Asymmetric Total Synthesis of Naturally Occurring (*R*)-(−)-Enantiomer of Tylophorine *via* Intramolecular Double Michael Reaction

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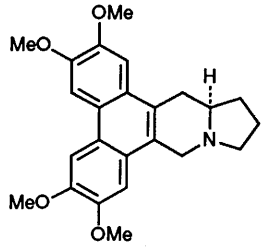
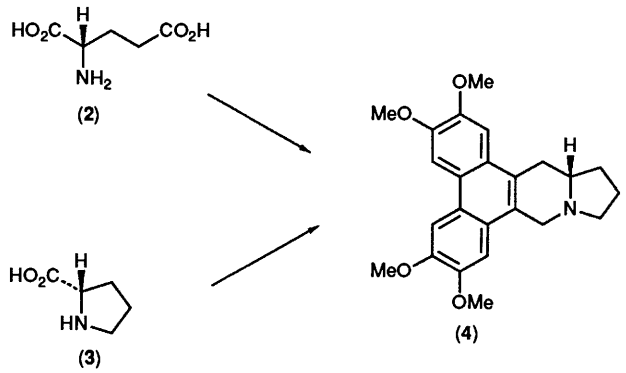
The first asymmetric total synthesis of the naturally occurring (*R*)-(−)-enantiomer (**1**) of tylophorine was achieved with high enantioselectivity *via* the intramolecular double Michael reaction of α,β-unsaturated esters (**10**) and (**20**), having two different chiral auxiliaries, with t-butyldimethylsilyl trifluoromethanesulphonate in the presence of triethylamine. (−)-Phenylmenthol and (2*R*,4*S*,5*R*)-(−)-4-(t-butyldimethylsiloxymethyl)-5-hydroxy-2-phenyl-1,3-dioxane, readily available from D-glucose, were used as chiral auxiliaries.

The absolute configuration of a phenanthroindolizidine alkaloid, (−)-tylophorine,[1,2] $[\alpha]_D^{27}$ −11.6° (*c* 1.07 in $CHCl_3$), was tentatively assigned as the (*S*)-form (**4**) on the basis of



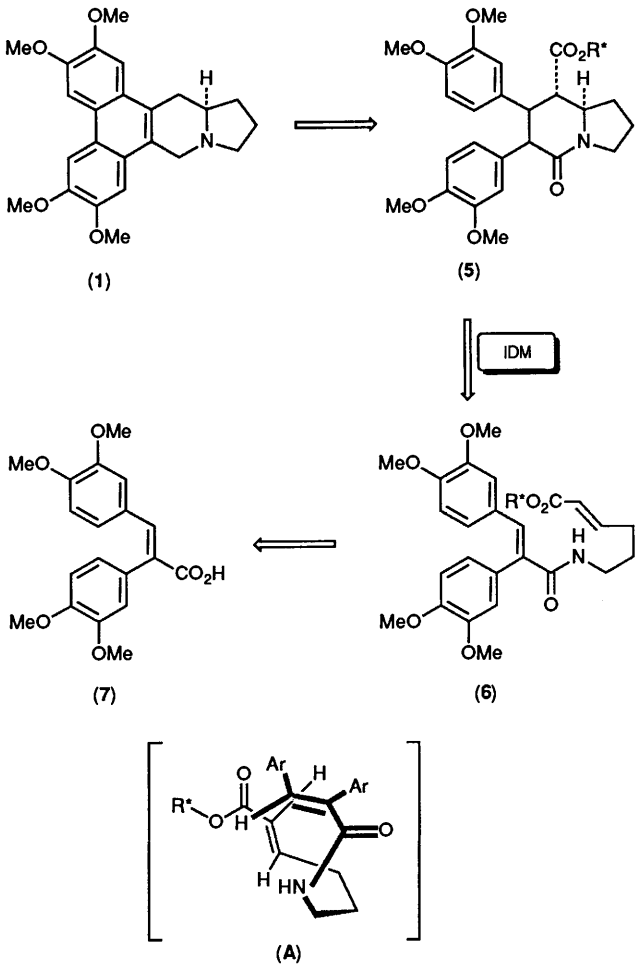
(1)

degradation studies.[3] However the (*S*)-isomer (**4**), prepared by syntheses (Scheme 1) starting from (*S*)-amino acids (**2**)[4] and (**3**),[5] showed dextrorotatory behaviour. Furthermore, Nordlander and Njorage[5] reported that the specific rotation of the (*S*)-isomer was $[\alpha]_D^{25}$ +73° (*c* 0.7 in $CHCl_3$) and that the value gradually decreased in solution. Synthesis of optically active



Scheme 1.

tylophorine has so far only been carried out using (*S*)-amino acids as chiral precursors as above and the synthesis of the naturally occurring enantiomer (**1**) has not been reported. Recently we developed a new methodology for the synthesis of quinolizidine and indolizidine derivatives by the intramolecular double Michael reaction.[6] A short synthesis of (±)-tylophorine was carried out by intramolecular double Michael reaction of the enone ester (**6**; R* = Et) derived from the acid (**7**).[7] Our attention then focussed on the asymmetric synthesis of



Scheme 2. IDM = Intramolecular double Michael reaction.

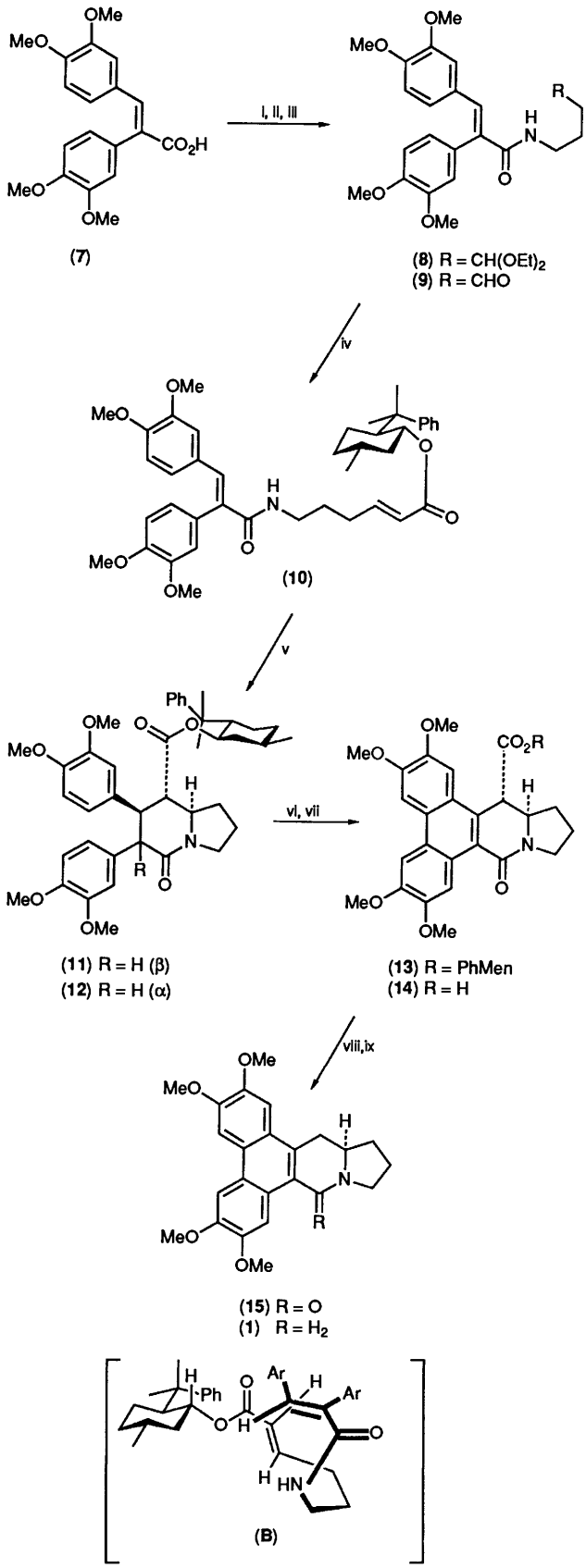
natural (*R*)-(−)-tylophorine (**1**) by exploitation of the above methodology. Since the intramolecular double Michael reaction was supposed to proceed *via* the conformation (**A**), the α,β-unsaturated amide should approach from the *si-re* face of the α,β-unsaturated ester in order to construct the (8a*R*)-indolizidine (**5**) (Scheme 2). We therefore speculated that the *re-si* face of the α,β-unsaturated ester should be hindered by the presence of a chiral auxiliary. Based on the above considerations, a highly enantioselective synthesis of the (*R*)-

(−)-enantiomer (**1**) was performed by way of the intramolecular double Michael reaction of the enone ester (**6**) possessing two different chiral auxiliaries.[8]

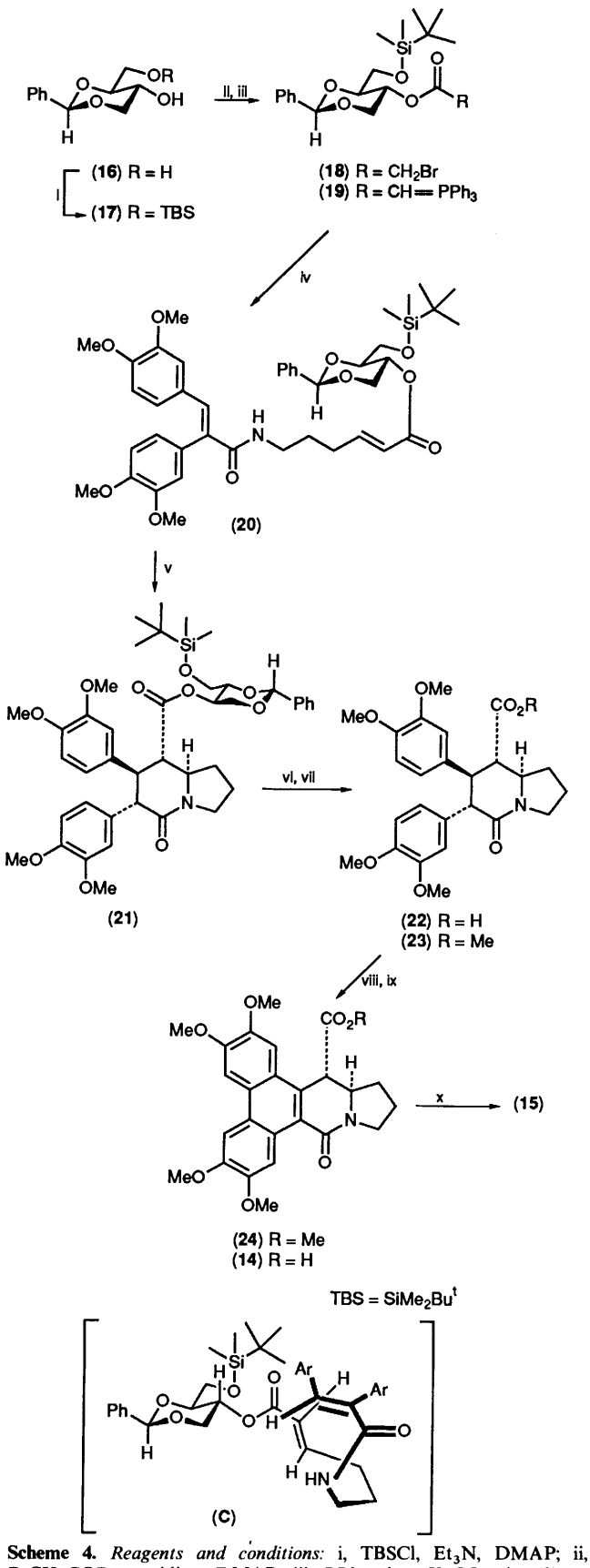
The (*E*)-acid (**7**)[9] was converted into the acid chloride and then condensed with 4-aminobutyraldehyde diethyl acetal to afford the amide (**8**) in quantitative yield. Deprotection of the acetal (**8**) with dilute acetic acid gave quantitatively the aldehyde (**9**), which was condensed with (−)-phenylmenthyl (triphenylphosphoranylidene)acetate[10] in refluxing acetonitrile to afford the (*E*,*E*)-ester (**10**), $[\alpha]_D^{25}$ +0.26° (*c* 1.49 in $CHCl_3$), in 79% yield. Reaction of the (*E*,*E*)-unsaturated ester (**10**) with t-butyldimethylsilyl trifluoromethanesulphonate (TBSOTf) in the presence of excess of triethylamine[6,7] in dichloromethane at −78 °C for 2 h produced a mixture of indolizidines (**11**) and (**12**) in the ratio *ca.* 4:1 in 92% yield. Treatment of the mixture (**11**) and (**12**) with sodium hydride in refluxing tetrahydrofuran (THF) for 2.5 h gave the single indolizidine (**11**), $[\alpha]_D^{26}$ +55.47° (*c* 4.46 in $CHCl_3$) in 78% yield. It was therefore assumed that the two products of the annulation were stereoisomers at the 6-position on the indolizidine ring. The stereochemistries at the three contiguous asymmetric centres, the 7-, 8-, and 8a-position, were tentatively assigned on consideration of the presumed conformation (**B**) of the transition state. The complete diastereofacial selectivity was made clear at the stage of the pentacyclic compound (**13**). Namely, oxidation of the epimeric mixture (**11**) and (**12**) using an excess of thallium(III) trifluoroacetate (TTFA) in the presence of boron trifluoride–diethyl ether in a mixture of dichloromethane and trifluoroacetic acid (TFA)[11] provided, in 55% yield, the phenanthroindolizidine (**13**), m.p. 252–254 °C; $[\alpha]_D^{26}$ −129.98° (*c* 0.748 in $CHCl_3$), as a single stereoisomer. The ^1H NMR spectrum (500 MHz; $CDCl_3$) of the product clearly indicated that the lactam (**13**) had been formed in >99% d.e. Hydrolysis of the ester (**13**) with potassium hydroxide in reluxing ethanol for 24 h gave the acid (**14**), m.p. 194–198 °C (decomp.); $[\alpha]_D^{26}$ −247.83° (*c* 1.5 in MeOH); $[\alpha]_D^{25}$ −258.11° (*c* 0.36 in $CHCl_3$), in 83% yield. Heating of the acid (**14**) in hexamethylphosphoramide (HMPA) at 230–240 °C gave rise to decarboxylation to produce (−)-tylophorin-9-one (**15**), m.p. 286–289 °C; $[\alpha]_D^{24}$ −214.65° (*c* 0.86 in $CHCl_3$), in 65% yield. Reduction of the lactam (**15**) with sodium bis(2-methoxyethoxy)aluminium hydride in refluxing dioxane for 2 h provided (*R*)-(−)-tylophorine (**1**), m.p. 274–276 °C (lit.,[12] m.p. 275 °C); $[\alpha]_D^{25}$ −76.5° (*c* 0.04 in $CHCl_3$) {lit.,[1] −11.6° (*c* 1.07 in $CHCl_3$); for (+)-form: lit.,[4] $[\alpha]_D^{23}$ +12° (*c* 0.7 in $CHCl_3$); lit.,[5] $[\alpha]_D^{21}$ +73° (*c* 0.7 in $CHCl_3$)}, in 87% yield (Scheme 3). The spectral data were identical with those of the authentic racemate.[7,13]

Thus the asymmetric synthesis of the natural enantiomer of tylophorine (**1**) was accomplished by an intramolecular double Michael reaction employing (−)-phenylmenthol as a chiral auxiliary. Supposing an antiplanar disposition between the conjugated double bond and the ester carbonyl bond of the α,β-unsaturated ester as well as a *syn*-planar arrangement between alkoxy α-hydrogen on the phenylmenthol and the ester carbonyl oxygen atom,[9,14] the above result would support the expected transition state (**B**).

On the basis of the above results, we anticipated that 1,3-*O*-benzylidene-L-erythritol (**16**),[15] readily available from D-glucose, would be a useful precursor to an alternative chiral auxiliary. Thus the primary alcohol group of the diol (**16**) was first protected with a t-butyldimethylsilyl group to give the monoether (**17**), which was acylated with bromoacetyl bromide in pyridine. Reaction of the bromoacetate (**18**), $[\alpha]_D^{26}$ −37.07° (*c* 2.49 in $CHCl_3$), thus obtained in 70% overall yield, with triphenylphosphine in benzene, followed by basic treatment of the resulting phosphonium salt, provided the ylide (**19**) in 92% overall yield.



Scheme 3. *Reagents and conditions:* i, $(COCl)_2$; ii, $H_2N[CH_2]_3CH(OEt)_2$, $NaHCO_3$; iii, aq. AcOH; iv, $Ph_3P{=}CHCO_2PhMen$; v, TBSOTf, Et_3N; vi, TTFA, $BF_3{\cdot}OEt_2$, TFA; vii, KOH; viii, HMPA, heat; ix, $NaAl(OCH_2CH_2OMe)_2H_2$. PhMen = 8-phenyl-*p*-menthan-3-yl.



Scheme 4. *Reagents and conditions:* i, TBSCl, Et_3N, DMAP; ii, $BrCH_2COBr$, pyridine, DMAP; iii, PPh_3 then K_2CO_3; iv, (**9**); v, TBSOTf, Et_3N; vi, KOH; vii, CH_2N_2; viii, TTFA, $BF_3{\cdot}OEt_2$, TFA; ix, KOH; x, HMPA, heat.

Wittig reaction of the ylide (**19**) with the aldehyde (**9**) in acetonitrile afforded the (*E,E*)-unsaturated ester (**20**), $[\alpha]_D^{27}$ −22.86° (*c* 1.84 in $CHCl_3$), in 85% yield as a single product. Treatment of the ester (**20**) with t-butyldimethylsilyl trifluoromethanesulphonate in the presence of excess of triethylamine[6,7] in dichloromethane at −78 to −5 °C for 2 h furnished, in 76% yield, the single indolizidine (**21**), $[\alpha]_D^{25}$ +42.35° (*c* 2.92 in $CHCl_3$), whose homogeneity was supported by 500 MHz ^1H NMR spectroscopy. The stereostructure of the product (**21**) was also deduced from consideration of the transition state (**C**) as in the case of the phenylmenthyl ester.

Hydrolysis of the ester (**21**), followed by esterification of the resulting acid (**22**) with excess of diazomethane, afforded the methyl ester (**23**), m.p. 177–178 °C; $[\alpha]_D^{24}$ +116.13° (*c* 2.87 in $CHCl_3$), in 98% overall yield. Oxidation of the methyl ester (**23**) by means of thallium(III) trifluoroacetate[11] produced the phenanthroindolizidine (**24**), $[\alpha]_D^{25}$ −253.5° (*c* 0.37 in $CHCl_3$), in 83% yield. The phenanthroindolizidine (**24**) was converted into (−)-tylophorin-9-one (**15**) in two steps, hydrolysis followed by decarboxylation as above (Scheme 4).

Conclusion.—The first asymmetric synthesis of the naturally occurring enantiomer of tylophorine (**1**) has thus been achieved by an intramolecular double Michael reaction, whose extraordinary high diastereoselection is noteworthy.

Experimental

General Methods.—M.p.s are determined on a Yanako micromelting-point apparatus and are uncorrected. ^1H NMR spectra were recorded on JEOL-PMX-60, JEOL-FX-90A, and JEOL-GX-500 spectrometers with tetramethylsilane as the internal standard. IR spectra were obtained on a Hitachi 260-10 spectrophotometer. Mass spectra were measured with Hitachi M-52 and JEOL DX-300 instruments. All reactions were run under an atmosphere of dry nitrogen or argon. Solvents were freshly distilled prior to use. Unless otherwise noted, all reaction mixtures were dried, after work-up, over anhydrous Na_2SO_4. Silica gel column chromatography was carried out with Wako gel C-200. High-performance liquid chromatography (HPLC) was carried out with a Gilson HPLC system Model 302/303 and monitored using UV and refractive index detectors. UV spectra were taken with a Hitachi 124 spectrophotometer. Optical rotations were meaured on a JASCO-DIP-340 polarimeter, while circular dichroism (CD) spectra were recorded on a JASCO J-400X spectropolarimeter. All new compounds described in this Experimental section were homogeneous on TLC and HPLC.

(E)-N-(4,4-*Diethoxybutyl*)-2,3-*bis*-(3,4-*dimethoxyphenyl*)-*acrylamide* (**8**).—To a stirred solution of the acid (**7**)[9] (316 mg, 0.92 mmol) in dry dichloromethane (11 ml) was added oxalyl dichloride (0.13 ml, 1.5 mmol) and the mixture was stirred for 4 h at ambient temperature. Evaporation of the solvent and the excess of reagent gave the corresponding acid chloride.

To a vigorously stirred mixture of 4-aminobutyraldehyde diethyl acetal (1.5 ml, 8.7 mmol), dichloromethane (8.7 ml), and saturated aq. sodium hydrogen carbonate (15 ml) was slowly added a solution of the above acid chloride in dichloromethane (5 ml) and the mixture was stirred for 4 h at ambient temperature. The organic layer was washed with saturated aq. sodium hydrogen carbonate, dried, and evaporated to give a residue, which was subjected to column chromatography on silica gel. Elution with hexane–ethyl acetate (1:1, v/v) afforded the *amide* (**8**) (447 mg, 100%) as yellowish needles, m.p. 62–64 °C (Found: C, 66.55; H, 7.45; N, 2.5. $C_{27}H_{37}NO_7$ requires C, 66.55; H, 7.65; N, 2.85%);

$\nu_{max}(CHCl_3)$ 3 450 (NH) and 1 650 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 1.15 (6 H, q, *J* 7.7 Hz, *J* 7.7 Hz, 2 × Me), 1.55 (4 H, m, $CH_2CH_2CH<$), 3.44 (4 H, 1, 2 × OCH_2), 3.58 (3 H, s, OMe), 3.80 (6 H, s, 2 × OMe), 3.92 (3 H, s, OMe), 5.60 (1 H, m, NH), 6.42–7.00 (6 H, m, 6 × ArH), and 7.71 (1 H, s, ArC*H*); *m/z* 487 (M^+) and 442 (M^+ − OEt).

(E)-2,3-*Bis*-(3,4-*dimethoxyphenyl*)-N-(3-*formylpropyl*)*acrylamide* (**9**).—A mixture of the amide (**8**) (840 mg, 1.72 mmol) and water (2 ml) in acetic acid (8 ml) was stirred for 3.5 h at 60 °C. After evaporation of the solvents, the residue was partitioned between benzene and saturated aq. sodium hydrogen carbonate. The organic phase was washed with saturated aq. sodium chloride, dried, and evaporated to give the aldehyde (**9**) (712 mg, 100%), which was used for the following reaction without further purification.

A part of the product was purified by silica gel column chromatography with benzene–acetone (8:1, v/v) as eluant to give the pure *aldehyde* (**9**) as yellowish scales, m.p. 109–111 °C; $\nu_{max}(CHCl_3)$ 1 720 (C=O) and 1 650 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 9.75 (1 H, s, CHO); *m/z* 413 (M^+) (Found: M^+, 413.1802. $C_{23}H_{27}NO_6$ requires *M*, 413.1767).

(E)-(+)-(1′R,3′R,4′S)-8′-*Phenyl*-p-*menthan*-3′-*yl* 6-[(E)-2,3-*Bis*-(3,4-*dimethoxyphenyl*)*acrylamido*]*hex*-2-*enoate* (**10**).—A solution of the aldehyde (**9**) (811 mg, 1.96 mmol) and (−)-8-phenyl-*p*-menthan-3-yl (triphenylphosphoranylidene)acetate[10] (1.56 g, 2.92 mmol) in acetonitrile (8 ml) was heated under reflux for 24 h. After evaporation of the solvent, the residue was taken up into benzene. The solution was washed successively with 5% hydrochloric acid, saturated aq. sodium hydrogen carbonate, and saturated aq. sodium chloride, dried, and evaporated to give a residue, which was chromatographed on silica gel. Elution with benzene–acetone (15:1, v/v) afforded the (E,E)-*ester* (**10**) (1.17 g, 79%) as a caramel-like residue, $[\alpha]_D^{25}$ +0.26° (*c* 1.49 in $CHCl_3$) (Found: C, 73.75; H, 7.65; N, 2.0. $C_{41}H_{51}NO_7$ requires C, 73.5; H, 7.65; N, 2.1%); $\nu_{max}(CHCl_3)$ 3 440 (NH), 1 700 (C=O), and 1 650 cm^{-1} (C=O); δ_H(500 MHz; $CDCl_3$) 0.84 (3 H, d, *J* 5.8 Hz, CH*Me*), 1.18 and 1.26 (each 3 H, each s, 2 × Me), 1.40–2.19 (4 H, m, 2 × CH_2), 3.28 (2 H, m, $NHCH_2$), 3.47 (3 H, s, OMe), 3.81 (6 H, s, 2 × OMe), 3.92 (3 H, s, OMe), 4.81 (1 H, dt, *J* 4.3 and 10.9 Hz, 3′-H), 5.21 (1 H, d, *J* 15.7 Hz, =$CHCO_2$), 5.59 (1 H, t, *J* 5.7 Hz, NH), 6.40–7.30 (6 H, m, 6 × ArH), and 7.73 (1 H, s, ArC*H*); λ_{max}(MeOH) 325 and 280 nm; *m/z* 669 (M^+).

(+)-(6S,7R,8S,8aR,1′R,3′R,4′S)-8′-*Phenyl*-p-*menthan*-3′-*yl* 6,7-*Bis*-(3,4-*dimethoxyphenyl*)-5-*oxoindolizidine*-8-*carboxylate* (**11**).—To a stirred solution of the above amide (**10**) (298 mg, 0.45 mmol) and triethylamine (0.65 ml, 4.67 mmol) in dry dichloromethane (9 ml) at −78 °C was added TBSOTf (0.5 ml, 2.17 mmol) and the mixture was stirred for 2 h at the same temperature. After addition of benzene (50 ml), the mixture was washed successively with saturated aq. sodium hydrogen carbonate, water, and saturated aq. sodium chloride, dried, and evaporated. The residue was subjected to silica gel column chromatography with benzene–acetone (4:1, v/v) as eluant to give an inseparable mixture of indolizidines (**11**) and (**12**) (274 mg, 92%), which was used for the next oxidation without further purification. A portion of the product was subjected to epimerisation as follows.

A mixture of the above indolizidines (**11**) and (**12**) (13 mg, 0.019 mmol) and 60% sodium hydride (3 mg, 0.075 mmol) in dry THF (1 ml) was heated under reflux for 2.5 h. After addition of benzene (10 ml), the mixture was washed successively with 5% aq. ammonium chloride, saturated aq. sodium hydrogen carbonate, and saturated aq. sodium chloride, dried, and evaporated. The residue was purified by short-column chromatography on silica gel with benzene–acetone (4:1, v/v) as eluant to afford the *title indolizidine* (**11**) (10.2 mg, 78%) as a powder, $[\alpha]_D^{26}$ +55.47° (*c* 4.46 in $CHCl_3$); $\nu_{max}(CHCl_3)$ 1 720 (C=O) and 1 635 cm^{-1} (C=O); δ_H(500 MHz; $CDCl_3$) 0.75 (3 H, d, *J* 5.4 Hz, CH*Me*), 0.89 and 1.08 (each 3 H, each s, 2 × Me), 2.69 (1 H, t, *J* 10.0 Hz, 7-H), 3.15 (1 H, t, *J* 12.0 Hz, 8-H), 3.71, 3.74, 3.78, and 3.82 (each 3 H, each s, 4 × OMe), 4.52 (1 H, dt, *J* 4.3 and 12.1 Hz, 3′-H), 6.37 and 6.45 (each 1 H, each d, *J* each 2.4 Hz, 2 × ArH), 6.51 and 6.54 (each 1 H, each dd, *J* each 2.4 and 8.1 Hz, 2 × ArH), 6.68 and 6.73 (each 1 H, each d, *J* each 8.1 Hz, 2 × ArH), and 7.20–7.30 (5 H, m, Ph); *m/z* 669 (M^+) (Found: M^+, 669.3661. $C_{41}H_{51}NO_7$ requires *M*, 669.3665).

(13aR,14S,1′R,3′R,4′S)-(−)-8′-*Phenyl*-p-*menthan*-3′-*yl* 2,3,6,7-*Tetramethoxy*-9-*oxo*-9,11,12,13,13a,14-*hexahydrophenanthro*[9,10-f]*indolizine*-14-*carboxylate* (**13**).—To a stirred solution of TTFA (44 mg, 0.08 mmol) in TFA (14 ml) at 0 °C were added quickly a solution of the epimeric mixture of indolizidines (**11**) and (**12**) (39 mg, 0.059 mmol) in dichloromethane (0.5 ml) and boron trifluoride–diethyl ether (0.13 ml, 1.06 mmol) and the resulting mixture was stirred for 2 h at 0 °C. After evaporation of the volatile materials, the residue was partitioned between dichloromethane and saturated aq. sodium hydrogen carbonate. The organic layer was dried and evaporated to give a residue, which was subjected to chromatography on silica gel. Elution with benzene–acetone (10:1, v/v) afforded the *phenanthroindolizine* (**13**) (22 mg, 55%) as a solid, m.p. 252–254 °C; $[\alpha]_D^{26}$ −129.98° (*c* 0.748 in $CHCl_3$); $\nu_{max}(CHCl_3)$ 1 710 (C=O) and 1 630 cm^{-1} (C=O); δ_H(500 MHz; $CDCl_3$) 0.72 (3 H, d, *J* 7.1 Hz, CH*Me*), 1.02 and 1.18 (each 3 H, each s, 2 × Me), 3.00 (1 H, dt, *J* 14.3 and 13.3 Hz, 13a-H), 3.67 (1 H, ddd, *J* 7.2, 7.4, and 12.0 Hz, 11-H), 3.76 (1 H, ddd, *J* 2.5, 8.6, and 12.0 Hz, 11-H), 3.98, 4.13, 4.14, and 4.18 (each 3 H, each s, 4 × OMe), 4.70 (1 H, dt, *J* 5.3 and 13.2 Hz, 3′-H), 6.88–7.10 (5 H, m, Ph), 7.22 (1 H, s, 1-H), 7.80 (2 H, s, 4- and 5-H), and 7.92 (1 H, s, 8-H); CD [θ] −8 046 (275 nm) (*c* 0.17 × 10^{-4} in EtOH); *m/z* 665 (M^+) (Found: M^+, 665.3400. $C_{41}H_{47}NO_7$ requires *M*, 665.3357).

(−)-*Tylophorin*-9-*one* (**15**).—(*a*) A mixture of the ester (**13**) (40 mg, 0.068 mmol) and potassium hydroxide (250 mg) in ethanol (5 ml) was heated for 24 h under reflux. After evaporation of the solvent, the residue was partitioned between water and diethyl ether. The aqueous layer was acidified with 10% hydrochloric acid and the resulting mixture was extracted with chloroform. The extract was washed with saturated aq. sodium chloride, dried, and evaporated to give the acid (**14**) (22 mg, 83%) as a yellowish solid, m.p. 194–198 °C (decomp.); $[\alpha]_D^{26}$ −247.83° (*c* 1.5 in MeOH); $[\alpha]_D^{25}$ −258.11° (*c* 0.36 in $CHCl_3$); $\delta_H(CDCl_3)$ 3.86, 4.05, 4.11, and 4.16 (each 3 H, each s, 4 × OMe) and 7.19, 7.43, 7.56, and 8.75 (each 1 H, each s, 4 × ArH), which was used for the next reaction without further purification.

A stirred solution of the above acid (**14**) (19 mg, 0.042 mmol) in HMPA (0.3 ml) was heated at 230–240 °C for 15 min. After dilution with benzene, the mixture was washed with saturated aq. sodium chloride, dried, and evaporated. The residue was purified by silica gel column chromatography with chloroform–acetone (20:1, v/v) as eluant to give (−)-tylophorin-9-one (**15**) (11 mg, 65%) as a yellowish powder, m.p. 286–289 °C; $[\alpha]_D^{24}$ −214.65° (*c* 0.86 in $CHCl_3$); $\nu_{max}(CHCl_3)$ 1 620 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 4.01 and 4.08 (each 3 H, each s, 2 × OMe), 4.10 (6 H, s, 2 × OMe), and 7.82, 7.76, 7.80, and 8.01 (each 1 H, each s, 4 × ArH); *m/z* 407 (M^+) (Found: M^+, 407.1729. $C_{24}H_{25}NO_5$ requires *M*, 407.1731). The spectral data were identical with those of the synthetic racemate.[7,13]

(*b*) A mixture of the (−)-methyl ester (**24**) (prepared as given below) (14 mg, 0.034 mmol) and potassium hydroxide (50 mg)

in ethanol (1 ml) was heated for 6 h under reflux. Similar work-up as above gave the acid (**14**) (12 mg, 81%) as a yellowish solid, m.p. 194–198 °C (decomp.); $[\alpha]_D^{25}$ −258.11° (*c* 0.36 in methanol), whose IR and NMR spectra were identical with those of the sample prepared by method (*a*). The acid (**14**) was converted, as the case of method (*a*), into (−)-tylophorin-9-one (**15**), identical with an authentic sample in all respects.

(2R,4S,5R)-(−)-4-(*t-Butyldimethylsiloxymethyl*)-2-*phenyl*-1,3-*dioxan*-5-*yl Bromoacetate* (**18**).—A mixture of the diol (**16**)[15] (880 mg, 4.19 mmol), t-butyldimethylsilyl chloride (TBSCl) (695 mg, 4.63 mmol), triethylamine (0.64 ml, 4.60 mmol), and 4-dimethylaminopyridine (DMAP) (21 mg, 0.17 mmol) in dimethylformamide (20 ml) was stirred for 0.5 h at room temperature. After addition of water, the mixture was extracted with benzene. The extract was washed with saturated aq. ammonium chloride, dried, and evaporated to give a residue, which was purified by column chromatography on silica gel. Elution with benzene–ethyl acetate (9:1, v/v) afforded the silyl ether (**17**) (1.309 g, 99.8%) as an oil, $\delta_H(CDCl_3)$ 0.03 (6 H, s, $SiMe_2$), 0.87 (9 H, s, Bu^t), 5.36 (1 H, s, 2-H), and 7.10–7.33 (5 H, m, Ph).

To a stirred solution of the silyl ether (**17**) (1.13 g, 3.5 mmol) in dichloromethane (40 ml) at 0 °C were added pyridine (0.35 ml, 4.3 mmol) and bromoacetyl bromide (0.35 ml, 4.13 mmol) and the mixture was stirred for 5.5 h at ambient temperature. After addition of 10% aqueous potassium hydrogen sulphate (ice cooling), the resulting mixture was extracted with diethyl ether. The extract was washed successively with saturated aq. sodium hydrogen carbonate and saturated aq. sodium chloride, dried, and evaporated. The residue was subjected to chromatography on silica gel with diethyl ether–hexane (1:19, v/v) as eluant to afford the *bromide* (**18**) (924 mg, 70%) as an oil, $[\alpha]_D^{26}$ −37.07° (*c* 2.49 in $CHCl_3$); $\nu_{max}(CHCl_3)$ 1 740 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 0.82 (9 H, s, Bu^t), 4.31 and 4.43 (each 1 H, each d, *J* 5.7 Hz, CH_2Br), 4.80–5.15 (1 H, m, 5-H), 5.47 (1 H, s, 2-H), and 7.20–7.55 (5 H, m, Ph); *m/z* 446 (M^+) (Found: M^+, 446.0943. $C_{19}H_{29}BrO_5Si$ requires *M*, 446.0947).

(6S,7R,8S,8aR,2′R,4′S,5′R)-(+)-4′-(*t-Butyldimethylsiloxymethyl*)-2′-*phenyl*-1′,3′-*dioxan*-5′-*yl* 6,7-*Bis*-(3,4-*dimethoxyphenyl*)-5-*oxoindolizidine*-8-*carboxylate* (**21**).—To a solution of the bromide (**18**) (527 mg, 1.18 mmol) in benzene (4 ml) was added a solution of triphenylphosphine (360 mg, 1.37 mmol) in benzene (2 ml) and the mixture was stirred for 24 h at ambient temperature before addition of light petroleum (b.p. range 30–60 °C). The solid formed was washed well with hexane and was then partitioned between 5% aq. potassium carbonate and benzene. The organic phase was washed with saturated aq. sodium chloride, dried, and evaporated to give the ylide (**19**) (683 mg, 92%) as a yellowish caramel-like residue, which was used for the following reaction without purification.

A mixture of the aldehyde (**9**) (99 mg, 0.24 mmol) and the ylide (**19**) (337 mg, 0.54 mmol) in acetonitrile (3.5 ml) was stirred for 24 h at ambient temperature. After evaporation, the residue was taken up into benzene. The benzene solution was washed successively with saturated aq. sodium hydrogen carbonate and saturated aq. sodium chloride, dried, and evaporated. The resulting residue was subjected to chromatography on silica gel with hexane–ethyl acetate (1:1, v/v) to afford the α,β-unsaturated ester (**20**) (155 mg, 85%) as an syrup, $[\alpha]_D^{27}$ −22.86° (*c* 1.84 in $CHCl_3$); $\nu_{max}(CHCl_3)$ 1 720 (C=O) and 1 660 cm^{-1} (C=O); δ_H(500 MHz; $CDCl_3$) 0.87 (9 H, s, Bu^t), 2.22 (2 H, q, *J* 6.7 Hz, $=CHCH_2$), 3.30–3.40 (2 H, m, $NHCH_2$), 3.50 (3 H, s, OMe), 3.82 (6 H, s, 2 × OMe), 3.92 (3 H, s, OMe), 4.41 (1 H, q, *J* 5.5 Hz, 4′-H), 4.98 (1 H, dt, *J* 6.5 and 9.7 Hz, 5′-H), 5.45 (1 H, s, 2′-H), 5.62 (1 H, br t, *J* 6.5 Hz, NH), 5.80 (1 H, d, *J* 15.5 Hz, COCH=), 6.48 (1 H, d, *J* 2.7 Hz, ArH), 6.96 (1 H, dt, *J* 6.7 and 15.5 Hz, $COCH=CH$), 7.30–7.54 (5 H, m, Ph), and 7.78 (1 H, s, $ArCH=$).

To a stirred solution of the α,β-unsaturated ester (**20**) (100 mg, 0.13 mmol) in dry dichloromethane (4 ml) at −78 °C were added triethylamine (0.40 ml, 2.87 mmol) and TBSOTf (0.32 ml, 1.39 mmol) and the mixture was stirred for 2 h at −78 to 5 °C. After dilution with benzene, the mixture was washed successively with saturated aq. sodium hydrogen carbonate and saturated aq. sodium chloride, and dried. Evaporation of the solvent gave a residue, which was subjected to chromatography on silica gel. Elution with benzene–acetone (4:1, v/v) afforded the *indolizidin*-5-*one* (**21**) (76 mg, 76%) as a powder, $[\alpha]_D^{25}$ +42.35° (*c* 2.92 in $CHCl_3$); $\nu_{max}(CHCl_3)$ 1 740 (C=O) and 1 630 cm^{-1} (C=O); δ_H(500 MHz; $CDCl_3$) 0.88 (9 H, s, Bu^t) 2.96 (1 H, t, *J* 11.0 Hz, 7-H), 3.33 (1 H, t, *J* 12.0 Hz, 8-H), 3.38, 3.45, 3.53, and 3.55 (each 3 H, each s, 4 × OMe), 4.87 (1 H, dt, *J* 5.0 and 10.0 Hz, 5′-H), 5.46 (1 H, s, 2′-H), 6.38 and 6.45 (each 1 H, each s, 2 × ArH), 6.54 (2 H, d, *J* 8.5 Hz, 2 × ArH), 6.76 (2 H, dt, *J* 3.0 and 8.5 Hz, 2 × ArH), and 7.35–7.50 (5 H, m, Ph); *m/z* 761 (M^+) (Found: M^+, 761.3560. $C_{42}H_{55}NO_{10}Si$ requires *M*, 761.3595).

(6S,7R,8S,8aR)-(+)-*Methyl* 6,7-*Bis*-(3,4-*dimethoxyphenyl*)-5-*oxoindolizidine*-8-*carboxylate* (**23**).—A mixture of the indolizidin-5-one (**21**) (38 mg, 0.05 mmol) and potassium hydroxide (225 mg) in ethanol (4.5 ml) was heated for 24 h under reflux. After evaporation of the solvent, the residue was partitioned between water and ether. The ice-cooled, aqueous phase was acidified with 10% hydrochloric acid and the resulting mixture was extracted with chloroform. The extract was washed with saturated aq. sodium chloride, dried, and evaporated to give the acid (**22**) as a powder (23 mg, 99%) which was used for the next reaction without purification.

To a solution of the acid (**22**) (28 mg, 0.06 mmol) in a mixture of chloroform and methanol (1:1, v/v; 3 ml) at 0 °C was added a solution of excess of diazomethane in diethyl ether. After 0.5 h, the mixture was evaporated to give a residue, which was subjected to silica gel column chromatography. Elution with benzene–acetone (3:1, v/v) afforded the *ester* (**23**) (29 mg, 99%) as plates, m.p. 177–178 °C; $[\alpha]_D^{24}$ +116.13° (*c* 2.87 in $CHCl_3$); $\nu_{max}(CHCl_3)$ 1 730 (C=O) and 1 630 cm^{-1} (C=O); δ_H(500 MHz; $CDCl_3$) 2.85 (1 H, dd, *J* 11.5 and 1.2 Hz, 7-H), 3.31 (1 H, t, *J* 11.5 Hz, 8-H), 3.45 (3 H, s, CO_2Me), 3.72, 3.74, 3.81, and 3.82 (each 3 H, each s, 4 × OMe), 3.69 (1 H, dt, *J* 11.5 and 5.5 Hz, 8a-H), 6.38 (1 H, d, *J* 1.8 Hz, ArH), 6.44 (1 H, d, *J* 1.8 Hz, ArH), 6.51 (2 H, dd, *J* 1.8 and 8.5 Hz, 2 × ArH), 6.69 (1 H, d, *J* 8.5 Hz, ArH), and 6.71 (1 H, d, *J* 8.5 Hz, ArH), *m/z* 469 (M^+) (Found: M^+, 469.2108. $C_{26}H_{31}NO_7$ requires *M*, 469.2100).

(13aR,14S)-(−)-*Methyl* 9-*Oxotylophorine*-14-*carboxylate* (**24**).—To a stirred solution of TTFA (270 mg, 0.496 mmol) in TFA (25 ml) at 0 °C were added a solution of the ester (**23**) (110 mg, 0.234 mmol) in dichloromethane (5 ml) and boron trifluoride–diethyl ether (0.6 ml, 4.89 mmol) and the resulting mixture was stirred for 16 h at 0–4 °C. After addition of sodium hydrosulphite (130 mg, 0.747 mmol), the mixture was stirred for 15 min at 0 °C and then concentrated under reduced pressure. The residue was partitioned between dichloromethane and saturated aq. sodium hydrogen carbonate. The organic phase was dried and evaporated to give a residue, which was purified by silica gel column chromatography. Elution with benzene–acetone (3:1, v/v) afforded the *phenanthroindolizine* (**24**) (91 mg, 83%) as a powder, $[\alpha]_D^{25}$ −253.5° (*c* 0.37 in $CHCl_3$); $\nu_{max}(CHCl_3)$ 1 730 (C=O) and 1 630 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 3.70 (3 H, s, CO_2Me), 3.94 and 4.08 (each 3 H, each s, 2 × OMe), 4.14 (6 H, s, 2 × OMe), and 7.20, 7.75, 7.78, and 8.81 (each 1 H, each s, 4 × ArH); *m/z*

465 (M^+) (Found: M^+, 465.1751. $C_{26}H_{27}NO_7$ requires M, 465.1788).

(−)-*Tylophorine* (**1**).—To a solution of (−)-tylophorin-9-one (**15**) (55 mg, 0.135 mmol) in dry dioxane (5 ml) was added a 3.4M solution of sodium bis-(2-methoxyethoxy)aluminium hydride in toluene (0.5 ml, 1.7 mmol) and the mixture was heated for 2 h under reflux. After evaporation of the solvents, the residue was diluted with water (10 ml) and then basified with 10% aq. sodium hydroxide. The mixture was extracted with chloroform, and the extract was washed with water, dried, and evaporated to give a solid, which was purified by HPLC on a 4.6 × 250 mm column of Dynamax microsorb silica 5 μm with chloroform–methanol (49:1, v/v) as eluant to afford (−)-tylophorine (**1**) (46 mg, 87%) as a powder, m.p. 274–276 °C (lit.,[12] 275 °C); $[\alpha]_D^{25}$ −76.5° (*c* 0.04 in $CHCl_3$) {lit.,[1] $[\alpha]_D^{27}$ −11.6° (*c* 1.07 in $CHCl_3$); for the (+)-form: lit.,[4] $[\alpha]_D^{23}$ +12° (*c* 0.7 in $CHCl_3$); lit.,[5] $[\alpha]_D^{21}$ +73° (*c* 0.7 in $CHCl_3$)}; $\delta_H(CDCl_3)$ 4.02 and 4.08 (each 6 H, each s, 4 × OMe), 7.14 and 7.29 (each 1 H, each s, 2 × ArH) and 7.79 (2 H, s, 2 × ArH); CD [θ] −8 235 (275 nm) (*c* 0.17 × 10^{-4} in EtOH); *m/z* 393 (M^+). The IR and NMR spectra were identical with those of the authentic racemate.[7,13]

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