Synthesis of chiral intermediates of quinine alkaloids and (+)-dihydroantirhine

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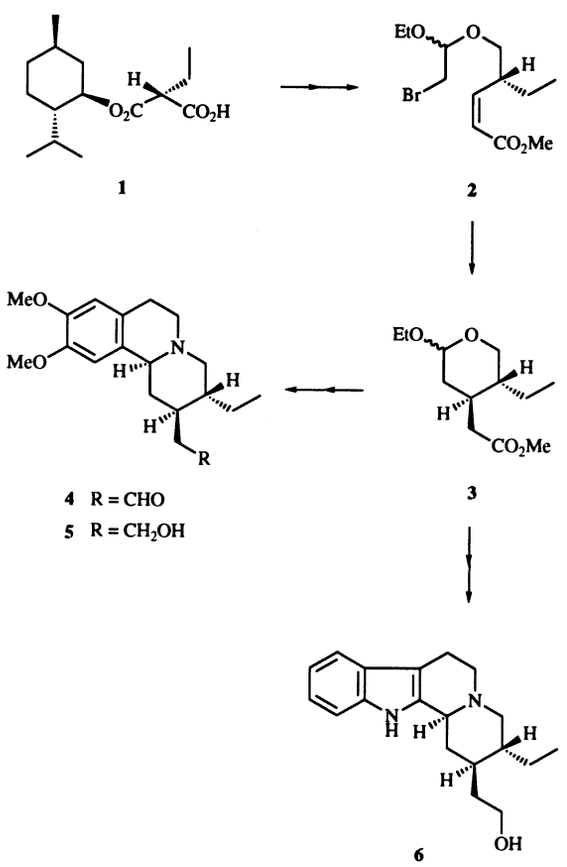
(4*R*,5*R*)-2-Ethoxy-5-ethyl-4-methoxycarbonylmethyl-3,4,5,6-tetrahydro-2*H*-pyran 3, which has been enantioselectively prepared, is converted into the *cis*-substituted lactone 11 by treatment with propanedithiol in the presence of boron trifluoride–diethyl ether. The product 11 is converted into the synthetic intermediate 7 of quinine alkaloids and the synthetic precursor 19 of (+)-dihydroantirhine 10.

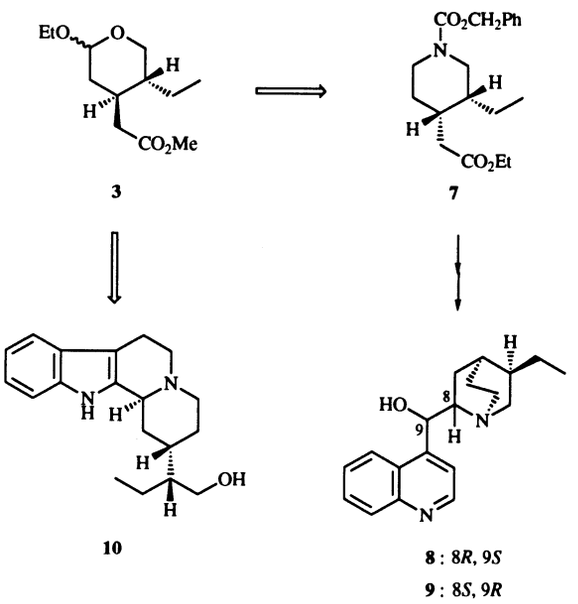
Previously, we achieved the stereocontrolled synthesis of the *trans*-substituted cyclic acetal **3** by cyclisation of the bromoacetal **2**, carried out by using organostannane[1] or nickel(II)-catalysed electroreduction (Scheme 1).[2] The substrate **2** was



Scheme 1

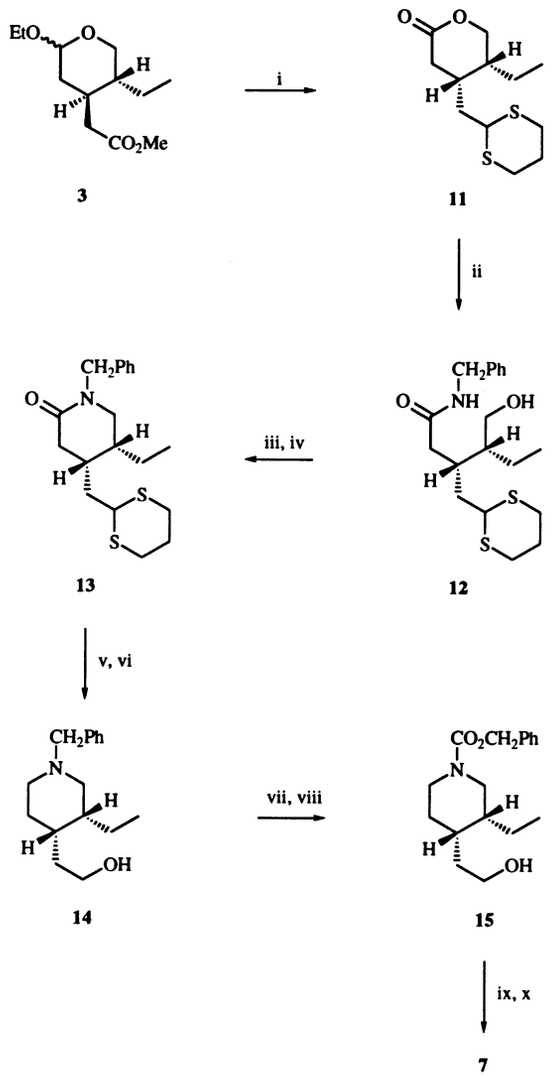
prepared from the chiral half ester **1**, which was diastereoselectively obtained through the crystallisation-induced asymmetric transformation.[3] The product **3** was converted into (−)-protoemetine **4**, (−)-protoemetinol **5**[1] and (−)-dihydrocorynantheol **6**.[4] We have conducted further studies to demonstrate the usefulness of **3** in alkaloid synthesis and describe here synthesis of quinine alkaloids, which are important in malerial therapy, and an indole alkaloid, (+)-dihydroantirhine.[5]

It was considered that the *cis*-substituted piperidine **7**, the synthetic intermediate of (+)-hydrocinchonine **8** and (−)-hydrocinchonidine **9**,[6] could be synthesised by insertion of a nitrogen atom between the alkoxy function and the ester function of **3** (Scheme 2). Furthermore, the introduction of a nitrogen atom between the acetal function and the ester function would lead to (+)-dihydroantirhine **10**, isolated from *Aspidosperma marcgrarianum*.[7]

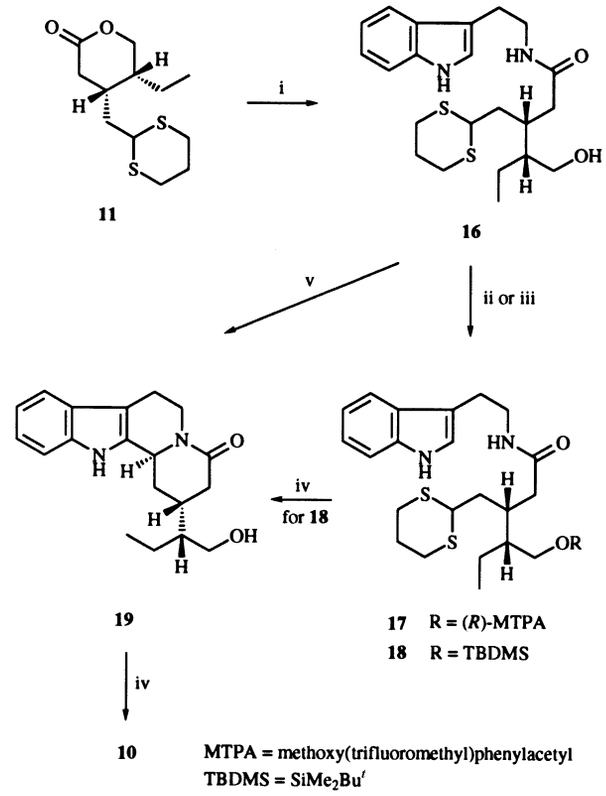


Scheme 2

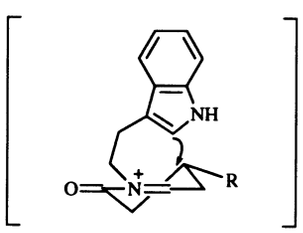
On the basis of the above considerations, the cleavage of the cyclic acetal function of **3**[1,2] was first examined. Treatment of **3** with propane-1,3-dithiol in the presence of a large excess of boron trifluoride–diethyl ether caused the formation of the thioacetal function as well as the lactone ring to give **11** (99%) (Scheme 3). The *cis*-substituted lactone **11** was heated with benzylamine in toluene to afford the amide **12** (85%). Transformation of **12** into the lactam **13** was carried out in 73% overall yield in two steps; mesylation followed by cyclisation using potassium hydride and 18-crown-6. Reaction of **13** with methyl iodide and sodium hydrogen carbonate in a mixture of acetonitrile and water[8] formed the corresponding aldehyde, which was reduced with lithium aluminium hydride in hot tetrahydrofuran. The piperidine derivative **14** was obtained in 70% overall yield in two steps. Direct conversion of the *N*-benzyl group of **14** into the carbamate group failed due to the presence of the hydroxy function. Therefore, the *N*-benzyl group of **14** was removed by hydrogenolysis using 10% palladium on activated carbon and ammonium formate[9] and the product was treated with benzyl chloroformate in the presence of sodium hydrogen carbonate in a mixture of benzene and water. The carbamate **15**, produced in 61% overall yield, was transformed in 84% overall yield into the ester **7** by Jones oxi-



Scheme 3 *Reagents and conditions:* i, $HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2$; ii, $PhCH_2NH_2$, heat; iii, MsCl, Et_3N; iv, KH, 18-crown-6; v, MeI, H_2O, MeCN, $NaHCO_3$; vi, $LiAlH_4$; vii, 10% Pd–C, HCO_2NH_4; viii, $ClCO_2CH_2Ph$, $NaHCO_3$; ix, Jones oxidation; x, EtOH, conc. H_2SO_4



Scheme 4 *Reagents and conditions:* i, tryptamine, heat; ii, MTPAOH, DCC, DMAP; iii, TBDMSCl, Et_3N, DMAP; iv, see ref. 10; v, MeI, H_2O, MeCN



20

dation followed by esterification. The racemate of **7** had been converted into (+)-hydrocinchonine **8** and (−)-hydrocinchonidine **9** by us.[6]

Next, the transformation of the *cis*-substituted lactone **11** into (+)-dihydroantirhine **10**[7] was investigated. Heating **11** with tryptamine in hot toluene provided the amide **16** in 91% yield (Scheme 4). The optical purity, >98% ee, was established from the 500 MHz NMR spectrum of its Mosher ester **17**. Protection of the hydroxy group of **16** with a *tert*-butyldimethylsilyl group afforded **18** (85%). The spectral properties of synthetic compound **18** were identical with those of the authentic compound.[10] The silyl ether **18** has been transformed into (+)-dihydroantirhine **10** *via* **19** by Suzuki and co-workers,[10] but in our route the tetracyclic compound **19** was directly synthesised from **16** by treatment with methyl iodide in a mixture of acetonitrile and water.[8] A mixture of **19** and its epimer was obtained in 64% yield in a ratio of 7:1. The desired compound **19** would be stereoselectively produced by ring closure through conformation **20** of the imine. Spectral data of **19**, $[\alpha]_D^{30}$ −41.3 ($CHCl_3$) [lit.,[10] $[\alpha]_D^{25}$ −21.7 ($CHCl_3$)], were consistent with reported values.[10,11]

Thus, the enantioselective syntheses of the intermediates **7** and **19** of quinine alkaloids and (+)-dihydroantirhine have been accomplished starting with **3**.

Experimental

General

Mps were measured on a Yanako micro melting-point apparatus and are uncorrected. IR Spectra were recorded on a JASCO IR-Report 100 spectrophotometer. NMR Spectra were measured for $CDCl_3$ solutions with Hitachi R-1200 and JNM-GX-500 spectrometers. Chemical shifts are recorded relative to internal $SiMe_4$; *J* values are given in Hz. Mass spectra were taken on JEOL-JMS-O1SG-2 and JEOL-DX-300 spectrometers. Optical rotations were determined on JASCO-DIP-340 and HORIBA SEPA-300 polarimeters. HPLC was carried out using a Gilson system and monitored by UV absorptions and refractive-index measurements.

All reactions were carried out under a positive atmosphere of dry Ar. Solvents were distilled prior to use: tetrahydrofuran, benzene and toluene were distilled from sodium–benzophenone, while dichloromethane was distilled from calcium hydride and stored over 4 Å molecular sieves. The organic extracts were dried over sodium sulfate unless otherwise indicated and the solvent was removed by rotary evaporation under reduced pressure. All new compounds described in the Experimental section were homogeneous on TLC and HPLC.

(−)-(4*S*,5*R*)-4-[(1,3-Dithian-2-yl)methyl]-5-ethyl-3,4,5,6-2*H*-tetrahydropyran-2-one 11

To a solution of the acetal **3**[1,2] (272 mg, 1.12 mmol) and propane-1,3-dithiol (0.169 cm^3, 1.69 mmol) in dry CH_2Cl_2 (5 cm^3) cooled with ice, was added boron trifluoride–diethyl ether (0.553 cm^3, 4.50 mmol). After the mixture had been stirred for 2.5 h at room temperature, it was directly subjected to chromatography on silica gel. Elution with ethyl acetate–hexane (3:7) provided the lactone **11** (290 mg, 99%) as an oil. Recrystallisation of this from benzene–diisopropyl ether–hexane gave prisms, mp 65–66 °C (Found: C, 55.2; H, 7.65; S, 24.3. $C_{12}H_{20}O_2S$ requires C, 55.35; H, 7.75; S, 24.6%); $[\alpha]_D^{23}$ −1.42 (*c* 0.70, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1730 (lactone); δ_H(500 MHz) 1.01 (3 H, t, *J* 7.3, CH_2Me), 1.27–1.45 (2 H, m, $CHCH_2Me$), 1.68 (1 H, ddd, *J* 14.5, 8.8 and 6.2, $CHCHHCH$), 1.83 (1 H, ddd, *J* 14.5, 8.8 and 5.0, $CHCHHCH$), 1.80–1.93 (2 H, m, 5-H, SCH_2CHH), 2.12–2.18 (1 H, m, SCH_2CHH), 2.41 (1 H, dd, *J* 17.2 and 8.2, 3-H), 2.43–2.51 (1 H, m, 4-H), 2.64 (1 H, dd, *J* 17.2 and 6.0, 3-H), 2.81–2.95 (4 H, m, 2 × SCH_2), 4.04 (1 H, dd, *J* 8.8 and 6.2, CHS_2) and 4.28 (2 H, d, *J* 4.9, 6-CH_2); *m/z* 260 (M^+).

(−)-(3*S*,4*R*)-*N*-Benzyl-4-hydroxymethyl-3-[(1,3-dithian-2-yl)-methyl]hexanamide 12

A mixture of the lactone **11** (45.9 mg, 0.176 mmol) and benzylamine (0.058 cm^3, 0.528 mmol) in toluene (1 cm^3) was heated under reflux for 16 h after which it was evaporated. The residue was chromatographed on silica gel with methanol–chloroform (1:19) as eluent to afford the amide **12** as an oil (55.1 mg, 85%); $[\alpha]_D^{26}$ −4.73 (*c* 1.06, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3440 (NH), 3380 (OH) and 1650 (amide); δ_H(500 MHz) 0.89 (3 H, t, *J* 7.3, 5-Me), 1.02–1.11 (1 H, m, 5-H), 1.20–1.29 (1 H, m, 5-H), 1.56–1.63 (1 H, m, 4-H), 1.72 (1 H, ddd, *J* 14.4, 7.5 and 6.4, $CHCHHCH$), 1.76 (1 H, ddd, *J* 14.4, 8.7 and 6.4, $CHCHHCH$), 1.79–1.88 (1 H, m, SCH_2CHH), 2.05–2.12 (1 H, m, SCH_2CHH), 2.13 (1 H, dd, *J* 14.1 and 5.5, 2-H), 2.39 (1 H, dd, *J* 14.1 and 7.9, 2-H), 2.49–2.56 (1 H, m, 3-H), 2.74–2.86 (4 H, m, 2 × SCH_2), 3.39 (1 H, dd, *J* 11.4 and 8.7, $OCHH$), 3.58 (1 H, dd, *J* 11.4 and 4.6, $OCHH$), 3.65–3.84 (1 H, m, OH), 4.02 (1 H, dd, *J* 8.7 and 6.9, CHS_2), 4.37 and 4.43 (each 1 H, each dd, *J* each 15.0 and 5.7, NCH_2Ph), 6.70 (1 H, br t, *J* 5.7, NH) and 7.23–7.34 (5 H, m, Ph); *m/z* (EI) 367.1645 (M^+, $C_{19}H_{29}NO_2S_2$ requires 367.1638).

(−)-(4*S*,5*R*)-*N*-Benzyl-4-[(1,3-dithian-2-yl)methyl]-5-ethylpiperidin-2-one 13

To a stirred solution of the amide **12** (99.2 mg, 0.270 mmol) and triethylamine (0.075 cm^3, 0.297 mmol) in dry benzene (1 cm^3) at 5 °C was added methanesulfonyl chloride (0.023 cm^3, 0.297 mmol). After the mixture had been stirred for 30 min at the same temperature it was diluted with benzene, washed with saturated aqueous sodium hydrogen carbonate and brine, dried and evaporated. After addition of dry benzene to the residue, the solvent was distilled off. To a suspension of potassium hydride (30% in oil; 310 mg, 2.70 mmol) and 18-crown-6 (10 mg, 0.038 mmol) in dry dimethoxyethane (5 cm^3) cooled with ice was slowly added a solution of the above product in dry dimethoxyethane (1 cm^3). After the mixture had been stirred for 30 min at room temperature, it was partitioned between saturated aqueous ammonium chloride and dichloromethane. The organic layer was separated, washed with brine, dried and evaporated to give a residue. This was subjected to chromatography on silica gel. Elution with ethyl acetate–hexane (7:3) afforded the lactam **13** (69.0 mg, 73%) as an oil, $[\alpha]_D^{26}$ −26.8 (*c* 1.26, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 1638 (lactam); δ_H(500 MHz) 0.79 (3 H, t, *J* 7.4, 5-CH_2Me), 1.16–1.36 (2 H, m, 5-CH_2), 1.60 (1 H, ddd, *J* 15.1, 9.5 and 5.5, 4-CHH), 1.72 (1 H, ddd, *J* 15.1, 9.5 and 4.1, 4-CHH), 1.74–1.82 (1 H, m, 5-H), 1.82–1.92 (1 H, m, SCH_2CHH), 2.10–2.17 (1 H, m, SCH_2CHH), 2.32–2.39 (1 H, m, 4-H), 2.41 (1 H, dd, *J* 17.6 and 6.8, 3-H), 2.52 (1 H, dd, *J* 17.6 and 6.3, 3-H), 2.79–2.95 (4 H, m, 2 × CH_2), 2.97 (1 H, dd, *J* 12.5 and 8.0, 6-H), 3.17 (1 H, dd, *J* 12.5 and 4.8, 6-H), 4.07 (1 H, dd, *J* 9.5 and 5.5, CHS_2), 4.49 and 4.66 (each 1H, each d, *J* each 14.6, NCH_2Ph) and 7.22–7.34 (5 H, m, Ph); *m/z* (EI) 349.1542 (M^+, $C_{19}H_{27}NOS_2$ requires 349.1534).

(+)-(3*R*,4*S*)-*N*-Benzyl-3-ethyl-4-(2-hydroxyethyl)piperidine 14

A mixture of the lactam **13** (62.8 mg, 0.018 mmol), methyl iodide (0.560 cm^3, 9.0 mmol) and sodium hydrogen carbonate (378 mg, 4.50 mmol) in acetonitrile–water (8:1; 4.5 cm^3) was stirred for 12 h at room temperature. After dilution with dichloromethane, the mixture was washed with brine, dried and evaporated to give the crude aldehyde; ν_{max}($CHCl_3$)/cm^{-1} 1722 (formyl) and 1628 (amide); δ_H(60 MHz) 0.70–0.95 (3 H, m, 5-CH_2Me), 0.97–1.04 (2 H, m, 5-CH_2), 1.55–3.40 (8 H, m), 4.43 and 4.77 (each 1 H, each d, *J* each 14.4, NCH_2Ph), 7.30 (5 H, s, Ph) and 9.76–9.90 (1 H, m, CHO).

To a suspension of lithium aluminium hydride (13.7 mg, 0.36 mmol) in dry tetrahydrofuran (5 cm^3) under reflux was added a solution of the above product in dry tetrahydrofuran (2 cm^3). After being heated for 23 h under reflux, the mixture was partitioned between 10% aqueous sodium hydroxide and dichloromethane. The organic layer was separated, dried and evaporated to afford a residue, which was chromatographed on silica gel. Elution with methanol–chloroform (1:19) yielded the amide **14** as an oil (31.2 mg, 70%), $[\alpha]_D^{26}$ +31.6 (*c* 0.297, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3350 (OH); δ_H(500 MHz) 0.82 (3 H, t, *J* 7.4, CH_2Me), 1.22–1.31 (2 H, m, 5-CH_2), 1.42–1.85 (6 H, m), 2.25–2.90 (4 H, m, 2- and 6-CH_2), 3.53–3.83 (5 H, m, NCH_2Ph and CH_2OH), 7.30 (1 H, t, *J* 7.2, ArH), 7.34 (2 H, t, *J* 7.2, 2 × ArH) and 7.34 (2 H, d, *J* 7.2, 2 × ArH); *m/z* (EI) 247.1925 (M^+, $C_{16}H_{25}NO$ requires 247.1936).

(+)-(3*R*,4*S*)-*N*-Benzyloxycarbony-3-ethyl-4-(2-hydroxyethyl)-piperidine 15

A mixture of the amine **14** (53.5 mg, 0.216 mmol), 10% palladium on activated carbon (60 mg) and ammonium formate (273 mg, 4.33 mmol) in benzene (2 cm^3) was heated for 1 h under reflux. After dilution with benzene followed by filtration through Celite, the filtrate was washed with 10% aqueous sodium hydroxide, dried (K_2CO_3) and evaporated to afford the crude amine; δ_H(60 MHz) 0.70–1.05 (3 H, m, CH_2Me), 1.05–2.10 (6 H, m), 2.30–3.20 (6 H, m) and 3.65 (2 H, t, *J* 7.2, CH_2OH).

To a stirred mixture of the above product and sodium hydrogen carbonate (54.4 mg, 0.648 mmol) in benzene–water (2:1; 5 cm^3) was added benzyl chloroformate (0.093 cm^3, 0.648 mmol). After the mixture had been stirred for 40 h at room temperature it was diluted with benzene, washed with water, dried and evaporated. Chromatography of the residue on silica gel with ethyl acetate–hexane (1:1) as eluent provided the alcohol **15** as an oil (38.7 mg, 61%), $[\alpha]_D^{27}$ +9.9 (*c* 0.31, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3620 and 3460 (OH) and 1680 (carbamate); δ_H(500 MHz) 0.80–1.02 (3 H, m, CH_2Me), 1.15–1.32 (2 H, m, 5-CH_2), 1.35–1.65 (6 H, m), 1.75–1.86 (1 H, m), 2.90–3.12 (2 H, m, 2- and 6-H), 3.63–3.75 (2 H, m, CH_2OH), 3.82–4.07 (2 H, m, 2- and 6-H), 5.09 and 5.14 (each 1H, each d, *J* each 12.8, OCH_2Ph) and 7.28–7.36 (5 H, m, Ph); *m/z* (EI) 291.1825 (M^+, $C_{17}H_{25}NO_3$ requires 291.1835).

(+)-Ethyl (3*R*,4*S*)-(*N*-benzyloxycarbonyl-3-ethyl-4-piperidyl)-acetate 7

To a stirred solution of the alcohol **15** (7.8 mg, 0.027 mmol) in acetone (2 cm^3) cooled with ice was added Jones reagent (0.017 cm^3, 0.11 mmol). After the mixture had been stirred for 40 min with ice cooling, it was treated with isopropyl alcohol (0.5 cm^3), diluted with dichloromethane, washed with water, dried and evaporated. The residue was taken up into ethanol (2 cm^3) to which concentrated sulfuric acid (0.1 cm^3) was added. After the mixture had been stirred for 20 h at room temperature it was poured into saturated aqueous sodium hydrogen carbonate cooled with ice and the mixture was thoroughly extracted with

dichloromethane. The combined extracts were washed with water, dried and evaporated to give a residue, which was purified by silica gel chromatography. Elution with ethyl acetate–hexane (1:5) gave the ester **7** as an oil (7.5 mg, 84%), $[\alpha]_D^{26}$ +5.7 (*c* 0.40, $CHCl_3$), the IR and ^1H NMR spectra and TLC behaviour of which were identical with those of the racemate of **7**.[6]

(−)-(3*S*,4*R*)-3-[(1,3-Dithian-2-yl)methyl]-4-hydroxymethyl-*N*-[2-(indol-3-yl)ethyl]hexanamide 16

A mixture of the lactone **11** (38.4 mg, 0.147 mmol) and tryptamine (57.6 mg, 0.295 mmol) in dry toluene (1 cm^3) was heated for 10 h under reflux. The reaction mixture was then subjected to chromatography on silica gel. Elution with ethyl acetate–hexane (1:1) followed by ethyl acetate–hexane (4:1) gave the alcohol **16** as a pale yellow oil (56.0 mg, 91%), $[\alpha]_D^{23}$ −10.2 (*c* 1.12, $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3470 (NH), 3420 (OH) and 1640 (amide); δ_H(500 MHz) 0.89 (3 H, t, *J* 7.3, CH_2Me), 0.97–1.08 (1 H, m, 5-H), 1.18–1.27 (1 H, m, 5-H), 1.26 (1 H, br s, OH), 1.57–1.62 (1 H, m, 4-H), 1.67 (1 H, ddd, *J* 14.4, 9.0 and 7.2, S_2CHCHH), 1.73 (1 H, ddd, *J* 14.4, 7.6 and 5.7, S_2CHCHH), 1.78–1.88 (1 H, m, SCH_2CHH), 2.03 (1 H, dd, *J* 14.4 and 4.6, 2-H), 2.04–2.11 (1 H, m, SCH_2CHH), 2.25 (1 H, dd, *J* 14.4 and 8.4, 2-H), 2.35–2.45 (1H, m, 3-H), 2.73–2.86 (4 H, m, 2 × CH_2), 2.99 (2 H, t, *J* 7.1, $ArCH_2$), 3.33 (1 H, dd, *J* 11.4 and 9.5, OCHH), 3.58 (1 H, dd, *J* 11.4 and 4.8, OCHH), 3.63 (2 H, dt, *J* 7.1 and 6.2, NCH_2CH_2), 3.98 (1 H, dd, *J* 7.6 and 7.2, CHS_2), 5.82 (1 H, br t, *J* 6.2, NH), 7.08 (1 H, d, *J* 2.1, ArH), 7.13, 7.21, 7.38 and 7.60 (each 1 H, each t, *J* each 8.1, 4 × ArH) and 8.17 (1 H, br s, NH); *m/z* (EI) 420.1883 (M^+, $C_{22}H_{32}N_2O_2S_2$ requires 420.1883).

(2*R*,3*S*)-3-[(1,3-Dithian-2-yl)methyl]-2-ethyl-4-{*N*-[2-(indol-3-yl)ethyl]carbamoyl}butyl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionate 17

To a stirred solution of the alcohol **16** (1.7 mg, 0.004 mmol), (*R*)-(+)-3,3,3-trifluoro-2-methoxy-2-phenylpropionic acid (9.5 mg, 0.040 mmol) and 4-dimethylaminopyridine (0.5 mg, 0.004 mmol) in dry dichloromethane (2 cm^3) cooled with ice was slowly added a solution of dicyclohexylcarbodiimide (6.7 mg, 0.032 mmol) in dry dichloromethane (1 cm^3). After the mixture had been stirred for 12 h at room temperature it was evaporated and the residue was taken up into diethyl ether. The mixture was filtered through Celite and evaporation of the filtrate gave a residue, which was chromatographed on silica gel. Elution with ethyl acetate–hexane (3:7) yielded the ester **17** as an oil (2.1 mg, 82%), $\nu_{max}(CHCl_3)/cm^{-1}$ 3540 (NH), 1758 (ester) and 1661 (amide); δ_H(500 MHz) 0.88 (3 H, t, *J* 7.4, CH_2Me), 1.16–1.25 (1 H, m, 2-CHH), 1.25–1.34 (1 H, m, 2-CHH), 1.46 (1 H, ddd, *J* 14.0, 8.8 and 4.9, S_2CHCHH), 1.68 (1 H, ddd, *J* 14.0, 8.8 and 4.0, S_2CHCHH), 1.68–1.73 (1 H, m, 2-H), 1.77–1.88 (1 H, m, SCH_2CHH), 1.89 (1 H, dd, *J* 14.2 and 7.8, 4-H), 2.00 (1 H, dd, *J* 14.2 and 5.8, 4-H), 2.05–2.12 (1 H, m, SCH_2CHH), 2.30–2.46 (1 H, m, 3-H), 2.75–2.86 (4 H, m, 2 × SCH_2), 2.96 (2 H, t, *J* 6.9, $ArCH_2$), 3.49 (3 H, s, OMe), 3.49–3.56 (1 H, m, CHHN), 3.58–3.66 (1 H, m, CHHN), 3.89 (1 H, dd, *J* 8.8 and 4.9, CHS_2), 4.08 (1 H, dd, *J* 11.5 and 4.8, 1-H), 4.32 (1 H, dd, *J* 11.5 and 7.3, 1-H), 5.57–5.64 (1 H, m, NH), 7.04 (1 H, d, *J* 2.7, ArH), 7.14 (1 H, br t, *J* 7.4, ArH), 7.21 (1 H, br t, *J* 7.4, ArH), 7.20–7.24 (1 H, m, ArH), 7.34–7.46 (2 H, m, 2 × ArH), 7.44–7.47 (2 H, m, 2 × ArH), 7.37 (1 H, br d, *J* 7.6, ArH), 7.61 (1 H, br d, *J* 7.6, ArH) and 8.03 (1 H, br s, NH); *m/z* (EI) 636.2274 (M^+, $C_{32}H_{39}F_3N_2O_4S_2$ requires 636.2303).

(−)-(3*S*,4*R*)-4-*tert*-Butyldimethylsiloxymethyl-3-[(1,3-dithian-2-yl)methyl]-*N*-[2-(indol-3-yl)ethyl]hexanamide 18

A mixture of the alcohol **16** (17.2 mg, 0.0409 mmol), *tert*-butyldimethylsilyl chloride (10.3 mg, 0.0686 mmol), 4-dimethylaminopyridine (1.0 mg, 0.0082 mmol) and triethylamine (0.024 cm^3, 0.172 mmol) in dichloromethane (2 cm^3) was stirred for 1 h at room temperature. After dilution with dichloromethane, the mixture was washed with brine, dried and evaporated. Silica gel chromatography of the residue with ethyl acetate–hexane (1:4) as eluent afforded the silyl ether **18** as an oil (18.6 mg, 85%), $[\alpha]_D^{23}$ −10.1 (*c* 0.846, $CHCl_3$) [lit.,[10] $[\alpha]_D^{25}$ −6.2 ($CHCl_3$)]; $\nu_{max}(CHCl_3)/cm^{-1}$ 3540 (NH) and 1654 (C=O); δ_H(500 MHz) 0.02 (6 H, s, 2 × SiMe), 0.86 (9 H, s, Bu^t), 0.89 (3 H, t, *J* 7.4, CH_2Me), 1.14–1.29 (2 H, m, 5-H_2), 1.47–1.54 (1 H, m, 4-H), 1.66 (1 H, ddd, *J* 14.1, 8.1 and 5.7, CHCHHCH), 1.76 (1 H, ddd, *J* 14.1, 8.8 and 4.9, CHCHHCH), 1.79–1.88 (1 H, m SCH_2CHH), 2.05–2.12 (1 H, m, SCH_2CHH), 2.09 (1 H, dd, *J* 14.2 and 6.9, 2-H), 2.35 (1 H, dd, *J* 14.2 and 7.0, 2-H), 2.36–2.43 (1 H, m, 3-H), 2.74–2.87 (4 H, m, 2 × SCH_2), 2.98 (2 H, *J* 6.8, $ArCH_2$), 3.49 (1 H, dd, *J* 10.5 and 7.5, OCHH), 3.56 (1 H, dd, *J* 10.5 and 4.8, OCHH), 3.55–3.66 (2 H, m, NCH_2), 4.02 (1 H, dd, *J* 8.8 and 5.7, CHS_2), 5.82–5.92 (1 H, m, NH), 7.07 (1 H, d, *J* 2.0, ArH), 7.12 (1 H, t, *J* 8.3, ArH), 7.20 (1 H, t, *J* 8.3, ArH), 7.37 (1 H, d, *J* 8.3, ArH), 7.61 (1 H, d, *J* 8.3, ArH) and 8.05 (1 H, br s, NH); *m/z* (EI) 534.2736 (M^+, $C_{28}H_{46}N_2O_2S_2Si$ requires 534.2771), the spectral data for which were consistent with those of the authentic compound.[10]

(−)-(1′*R*,2*R*,12b*S*)-2-[1-(Hydroxymethyl)propyl]-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-4-one 19

A mixture of the alcohol **16** (19.5 mg, 0.0464 mmol), methyl iodide (0.30 cm^3, 0.48 mmol) and acetonitrile–water (4:1; 0.5 cm^3) was stirred for 60 h at room temperature and then poured into 10% aqueous ammonia. The mixture was thoroughly extracted with dichloromethane. The combined extracts were dried (potassium carbonate) and evaporated to give a residue which was subjected to chromatography on silica gel. Elution with ethyl acetate–dichloromethane (4:1) afforded a 7:1 mixture of two diastereoisomers as a powder (7.2 mg, 64%). Further purification by HPLC using Microsorb Si (4.6 × 250 mm, 5 μm) with ethyl acetate as eluent provided the major isomer **19** as a powder, $[\alpha]_D^{30}$ −41.3 (*c* 0.103, $CHCl_3$) [lit.,[10] $[\alpha]_D^{25}$ −21.7 ($CHCl_3$)]; $\nu_{max}(CHCl_3)/cm^{-1}$ 3470 (NH), 3350 (OH) and 1620 (C=O); δ_H(500 MHz) 0.91 (3 H, t, *J* 7.5, CH_2Me), 1.24–1.32 (1 H, m, CHHMe), 1.26 (1 H, br s, OH), 1.33–1.40 (1 H, m, 2-CH), 1.44–1.52 (1 H, m, CHHMe), 1.83–1.92 (1 H, m, 2-H), 2.18 (1 H, ddd, *J* 15.8, 10.3 and 5.7, 1-H), 2.30 (1 H, dd, *J* 17.0 and 10.4, 3-H), 2.32–2.38 (1 H, m, 1-H), 2.52 (1 H, ddd, *J* 17.0, 5.9 and 1.9, 3-H), 2.68–2.74 (1 H, m, 7-H), 2.92–3.04 (2 H, m, 6- and 7-H), 3.72 (1 H, dd, *J* 11.0 and 5.0, CHHOH), 3.81 (1 H, dd, *J* 11.0 and 3.8, CHHOH), 4.94–4.98 (1 H, m, 12b-H), 5.00–5.05 (1 H, m, 6-H), 7.11 (1 H, t, *J* 8.0, ArH), 7.18 (1 H, t, *J* 8.0, ArH), 7.33 (1 H, d, *J* 8.0, ArH), 7.48 (1 H, d, *J* 8.0, ArH) and 8.06 (1 H, br s, NH); *m/z* (EI) 312.1820 (M^+, $C_{19}H_{24}N_2O_2$ requires 312.1838), the spectral data for which were consistent with those of the authentic compound.[10]

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11 There is a large discrepancy between the optical rotation obtained by the present work and the literature value. The compound **19**, previously reported, had been synthesised from labile (*R*)-1,2-isopropylideneglyceraldehyde.[10]

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