:*E* 16:1).

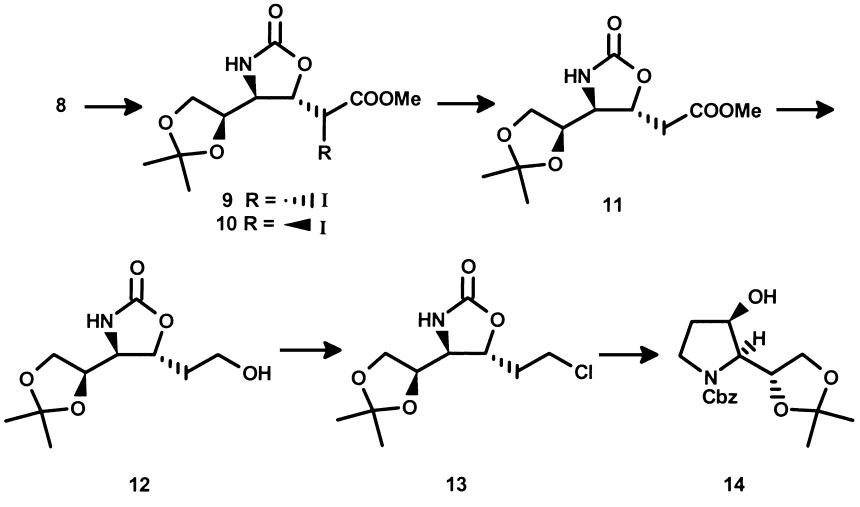
The use of K_2CO_3/toluene (entry 5), suggested by Koskinen et al.[13] was also tested: the reaction gave the *Z*-isomer with a good selectivity but in yield lower than those previously obtained.

The electron poor *Z*-allyl amine **8** was then subjected to an iodocyclocarbamation reaction[14] using an excess of I_2 in CH_3CN. After the time required for consumption of α,β-unsaturated ester (12 h), we obtained a complex mixture of products, coming not only from the iodocyclocarbamation reaction but also from iodoetherification reactions[15] and removal of the acetonide group. Among various attempts to suppress these side reactions, we found that the use of AgOTf:$NaHCO_3$:I_2 (2:4:2) in CH_3CN could solve the problem. Under these conditions, the cyclization occurred within 2 h in a chemo- and stereoselective

Table 1
Selective formation of the *Z*-α,β-unsaturated ester **8**

Entry	Conditions	Yield	Z/E ratio
1	$Ph_3PCHCOOMe$ 0 °C, MeOH	88	2:1
2	$(PhO)_2POCH_2COOMe$ Triton B, -78 °C	65	14:1
3	$(PhO)_2POCH_2COOMe$ $K(HMDS)_2$, 18-crown-6, -78 °C, THF	72	15:1
4	$(CF_3CH_2O)_2POCH_2COOMe$ $K(HMDS)_2$, 18-crown-6, -78 °C, THF	93	16:1
5	$(CF_3CH_2O)_2POCH_2COOMe$ K_2CO_3, 18-crown-6, -20 °C →0 °C, PhMe	66	15:1

fashion to give the epimeric iodo *trans* oxazolidin-2-ones **9** and **10** in 81% yield (based on the recovery of 20% of **8**) and a ratio of 92:8 (Scheme 3).



Scheme 3.

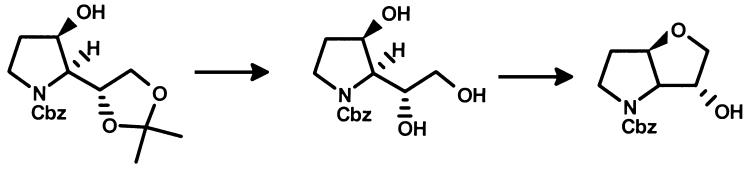
The *trans* orientation of the cyclic carbamates **9** and **10** was confirmed by the coupling constant between H-4 and H-5 ($J_{4,5}$=3.5 Hz) in the ^{1}H NMR spectrum. This is in agreement with our earlier results[8] and those reported in the literature.[16] The stereochemical course of this iodine mediated cyclization can be qualitatively explained on the basis of the allylic 1,3 strain,[17] in accord with our previous observations.[8]

Reductive removal of the iodo group was achieved directly on the epimeric mixture of **9** and **10**, under radical-induced conditions (*n*-Bu_3SnH/AIBN), to give the ester **11** (93% yield), which was converted by $LiAlH_4$ reduction into the alcohol **12** (94% yield). Attempts to reduce directly the epimeric mixture of **9** and **10** to the alcohol **12**, using different reducing reagents and conditions, were frustrated by the low yield obtained (40% yield).

The synthetic strategy then required conversion of the hydroxy function in **12** into the chloride function as in **13**. Initial attempts to perform directly the transformation under standard conditions[18]

($Ph_3P/CCl_4/CH_2Cl_2$) were unsuccessful, a mixture of products being obtained, presumably due to the instability of the acetonide under these conditions. The use[19] of K_2CO_3 (2 equiv.) increased the yield of compound **13** to 40%. However, nearly a quantitative yield (98%) of **13** was obtained when the reaction was perfomed[20] in dry pyridine, using substrate:Ph_3P:CCl_4 in the optimal ratio of 1:4:2. Subsequently, compound **13**, by treatment with a solution of NaOH in MeOH/H_2O (75°C), underwent cleavage of the cyclic urethane and displacement of chlorine by nitrogen, giving the corresponding pyrrolidine which was isolated as the *N*-Cbz derivative **15** in 68% yield (Scheme 3). Having assembled all the stereogenic centers and functional groups, the conversion of the 1,2-dihydroxy group into the β-hydroxy acid completed the synthesis.

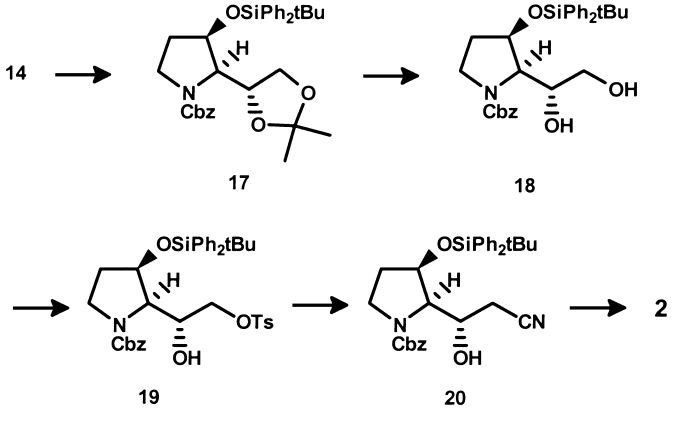
The acetonide was treated with CF_3COOH in THF/H_2O to give in good yield (85%) the free triol **15** (Scheme 4). Attempts to activate regioselectively the primary hydroxy group as the tosylate failed: under the conditions studied (TsCl/CH_2Cl_2/Py or TsCl/Py) the main product was the azabicyclo[3.3.0]-octane **16**, presumably by initial tosylation of the primary alcohol followed by five membered ring formation.[21]



14 15 16

Scheme 4.

Therefore, we protected the free hydroxy group in the pyrrolidine **14** as the *tert*-butyldimethylsilyl ether **17** (*t*-Bu(Me)$_2$SiCl, imidazole, 97% yield) and cleaved selectively the acetonide using $FeCl_3 \cdot 3H_2O$[22] adsorbed on silica gel, to obtain the diol **18** in 93% yield (Scheme 5). Treatment of the diol **18** with TsCl in CH_2Cl_2/Py gave the tosylate **19** in 86% yield, which was converted into the nitrile **20** following standard methodology (NaCN, DMF, 83% yield).



17 18 19 20

Scheme 5.

The title compound was finally obtained from **20** by catalytic hydrogenolysis (5% Pd/C, EtOAc) to remove the Cbz group, followed by acid hydrolysis to give **2**, which showed analytical data in agreement with those already reported.[7]

In summary we have presented a convenient preparation of (−)-detoxinine, the core unit of detoxin D_1, starting from L-ascorbic acid. The present method, characterized by the use of an inexpensive starting material and by an easy and stereoselective introduction of all stereogenic centers, proves to be a suitable alternative to the known procedures.

Moreover, the above synthetic approach appears very appealing for the preparation of analogues of detoxin D_1, as potential candidates against the cytotoxicity of some antibiotics.

3. Experimental

Melting points were determined in open capillaries using a Büchi apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were run on a Varian Gemini 300 spectrometer at 300 MHz and 75 MHz, respectively, in $CDCl_3$, unless otherwise reported. Chemical shifts (δ scale) are relative to TMS as internal reference. Proton and carbon signals were correlated by COSY and/or HECTOR experiments, when it was required for unambiguous assignments. ^1H and ^{13}C NMR spectra for compounds **15**–**20**, due to the restricted rotation of the N–CO bond, were characterized by the signals of both conformers. Only the signals of the major conformer are reported. Optical rotations were determined on a Perkin–Elmer 243 polarimeter at 23°C (concentration g/100 ml). All solvents were dried prior to use.[23] Thin layer chromatography was performed on Merck silica gel 60 F_{254} glass plates.

*3.1. (2*S*,3*R*)-1,2-Isopropylidendioxy-butan-3,4-diol **4***

To a stirred solution of the α-hydroxy ester[9] **3** (10.2 g, 0.05 mol), triphenylphosphine (26.3 g, 0.1 mol), and benzoic acid (2.2 g, 0.1 mol) in dry THF (300 ml), DIAD (19.7 ml, 0.1 mol) in THF (50 ml) was added dropwise at −5°C over 30 min. The slightly yellow solution was stirred at room temperature for 24 h, whereupon the volatile components were removed under reduced pressure and the residue purified according to Abushanab et al.,[9] to give the corresponding diester (12.8 g, 83%) as a colorless oil.

To a cooled (−15°C) and stirred solution of the above compound (12.32 g, 0.04 mol) in dry THF (200 ml) was added dropwise a solution of $LiAlH_4$ (1 M in THF, 60 ml, 0.060 mol). After the addition was complete the mixture was stirred at room temperature for 1 h and heated at reflux for 3 h. The mixture was cooled at 0°C and EtOAc (150 ml) was added dropwise over 10 min and stirred at the same temperature for 30 min, before adding cautiously H_2O. The mixture was filtered over a pad of Celite, dried over Na_2SO_4 and concentrated to a light, yellow oil. The oil was distilled (bp 103–110°C, 0.2 mmHg; lit.[9] bp 110–120°C, 0.3 mmHg) to provide **4** (6.0 g, 92%). $[\alpha]_D$=−7.53 (c=3.2, EtOH); lit.[9] $[\alpha]_D$=−7.61 (c=6.5, EtOH).

*3.2. (2*R*,3*S*)-3-Azido-4-*tert*-butyldimethylsilyloxy-1,2-isopropylidendioxy-butane **5***

To a cooled (−5°C) solution of diol **4** (5.0 g, 30.9 mmol) and imidazole (2.24 g, 32.9 mmol) in dry THF (60 ml) was added *tert*-butyldimethylsilylchloride (4.66 g, 30.9 mmol) in small portions and the reaction mixture was stirred for 3 h at the same temperature. After this time H_2O (10 ml) and Et_2O (100 ml) were added and the organic layer was extracted with HCl 1N (2×25 ml), H_2O (50 ml), satd $NaHCO_3$ (2×25 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a colorless oil. The residue was dissolved in dry CH_2Cl_2 (60 ml), then triethylamine (5.50 ml, 39.5 mmol) and methanesulfonyl chloride (2.8 ml, 36.2 mmol) were added at −5°C. The reaction mixture was stirred at room temperature for 1 h. After dilution with Et_2O, the mixture was washed with HCl 1N (2×25 ml), H_2O (50 ml), satd aqueous $NaHCO_3$ (50 ml) and brine. Drying followed by evaporation gave the corresponding mesylate as an oil. The residue was dissolved in dry DMF (100 ml) and sodium azide (16.12 g, 0.248 mol) was added. The mixture was stirred at 95°C for 10 h, cooled to room temperature, and added to a satd aqueous solution of $NaHCO_3$. The solution was extracted with EtOAc (3×150 ml)

and the combined organic layers were washed with brine. Drying followed by evaporation gave a yellow oil. The residue was purified by silica gel column chromatography (*n*-hexane:EtOAc 95:5) to give **5** (6.9 g, 76%) as a colorless oil; $[\alpha]_D$=21.9 (c=0.93, $CHCl_3$); ^{1}H NMR δ 4.19 (1H, q, *J*=6.5 Hz, CHO), 4.05, 3.85 (1H each, dd, *J*=8.5 and 6.5 Hz, CH_2O), 3.79 (1H, dd, *J*=10.0 and 6.5 Hz, CH_AH_BOSi), 3.75 (1H, d, *J*=5.5 Hz, CH_AH_BOSi), 3.39 (1H, q, *J*=6.0 Hz, CHN), 1.46, 1.37 (3H each, s, 2×Me), 0.91 (9H, s, 3×Me), 0.09 (6H, s, 2×MeSi); ^{13}C NMR δ 109.60 (s, COO), 75.66 (d, CHO), 66.43 (t, CH_2O), 64.13 (d, CHN), 63.29 (t, CH_2OSi), 26.33, 25.34 (q each, 2×Me), 25.70 (q, Me_3), 18.20 (s, SiC), −5.55 (q, Me_2Si). Anal. calcd for $C_{13}H_{27}N_3O_3Si$: C 51.80, H 9.03, N 13.94. Found: C 51.65, H 9.05, N 13.97.

3.3. (2R,3S)-3-N-Benzyloxycarbonyl-4-tert-butyldimethylsilyloxy-1,2-isopropylidendioxy-butane **6**

A solution of azide **5** (6.78 g, 22.53 mmol) in abs. EtOH (150 ml) was hydrogenated (1 atm) over 10% Pd/C (0.678 g) for 6 h. After that time the mixture was filtered over Celite and concentrated under reduced pressure.

To a solution of the above crude amine in dry THF (150 ml) were added Et_3N (4.09 ml, 29.37 mmol) and *N*-(benzyloxycarbonyloxy) succinimide (7.28 g, 29.21 mmol) and the mixture was stirred overnight. After that time the mixture was concentrated under reduced pressure and purified by silica gel column chromatography (*n*-hexane:EtOAc 90:10) to give **6** (8.94 g, 97%) as a colorless oil. $[\alpha]_D$=−2.6 (c=0.33, $CHCl_3$); ^{1}H NMR δ: 7.35 (5H, br s, C_6H_5), 5.13, 5.07 (1H each, d, *J*=12.0 Hz, $COOCH_2$), 4.99 (1H, br d, *J*=8.5 Hz, NH), 4.38 (1H, td, *J*=7.0 and 2.0 Hz, CHO), 4.03 (1H, dd, *J*=8.0 and 7.0 Hz, CH_AH_BO), 3.77 (1H, tdd, *J*=8.5, 5.0 and 2.0 Hz, CHN), 3.72 (1H, t, *J*=7.5 Hz, CH_AH_BO), 3.69 (1H, dd, *J*=10.0 and 5.0 Hz, CH_CH_DOSi), 3.58 (1H, dd, *J*=10.0 and 8.0 Hz, CH_CH_DOSi), 1.41, 1.34 (3H each, s, 2×Me), 0.88 (9H, s, 3×Me), 0.05 (6H, s, 2×MeSi); ^{13}C NMR δ: 156.37 (s, CO), 136.43, 128.51, 128.12, 128.06 (s, d×2, d, d×2, C_6H_5), 109.10 (s, COO), 73.55 (d, CHO), 66.86, 66.20 (t each, 2×CH_2O), 62.78 (t, CH_2OSi), 52.75 (d, CHN), 26.34, 25.02 (q each, 2×Me), 25.81 (q, 3×Me), 18.27 (s, SiC), −5.45, −5.54 (q each, 2×MeSi). Anal. calcd for $C_{21}H_{35}NO_5Si$: C 61.58, H 8.61, N 3.42. Found: C 61.76, H 8.63, N 3.41.

3.4. (2R,3S)-3-N-Benzyloxycarbonyl-1,2-isopropylidendioxy-butan-4-ol **7**

Tetrabutylammonium fluoride (1 M in THF, 21.9 ml, 21.9 mmol) was added dropwise to a solution of silyl ether **6** (8.54 g, 20.88 mmol) in THF (85 ml) at 0°C. The solution was stirred at room temperature for 2 h, whereupon a satd solution of NH_4Cl (20 ml) was added and the mixture stirred for 10 min. The mixture was diluted with EtOAc (200 ml), and the aqueous layer was extracted with EtOAc (3×50 ml). The combined extracts were washed with brine, H_2O, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (eluent *n*-hexane:EtOAc 25:75) of the residue gave pure **7** (6.04 g, 99%) as a colorless oil; $[\alpha]_D$=−23.6 (c=1.54, MeOH); ^{1}H NMR δ: 7.36 (5H, br s, C_6H_5), 5.32 (1H, br d, *J*=8.0 Hz, NH), 5.14, 5.09 (1H each, d, *J*=12.0 Hz, $COOCH_2$), 4.35 (1H, td, *J*=7.0 and 2.0 Hz, CHO), 4.04, 3.74 (1H each, dd, *J*=8.0 and 7.0 Hz, CH_2O), 3.81 (2H, br d, *J*=8.0 Hz, CH_2OH), 3.80 (1H, m, CHN), 1.42, 1.35 (3H each, s, 2×Me); ^{13}C NMR δ: 156.92 (s, CO), 136.24, 128.55, 128.21, 128.04 (s, d×2, d, d×2, C_6H_5), 109.57 (s, COO), 75.85 (d, CHO), 67.11 (t, CH_2O), 64.35 (t, CH_2OH), 52.55 (d, CHN), 26.24, 24.99 (q each, 2×Me). Anal. calcd for $C_{15}H_{21}NO_5$: C 61.00, H 7.17, N 4.74. Found: C 60.83, H 7.18, N 4.72.

3.5. *Methyl (4*S,*5*R,Z*)-3-*N-*benzyloxycarbonyl-5,6-isopropylidendioxy-2-hexenoate* **8**

Oxalyl chloride (3 ml, 33 mmol) was dissolved in dry CH_2Cl_2 (50 ml), the mixture was cooled to −63°C, and a solution of dry DMSO (5.61 ml, 66 mmol) in CH_2Cl_2 (10 ml) was then added dropwise during 15 min. The aminoalcohol **7** (6.0 g, 20.0 mmol) in CH_2Cl_2 (20 ml) was added dropwise during 10 min, the resulting slightly cloudy solution was stirred for 10 min at −63°C, and a solution of *N*,*N*-diisopropylethyl amine (20.9 ml, 0.12 mol) in CH_2Cl_2 (50 ml) was added dropwise during 15 min. After 15 min, the reaction was quenched by adding water (5.0 ml) to the stirred reaction mixture at −63°C. The resulting slurry was poured into Et_2O (300 ml) and washed with 20% aqueous $KHSO_4$ (2×100 ml). The layers were separated and the aqueous layer was back-extracted with Et_2O (2×100 ml). The combined organic layers were washed with brine solution (2×50 ml), dried over Na_2SO_4 and filtered. The solvent was removed under vacuum to afford the crude aldehyde as an oil, which was immediately used in the next reaction.

To a solution of 18-crown-6 (26.45 g, 0.1 mol) and methyl[bis(2,2,2-trifluoroethyl) (methoxycarbonylmethyl) phosphonate (6.36 g, 20.0 mmol) in dry THF (400 ml) at −65°C was added under nitrogen with stirring during 15 min a solution of $KN(TMS)_2$ (0.5 M in THF, 40.0 ml). The mixture was stirred for 20 min at the same temperature, cooled to −78°C and a solution of the above crude aldehyde in THF (10 ml) was added dropwise. The solution was stirred at −78°C for 45 min, whereupon a satd solution of NH_4Cl (15 ml) was added cautiously. The mixture was diluted with EtOAc (100 ml), separated and the aqueous layer was extracted with EtOAc (3×100 ml). The combined extracts were washed with brine, H_2O, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography (eluent hexane:EtOAc 75:25) of the residue gave pure α,β-unsaturated ester **8** (6.49 g, 93%) as a solid; mp 48–49°C; $[\alpha]_D$=−30.9 (c=0.33, $CHCl_3$); ^{1}H NMR δ: 7.35 (5H, br s, C_6H_5), 6.17 (1H, dd, *J*=11.5 and 8.0 Hz, C*H*=CHCO), 5.91 (1H, br d, *J*=11.5 Hz, CH=C*H*CO), 5.42 (1H, br t, *J*=8.5 Hz, CHN), 5.31 (1H, br d, *J*=9.0 Hz, NH), 5.12, 5.08 (1H each, d, *J*=12.0 Hz, $COOCH_2$), 4.38 (1H, br t, *J*=6.5 Hz, CHO), 4.11 (1H, dd, *J*=11.0 and 6.5 Hz, CH_AH_BO), 3.80 (1H, dd, *J*=11.0 and 6.0 Hz, CH_AH_BO), 3.73 (3H, br s, OMe), 1.46, 1.32 (3H each, s, 2×Me); ^{13}C NMR δ: 174.75 (s, *C*OOMe), 154.17 (s, CON), 148.08 (d, *C*H=CHCO), 137.15, 128.54, 128.22, 128.19 (s, d×2, d, d×2, C_6H_5), 120.49 (d, CH=*C*HCO), 109.91 (s, COO), 77.67 (d, CHO), 67.01 (t, CH_2O), 66.31 (t, *C*H_2OCO), 51.52 (d, CHN), 50.23 (q, OMe), 26.28, 24.62 (q each, 2×Me). Anal. calcd for $C_{18}H_{23}NO_6$: C 61.88, H 6.64, N 4.01. Found: C 61.71, H 6.65, N 4.00.

3.6. *Methyl (4*R,*5*R,*1′*R*)-α-iodo-4-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-oxo-5-oxazolidineacetate* **9** *and methyl (4*R,*5*R,*1′*S*)-α-iodo-4-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-oxo-5-oxazolidineacetate* **10**

To a solution of the α,β-unsaturated ester **8** (5.25 g, 15 mmol), AgOTf (7.8 g, 30 mmol) and $NaHCO_3$ 5.06 g, 60 mmol) in dry CH_3CN (90 ml), I_2 (9.53 g, 37.5 mmol) was added in one portion at room temperature. The reaction mixture was stirred at the same temperature for 2 h, then diluted with $CHCl_3$ (200 ml) and extracted with an aqueous solution of $Na_2S_2O_3$ (0.3 M, 2×150 ml). The aqueous layers were extracted with $CHCl_3$ (2×50 ml) and the combined extracted were dried over Na_2SO_4, filtered and evaporated to dryness under vacuum. The ^{1}H NMR spectra of the crude mixture showed the presence of **9** and **10** in a ratio 92:8 by integration. The residue was passed through a short silica gel column (EtOAc:*n*-hexane 7:3) to give an inseparable mixture of **9** and **10** (3.75 g, 81% based on the recovery of 20% of **8**).

9: ^{1}H NMR δ: 5.52 (1H, br s, NH), 4.69 (1H, dd, *J*=7.0, and 3.5 Hz, CHOCO), 4.61 (1H, d, *J*=7.0 Hz, CHI), 4.22 (1H, dt, *J*=7.0 and 4.5 Hz, CHO), 4.11 (1H, dd, *J*=9.0 and 7.0 Hz, CH_AH_BO), 3.87 (1H, dd,

J=9.0 and 4.5 Hz, CH_AH_BO), 3.79 (3H, s, OMe), 3.78 (1H, br d, *J*=4.0 Hz, CHN), 1.44, 1.35 (3H each, s, 2×Me); ^{13}C NMR δ: 169.07 (s, *C*OOMe), 158.01 (s, NCO), 110.31 (s, COO), 77.98 (d, CHOCO), 76.07 (d, CHO), 65.65 (t, CH_2O), 58.05 (d, CHN), 53.40 (q, OMe), 26.21, 24.87 (q each, 2×Me), 19.82 (d, CHI).

10: ^1H NMR δ: 5.46 (1H, br s, NH), 4.66 (1H, dd, *J*=8.0, and 3.5 Hz, CHOCO), 4.55 (1H, d, *J*=8.0 Hz, CHI), 4.22 (1H, dt, *J*=7.0 and 4.5 Hz, CHO), 4.11 (1H, dd, *J*=9.0 and 7.0 Hz, CH_AH_BO), 3.85 (1H, dd, *J*=9.0 and 4.5 Hz, CH_AH_BO), 3.82 (1H, br t, *J*=4.0 Hz, CHN), 3.79 (3H, s, OMe), 1.44, 1.35 (3H each, s, 2×Me); ^{13}C NMR δ: 169.13 (s, *C*OOMe), 157.87 (s, NCO), 110.34 (s, COO), 77.62 (d, *C*HOCO), 75.91 (d, CHO), 68.51 (t, CH_2O), 59.00 (d, CHN), 53.34 (q, OMe), 27.79, 24.96 (q each, 2×Me), 19.71 (d, CHI).

*3.7. Methyl (4*R*,5*R*)-4-[(4*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-oxo-5-oxazolidineacetate **11***

Tributyltin hydride (4.68 ml, 17.66 mmol) was added to a solution of AIBN (0.164 g, 1 mmol) in dry toluene (55 ml) under nitrogen and the clear solution brought to reflux. A solution of iodo ester **9** and **10** (3.4 g, 8.83 mmol) in toluene (80 ml) was added and the solution was refluxed for 3 h and concentrated under vacuum. The residue was purified by silica gel column chromatography (*n*-hexane:EtOAc 30:70) to give **11** (2.13 g, 93%) as a white solid; mp 137°C; $[\alpha]_D$=49.7 (c=1.61, $CHCl_3$); ^1H NMR δ: 5.50 (1H, br s, NH), 4.70 (1H, ddd, *J*=8.0, 5.5 and 3.5 Hz, CHOCO), 4.20 (1H, ddd, *J*=6.5, 6.0 and 4.5 Hz, CHO), 4.11 (1H, dd, *J*=9.0 and 6.5 Hz, CH_AH_BO), 3.83 (1H, dd, *J*=9.0 and 4.5 Hz, CH_AH_BO), 3.73 (3H, s, OMe), 3.58 (1H, dd, *J*=6.0 and 3.5 Hz, CHN), 2.86 (1H, dd, *J*=16.5 and 5.5 Hz, CH_CH_DCO), 2.75 (1H, dd, *J*=16.5 and 8.0 Hz, CH_CH_DCO), 1.45, 1.35 (3H each, s, 2×Me). ^{13}C NMR δ: 169.40 (s, *C*OOMe), 157.96 (s, NCO), 110.32 (s, COO), 76.34 (d, CHO), 74.20 (d, CHOCO), 65.70 (t, CH_2O), 59.69 (d, CHN), 52.15 (q, OMe), 38.81 (t, CH_2CO), 26.48, 24.51 (q each, 2×Me). Anal. calcd for $C_{11}H_{17}NO_6$: C 50.96, H 6.61, N 5.40. Found: C 50.85, H 6.59, N 5.39.

*3.8. (4*R*,5*R*)-4-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-5-(2-hydroxyethyl)-2-oxo-oxazolidine **12***

To a well stirred and cooled (−15°C) solution of the ester **11** (1.8 g, 6.95 mmol) in dry THF (30 ml) was added dropwise $LiAlH_4$ (1 M in THF, 6.95 ml), and the solution was stirred at the same temperature for 3 h. After that time EtOAc (60 ml) was added and the mixture was stirred at the same temperature for 10 min, before adding cautiously H_2O. The solution was diluted with EtOAc (100 ml), filtered through a short pad of Celite, and concentrated under reduced pressure. The crude alcohol was purified by silica gel column chromatography ($CHCl_3$:MeOH 93:7) to give **12** (1.52 g, 95%); mp 107°C; $[\alpha]_D$=93.0 (c=1.1, MeOH); ^1H NMR δ: 5.64 (1H, br s, NH), 4.54 (1H, dt, *J*=8.0 and 5.0 Hz, CHOCO), 4.14 (1H, dt, *J*=6.5 and 5.0 Hz, CHO), 4.08 (1H, dd, *J*=9.0 and 6.5 Hz, CH_AH_BO), 3.83 (2H, t, *J*=6.0 Hz, CH_2OH), 3.75 (1H, dd, *J*=9.0 and 6.5 Hz, CH_AH_BO), 3.60 (1H, t, *J*=6.0 Hz, CHN), 1.97 (1H, ddt, *J*=15.0, 8.0 and 6.0 Hz, CH_CH_D), 1.88 (1H, dtd, *J*=15.0, 6.0 and 5.0 Hz, CH_CH_D), 1.44, 1.34 (3H each, s 2×Me); ^{13}C NMR δ: 158.46 (s, NCO), 110.30 (s, COO), 76.67 (d, CHOCO), 76.14 (d, CHO), 65.64 (t, CH_2O), 59.92 (d, CHN), 58.41 (q, CH_2OH), 37.64 (t, CH_2O), 26.46, 24.87 (q each, 2×Me). Anal. calcd for $C_{10}H_{17}NO_5$: C 51.94, H 7.41, N 6.06. Found: C 52.03, H 7.39, N 6.03.

*3.9. (4*R*,5*R*)-4-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl]-5-(2-chloroethyl)-2-oxo-oxazolidine **13***

To a solution containing the alcohol **12** (1.45 g, 6.3 mmol) in dry pyridine (90 ml), was added at room temperature triphenylphosphine (6.68 g, 25.2 mmol) followed by carbon tetrachloride (1.015 ml, 12.6

mmol). The mixture was protected by moisture and stirred at 45°C for 15 h then cooled at 0°C and abs. ethanol (60 ml) was added. The mixture was stirred for 15 min and concentrated at reduced pressure. The residue was purified by flash chromatography (eluent $CHCl_3$:MeOH 97:3) to give the compound **13** (1.47 g, 98% yield) as a white solid; mp 94°C; $[\alpha]_D$=61.2 (c=0.59, $CHCl_3$); ^{1}H NMR δ: 6.18 (1H, br s, NH), 4.61 (1H, dt, *J*=9.5 and 4.0 Hz, CHOCO), 4.18 (1H, dt, *J*=7.0 and 5.0 Hz, CHO), 4.12 (1H, dd, *J*=9.0 and 7.0 Hz, C*H*$_A$H$_B$O), 3.77 (1H, dd, *J*=9.0 and 5.0 Hz, CH$_A$*H*$_B$O), 3.73 (1H, ddd, *J*=11.0, 6.5 and 5.0 Hz, C*H*$_C$H$_D$Cl), 3.69 (1H, ddd, *J*=11.0, 9.0 and 5.0 Hz, CH$_C$*H*$_D$Cl) 3.54 (1H, t, *J*=5.0 Hz, CHN), 2.10 (1H, ddt, *J*=15.0, 9.5 and 5.0 Hz, C*H*$_E$H$_F$), 2.01 (1H, dddd, *J*=15.0, 9.0, 6.5 and 4.0 Hz, CH$_E$*H*$_F$), 1.45, 1.35 (3H each, s, 2×Me); ^{13}C NMR δ: 158.46 (s, NCO), 110.37 (s, COO), 76.21 (d, CHO), 75.04 (d, CHO), 65.40 (t, CH_2O), 59.50 (d, CHN), 38.89 (t, CH_2Cl), 38.12 (t, CH_2), 26.40, 24.74 (q each, 2×Me). Anal. calcd for $C_{10}H_{16}ClNO_4$: C 48.10, H 6.46, N 5.61. Found: C 48.19, H 6.48, N 5.61.

3.10. (2S,3R)-1-(Benzyloxycarbonyl)-2-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-hydroxy-pyrrolidine ***14***

To a solution of chloride **13** (1.02 g, 4.06 mmol) in 50 ml of MeOH:H_2O (3:1) was added NaOH (0.48 g, 12.0 mmol) and the solution was heated at 75°C overnight. The solvents were evaporated under reduced pressure and the residue was dissolved in $CHCl_3$ (100 ml), filtered and concentrated. The residue was dissolved in dry THF (10 ml) followed by addition of Et_3N (0.21 ml, 1.5 mmol) and dibenzyl dicarbonate (0.43 g, 1.5 mmol). The mixture was stirred overnight, concentrated under reduced pressure and purified by silica gel column chromatography (EtOAc:*n*-hexane 6:4) to give **14** (0.873 g, 68%) as a colorless oil; $[\alpha]_D$=−40.9 (c=1.53, $CHCl_3$); ^{1}H NMR δ: 7.35 (5H, br s, C_6H_5), 5.14, 5.11 (1H each, d, *J*=12.5 Hz, OC*H*$_2$C$_6$H$_5$), 4.44 (1H, p, *J*=7.5 Hz, CH$_2$CH$_2$C*H*O), 4.35 (1H, t, *J*=7.0 Hz, CHO), 4.08 (1H, br t *J*=8.0 Hz, C*H*$_A$H$_B$O), 4.05 (1H, br d, *J*=8.0 Hz, CH$_A$*H*$_B$O), 3.97 (1H, br d, *J*=7.0 Hz, OH), 3.74 (1H, *J*=8.0 Hz, CHN), 3.58 (1H, ddd, *J*=9.5, 6.0 and 5.0 Hz, C*H*$_C$H$_D$N), 3.50 (1H, dt, *J*=9.5 and 5.0 Hz, CH$_C$*H*$_D$N), 2.06 (1H, dq, *J*=12.0 and 8.0 Hz, C*H*$_E$H$_F$), 1.81 (1H, m, CH$_E$*H*$_F$), 1.40, 1.35 (3H each, s, 2×Me); ^{13}C NMR δ: 157.01 (s, CO), 136.42, 128.50, 128.08, 127.85 (s, d×2, d, d×2, C_6H_5), 108.87 (s, COO), 75.13 (d, CHO), 71.45 (d, CHN), 66.94, 66.16 (t each, 2×CH_2O), 58.78 (d, CHN), 44.35 (t, CH_2N), 33.38 (t, CH_2), 26.21, 25.28 (q each, 2×Me). Anal. calcd for $C_{17}H_{23}NO_5$: C 63.53, H 7.21, N 4.36. Found: C 63.41, H 7.22, N 4.35.

3.11. (2S,3R)-1-(Benzyloxycarbonyl)-2-[(1R)-1,2-dihydroxyethyl]-3-hydroxy-pyrrolidine ***15***

To a solution of the acetonide **14** (0.777 g, 2.42 mmol) in 5:1 THF:H_2O (12 ml) at 0°C was added trifluoroacetic acid (0.4 ml). The resulting mixture was allowed to warm to room temperature and left overnight. The solvent was removed under reduced pressure and the residue purified by silica gel column chromatography ($CHCl_3$:MeOH 9:1) to give the triol **15** (0.606 g, 92%) as a white solid; mp 30–31°C; $[\alpha]_D$=−38.1 (c=1.16, MeOH); ^{1}H NMR δ: 7.29 (5H, br s, C_6H_5), 5.07 (2H, s, $COOCH_2$), 4.44 (1H, q, *J*=6.5 Hz, CH$_2$CH$_2$C*H*O), 4.04 (1H, m, C*H*OH), 3.91 (1H, dd, *J*=6.5 and 2.5 Hz, CHN), 3.62 (1H, dt, *J*=12.0 and 7.0 Hz, C*H*$_A$H$_B$O), 3.54 (1H, m, CH$_A$*H*$_B$O), 3.53 (1H, m, C*H*$_C$H$_D$N), 3.48 (1H, dt, *J*=11.0 and 7.0 Hz, CH$_C$*H*$_D$N), 2.03, 1.95 (1H each, br p, *J*=7.0 Hz, CH_2); ^{13}C NMR δ: 157.61 (s, NCO), 136.14, 128.57, 128.23, 127.92 (s, 2×d, 2×d, d, C_6H_5), 71.56, 71.14 (d each, 2×CHOH), 67.64 (t, COO*C*H$_2$), 63.65 (t, CH_2O), 62.17 (d, CHN), 44.90 (t, CH_2N), 33.01 (t, CH_2). Anal. calcd for $C_{14}H_{19}NO_5$: C 59.78, H 6.81, N 4.98. Found: C 59.90, H 6.79, N 4.99.

3.12. (1R,4R,5R)-N-(Benzyloxycarbonyl)-4-hydroxy-2-oxa-6-azabicyclo[3.3.0]octane **16**

Freshly distilled pyridine (0.36 ml) and *p*-toluenesulfonyl chloride (0.509 g, 2.67 mmol) were added to a solution of **15** (0.5 g, 1.78 mmol) in dry CH_2Cl_2 (5 ml) at −15°C under N_2 atmosphere. The mixture was stirred for 10 h at the same temperature, diluted with CH_2Cl_2 (10 ml) and then acidified (pH 3–4) with 1N HCl. The organic layer was washed with water, brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc:*n*-hexane 6:4) to give the azabicyclo **16** (0.24 g, 61%) as an oil; $[\alpha]_D$=−37.9 (c=1.28, MeOH); ^{1}H NMR δ: 7.40–7.30 (5H, m, C_6H_5), 5.17, 5.11 (1H each, d, *J*=12.0 Hz, COOC*H*$_2$), 4.77 (1H, q, *J*=5.0 Hz, CH_2CHOCH_2), 4.45 (1H, br t, *J*=4.5 Hz, C*H*OH), 4.14 (1H, br d, *J*=5.0 Hz, CHN), 4.01 (1H, dd, *J*=9.5 and 4.5 Hz, CH_AH_BO), 3.74 (1H, dd, *J*=9.5 and 4.0 Hz, CH_AH_BO), 3.71 (1H, m, CH_CH_DN), 3.33 (1H, dt, *J*=11.0 and 6.5 Hz, CH_CH_DN), 3.11 (1H, br s, OH), 2.07 (1H, br dd, *J*=13.0 and 6.5 Hz, CH_EH_F), 1.83 (1H, ddd, *J*=13.0, 7.0 and 2.0 Hz, CH_EH_F); ^{13}C NMR δ: 155.12 (s, NCO), 136.44, 128.54, 128.25, 127.90 (s, d×2, d, d×2, C_6H_5), 81.73 (d, CH_2CHOCH_2), 76.75 (d, CHOH), 74.31 (t, CH_2O), 70.77 (d, CHN), 67.15 (t, COOCH_2), 45.19 (t, CH_2N), 31.64 (t, CH_2). Anal. calcd for $C_{14}H_{17}NO_4$: C 63.87, H 6.51, N 5.32. Found: C 63.67, H 6.50, N 5.32.

3.13. (2R,3R)-1-(Benzyloxycarbonyl)-2-[(4R)-2,2-dimethyl-1,3-dioxolan-4-yl]-3-tert-butyldiphenylsilyloxypyrrolidine **17**

To a stirred solution of **14** (0.96 g, 3 mmol) and imidazole (0.51 g, 7.5 mmol) in dry THF (10 ml) was added *tert*-butyldiphenylsilylchloride (0.917 ml, 3.5 mmol). The mixture was stirred overnight at room temperature, then poured into 10 ml of satd brine and extracted with ethyl acetate (3×50 ml). The combined extracts were washed with water, dried over Na_2SO_4 and concentrated under reduced pressure to give crude silyl ether, which was purified by silica gel chromatography (EtOAc:*n*-hexane 5:95) to give **17** (1.65 g, 98%); $[\alpha]_D$=−7.3 (c=1.23, $CHCl_3$); ^{1}H NMR δ: 7.65 (4H, td, *J*=9.0 and 2.0 Hz, SiC_6H_5), 7.38 (6H, m, SiC_6H_5), 7.29 (5H, m, C_6H_5), 5.07, 5.03 (1H each, d, *J*=12.0 Hz, $COOCH_2$), 4.50 (1H, m, CHOSi), 4.33 (1H, dt, *J*=10.0 and 7.5 Hz, CHO), 3.93 (2H, m, CH_2O), 3.38 (1H, td, *J*=10.0 and 2.0 Hz, CH_AH_BN), 3.26 (1H, br q, *J*=10.0 Hz, CH_AH_BN), 2.22 (1H, br p, *J*=10.0 Hz, CH_CH_D), 1.75 (1H, br qd, *J*=10.0 and 2.0 Hz, CH_CH_D), 1.39, 1.31 (3H each, s, 2×Me), 1.08 (9H, s, Me_3); ^{13}C NMR δ: 153.24 (s, CO), 135.83, 135.64, 133.88, 133.60, 130.01, 129.95, 127.87, 127.73 (d×2, d×2, s, s, d, d, d×2, d×2, 2×C_6H_5), 135.93, 128.46, 127.94, 127.91 (s, d×2, d×2, d, C_6H_5), 108.74 (s, COO), 74.52, 74.35 (d each, 2×CHO), 72.43 (t, CH_2O), 67.09 (t, COOCH_2), 58.79 (d, CHN), 44.06 (t, CH_2N), 31.28 (t, CH_2), 267.03 (q, Me_3), 26.30, 26.05 (q each, 2×Me), 19.27 (s, SiC). Anal. calcd for $C_{33}H_{41}NO_5Si$: C 70.81, H 7.38, N 2.50. Found: C 71.01, H 7.36, N 2.49.

3.14. (2R,3R)-1-(Benzyloxycarbonyl)-2-[(1R)-1,2-dihydroxyethyl]-3-tert-butyldiphenylsilyloxypyrrolidine **18**

A mixture of acetonide **17** (1.12 g, 2.0 mmol) and $FeCl_3/SiO_2$[21] (60 mg) in 15 ml of $CHCl_3$ was stirred at room temperature for 16 h. After that time, the mixture was filtered, the filtrate was concentrated under reduced pressure and the residue was purified by silica gel chromatography (EtOAc:*n*-hexane 1:1) to give **18** (0.793 g, 93% based on recovery of 18% of **17**); $[\alpha]_D$=−24.8 (c=1.7, MeOH); ^{1}H NMR δ: 7.65 (4H, td, *J*=7.0 and 1.5 Hz, SiC_6H_5), 7.41 (6H, m, SiC_6H_5), 7.31 (5H, br s, C_6H_5), 5.09 (2H, s, $COOCH_2$), 4.43 (1H, dt, *J*=9.0 and 8.0 Hz, CHOSi), 4.32 (1H, ddd, *J*=7.5, 5.0 and 2.0 Hz, C*H*OH), 4.10 (1H, br s, OH), 3.94 (1H, dd, *J*=8.0 and 2.0 Hz, CHN), 3.64 (1H, dd, *J*=11.5 and 7.5 Hz, CH_AH_BO), 3.55 (1H,

dd, *J*=11.5 and 5.0 Hz, CH_AH_BO), 3.45 (1H, td, *J*=10.0 and 3.0 Hz, CH_CH_DN), 3.27 (1H, td, *J*=10.0 and 8.0 Hz, CH_CH_DN), 2.69 (1H, br s, OH), 2.11 (1H, dq, *J*=11.5 and 9.5 Hz, CH_EH_F), 1.82 (1H, dtd, *J*=11.5, 8.0 and 3.0 Hz, CH_EH_F), 1.09 (9H, s, Me_3); ^{13}C NMR δ: 157.16 (s, CO), 136.20, 128.52, 128.17, 127.89 (s, d×2, d, d×2, C_6H_5), 135.71, 135.58, 133.09, 132.40, 130.23, 130.13, 128.01, 127.84 (d×2, d×2, s, s, d, d, d×2, d×2, 2×SiC_6H_5), 72.51 (d, CHOSi), 70.66 (d, CHOH), 67.51 (t, $COOCH_2$), 63.20 (t, CH_2O), 60.0 (d, CHN), 44.08 (t, CH_2N), 32.66 (t, CH_2), 26.95 (q, 3×Me), 19.06 (s, SiC). Anal. calcd for $C_{30}H_{37}NO_5Si$: C 69.33, H 7.18, N 2.70. Found: C 69.30, H 7.19, N 2.69.

*3.15. (2*R*,3*R*)-1-(Benzyloxycarbonyl)-2-[(1*R*)-2-*p*-toluenesulfonyloxy-ethyl-1-ol]-3-*tert*-butyldiphenylsilyloxypyrrolidine **19***

To a solution of diol **18** (0.555 g, 1.065 mmol) in dry CH_2Cl_2 (3 ml) was added freshly distilled pyridine (0.213 ml) and *p*-toluenesulfonyl chloride (0.406 g, 2.13 mmol) at −5°C. The mixture was stirred at the same temperature for 10 h then diluted with CH_2Cl_2 (30 ml) and treated with 1N HCl (2×15 ml), H_2O, satd $NaHCO_3$, brine and dried over Na_2SO_4. The residue was purified by silica gel chromatography (EtOAc:*n*-hexane 3:7) to give **19** (0.618 g, 86%) as a colorless oil; $[\alpha]_D$=−20.4 (c=1.5, MeOH); ^{1}H NMR δ: 7.80 (2H, d *J*=8.0 Hz, $SO_2C_6H_4$), 7.68 (4H, dd, *J*=7.5 and 1.5 Hz, SiC_6H_5), 7.62 (4H, td, *J*=7.5 and 1.5 Hz, SiC_6H_5), 7.48 (2H, m, SiC_6H_5), 7.48–7.28 (5H, m, C_6H_5), 7.31 (2H, d, *J*=8.0 Hz, $SO_2C_6H_4$), 5.07 (2H, s, $COOCH_2$), 4.74 (1H, q, *J*=4.0 Hz, CHOSi), 4.41 (1H, q, *J*=2.0 Hz, CHO), 4.35, 4.13 (1H each, dd, *J*=12.0 and 2.0 Hz, CH_2O), 3.81 (1H, dt, *J*=11.0 and 8.5 Hz, CH_AH_BN), 3.56 (1H, dd, *J*=4.5 and 2.0 Hz, CHN), 3.43 (1H, dt *J*=11.0 and 6.0 Hz, CH_AH_BN), 2.42 (3H, s, Me), 2.05, 1.62 (1H each, tdd, *J*=9.0, 6.0 and 4.0 Hz, CH_2), 1.06 (9H, s, 3×Me); ^{13}C NMR δ: 152.44 (s, NCO), 136.10, 128.54, 128.16, 127.83 (s, d×2, d, d×2, C_6H_5), 134.79, 131.52, 129.82, 128.16 (s, s, d×2, d×2, SiC_6H_5), 135.71, 133.29, 132.18, 130.62, 130.57, 128.21, 127.96 (d×4, s, s, d, d, d×2, d×2, SiC_6H_5), 76.86 (d, CHOSi), 71.88 (d, CHO), 67.13 (t, $COOCH_2$), 62.77 (t, CH_2O), 60.88 (d, CHN), 44.94 (t, CH_2N), 32.33 (t, CH_2), 26.86 (q, Me_3), 21.65 (q, Me_3), 19.03 (s, SiC). Anal. calcd for $C_{37}H_{43}NO_7SSi$: C 65.95, H 6.43, N 2.08. Found: C 65.80, H 6.38, N 2.07.

*3.16. (2*R*,3*R*)-1-(Benzyloxycarbonyl)-2-[(1*R*)-2-cyano-ethyl-1-ol]-3-*tert*-butyldiphenylsilyloxypyrrolidine* **20**

A mixture of **19** (0.60 g, 0.9 mmol) and sodium cyanide (0.348 g, 7.2 mmol) in dry DMF (20 ml) was stirred for 4 h at 45°C. Then the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (EtOAc:*n*-hexane 4:6) to give the nitrile **20** (0.264 g, 83%); $[\alpha]_D$=−27.9 (c=0.76, MeOH); ^{1}H NMR δ: 7.67 (4H, td, *J*=7.0 and 1.5 Hz, SiC_6H_5), 7.42 (6H, m, SiC_6H_5), 7.28 (5H, br s, C_6H_5), 5.10 (2H, s, $COOCH_2$), 4.49 (1H, dt, *J*=9.0 and 7.5 Hz, CHOSi), 4.33 (1H, m, CHOH), 4.11 (1H, dd, *J*=7.5 and 2.0 Hz, CHN), 3.57 (1H, br s, OH), 3.49 (1H, td, *J*=10.0 and 3.0 Hz, CH_AH_BN), 3.36 (1H, td, *J*=10.0 and 7.5 Hz, CH_AH_BN), 2.79 (1H, dd, *J*=11.0 and 7.0 Hz, CH_CH_DCN), 2.75 (1H, dd, *J*=11.0 and 6.0 Hz, CH_CH_DCN), 2.11, 1.89 (1H each, m, CH_2); ^{13}C NMR δ: 157.44 (s, CO), 137.00, 128.45, 127.94, 127.78 (s, d×2, d, d×2, C_6H_5), 135.71, 135.48, 132.89, 132.42, 130.13, 128.09, 127.81 (d×2, d×2, s, s, d, d, d×2, d×2, 2×SiC_6H_5), 118.62 (s, CN), 74.26 (d, CHOSi), 70.55 (d, CHOH), 67.43 (t, $COOCH_2$), 60.01 (d, CHN), 45.84 (t, CH_2N), 32.88 (t, CH_2), 27.89 (t, CH_2CN), 26.91 (q, 3×Me), 19.07 (s, SiC). Anal. calcd for $C_{31}H_{36}N_2O_4Si$: C 70.42, H 6.86, N 5.30. Found: C 70.49, H 6.85, N 5.28.

3.17. (−)-Detoxinine **2**

A solution of **20** (0.2 g. 0.38 mmol) in dry EtOAc (4 ml) was hydrogenated (1 atm) in the presence of catalytic 5% Pd/C for 5 h. After that time the mixture was filtered over Celite and concentrated under reduced pressure. A solution of the above crude amine in 4N HCl was heated to 50°C and the temperature was slowly increased to 75°C over 2.5 h. After 12 h the mixture was concentrated under reduced pressure and the brown residue was purified by cation exchange chromatography (Dowex 50X8-200), eluting with 1N NH_4Cl. The residue was triturated with abs. EtOH to give (−)-**2** (45 mg, 68%). Mp 224–227°C; $[\alpha]_D$=−4.5 (c=0.4, H_2O); (lit.[7] mp 227–229°C; $[\alpha]_D^{20}$=−4.4 (c=0.5, H_2O); lit.[5c] mp 225–228°C; $[\alpha]_D^{23}$=−4.8 (c=0.5, H_2O); ^1H and ^{13}C NMR spectra as reported.[7]

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