Stereocontrolled Construction of Octahydroquinolizines, Octahydroindolizines, Hexahydrobenzo[*a*]quinolizines, and an Octahydroindolo[2,3-*a*]quinolizine by an Intramolecular Double Michael Reaction: Synthesis of (±)-Epilupinine

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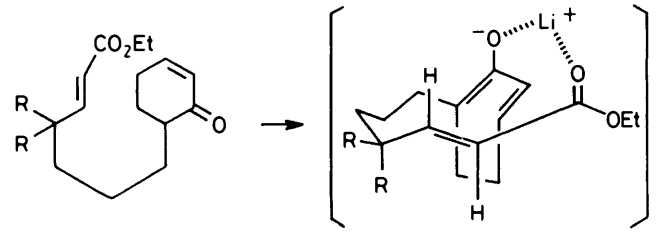
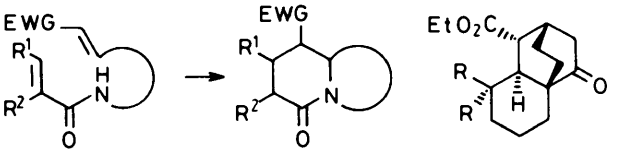
Stereocontrolled one-step syntheses of octahydroquinolizine and octahydroindolizine derivatives from α,β-unsaturated enamide esters was achieved under two different conditions; heating in the presence of chlorotrimethylsilane, triethylamine, and zinc chloride at 180—185 °C, and treatment with dimethyl-t-butylsilyl trifluoromethanesulphonate in the presence of triethylamine at −78 to 20 °C. A simple synthesis of an alkaloid, (±)-epilupinine, was accomplished. Hexahydrobenzo[*a*]-quinolizin-4-ones and an octahydroindolo[2,3-*a*]quinolizin-4-one were also constructed by the same method.

Recently we reported a stereoselective synthesis of spiro-fused bicyclo[2.2.2]octanes (**2**) by the intramolecular double-Michael reaction of α,β-unsaturated enone esters (**1**) using lithium bases *via* possible chelated intermediates,[1] and its application to the synthesis of (+)-atisirene.[2] The success of the work prompted us to investigate extensions of the above strategy for the synthesis of heteropolycyclic compounds. Thus we envisaged construction of bicyclic systems (**4**), having an angular nitrogen, from α,β-unsaturated enamide esters (**3**), and we now describe the novel annelation to the important ring systems in alkaloid syntheses.[3]



(1) R = H and/or Me

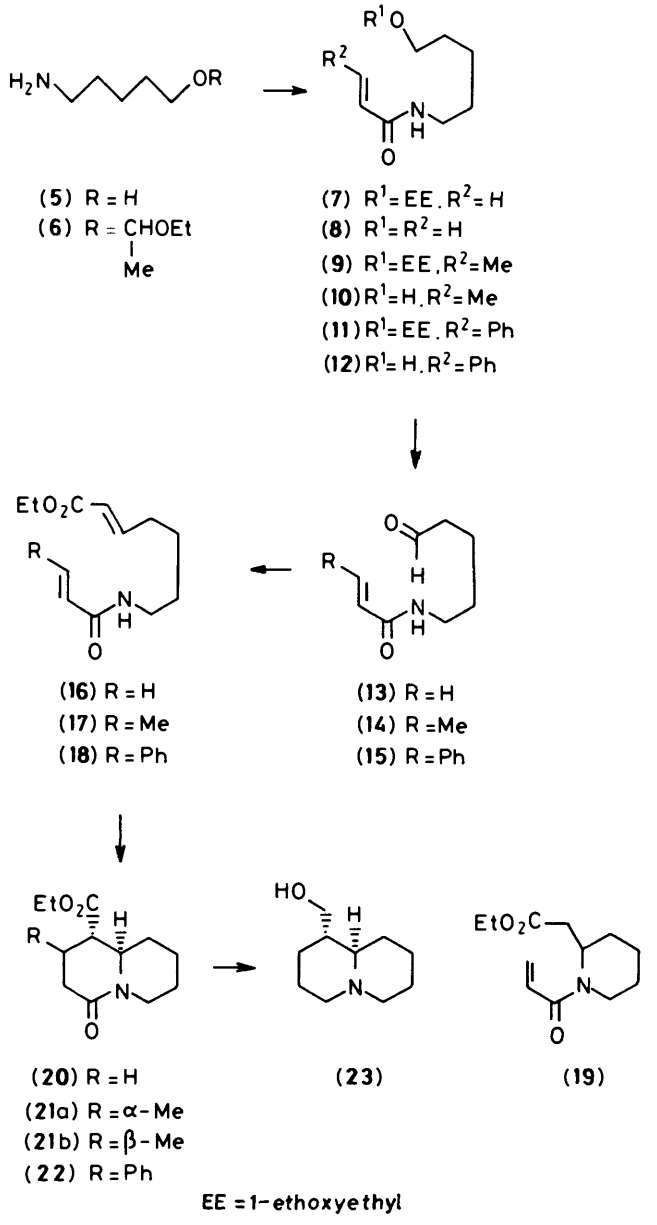


(3) (4) (2)

EWG = electron-withdrawing group

In the synthesis of simple octahydroquinolizine derivatives, the hydroxy group of the 5-aminopentan-1-ol (**5**) was protected with an ethoxyethyl group by means of ethyl vinyl ether in the presence of a small excess of hydrochloric acid in dichloromethane. Schotten–Baumann reaction of the amine (**6**) with α,β-unsaturated acyl chlorides carried out in a mixture of saturated aqueous sodium hydrogen carbonate and dichloromethane afforded the corresponding enamides (**7**), (**9**), and (**11**). Removal of the ethoxyethyl group with acetic acid in aqueous tetrahydrofuran (THF) gave the alcohols (**8**), (**10**), and (**12**), which were oxidised utilizing (pyridine)$_2$–chromium(VI) oxide complex in dichloromethane[4] to the aldehydes (**13**), (**14**), and (**15**). Emmons reaction[5] of the aldehyde (**13**) with ethyl (diethoxyphosphonyl) acetate and sodium hydride produced the desired α,β-unsaturated ester (**16**) together with a considerable amount of a piperidine derivative (**19**). On the other hand, reaction with the stabilised phosphorus ylide (ethoxycarbonylmethylene)triphenylphosphorane gave only the (*E*)-ester (**16**). Thus the substrates (**16**), (**17**), and (**18**) of the annelation reaction were readily prepared from the commercially available substance (**5**) in good yield. Annelation reaction carried out under basic conditions using lithium di-isopropylamide, lithium hexamethyldisilazide, potassium t-butoxide, sodium hydride, and triethylamine resulted in failure and only the piperidine derivative (**19**) was formed. It was clear from the above results that the enamide group does not work as a Michael acceptor under these conditions. In order to activate the enamide moiety, therefore the annelation reaction was then investigated using Lewis acid catalysis. However, treatment using simple Lewis acids such as aluminium chloride, magnesium chloride, zinc chloride, tin(IV) chloride, and boron trifluoride–diethyl ether was fruitless. After numerous attempts, the annelation was effectively performed under two different conditions; heating in the presence of chlorotrimethylsilane, triethylamine, and zinc chloride[6] at 180—185 °C or treatment with dimethyl-t-butylsilyl trifluoromethanesulphonate in the presence of triethylamine at −78 to 20 °C.[7]

Heating of the enamide ester (**16**) with excess of chlorotrimethylsilane, triethylamine, and zinc chloride in toluene in a sealed tube for 10 h at 185 °C produced the octahydroquinolizin-4-one (**20**) in 55% yield. Reflux of a mixture of the enamide ester (**16**) and the same reagents in *o*-dichlorobenzene also gave the same result. However, heating of the mixture below 150 °C yielded no quinolizin-4-one. The annelation product (**20**) was obtained as a single

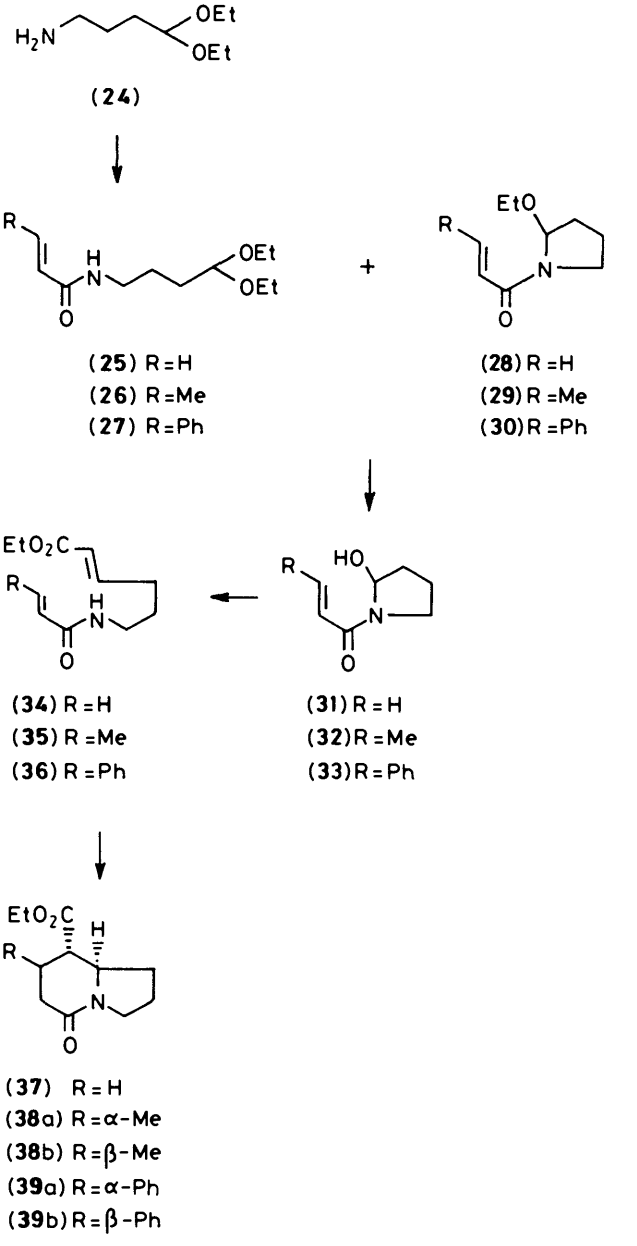


Scheme 1.

stereoisomer and its stereochemistry was determined by its conversion into a natural product; reduction of compound (**20**) with lithium aluminium hydride in refluxing THF gave, in 77% yield, (±)-epilupinine (**23**),[8] whose spectral data were identical with those of an authentic sample. It was therefore shown that the stereochemistry of the (*E*)-α,β-unsaturated ester group was retained during the annelation (Scheme 1).

On being heated with chlorotrimethylsilane, triethylamine, and zinc chloride in toluene at 185 °C, the (*E*,*E*)-but-2-enamide (**17**) afforded two octahydroquinolizin-4-ones (**21a** and **b**) in 58 and 17% yield, respectively, after chromatographic purification. These must be the stereoisomers at C-2. In the n.m.r. spectra, the signal due to the methyl group at C-2 of the major product was observed at δ 0.94 as a doublet with *J* 8 Hz, while that of the minor product resonated at δ 1.01, also as a doublet with *J* 8 Hz. Therefore the structure of the major product was assigned as (**21a**) having the axially oriented methyl group.[9] The same reaction of the (*E*,*E*)-3-phenylpropenamide (**18**) afforded a mixture of two octahydroquinolizin-4-ones (**22**), in 79% yield, which were inseparable on column chromatography. The isomeric ratio of 4:9 was determined on the basis of integrations of the signals due to the methyl group of the ethyl ester observed at δ 0.83 and 1.14.

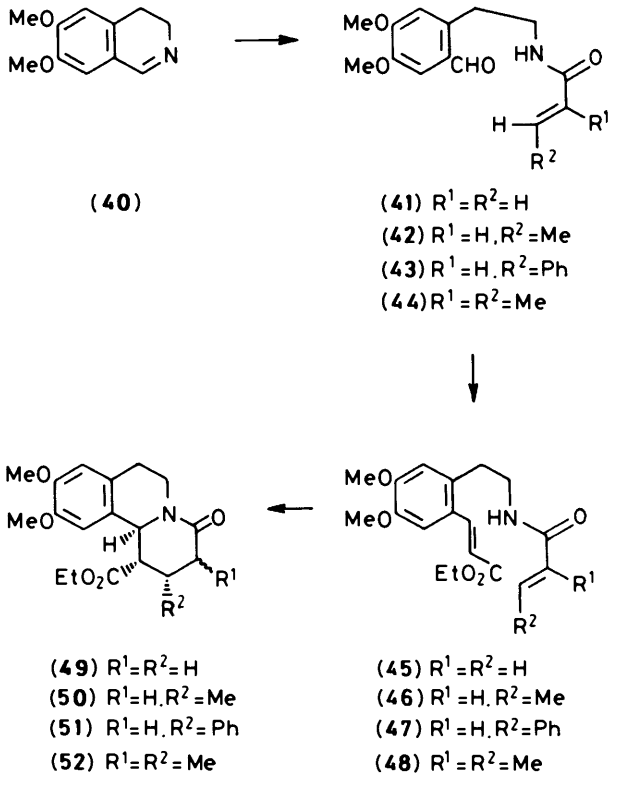
In order to synthesise octahydroindolizines, the commercially available amino acetal (**24**) was condensed with α,β-unsaturated acyl halides in the presence of sodium hydrogen carbonate as previously described, to give mixtures of enamides (**25**)—(**27**) and 2-ethoxypyrrolidine derivatives (**28**)—(**30**). Treatment of the mixtures with dil. hydrochloric acid yielded the 2-hydroxypyrrolidines (**31**)—(**33**). Wittig reaction with (ethoxycarbonylmethylene)triphenylphosphorane produced three enamide (*E*)-esters (**34**)—(**36**) in good yield. Heating of the propenamide (**34**) in the presence of chlorotrimethylsilane, triethylamine, and zinc chloride in toluene at 185 °C gave the octahydroindolizin-5-one (**37**) in 55% yield as a single stereoisomer. Annelation reaction of the but-2-enamide (**35**) under the same reaction conditions gave two octahydroindolizin-5-ones, (**38a**) in 72 and (**38b**) in 7% yield respectively. The stereochemistry of the products was also determined by the chemical shift due to the methyl group at C-



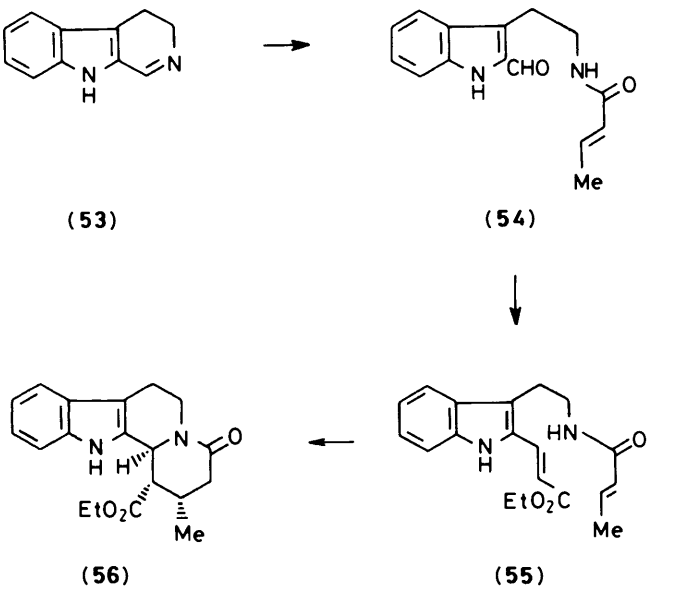
Scheme 2.

7;[9] δ 0.99 (d, *J* 6 Hz) for the major isomer (**38a**) and δ 1.06 (d, *J* 7 Hz) for the minor isomer (**38b**). Similarly, two octahydroindolizin-5-ones (**39a** and **b**) were obtained in 75 and 11% yield, respectively, from the 3-phenylpropenamide (**36**) (Scheme 2). From the above results, the structure of the major product was deduced as (**39a**) possessing the axially oriented phenyl group, whereas the minor isomer was assigned structure (**39b**).

Octahydroquinolizine and octahydroindolizine ring systems are common frameworks of alkaloids. Furthermore hexahydrobenzo[*a*]quinolizine and octahydroindolo[2,3-*a*]quinolizine ring systems appear in a wide variety of alkaloids. The development of simple synthetic procedures towards these ring systems still continues because some of the natural products and synthetic compounds possess medicinal activity.[10] Therefore the above method was applied for the construction of these derivatives. Formation of the formyl enamides (**41**)—(**44**) was achieved by the reaction of 3,4-dihydro-6,7-dimethoxyisoquinoline (**40**) with α,β-unsaturated acyl chlorides in a mixture of dichloromethane and saturated aqueous sodium hydrogen carbonate at room temperature. Wittig reaction as previously described gave four different substrates (**45**)—(**48**) for the annelation reaction. On heating of the mixture of the propenamide (**45**), chlorotrimethylsilane, triethylamine, and zinc chloride in toluene at 180—185 °C, the hexahydrobenzo[*a*]quinolizine (**49**) was produced in 44% yield. The signal due to the hydrogen at the angular C-11b position, observed at δ 5.03 as a doublet with *J* 8 Hz, suggested the stereochemistry of the product as that shown in structure (**49**). Interestingly, both the but-2-enamide (**46**) and the 3-phenylpropenamide (**47**) formed hexahydrobenzo[*a*]quinolizines (**50**) and (**51**), respectively, in 52 and 48% yield, each as a single stereoisomer. Mechanistic and steric hindrance considerations indicate that the preferentially formed isomers of compounds (**50**) and (**51**) would possess the all-*cis* relative configuration about the angular hydrogen at C-11b, the CO_2Et group at C-1, and the substituent at C-2 as in the



Scheme 3.



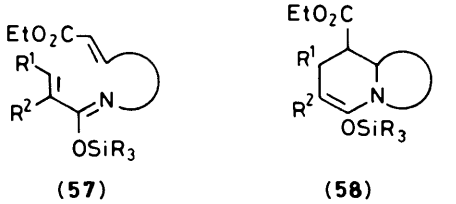
Scheme 4.

case of the above octahydroquinolizines and octahydroindolizines. On the other hand, the 2-methylbut-2(*E*)-enamide (**48**) was converted into two hexahydrobenzo[*a*]quinolizines (**52**) in 25 and 41% yield (Scheme 3). Treatment of the major product with sodium hydride in hot THF caused epimerisation to the minor product. Therefore they must be stereoisomers at C-3.

The enamide ester (**55**) was prepared from 3,4-dihydro-β-carboline (**53**) *via*-formyl derivative (**54**) and was similarly subjected to the annelation reaction; the octahydroindolo[2,3-*a*]quinolizine (**56**) was formed in 66% yield (Scheme 4).

It was further found that the annelation proceeds more stereoselectively under milder conditions on treatment with a trialkylsilyl trifluoromethanesulphonate in the presence of triethylamine. Thus, reaction of the enamide ester (**47**) with trimethylsilyl trifluoromethanesulphonate and triethylamine in dichloromethane at room temperature produced the hexahydrobenzo[*a*]quinolizine (**51**) in 75% yield, and similar reaction using dimethyl-t-butylsilyl trifluoromethanesulphonate gave the same product in 83% yield. It was observed that the latter reaction proceeded more rapidly than that with the trimethylsilyl compound, to give the clean product. When the enamide ester (**35**) was treated with dimethyl-t-butylsilyl trifluoromethanesulphonate and triethylamine in dichloromethane at 20 °C, the two stereoisomers (**38a**) and (**38b**) were obtained in 78 and 5% yield after chromatographic separation. The reaction proceeded even at −78 °C and one product, (**38a**), was obtained in 75% yield after 1 h reaction at this temperature. Similarly, the octahydroquinolizin-4-one (**20**), the synthetic precursor of (±)-epilupinine (**23**), was synthesised in 92% yield from enamide ester (**16**).

Both reagent mixtures, chlorotrimethylsilane–triethylamine–zinc chloride and dimethyl-t-butylsilyl trifluoromethanesulphonate–triethylamine, are used for the synthesis of cross-con-



jugated dienol silyl ethers from α,β-unsaturated ketones.[6,7,11] However, no formation of 1-azadienes such as (**57**) was observed in either reaction. The reaction with dimethyl-t-butylsilyl trifluoromethanesulphonate and triethylamine directly produced the annelation products at −78 °C after a short period without formation of the silyl enol ether (**58**). In conjunction with our stereochemical observations, therefore, it is considered that neither reaction is the intramolecular Diels–Alder reaction of 1-azadienes[12] as first thought. Although further investigations are required to clarify the reaction mechanism, the annelation could be regarded as two sequential Michael reactions.

Experimental

General Methods.—M.p.s are uncorrected. I.r. spectra were recorded for $CHCl_3$ solutions on a Hitachi 260-10 spectrophotometer. N.m.r. spectra were measured for $CDCl_3$ solutions on JEOL JNM-PMX-60 and JEOL-PS-100 spectrometers. Chemical shifts are reported as δ_H values relative to internal $SiMe_4$. Ordinary mass spectra were taken on a Hitachi M-52G instrument, and accurate mass spectra with a JEOL-JMS-01SG-2 spectrometer. High-pressure liquid chromatography (h.p.l.c.) was carried out using a Hitachi 635 instrument monitored by u.v. absorption and refractive-index measurements. All new compounds described in the Experimental section were homogeneous on t.l.c. and h.p.l.c.

1-*Amino*-5-(1-*ethoxyethoxy*)*pentane* (**6**).—To a stirred solution of 5-aminopentan-1-ol (**5**) (1.03 g) in dichloromethane (40 ml) were slowly added a small excess of ethereal hydrogen chloride and a solution of ethyl vinyl ether (1 g) in dichloromethane (1 ml). The mixture was stirred for 5 h at 4 °C and for 1 h at 10 °C before being poured into 10% aqueous ammonia. The organic layer was washed with saturated aqueous sodium chloride, dried (Na_2SO_4), and evaporated to give the *amine* (**6**) (1.66 g, 95%) as an oil, which was used in the next reaction without further purification. The *product* had $\nu_{max.}$($CHCl_3$) 3 410 cm^{-1} (NH_2); δ 1.16 (3 H, t, *J* 7 Hz, OCH_2Me), 1.26 (3 H, d, *J* 6 Hz, $CHMe$), 1.20—1.80 (6 H, m, 3 × CH_2), 2.53—2.86 (2 H, br s, NH_2), 3.30—3.83 (6 H, m, 2 × CH_2 and NCH_2), and 4.63 (1 H, q, *J* 6 Hz, C*H*Me); *m/z* 130 (M^+ − OEt) (Found: M^+ − OEt, 130.1223. $C_7H_{16}NO$ requires *m/z* 130.1230).

N-(5-*Hydroxypentyl*)*acrylamide* (**8**).—To a vigorously stirred, ice-cooled mixture of the amine (**6**) (1 g), saturated aqueous sodium hydrogen carbonate (10 ml), and dichloromethane (10 ml) was added dropwise a solution of acryloyl chloride (1 g) in dichloromethane (10 ml), and the mixture was stirred for 2 h at the same temperature. The organic solution was washed successively with saturated aqueous sodium hydrogen carbonate, 10% aqueous potassium hydrogen sulphate, and saturated aqueous sodium chloride, dried (Na_2SO_4), and evaporated. The residue was subjected to silica gel column chromatography. Elution with benzene–acetone (85:15 v/v) gave the *amide* (**7**) (1.13 g, 86%) as an oil, $\nu_{max.}$ 3 450 (NH) and 1 670 cm^{-1} (C=O); δ 1.16 (3 H, t, *J* 7 Hz, OCH_2Me), 1.26 (3 H, d, *J* 6 Hz, $CHMe$), 1.20—1.80 (6 H, m, 3 × CH_2), 3.16—3.93 (6 H, m, 2 × OCH_2 and NCH_2), 4.63 (1 H, q, *J* 6 Hz, C*H*Me), 5.70 (1 H, dd, *J* 6 and 12 Hz, CH_2=C*H*CO), and 6.16—6.26 (2 H, m, CH_2=CHCO); *m/z* 156 (M^+ − CHMeOEt) (Found: M^+ − CHMeOEt, 156.0998. $C_8H_{14}NO_2$ requires *m/z*, 156.1023).

The amide (**7**) (1 g) was dissolved in a mixture of acetic acid–THF–water (3:2:1 v/v; 20 ml) and the mixture was stirred for 7 h at room temperature. After concentration of the reaction mixture under reduced pressure, the residue was taken up into chloroform, and the solution was washed successively with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride. The solution was dried (Na_2SO_4) and the solvent was evaporated off to give a residue, which was chromatographed on silica gel. Elution with benzene–ethyl acetate (1:1 v/v) gave the *alcohol* (**8**) (570 mg, 83%) as an oil, $\nu_{max.}$ 3 450 and 3 400 (NH and OH) and 1 670 cm^{-1} (C=O); δ 1.20—1.80 (6 H, m, 3 × CH_2), 3.26 (2 H, t, *J* 6 Hz, NCH_2), 3.75 (2 H, t, *J* 6 Hz, OCH_2), 5.70 (1 H, dd, *J* 6 and 12 Hz, CH_2=C*H*CO), and 6.10—6.23 (2 H, m, CH_2=CHCO) (Found: M^+, 157.1122. $C_8H_{15}NO_2$ requires *M*, 157.1102).

(E)-N-(5-*Hydroxypentyl*)*crotonamide* (**10**).—Condensation of the amine (**6**) (1.44 g) and crotonoyl chloride (1.5 g) as above gave the amide (**9**) (1.60 g, 85%), $\nu_{max.}$ 3 450 (NH) and 1 672 cm^{-1} (C=O); δ 1.19 (3 H, t, *J* 7 Hz, OCH_2Me), 1.27 (3 H, d, *J* 6 Hz, $CHMe$), 1.20—1.75 (6 H, m, 3 × CH_2), 1.85 (3 H, dd, *J* 3 and 7 Hz, =$CHMe$), 3.20—3.80 (6 H, m, 2 × OCH_2 and NCH_2), 4.65 (1 H, q, *J* 6 Hz, C*H*Me), 5.77 (1 H, dq, *J* 16 and 3 Hz, C*H*=CHMe), and 6.80 (1 H, dq, *J* 16 and 7 Hz, =C*H*Me).

Removal of the ethoxyethyl group of the amide (**9**) (950 mg) as above gave the *alcohol* (**10**) (581 mg, 82%), $\nu_{max.}$ 3 450 and 3 400 (NH and OH) and 1 670 cm^{-1} (C=O); δ 1.82 (3 H, dd, *J* 3 and 7 Hz, =$CHMe$), 5.75 (1 H, dq, *J* 16 and 3 Hz, C*H*=CHMe), and 6.78 (1 H, dq, *J* 16 and 7 Hz, =C*H*Me) (Found: M^+, 171.1227. $C_9H_{17}NO_2$ requires *M*, 171.1227).

N-(5-*Hydroxypentyl*)*cinnamamide* (**12**).—Condensation of the amine (**6**) (700 mg) and cinnamoyl chloride (1 g) as previously gave the amide (**11**) (764 mg, 82%), $\nu_{max.}$ 3 448 (NH) and 1 660 cm^{-1} (C=O); δ 1.18 (3 H, t, *J* 7 Hz, OCH_2Me), 1.28 (3 H, d, *J* 6 Hz, $CHMe$), 1.30—1.80 (6 H, m, 3 × CH_2), 3.20—3.90 (6 H, m, 2 × OCH_2 and NCH_2), 4.63 (1 H, q, *J* 6 Hz, C*H*Me), 6.45 (1 H, d, *J* 16 Hz, COCH=), 7.20—7.45 (5 H, m, Ph), and 7.56 (1 H, d, *J* 16 Hz, =C*H*Ph). Deprotection of the amide (**11**) (173 mg) was previously afforded the *alcohol* (**12**) (120 mg, 91%), δ 6.33 (1 H, d, *J* 16 Hz, COCH=) and 7.56 (1 H, d, *J* 16 Hz, =C*H*Ph) (Found: M^+, 233.1402. $C_{14}H_{19}NO_2$ requires *M*, 233.1414).

Ethyl (E)-7-*Acrylamidohept*-2-*enoate* (**16**).—To a solution of pyridine (3.62 g) in dry dichloromethane (40 ml) was added chromium(VI) oxide (2.29 g) and the mixture was stirred for 1 h at room temperature. After addition of a solution of the alcohol (**8**) (600 mg) in dry dichloromethane (10 ml), the resulting mixture was stirred for 30 min at room temperature and was then diluted with ether (200 ml). After filtration through Celite, the filtrate was washed successively with 5% aqueous sodium hydroxide, 5% hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and saturated aqueous sodium chloride, and dried (Na_2SO_4). Evaporation of the solvent gave the crude aldehyde (**13**) (480 mg) which was subjected to the following reaction without purification.

A mixture of the crude aldehyde (**13**) (480 mg) and (ethoxycarbonylmethylene)triphenylphosphorane (1.06 g) in acetonitrile (10 ml) was stirred for 10 h at room temperature and was then refluxed for 30 min. After evaporation of the solvent, the residue was taken up into chloroform, and the solution was washed successively with 5% hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and saturated aqueous sodium chloride, and dried (Na_2SO_4). Evaporation of the solvent gave a residue, which was purified by silica gel column chromatography. Elution with benzene–acetone (9:1 v/v) afforded the *ester* (**16**) (644 mg, 75%) as an oil, δ 1.26 (3 H, t, *J* 7 Hz, OCH_2Me), 1.40—1.65 (4 H, m, 2 × CH_2), 2.05—2.30 (2 H, m, 4-H_2), 3.18—3.43 (2 H, m, 7-H_2), 4.15 (2 H, q, *J* 7 Hz, OCH_2), 5.50—6.39 (3 H, m, 2-H and =CH_2), and 6.90 (1 H, dt, *J* 16 and 7 Hz, 3-H) (Found: M^+, 225.1379. $C_{12}H_{19}NO_3$ requires *M*, 225.1366).

Ethyl (E)-7-*Crotonamidohept*-2-*enoate* (**17**).—Following the above procedure, the alcohol (**10**) (388 mg) was transformed into the (E)-α,β-*unsaturated ester* (**17**) (336 mg, 62%), $\nu_{max.}$ 3 448 (NH) and 1 700 and 1 670 cm^{-1} (C=O); δ 1.26 (3 H, t, *J* 7 Hz, OCH_2Me), 1.40—1.60 (4 H, m, 2 × CH_2), 1.84 (3 H, dd, *J* 3 and 7 Hz, =CH*Me*), 2.05—2.30 (2 H, m, 4-H_2), 3.10—3.40 (2 H, m, 7-H_2), 4.15 (2 H, q, *J* 7 Hz, OCH_2), 5.69—5.86 (2 H, m, 2 × COCH=), and 6.60—7.03 (2 H, m, 2 × COCH=C*H*) (Found: 239.1532. $C_{13}H_{21}NO_3$ requires *M*, 239.1521).

Ethyl (E)-7-*Cinnamamidohept*-2-*enoate* (**18**).—The alcohol (**12**) (200 mg) was similarly converted into the (E)- α,β-*unsaturated ester* (**18**) (188 mg, 73%), $\nu_{max.}$ 3 452 (NH) and 1 710 and 1 665 cm^{-1} (C=O); δ 1.27 (3 H, t, *J* 7 Hz, OCH_2Me), 1.45—1.60 (4 H, m, 2 × CH_2), 2.05—2.30 (2 H, m, 4-H_2), 3.30—3.50 (2 H, m, 7-H_2), 4.15 (2 H, q, *J* 7 Hz, OCH_2), 5.79 (1 H, dt, *J* 17 and 2 Hz, 2-H), 6.35 (1 H, d, *J* 17 Hz, C*H*=CHPh), 6.90 (1 H, dt, *J* 7 and 17 Hz, 3-H), 7.22—7.50 (5 H, m, Ph), and 7.58 (1 H, d, *J* 17 Hz, =C*H*Ph) (Found: M^+, 301.1670. $C_{18}H_{23}NO_3$ requires *M*, 301.1676).

N-*Acryloylpyrrolidin*-2-*ol* (**31**).—To a vigorously stirred, ice-cooled mixture of the amino acetal (**24**) (1 g), dichloromethane (10 ml), and saturated aqueous sodium hydrogen carbonate (10 ml) was added dropwise a solution of acryloyl chloride (1 g) in dichloromethane (5 ml), and the mixture was stirred for 1 h at room temperature. The organic layer was dried (K_2CO_3) and evaporated to give a mixture of the enamides (**25**) and (**28**) as a syrup, which was used immediately in the following reaction.

A mixture of the above product and 3% hydrochloric acid (10 ml) in acetone (20 ml) was stirred for 3 h at room temperature. After neutralisation by addition of saturated aqueous sodium hydrogen carbonate, followed by concentration under reduced pressure, the resulting mixture was extracted with chloroform. The extract was dried (K_2CO_3) and evaporated to give a residue, which was chromatographed on silica gel and eluted with benzene–acetone (4:1 v/v) to afford the *pyrrolidine* (**31**) [744 mg, 85% from (**24**)] as an oil (Found: C, 56.85; H, 7.5; N, 9.3. $C_7H_{11}NO_2 \cdot \frac{1}{3}H_2O$ requires C, 57.1; H, 8.0; N, 9.5%); $\nu_{max.}$ 3 440 (OH) and 1 640 cm^{-1} (C=O); δ 1.80—2.20 (4 H, m, 3- and 4-H_2), 3.30—3.70 (2 H, m, 5-H_2), 4.50 (1 H, br s, OH), 5.40—5.86 (1 H, m, 2-H), 5.66 (1 H, dd, *J* 6 and 12 Hz, COCH=), and 6.30—6.50 (2 H, m, =CH_2); *m/z* 141 (M^+) (Found: M^+, 141.0784. $C_7H_{11}NO_2$ requires *M*, 141.0789).

N-*Crotonoylpyrrolidin*-2-*ol* (**32**).—The amino acetal (**24**) (1 g) was similarly converted into the *pyrrolidine* (**32**) (988 mg, 74%), $\nu_{max.}$ 3 400 (OH) and 1 659 cm^{-1} (C=O); δ 1.80—2.15 (7 H, m, =CH*Me* and 3- and 4-H_2), 3.40—3.93 (2 H, m, 5-H_2), 4.25 (1 H, br s, OH), 5.53—5.73 (1 H, m, 2-H), 6.03 (1 H, dd, *J* 2 and 16 Hz, COCH=), and 6.80 (1 H, dq, *J* 16 and 7 Hz, =C*H*Me) (Found: M^+, 155.0917. $C_8H_{13}NO_2$ requires *M*, 155.0945).

N-*Cinnamoylpyrrolidin*-2-*ol* (**33**).—Similarly, the amino acetal (**24**) (1 g) was converted into the *hydroxypyrrolidine* (**33**) (1.01 g, 75%), $\nu_{max.}$ 3 400 (OH) and 1 650 cm^{-1} (C=O); δ 1.90—2.25 (4 H, m, 3- and 4-H_2), 3.45—3.90 (2 H, m, 5-H_2), 4.25 (1 H, br s, OH), 5.55—5.80 (1 H, m, 2-H), 6.57 (1 H, d, *J* 16 Hz, COCH=), 7.25—7.62 (5 H, m, Ph), and 7.67 (1 H, d, *J* 16 Hz, =C*H*Ph) (Found: M^+, 217.1100. $C_{13}H_{15}NO_2$ requires *M*, 217.1102).

Ethyl (E)-6-*Acrylamidohex*-2-*enoate* (**34**).—A mixture of the hydroxypyrrolidine (**31**) (55 mg) and (ethoxycarbonylmethylene)triphenylphosphorane (135 mg) in acetonitrile (5 ml) was stirred for 10 h at room temperature and then refluxed for 1 h. After evaporation of the solvent, the residue was chromatographed on silica gel. Elution with benzene–acetone (93:7 v/v) gave the α,β-*unsaturated enamide ester* (**34**) (74 mg, 90%) as a solid, m.p. 128—131 °C; $\nu_{max.}$ 3 460 (NH), and 1 715 and 1 680 cm^{-1} (C=O); δ 1.26 (3 H, t, *J* 7 Hz, OCH_2Me), 1.76 (2 H, quintet, *J* 7 Hz, 5-H_2), 2.20 (2 H, br q, *J* 7 Hz, 4-H_2), 3.60 (2 H, br q, *J* 7 Hz, 6-H_2), 4.13 (2 H, q, *J* 7 Hz, OCH_2), 5.63 (1 H, dd, *J* 6 and 12 Hz, COC*H*=CH_2), 5.80 (1 H, d, *J* 16 Hz, 2-H), 6.20—6.31 (2 H, m, CH=CH_2), 6.95 (1 H, dt, *J* 16 and 7 Hz, 3-H), and 7.75 (1 H, m, NH); *m/z* 211 (M^+) (Found: M^+, 211.1180. $C_{11}H_{17}NO_3$ requires *M*, 211.1207).

Ethyl (E)-6-*Crotonamidohex*-2-*enoate* (**35**).—Wittig reaction of the pyrrolidine (**32**) (224 mg) under the same reaction conditions as above yielded the *enamide* (**35**) (224 mg, 69%) as an oil, $\nu_{max.}$ 3 450 (NH) and 1 710 and 1 678 cm^{-1} (C=O); δ 1.27 (3 H, t, *J* 7 Hz, OCH_2Me), 1.68 (2 H, quintet, *J* 7 Hz, 5-H_2), 1.85 (3 H, dd, *J* 3 and 7 Hz, =CH*Me*), 2.12 (2 H, br q, *J* 7 Hz, 4-H_2), 3.30 (2 H, br q, *J* 7 Hz, 6-H_2), 4.14 (2 H, q, *J* 7 Hz, OCH_2), 5.80 (1 H, dq, *J* 16 and 3 Hz, NCOCH=), 5.81 (1 H, dt, *J* 16 and 2 Hz, O_2CCH=), 6.00—6.25 (1 H, m, NH), and 6.60—7.04 (2 H, m, 2 × =CH) (Found: M^+, 225.1357. $C_{12}H_{19}NO_3$ requires *M*, 225.1364).

Ethyl (E)-6-*Cinnamamidohex*-2-*enoate* (**36**).—Similarly, the hydroxypyrrolidine (**33**) (217 mg) was transformed into the *ester* (**36**) (252 mg, 88%), $\nu_{max.}$ 3 450 (NH) and 1 710 and 1 660 cm^{-1} (C=O); δ 1.26 (3 H, t, *J* 7 Hz, OCH_2Me), 1.60—1.87 (2 H, m, 5-H_2), 2.29 (2 H, br q, *J* 7 Hz, 4-H_2), 3.41 (2 H, br q, *J* 7 Hz, 6-H_2), 4.16 (2 H, q, *J* 7 Hz, OCH_2), 5.82 (1 H, dt, *J* 17 and 2 Hz, 2-H), 6.38 (1 H, d, *J* 16 Hz, NCOCH=), 6.92 (1 H, dt, *J* 17 and 7 Hz, 3-H), 6.22—6.50 (5 H, m, Ph), and 7.60 (1 H, d, *J* 16 Hz, =C*H*Ph) (Found: M^+, 287.1536. $C_{17}H_{21}NO_3$ requires *M*, 287.1511).

N-(2-*Formyl*-4,5-*dimethoxyphenethyl*)*acrylamide* (**41**).—To a vigorously stirred mixture of 3,4-dihydro-6,7-dimethoxyisoquinoline (**40**) (243 mg), dichloromethane (2 ml), and saturated aqueous sodium hydrogen carbonate (2 ml) was added dropwise a solution of acryloyl chloride (250 mg) in dichloromethane (2 ml), and the mixture was stirred for 50 min. After addition of benzene (10 ml) the organic layer was washed successively with 10% ammonia and saturated aqueous sodium chloride, dried (Na_2SO_4), and evaporated. The residue was subjected to chromatography on silica gel, and elution with benzene–acetone (9:1 v/v) gave the *aldehyde* (**41**) (213 mg, 64%) as a solid. Recrystallisation from methanol afforded yellowish scales, m.p. 135—137 °C; $\nu_{max.}$ 3 450 (NH) and 1 690 and 1 675 cm^{-1} (C=O); δ 3.22 (2 H, br t, *J* 7 Hz, ArCH_2), 3.54 (2 H, br q, *J* 7 Hz, NCH_2), 3.92 (6 H, s, 2 × OMe), 5.60 (1 H, dd, *J* 16 and 5 Hz, COCH=), 6.09 (1 H, d, *J* 16 Hz, =CH*H*), 6.17 (1 H, d, *J* 5 Hz, =C*H*H), 6.74 and 7.28 (each 1 H, each s, 2 × ArH), and 10.00 (1 H, s, CHO); *m/z* 263 (M^+) (Found: M^+, 263.1182. $C_{14}H_{17}NO_4$ requires *M*, 263.1157).

N-(2-*Formyl*-4,5-*dimethoxyphenethyl*)*crotonamide* (**42**).—Similarly, the 3,4-dihydroisoquinoline (**40**) (500 mg) was converted into the *aldehyde* (**42**) (550 mg, 90%), m.p. 143—144 °C; δ 1.83 (3 H, dd, *J* 2 and 7 Hz, =CH*Me*), 3.21 (2 H, br t, *J* 7 Hz, ArCH_2), 3.55 (2 H, br q, *J* 7 Hz, NCH_2), 3.91 and 3.94 (each 3 H, each s, 2 × OMe), 5.72 (1 H, dq, *J* 16 and 2 Hz, COCH=), 6.58—7.00 (3 H, m, =C*H*Me and 2 × ArH), and 10.03 (1 H, s, CHO) (Found: M^+, 277.1324. $C_{15}H_{19}NO_4$ requires *M*, 277.1314).

Ethyl 2-(2-*Acrylamidoethyl*)-4,5-*dimethoxycinnamate* (**45**).—A mixture of the aldehyde (**41**) (157 mg) and ethoxycarbonylmethylene)triphenylphosphorane (291 mg) in acetonitrile (5 ml) was stirred for 12 h before being evaporated to dryness. The residue was purified by column chromatography on silica gel

with benzene–acetone (9:1 v/v) as eluant to give the *enamide ester* (**45**) (140 mg, 70%) as a solid. Recrystallisation from methanol afforded yellowish scales, m.p. 127—128 °C; $\nu_{max.}$ 3 450 (NH), 1 700 and 1 670 (C=O), and 1 630 cm^{-1} (C=C); δ 1.33 (3 H, t, *J* 7 Hz, OCH_2Me), 2.95 (2 H, br t, *J* 7 Hz, $ArCH_2$), 3.32—3.64 (2 H, m, NCH_2), 3.87 (6 H, s, 2 × OMe), 4.26 (2 H, q, *J* 7 Hz, OCH_2), 6.26 (1 H, dd, *J* 16 and 5 Hz, $COCH{=}CH_2$), 6.09 (1 H, d, *J* 16 Hz, =C*H*H), 6.19 (1 H, d, *J* 5 Hz, =CH*H*), 6.26 (1 H, d, *J*, 16 Hz, =C*H*CO_2Et), 6.68 and 7.04 (each 1 H, each s, 2 × ArH), and 7.88 (1 H, d, *J* 16 Hz, ArC*H*=) (Found: M^+, 333.1581. $C_{18}H_{23}NO_5$ requires *M*, 333.1576).

Ethyl 2-(2-*Crotonamidoethyl*)-4,5-*dimethoxycinnamate* (**46**).—The aldehyde (**42**) (305 mg) was converted as above into the *ester* (**46**) (336 mg, 88%), m.p. 133—134 °C; $\nu_{max.}$ 3 450 (NH), 1 700 and 1 680 (C=O), and 1 630 cm^{-1} (C=C); δ 1.33 (3 H, t, *J* 7 Hz, OCH_2Me), 1.82 (3 H, dd, *J* 2 and 8 Hz, =CH*Me*), 2.94 (2 H, br t, *J* 7 Hz, $ArCH_2$), 3.35—3.57 (2 H, m, NCH_2), 3.84 and 3.89 (each 3 H, each s, 2 × OMe), 4.24 (2 H, q, *J* 7 Hz, OCH_2), 5.71 (1 H, dq, *J* 16 and 2 Hz, NCOCH=), 6.26 (1 H, d, *J* 16 Hz, O_2CCH=), 6.69 (1 H, s, ArH), 6.80 (1 H, dq, *J* 16 and 8 Hz, =C*H*Me), 7.04 (1 H, s, ArH), and 7.89 (1 H, d, *J* 16 Hz, ArC*H*=) (Found: M^+, 347.1716. $C_{19}H_{25}NO_5$ requires *M*, 347.1731).

Ethyl 2-(2-*Cinnamamidoethyl*)-4,5-*dimethoxycinnamate* (**47**).—The 3,4-dihydroisoquinoline (**40**) (1 g) was converted into the *aldehyde* (**43**) (1.15 g, 77%), m.p. 128—131 °C; δ 9.93 (1 H, s, CHO) (Found: M^+, 339.1485. $C_{20}H_{21}NO_4$ requires *M*, 339.1470).

Wittig reaction of compound (**43**) (1.12 g) gave the *ester* (**47**) (991 mg, 73%), m.p. 151—153 °C; $\nu_{max.}$ 3 440 (NH), 1 700 and 1 660 (C=O), and 1 620 cm^{-1} (C=C); δ 1.31 (3 H, t, *J* 8 Hz, OCH_2Me), 3.00 (2 H, t, *J* 7 Hz, $ArCH_2$), 3.46—3.65 (2 H, m, NCH_2), 3.86 and 3.88 (each 3 H, each s, 2 × OMe), 4.22 (2 H, q, *J* 8 Hz, OCH_2), 5.70 (1 H, br s, NH), 6.25 and 6.29 (each 1 H, each d, each *J* 16 Hz, 2 × COCH=), 6.70 and 7.06 (each 1 H, each s, 2 × ArH), 7.20—7.45 (5 H, m, Ph), and 7.60 and 7.93 (each 1 H, each d, each *J* 16 Hz, 2 × C*H*=CHCO) (Found: M^+, 409.1928. $C_{24}H_{27}NO_5$ requires *M*, 409.1888).

Ethyl 4,5-*Dimethoxy*-2-[2-(2-*methylcrotonamido*)*ethyl*]*cinnamate* (**48**).—Similarly the 3,4-dihydroisoquinoline (**40**) (500 mg) was converted into the *aldehyde* (**44**) (418 mg, 65%), δ 10.10 (1 H, s, CHO) (Found: M^+, 291.1436. $C_{16}H_{21}NO_4$ requires *M*, 291.1469).

Wittig reaction of compound (**44**) (167 mg) yielded the *ester* (**48**) (153 mg, 74%), m.p. 123—125 °C (from chloroform–n-hexane); $\nu_{max.}$ 3 450 (NH), 1 700 and 1 660 (C=O), and 1 628 cm^{-1} (C=C); δ 1.33 (3 H, t, *J* 8 Hz, OCH_2Me), 1.70 (3 H, br d, *J* 8 Hz, *Me*CH=), 1.75 (3 H, s, =CMe–), 2.93 (2 H, t, *J* 8 Hz, $ArCH_2$), 3.30—3.63 (2 H, m, NCH_2), 3.78 and 3.81 (each 3 H, each s, 2 × OMe), 4.23 (2 H, q, *J* 8 Hz, OCH_2), 5.73—6.13 (2 H, m, =C*H*Me and NH), 6.46 (1 H, d, *J* 16 Hz, =CHCO), 6.65 and 7.00 (each 1 H, each s, 2 × ArH), and 7.83 (1 H, d, *J* 16 Hz, ArC*H*=) (Found: M^+, 361.1881. $C_{20}H_{27}NO_5$ requires *M*, 361.1888).

Ethyl (E)-3-[3-(2-*Crotonamido*)*ethylindol*-2-*yl*]*acrylate* (**55**).—Similarly, 3,4-dihydro-β-carboline (**53**) (250 mg) was converted, in two steps, into the *ester* (**55**) (297 mg, 62%), m.p. 194—195 °C; $\nu_{max.}$ 3 485—3 460 (NH), 1 700 and 1 682 (C=O), and 1 632 cm^{-1} (C=C); δ 1.34 (3 H, t, *J* 6 Hz, OCH_2Me), 1.79 (3 H, dd, *J* 2 and 5.8 Hz, =CH*Me*), 3.14 (2 H, t, *J* 5.7 Hz, $ArCH_2$), 3.43—3.69 (2 H, m, NCH_2), 4.25 (2 H, q, *J* 6 Hz, OCH_2), 5.66 (1 H, dd, *J* 2 and 16 Hz, COCH=), 6.17 (1 H, d, *J* 16 Hz, COCH=), 6.81 (1 H, dq, *J* 16 and 5.8 Hz, =C*H*Me), 7.71 (1 H, d, *J* 16 Hz, ArC*H*=), and 8.42 (1 H, br s, NH) (Found: M^+, 326.1629. $C_{19}H_{21}N_2O_3$ requires *M*, 326.1629).

Ethyl (±)-(1RS,9aSR)-1,2,3,6,7,8,9,9a-*Octahydro*-4-*oxo*-9a*H*-*quinolizine*-1-*carboxylate* (**20**).—(A) A mixture of the enamide ester (**16**) (40 mg), zinc chloride (40 mg), triethylamine (0.5 ml), and chlorotrimethylsilane (0.5 ml) in dry toluene (5 ml) was heated for 10 h at 185 °C in a sealed tube. After the mixture had cooled and been treated with benzene (10 ml), it was washed successively with 5% hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and saturated aqueous sodium chloride and dried (Na_2SO_4). Evaporation of the solvents gave a residue, which was purified by chromatography on silica gel. Elution with benzene–acetone (9:1 v/v) gave the *octahydroquinolizin*-4-*one* (**20**) (22 mg, 55%) as a syrup, $\nu_{max.}$ 1 720 and 1 620 cm^{-1} (C=O); δ 1.27 (3 H, t, *J* 8 Hz, OCH_2Me), 1.20—2.60 (12 H, m), 3.50—3.68 (1 H, m), 4.17 (2 H, q, *J* 8 Hz, OCH_2), and 4.70—4.84 (1 H, m) (Found: M^+, 225.1325. $C_{12}H_{19}NO_3$ requires *M*, 225.1366).

(B) To a stirred solution of the enamide ester (**16**) (30 mg) and triethylamine (0.1 ml) in dry dichloromethane (1 ml) at −78 °C was added dimethyl-t-butylsilyl trifluoromethanesulphonate (0.08 ml), and the mixture was stirred for 1 h at −78 °C under argon. After addition of benzene (10 ml), the mixture was washed successively with saturated aqueous sodium hydrogen carbonate and saturated aqueous sodium chloride and dried (Na_2SO_4). After evaporation of the solvent, the residue was subjected to column chromatography as above to give the quinolizidin-4-one (**20**) (30.4 mg, 92%), which was identical with the above sample on spectral and chromatographic comparison.

Ethyl (±)-(1RS,2RS,9aSR)- *and* (±)-(1RS,2SR,9aSR)-1,2,3,6,7,8,9,9a-*Octahydro*-2-*methyl*-4-*oxo*-9a*H*-*quinolizine*-1-*carboxylate* (**21a**) *and* (**21b**).—Following method A, the enamide ester (**17**) (57 mg) was transformed into the *octahydroquinolizin*-4-*ones* (**21a**) (33 mg, 58%) as a syrup, $\nu_{max.}$ 1 722 and 1 620 cm^{-1} (C=O); δ 0.94 (3 H, d, *J* 8 Hz, 2-Me), 1.26 (3 H, t, *J* 8 Hz, OCH_2Me), 1.15—2.60 (11 H, m), 3.50—3.68 (1 H, m), 4.17 (2 H, q, *J* 8 Hz, OCH_2), and 4.70—4.85 (1 H, m); *m*/*z* 239 (M^+) (Found: M^+, 239.1535. $C_{13}H_{21}NO_3$ requires *M*, 239.1521); and (**21b**) (9.7 mg, 17%) as a syrup, $\nu_{max.}$ 1 720 and 1 620 cm^{-1} (C=O); δ 1.01 (3 H, d, *J* 8 Hz, 2-Me), 1.25 (3 H, *J* 8 Hz, OCH_2Me), 1.20—2.85 (11 H, m), 3.26—3.55 (1 H, m), 4.16 (2 H, q, *J* 8 Hz, OCH_2), and 4.70—4.85 (1 H, m) (Found: M^+, 239.1515).

Ethyl (±)-(1RS,2RS,9aSR)- *and* (±)-(1RS,2SR,9aSR)-1,2,-3,6,7,8,9,9a-*Octahydro*-4-*oxo*-2-*phenyl*-9a*H*-*quinolizine*-1-*carboxylate* (**22**).—Following method A, the enamide ester (**18**) (54 mg) was transformed into a mixture of two *octahydroquinolizin*-4-*ones* (**22**) (43 mg, 79%) in the ratio 4:9 as a syrup, $\nu_{max.}$ 1 726 and 1 622 cm^{-1} (C=O); δ 0.83 and 1.14 [3 H (4:9), each t, each *J* 8 Hz, OCH_2], 1.30—2.90 (11 H, m), 3.05—3.62 (1 H, m), 3.83 and 4.04 [2 H (4:9), each q, *J* 8 Hz, OCH_2], 4.70—5.00 (1 H, m), and 7.05—7.30 (5 H, m, Ph) (Found: M^+, 301.1657. $C_{18}H_{23}NO_3$ requires *M*, 301.1676).

Ethyl (±)-(8RS,8aSR)-1,2,3,5,6,7,8,8a-*Octahydro*-5-*oxoindolizine*-8-*carboxylate* (**37**).—Following method A, the enamide ester (**34**) (40 mg) was converted into the *octahydroindolizin*-5-*one* (**37**) (22 mg, 55%) as a syrup, $\nu_{max.}$ 1 722 and 1 620 cm^{-1} (C=O); δ 1.28 (3 H, t, *J* 8 Hz, OCH_2Me), 1.50—2.65 (9 H, m, 1-, 2-, 6-, and 7-H_2 and 8-H), 3.42—3.71 (3 H, m, 3-H_2 and 8a-H), and 4.20 (2 H, q, *J* 8 Hz, OCH_2Me) (Found: M^+, 211.1222. $C_{21}H_{17}NO_3$ requires *M*, 211.1207).

Ethyl (±)-(7RS,8RS,8aSR)- *and* (±)-(7RS,8SR,8aRS)-1,2,3,5,6,7,8,8a-*Octahydro*-7-*methyl*-5-*oxoindolizine*-8-*carboxylate* (**38a**) *and* (**38b**).—(A) Following method A, the enamide ester (**35**) (50 mg) was converted into the *octahydroindolizin*-5-*one* (**38a**) (36 mg, 72%) as a syrup, $\nu_{max.}$ 1 721 and 1 620 cm^{-1}

(C=O); δ 0.99 (3 H, d, *J* 6 Hz, 7-Me), 1.28 (3 H, t, *J* 8 Hz, OCH_2Me), 1.54—2.75 (8 H, m, 1-, 2-, and 6-H_2 and 7- and 8-H), 3.40—3.77 (3 H, m, 3-H_2 and 8a-H), and 4.20 (2 H, q, *J* 8 Hz, OCH_2) (Found: M^+, 225.1376. $C_{12}H_{19}NO_3$ requires *M*, 225.1364); and its *epimer* (**38b**) (3.5 mg, 7%) as a syrup, $\nu_{max.}$ 1 720 and 1 620 cm^{-1} (C=O), δ 1.06 (3 H, d, *J* 7 Hz, 7-Me), 1.25 (3 H, t, *J* 8 Hz, OCH_2Me), 1.40—2.90 (8 H, m, 1-, 2-, and 6-H_2 and 7- and 8-H), 3.40—3.77 (3 H, m, 3-H_2 and 8a-H), and 4.14 (2 H, q, *J* 8 Hz, OCH_2) (Found: M^+, 225.1371).

(B) Following method B carried out at −78 °C, the enamide ester (**35**) (23 mg) was selectively converted into the indolizin-5-one (**38a**) (17 mg, 75%), whose spectral data and t.l.c. behaviour were identical with those of the above sample (**38a**).

(C) Following method B carried out at 20 °C, the enamide ester (**35**) (60 mg) was converted into two indolizin-5-ones (**38a**) (46 mg, 78%) and (**38b**) (3 mg, 5%), whose spectral data and t.l.c. behaviour were identical with those of the above samples, respectively.

Ethyl (±)-(7RS,8RS,8aSR)- *and* (±)-(7RS,8SR,8aRS)-1,2,3,-5,6,7,8,8a-*Octahydro*-5-*oxo*-7-*phenylindolizine*-8-*carboxylate* (**39a**) *and* (**39b**).—Following method A, the enamide ester (**36**) (90 mg) was transformed into the *octahydroindolizin*-5-*one* (**39a**) (67.5 mg, 75%) as a syrup, $\nu_{max.}$ 1 722 and 1 622 cm^{-1} (C=O); δ 0.86 (3 H, t, *J* 8 Hz, OCH_2Me), 1.50—3.70 (11 H, m), 3.86 (2 H, q, *J* 8 Hz, OCH_2), and 7.10—7.35 (5 H, m, Ph) (Found: M^+, 287.1506. $C_{17}H_{21}NO_3$ requires *M*, 287.1511); and its *epimer* (**39b**) (10 mg, 11%) as a syrup, $\nu_{max.}$ 1 721 and 1 621 cm^{-1} (C=O); δ 1.06 (3 H, t, *J* 8 Hz, OCH_2Me), 1.40—3.65 (11 H, m), 4.00 (2 H, q, *J* 8 Hz, OCH_2), and 7.10—7.30 (5 H, m, Ph) (Found: M^+, 287.1525).

Ethyl (±)-(1RS,11bRS)-1,3,4,6,7,11b-*Hexahydro*-9,10-*dimethoxy*-4-*oxo*-2H-*benzo*[a]*quinolizine*-1-*carboxylate* (**49**).—The enamide ester (**45**) (50 mg) was transformed, following method A, into the *hexahydrobenzo*[a]*quinolizin*-4-*one* (**49**) (22 mg, 44%) as a syrup, $\nu_{max.}$ 1 720 and 1 620 cm^{-1} (C=O); δ 1.33 (3 H, t, *J* 7 Hz. OCH_2Me), 3.80 and 3.85 (each 3 H, each s, 2 × OMe), 5.03 (1 H, d, *J* 8 Hz, 11b-H), and 6.60 (2 H, br s, 2 × ArH) (Found: M^+, 333.1581. $C_{18}H_{23}NO_5$ requires *M*, 333.1576).

Ethyl (±)-(1RS,2RS,11bRS)-1,3,4,6,7,11b-*Hexahydro*-9,10-*dimethoxy*-2-*methyl*-4-*oxo*-2H-*benzo*[a]*quinolizine*-1-*carboxylate* (**50**).—Following method A, the enamide ester (**46**) (41 mg) was transformed into the *hexahydrobenzo*[a]*quinolizin*-4-*one* (**50**) (21 mg, 52%) as crystals, m.p. 158—159 °C; $\nu_{max.}$ 1 730 and 1 630 cm^{-1} (C=O); δ 1.09 (3 H, d, *J* 7 Hz, 2-Me), 1.32 (3 H, t, *J* 8 Hz, OCH_2Me), 3.78 and 3.83 (each 3 H, each s, 2 × OMe), 4.26 (2 H, q, *J* 8 Hz, OCH_2), 5.00 (1 H, d, *J* 8 Hz, 11b-H), and 6.51 and 6.61 (each 1 H, each s, 2 × ArH) (Found: M^+, 347.1764. $C_{19}H_{25}NO_5$ requires *M*, 347.1731).

Ethyl (±)-(1RS,2RS,11bRS)-1,3,4,6,7,11b-*Hexahydro*-9,10-*dimethoxy*-4-*oxo*-2-*phenyl*-2H-*benzo*[a]*quinolizine*-1-*carboxylate* (**51**).—(A) A mixture of the enamide ester (**47**) (56 mg), triethylamine (0.5 ml), zinc chloride (50 mg), and chlorotrimethylsilane (0.5 ml) in dry *o*-dichlorobenzene (10 ml) was refluxed for 17 h under argon. After having cooled, the reaction mixture was worked up and purified as in method A above to give the *hexahydrobenzo*[a]*quinolizin*-4-*one* (**51**) (27 mg, 48%) as crystals, m.p. 154—157 °C; $\nu_{max.}$ 1 725 and 1 630 cm^{-1} (C=O); δ 0.74 (3 H, t, *J* 8 Hz, OCH_2Me), 3.61 (2 H, q, *J* 8 Hz, OCH_2), 3.80 and 3.82 (each 3 H, each s, 2 × OMe), 5.00—5.29 (2 H, m, 11b-H and 6β-H), 6.57 and 6.65 (each 1 H, each s, 2 × ArH), and 7.16—7.40 (5 H, m, Ph) (Found: M^+, 409.1859. $C_{24}H_{27}NO_5$ requires *M*, 409.1888).

(B) Reaction of the enamide ester (**47**) (40 mg) with dimethyl-t-butylsilyl trifluoromethanesulphonate (0.04 ml) in the presence of triethylamine (0.05 ml) in dry dichloromethane (3 ml) for 1 h at room temperature gave the hexahydroquinolizin-4-one (**51**) (33 mg, 83%), identical with the above material.

(C) Reaction of the enamide ester (**47**) (40 mg) with trimethylsilyl trifluoromethanesulphonate (0.04 ml) in the presence of triethylamine (0.05 ml) in dry dichloromethane (3 ml) for 1 h at room temperature gave the hexahydroquinolizin-4-one (**51**) (30 mg, 75%), identical with the above sample.

Ethyl (±)-(1RS,2RS,11bRS)-1,3,4,6,7,11b-*Hexahydro*-9,10-*dimethoxy*-2,3-*dimethyl*-4-*oxo*-2H-*benzo*[a]*quinolizine*-1-*carboxylate* (**52**).—A mixture of the enamide ester (**48**) (150 mg), triethylamine (1 ml), zinc chloride (100 mg), and chlorotrimethylsilane (1 ml) in dry *o*-dichlorobenzene (5 ml) was refluxed for 16 h; work-up and purification as previously described yielded one isomer of the *hexahydroquinolizin*-4-*one* (**52**) (37 mg, 25%) as a solid, $\nu_{max.}$ 1 730 and 1 625 cm^{-1} (C=O); δ (3 H, d, *J* 7 Hz, 2-Me), 1.23 (3 H, d, *J* 7 Hz, 3-Me), 1.35 (3 H, t, *J* 7 Hz, OCH_2Me), 3.76 and 3.84 (each 3 H, each s, 2 × OMe), 4.50 (2 H, q, *J* 7 Hz, OCH_2), 5.04 (1 H, d, *J* 9 Hz, 11b-H), and 6.43 and 6.61 (each 1 H, each s, 2 × ArH) (Found: M^+, 361.1881. $C_{20}H_{27}NO_5$ requires *M*, 361.1888); and the *isomer* at C-3 (61 mg, 41%) as needles, m.p. 166—168 °C, $\nu_{max.}$ 1 730 and 1 625 cm^{-1} (C=O); δ 0.88 (3 H, t, *J* 7 Hz, OCH_2Me), 1.15 (3 H, d, *J* 7 Hz, 2-Me), 1.32 (3 H, d, *J* 7 Hz, 3-Me), 3.80 and 3.83 (each 3 H, each s, 2 × OMe), 4.68—5.16 (2 H, m, 11b- and 6β-H), and 6.56 and 6.63 (each 1 H, each s, 2 × ArH) (Found: M^+, 361.1876).

Ethyl (±)-(1RS,2RS,12bRS)-1,2,3,4,6,7,12,12b-*Octahydro*-2-*methyl*-4-*oxoindolo*[2,3-a]*quinolizine*-1-*carboxylate* (**56**).—Following the same procedure as above, the enamide ester (**55**) (33 mg) was converted into the *octahydroindolo*[2,3-a]*quinolizin*-4-*one* (**56**) (22 mg, 66%) as a syrup, $\nu_{max.}$ 3 450 (NH) and 1 720 and 1 630 cm^{-1} (C=O); δ 1.02 (3 H, d, *J* 5 Hz, 2-Me), 1.39 (3 H, t, *J* 7 Hz, OCH_2Me). 4.39 (2 H, q, *J* 7 Hz, OCH_2), 4.98—5.27 (2 H, m, 6β-and 12b-H), and 8.17 (1 H, br s, NH) (Found: M^+, 326.1659. $C_{19}H_{22}N_2O_3$ requires *M*, 326.1629).

(±)-*Epilupinine* (**23**).—To a stirred, refluxing suspension of lithium aluminium hydride (20 mg) in dry THF (0.5 ml) was slowly added a solution of the octahydroquinolizin-4-one (**20**) (20 mg) in dry THF (1 ml), and the mixture was refluxed for 3 h. After the mixture had cooled, water (0.02 ml), 15% aqueous sodium hydroxide (0.02 ml), and water (0.06 ml) were added successively. After the mixture had been filtered through Celite, the combined filtrate and washings (ether) were dried (Na_2SO_4) and evaporated to give a residue, which was subjected to chromatography on alumina (grade III). Elution with chloroform–ether (1:1 v/v) afforded (±)-epilupinine (**23**) (11.5 mg, 77%) as a syrup, whose n.m.r. and mass spectra were identical with those of an authentic sample.

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