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SYNTHETIC STUDIES OF THE DETOXIN COMPLEX. I. TOTAL SYNTHESIS OF (-) DETOXININE.

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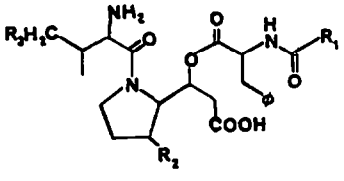
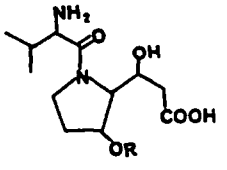
Abstract. A total synthesis of (-) detoxinine (1), the parent amino acid of the detoxin complex is reported. Two different routes to key intermediate 8a were developed: one from an acyclic precursor and the other from L-proline. The elaboration of 8a to 1 employed a stereoselective aldol condensation.

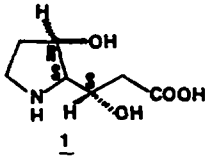
The synthesis of highly functionalized, unusual amino acids that are found as components of biologically important peptides is of great interest.[1] The detoxin complex,[2] made up of metabolites produced by Streptomyces caespitosus var. detoxicus 7072 GC_1, is a selective antagonist of the antibiotic blasticidin S and is of interest for its detoxification effect against the antibiotic both in animal and plant cells (Figure 1). The parent component of the complex belongs to a new class of depsipeptides which contains a (2S, 3R, 1'S)-2-(2'-carboxy-1'-hydroxyethyl)-3-hydroxypyrrolidine unit, (-) detoxinine (1).



	R_1	R_2	R_3
DETOXIN E_1	$CH(CH_3)CH_2CH_3$	$COOCH_3$	CH_3
D_1	$CH(CH_3)CH_2CH_3$	$OCOCH_3$	H
C_1	CH_3	$OCOCH_3$	H
C_2	CH_2CH_3	$OCOCH_3$	H
C_3	$CH(CH_3)_2$	$OCOCH_3$	H
B_1	CH_3	H	H
B_3	$CH(CH_3)_2$	H	H



	R
DETOXIN A_1	$COCH_3$
VALYLDETOXININE	H



1

DETOXININE

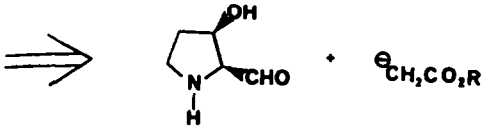
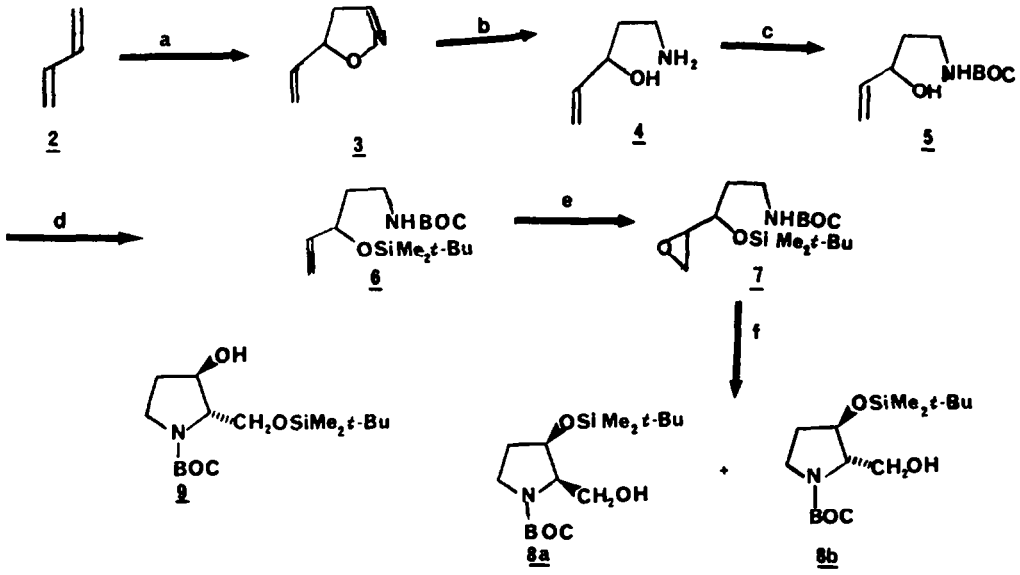


FIGURE 1

Detoxinine has been synthesized recently.[3] However, one approach involves a nonstereoselective route,[3a] while the other utilizes an expensive starting material.[3b] We now report a different route to 1, employing a stereoselective aldol condensation as the key step (Figure 1).

Scheme 1



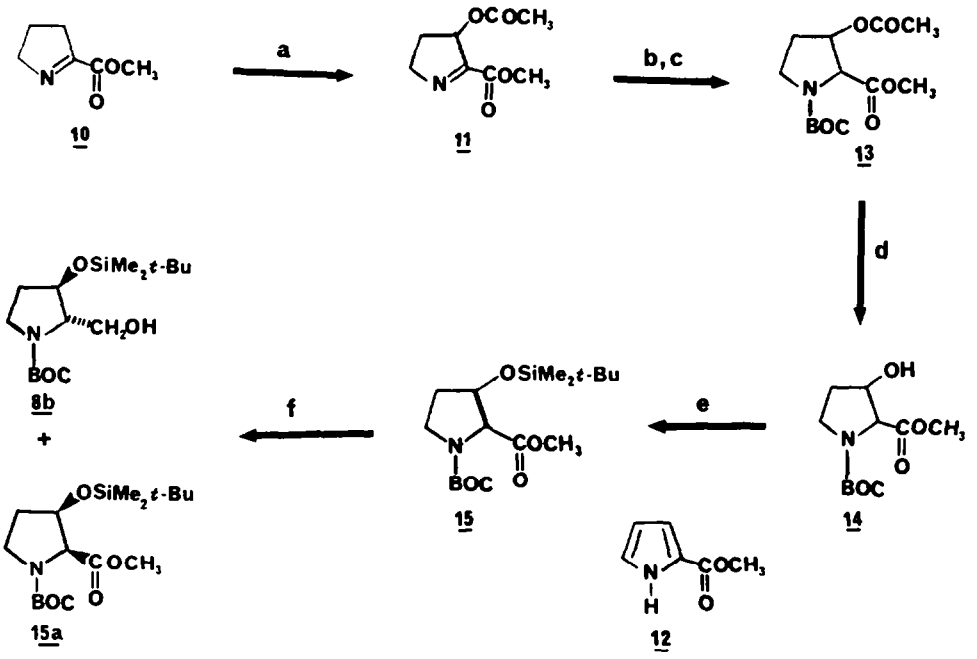
[a]CH_3NO_2, TMS-Cl, NEt_3, TFA; [b]$LiAlH_4$, Et_2O, RT→Δ; [c]$(Boc)_2O$, NEt_3, CH_2Cl_2; [d]t-$BuMe_2SiCl$, Im, DMF; [e]MCPBA, $NaHCO_3$, CH_2Cl_2; [f]$Mg(OTF)_2$, $NaHCO_3$, CH_2Cl_2 or $BF_3.Et_2O$, CH_2Cl_2, -78°C.

We first prepared the required aldehyde via the novel Lewis acid mediated cyclization of a suitably substituted linear precursor to form the pyrrolidine ring of detoxinine. Compound 4 (Scheme 1) was synthesized according to the procedure of Das and Torssell,[4] from butadiene (2) and nitromethane, followed by lithium aluminum hydride reduction of the resulting 5-vinyl-2-isoxazoline (3). Compound 4 was then converted to its tert-butyloxycarbonyl (Boc) derivative (5) under standard conditions. Sharpless[5] kinetic resolution was attempted but this reaction was too slow to be useful. Conversion of compound 5 to its silyl ether 6,[6] followed by epoxidation of the double bond with m-chloroperbenzoic acid afforded a 1:1 mixture of threo- and erythro-epoxides (7) in 82.5% yield. Treatment of 7 with magnesium triflate,[7] in methylene chloride, led to the formation of cis (8a) and trans pyrrolidines (8b) as a 1:1 separable mixture in 62% yield. Use of boron trifluoride etherate at -78°C, in methylene chloride, gave the isomeric pyrrolidines in 91% yield. Similar Lewis acid catalyzed cyclizations have been reported for the construction of substituted tetrahydrofurans.[8] When ether was used as the solvent in this reaction, significant formation of a secondary alcohol (9) resulting from a 1,5 silyl migration was observed.

Compounds 8a and 8b were also synthesized from L-proline. L-Proline was converted to methyl pyrroline carboxylate (10) (Scheme 2) using the procedure of Häusler and Schmidt.[9] Allylic acetoxylation of this compound had been reported[10], but we found that the use of methylene chloride instead of benzene as the solvent accelerated the reaction and afforded higher yields. Thus, treatment of 10 with one equivalent of lead tetraacetate, in methylene chloride, at reflux for 4 h resulted in the corresponding allylic acetate (11) contaminated (8-10%) with the pyrrole methyl ester (12). Because of the instability of this acetate, the mixture was not

purified but used directly in the next step. Reduction of the aldimine functionality in 11 using sodium cyanoborohydride[11] under acidic conditions, or preferably dimethylamine borane[12] in acetic acid, afforded the free amine which was conveniently converted to its Boc derivative (13) by treatment with di-tert-butyl dicarbonate in methylene chloride containing triethylamine. The overall yield for this three step sequence, with dimethylamine borane as the reducing agent, was

Scheme 2

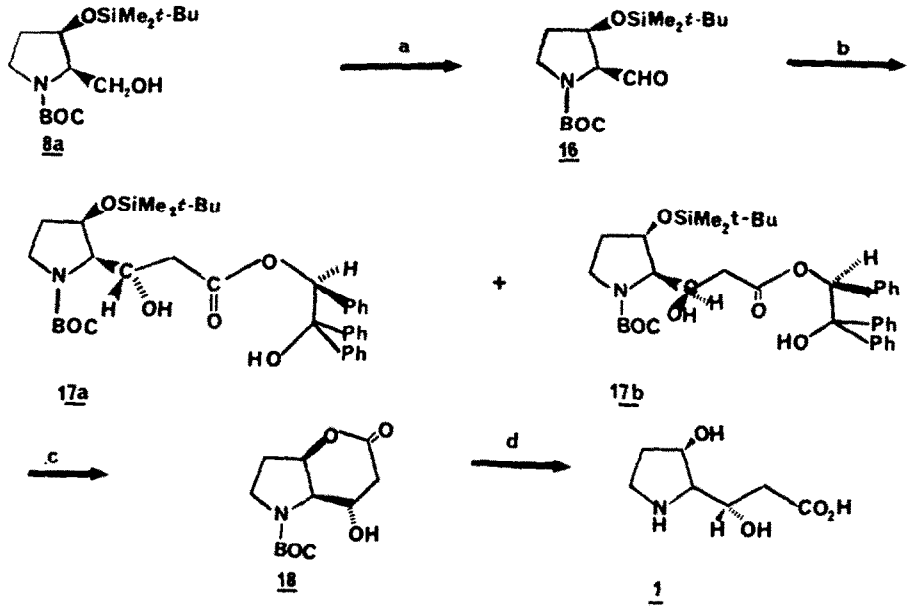


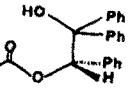
[a] $Pb(OAc)_4$, CH_2Cl_2, Δ; [b] $NaCNBH_3$, PH 5-6 or $BH_3.NMe_2$, HOAc; [c] $(Boc)_2O$, NEt_3, CH_2Cl_2; [d] K_2CO_3, MeOH; [e] t-$BuMe_2SiCl$, Im, DMF; [f] $NaBH_4$, LiCl, EtOH, THF.

typically 65-74%. Our efforts to separate the cis- and trans-proline derivatives at this stage met with little success. Treatment of 13 with potassium carbonate in methanol led to an almost quantitative conversion to 14. Silylation under standard conditions,[6] followed by reduction[13] of the silyl derivative 15, gave the trans-alcohol (8b) and the unreacted cis-ester (15a). The cis-ester (15a) could be reduced to the corresponding alcohol (8a) by lithium aluminum hydride, at low temperature.

Further elaboration of alcohol 8a to (-) detoxinine (1) is outlined in Scheme 3. Oxidation using Swern conditions[14] (trifluoroacetic anhydride and dimethylsulfoxide) gave pyrrolidinal 16. This aldehyde proved stable to purification by flash column chromatography. Aldol condensation of aldehyde 16 with the chiral enolate[15] derived from S-mandelic acid afforded a 3:1 chromatographically separable mixture of 17a and 17b, the best ratio obtained. Use of the lithium enolate at -78°C for 8 h gave a 2:1 ratio of products in favor of the desired isomer. Treatment of 17a with tetrabutylammonium fluoride for 15 min afforded 18 in 85% yield. ^{1}H-Nmr analysis of 18 in the presence of chiral shift reagent,[14] tris [3-(heptafluoropropylhydroxymethylene)-d-camphorato] europium III [Eu(hfc)$_3$] indicated the enantiomeric excess to be 60%. This was also confirmed by Horeau's method.[17] Reaction of 18 with trifluoroacetic acid followed by ion-exchange

Scheme 3



[a]TFAA, DMSO, NEt_3, -78°C; [b]1.  , LDA, THF, 2. $MgBr_2$; [c]$(n\text{-}Bu)_4NF$, THF; [d]1. TFA, 2. Dowex ion exchange resin, 1N NH_4OH.

chromatography using 1N NH_4OH as eluant gave detoxinine (1) identical in all respects with the natural product. Current investigations are underway towards the synthesis of other members of the detoxin complex.

EXPERIMENTAL

General. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H-Nmr spectra were recorded on a Bruker WM 250 (250 MHz) Fourier transform spectrometer. All samples were run in deuterio chloroform except for compounds 18 and 1 that were run in deuterated benzene and deuterium oxide respectively. Chemical shifts are in parts per million (δ) relative to tetramethylsilane. Coupling constants (J values) are in Hertz (Hz). Multiplicities are designated as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br). Infrared spectra (IR) were run on a Perkin-Elmer Model 281A or 281B spectrometers. Analytical thin layer chromatography (TLC) was performed on Merck silica gel 60F-254 plates (250 μl). Visualization was effected with ultraviolet light, ninhydrin (3% w/v) in 95% ethanol containing 2% acetic acid, and phosphomolybdic acid reagent (7% w/v) in 95% ethanol. Chromatography was performed on Merck silica gel 60 (230-400 mesh) under a slight positive pressure. Elemental analyses were performed by Mic Anal Organic Microanalysis labs, Tucson, AZ. Optical rotations were recorded on a *Perkin-Elmer Model 241 Polarimeter*, at the sodium D line, and ambient temperatures. High resolution mass spectra (HRMS) were obtained on a Hitachi-Perkin Elmer RMH-2 high resolution, double focusing, electron-impact spectrometer or a vacuum generator's V.G. 707H spectrometer interfaced with a Kratos DS-50-S data system.

All solvents used were reagent grade. Tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone; dichloromethane was distilled from calcium hydride.

1-(N-tert-Butyloxycarbonylamino)-3-hydroxy-pent-4-ene (5). To a cooled (0°C) solution of amino alcohol 4 (2.955 g; 29.5 mmol) in methylene chloride (200 ml), triethylamine (4.5 ml) and di-tert-butyl dicarbonate (7.1 g; 32.53 mmol) were added with stirring. The solution was stirred at 0°C for 6 h and made acidic with saturated citric acid solution. The methylene chloride layer

was washed with water, brine, dried (Na_2SO_4) and concentrated. Purification by flash chromatography using methylene chloride: acetone (95:5) as eluant afforded product 5 (5.0362 g, 84.8% yield). R_f 0.23 [methylene chloride:acetone (95:5)]; IR (neat) 3365, 3085, 1700, 1505, 1360, 1280, 1260, 1170, 980, 920, 860, 780, 730 cm^{-1}; ^{1}H-Nmr: 1.45 (9H, s, Boc), 1.61-1.77 (2H, m, $-CH_2-$), 3.05-3.09 (1H, m, $-NCH_2$), 3.11-3.22 (1H, m), 3.40-3.46 (1H, m, -OH), 4.19 (1H, ddd, J^1=1.4, J^2=5.6, J^3=7.9), 4.88 (1H, m, -NH), 5.11 (1H, dt, J^1=10.4, J^2=1.4), 5.27 (1H, dt, J^1=17.2, J^2=1.4), 5.89 (1H, ddd, J^1=5.6, J^2=10.4, J^3=17.2); HRMS, M^++1, Calcd. for $C_{10}H_{19}NO_3$: 202.1440. Found: 202.1403.

1-(N-tert-Butyloxycarbonylamino)-3-(t-butyldimethylsilyloxy)-pent-4-ene (6). To a stirred solution of compound 5 (2.5294 g; 12.568 mmol) in dry DMF (6.3 ml) were added tert-butyldimethylsilyl chloride (2.368 g; 15.71 mmol) and imidazole (2.139 g; 31.42 mmol). The reaction mixture was stirred for 24 h at ambient temperature. Water (10 ml) was added to it and the solution was extracted with ethyl acetate. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography of the crude mixture using petroleum ether:ether (90:10) as eluant afforded product 6 (3.92 g; 98.9% yield). R_f 0.25 [petroleum ether:ether (90:10)]; IR (neat) 3360, 3080, 1720, 1505, 1380, 1355, 1250, 1165, 825, 765 cm^{-1}; ^{1}H-Nmr: 0.03-0.07 (6H, m, $-SiMe_2$), 0.86-0.92 (9H, m, -Si-*t*-Bu), 1.43 (9H, s, Boc), 1.61-1.74 (2H, m, $-CH_2$), 3.20 (2H, m, $-NCH_2$), 4.26 (1H, m), 5.05-5.10 (2H, m), 5.19 (1H, dt, J^1=16.9, J^2=1.5), 5.80 (1H, ddd, J^1=5.7, J^2=10.4, J^3=16.9). Anal. Calcd. for $C_{15}H_{33}NO_3Si$: C, 60.90; H, 10.54; N, 4.44. Found: C, 60.99; H, 10.99; N, 4.43.

1-(N-tertBbutyloxycarbonylamino)-3-(t-butyldimethylsilyloxy)-4-oxiranyl pentane (7). To a stirred solution of 6 (3.1339 g; 9.9325 mmol) in methylene chloride (50 ml) at 0°C, were added sodium bicarbonate (0.8334 g; 9.932 mmol) and m-chloroperbenzoic acid (4.2851 g; 19.865 mmol). The mixture was allowed to warm to room temperature and then stirred for 48 h. The organic layer was washed with $NaHCO_3$, water, citric acid, dried (Na_2SO_4) and concentrated. The crude mixture was chromatographed using petroleum ether:ether (80:20) as eluant to yield epoxide 7, (2.7157 g; 82.5% yield) as an oil. R_f 0.31 [petroleum ether:ether (80:20)]; IR (neat) 3360, 1720, 1520, 1380, 1360, 1245, 1160, 1015, 930, 840, 770, 665 cm^{-1}; ^{1}H-Nmr: 0.06-0.13 (6H, m, $-SiMe_2$), 0.84-1.00 (9H, m, Si-*t*-Bu), 1.43 (9H, s, Boc), 1.67-1.85 (2H, m, $-CH_2$), 2.5-2.7 (1H, m), 2.72-2.75 (1H, m), 2.84-3.00 (1H, m), 3.2-3.45 (2H, m, $-NCH_2$), 3.60-3.75 (1H, m), 4.85-4.95 (1H, m, -NH). Anal. Calcd. for $C_{16}H_{33}NO_4Si$: C, 57.96; H, 10.03; N, 4.23. Found: C, 58.18; H, 10.11; N, 4.06.

Cyclization of 7: Method A. To a stirred solution of silyl epoxide 7 (0.1 g; 0.301 mmol) in anhydrous methylene chloride (10 ml) at 0°C, magnesium triflate (0.116 g; 0.36 mmol) and sodium bicarbonate (0.034 g) were added. The reaction mixture was allowed to warm to room temperature and stirred at this temperature for 4 h. The organic layer was then washed with brine, dried (Na_2SO_4) and concentrated. The resulting oil was chromatographed using methylene chloride:acetone (98:2) as eluant to afford the cis-alcohol 8a (0.032 g; 32% yield) and the trans-alcohol 8b (0.030 g, 30% yield).

Compound 8a: IR (neat) 3440, 1680, 1660, 1450, 1400, 1245, 1160, 1120, 1080, 1000, 875, 775, 660 cm^{-1}; ^{1}H-Nmr: 0.08-0.12 (6H, m, $-SiMe_2$), 0.88-0.91 (9H, m, -Si-*t*-Bu), 1.46 (9H, s, Boc), 1.77-1.95 (2H, m, $-CH_2$), 3.37-3.47 (2H, m, $-NCH_2$), 3.65-3.72 (1H, m), 3.82-3.85 (2H, m, $-OCH_2$), 4.37-4.48 (2H, m). Anal. Calcd. for $C_{16}H_{33}NO_4Si$: C, 57.96; H, 10.03; N, 4.23. Found: C, 57.97; H, 10.28; N, 4.39.

Compound 8b: IR (neat) 3440, 1680, 1660, 1400, 1280, 1235, 1155, 1100, 1030, 1000, 905, 825, 775, 660 cm^{-1}; ^{1}H-Nmr: 0.07 (6H, d, J=2.2, $-SiMe_2$), 0.87 (9H, s, -Si-*t*-Bu), 1.46, 1.45 (9H, s, Boc), 1.66-1.95 (2H, m, $-CH_2$), 3.29-3.39 (1H, m), 3.47-3.53 (3H, m), 3.57-3.72 (1H, m), 3.98, 4.28 (1H, m), 4.37-4.4 (1H, m, -OH, D_2O exchangeable). Anal. Calcd. for $C_{16}H_{33}NO_4Si$: C, 57.96; H, 10.03; N, 4.23. Found: C, 57.91; H, 10.07; N, 4.00.

Method B. The solution of epoxide 7 (5.097 g; 15.38 mmol) in dry methylene chloride (30 ml) was added dropwise to a precooled (-78°C) solution of freshly distilled boron trifluoride etherate (2.3 ml) in methylene chloride (270 ml). It was stirred at -78°C for 2 min and then quenched with 5 ml of saturated aqueous ammonium chloride solution. The solution was allowed to warm to 0°C. The methylene chloride layer was washed with water, aqueous $NaHCO_3$, brine, dried (Na_2SO_4) and concentrated. Purification was carried out as previously described to afford 8a (2.3965 g; 47.0% yield) and 8b (2.2482g; 44.1% yield) as oils.

Methyl 3-acetoxy-1-pyrroline-2-carboxylate (11). To a stirred solution of methyl-1-pyrroline-2-carboxylate (10) (1.949 g; 15.35 mmol), in dry methylene chloride (30 ml), was added freshly recrystallized lead tetraacetate (7.48 g, 16.87 mmol) in small portions at 0°C under N_2 atmosphere. The reaction mixture was stirred at 0°C for 15 min and then refluxed for 4 h. The precipitate of lead oxide was collected and washed with dry methylene chloride (2x5 ml). The combined organic layers were concentrated in vacuo to afford a quantitative recovery (2.8 g) of 11.

Methyl N-tert-butyloxycarbonyl-3-acetoxyprolinate (13). To a solution of the above crude reaction mixture in glacial acetic acid (20 ml), dimethylamine borane (1.36 g; 23.08 mmol) was added at 5°C. The reaction mixture was stirred at room temperature for 2 h, and the solvents were removed in vacuo. The residue was then dissolved in methylene chloride (20 ml) and cooled to 0°C. Triethylamine (6 ml) and di-tert-butyl dicarbonate (4.02 g; 18.42 mmol) were added to this residue. The reaction mixture was stirred at 0° for 1 h and at room temperature for 40 h. The solution was made acidic with a saturated solution of citric acid and an additional amount of methylene chloride (20 ml) was added. The organic layer was then washed with water, brine, dried (Na_2SO_4) and concentrated. Purification of the crude product by chromatography, using hexane-acetone (80:20) as eluant, afforded 13 (3.264 g; 74.4% yield) as an oil. IR (neat): 1760, 1730, 1715, 1410, 1340, 1280 cm^{-1}; ^{1}H-Nmr: 1.4, 1.5 (9H, s, Boc), 2.1 (3H, s, $-OCOCH_3$), 2.15-2.25 (2H, m, $-CH_2$), 3.5 (2H, m), 3.9 (3H, s, $-COOCH_3$), 4.52 and 4.6 (1H, two sets of d) and 5.45 (1H, q, J=6).

Methyl N-tert-butyloxycarbonyl-3-hydroxyprolinate (14). A mixture of compound 13 (1.0088 g; 3.527 mmol), methanol (25 ml) and potassium carbonate (0.975 g) was stirred at room temperature for 5 h. The solvent was removed in vacuo and the residue was dissolved in ethyl acetate and water. The organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated. The resulting oil was purified by flash chromatography using chloroform: acetone (90:10) as eluant to afford 0.8208 g (95% yield) of 14; ^{1}H-Nmr: 1.43, 1.45 (9H, s), 1.9-2.2 (2H, m), 3.23 (1H, d), 3.45-3.7 (2H, m), 3.78 (3H, s), 4.3-4.5 (1H, m) and 4.6-4.75 (1H, m).

Methyl N-tert-butyloxycarbonyl-3-t-butyldimethylsilyloxyprolinate (15). To a stirred solution of compound 14 (0.665 g; 2.71 mmol) in DMF (3.6 ml), t-butyldimethylsilyl chloride (0.814 g; 5.40 mmol) and imidazole (0.738 g; 10.85 mmol) were added. The solution was stirred at room temperature for 48 h. Water (10 ml) was then added and the mixture was extracted with ethyl acetate. The organic layer was then washed with brine, dried (Na_2SO_4) and concentrated. The resulting oil was purified by flash column chromatography using petroleum ether:ether (80:20) as the eluant to afford 15 (0.922 g; 95% yield); ^{1}H-Nmr: 0.05-0.17 (6H, m), 0.75-0.93 (9H, m), 1.35 and 1.48 (9H, s), 1.98 (2H, q), 3.3-3.5 (1H, m), 3.55-3.7 (1H, m), 3.72 and 3.75 (3H, two sets of s), 4.30 (1H, two sets of d) and 4.5-4.6 (1H, m).

Reduction of 15. To a suspension of sodium borohydride (0.026 g) and lithium chloride (0.028 g) in absolute ethanol (3 ml) at 0°C, a solution of 15 (0.1186 g; 0.33 mmol) in THF (2 ml) was added dropwise with vigorous stirring. After completion of the addition, the reaction mixture was allowed to warm to room temperature. It was stirred at this temperature for 24 h. The slurry was separated by filtration and the filtrate was concentrated in vacuo. The resulting oil was purified by flash chromatography using chloroform:acetone (97:3) as eluant. Two products were isolated: the hydroxy silyl ether 8b (0.04 g) and the cis-ester 15a (0.072 g). Compound 8b had identical spectral data to the sample prepared above.

N-tert-Butyloxycarbonyl-3-t-butyldimethylsilyloxyprolinal (16). To a precooled (-78°C) solution of methylene chloride (3 ml) and dimethylsulfoxide (0.43 ml; 6.06 mmol), trifluoroacetic anhydride (0.64 ml; 4.53 mmol) in methylene chloride (1.5 ml) was added dropwise. After 10 min, alcohol 8a (1.0 g; 3.016 mmol) in methylene chloride (3 ml) was added over a period of 5 min. The reaction mixture was stirred at -78°C for 1 h after which time triethylamine (1.20 ml; 8.61 mmol) was added and the resulting solution was warmed to 0°C and stirred for 45 min.. The reaction mixture was poured into a separatory funnel containing brine (3 ml) and extracted with ether (2x20 ml). The organic layer was dried (Na_2SO_4) and concentrated. Purification by flash column chromatography using methylene chloride:acetone (99:1) as eluant afforded pure aldehyde (0.878 g; 88% yield) as a clear, colorless oil. Using the same procedure compound 8b could also be oxidized to the corresponding aldehyde.

Compound 16: IR (neat) 1730, 1680, 1400, 1370, 1290, 1260, 1170, 1115, 1050, 1000, 900, 835 cm^{-1}; ^{1}H-Nmr: 0.02-0.07 (6H, m, $-SiMe_2$), 0.79-0.90 (9H, m, $-Si$-*t*-Bu), 1.39 and 1.46 (9H, s, Boc), 1.84-1.95 (2H, m, $-CH_2$), 3.59-3.70 (2H, m, $-NCH_2$), 3.94 (dd, J^1=3.2, J^2=5.1) and 4.07 (1H, dd, J^1=2.7, J^2=5.1), 4.64-4.69 (1H, m), 9.38 (d, J=3.2) and 9.44 (d, J=2.7); HRMS, M^++1, Calcd. for $C_{16}H_{31}NO_4Si$: 330.2030. Found: 330.1951.

Preparation of (S)-2-acetoxy-1,1,2-triphenylethanol. To a solution of (S) (+) methyl mandelate (0.25 g; 1.5 mmol) in anhydrous ether (1.6 ml) was added a solution of phenyl magnesium bromide (1.75 ml of 3.0 M solution, 5.25 mmol) at room temperature. The reaction mixture was refluxed for 2 h and then cooled. It was then quenched with saturated aqueous ammonium chloride solution. The layers were separated and the aqueous layer was extracted with ethyl acetate (3x15 ml). The combined organic layers were dried (Na_2SO_4) and concentrated. Purification by flash chromatography using petroleum ether:ether (75:25) as eluant gave (S)-2-hydroxy-1,1,2-triphenyl ethanol (0.34 g; 80% yield) as a solid, mp 111-117°C; IR ($CHCl_3$) 3400, 2950, 1160, 1025, 820 cm^{-1}; ^{1}H-Nmr: 1.14 (1H, s), 2.45 (1H, d, J=3), 5.61 (1H, d, J=3) and 6.9-7.8 (15H, m).

A solution of the above diol (0.320 g; 1.1 mmol) in methylene chloride (7 ml) and pyridine (0.13 ml; 1.6 mmol) was cooled to 0°C and then acetyl chloride (0.09 ml, 1.27 mmol) was added. The reaction mixture was warmed to room temperature and a white precipitate began to form. The mixture was further stirred at room temperature for 12 h. Removal of the solvent followed by recrystallization from acetone yielded a pure product (0.225 g; 62% yield); mp 244-245°C; $[\alpha]_D^{26}$ -192° (c 0.26, py), lit[15] $[\alpha]_D^{20}$ -209° (c 1.3, py); IR (KBr) 3450, 3000, 1700, 1480, 1360, 1240, 1160, 1020, 885, 830, 755, 730 and 690 cm^{-1}; ^{1}H-Nmr: 2.0 (3H, s), 2.85 (1H, s), 6.70 (1H, s) and 7.0-7.6 (15H, m).

Aldol Condensation of 16. To a stirred suspension of (S)-2-acetoxy-1,1,2-triphenylethanol (0.236 g; 0.71 mmol) in THF (6 ml) at -78°C was added a solution of lithium diisopropylamide in THF, prepared from diisopropylamine (0.24 ml; 1.71 mmol) and n-butyllithium (1.12 ml of 1.4 M solution, 1.56 mmol). The mixture was warmed to 0°C to give a clear yellow solution. The solution was then cooled to -78°C and a solution of magnesium bromide in THF (7.1 ml), prepared from magnesium turnings (48.6 mg; 2.00 mmol) and 1,2-dibromoethane (0.09 ml; 1.0 mmol) in THF (10 ml) was added. The mixture was stirred at -78°C for 1 h. The solution of aldehyde 16 (0.2342 g; 0.71 mmol) in THF (6 ml) was added dropwise to the solution of the enolate at -78°C and stirred at this temperature for 12 h. The resulting mixture was then quenched with saturated ammonium chloride solution (2 ml) and the solution was allowed to warm to 0°C. The organic layer was washed with water, brine, dried (Na_2SO_4) and concentrated. Purification by flash chromatography using methylene chloride:acetone (99:1) as eluant afforded 17a (0.142 g, 30.2% yield) and 17b (0.047 g, 10.0 % yield) as clear oils which slowly solidified.

Compound 17a: R_f 0.113 [methylene chloride:acetone (95:5)]; mp 90-92°C; $[\alpha]_D^{24}$ -102.9° (c 1.0, $CHCl_3$); IR ($CHCl_3$) 3590, 3440, 3070, 1735, 1690, 1495, 1450, 1400, 1370, 1260, 1160, 1125, 1085, 1035, 1005, 905, 835 cm^{-1}; ^{1}H-Nmr: 0.04-0.08 (6H, m, $-SiMe_2$), 0.85-0.87 (9H, m, -Si-*t*-Bu), 1.47 and 1.42 (9H, s, Boc), 1.75-1.81 (2H, m, $-CH_2$), 2.52-2.71 (2H, m), 3.33-3.54 (3H, m), 3.85 (1H, brs, -OH, D_2O exchangeable), 4.02-4.11 (1H, m), 4.32-4.43 (2H, m), 6.71 and 6.76 (1H, s), 7.00-7.61 (15H, m, Ar). Anal. Calcd. for $C_{38}H_{51}NO_7Si$: C, 68.95; H, 7.77; N, 2.12. Found: C, 68.99; H, 7.84; N, 2.15.

Compound 17b: R_f 0.225 [methylene chloride:acetone (95:5)]; mp 82-84°C; $[\alpha]_D^{24}$ -71.8° (c 1.3, $CHCl_3$); IR ($CHCl_3$) 3590, 3440, 3070, 1740, 1690, 1395, 1450, 1400, 1370, 1260, 1170, 1125, 1080, 1000, 900, 835 cm^{-1}; ^{1}H-Nmr: 0.07 (6H, s, $SiMe_2$), 0.86 (9H, s, -Si-*t*-Bu), 1.44, 1.48 (9H, s, Boc), 1.74-2.00 (2H, m, $-CH_2$), 2.4-2.59 (2H, m), 3.22-3.43 (2H, m, $-NCH_2$), 3.78 (1H, br s, -OH, D_2O exchangeable), 3.90-3.94 (1H, m), 4.09-4.22 (1H, m), 4.39-4.47 (2H, m), 4.74-4.77 (1H, m, -OH, D_2O exchangeable), 6.68 (1H, s), 7.03-7.58 (15H, m, Ar).

N-tert-Butyloxycarbonyl-(3aα, 7α, 7aα)-hexahydro-7-hydroxy-5-oxo-pyrano[3,2-b]pyrrole-1(2H)-carboxylic acid (18). To a solution of 17a (62.5 mg; 0.094 mmol) in THF (1.0 ml) at 0°C was added dropwise solution of tetrabutylammonium fluoride (1M in THF; 0.13 ml; 0.13 mmol). The solution was stirred at 0° for 30 min and then concentrated in vacuo. Purification by flash column chromatography using methylene chloride:acetone (98:2) as eluant afforded pure 18 (20.6 mg; 84.8% yield). Using the same procedure, 17b could also be converted to the other isomer. Compound 18: $[\alpha]_D^{23}$ -6.5° (c 1.0, $CHCl_3$); IR (neat) 3470, 1760, 1670, 1410, 1385, 1310, 1282, 1165, 1135 cm^{-1}; ^{1}H-Nmr (d_6-benzene): 1.02-1,17 (1H, m), 1.48 (9H, s, Boc), 1.56-1.67 (1H, m, -CH), 2.23 (1H, dd, J^1=15 Hz, J^2=12.2, -CH-CO-), 2.83 (1H, dd, J^1=15, J^2=4.2, -CH-CO-), 3.03 (1H, m), 3.18 (1H, m), 3.50 (1H, t, J=4, -N-CH-), 3.77-3.87 (2H, m, -CHOH, -CHO) and 5.21 (1H, br s, -OH).

(3R)-3-Hydroxy-3[(2R, 3S)-3-hydroxy-2-pyrrolidinyl]propanoic acid (1). Compound 1 was prepared from 18 in 78% yield using the procedure described by Hausler[3a] for the racemic compound. Compound 1, mp > 200° (dec); $[\alpha]_D^{23}$ -4.1° (c 0.5, H_2O), lit[3b] $[\alpha]_D$ -4.8° (c 0.5, H_2O); IR (KBr) 3300 (br), 2800 (br), 1640, 1545, 1410, 1340, 1140, 1020, 760, 620 cm^{-1}; ^{1}H-Nmr (D_2O): 2.10-2.26 (2H, m, $-CH_2$), 2.42 (1H, dd, J^1=7.6, J^2=15.6, -CH-CO-), 2.63 (1H, dd, J^1=4.5, J^2=15.6, -CH-CO-), 3.42-3.52 (3H, m, -N-CH-, $-N-CH_2$), 4.28-4.36 (1H, m, -CH-O), 4.70-4.77 (1H, m, -O-CH-).

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