Tetrahedron Vol 49, No 4, pp 785-802, 1993
Printed in Great Britain

0040-4020/93 $6 00+ 00

Total Synthesis of (+)-Valyldetoxinine and (–)-Detoxin D_1

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

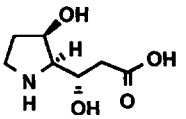
†Department of Chemistry, Ewha Womans University, Seoul 120-750, Korea
Department of Chemistry, University of Pennsylvania, Philadelphia, PA 19104-6323, USA

(*Received in USA* 18 *August* 1992, *accepted* 11 *November* 1992)

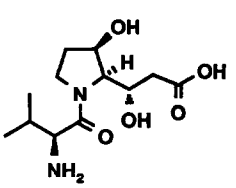
Abstract *The detoxin complex, metabolues produced by Streptomyces caespitosus var detoxicus 7072 GC_1, is a selective antagonist of the antibiotic blasticidin S Two approaches toward the total synthesis of (+)-valyldetoxinine and (–)-detoxin D_1 are described. These routes involve a 2,3-disubstituted pyrrolidine as a common intermediate and utilize glucose as the chiral precursor*

The synthesis of highly functionalized unusual amino acids, which are found as components of biologically important peptides is of great interest [1] In 1968, Yonehara and coworkers first reported the production, isolation and the biological activities of some members of the detoxin complex [2] The organism which produces the detoxins was isolated from soils and was classified as a species of *Streptomyces caespitosus* var *detoxicus* 7072 GC_1. 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 The detoxins also exhibit antimicrobial activity against some microorganisms [3,4] After several members of the detoxins were isolated and identified,[5] structure-activity relationships (SARs) were investigated by using *Bacillus cereus* as a test organism Detoxin D_1 was found to be the most active congener Valyldetoxinine, which lack an acyl phenylalanyl moiety was 5000 times less effective The parent component of the complex is a β-hydroxy-γ-amino acid, (–)-detoxinine Five research groups have reported syntheses of detoxinine[6-11] and detoxins B_1 and B_3 [12] Häusler synthesized (–)-detoxin D_1 by extending his synthesis of racemic detoxinine [13] The synthetic challenges and unique biological activities of the detoxin complex led us to investigate stereocontrolled approaches to valyldetoxinine, and detoxin D_1 [14]

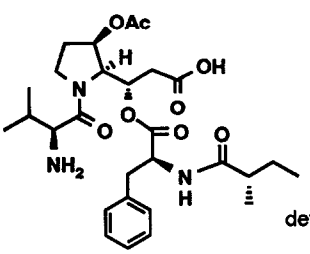
Carbohydrates are one of nature's richest sources of chirality to produce enantiomerically pure compounds They are recognized as readily available, highly functional molecules containing several asymmetric centers [15] Currently, several approaches, which employed D-glucose as the source of chirality,



detoxinine
1



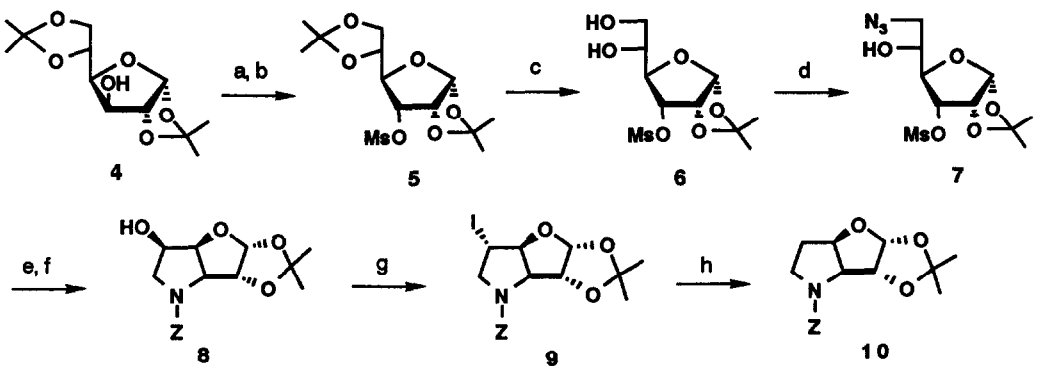
valyldetoxinine
2



detoxin D_1
3

have utilized this carbohydrate to prepare the pyrrolidinol ring.[16-19] As shown in **Scheme 1**, we constructed the pyrrolidinol ring by a modification of methodology previously employed by our group for the synthesis of 1,4-dideoxy-1,4-imino-D-lyxitol hydrogen chloride [16] The key step of this approach is the formation of the pyrrolidine ring in structure **8** *via* cyclization by attack of an amino group on a mesylate in the furanose ring The synthesis began with diacetone D-glucose (**4**), which was oxidized with pyridinium chlorochromate (PCC) in the presence of molecular sieves in CH_2Cl_2 The crude ketone was then treated with sodium borohydride in ethanol to give the α-D-allofuranose (82% yield). Treatment of this product with methanesulfonyl chloride in pyridine gave mesylate **5** (95% yield).[20,21] Subsequent mild hydrolysis using a resin selectively removed the isopropylidene group at C-5 and C-6 to afford 1,2-O-isopropylidene-3-O-methanesulfonyl-α-D-allofuranose (**6**) in 59% yield. The use of dilute aqueous sulfuric acid instead of the resin increased the yield to 74%. Conversion of the primary alcohol (**6**) into the corresponding bromide was achieved with carbon tetrabromide and triphenylphosphine in THF (94% yield). Displacement of the bromide with sodium azide in DMF afforded intermediate **7** in 96% yield Alternatively, the alcohol (**6**) was treated with carbon tetrabromide, triphenylphosphine, and lithium azide in DMF to provide the same product (**7**) in 96% [22] The azide function in **7** was reduced to a primary amine in ethanol using a catalytic amount of palladium on carbon under a hydrogen atmosphere (30 psi). Subsequent cyclization with sodium acetate and protection of the resulting secondary amine with benzyl chloroformate and triethylamine in THF afforded product **8** in 50% yield When the secondary amine was treated with sodium carbonate in a mixture of acetone and water, the yield increased to 78% overall Compound **8** was deoxygenated at C-5 *via* reductive radical cleavage of a halide Treatment of **8** with 2,4,5-triiodoimidazole (ImI_3)[23] and triphenylphosphine in refluxing toluene gave the corresponding iodide (**9**) in 99% yield with inversion of configuration Free radical reduction of the iodide with tributyltin hydride was initiated with azobis(isobutyronitrile) (AIBN) in benzene under reflux, and proceeded to completion to give compound **10** in 97% yield

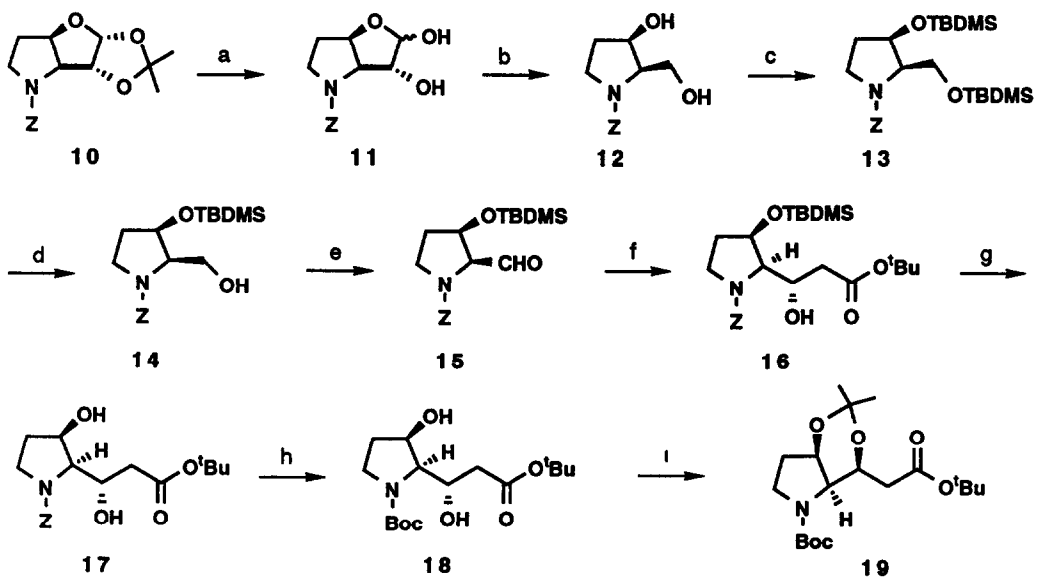
Scheme 1



[a] 1 PCC, molecular sieves, CH_2Cl_2, 2 $NaBH_4$, EtOH, 82%, [b] MsCl, Pyr , 95%, [c] Dowex 50X4-400, dioxane, MeOH, H_2O, 0 °C, 59% or $H_2SO_{4(aq)}$, 74%, [d] 1 Ph_3P, CBr_4, THF, 2 NaN_3, DMF, 90%, or Ph_3P, CBr_4, LiN_3, DMF, 96%, [e] 1 Pd/C, H_2 or Raney Ni, H_2, 2 NaOAc, EtOH, reflux, [f] benzyl chloroformate, Et_3N, THF, 50% from **7** or benzyl chloroformate, H_2O, acetone, Na_2CO_3, 78% from **7**, [g] ImI_3, imidazole, Ph_3P, toluene, 99%, [h] *n*-Bu_3SnH, benzene, AIBN, 97%

The isopropylidene group at C-1 and C-2 of **10** was hydrolyzed using an ion-exchange resin in a mixture of dioxane and water to give lactol **11** as shown in **Scheme 2.** Cleavage of the vicinal hydroxyl groups was achieved with sodium metaperiodate in dioxane and water Immediate reduction of the aldehyde function using sodium borohydride in methanol afforded the 1,3-diol **12** in 95% from **10.** Both primary and secondary hydroxyl groups of **12** were protected as their silyl ethers in 98% yield. Selective removal of the primary silyl group of the diprotected intermediate **13** was accomplished in 83% yield using aqueous acetic acid and tetrahydrofuran (THF). A modified Parikh-Doering reaction[24] using sulfur trioxide-pyridine complex, in the presence of dimethyl sulfoxide (DMSO) and triethylamine, gave the required aldehyde (**15,** 80% yield) to be used in the aldol condensation The aldehyde (**15**) was treated with the lithium salt of *tert*-butyl acetate to afford only one diastereomer (**16**) in 87% yield A series of transformations were conducted to prove the stereochemistry at the β-hydroxy center of the side chain. The β-hydroxy ester **16** was desilylated using tetrabutylammonium fluoride (TBAF) in THF to afford **17** in 98% yield The Z group was removed by a standard procedure, followed by Boc group protection to give derivative **18** in 54% yield. The resulting 1,3-diol (**18**) was ketalized using 2,2-dimethoxypropane to give intermediate **19,** previously converted to (–)-detoxinine [7,11] The physical data of compound **19** was compared with previously reported data [7,11]

Scheme 2

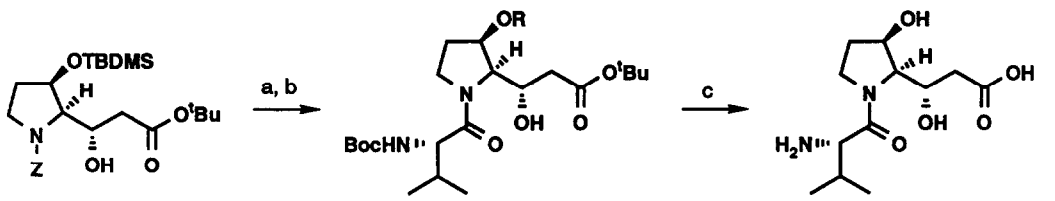


[a] Dowex 50X4-400, dioxane, H_2O, 40 °C, [b] 1 $NaIO_4$, dioxane, H_2O, 0 °C, 2 $NaBH_4$, MeOH, 0 °C to rt, 95%, [c] TBDMSCl, Im, DMF, 0 °C to rt, 98%, [d] AcOH, H_2O, THF, 0 °C to rt, 83%, [e] SO_3•Py, CH_2Cl_2, Et_3N, DMSO, 0 °C to rt, 80%, [f] $LiCH_2CO_2{}^tBu$, THF, -78 °C, 87%, [g] TBAF, THF, 0 °C, 98%, [h] 1 H_2, Pd/C, MeOH, rt, 2 $(Boc)_2O$, Et_3N, DMAP, THF, rt, 54%, [i] 2,2-dimethoxypropane, *p*-TsOH•H_2O, THF, Δ, 96%

The elaboration of the β-hydroxy ester **16** to complete the total synthesis of (+)-valyldetoxinine (**1**) is shown in **Scheme 3** Compound **16** was catalytically hydrogenated with palladium on carbon under an atmosphere of hydrogen Subsequent coupling with *tert*-butoxycarbonyl protected L-valine, in the presence of

dicyclohexylcarbodiimide and a racemization suppressing reagent, 1-hydroxybenzotriazole hydrate (HOBT), in CH_2Cl_2, produced the fully protected valyldetoxinine precursor **20** in 75% yield. Removal of the *tert*-butyldimethylsilyl group was first tried under acidic conditions (48% aqueous HF in acetonitrile). The reaction was sluggish and partial epimerization was observed. Treatment of **20** with 1.1 M tetrabutylammonium fluoride in THF ensured the formation of **21** in 3 min (96% yield). Since deprotection of both the Boc and *tert*-butyl ester groups with trifluoroacetic acid did not give satisfactory results, compound **21** was treated with dry hydrogen chloride in ethyl acetate to afford the corresponding valyldetoxinine hydrochloride in 89% yield The hydrochloride salt was purified by ion-exchange chromatography to afford (+)-valyldetoxinine (**2**) in 92% yield

Scheme 3



16 **20** R = TBDMS, **21** R = H Valyldetoxinine **2**

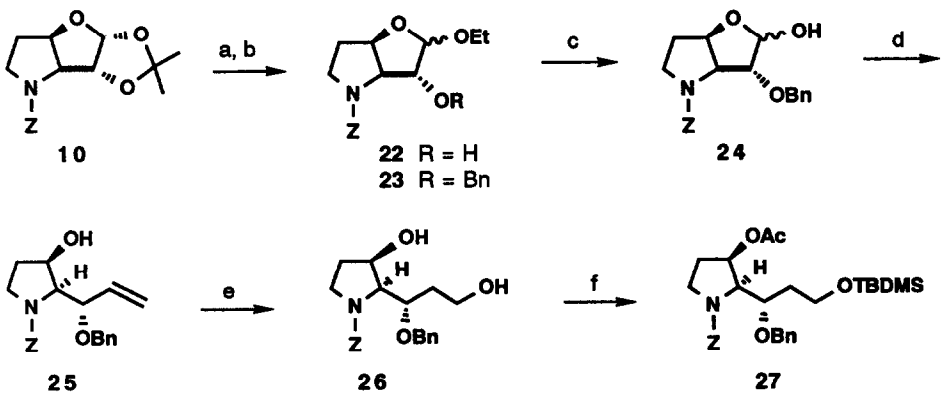
[a] 1 H_2, Pd/C, MeOH, rt, 2 Boc-L-Val-OH, DCC, HOBT, CH_2Cl_2, 0 °C to rt, 75%, [b] TBAF, THF, 0 °C, 96%, [c] 1 dry HCl, EtOAc, rt, 89%, 2 ion-exchange, 92%

The (+)-valyldetoxinine (**2**) exists as a rotameric mixture in solution To investigate the rotamer population, a variable temperature ^{13}C NMR spectroscopic study was conducted At 300 °K, two sets of ^{13}C peaks were observed in the spectrum of **2** At 335 °K the intensities of the minor peaks diminished When the temperature reached 353 °K, the intensities of the minor peaks were greatly decreased This study confirms the coexistence of rotamers of (+)-valyldetoxinine (**2**) in solution at room temperature These results agree with previous reports[5,25] on the structure determination of the detoxin complex by degradative and spectroscopic methods, in which valyldetoxinine was shown to exhibit a doubling pattern of the ^{13}C resonances due to the *syn-anti* isomerism of the amide bond

The synthesis of (–)-detoxin D_1 from intermediate **10** is summarized in Schemes **4** and **5**. To avoid elimination of the β-hydroxyl group and facilitate the subsequent esterification, we chose to mask the acid function of detoxin D_1 (**3**) as a silyl protected alcohol The synthesis of the key intermediate **27** required a one carbon chain extension from the hemiacetal in the lactol **24** The successful formation of the fully protected pyrrolidinol **27** is shown in **Scheme 4** Treatment of the protected amine **10** with ethanol in the presence of 15% HCl/Et_2O at room temperature gave the ethyl glycoside **22**, which was treated with benzyl bromide and potassium hydride to afford the benzyl ether **23** in 84% yield from **10** Hydrolysis of the ethyl glycoside **23** with aqueous TFA gave the corresponding lactol **24** in 90% yield Several attempts to generate the methyl enol ether from **24** using the Wittig reaction or Peterson olefination were unsuccessful Therefore, we decided to prepare the terminal olefin **25** To this end, lactol **24** was treated with methylenetriphenylphosphorane to afford compound **25** in 71% yield [17] Since detoxin D_1 (**3**) contains a free carboxylic acid, our first strategy

was to bring up a precursor which could be easily oxidized to an acid. Therefore, after acetylation of the secondary alcohol of **25**, direct conversion of the terminal olefin into the corresponding aldehyde was attempted using Brown's method [26,27] Unfortunately, this method gave disappointing results, thus forcing us to develop an alternate strategy. Treatment of olefin **25** with disiamylborane, followed by oxidation using 30% hydrogen peroxide and 2 N aqueous NaOH led to the 1,5-diol **26** in 83% yield. The primary alcohol of compound **26** was protected as its corresponding silyl ether using conditions for the selective protection of a primary hydroxyl group over a secondary [28] Thus, 1,5-diol **26** was transformed into the fully protected compound **27** by *tert*-butyldimethylsilylation and acetylation in one step (91% yield)

Scheme 4

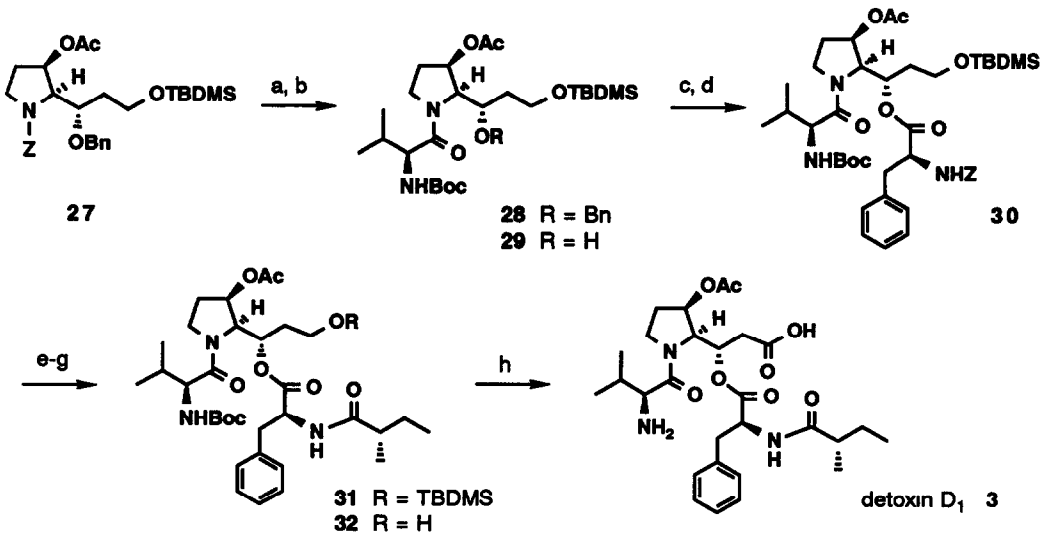


[a] EtOH, 15% HCl/Et_2O, 94%, [b] BnBr, KH, DMF, 89%, [c] TFA, H_2O, 90%, [d] $Ph_3P{=}CH_2$, THF, 71%, [e] disiamylborane, then H_2O_2, NaOH, 83%, [f] TBDMSCl, Et_3N, DMAP, CH_2Cl_2, then Ac_2O, Et_3N, 91%

The completion of the synthesis is detailed in **Scheme 5**. The elaboration of the key intermediate **27** to a protected precursor of detoxin D_1 (**3**) was carried out using appropriate peptide and ester coupling reagents. The benzoxycarbonyl protecting group of **27** was selectively removed by catalytic hydrogenolysis using Raney Ni as a catalyst under an atmosphere of hydrogen (40 psi) Coupling of the resulting secondary amine with Boc-Valine was then accomplished by using N,N-bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl) [29] A preactivation protocol gave the best yield Boc-L-Valine was treated with BOP-Cl at -15 °C, and after 20 min, the secondary amine was added to afford the coupled product **28** in 90% yield from **27** [30] Catalytic hydrogenation of the benzyl ether **28** in ethanol in the presence of palladium black, under 45 psi of hydrogen, gave the corresponding alcohol **29** With alcohol **29** in hand, a convergent approach for the synthesis of the protected precursor of detoxin D_1 (**3**) was examined Attempts to couple (S)-2-methylbutyryl-L-phenylalanine[13] with the hydroxyl group of intermediate **29**, 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 (**3**) Treatment of dipeptide **29** with Z-L-phenylalanine, in the presence of dicyclohexylcarbodiimide (DCC), a catalytic amount of 4-dimethylaminopyridine (DMAP), and 10-camphorsulfonic acid (CSA), in

Scheme 5



[a] Raney Ni, H_2, EtOAc, MeOH, [b] Boc-valine, BOP-Cl, Et_3N, CH_2Cl_2, 90%, [c] H_2, palladium black, EtOH, [d] Z-phenylalanine, DCC, DMAP, 10-camphorsulfonic acid (CSA), CH_2Cl_2, 88%, [e] Pd/C, H_2, EtOAc, MeOH, [f] (S)-2-methylbutyric acid, 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

CH_2Cl_2, afforded the depsipeptide **30** in 88% yield. Removal of the benzoxycarbonyl protecting group by catalytic hydrogenolysis, and subsequent treatment with (S)-2-methylbutyric acid in the presence of BOP reagent and N,N-diisopropylethylamine (DIEA), afforded the depsipeptide **31** in 70% yield [31] The next step was the deprotection of the *tert*-butyldimethylsilyl protecting group, which was accomplished in 99% yield by using acetic acid : THF . H_2O (3 . 1 . 1). To synthesize detoxin D_1 (**3**), the primary alcohol in depsipeptide **32** had to be oxidized to a carboxylic acid This operation was carried out in two steps The primary alcohol **32** was first converted to the aldehyde by a Swern oxidation using trifluoroacetic anhydride (TFAA) as the DMSO activator.[32] The unstable aldehyde was immediately oxidized to the carboxylic acid, using a procedure developed by Masamune for oxygen-rich molecules containing acid-sensitive groups [33] Treatment of the aldehyde with 1 M potassium permanganate in *tert*-butyl alcohol, using 5% sodium hydrogen phosphate, produced the corresponding acid, which was used directly in the subsequent TFA deprotection and ion exchange purification to give detoxin D_1 (**3**) in 70% yield Synthetic detoxin D_1 was identified by comparison of its physical data with that reported by Häusler [13]

EXPERIMENTAL[34]

General Procedure

All solvents were reagent grade and distilled before use Analytical thin-layer chromatography (TLC) was performed on Merck silica gel (60 F 254) plates (0 25 mm) Visualization was effected with ultraviolet light or any of the following reagents ninhydrin, phosphomolybdic acid, 2,4-dinitrophenylhydrazine,

anisaldehyde, potassium permanganate. Chromatography was carried out on Merck silica gel 60 (particle size 240-400 mesh). Melting points (mp) were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected ^1H and ^{13}C NMR spectra were recorded on a Brucker/IBM AC-250 (250 MHz) or a Bruker AMX–500 (500 MHz) spectrometer Chemical shifts were measured in parts per million (δ) relative to tetramethylsilane (TMS) or chloroform as the internal standard 3-(Trimethylsilyl)-1-propane sulfonic acid sodium salt hydrate was the internal standard for deuterium oxide Coupling constants (J values) are in Hertz (Hz) Multiplicities are designated as singlet (s), broad singlet (br s), doublet (d), triplet (t), quartet (q), and multiplet (m) Infrared spectra (IR) were obtained on a Perkin-Elmer Model 281-B spectrometer Absorptions are reported in wave numbers (cm^{-1}), and their intensities are designated as strong (s), medium (m), weak (w), and broad (br) The spectra are calibrated against the 1601 cm^{-1} band of a polystyrene film. Optical rotations (in degrees, °) were recorded on a Perkin-Elmer Model 241 polarimeter at the sodium D line Concentration were reported in g/100 ml High resolution mass spectra (HRMS) were obtained on either a VG 70-70 HS or a VG ZAB-E, using either ammonia Chemical Ionization (CI) or Fast Atom Bombardment (FAB) The mass spectrometers were interfaced to VG/DEC 11-73 data systems

1,2-O-Isopropylidene-3-O-methanesulfonyl-α-D-allofuranose (6).

Compound **5** (17 80 g, 52 66 mmol) was dissolved in methanol (120 mL) and dioxane (100 mL) at ambient temperature Additional dioxane (20 mL) was added to the mixture to dissolve all solids, followed by 0 8% aqueous H_2SO_4 solution (240 mL) The mixture was stirred for 23 h at ambient temperature, and then concentrated after neutralization with saturated sodium carbonate (Na_2CO_3) solution The aqueous material was extracted with ethyl acetate (5 × 100 mL) The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated The residue was purified by silica gel flash-column chromatography to afford compound **6** as white crystals (11 54 g, 74% yield) [16] TLC (EtOAc) R_f 0.45, mp 96-97 °C, $[\alpha]_D^{22}$ +99 3 (*c* 0 61, $CHCl_3$), ^{13}C NMR ($CDCl_3$) δ 26 6, 26 7, 38 8, 62 7, 71 2, 75 8, 77.6, 77 8, 104.1, 113 8

6-Azido-6-deoxy-1,2-O-isopropylidene-3-O-methanesulfonyl-α-D-allofuranose (7).

Carbon tetrabromide (CBr_4, 6 670 g, 20 11 mmol) was added to a solution of compound **6** (5 000 g, 16 67 mmol) in THF (50 mL) at ambient temperature, under an atmosphere of nitrogen The mixture was cooled to -15 °C and triphenylphosphine was added in portions over a period of 10 min. The mixture was then warmed to ambient temperature After 3 h, carbon tetrabromide (0 5559 g, 1 676 mmol) and triphenylphosphine (2 198 g, 8 381 mmol) were added again and the mixture was stirred for 8 h The precipitate formed was removed by filtration and the filtrate was washed with saturated NaCl solution The organic layer was dried over anhydrous Na_2SO_4, evaporated, and the residue purified by silica gel flash-column chromatography using ether petroleum ether (1 2, 1 1, 2 1) as eluants to afford the bromide as white crystals (5 688 g, 94% yield) TLC (EtOAc petroleum ether, 1 2) R_f 0 32, mp 90-92 °C, $[\alpha]_D^{22}$ +74 0° (*c* 1 59, $CHCl_3$), IR ($CHCl_3$) 3580(w), 3030(w), 3000(m), 2940(w), 2910(w), 1465(w), 1410(w), 1370(s), 1230(m), 1180(s), 1165(s), 1120(s), 1080(m), 1050(s), 1020(s), 970(s), 870(s), 835(s) cm^{-1}, ^1H NMR ($CDCl_3$) δ 1 38 (3H, s) 1 59 (3H, s), 2 60 (1H, d, J 4 8 Hz), 3 16 (3H, s), 3 51 (1H, dd, J^1 10 7 Hz, J^2 7 2 Hz), 3 61 (1H, dd, J^1 10 7 Hz, J^2 4 0 Hz), 4 03 (1H, m), 4 21 (1H, dd, J^1 8 3 Hz, J^2 5 3 Hz), 4 81 (1H, m), 4 88 (1H, dd, J^1 8 3 Hz, J^2 4 8 Hz), 5 82 (1H, d, J 3 6 Hz), ^{13}C NMR ($CDCl_3$) δ 26 7, 26 7, 34 6, 38 8, 71 2, 76 3, 77 5, 77 9, 104 0, 113 9, HRMS calcd for $C_{10}H_{17}BrO_7S$ ($M+NH_4$) 378 0222, found 378 0243 To a solution of the above bromide (1 00 g, 2 77 mmol) in DMF (10 0 mL) was added sodium azide (NaN_3, 0 450 g, 6 92 mmol) The suspension was warmed to 45 °C and stirred for 8 h under an argon atmosphere The reaction mixture was diluted with ethyl acetate (10 mL) followed by successive washings of saturated NaCl solution (5 mL) and NH_4Cl (5 mL) The organic layer was dried over anhydrous Na_2SO_4 and concentrated The remaining DMF was then removed by distillation *in vacuo* The residue (yellow oil) was purified by silica gel flash-column chromatography using ether petroleum ether (1 1, 3 1, 4 1) as eluants to give compound **7** as a

colorless viscous oil (0 860 g, 96%):[16] TLC (EtOAc. petroleum ether, 1 2) R_f 0 32, ^{13}C NMR ($CDCl_3$) δ 26 5, 26 6, 38 7, 52 5, 70.1, 75.6, 77.4, 77.7, 103.9, 113.7.

N-Benzyloxycarbonyl-3,6-dideoxy-3,6-imino-1,2-O-isopropylidene-α-D-glucofuranose (8).

Compound 7 (3 18 g, 9 84 mmol) was dissolved in ethyl acetate (26 mL) Raney nickel (1 27 g) in methanol (26 mL) was added to the reaction flask. The reaction mixture was stirred at ambient temperature under a slight positive pressure of hydrogen for 24 h. The Raney nickel catalyst was removed by filtration and washed with methanol After the solvent was evaporated, the remaining water was removed by azeotropic distillation with acetonitrile The residue was dissolved in absolute ethanol (44 mL) Sodium acetate (0 96 g, 8 85 mmol) was added to the solution which was then refluxed for 15 h. After the solvent was evaporated, the remaining water was removed by azeotropic distillation with acetonitrile, and the product was then dissolved in acetone water (17 5 mL : 4.4 mL) under an argon atmosphere. After the reaction mixture was cooled to -10 °C, benzyl chloroformate (1.40 mL, 9.83 mmol) was added and the reaction mixture was stirred for another hour After the addition of sodium carbonate (0.62 g, 5 9 mmol), the temperature was increased to 0 °C After 2 h, the reaction mixture was filtered and concentrated. The residue was dissolved in ethyl acetate (250 mL) and this solution was washed consecutively with 10% citric acid (2 × 10 mL), 5% $NaHCO_3$ (10 mL), and saturated NaCl solution (15 mL) The organic layer was dried (Na_2SO_4) and the organic solvent was removed. The crude product was purified by flash silica gel chromatography using ethyl acetate/petroleum ether (2 5) as eluant to give 2 56 g (78% yield) of compound **8** as a white foam.[16] TLC (EtOAc petroleum ether, 1 1) R_f 0.26; ^{13}C NMR ($CDCl_3$) δ 26 6, 26 7, 27 2, 50.1, 65 3, 65 5, 67 3, 70 4, 70.8 81.7, 82 5, 84 2, 85 3, 106 1, 112 8, 128 0, 128 1, 128 2, 128 5, 136 2, 136 3, 154 1, 154 5

N-Benzyloxycarbonyl-3,6-imino-5-iodo-1,2-O-isopropylidene-3,5,6-trideoxy-α-D-glucofuranose (9).

To a solution of compound **8** (2 14 g, 6 38 mmol) in dry toluene (120 mL) was added triphenylphosphine (Ph_3P, 3 35 g, 12 7 mmol) and triiodoimidazole [ImI_3, 2 86 g, 6 38 mmol] The yellow solution was refluxed under an argon atmosphere for 2 h Additional Ph_3P (1 67 g, 6.38 mmol) and ImI_3 (1 43 g, 3 19 mmol) were added and the reaction refluxed for another 2 h The reaction mixture was cooled, diluted with toluene (120 mL) and stirred vigorously with saturated $NaHCO_3$ (120 mL) Iodine (I_2) was added to the reaction mixture until the dark yellow color in toluene persisted Excess I_2 was reduced by sodium thiosulfate and the two layers were separated. The organic layer was washed with saturated NaCl solution (100 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure The residue was purified by silica gel flash-column chromatography (petroleum ether ether, 3 1) to afford compound **9** as white crystals (2 81 g, 99% yield) TLC (EtOAc petroleum ether, 1 3) R_f 0 58, mp 83-84 °C, $[\alpha]_D^{24}$ -54.8° (*c* 0 87, $CHCl_3$), IR (KBr) 3050(w), 3020(w), 2980(w), 2940(w), 2860(w), 1715(s), 1580(w), 1495(w), 1460(m), 1410(s), 1380(m), 1370(m), 1360(s), 1335(m), 1305(m), 1285(m), 1255(m), 1210(s), 1180(m), 1150(m), 1140(m), 1115(s), 1085(s), 1040(m), 1010(s), 970(m), 950(w), 905(m), 885(w), 825(w), 800(w), 740(m), 730(m), 690(m) cm^{-1}, ^1H NMR ($CDCl_3$) δ 1 30 (1 31) (3H, s), 1 51 (1 52) (3H, s), 3.90 (3 94) (1H, dd, J^1 4 3 Hz, J^2 13 2 Hz), 3 98 (4 06) (1H, d, J 13.2 Hz), 4 08 (1H, m), 4 67 (4 85) (1H, d, J 3 4 Hz), 4 70 (1H, d, J 3 6 Hz), 5 06, 5 08 (1H, d, J 3 6 Hz), 5 18-5 29 (2H, m), 5 83 (5 84) (1H, d, J 3 5 Hz), 7 32-7 41 (5H, m), ^{13}C NMR ($CDCl_3$) δ 22 2, 22 5, 26.5, 26 6, 27.3, 55 5, 55 6, 65 7, 66 1, 67 4, 82 8, 83 7, 88 8, 89 8, 106 9, 106 9, 112 8, 127 7, 127 9, 128.1, 128.2, 128.6, 136 2, 136 4, 154 6, 154 7, HRMS calcd for $C_{17}H_{20}INO_5$ (M) 445 038, found 445 039 The ^1H value in parentheses are for the rotamers

N-Benzyloxycarbonyl-3,6-imino-1,2-O-isopropylidene-3,5,6-trideoxy-α-D-glucofuranose (10).

Tributyltin hydride (17 9 g, 16 6 mL, 61 5 mmol) and AIBN (0 461 g, 3 39 g) were added to dry

benzene (200 mL) The system was flushed with argon and the clear solution brought to reflux A solution of iodide **9** (13.7 g, 30.8 mmol) in dry benzene (300 mL) was then added. The reaction mixture was refluxed for 3 h under an argon atmosphere followed by removal of the solvent The residue was purified by silica gel flash-column chromatography to give compound **10** as a white solid (9.50 g, 97% yield)· TLC (EtOAc petroleum ether, 1·3) R_f 0 33, mp 84-85 °C, lit.[17] mp 88-89 °C; $[\alpha]_D^{22}$ -64.1° (*c* 0.39, $CHCl_3$), lit [17] $[\alpha]_D^{20}$ -62 8° ($CHCl_3$), ^{13}C NMR ($CDCl_3$) δ 26.5, 26.6, 27 1, 30 0, 30.3, 45.2, 45.5, 67.0, 67.3, 67 7, 82 3, 83.2, 83.4, 84.6, 106 1, 111 8, 127.9, 128.0, 128.1, 128.5, 136.5, 136 6, 154.4, 154.7.

N-Benzyloxycarbonyl-3,6-imino-3,5,6-trideoxy-α-D-glucofuranose (11).

To a solution of compound **10** (9 50 g, 29 5 mmol) in dioxane (350 mL) and water (350 mL) was added freshly activated Dowex 50X4-400 ion-exchange resin (H^+, 95 g) The reaction mixture was warmed to 40 °C and stirred for 48 h The resin was removed by filtration, washed thoroughly with water and ethyl acetate The combined solvents were removed *in vacuo* and the remaining water was removed by azeotropic distillation with toluene The crude diol **11** (oil) was subjected to the next step without further purification TLC (EtOAc) R_f 0 52, $[\alpha]_D^{24}$ -91.9° (*c* 0 54, $CHCl_3$), IR ($CHCl_3$) 3400(br), 3100(w), 3040(w), 3020(w), 2990(w), 2980(m), 2900(w), 1690(s), 1585(w), 1540(w), 1500(w), 1450(s), 1420(s), 1350(s), 1235(m), 1185(m), 1115(s), 1040(s), 1010(s), 960(m), 910(m), 840(w), 680(w), 645(w) cm^{-1}, ^1H NMR ($CDCl_3$) δ 1 82-1 93 (1H, m), 2 00-2 10 (1H, m), 3 32-3 77 (3H, m), 3 99-4 50 (2H, m), 4.15 (1H, m), 4 91-4 95 (1H, m), 5 05-5 39 (2H, m), 5 38 (1H, m), 7 30-7 41 (5H, m), ^{13}C NMR ($CDCl_3$) δ 31 0, 45 1, 67 4, 68 9, 75 9, 79 9, 98 3, 127 9, 128 2, 128 5, 136 2, 155 3 (only peaks correspond to the major isomer are shown for clarity), HRMS calcd for $C_{14}H_{18}NO_5$ (M + H) 280 1185, found 280 1194

(2R,3R)-N-Benzyloxycarbonyl-3-hydroxy-2-hydroxymethylpyrrolidine (12).

Sodium periodate (15 9 g, 74 4 mmol) was added to a solution of crude diol **11** in dioxane (90 mL) and water (270 mL) at 0 °C The mixture was stirred for 3.5 h at 0 °C The reaction mixture was diluted with ether (150 mL), the layers separated, and the aqueous layer extracted with ether (3 × 150 mL) The combined organic layers were washed with saturated NaCl solution (200 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and the remaining water was removed by azeotropic distillation with toluene The resulting crude aldehyde was dissolved in methanol (300 mL) and the solution cooled to 0 °C Sodium borohydride (2 36 g, 62 5 mmol) was added slowly to the reaction mixture and the solution warmed to ambient temperature and stirred for 10 h The reaction mixture was diluted with saturated NaCl solution (200 mL), concentrated, and acidified to pH 4 with 1 N HCl, and extracted with ethyl acetate (3 × 200 mL) The combined organic layers were dried over Na_2SO_4, the solvent concentrated, and the residue purified by silica gel flash-column chromatography using EtOAc as an eluant to afford 7 10 g (95% yield for three steps from **10**) of product **12** as a colorless oil TLC (EtOAc) R_f 0 34, $[\alpha]_D^{22}$ -49 2° (*c* 0 56, $CHCl_3$), IR ($CHCl_3$) 3400(br), 3100(w), 3080(w), 3040(w), 3000(m), 2990(m), 2980(m), 2900(m), 1700(s), 1590(w), 1550(w), 1500(m), 1450(s), 1420(s), 1360(s), 1340(s), 1230(m), 1180(m), 1170(m), 1120(s), 1080(s), 1070(s), 1040(m), 990(m), 960(w), 910(w) cm^{-1}, ^1H NMR ($CDCl_3$) δ 1 89-2 04 (2H, m), 3 41 (2H, m), 3 51 (2H, m), 3 88 (2H, m), 3 98 (1H, m), 4 50 (1H, m), 5 13 (1H, m), 7 30-7 37 (5H, m), ^{13}C NMR ($CDCl_3$) δ 32 3, 32 9, 44 5, 44 7, 59 9, 61 5, 61 9, 62 7, 67 1, 72 5, 73 0, 127 9, 128 1, 128 5, 136 4, 155 2, 156 1, HRMS calcd for $C_{13}H_{17}NO_4$ (M) 251 1153, found 251 1125

(2R,3R)-N-Benzyloxycarbonyl-3-[(1,1-dimethylethyl)dimethylsilyl]oxy-2-[(1,1-dimethylethyl)dimethylsilyl]oxymethylpyrrolidine (13).

To a solution of diol **12** (7 100 g, 28 25 mmol) in dry DMF (170 mL), at 0 °C and under an atmosphere of argon, was added imidazole (13 46 g, 197 8 mmol) After the reagents were dissolved, *tert*-butyldimethylsilyl chloride (12 78 g, 84 76 mmol) was added The reaction was stirred for 30 min at 0 °C and

allowed to warm to room temperature. After 3 h, the reaction was diluted with ether (170 mL). The mixture was washed with saturated NaCl (170 mL), 5% HCl (2 × 45 mL), 5% $NaHCO_3$ (45 mL) and saturated NaCl (45 mL). The organic layer was dried (Na_2SO_4) and concentrated. The resulting crude product was purified using silica gel flash-column chromatography eluting with ethyl acetate petroleum ether (5·95) Pure **13** was obtained as a colorless oil (13.26 g, 98% yield): TLC (EtOAc.petroleum ether, 1 19) R_f 0 33; $[\alpha]_D^{22}$ -31 6° (*c* 1 53, $CHCl_3$), IR ($CHCl_3$) 3000(w), 2960(s), 2930(s), 2890(m), 2860(m), 1690(s), 1495(w), 1470(m), 1460(m), 1420(m), 1375(w), 1360(m), 1325(m), 1300(w), 1280(w), 1250(m), 1180(w), 1130(m), 1120(s), 1090(s), 1055(m), 1010(m), 1000(m), 935(w), 890(m), 870(m), 830(s) cm^{-1}; ^1H NMR ($CDCl_3$) δ -0 07-0.03 (6H, m), 0 67 (9H, s), 0.85 (9H, d, J 13.7 Hz), 0.89 (9H, s), 1 62 (1H, m), 2.08 (1H, m), 3 40-3 52 (2H, m), 3.74 (1H, m), 3.90 (2H, m), 4 35 (1H, m), 5 08-5.19 (2H, m), 7.30-7.37 (5H, m); ^{13}C NMR ($CDCl_3$) δ -5 6, -5.1, -4 8, 18.0, 18 1, 25.7, 25.8, 32 1, 32 8, 44 2, 44 4, 59.0, 59 9, 61 0, 61 4, 66 5, 66 8, 71 2, 71.8, 127.7, 127 8, 128 0, 128 2, 128 4, 136 9, 137 1, 154 9, 155 2, HRMS calcd for $C_{25}H_{46}NO_4Si_2$ (M + H) 479 2965, found. 480.2973

(2R,3R)-N-Benzyloxycarbonyl-3-[(1,1-dimethylethyl)dimethylsilyl]oxy-2-hydroxymethyl-pyrrolidine (14).

To a solution of compound **13** (9 00 g, 18 8 mmol) in THF (38 mL) at 0 °C were added water (38 mL) and acetic acid (114 mL). The reaction was stirred for 2 h at 0 °C and allowed to warm to room temperature After 10 h, the reaction was concentrated under reduced pressure. The excess water was removed by azeotropic distillation with toluene. The crude product was purified by silica gel flash-column chromatography eluting with ether:petroleum ether (1.6, 1:3). Pure **14** was obtained as a colorless oil (5.79 g, 83% yield) TLC (EtOAc·petroleum ether, 1:5) R_f 0.27, $[\alpha]_D^{23}$ -35.8° (*c* 0.84, $CHCl_3$), IR ($CHCl_3$) 3100(w), 3000(w), 2960(s), 2940(s), 2900(m), 2860(m), 1810(w), 1680(s), 1500(w), 1470(m), 1460(m), 1430(s), 1390(w), 1360(s), 1340(m), 1310(w), 1260(m), 1180(m), 1130(s), 1090(m), 1060(m), 1000(m), 940(w), 910(w), 840(s) cm^{-1}, ^1H NMR (DMSO-d_6, 340 °K) δ 0 08 (9H, s), 0 88 (9H, s), 1 88 (1H, m), 1 94 (1H, m), 3 36-3.41 (2H, m), 3.61-3 71 (3H, m), 4.04 (1H, br s), 4 42 (1H, m), 5.04-5.11 (2H, m), 7 28-7 36 (5H, m), ^{13}C NMR ($CDCl_3$) δ -5.2, -4 7, 17 9, 25 7, 31 8, 33.2, 43.8, 44 5, 62 1, 63 4, 63 8, 67 2, 73 0, 73 7, 127 9, 128 1, 128 5, 136 5, 156 5, HRMS calcd for $C_{19}H_{32}NO_4Si$ (M + H) 366 2101, found 366 2094

(2S,3R)-N-Benzyloxycarbonyl-3-[(1,1-dimethylethyl)dimethylsilyl]oxy-2-prolinal (15).

To a solution of compound **14** (2.20 g, 6 02 mmol) in dichloromethane (30 mL), at 0 °C and under an argon atmosphere, were added triethylamine (4 87 g, 6 71 mL) and DMSO (3 39 g, 3 08 mL) After the addition of sulfur trioxide-pyridine complex, the reaction was allowed to warm to room temperature and stirred for 6 h The reaction mixture was treated with ether (120 mL) and saturated NaCl solution (30 mL) The organic layer was separated, washed successively with 5% HCl (30 mL), saturated NaCl (30 mL), 5% $NaHCO_3$ (30 mL), and saturated NaCl solution (30 mL) The resulting organic layer was dried (Na_2SO_4) and concentrated under reduced pressure The crude material was purified by silica gel flash-column chromatography eluting with petroleum ether ether (6 1) Pure aldehyde **15** (1 74 g, 80% yield) was obtained as a colorless oil which solidified upon refrigeration TLC (EtOAc petroleum ether, 1 4) R_f 0 44, $[\alpha]_D^{22}$ -73 5° (*c* 0 82, $CHCl_3$), IR ($CHCl_3$) 3020(w), 3000(w), 2950(m), 2920(m), 2900(w), 2850(m), 1735(s), 1700(s), 1490(w), 1460(m), 1450(m), 1415(s), 1355(s), 1290(w), 1250(m), 1180(w), 1110(s), 1080(m), 1045(s), 990(m), 930(w), 920(w), 890(w), 830(s) cm^{-1}, ^1H NMR ($CDCl_3$) δ 0 04 (0 06) (3H, s), 0 85 (0 86) (3H, s), 1 87-2 00 (2H, m), 3 64-3 77 (2H, m), 4 11 (4 19) (1H, dd, J^1 2 8 Hz, J^2 5 5 Hz), 4 70 (1H, m), 5 11-5 21 (2H, m), 7 27-7 40 (5H, m) 9 44 (9 52) (1H, d, J 2 8 Hz), ^{13}C NMR ($CDCl_3$) δ -5 4, -5 3, -4 8, 17 9, 25 5, 25 5, 33 8, 34 4, 44 6, 45 2, 67 3, 68 7, 68 9, 74 2, 75 3, 128 0, 128 0, 128 1, 128 5, 136 1, 136 4, 154 5, 155 3, 200 4, 200 5, HRMS calcd for $C_{19}H_{33}N_2O_4Si$ (M + NH_4) 381 2209, found 381 2219

The ^1H value in parentheses are for the rotamers.

***tert*-Butyl (3S)-3-[(2R,3R)-1-benzyloxycarbonyl-3-[(*tert*-butyldimethylsilyl)oxy]-2-pyrrolidinyl]-3-hydroxypropionate (16).**

To a solution of aldehyde **15** (1 50 g, 4.12 mmol) in THF (10 mL) was added a solution of lithio *tert*-butyl acetate (1.26 g, 10.3 mmol) in THF (10 mL) dropwise at -78 °C in a dry ice-acetone bath, under an argon atmosphere and the reaction mixture was stirred for 20 min. Saturated NaCl solution (20 mL) was added to the mixture, and the organic phase was washed with 5% HCl (10 mL), saturated NaCl (10 mL), 5% $NaHCO_3$ (10 mL), and saturated NaCl (10 mL) solution, successively. The organic layer was dried (Na_2SO_4) and concentrated The residue was purified using silica gel flash-column chromatography eluting with ether petroleum ether (1 5, 1 4, 1 3) Pure compound **16** (1 71 g, 87% yield) was obtained as a colorless oil TLC (EtOAc:petroleum ether, 1:4) R_f 0 40; $[\alpha]_D^{22}$ -35.8° (*c* 0.55, $CHCl_3$); IR ($CHCl_3$) 3520(w), 3030(w), 3000(w), 2980(m), 2960(m), 2900(m), 2860(m), 1700(s), 1495(w), 1470(m), 1460(m), 1450(m), 1410(s), 1395(m), 1370(s), 1360(s), 1345(m), 1310(m), 1260(s), 1155(s), 1120(s), 1085(s), 1005(m), 900(m), 835(s) cm^{-1}, ^1H NMR ($CDCl_3$) δ 0 10 (3H, s), 0.11 (3H, s), 0 91 (9H, s), 1 45 (9H, s), 2 06 (2H, m), 2 48 (1H, dd, J^1 9 5 Hz, J^2 15 7 Hz), 2 65 (1H, d, J 15 1 Hz), 3.32 (1H, br s), 3 52 (2H, m), 3 91 (1H, m), 4 41 (2H, m), 5 13 (1H, dd, J^1 12 5 Hz, J^2 23 1 Hz), 7.30-7 37 (5H, m); ^{13}C NMR ($CDCl_3$) δ -5 1, -4 7, 18 0, 25.7, 28 1, 32 4, 33 1, 40 5, 40 8, 44 2, 61 3, 62 8, 67 1, 68 5, 72 1, 72 8, 80.4, 127 6, 128 0, 128 5, 136 6, 156 6, 171 6, HRMS calcd for $C_{25}H_{42}NO_6Si$ (M + H) 480 2781, found 480 2845

***tert*-Butyl (3S)-3-[(2S,3R)-1-benzyloxycarbonyl-3-hydroxy-2-pyrrolidinyl]-3-hydroxypropionate (17)**

A mixture of compound **16** (0 300 g, 0 625 mmol) and 1.1 M *n*-tetrabutylammonium fluoride (1 02 mL, 1 13 mmol) in THF (6 3 mL) was stirred at 0 °C for 10 min After addition of a saturated NaCl solution (7 mL), the mixture was extracted with ethyl acetate (3 × 7 mL) The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure The crude product was purified by silica gel flash-column chromatography using ethyl acetate.petroleum ether (1 2, 2 1) as eluants to give **17** (0.223 g, 98% yield) as a colorless oil TLC (EtOAc·petroleum ether, 1·1) R_f 0.36; $[\alpha]_D^{22}$ -59 4 (*c* 0 66, $CHCl_3$), IR ($CHCl_3$) 3510(br), 2990(w), 2930(w), 1685(s), 1475(w), 1450(w), 1390(s), 1370(s), 1340(m), 1300(w), 1280(w), 1245(m), 1150(s), 1120(m), 1070(m), 1000(w), 965(w), 885(w), 835(w) cm^{-1}, ^1H NMR ($CDCl_3$) δ 1 46 (9H, s), 1 66 (1H, m), 2 04 (1H, m), 2.55-2 69 (2H, m), 3 02 (1H, br s), 4 14 (1H, br s), 3 53 (2H, m), 3 98 (1H, dd, J^1 3 6 Hz, J^2 7 2 Hz), 4 46 (2H, m), 5 08-5 17 (2H, m), 7 32-7 37 (5H, m), HRMS calcd for $C_{19}H_{28}NO_6$ (M + H) 366 1916, found 366 1941

***tert*-Butyl (3S)-3-[(2S,3R)-1-*tert*-butoxycarbonyl-3-hydroxy-2-pyrrolidinyl]-3-hydroxypropionate (18).**

To a solution of compound **17** (0 208 g, 0 569 mmol) in methanol (8 mL) was added 10% palladium on carbon (0 0200 g), and the solution flushed three times with hydrogen gas The reaction mixture was shaken for 3 h at ambient temperature, under a hydrogen atmosphere in a Parr hydrogenator (40 psi) The catalyst was removed by filtration over Celite and washed thoroughly with methanol The solution was concentrated, and the resulting secondary amine was subjected to the next step without further purification To a solution of the secondary amine in THF (6 mL) were added triethylamine (0 087 mL, 0 0634 g, 0 636 mmol) and di-*tert*-butyldicarbonate (0 149 g, 0 683 mmol), followed by 4-dimethylaminopyridine (0 0139 g, 0 114 mmol) at ambient temperature, under an argon atmosphere The mixture was stirred for 2 h under the same conditions, and then concentrated The residue was purified by silica gel flash-column chromatography eluting with ethyl acetate petroleum ether (1 2, 1 1) to afford compound **18** (0 102 g, 54% yield) as a white solid TLC (EtOAc petroleum ether, 1 1) R_f 0 42, mp 97-98 °C, lit [11] mp 122-123 °C, $[\alpha]_D^{22}$ -57 5° (*c* 0 47, $CHCl_3$), lit [11]

$[\alpha]_D^{26}$ -53 0° (*c* 3 44, $CHCl_3$).

***tert*-Butyl[4S-(4α,4aα,7aα)]-5-(*tert*-butoxycarbonyl)-hexahydro-2,2-dimethyl-1,3-dioxino-[5,4-*b*]pyrrole-4-acetate (19).**

To a solution of compound **18** (0 0150 g, 0.0452 mmol) in THF (1 mL) were added dry 2,2-dimethoxypropane (0.0556 mL, 0.0471 g, 0.452 mmol), *p*-toluenesulfonic acid (0 0017 g, 0.0090 mmol), and freshly activated 3 Å molecular sieves. The reaction mixture was brought to reflux for 1 5 h, under an argon atmosphere After evaporation of the solvent, the residue was purified by silica gel flash-column chromatography eluting with ether·petroleum ether (1:4) to afford compound **19** (0 0161 g, 96% yield) as a white solid· TLC (EtOAc:petroleum ether, 1:5) R_f 0.41; mp 92-93 °C, lit.[7] 90-91 °C, lit.[11] 90-90 5 °C, $[\alpha]_D^{22}$ -97 5° (*c* 0 49, $CHCl_3$), lit.[7] -100.0° (*c* 1 8, $CHCl_3$), lit.[11] -103 0° (*c* 2.23, $CHCl_3$)

***tert*-Butyl (3S)-3-[(2R,3R)-1-[N-(*tert*-butoxycarbonyl)-L-valyl]-3-[(*tert*-butyldimethylsilyl)oxy]-2-pyrrolidinyl]-3-hydroxypropionate (20).**

To a solution of compound **16** (0 5300 g, 1.105 mmol) in methanol (11 mL) was added 10% palladium on carbon (0 0530 g), and the solution flushed with hydrogen gas The reaction mixture was shaken for 2 5 h at ambient temperature, under a hydrogen atmosphere in a Parr hydrogenator (45 psi). The catalyst was removed by filtration through Celite and washed thoroughly with methanol The filtrate was concentrated to afford the crude amine which was azeotropically dried with toluene (2 × 10 mL). To a stirred solution of the amine in CH_2Cl_2 (11 mL) at 0 °C in an ice bath was added sequentially Boc-L-valine (0 2880 g, 1.326 mmol), 1-hydroxybenzotriazole hydrate (0 1886 g, 1.381 mmol), and dicyclohexylcarbodiimide (0.2745 g, 1 326 mmol), under an argon atmosphere The reaction mixture was stirred at 0 °C for 1 h and at ambient temperature for 8 h. After filtration of the precipitated urea, followed by washing with ethyl acetate (3 × 20 mL), the filtrate was washed sequentially with saturated NaCl (10 mL), 5% HCl (10 mL), 5% $NaHCO_3$ (10 mL), and then saturated NaCl (10 mL) solution. The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by silica gel flash-column chromatography using ethyl acetate:petroleum ether (9:1, 6.1, 4 1) to afford compound **20** (0 4487 g, 75% yield) as a white foam: TLC (EtOAc·petroleum ether, 1 2) R_f 0 62, $[\alpha]_D^{22}$ -37 66° (*c* 0 47, $CHCl_3$), IR ($CHCl_3$). 3440(w), 2990(m), 2960(m), 2940(m), 2900(w), 2860(w), 1725(s), 1710(s), 1640(m), 1500(m), 1460(m), 1455(m), 1425(m), 1390(m), 1370(s), 1310(w), 1255(m), 1155(s), 1035(w), 1015(w), 1000(w), 895(w), 835(m) cm^{-1}, ^1H NMR ($CDCl_3$) δ 0 087, 0 094(6H, s), 0 89 (3H, s), 0 91 (d, 3H, J 6 7 Hz), 1 00 (d, 3H, J 6 8 Hz), 1 40, 1 43 (s, 18H), 1 99 (1H, dt, J^1 6 8 Hz, J^2 13 3 Hz), 2 09 (1H, d), 2 36 (1H, dd, J^1 9 5 Hz, J^2 15 9 Hz), 2 59 (1H, dd, J^1 3 2 Hz, J^2 15 9 Hz), 3 63 (1H, m), 3 72 (1H, m), 4 21 (1H, dd, J^1 4 6 Hz, J^2 6 8 Hz), 4 31-4.39 (3H, m), 5.22 (1H, d, J 9 3 Hz), ^{13}C NMR ($CDCl_3$) δ -5 1, -4 7, 17 1, 17 9, 19 6, 25 7, 28 1, 28 3, 31 4, 33 3, 41 2, 45 1, 56 4, 62 1, 68 3, 71 3, 79 4, 80 4, 155 9, 171 3, 173 4, HRMS calcd for $C_{19}H_{28}NO_6$ (M + H) 545 3622, found 545 3683

***tert*-Butyl (3S)-3-[(2S,3R)-1-[N-(*tert*-butoxycarbonyl)-L-valyl]-3-hydroxy-2-pyrrolidinyl]-3-hydroxypropionate (21).**

To a solution of compound **20** (0 3413 g, 0 6264 mmol) in THF (6 3 mL) was added 1 1 M tetrabutylammonium fluoride in THF (0 854 mL) at 0 °C The reaction was stirred for 3 min, and then concentrated under reduced pressure The residue was purified using silica gel flash-column chromatography eluting with ethyl acetate petroleum ether (1·1) to afford pure **21** (0 2585 g, 96% yield) as a white foam TLC (EtOAc petroleum ether, 1 1) R_f 0 18, $[\alpha]_D^{22}$ -45 0° (*c* 0 49, $CHCl_3$), IR ($CHCl_3$) 3440(w), 3040(w), 2990(m), 2940(w), 2910(w), 2880(w), 1705(s), 1640(s), 1500(m), 1420(m), 1395(m), 1370(m), 1340(w), 1310(w), 1235(m), 1160(s), 1095(m), 1045(w), 1015(w), 955(w), 865 (w), 840(w) cm^{-1}, ^1H NMR ($CDCl_3$)

δ 0 93 (3H, d, J 6 8 Hz), 1 02 (3H, d, J 6 7 Hz), 1 43 (9H, s), 1.45 (9H, s), 2.01 (1H, dt, J^1 6 5 Hz, J^2 13 1 Hz), 2 09 (1H, dt, J^1 6.4 Hz, J^2 13 2 Hz), 2.19 (1H, dt, J^1 7 1 Hz, J^2 14 5 Hz), 2 47 (1H, dd, J^1 9 9 Hz, J^2 16 6 Hz), 2 61 (1H, dd, J^1 2 8 Hz, J^2 16 6 Hz), 3.04 (1H, d, J 6 1 Hz,), 3 66 (1H, m), 3 80 (1H, m), 4 10 (1H, d, J 2.6 Hz), 4 27 (1H, dd, J^1 4 6 Hz, J^2 6.6 Hz), 4 36 (1H, dd, J^1 5 6 Hz, J^2 9 1 Hz), 4 44-4 52 (2H, m), 5 23 (1H, d, J 9 1 Hz), ^{13}C NMR ($CDCl_3$) δ 17 2, 19.7, 28 1, 28 4, 31.5, 33 8, 40 1, 457, 68 5, 71 4, 79 6, 81 5, 155 9, 173 0, 173.4, HRMS calcd for $C_{21}H_{39}N_2O_7$ (M + H) 431 2757, found 431 2778

(+)-Valydetoxinine (2).

Under an argon atmosphere, **21** (0 0960 g, 0 223 mmol) was dissolved in dry ethyl acetate saturated with dry HCl (3 mL), and the resulting mixture was stirred for 30 min at ambient temperature The reaction mixture was concentrated, and the resulting crude material was triturated with *tert*-butylmethyl ether (2 × 3 mL) to afford the acid chloride salt (0 0617 g, 89% yield) as a white solid: TLC ($CHCl_3$ MeOH H_2O, 70 30·5) R_f 0 36, mp 110 °C (decomposed), $[\alpha]_D^{22}$ -63 1° (*c* 0 32, MeOH); IR ($CHCl_3$) 3700-2300(br), 1960(s), 1720(s), 1570(m), 1480(s), 1440(s), 1375(s), 1320(m), 1289(m), 1250(s), 1220(s), 1180(s), 1160(s), 1115(m), 1070(m), 1050(s), 1025(s), 1010(m), 960(s), 930(m), 875(w), 855(w), 815(w), 800(w), 725(m), 680(m) cm^{-1}, ^{1}H NMR (MeOD-d_4) δ 1.01 (5H, d, J 7 0 Hz), 1 12 (5H, d, J 7.0 Hz), 2.17-2 32 (3H, m), 2.54 (1H, dd, J^1 3 6 Hz, J^2 16.3 Hz), 2 65 (1H, dd, J^1 7 2 Hz, J^2 16 3 Hz), 3 59 (1H, m), 3.98 (1H, m), 4 21 (1H, d, J 4 8 Hz), 4 27 (1H, m), 4 34 (1H, dt, J^1 3 8 Hz, J^2 7 4 Hz), 5 25 (1H, t, J 4 4 Hz), ^{13}C NMR (MeOD-d_4) δ 171 8, 170 3, 80 7, 67 4, 64.4, 58.5, 47.3, 35.8, 33.2, 30.5, 19 2, 17.0, HRMS calculated for $C_{12}H_{21}N_2O_4$ (M - HCl - OH) 257.1501, found 257.1492. Valyldetoxinine HCl (0.0332 g, 0 0107 mmol) was dissolved in 1 M NH_4OH (2 mL) and the solution stirred for 30 min The solvent was evaporated and the resulting crude solid was placed on an ion exchange column (Dowex 50×2-400) and eluted with 0 02-0 2 M ammonium carbonate (pH 7 0) The collected fractions were concentrated to afford (+)-valyldetoxinine (**2**, 0 0270 g, 92% yield) as a white solid TLC ($CHCl_3$ MeOH H_2O, 70 30 5) R_f 0 09 , mp 109-111 °C, $[\alpha]_D^{22}$ +25 0° (*c* 0 52, MeOH), IR (KBr) 3700-2300(br), 2100(w), 1640(s), 1560(s), 1440(s), 1390(s), 1260(m), 1185(m), 1110(m), 1080(m), 1020(m), 890(w) cm^{-1}, ^{1}H NMR (MeOD-d_4) δ 1 00 (1 06) (1H, d, J 6 9 Hz), 1 05 (1 13) (1H, d, J 6 9 Hz), 1 97 (1H, ddd, J^1 10 0 Hz, J^2 12 3 Hz, J^3 19 3 Hz), 2 08 (2 20) (1H, m), 2 18 (1H, m), 2 43-2 47 (1H, m), 2 56 (2 79) (1H, dd, J^1 3 2 Hz, J^2 15 5 Hz), 3 50 (3 66) (2H, m), 4 01 (4 19) (1H, d, J 7 1 Hz), 4 04 (4 41) (1H, m), 4 06 (4 24) (1H, dd, J^1 3 6 Hz, J^2 6 5 Hz), 4 35 (4 44) (1H, dt, J^1 7 0 Hz, J^2 10 0 Hz), ^{13}C NMR (MeOD-d_4) δ 17 3, 18 2, 18 9, 19 5, 30 4, 31 3, 31 8, 33 5, 42 9, 44 0, 46 8, 49 7, 49 9, 58 0, 58 8, 63 7, 64 1, 67 2, 69 0, 71 3, 72 4, 171 0, 171 4, 178 8, 179 6, HRMS calcd for $C_{12}H_{23}N_2O_5$ (M + H) 275 1607, found 275 1631 The ^{1}H value in parentheses are for the rotamers

Ethyl N-[(Benzyloxy)carbonyl]-3,6-imino-3,5,6-trideoxy-D-glucofuranoside (22).

To a solution of compound **10** (0 10 g, 0 313 mmol) in anhydrous ethanol (1 25 mL) was added 15% hydrogen chloride/ether (1 25 mL) and the resulting mixture was stirred at ambient temperature for 15 h The solution was concentrated *in vacuo*, and the residue was dissolved in ethyl acetate (50 mL) The ethyl acetate solution was then washed with 5% $NaHCO_3$ (5 mL) and saturated NaCl (5 mL) solutions The organic layer was dried (Na_2SO_4), filtered, and concentrated The resulting crude oil was purified by column chromatography, eluting with ethyl acetate/petroleum ether (1 2, 1 1) to afford a trideoxyglucofuranoside (0 091 g) in 94% yield TLC (EtOAc petroleum ether, 40 60) R_f 0 35, IR ($CHCl_3$) 3460-3420 (br), 3000 (m), 2920 (m), 1710-1680 (s), 1430 (s), 1370 (s), 1200 (w), 1120 (s), 1015 (s), 920 (m), 850 (w) cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 1 1-1 2 (3H, t, J 6 5 Hz), 1 8-2 1 (2H, m), 3 35-3 75 (4H, m), 4 05-4 35 (2H, m), 4 98-5 02 (2H, m), 5 1-5 2 (2H, m), 7 4 (5H, br s), HRMS calcd for $C_{16}H_{22}O_5N$ (M + H) 308 1498, found 308 1495

Ethyl N-[(Benzyloxy)carbonyl]-2-O-benzyl-3,6-imino-3,5,6-trideoxy-D-glucofuranoside (23).

Trideoxyglucofuranoside **22** (0.41 g, 1.33 mmol) was dissolved in DMF (5.3 mL), and treated with 35% KH (0 152 g, 1.33 mmol). Stirring at ambient temperature was continued for 30 min, and benzyl bromide (0.32 mL, 2.66 mmol) was added to the mixture After the reaction was completed, the reaction mixture was quenched with a small amount of water and concentrated. The residue was dissolved in ethyl acetate (150 mL) and the ethyl acetate solution was washed successively with 10 mL each of 5% HCl, 5% $NaHCO_3$, and saturated NaCl. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting crude oil was purified by column chromatography eluting with ethyl acetate/petroleum ether (20:80) to afford compound **23** (0.47 g) in 89%yield: TLC (EtOAc:petroleum ether, 40:60) R_f 0.76, IR ($CHCl_3$) 3000 (m), 2920 (m), 1705 (s), 1430 (m), 1365 (m), 1120 (m), 1095 (m), 1010 (w), 920 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.1-1 2 (3H, m), 1.8-2.1 (2H, m), 3.35-3.80 (4H, m), 4.0-4.9 (4H, m), 4.95-5.05 (2H, m), 5 1-5.2 (2H, m), 7 1-7.4 (10H, br s); HRMS calcd for $C_{23}H_{28}O_5N$ (M + H) 398.1967, found 398 1954.

N-[(Benzyloxy)carbonyl]-2-O-benzyl-3,6-imino-3,5,6-trideoxy-D-glucofuranose (24).

A solution of compound **23** (0.210 g, 0 528 mmol) in 50% aqueous TFA (2 6 mL) was stirred at 50 °C for 5 h. Evaporation of the solvent gave an oil, which was dissolved in ethyl acetate (75 mL) The solution was washed with 5% $NaHCO_3$ (5 mL), and saturated NaCl (5 mL) solutions, then dried over Na_2SO_4, and concentrated The resulting crude oil was purified by column chromatography, eluting with ethyl acetate/petroleum ether (40 60), to afford compound **24** (0 176 g, 86%) as an oil; TLC (acetone·hexane, 30 70) R_f 0 27, IR ($CHCl_3$) 3560-3400 (br), 2980 (m), 1740-1690 (s), 1425 (s), 1365 (s), 1325 (w), 1200 (w), 1120 (s), 1070 (m), 920 (w), 845 (w) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1 7-2 1 (2H, m), 3 2-3 8 (2H, m), 3 9-4 7 (4H, m), 4 8-4 95 (1H, m), 5 1-5 2 (2H, m), 5 30-5.45 (1H, m), 7.1-7.4 (10H, br s), HRMS calcd for $C_{21}H_{24}O_5N$ (M + H) 370 1654, found 370 1595.

(2S,3R)-1-[(Benzyloxy)carbonyl]-2-[(S)-1-(benzyloxy)-2-propenyl]-3-hydroxypyrrolidine (25).

Methyltriphenylphosphonium bromide (5 299 g, 14.83 mmol) was suspended in dry THF (14 mL) in a flame-dried flask equipped with a magnetic stirrer To this stirred suspension was added dropwise, under argon, a solution of *n*-butyllithium in hexane (9 26 mL, 1.6 M). The bright yellow mixture was stirred at room temperature until no solid remained (~30 min) Compound **24** (1 177 g, 3 19 mmol), dissolved in 7 2 mL of THF, was then added to the reaction mixture, and stirring was continued at 45 °C for 5 h After quenching with saturated aqueous NH_4Cl solution, the mixture was extracted with ethyl acetate The organic solution was washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated to give an oily residue which was subjected to column chromatography, eluting with acetone hexane (20 80) to afford the desired pyrrolidinol **25** (0 832 g) in 71% yield TLC (acetone·hexane, 30 70) R_f 0 37, $[\alpha]_D^{24}$ -32 3° (*c* 0 4, $CHCl_3$), lit [17] $[\alpha]_D^{20}$ -25 2° ($CHCl_3$); IR ($CHCl_3$) 3580-3480 (br), 3020 (w), 2975 (w), 2920 (w), 1705 (s), 1425 (s), 1370 (m), 1345 (w), 1120 (m), 1075 (m), 945 (w) cm^{-1}, ^1H NMR ($CDCl_3$) δ 1 9-2 1 (2H, m), 3 18 (1H, br s), 3 4-3 6 (2H, m), 4 1-4 2 (1H, m), 4 30-4 48 (1H, m), 4 50-4 65 (3H, m), 5 05 (2H, s), 5 15-5 25 (2H, m), 5 9-6 1 (1H, m), 7 3 (10H, br s), HRMS calcd for $C_{22}H_{26}O_4N$ (M + H) 368 1862, found 386 1892

(3S)-3-Benzyloxy-3-[(2S,3R)-1-[(benzyloxy)carbonyl]-3-hydroxy-2-pyrrolidinyl]-1-propanol (26).

To a magnetically stirred, cold (-10 °C) solution of disiamylborane (8 1 mmol, from 4 1 mL of 2 M solution of borane-methyl sulfide complex in THF and 8.1 mL of 2 M solution of 2-methyl-2-butene in THF) was added, under argon, a solution of olefin **25** (0 4792 g, 1 31 mmol) in THF (1 mL) The cooling bath was

removed and the stirring was continued for 3 h. At 0 °C, the reaction mixture was treated simultaneously with solutions of 2 N NaOH (7 4 mL) and 30% H_2O_2 (4.6 mL) over a period of 15 min and with stirring. The mixture was brought to room temperature and stirred for another 8 h. It was then treated with a saturated solution of NH_4Cl. After evaporation of the solvent, the residue was extracted with ethyl acetate (150 mL) The ethyl acetate solution was washed with 15 mL each of 5% $NaHCO_3$, H_2O, and saturated NaCl, dried, and concentrated The crude 1,5-diol was purified by chromatography on silica gel using 35% acetone/hexane as the solvent The product was azeotropically dried using toluene. The last traces of the solvent were removed under reduced pressure to give 0.4202 g of **26** in 83% yield TLC (acetone hexane, 40 60) R_f 0 32, $[\alpha]_D^{24}$ -48 5° (*c* 3 3, $CHCl_3$), IR ($CHCl_3$) 3580-3400 (br), 3020 (w), 2980 (w), 2920 (w), 1700 (s), 1460 (m), 1430 (s), 1370 (m), 1340 (m), 1120 (m), 1080 (s), 920 (w) cm^{-1}, ^1H NMR ($CDCl_3$) δ 1.9-2 1 (4H, m), 3 41-3 80 (4H, m), 4 1-4 3 (2H, m), 4 48-4 70 (3H, m), 5 05-5 15 (2H, m), 7 4 (10H, br s), HRMS calcd for $C_{22}H_{28}O_5N$ (M + H) 386 1967, found 386 1955

(S)-1-[(2R,3R)-3-Acetoxy-1-[(benzyloxy)carbonyl]-2-pyrrolidinyl]-1-benzyloxy-3-[(*tert*-butyldimethylsilyl)oxy]-propane (27).

Diol **26** (0 1317 g, 0 341 mmol) was dissolved in CH_2Cl_2 (3 3 mL) at ambient temperature, and treated sequentially with Et_3N (0.057 mL, 0.409 mmol), *tert*-butyldimethylsilyl chloride (0 054 g, 0 358 mmol), and 4-dimethylaminopyridine (DMAP) (4 2 mg, 0 0341 mmol). The mixture was stirred for 18 h and then cooled to -10 °C To this mixture were added Et_3N (0 052 mL, 0 375 mmol) and Ac_2O (0 064 mL, 0.682 mmol) After the reaction was completed (2 h), it was diluted with ether (70 mL), and washed with 10% HCl (5 mL), 5% $NaHCO_3$ (5 mL), and saturated NaCl (5 mL) solutions The organic layer was dried (Na_2SO_4), filtered, and concentrated The resulting crude oil was purified by column chromatography eluting with ether/petroleum ether (10 90) to give acetate **27** (0 168 g, 91% yield) as an oil. TLC (EtOAc petroleum ether, 20 80) R_f 0 44, $[\alpha]_D^{23}$ -32 2° (*c* 0 6, $CHCl_3$), IR ($CHCl_3$) 2980 (s), 2960 (s), 2880 (m), 1750 (s), 1710-1690 (s), 1420 (s), 1370 (m), 1250 (s), 1100 (s), 1070 (m), 840 (m) cm^{-1}, ^1H NMR ($CDCl_3$) δ 0 05 (6H, s), 0 95 (9H, s), 1 61-1 95 (2H, m), 2 0 (3H, s), 2 21-2 32 (2H, m), 3 45-3 60 (3H, m), 3.70-4 05 (2H, m), 4 3-4 7 (3H, m), 5 05-5 15 (2H, m), 5 15-5 30 (1H, m), 7 4 (10H, br s), HRMS calcd for $C_{30}H_{44}O_6NSi$ (M + H) 542 2938, found 542 2919

(S)-1-[(2R,3R)-3-Acetoxy-1-[N-(*tert*-butoxycarbonyl)-L-valyl]-2-pyrrolidinyl]-1-benzyloxy-3-[(*tert*-butyldimethylsilyl)oxy]-propane (28).

To a suspension of Raney nickel (0 134 g) in CH_3OH/EtOAc (1 1, 3 1 mL), was added acetate **28** (0 2226 g, 0 41 mmol) in CH_3OH/EtOAc solution (1 1, 1 mL) The solution was stirred for 2 h under an atmosphere of hydrogen (40 psi) The reaction mixture was filtered through Celite The Celite was washed with CH_3OH, and the filtrate was concentrated The resulting pyrrolidine was used directly in the next step Boc-Valine (0 1161 g, 0 534 mmol) was dissolved in CH_2Cl_2 (5 3 mL), and the solution was cooled to -15 °C BOP-Cl (0.136 g, 0.534 mmol) was added, followed by the dropwise addition of Et_3N (0 075 mL, 0 534 mmol) The reaction mixture was stirred at -15 °C for 0 5 h. The solution was then concentrated to 10 mL and the above pyrrolidine (0 1670 g, 0 41 mmol) and Et_3N (0 063 mL, 0 452 mmol) were added The solution was kept at 0 °C for 8 h, and then diluted with ether (150 mL) The organic layer was washed with 10% HCl (10 mL), 5% $NaHCO_3$ (10 mL), and saturated NaCl (10 mL) solutions The organic layer was dried (Na_2SO_4), filtered, and concentrated The residue was purified by column chromatography eluting with ethyl acetate petroleum ether (10 90 to 20 80) Compound **28** (0 2256 g, 90% yield) was obtained as an oil TLC (EtOAc petroleum ether, 20 80) R_f 0 36 , $[\alpha]_D^{24}$ -27 4° (*c* 6 4, $CHCl_3$), IR ($CHCl_3$) 3460 (w), 2990 (m), 2960 (m), 2880 (m), 1750 (s), 1720 (s), 1650 (s), 1505 (m), 1435 (m), 1380 (s), 1250 (s), 1170 (m), 1100 (s),

845 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.04 (6H, s), 0.89 (9H, s), 0.92 (3H, d, J 6 7 Hz), 0.99 (3H, d, J 6 8 Hz), 1 4 (9H, s), 1 60-1.95 (2H, m), 2 0 (3H, s), 2.20-2 35 (2H, m), 3.55-3 71 (4H, m), 3 91-3 98 (1H, m), 4 2-4.3 (1H, m), 4 55 (2H, s), 4 65 (1H, dd), 5.1-5.2 (2H, m), 7 25 (5H, br s); HRMS calcd for $C_{32}H_{55}O_7N_2Si$ (M + H) 607 3778, found 607 3843

N-[(Benzyloxy)carbonyl]-3-phenyl-L-alanine, (S)-1-[(2S,3R)-3-Acetoxy-1-[N-(*tert*-butoxycarbonyl)-L-valyl]-2-pyrrolidinyl]-3-[(*tert*-butyldimethylsilyl)oxy]-propyl Ester (30).

A mixture of compound **28** (0 292 g, 0.482 mmol), EtOH (2.41 mL) and Pd black (0 146 g) was hydrogenated (45 psi) at room temperature in a Parr hydrogenator After 24 h, the solution was filtered through Celite, dried (Na_2SO_4), and concentrated A mixture of the resulting alcohol and N-(benzyloxy)carbonyl-L-phenylalanine (0.188 g, 0 626 mmol) was azeotropically dried with benzene (3 x10 mL). To this mixture, in CH_2Cl_2 (2 4 mL), at 0 °C with stirring, DCC (0 159 g, 0 771 mmol), DMAP (17 7 mg, 0 145 mmol) and CSA (33 6 mg, 0.145 mmol) were added sequentially. The reaction was allowed to warm to room temperature and was then stirred overnight The solid formed was collected by filtration and washed with EtOAc The filtrate was concentrated under reduced pressure and diluted with ether (150 mL) The reaction mixture was filtered again, and the collected solid was washed with ether The ether layer was washed with 5% HCl (10 mL), 5% $NaHCO_3$ (10 mL), and saturated NaCl (10 mL) solution The organic layer was dried (Na_2SO_4), filtered, and concentrated The resulting crude oil was purified by column chromatography, eluting with ethyl acetate/petroleum ether (15 85) Ester **30** (0 339 g, 88%) was obtained as an oil TLC (EtOAc petroleum ether, 30 70) R_f 0 44, $[\alpha]_D^{23}$ -38.2° (*c* 1.5, $CHCl_3$), IR ($CHCl_3$) 3460 (w), 2980 (m), 2950 (m), 2880 (m), 1750-1720 (s), 1655 (s), 1505 (s), 1380 (m), 1250 (m), 1170 (m), 1105 (w), 845 (m) cm^{-1}, ^1H NMR ($CDCl_3$) δ 0 02 (6H, s), 0.9 (9H, s), 0 99 (3H, d, J 9 0 Hz), 1 3 (3H, d, J 7 0 Hz), 1 42 (9H, s), 1 58-1 98 (2H, m), 2 05 (3H, s), 2 0-2 2 (2H, m), 2 95-3 20 (2H, m), 3.43-3 75 (4H, m), 4 28-4 35 (1H, m), 4 55-4 72 (2H, m), 5 05-5 15 (3H, m), 5 23 (1H, d, J 9.1 Hz), 5 45 (1H, m), 7 1-7 35 (10H, br s), HRMS calcd for $C_{42}H_{64}O_{10}N_3Si$ (M + H) 798 4360, found 798 4421

N-[(2S)-2-Methyl-1-oxobutyl]-3-phenyl-L-alanine, (S)-1-[(2S, 3R)-3-Acetoxy-1-[N-(*tert*-butoxycarbonyl)-L-valyl]-2-pyrrolidinyl]-3-[(*tert*-butyldimethylsilyl)oxy]-propyl Ester (31).

Ester **30** (75 1 mg, 0 094 mmol) in a mixture of CH_3OH and EtOAc (1 1, 0 97 mL) was stirred with 10% Pd/C (16 mg) under an atmosphere of hydrogen (35 psi) for 5 h The solution was then filtered through Celite, dried (Na_2SO_4), and concentrated To a solution of the resulting free amine (62.3 mg, 0 094 mmol) and (S)-2-methylbutyric acid (0.012 ml, 0 113 mmol), in CH_2Cl_2 (0 94 mL) and at 0 °C, were added BOP (49 9 mg, 0 113 mmol) and DIEA (0.034 mL, 0 197 mmol) After 30 min, the solution was brought to room temperature, and stirred for 3 h After this time, the reaction mixture was treated with 2 mL of saturated NaCl solution, and then extracted with 35 mL EtOAc The organic layers were combined and washed successively with 5% HCl, saturated NaCl, 5% $NaHCO_3$ and saturated NaCl solutions The organic layer was dried (Na_2SO_4), filtered, and concentrated The resulting crude oil was purified by column chromatography, eluting with ethyl acetate petroleum ether (10 90, 20 80) to afford 49 1 mg (70%) of compound **31** as a foam TLC (EtOAc petroleum ether, 30 70) R_f 0 31, $[\alpha]_D^{24}$ -22 7° (*c* 0 81, $CHCl_3$); IR ($CHCl_3$) 3460 (w), 2990 (m), 2960 (m), 2880 (m), 1755 (s), 1720 (s), 1660 (s), 1510 (s), 1430 (m), 1380 (m), 1245 (s), 1180 (s), 1105 (w), 845 (m) cm^{-1}, ^1H NMR ($CDCl_3$) δ 0 02 (6H, s), 0 89 (9H, s), 0 7-0 93 (9H, m), 1 04 (3H, d, J 8 0 Hz), 1 45 (9H, s), 1 25-1 60 (2H, m), 1 70-1 81 (2H, m), 1.9-2 1 (2H, m), 2 08 (3H, s), 2 20-2 35 (1H, m), 2 9-3 28 (2H, m), 3 45-3 85 (4H, m), 4 3-4 4 (1H, m), 4 65-4 90 (2H, m), 5 1-5 2 (1H, m), 5 25 (1H, d, J 8 5 Hz), 5 41-5 52 (1H, m), 5 78 (1H, d, J 6 0 Hz), 7 15-7 30 (5H, br s), HRMS calcd for $C_{39}H_{66}O_9N_3Si$ (M + H) 748 4568, found 748 4520

N-[(2S)-2-Methyl-1-oxobutyl]-3-phenyl-L-alanine, (S)-1-[(2S,3R)-3-Acetoxy-1-[N-(*tert*-butoxycarbonyl)-L-valyl]-2-pyrrolidinyl]-3-hydroxypropyl Ester (32).

To compound **31** (87 3 mg, 0.116 mmol), in THF (0 5 mL), was added HOAc and H_2O (3.1, 2 mL) After 16 h, the reaction mixture was concentrated under reduced pressure. The excess water was removed by azeotropic distillation with toluene The crude oil was then purified by column chromatography, eluting with acetone hexane (25 75) to afford alcohol **32** (73 6 mg, 99% yield) as a white foam, TLC (acetone hexane, 40 60) R_f 0 41 , $[\alpha]_D^{24}$ -27° (*c* 1 1, $CHCl_3$), IR ($CHCl_3$) 3580-3400 (br), 3000 (m), 2960 (m), 2900 (m), 1755 (s), 1720 (s), 1660 (s), 1580 (s), 1430 (w), 1380 (m), 1245 (s), 1180 (s), 1105 (w), 845 (m) cm^{-1}, ^1H NMR ($CDCl_3$) δ 0 8 (9H, m), 1.04 (3H, d, J 8 0 Hz), 1 25-1 60 (2H, m), 1 45 (9H, s), 1.70-1 85 (2H, m), 1 9-2 1 (2H, m), 2 08 (3H, s), 2 20-2 35 (1H, m), 2 85 (1H, br s), 2 90-3 28 (2H, m), 3 50-3 85 (4H, m), 4 3-4 4 (1H, m), 4 70-4 81 (2H, m), 5 11-5 25 (2H, m), 5 35-5 41 (1H, m), 5 85 (1H, d, J 7 5 Hz), 7 15-7 35 (5H, br s), HRMS calcd for $C_{33}H_{52}O_9N_3$ (M + H) 634 3703, found 634 3765

Detoxin D_1 (3).

To a solution of DMSO (0 07 mL, 0 99 mmol) in CH_2Cl_2 (0 4 mL), at -78 °C, was added, dropwise, trifluoroacetic anhydride (0 07 mL, 0 50 mmol) in CH_2Cl_2 (0 2 mL) The resulting mixture was stirred at -78 °C for 20 min and alcohol **32** (43 2 mg, 0 201 mmol) in CH_2Cl_2 (1 6 mL) was added dropwise After 2 5 h, triethylamine (0 042 mL, 0 3 mmol) in CH_2Cl_2 (0 1 mL) was added dropwise. After 1 h at ambient temperature, the reaction was diluted with ether (20 mL) The organic solution was washed with 5% HCl (2 mL), 5% $NaHCO_3$ (2 mL), and saturated NaCl (2 mL) solutions The organic layer was dried (Na_2SO_4), filtered, and concentrated The resulting unstable aldehyde was dissolved in *tert*-butyl alcohol (0 42 mL) and treated with 5% NaH_2PO_4 (0 28 mL) and 1 M $KMnO_4$ (0 42 mL) solutions After 0.5 h, the solution was diluted with ether (10 mL) and cooled to 0 °C A saturated solution of Na_2SO_3 was added dropwise (0 2 mL) To the resulting solution was added 10% HCl until the aqueous layer was pH 3 The aqueous layer was extracted with EtOAc The combined organic layers were dried (Na_2SO_4), filtered, and concentrated At 0 °C and under an argon atmosphere, the resulting acid was dissolved in dry CH_2Cl_2 (0 69 mL) Trifluoroacetic acid (0 11 mL, 1 37 mmol) was added *via* a syringe The reaction mixture was stirred at 0 °C for 2 h and then concentrated The crude solid was placed on an ion exchange column (Dowex-50Wx2, 200-400 mesh) and eluted with 0 05-0 2 M ammonium carbonate (pH 7 0) The collected fractions were concentrated and the remaining water was removed by azeotropic distillation with absolute ethanol until a white powder resulted Recrystallization from chloroform/hexane afforded detoxin D_1 (26 1 mg, 70%) as a white solid TLC ($CHCl_3$ MeOH H_2O, 7 5 1) R_f 0 75, mp 150-152 °C, lit [13] mp 120 °C, lit [35] mp 156-158 °C, $[\alpha]_D^{23}$ -41° (*c* 0 2, MeOH), lit [13] $[\alpha]_D^{25}$ -40° (*c* 0 53, MeOH), lit [35] $[\alpha]_D^{25}$ -16° (*c* 1, MeOH), IR ($CHCl_3$) 3460 (w), 3400-3200 (br), 3000 (m), 2960 (m), 2900 (m), 1750 (s), 1670 (s), 1600 (s), 1510 (w), 1370 (m), 1250 (m), 1095 (w), 980 (w) cm^{-1}, ^1H NMR (DMSO-d_6) δ 0 76 (3H, t), 0 84 (3H, d, J 5 7 Hz), 0 86 (3H, d, J 9 0 Hz), 0 94 (3H, d, J 9 0 Hz), 1 25 (1H, m), 1 46 (1H, m), 1 75-2 05 (2H, m), 1 99 (3H, s), 2 12 (1H, m), 2 22 (1H, m), 2 30 (1H, m), 2 60 (1H, m), 2 88 (1H, m), 3 10 (1H, dd, J^1 5 2 Hz, J^2 13 6 Hz), 3 32 (1H, d, J 4 8 Hz), 3 47-3 61 (1H, m), 3 66-3 78 (1H, m), 4 49 (1H, m), 4 69 (1H, d, J 4 0 Hz), 5 09 (1H, m), 5 43 (1H, m), 7 13-7 35 (5H, m), 8 15 (1H, m), ^{13}C NMR (MeOD-d_4) δ (12 3, 12 4), (17 2, 17 5), 17 7, (19 2, 19 8), 20 9, (28 0, 28 2), 31 0, (31 2, 31 9), (37 9, 38 4), (39 9, 40 1), 43 6, (44 8, 46 0), (54 1, 54 6), (57 8, 57 9), (58 6, 59 7), (72 2, 72 7), (73 4, 73 5), 127 7, 127 8, 129 4, 129 5, 130 4, 138 6, 170 4, (171 5, 171 7), (172 1, 172 4), 176 6, (178 9, 179 2), HRMS calcd for $C_{28}H_{42}O_8N_3$ (M + H) 548 2971, found 548 2998 The ^{13}C value in parentheses are for the rotamers These values are in agreement with those reported by Hausler [13]

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

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