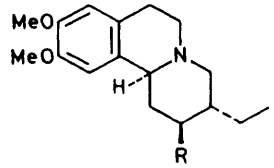
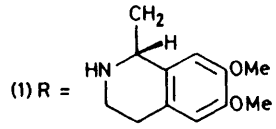
Studies on the Syntheses of Heterocyclic Compounds. Part 875.[1] The Total Stereoselective Retro Mass Spectral Synthesis of (±)-Emetine

By **Tetsuji Kametani,* Samuel A. Surgenor,** and **Keiichiro Fukumoto,** Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

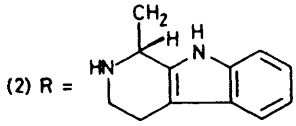
Addition of 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (5) to 3-methoxycarbonyl-1,6,7,11b-tetrahydro-9,10-dimethoxybenzo[*a*]quinolizin-4-one (4) produced 2-[3,4-dihydro-6,7-dimethoxy-1-isoquinolyl)methyl]-3-methoxycarbonyl-1,2,3,6,7,11b-hexahydro-9,10-dimethoxybenzo[*a*]quinolizin-4-one (6A). The same reaction of 3,4-dihydro-1-methyl-9*H*-pyrido[3,4-*b*]indole (15) with (4) afforded 2-(3,4-dihydro-9*H*-pyrido[3,4-*b*]-1-indolyl)methyl]-1,2,3,6,7,11b-hexahydro-9,10-dimethoxy-3-methoxycarbonylbenzo[*a*]quinolizin-4-one (16). The former Michael adduct (6A) was converted into (±)-emetine (1) in six steps.

In view of the success with which the Retro Mass Spectral method has been applied to the synthesis of a wide range of alkaloids,[2] it was decided to investigate a synthetic route to the benzo[*a*]quinolizine derivatives



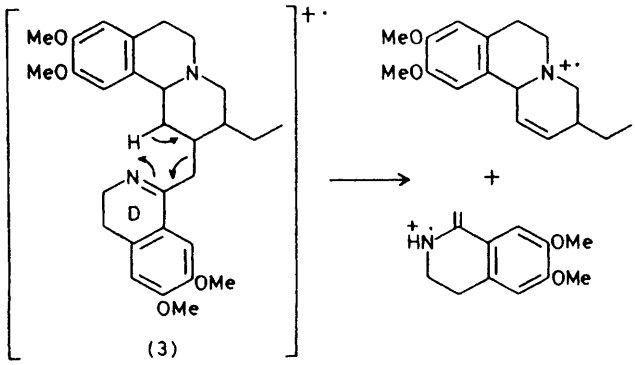


(1) R =



(2) R =

involving this method. The development of facile synthetic procedures for such derivatives, *e.g.* (1) and (2), is of continuing interest due to the biological activities possessed by some of the natural products and synthetic compounds.[3] Emetine (1) in particular, is an attractive target molecule for a synthesis based on the Retro Mass Spectral method; namely, and in accord with the nature of the method, it has been observed that the main mass spectral fragmentation process for the emetine bases in which ring D is incorporated in a 3,4-dihydroisoquinoline moiety, *e.g.* *O*-methylpsychotrine (3), is as shown in Scheme 1.[4] It was thus envisaged that utilisation of the feasible synthetic equivalents of these mass spectral fragments, the αβ-unsaturated ester (4) and the 3,4-dihydro-1-methylisoquinoline (5), in a Michael reaction (exploiting the enamine character of the latter [5]) would enable a synthesis of (±)-emetine *via* the Retro Mass Spectral adduct (6) to be achieved.



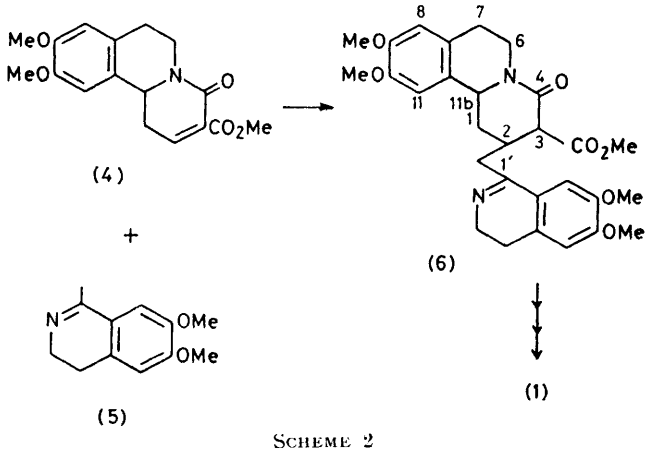
(3)

SCHEME 1

Here we report a facile total stereoselective synthesis of emetine (1) achieved on the basis of the above reasoning. The results of an attempt to carry out an analogous synthesis of deoxytubulosine (2) are also presented.[6]

RESULTS AND DISCUSSION

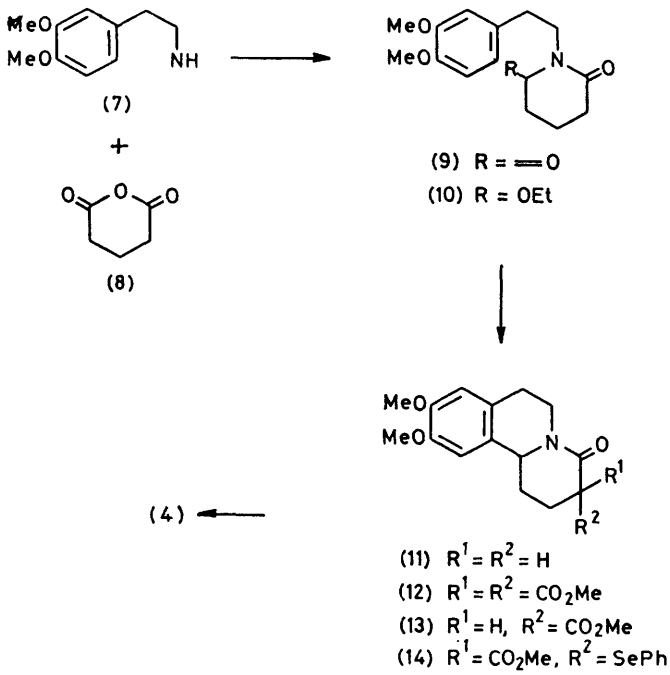
The requisite αβ-unsaturated ester lactam (4) was prepared *via* the known quinolizinone (11) (Schemes 2 and 3).[7,8] Thus, heating a mixture of 3,4-dimethoxyphenethylamine (7) and glutaric anhydride (8) at 100 °C and



SCHEME 2

treatment of the product with refluxing acetyl chloride afforded the imide (9) in 71% yield.[7] By the method of Speckamp,[9] this imide was converted into 1,2,3,6,7,11b-hexahydro-9,10-dimethoxybenzo[*a*]quinolizin-4-one (11). Thus low-temperature sodium borohydride reduction of imide (9) in ethanol in the presence of hydrochloric acid yielded the ethoxypiperidine (10) which on treatment with toluene-*p*-sulphonic acid in refluxing benzene

produced the benzoquinolizinone (11) * in 99% overall yield. Treatment of this lactam (11) in tetrahydrofuran with one equivalent of lithium di-isopropylamide (LDA) and one equivalent of methyl chloroformate led to pro-

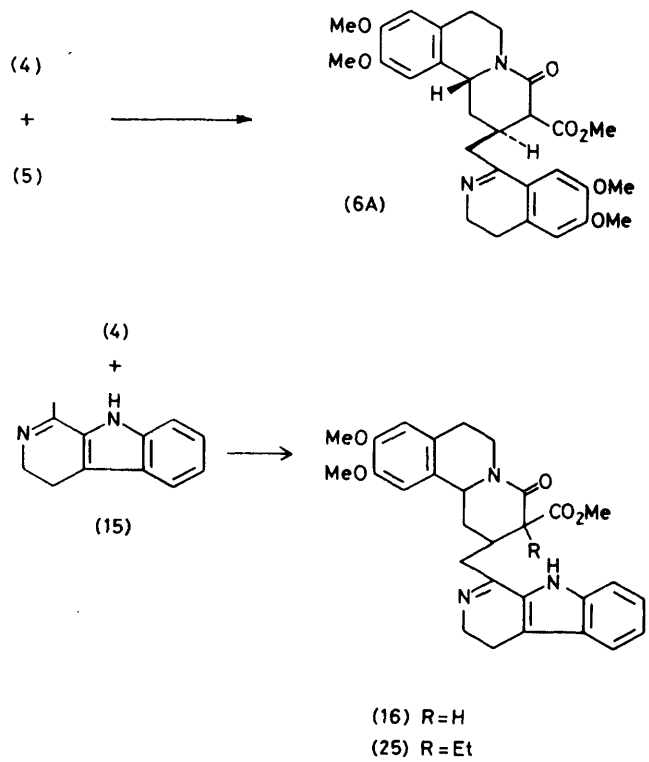


SCHEME 3

duction of the αα-disubstituted derivative (12) in 50% yield rather than to formation of the desired mono-methoxycarbonyl compound (13). Using two equivalents of LDA and an excess of methyl chloroformate the diester (12) could be obtained in 93.3% yield after recrystallisation. The required monoester (13) was produced as a mixture of diastereoisomers on hydrolysis of the diester in methanol containing 1 equivalent of potassium hydroxide. For the purposes of complete characterisation, a single stereoisomer was obtained as crystals by careful chromatography on silica gel. Introduction of αβ-unsaturation was brought about through an α-selenation–oxidative elimination sequence;[10] treatment of the mixture of diastereoisomeric monoesters (13) in benzene–dimethylformamide with sodium hydride followed by addition of phenylselenyl chloride yielded a mixture of the diastereoisomeric α-phenylseleno-derivatives (14) in 90.4% yield. Again for characterisation purposes only, a crystalline sample of a single isomer was obtained by chromatography on silica gel. Oxidative elimination proceeded smoothly at room temperature on treatment of the above mixture with an excess of sodium metaperiodate in aqueous methanol. Short-column chromatography (SiO–$CHCl_3$) of the crude product afforded the required Retro Mass Spectral synthon (4) as a pale yellow gum in 89.7% yield, all attempts at crystallisation failing. The molecular ion peak was observed at *m/e* 317 in the mass spectrum, and carbonyl bands appeared at 1 740 and 1 620 cm^{-1} in the i.r. spectrum. The olefinic proton was observed as a broad doublet (*J* 3 Hz) at δ 7.50 in the n.m.r. spectrum.

When a mixture of the above product (4) and 2 equivalents of the other Retro Mass Spectral synthon, 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (5),[11] in dry methanol solution was maintained under nitrogen at room temperature in the dark for 94 h, the Michael adduct (6A) was produced as a fine white precipitate in 55.7% yield (Scheme 4). It was evident from the n.m.r. spectrum and from the t.l.c. behaviour that this product was a single diastereoisomer. As is to be expected of a Retro Mass Spectral product, this adduct showed only a very small molecular ion peak (*m/e* 522) in its mass spectrum with the largest peaks (*m/e* 205 and 317) corresponding to the molecular weights of the two synthons. That the partial stereochemistry of this product is as represented in formula (6A) was demonstrated by subsequent reactions. No other isomer or other major product could be detected in, or isolated from, the remaining reaction mixture.

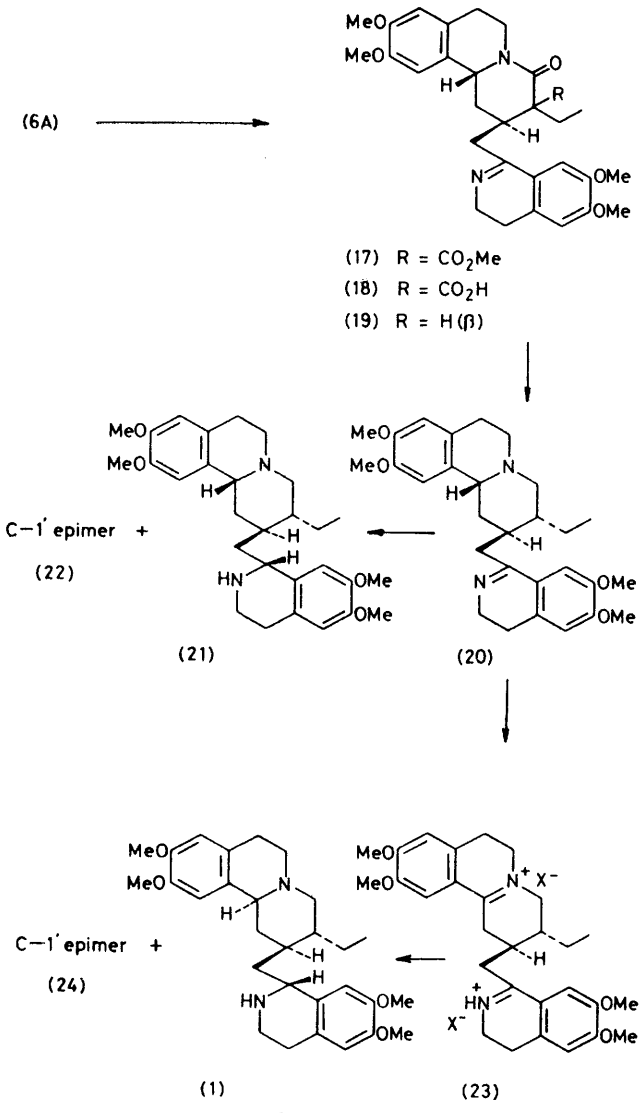
A potential intermediate for an analogous synthesis of deoxytubulosine (2), the hexacyclic Michael adduct (16), was produced when the 3,4-dihydro-β-carboline (15)[12] was substituted for the 3,4-dihydroisoquinoline in the above addition reaction. Two stereoisomers of this derivative (16), in an approximate ratio of 3.5 : 1, were formed in 79.1% yield. The mass spectrum of the



SCHEME 4

*Although the melting point (116—118 °C) of this compound differs considerably from that already reported (ref. 8; m.p. 87.5—90.5 °C), all spectral and analytical data are in accord with the structure.

major isomer, isolated by fractional crystallisation of the crude product, displayed a very small molecular ion peak (*m/e* 501) and two main peaks (*m/e* 184 and 317) in analogy with the 'emetine Michael adduct' (6A).



SCHEME 5

Short-column chromatography (20 : 1) of the residue obtained on evaporation of the mother liquor afforded a *ca.* 1 : 1 mixture of the two stereoisomers. However, further chromatography on a column of silica gel (using a 50 : 1 silica : compound ratio which was deemed necessary to achieve separation) led to extensive decomposition with the result that a pure sample of the minor isomer could not be isolated.

Conversion of the adduct (6A) into (±)-emetine (1) was carried out as shown in Scheme 5. Treatment of (6A), in benzene–dimethylformamide at room temperature, with one equivalent of sodium hydride followed by addition of one equivalent of ethyl iodide afforded the 3-ethyl derivative (17) as colourless needles in 77.5% yield. Hydrolysis in refluxing methanolic potassium hydroxide gave an almost quantitative yield of the carboxylic acid. Although the relative configuration at C-2 and C-3 in these compounds (6A), (17), and (18) remains obscure, a single diastereoisomer was obtained in each case. Heating the acid (18) in dimethylformamide at 180—185 °C for 30 min furnished the decarboxylated product (19) as a single compound in 79.2% yield. This product was isolated directly from the reaction mixture as colourless crystals and although it could not successfully be recrystallised, a satisfactory elemental analysis was obtained. N.m.r. spectroscopy and t.l.c. behaviour demonstrated that this product was a single diastereoisomer. Reduction to the emetine-type base was carried out in two straightforward steps.* Room temperature reduction of the lactam (19) with Red-al in benzene afforded the amine (20) quantitatively as a pale yellow oil (*m/e* 478) which was used without further purification, and sodium borohydride reduction of this derivative produced, in 95.6% yield, *ca.* 1.4 : 1 mixture of the emetine isomers (21) and (22) which were separated by chromatography on silica gel. Although the isomer of higher R_F was indistinguishable from (±)-emetine by t.l.c. analysis,† comparison of the n.m.r. spectra revealed small differences in all the main chemical shifts (see Experimental section) indicating this product to be a diastereoisomer of (±)-emetine. That it was the C-11b epimer (21) was demonstrated by subsequent work. The other product was thus deduced to be C-11b-*epi*-isometine (22).

Treatment of compound (20), the C-11b epimer of *O*-methylpsychotrine (3), with mercury(II) acetate in aqueous acetic acid, according to the method of Openshaw and Whittaker,[15] furnished the dehydration product (23) which was isolated as the perchlorate salt. Reduction of this derivative with sodium borohydride afforded, in 75.5% yield from (20), *ca.* 1 : 1.3 mixture of (±)-emetine (1) and (±)-isoemetine (24) which were separated by chromatography on silica gel. This synthetic emetine was identical to an authentic sample ‡ (t.l.c., i.r., and n.m.r. spectra). The medicinally useless isoemetine can, of course, be converted, *via* *O*-methylpsychotrine (3), into emetine.[15] This last reaction sequence described above, dehydrogenation–reduction, demonstrates that compound (20) is the thermodynamically less stable *cis*-quinolizidine, and therefore that the preceding compounds back to the Michael adduct also have the β-C-11b-H configuration as represented in formula (6A) to (20) in Scheme 5. We have thus achieved a simple and efficient stereoselective synthesis

* Reduction of such derivatives to the emetine-type base has previously been carried out in one step using lithium aluminium hydride (ref. 13).

† In t.l.c. analysis of a mixture of emetine and isometine, emetine is the fast-moving component. Also, the β1′-H epimer in a range of C-1′ diastereoisomeric pairs was shown [14] to have the higher R_F.

‡ Commercial emetine dihydrochloride from Tokyo Kasei Kogyo Co., Ltd., Tokyo.

of (±)-emetine based on the Retro Mass Spectral method.

The potential deoxytubulosine intermediate (16) has been prepared by Michael addition in *ca.* 80% yield (disregarding the fact that two stereoisomers were produced) as already described. However, an attempt to carry out an analogous synthesis of (±)-deoxytubulosine (2) failed due to our inability to achieve the required C3-ethylation [(16) to (25)] of this potential intermediate. Attempted ethylation of the major isomer of (16), under the conditions which were successfully used to convert (6A) into (17), and under a variety of other conditions (using or LDA at various temperatures), led to complex reaction products from which none of the required derivative (25) was obtained.

EXPERIMENTAL

M.p.s were taken with a Yanagimoto micro-apparatus (MP-S2). I.r. spectra were recorded on a Hitachi 215 spectrophotometer, n.m.r. spectra with a JEOL JNM-PMX-60 spectrophotometer (using tetramethylsilane as internal standard), and mass spectra on Hitachi M-52G and JEOL JMS-01SG-2 spectrometers.

N-(3,4-*Dimethoxyphenethyl*)*glutarimide* (9).—A mixture of 3,4-dimethoxyphenethylamine (7) (5.9 g) and glutaric anhydride (8) (3.7 g) was heated at 95—100 °C for 1.5 h. To the viscous brown syrup, after cooling, was added acetyl chloride (20 ml) and the mixture was stirred under reflux for 1.5 h. Evaporation of the excess of acetyl chloride under reduced pressure and addition of water to the residue produced a fine white crystalline solid which was collected by filtration and recrystallised from benzene to afford the glutarimide (9) (6.4 g, 71%), m.p. 113.5—114.5 °C (lit.,[7] 114—115 °C), $\nu_{max.}$ ($CHCl_3$) 1 720 and 1 665 cm^{-1}; δ($CDCl_3$) 6.87 (2 H, s, arom.), 4.03 (2 H, t, *J* 7 Hz, CH_2N), 3.88 (6 H, s, 2 OMe), 2.97—2.47 (6 H, m, $CH_2CH_2CH_2$ and Ar CH_2) and 2.13—1.68 (2 H, m, $CH_2CH_2CH_2$).

N-(3,4-*Dimethoxyphenethyl*)-6-*ethoxy*-2-*piperidone* (10).—To a stirred solution of the glutarimide (9) (1.5 g) in 95% ethanol (150 ml) at −15 to −20 °C was added sodium borohydride (1.5 g). At regular intervals (*ca.* 15 min), 10 drops of 4M-hydrochloric acid were added during 4 h, with stirring. The excess of sodium borohydride was destroyed by slow addition of hydrochloric acid to the cooled reaction mixture, until pH 3 was reached. The mixture was then stirred for an additional 60 min at 5—10 °C, neutralised with ethanolic 1% potassium hydroxide, and evaporated. Extraction of the residue with chloroform, followed by evaporation, afforded the amide (10) as a pale yellow oil, δ(CCl_4) 6.75 (2 H, s, arom.), 3.80 (6 H, s, 2 OMe), 3.55 (2 H, q, *J* 7 Hz, CH_2CH_3), and 1.18 (3 H, t, *J* 7 Hz, CH_2CH_3), which was used without further purification.

1,2,3,6,7,11b-*Hexahydro*-9,10-*dimethoxybenzo*[a]*quinolizin*-4-*one* (11).—To a solution of the above amide (10) in benzene (300 ml) was added toluene-*p*-sulphonic acid (420 mg) and the mixture was stirred under reflux for 3 h. After cooling, the benzene solution was washed with saturated aqueous sodium hydrogen carbonate and with saturated aqueous sodium chloride, dried (Na_2SO_4), and evaporated to give the benzoquinolizinone (11) as a pale yellow oil which crystallised (m.p. 111—112 °C, 1.4 g, 99% from the glutarimide) on trituration with hexane. A sample recrystallised from ether in square colourless plates had m.p. 116—118 °C (lit.,[8] 87.5—90.5 °C), $\nu_{max.}$ ($CHCl_3$) 1 620 cm^{-1}; δ(CCl_4) 6.62 and 6.53 (2 H, 2s, arom.), 5.10—4.33 (2 H, m, 11b-H and 6-H), 3.77 (6 H, s, 2 OMe), and 2.97—1.53 (9 H, m, other H); *m/e* 261 (M^+) (Found: C, 68.7; H, 7.35; N, 5.2. Calc. for $C_{15}H_{19}NO_3$: C, 68.95; H, 7.35; N, 5.35%).

1,2,3,6,7,11b-*Hexahydro*-9,10-*dimethoxy*-3,3-*bismethoxycarbonylbenzo*[a]*quinolizin*-4-*one* (12).—To a stirred solution of di-isopropylamine (23.8 ml, 168.5 mmol) in dry tetrahydrofuran (100 ml) at −50 °C under nitrogen was added n-butyl-lithium in hexane solution (110 ml; 1.54M). After stirring at −50 °C for 30 min, the lactam (11) (20 g, 76.6 mmol) in dry tetrahydrofuran (250 ml) was added over 30 min. After 1 h, a solution of methyl chloroformate (25 g, 264.5 mmol) in dry tetrahydrofuran (50 ml) was added over 30 min to the cooled solution. The reaction mixture was stirred under nitrogen at −50 °C for 1 h and then allowed to reach room temperature whereupon it was left overnight. Saturated aqueous ammonium chloride (25 ml) was then added and the mixture concentrated under reduced pressure. The residue was partitioned between water (200 ml) and chloroform (200 ml). The aqueous layer was further extracted with chloroform and the combined organic solution was washed with water and saturated aqueous sodium chloride, dried (Na_2SO_4), and evaporated to give a red syrup which crystallised on trituration with ether. The resulting pale yellow solid was recrystallised from methanol to afford the *diester* (12) (26.95 g, 93.3%) as colourless needles, m.p. 142—143 °C, $\nu_{max.}$ ($CHCl_3$) 1 745, 1 730, and 1 645 cm^{-1}; δ($CDCl_3$) 6.67 (2 H, s, arom.), 5.10—4.47 (2 H, m, 11b-H and 6-H), 3.88 (9 H, s, 3 OMe), and 3.77 (3 H, s, OMe); *m/e* 377 (M^+) (Found: C, 60.3; H, 6.25; N, 3.8. $C_{19}H_{23}NO_3$ requires C, 60.45; H, 6.15; N, 3.7%).

1,2,3,6,7,11b-*Hexahydro*-9,10-*dimethoxy*-3-*methoxycarbonylbenzo*[a]*quinolizin*-4-*one* (13).—To a solution of the diester (12) (15 g, 39.79 mmol) in methanol (600 ml) warmed to obtain complete solution, was added potassium hydroxide (88%, 2.532 g, 39.79 mmol). After stirring for 40 h at room temperature, the solution was poured into 50% saturated aqueous sodium chloride (600 ml) and extracted with chloroform (3 × 200 ml). The combined organic solution was washed with water, and saturated sodium chloride solution, dried (Na_2SO_4), and evaporated to give a yellow syrup (13.7 g). Chromatography on a column of silica gel (300 g) and elution with chloroform afforded a diastereoisomeric mixture of the *monoester* (13) as a colourless syrup (11.9 g, 93.8%). A portion (*ca.* 500 mg) of this mixture was rechromatographed on silica gel (25 g). Elution with chloroform provided a sample of the faster-moving diastereoisomer as a white solid which was recrystallised from di-isopropyl ether as fans of colourless needles, m.p. 117—118 °C, $\nu_{max.}$ ($CHCl_3$) 1 740 and 1 640 cm^{-1}; δ($CDCl_3$) 6.59 and 6.54 (2 H, 2s, arom.), 5.07—4.48 (2 H, m, 11b-H and 6-H), 3.83 (6 H, s, 2 OMe), and 3.73 (3 H, s, OMe); *m/e* 319 (M^+) (Found: C, 63.85; H, 6.7; N, 4.2. $C_{17}H_{21}NO_5$ requires C, 63.95; H, 6.65; N, 4.4%).

1,2,3,6,7,11b-*Hexahydro*-9,10-*dimethoxy*-3-*methoxycarbonyl*-3-*phenylselenobenzo*[a]*quinolizin*-4-*one* (14).—To a stirred solution of the above diastereoisomeric mixture of monoesters (13) (10.5 g, 32.92 mmol) in dry benzene (120 ml) and dry dimethylformamide (60 ml) under nitrogen was added sodium hydride (50% in oil; 1.74 g, 36.21 mmol). After stirring the mixture for 6 h at room temperature, a solution of phenylselenenyl chloride (6.93 g, 36.21 mmol) in dry benzene (100 ml) was added rapidly dropwise. The

mixture was stirred for 1 h at room temperature and then diluted with benzene (600 ml). The organic solution was washed with 5% hydrochloric acid, water, and saturated aqueous sodium chloride, dried (Na_2SO_4), and evaporated to give a viscous red oil. Chromatography on a column of silica gel and elution with chloroform afforded a diastereoisomeric mixture of the *phenylseleno-derivative* (14) as a pale yellow syrup (14.1 g, 90.4%). A portion (*ca.* 500 mg) of this mixture was rechromatographed on silica gel (25 g). Elution with chloroform provided a sample of the faster-moving diastereoisomer as a white solid which was recrystallised from benzene–hexane to afford colourless needles, m.p. 141.5—142.5 °C, $\nu_{max.}$ ($CHCl_3$) 1 720 and 1 635 cm^{-1}; $\delta(CDCl_3)$ 7.87—7.19 (5 H, m, SeC_6H_5), 6.60 and 6.53 (2 H, 2s, arom.), and 3.86, 3.80, and 3.68 (9 H, 3s, 3 OMe); *m/e* 474 (M^+) (Found: C, 58.0; H, 5.35; N, 2.65. $C_{23}H_{25}NO_5Se$ requires C, 58.25; H, 5.3; N, 2.95%).

1,6,7,11b-*Tetrahydro*-9,10-*dimethoxy*-3-*methoxycarbonylbenzo*[a]*quinolizin*-4-*one* (4).—To a stirred solution of the above diastereoisomeric mixture of phenylseleno-derivatives (14) (2 g, 4.22 mmol) in methanol (120 ml) and water (15 ml) was added sodium hydrogencarbonate (709 mg, 8.44 mmol) and sodium metaperiodate (1.8 g, 8.44 mmol). The mixture was vigorously stirred for 30 min at room temperature and the resultant slurry poured into a mixture of 50% saturated aqueous sodium hydrogen carbonate (300 ml) and chloroform (200 ml). The aqueous layer was further extracted with chloroform and the combined organic solution was washed with water and saturated aqueous sodium chloride, dried (Na_2SO_4), and evaporated to give a yellow gum. Chromatography on a column of silica gel (10 : 1) and elution with chloroform afforded the αβ-*unsaturated ester lactam* (4) (1.2 g, 89.7%) as a pale yellow gum, $\nu_{max.}$ ($CHCl_3$) 1 740, 1 665, and 1 620 cm^{-1}; $\delta(CDCl_3)$ 7.50 (1 H, d, *J* 3 Hz, 2 CH), 6.70 and 6.63 (2 H, 2s, arom.), and 3.90 (9 H, s, 3 OMe); *m/e* 317 (M^+) (Found: M^+ 317.123 5. $C_{17}H_{19}NO_5$ requires M^+, 317.126 2).

2-[(3,4-*Dihydro*-6,7-*dimethoxy*-1-*isoquinolyl*)*methyl*]-1,2,3,5,7,11b-*hexahydro*-9,10-*dimethoxy*-3-*methoxycarbonylbenzo*[a]*quinolizin*-4-*one* (6A).—To a solution of the αβ-unsaturated ester (4) (1.2 g, 3.79 mmol) in dry methanol (30 ml) was added 3,4-dihydro-6,7-dimethoxy-1-methylisoquinoline (5) [11] (1.5 g, 7.32 mmol). The solution was maintained in the dark at room temperature under nitrogen for 94 h. The resultant fine white precipitate was filtered off to afford the *pentacyclic Michael adduct* (6A) (1.1 g, 55.7%). A sample recrystallised from methanol in fine colourless needles had m.p. 98—103 °C, $\nu_{max.}$ ($CHCl_3$) 1 740, 1 640, 1 605, and 1 570 cm^{-1}; $\delta(CDCl_3)$ 7.28, 7.03, 6.67, and 6.58 (4 H, 4s, arom.), 3.87 (6 H, s, 2 OMe), 3.78 (3 H, s, OMe), and 3.70 (6 H, s, 2 OMe); *m/e* 522 (M^+) (Found: C, 65.05; H, 6.45; N, 4.5. $C_{29}H_{34}N_2O_7 \cdot CH_3OH$ * requires C, 64.95; H, 6.9; N, 5.05%).

2-[(3,4-*Dihydro*-9H-*pyrido*[3,4-*b*]-1-*indolyl*)*methyl*]-1,2,3,6,7,11b-*hexahydro*-9,10-*dimethoxy*-3-*methoxycarbonylbenzo*[a]*quinolizin*-4-*one* (16).—To a solution of the αβ-unsaturated ester (4) (2 g, 6.31 mmol) in dry methanol (50 ml) was added 3,4-dihydro-1-methyl-9*H*-pyrido[3,4-*b*]indole (15) [12] (2.4 g, 13.04 mmol). The solution was maintained at room temperature in the dark under nitrogen for 86 h. The solvent was evaporated off and the pale yellow semi-solid residue taken up in warm chloroform Addition of a small amount of ether induced crystallisation, and filtration afforded the pure *hexacyclic Michael adduct* (16) (1.39 g, 44%). A sample recrystallised from chloroform–ether as very fine colourless needles had m.p. 195—197 °C (decomp.), $\nu_{max.}$ ($CHCl_3$) 3 350, 1 730, and 1 640 cm^{-1}; $\delta(CDCl_3)$ 9.38 (1 H, s, NH), 7.68—6.87 (4 H, m, indole arom.), 6.50 (2 H, s, arom.), and 3.83, 3.78, and 3.65 (9 H, 3s, 3 OMe); *m/e* 501 (M^+) (Found: C, 69.0; H, 6.05; N, 7.7. $C_{29}H_{31}N_3O_5$ requires C, 69.45; H, 6.25; N, 8.4%). Evaporation of the original mother-liquor and chromatography of the residue on a column of silica gel (20 : 1), eluting with 2% methanol in chloroform, afforded a mixture of the above product and its diastereoisomer as a pale yellow amorphous solid (1.11 g, 35.1%). T.l.c. (SiO_2; 10% MeOH in $CHCl_3$) and the n.m.r. spectrum (main chemical shifts the same as for the above pure single isomer) indicated *ca.* 1 : 1 mixture of the two diastereoisomers of the Michael adduct (16). Total yield of adduct (16) 2.5 g (79.1%) with isomer ratio *ca.* 3.5 : 1.

2-[(3,4-*Dihydro*-6,7-*dimethoxy*-1-*isoquinol*)*methyl*]-3-*ethyl*-1,2,3,6,7,11b-*hexahydro*-9,10-*dimethoxy*-3-*methoxycarbonylbenzo*[a]*quinolizin*-4-*one* (17).—To a stirred solution of the addition product (6A) (3 g, 5.75 mmol) in a mixture of dry benzene (100 ml) and dry dimethylformamide (50 ml) under nitrogen was added sodium hydride (50% in oil; 303.5 mg, 6.32 mmol). After 90 min, ethyl iodide (986 mg, 6.32 mmol) in dry benzene (10 ml) was added rapidly dropwise, and the mixture stirred under nitrogen at room temperature for 5 h. The reaction mixture was diluted with benzene (900 ml), washed with water and saturated aqueous sodium chloride, dried (Na_2SO_4), and evaporated to give pale yellow crystals. Filtration from ether afforded the pure *ethyl derivative* (17) as fine white crystals (2.45 g, 77.5%). A sample recrystallised from benzene–hexane as colourless needles had m.p. 170—171 °C, $\nu_{max.}$ ($CHCl_3$) 1 740, 1 640, and 1 620 cm^{-1}; $\delta(CDCl_3)$ 6.93 and 6.72 (2 H, 2s, arom.), 6.59 (2 H, s, arom.), 3.93, 3.81, and 3.72 (9 H. 3s, 3 OMe), 3.86 (6 H, s, 2 OMe), and 0.59 (3 H, t, *J* 7.5 Hz, CH_2CH_3); *m/e* 550 (M^+) (Found: C, 67.45; H, 7.05; N, 5.0. $C_{31}H_{38}N_2O_7$ requires C, 67.6; H, 6.95; N, 5.1%).

2-[(3,4-*Dihydro*-6,7-*dimethoxy*-1-*isoquinolyl*)*methyl*]-3-*ethyl*-1,3,4,6,7,11b-*hexahydro*-9,10-*dimethoxy*-4-*oxo*-2H-*benzo*[a]*quinolizine*-3-*carboxylic Acid* (18).—The 3-ethyl derivative (17) (600 mg, 1.09 mmol) was dissolved in 10% methanolic potassium hydroxide (30 ml) and the solution was heated under reflux for 4 h. The mixture was cooled and diluted to 150 ml with water and the solution washed with chloroform. The aqueous solution was acidified (pH 6) with acetic acid and extracted with chloroform (2 × 100 ml). The combined extract was washed with saturated aqueous sodium chloride, dried (Na_2SO_4), and evaporated to give a white solid. Filtration from ether afforded the pure *carboxylic acid* (18) as white crystals (575 mg, 98.3%). A sample recrystallised from chloroform as colourless needles had m.p. 186—188 °C (decomp.), $\nu_{max.}$ ($CHCl_3$) 2 800—2 200, 1 730, 1 650, 1 600, and 1 560 cm^{-1}; $\delta([^2H_6]$-DMSO) 7.37, 7.18, 6.73, and 6.62 (4 H, 4s, arom.), 3.93, 3.79, 3.72, and 3.51 (12 H, 4s, 4 OMe), and 0.53 (3 H, t, *J* 7.5 Hz, CH_2CH_3); *m/e* 492 ($M^+ - CO_2$) (Found: C, 54.95; H, 5.75; N, 4.05. $C_{30}H_{36}N_2O_7 \cdot 1.2CHCl_3$ † requires C, 55.1; H, 5.5; N, 4.1%).

2-[(3,4-*Dihydro*-6,7-*dimethoxy*-1-*isoquinolyl*)*methyl*]-3-*ethyl*-1,2,3,6,7,11b-*hexahydro*-9,10-*dimethoxybenzo*[a]-*quinolizin*-4-*one* (19).—The carboxylic acid (18) (150 mg, 0.28 mmol) in dry dimethylformamide (3 ml) was heated at

* A signal corresponding to methanol (1 equiv.) was observed in the n.m.r. spectrum, δ 3.43 (3 H, s).

† A signal corresponding to chloroform (*ca.* 1.5 equiv.) was observed in the n.m.r. spectrum, δ 8.38 (s).

180—185 °C for 30 min under nitrogen. The solution was cooled and poured into benzene (100 ml). This solution was washed with dilute aqueous sodium hydrogencarbonate, water, and saturated aqueous sodium chloride, dried (Na_2SO_4), and evaporated to give the pure *decarboxylated product* (19) as a fine white crystals (109 mg, 79.2%), m.p. 149—151 °C, $\nu_{max.}$ ($CHCl_3$) 1 620 and 1 570 cm^{-1}; δ($CDCl_3$) 7.03 and 6.77 (2 H, 2s, arom.), 6.65 (2 H, s, arom.), 4.02, 3.97, 3.90, and 3.84 (12 H, 4s, 4 OMe), and 0.92 (3 H, t, *J* 7.5 Hz, CH_2CH_3); *m/e* 492 (M^+) (Found: M^+, 492.258 6; C, 70.85; H, 7.5; N, 5.45. $C_{29}H_{36}N_2O_5$ requires M^+, 492.262 2; C, 70.7; H, 7.35; N, 5.7%).

2-[(3,4-*Dihydro*-6,7-*dimethoxy*-1-*isoquinolyl*)*methyl*]-3-*ethyl*-1,3,4,6,7,11b-*hexahydro*-9,10-*dimethoxy*-2H-*benzo*[a]-*quinolizine* (20).—To a solution of the lactam (19) (50 mg) in dry benzene (4 ml) was added Red-al (70% in toluene solution 0.6 ml). The mixture was stirred under nitrogen at room temperature for 90 min. The excess of Red-al was destroyed by cautious addition of 10% aqueous sodium hydroxide under cooling with ice. The mixture was filtered and the benzene solution washed with 10% aqueous sodium hydroxide, dried (Na_2SO_4), and evaporated to afford the *amine* (20) (50 mg, quantitative) as a pale yellow oil, δ($CDCl_3$) 7.05 and 6.74 (2 H, 2s, arom.), 6.57 (2 H, s, arom.), 3.96, 3.89, 3.83, and 3.71 (12 H, 4s, 4 OMe), and 0.85 (3 H, t, *J* 7 Hz, CH_2CH_3); *m/e* 478 (M^+), which was used without further purification.

11b-epi-*Emetine* (21) *and* 11b-epi-*Isoemetine* (22).—To the above amine (20) (50 mg) in methanol (4 ml) was added sodium borohydride (100 mg) and the mixture stirred at room temperature for 30 min. The mixture was evaporated and the residue was taken up in chloroform. This mixture was washed with water and saturated aqueous sodium chloride, and the organic solution was dried (Na_2SO_4) and evaporated to give a mixture of the emetine diastereoisomers (21) and (22) as a pale yellow oil (55 mg, quantitative). Chromatography on a column of silica gel (2 g) and elution with 2% methanol in chloroform afforded 11b-*epi*-emetine (21) (28 mg, 55.8%) as a colourless gum, $\nu_{max.}$ ($CHCl_3$) 1 665 and 1 600 cm^{-1}; δ($CDCl_3$) 6.74 (1 H, s, arom.), 6.54br (3 H, s, arom.), 3.84 (12 H, s, 4 OMe), and 0.86 (3 H, t, *J* 5.5 Hz, CH_2CH_3); *m/e* 480 (M^+). Further elution with 4% methanol in chloroform afforded 11b-*epi*-isometine (22) (20 mg, 39.8%) as a pale yellow gum, $\nu_{max.}$ ($CHCl_3$) 1 660, 1 600 cm^{-1}; δ($CDCl_3$) 6.68br (4 H, s, arom.), 3.87 (12 H, s, 4 OMe), and 0.96 (3 H, t, *J* 5.5 Hz, CH_2CH_3).

(±)-*Emetine* (1) *and* (±)-*Isoemetine* (24).—To a solution of 11b-*epi*-*O*-methylpsychotrine (20) (120 mg, 0.25 mmol) in acetic acid (90% aq.; 4 ml) was added mercury(II) acetate (323 mg, 1 mmol). The mixture was stirred and heated at 100—110 °C for 50 min under nitrogen. The reaction mixture was cooled and filtered to remove mercury(I) acetate. The yellow filtrate was diluted to 15 ml with dilute acetic acid and saturated with hydrogen sulphide. Filtration through Celite and evaporation of the yellow filtrate gave a red gum which was taken up in water (5 ml) and acidified (pH 2) with 70% perchloric acid. The yellow perchlorate salt (23) was collected by filtration and used without further purification. To this perchlorate in methanol (10 ml) was added sodium borohydride (500 mg) portionwise. After stirring for 30 min at room temperature, work-up as described above gave the crude product as a yellow gum (130 mg). Chromatography on a column of silica gel (6 g) and elution with chloroform removed some coloured material. Elution with 2% methanol in chloroform afforded (±)-emetine(1) (40 mg, 33.2%) as a colourless gum, $\nu_{max.}$ ($CHCl_3$) 1 610 cm^{-1}; δ($CDCl_3$) 6.73 (1 H, s, arom.), 6.54br (2 H, s, arom.), 6.47 (1 H, s, arom.), 3.83 (9 H, s, 3 OMe), 3.80 (3 H, s, OMe), and 0.90 (3 H, t, *J* 5.5 Hz, CH_2CH_3); *m/e* 480 (M^+). The hydrochloride salt was prepared and recrystallised from methanol–ether in colourless granules, m.p. 223—226 °C (lit.,[13] 225—238 °C; lit.,[16] 237—241 and 239—242 °C; lit.,[17] 261—263 °C). Further elution with 4% methanol in chloroform afforded (±)-isoemetine (24) (51 mg, 42.3%) as a colourless gum, $\nu_{max.}$ ($CHCl_3$) 1 610 cm^{-1}; δ($CDCl_3$) 6.77 (1 H, s, arom.), 6.63 (3 H, s, arom.), 3.88 (12 H, s, 4 OMe), and 1.02br (3 H, t, CH_2CH_3).

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