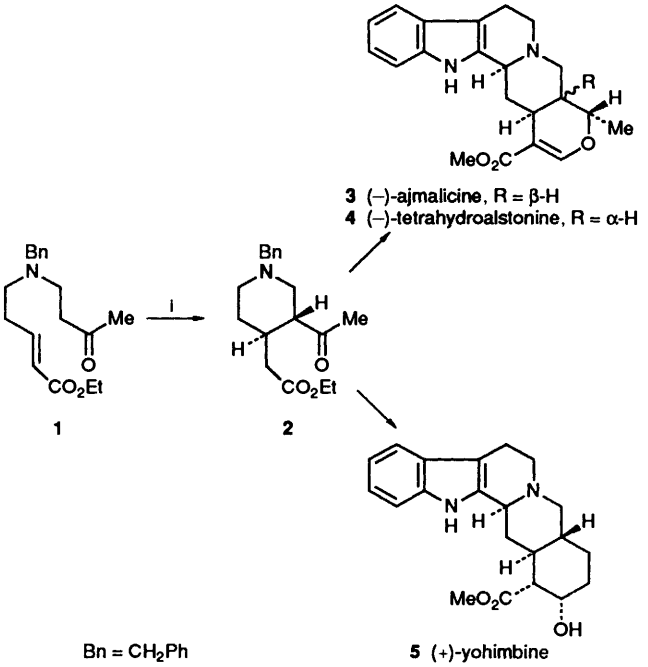
Heterocycles in Asymmetric Synthesis. Part 2.† Efficient Asymmetric Approaches to Heteroyohimbine, Yohimbine and Related Alkaloids

Yoshiro Hirai, Takashi Terada, Takao Yamazaki and Takefumi Momose*
Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama 930-01, Japan

Asymmetric syntheses of heteroyohimbine, yohimbine, and related alkaloids are reported. The piperidine derivative ethyl (−)-(3-acetyl-1-benzylpiperidin-4-yl)acetate (−)-**2**, which was obtained by an asymmetric intramolecular Michael reaction of the acyclic compound ethyl 5-[benzyl-(3-oxobutyl)-amino]pent-2-enoate **1**, was stereoselectively converted into the (−)-lactone methyl (1*S*,4a*R*,8a*R*)-3,4,4a,5,6,7,8,8a-octahydro-1-methyl-3-oxo-1*H*-pyrano[3,4-*c*]pyridine-7-carboxylate (−)-**7** and (+)-olefin methyl [(*R*)-3-(*Z*)-ethylidene-1-methoxycarbonylpiperidin-4-yl]acetate **15**. The (−)-lactone (−)-**7** was transformed into (−)-ajmalicine **3** in 5 steps. The (+)-olefin (+)-**15** is the precursor in a published route to (−)-tetrahydroalstonine. The (−)-piperidine (−)-**2** was also converted into the α,β-unsaturated ketone *t*-butyl (4a*R*,8a*R*)-(−)-1,2,3,4,4a,5,6,8a-octahydro-6-oxoisoquinoline-2-carboxylate (−)-**30** in 6 steps. Stereoselective introduction of the methoxycarbonyl group into this last compound, followed by stereoselective reduction of the ketone moiety with L-Selectride, afforded the D/E-ring system of (+)-yohimbine. This can be converted into yohimbine by following the established sequence. The conversion of the (−)-piperidine derivative (−)-**2** ethyl [(4*R*,5*R*)-5-ethyl-2-oxopiperidin-4-yl]acetate (+)-**21** for the synthesis of (−)-emetine **23** was also accomplished.

In the preceding paper, we described the design of the substrate for the preparation of the functionalized piperidine system **2**, thus obtained with high enantioselectivity *via* an asymmetric intramolecular Michael reaction from the acyclic compound **1**. We anticipated that this piperidine derivative **2** would be a suitable precursor for the synthesis of the D/E-ring system of a range of structurally and biologically important *Rauwolfia* alkaloids and designed synthetic routes to these alkaloids from substrate **2**. We would now like to disclose synthetic work which provides an entry into the *Rauwolfia* alkaloids (−)-ajmalicine **3**, (−)-tetrahydroalstonine **4**, and (+)-yohimbine **5**, and related alkaloids (Scheme 1).



Scheme 1 *Reagent:* i, chiral base

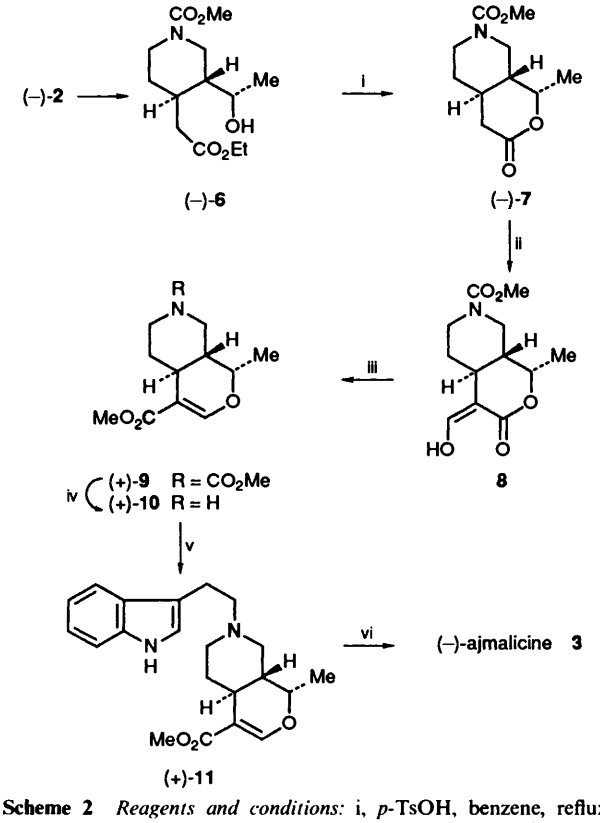
Results and Discussion

Synthesis of (−)-*Ajmalicine* **3** *and* (−)-*Tetrahydroalstonine* **4**.—We initially engaged in the synthesis of two heteroyohimbine alkaloids, (−)-ajmalicine **3** and (−)-tetrahydroalstonine **4**,[1] which are stereoisomeric at the D/E-ring fusion, from a single piperidine (−)-**2** obtained by the intramolecular Michael reaction of the acyclic compound **1** as shown in Schemes 2 and 3.

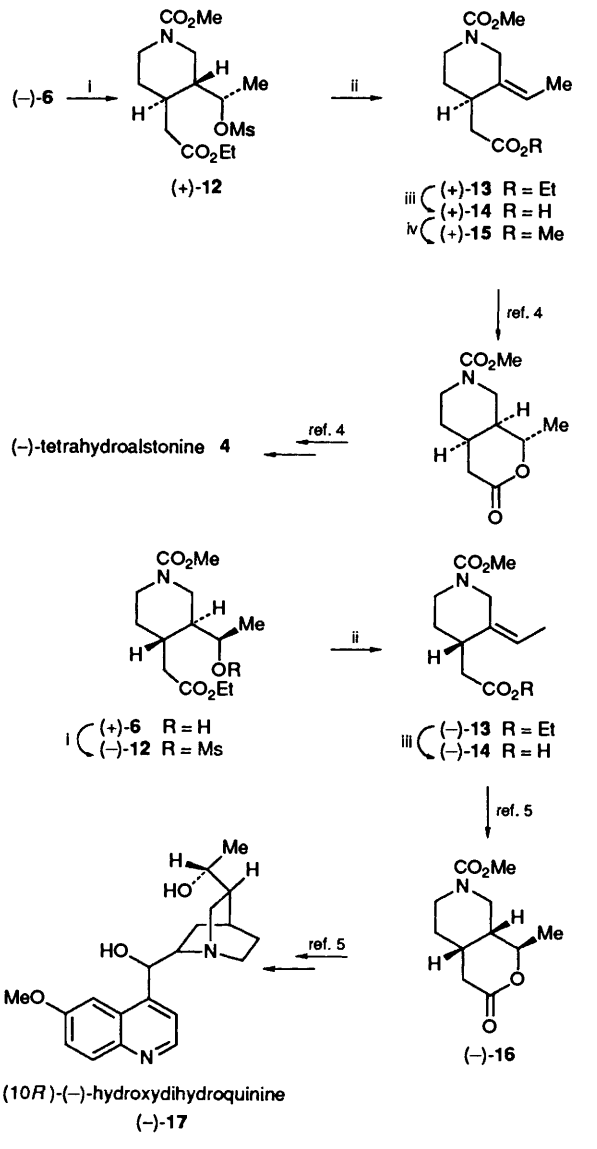
The alcohol (−)-**6** was readily derived[2] from ketone (−)-**2**, and heating of compound (−)-**6** in benzene in the presence of toluene-*p*-sulfonic acid (*p*-TsOH) gave the lactone (−)-**7** in 73% overall yield from (−)-**2**. Completion of the E-ring functionality required installation of the C-22 methoxycarbonyl group and introduction of the alkoxyacrylate chromophore. This has been achieved according to the following sequences. Reaction of the lactone (−)-**7** with methyl formate in dioxane in the presence of triphenylmethylsodium gave the α-formyllactone **8**, which was subjected to acid-catalysed methanolysis to provide the alkoxyacrylate (+)-**9** in 57% yield. Cleavage of the carbamoyl group in compound (+)-**9** was effected by treatment with trimethylsilyl iodide (TMSI) to give the secondary amine (+)-**10** in 62% yield. The conversion of amine (+)-**10** into (−)-ajmalicine **3** was carried out according to the method of Uskokovic:[3] condensation of amine (+)-**10** with tryptophyl bromide afforded seco-ajmalicine (+)-**11**, which was cyclized by treatment with mercury(II) acetate followed by reduction with $NaBH_4$ to furnish compound **3** in 18% yield. Synthetic (−)-ajmalicine **3** had a value of $[\alpha]_D^{26}$ −54.8° (*c* 0.1, $CHCl_3$) similar to that $\{[\alpha]_D^{25}$D −60° ($CHCl_3$)}‡ of natural (−)-ajmalicine, and possessed the spectral properties identical with those of the natural product.

We next examined the synthesis of (−)-tetrahydroalstonine **4** from compound (−)-**6**. For the elaboration of the tetrahydroalstonine skeleton, it was necessary to epimerize the C-20 proton in ajmalicine **3**. This was achieved *via* the olefin (+)-**15**

† Part 1 is the preceding paper.
‡ Commercially available ajmalicine (Nacalai Tesque Inc.) was used for measurement of optical rotation.



Scheme 2 *Reagents and conditions:* i, *p*-TsOH, benzene, reflux; ii, triphenylmethylsodium, methyl formate; iii, HCl–MeOH; iv, TMSI; v, tryptophyl bromide; vi, $Hg(OAc)_2$, then $NaBH_4$



Scheme 3 *Reagents and conditions:* i, MsCl, pyridine; ii, NaI, acetone, then DBU, benzene, reflux; iii, 1 mol dm^{-3} NaOH, EtOH, 0 °C; iv, CH_2N_2

as described in Scheme 3. Treatment of the alcohol (−)-**6** with methanesulfonyl chloride (MsCl) in pyridine gave the mesate (+)-**12**. The base-induced β-elimination of the iodide derived from intermediate (+)-**12** proceeded stereoselectively to give, in 77% yield, the olefin (+)-**13** having *Z*-configuration* at the exocyclic double bond. Hydrolysis of the ester (+)-**13** with 1 mol dm^{-3} NaOH, followed by esterification of the resulting acid (+)-**14**, afforded the methyl ester (+)-**15** in 75% yield. Conversion of methyl ester (+)-**15** into (−)-tetrahydroalstonine **4** through the lactone (+)-**16**, obtained from hydroboration of (+)-**15**, has been reported.[4] The acid (−)-**14**, the enantiomer of (+)-**14**, was derived from the alcohol (+)-**6** by the same procedure as that described above. The acid (−)-**14** has also been converted into a dihydrocinchonine mimic **17**, *via* the *cis*-lactone (−)-**16**.[5]

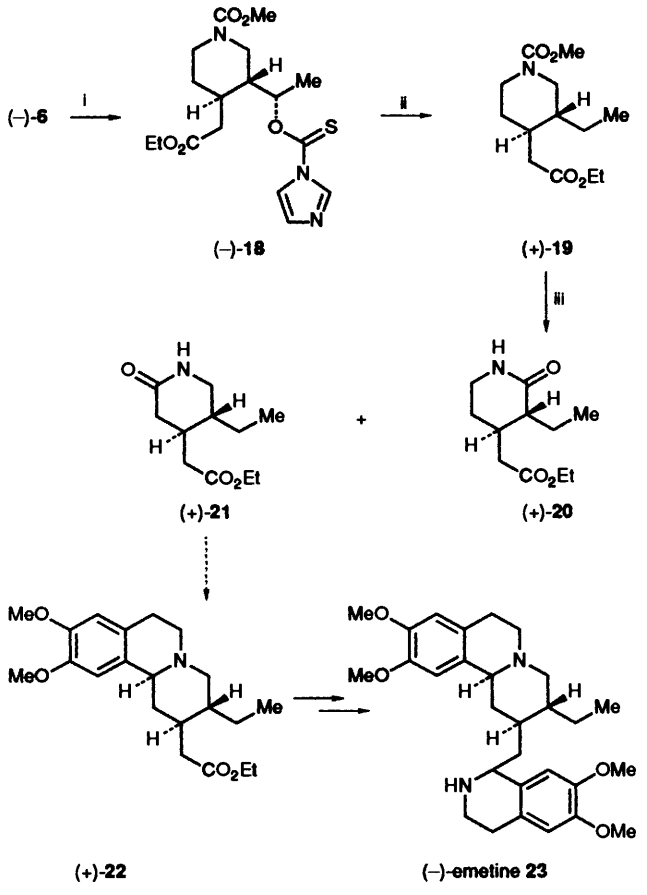
Our next effort was directed towards the conversion of the alcohol (−)-**6** into an emetine precursor. Treatment of the alcohol (−)-**6** with 1,1′-thiocarbonyldiimidazole afforded the ester (−)-**18**, which was then reduced with tributyltin hydride[6] to give the deoxygenated piperidine derivative (+)-**19** in 89% yield. Ruthenium dioxide oxidation[7] of the piperidine (+)-**19** furnished a mixture of the lactams (+)-**20** and (+)-**21**[8] (ratio ~1:1.1) which was fractionated by flash column chromatography. The racemate of the lactam (+)-**21** has been shown to lead to the emetine precursor (±)-**22**.[9] Since the conversion of (+)-**22** or its racemate into (−)-emetine **23** or its racemate has also been reported,[10] lactam (+)-**21** could be an important intermediate for the synthesis of (−)-emetine **23** (Scheme 4).

* The *Z*-configuration of the double bond in the compounds (+)-**13**, (+)-**14**, and (+)-**15** was determined by comparison of the ^{13}C NMR spectrum of (+)-**15** with that of an authentic sample: cf. ref. 4.

Synthesis of (+)-*Yohimbine* **5**.—Next, our attention was focussed on the enantioselective synthesis of yohimbine. The yohimbine alkaloids have received considerable attention because of their varied range of pharmacological activities,[11] and a number of syntheses of yohimbine, the most important member of the yohimboid class of alkaloids, have been reported.[12] However, there is no documented example of its asymmetric synthesis.[13]

Our strategy[14] involved the stereoselective conversion of the piperidine derivative (−)-**2** into the D/E-ring segment **35**. This was effected as shown in Scheme 5.

Debenzylation of substrate (−)-**2** over palladium(II) hydroxide under hydrogen, followed by treatment of intermediate **24** with di-*t*-butyl dicarbonate [$(Boc)_2O$] in diethyl ether in the presence of pyridine, gave the urethane (−)-**25** in 92% yield. Cyclization of compound (−)-**25** by treatment with lithium diisopropylamide (LDA) proceeded smoothly *via* kinetic deprotonation to give the bicyclic diketone (−)-**26** in 99% yield. Treatment of dione (−)-**26** with a catalytic amount of *p*-TsOH in dry methanol afforded a 1:3.8 mixture of the vinylogous esters (+)-**27** and (−)-**28** in 85% combined yield. The regioselectivity in favour of isomer (−)-**28** may be, in part, a

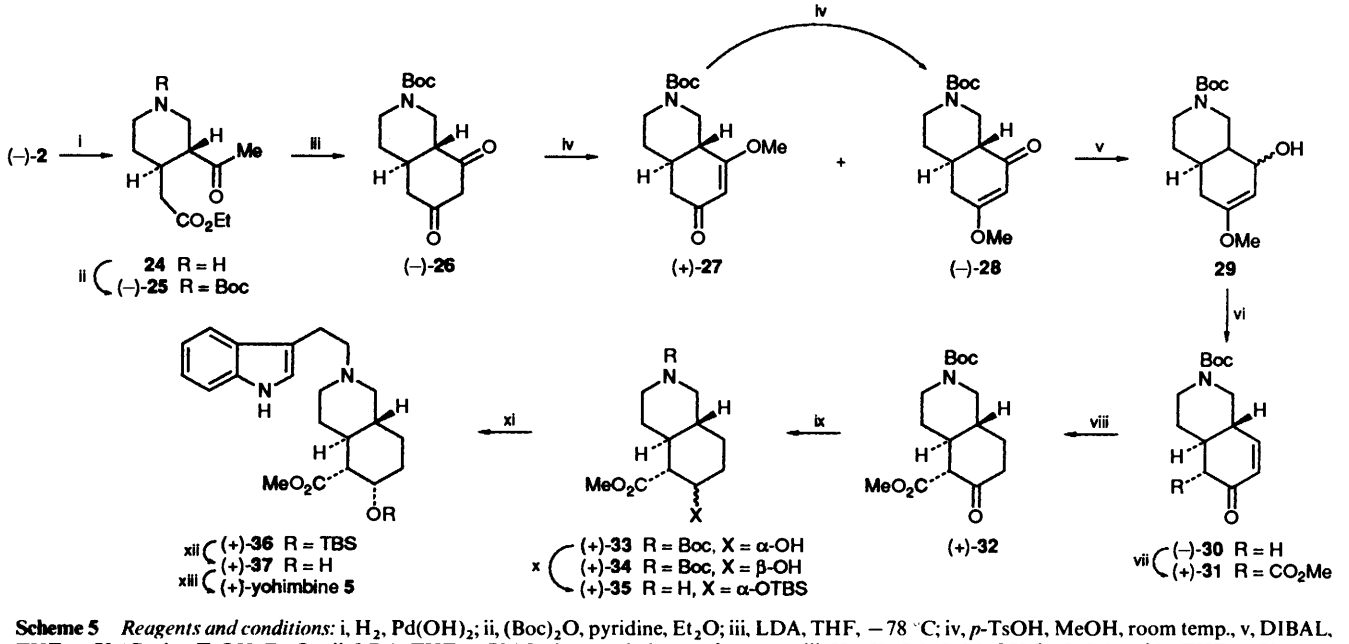


Scheme 4 *Reagents and conditions:* i, 1,1′-thiocarbonyldiimidazole; ii, tributyltin hydride, benzene, reflux; iii, ruthenium dioxide, $NaIO_4$

result of an unfavourable 1,3-strain between the methoxy group and the C-8a proton in isomer (+)-**27**. The minor ester (+)-**27** separated was equilibrated to the parent mixture under the same conditions as mentioned above. Thus, the desired isomer (−)-**28** could eventually be obtained pure by repetition of this procedure. Reduction of (−)-**28** with diisobutylaluminum hydride (DIBAL) and subsequent treatment of the resulting alcohol **29** with a catalytic amount of *p*-TsOH in dry diethyl ether gave the α,β-unsaturated ketone (−)-**30** in 72% yield. Treatment of the lithium enolate of enone (−)-**30** with methyl cyanoformate[15] afforded the β-keto ester (+)-**31** in 84% yield, catalytic hydrogenation of which over 5% Pd–C under hydrogen, followed by reduction of the resulting ketone (+)-**32*** with $NaBH_4$ in methanol at −15 °C produced the alcohols (+)-**33** and (+)-**34** in 70% combined yield in the ratio 1:2.2. Reduction of ketone, (+)-**32** with zinc borohydride also gave preferentially the undesired alcohol (+)-**34** (**33**:34 1:5.3). In marked contrast to these results, a better result was obtained with lithium tri-*sec*-butylborohydride (L-Selectride). Treatment of ketone (+)-**32** with L-Selectride in tetrahydrofuran (THF) at −78 °C gave the desired alcohol (+)-**33** as the sole product in 73% yield, the stereoselectivity being consistent with the prediction based on steric control.[16] Treatment of the alcohol (+)-**33** with *t*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) caused cleavage[17] of the Boc group and spontaneous protection of the hydroxy group to give the secondary amine (+)-**35** in 91% yield. Alkylation of amine (+)-**35** with tryptophyl bromide in MeCN in the presence of potassium carbonate, followed by desilylation (HF–MeCN) of intermediate **36** afforded seco-yohimbine (+)-**37**, m.p. 116–118 °C; $[\alpha]_D^{26}$ +43.8° (*c* 1.07, MeOH), in 76% yield. The structure of product (+)-**37** was confirmed by its direct comparison with an authentic sample derived[18,19] from natural yohimbine. Total synthesis of yohimbine *via* the racemate of compound (+)-**37** has already been accomplished by G. Stork,[12b] and S. Sakai and co-workers[19] also have reported the conversion of compound (+)-**37** into (+)-yohimbine **5** by a similar method. The formal asymmetric synthesis of (+)-yohimbine **5** has therefore been completed.

The enantioselective synthesis of (−)-ajmalicine **3**, (−)-tetrahydroalstonine **4**, and (+)-yohimbine **5** has thus been achieved starting from a single piperidine derivative (−)-**2** obtained by an asymmetric intramolecular Michael reaction. Since the piperidine derivative (+)-**2**,[2] the enantiomer of (−)-**2**, has also

* The transformation of the (±)-*N*-cyano analogue of compound (+)-**32** to (±)-yohimbine has been reported previously by Stork and Guthikonda: ref. 12*b*.



Scheme 5 *Reagents and conditions:* i, H_2, $Pd(OH)_2$; ii, $(Boc)_2O$, pyridine, Et_2O; iii, LDA, THF, −78 °C; iv, *p*-TsOH, MeOH, room temp., v, DIBAL, THF, −78 °C; vi, *p*-TsOH, Et_2O; vii, LDA, THF, −78 °C, then methyl cyanoformate; viii, H_2, 5% Pd–C, MeOH; ix, L-Selectride, THF, −78 °C; x, TBSOTf, CH_2Cl_2; xi, tryptophyl bromide, K_2CO_3, MeCN; xii, HF, MeCN; xiii, $Hg(OAc)_2$, 1% AcOH, then $NaBH_4$

been obtained from substrate **1**, this constitutes a route to both enantiomers of the several alkaloids described above.

The design of versatile chiral building blocks and its asymmetric synthesis provides an important methodology in the asymmetric synthesis of natural products. These issues constitute the basis of current investigation in our laboratory, the results of which will be reported in due course.

Experimental

Optical rotations were measured with a JASCO DIP-140 polarimeter. IR spectra were recorded on a JASCO A-102 grating spectrophotometer and were calibrated with the 1601 cm^{-1} absorption of polystyrene. NMR spectra were taken on JEOL GX-270 and Varian XL-200 spectrometers for solutions in deuteriochloroform. Chemical shifts are reported in parts per million (δ) downfield from internal tetramethylsilane. *J*-Values are given in Hz. Mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained on a JEOL JMS D-200 spectrometer. M.p.s were determined with a Yanagimoto micro melting point apparatus and are uncorrected. Elemental analyses were performed by the micro analytical laboratory of this University. All reactions were carried out in flame-dried flasks under argon except in those cases where water was present. Reagents and solvents were dried and distilled before use. Column chromatography was performed with 270-400 mesh silica gel (Merck-9385). Ether refers to diethyl ether.

Methyl (1S,4aR,8aR)-3,4,4a,5,6,7,8,8a-*Octahydro*-1-*methyl*-3-*oxo*-1H-*pyrano*[3,4-c]*pyridine*-7-*carboxylate* (−)-**7**.—A catalytic amount of *p*-TsOH monohydrate (0.14 g, 0.74 mmol) was added to a solution of the alcohol (−)-**6** (2.01 g, 7.36 mmol) in benzene (50 cm^3) and the mixture was heated under reflux for 11 h. The reaction mixture was washed with saturated aq. $NaHCO_3$ and dried ($MgSO_4$). The organic solvent was removed under reduced pressure and the resulting residue was subjected to column chromatography [silica gel, 70 g; elution with benzene–CH_2Cl_2 (1:1)] to give the lactone (−)-**7** (1.67 g, 7.35 mmol) as crystals, m.p. 74–77 °C (from Et_2O) (Found: C, 58.0; H, 7.4; N, 6.3. Calc. for $C_{11}H_{17}NO_4$: C, 58.13; H, 7.54; N, 6.16%); $[\alpha]_D^{26}$ −53.3° (*c* 1.1, MeOH); ν_{max}(neat)/cm^{-1} 1725 (ester CO) and 1690 (carbamate CO); δ_H 1.13–1.37 (1 H, m, 5-H^{ax}), 1.30 [3 H, d, *J* 6.8, C*H*(OH)Me], 1.76–2.05 (3 H, m), 2.11 (1 H, dd, *J* 17.8 and 11.3, CH*H*CO_2Et), 2.50 (1 H, br t, *J* 13.2, 6-H^{ax}), 2.73 (1 H, dd, *J* 17.8 and 4.9, C*H*HCO_2Et), 2.70–2.85 (1 H, m, 8-H^{ac}), 3.71 (3 H, s, NCO_2Me), 4.03–4.40 (2 H, br, 6- and 8-H^{eq}), and 4.70 (1 H, m, CMe*H*CO_2); *m/z* 227 (M^+).

Methyl (1S,4aS,8aR)-3,4,4a,5,6,7,8,8a-*Octahydro*-4-*hydroxymethylene*-1-*methyl*-3-*oxo*-1H-*pyrano*[3,4-c]*pyridine*-7-*carboxylate* (−)-**8**.—Triphenylmethylsodium [20.6 cm^3; 0.53 mol dm^{-3} in benzene–ether (1:1)] was added to a solution of the lactone (−)-**7** (495 mg, 2.18 mmol) in 1,4-dioxane (30 cm^3) at 0 °C. After the mixture had been stirred for 10 min at room temperature, methyl formate (4.87 g, 81.1 mmol) was added dropwise and the mixture was stirred for 16 h at room temperature. The reaction flask was cooled in an ice-bath, and ice–water (15 cm^3) and ether (30 cm^3) were added. The ether phase was separated and the aq. phase was extracted with ether (30 cm^3). The aq. solution was acidified with glacial acetic acid and was then neutralized with saturated aq. $NaHCO_3$. The neutral solution was saturated with NaCl and extracted with CH_2Cl_2 (30 cm^3 × 3). The CH_2Cl_2 extracts were combined, dried ($MgSO_4$), and concentrated under reduced pressure to give the α-hydroxymethylenelactone **8** (508.6 mg, 1.99 mmol) as an oil. This α-hydroxymethylene lactone **8** was used for the next step without purification; ν_{max}(neat)/cm^{-1} 1700 (ester CO) and 1655 (carbamate CO).

Dimethyl (1S,4aS,8aR)-4a,5,6,7,8,8a-*Hexahydro*-1-*methyl*-1H-*pyrano*[3,4-c]*pyridine*-4,7-*dicarboxylate* (+)-**9**.—A solution of lactone **8** (508.6 mg, 1.99 mmol) in 10% methanolic hydrogen chloride (30 cm^3) was refluxed for 12 h. The solution was concentrated under reduced pressure to dryness. The residue was treated with saturated aq. $NaHCO_3$ (10 cm^3) and extracted with CH_2Cl_2. The CH_2Cl_2 phase was dried ($MgSO_4$), and concentrated under reduced pressure to give a residue, which was subjected to column chromatography [silica gel, 23 g; elution with benzene–CH_2Cl_2 (1:1)] to give *compound* (+)-**9** (334 mg, 1.24 mmol) as an oil (Found: M^+, 269.1303. $C_{13}H_{19}NO_5$ requires M, 269.1262); $[\alpha]_D^{26}$ +102.0° (*c* 1.1, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1720sh (ester CO), 1700 (carbamate CO) and 1615 (C=C); δ_H 1.00–1.20 (1 H, m, 5-H^{ax}), 1.13 (3 H, d, *J* 6.6, CH*Me*), 1.74 (1 H, t, *J* 11.5 and 4.5, 5-H^{eq}), 2.18–2.33 (1 H, m, 8a-H), 2.49 (1 H, br t, *J* 13.6, 6-H^{ax}), 2.66 (1 H, dq, *J* 13.6 and 3.0, 4a-H), 2.83 (1 H, br t, *J* 13.6, 8-H^{ax}), 3.69 (6 H, s, CO_2Me × 2), 3.95–4.35 (2 H, br, 6- and 8-H^{eq}), 4.32–4.45 (1 H, m, C*H*Me) and 7.47 (1 H, d, *J* 1.7, 3-H).

Methyl (1S,4aS,8aR)-4a,5,6,7,8,8a-*Hexahydro*-1-*methyl*-1H-*pyrano*[3,4-c]*pyridine*-4-*carboxylate* (+)-**10**.—A solution of diester (+)-**9** (46.8 mg, 0.174 mmol) and TMSI (41.7 mg, 0.209 mmol) in $CHCl_3$ (0.5 cm^3) was heated at 55 °C for 4 h. MeOH (28.2 mm^3) was added and the reaction mixture was concentrated under reduced pressure. MeOH (1 cm^3) and sodium methoxide (4.7 mg, 0.087 mmol) were added and the mixture was stirred for 10 min. After removal of the solvent, the residue was partitioned between CH_2Cl_2 (10 cm^3) and water (5 cm^3). The CH_2Cl_2 phase was separated, dried (K_2CO_3), and concentrated under reduced pressure. The resulting residue was subjected to column chromatography [silica gel, 2 g; elution with $CHCl_3$–MeOH (20:1)] to give *ester* (+)-**10** (22.7 mg, 0.1075 mmol) as a yellow oil (Found: M^+, 211.1161. $C_{11}H_{17}NO_3$ requires M, 211.1207); $[\alpha]_D^{26}$ +98.4° (*c* 1.2, $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 1695 (CO) and 1615 (C=C); δ_H 1.11 (3 H, d, *J* 6.8, CH*Me*), 3.68 (3 H, s, CO_2Me), 4.25–4.38 (1 H, m, C*H*Me) and 7.46 (1 H, d, *J* 2.0, 3-H).

Seco-ajmalicine (+)-**11**.—K_2CO_3 (85.1 mg, 0.616 mmol) was added to a solution of the secondary amine (+)-**10** (108.4 mg, 0.513 mmol) in acetonitrile (10 cm^3) and the mixture was heated at 60 °C for 12 h, then was filtered, and the filtrate was concentrated under reduced pressure. The residue was subjected to column chromatography (silica gel, 6 g; elution with $CHCl_3$) to give *seco-ajmalicine* (+)-**11** (163.9 mg, 0.4624 mmol) as yellow crystals (m.p. 73–80 °C) (Found: M^+, 354.1904. $C_{21}H_{26}N_2O_3$ requires M, 354.1942); $[\alpha]_D^{26}$ +50.5° (*c* 1.0, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1705 (CO) and 1616 (C=C); δ_H 1.15 (3 H, d, *J* 6.6, CH*Me*), 1.82 (1 H, t, *J* 10.5), 1.9–2.1 (1 H, m), 2.1–2.2 (2 H, m), 2.6–2.8 (3 H, m), 2.9–3.1 (3 H, m), 3.18 (1 H, br d, *J* 11.7), 3.71 (3 H, s, CO_2Me), 4.37 (1 H, dq, *J* 3.9 and 2.7, C*H*Me), 7.04 (1 H, d, *J* 2.4, indole 2-H), 7.1–7.3 (2 H, m, ArH), 7.37 (1 H, d, *J* 7.8, ArH), 7.49 (1 H, d, *J* 2.0, 3-H), 7.62 (1 H, d, *J* 7.8, ArH) and 7.99 (1 H, br s, NH).

Ajmalicine **3**.—A mixture of compound (+)-**11** (64.7 mg, 0.183 mmol) and mercury(II) acetate (607.6 mg, 1.907 mmol) in 5% aq. acetic acid (9 cm^3) was heated at 100 °C for 3 h, after which it was treated with hydrogen sulfide, filtered through a layer of Celite, and concentrated under reduced pressure. The pH of the solution was brought to ~6 by addition of $NaHCO_3$ and the solution was stirred with $NaBH_4$ (38.1 mg, 1.008 mmol) at room temperature for 20 h. The reaction mixture was then extracted with CH_2Cl_2, and the extract was dried (K_2CO_3), and concentrated under reduced pressure. The resulting residue was

subjected to column chromatography (silica gel, 3 g; elution with $CHCl_3$) to give the unchanged starting material (10 mg, 0.028 mmol) and crystalline ajmalicine **3** (12.9 mg, 0.037 mmol), m.p. 236–239 °C (decomp.), which was recrystallized from MeOH; $[\alpha]_D^{26}$ −54.8° (*c* 0.1, $CHCl_3$). The IR (KBr) and ^1H NMR spectra, and specific rotation of this synthetic (−)-ajmalicine **3** were identical with those of the natural product.

Ethyl (3R,4R,1′S)-{1-*Methoxycarbonyl*-3-[1′-(*methylsulfonyloxy*)*ethyl*]*piperidin*-4-*yl*}*acetate* (+)-**12**.—Methanesulfonyl chloride (109.2 mg, 0.794 mmol) was added to a solution of the alcohol (−)-**6** (216.8 mg, 0.953 mmol) in pyridine (4 cm^3) at room temperature. After being stirred for 2 h, the mixture was concentrated under reduced pressure to give an oil, which was treated with CH_2Cl_2 and saturated aq. $NaHCO_3$. The CH_2Cl_2 phase was washed successively with water, 10% HCl, and then water, and dried ($MgSO_4$). The organic phase was concentrated under reduced pressure to give an oil, which was subjected to column chromatography [silica gel, 10 g; elution with benzene–CH_2Cl_2 (1:2)] to afford the mesate (+)-**12** (270 mg, 0.769 mmol) as an oil (Found: C, 47.9; H, 7.1; N, 3.7. Calc. for $C_{14}H_{25}NO_7S$: C, 47.85; H, 7.17; N, 3.99%); $[\alpha]_D^{26}$ +10.2° (*c* 1.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1725 (ester CO) and 1700 (carbamate CO); δ_H 1.26 (3 H, t, *J* 7.1, OCH_2Me), 1.3–1.4 (1 H, m, 5-H^{ax}), 1.51 (3 H, d, *J* 6.6, $CHMe$), 1.50–1.65 (1 H, m, 5-H^{eq}), 1.65–1.85 (2 H, m), 1.99–2.13 (1 H, m, 4-H), 2.32 (1 H, dd, *J* 15.1 and 8.3, $CHHCO$), 2.64 (1 H, dd, *J* 15.1 and 3.9, $CHHCO$), 2.77–2.95 (2 H, m), 3.06 (3 H, s, SO_2Me), 3.70 (3 H, s, NCO_2Me), 3.90–4.10 (1 H, br, 2-H^{eq}), 4.14 (2 H, q, *J* 7.1, OCH_2Me) and 5.10 (1 H, dq, *J* 13.0 and 2.9 Hz, $CHOMs$); *m*/*z* 351 (M^+).

Ethyl (3S,4S,1′R)-{1-*Methoxycarbonyl*-3-[1′-(*methylsulfonyloxy*)*ethyl*]*piperidin*-4-*yl*}*acetate* (−)-**12**.—The mesate (−)-**12** (197.5 mg) was obtained from the alcohol (+)-**6** (179.6 mg) by the same procedure as that described for mesate (+)-**12** (Found: C, 48.0; H, 7.1; 4.0%); $[\alpha]_D^{26}$ −10.4° (*c* 1.2, $CHCl_3$). The IR (neat) and ^1H NMR spectra of this sample were identical with those of its enantiomer (+)-**12**.

Ethyl [(R)-3-(Z)-*Ethylidene*-1-*methoxycarbonylpiperidin*-4-*yl*]*acetate* (+)-**13**.—NaI (1.21 g, 8.09 mmol) was added to a solution of mesate (+)-**12** (0.71 g, 2.02 mmol) in acetone (10 cm^3). The reaction mixture was heated under reflux for 60 h and then concentrated under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 (10 cm^3) and the CH_2Cl_2 solution was washed successively with saturated aq. $NaHCO_3$, saturated aq. $Na_2S_2O_4$, and water, and dried ($MgSO_4$). The organic phase was concentrated under reduced pressure and the resulting residue was dissolved in benzene (40 cm^3). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) (0.37 g, 2.43 mmol) was added and the mixture was heated under reflux for 21 h, and then poured into ice–water (20 cm^3). The separated organic phase was washed successively with 10% HCl and water, dried ($MgSO_4$), and concentrated under reduced pressure. The resulting residue was subjected to column chromatography [silica gel, 17 g; elution with benzene–CH_2Cl_2 (1:1)] to give compound (+)-**13** (396.7 mg, 1.55 mmol) as an oil (Found: C, 60.8; H, 8.05; N, 5.1. Calc. for $C_{13}H_{21}NO_4$: C, 61.15; H, 8.29; N, 5.49%); $[\alpha]_D^{26}$ +19.5° (*c* 1.1, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1730 (ester CO) and 1700 (carbamate CO); δ_H 1.25 (3 H, t, *J* 7.0, OCH_2Me), 1.2–1.4 (1 H, m, 5-H^{ax}), 1.68 (3 H, d, *J* 6.6, =CHMe), 1.70–1.85 (1 H, m, 5-H^{eq}), 2.32 (1 H, dd, *J* 15.0 and 7.7, $CHHCO_2Et$), 2.58 (1 H, dd, *J* 15.0 and 7.1, $CHHCO_2Et$), 2.62–2.77 (1 H, m, 4-H), 3.20–3.35 (1 H, m), 3.60–3.85 (2 H, m), 3.69 (3 H, s, OMe), 4.13 (2 H, q, *J* 7.0, OCH_2Me), 4.37 (1 H, br d, *J* 13.9, 6-H^{eq}) and 5.25 (1 H, q, *J* 6.6, $=CHMe$); δ_C 12.9 (q), 14.3 (q), 32.1 (t), 37.4 (t), 38.4 (d), 42.8 (t), 43.3 (t), 52.6 (q), 60.4 (t), 118.2 (d), 135.2 (s), 157.5 (s) and 172.5 (s); *m*/*z* 255 (M^+).

Ethyl [(S)-3-(Z)-*Ethylidene*-1-*methoxycarbonylpiperidin*-4-*yl*]*acetate* (−)-**13**.—As described for isomer (+)-**13**, compound (−)-**12** (147.8 mg) was transformed into compound (−)-**13** (82 mg) (Found: C, 60.9; H, 8.3; N, 5.2%); $[\alpha]_D^{26}$ −19.9° (*c* 1.1, $CHCl_3$). The IR (neat) and ^1H NMR spectra of this sample were identical with those of its enantiomer (+)-**13**.

[(R)-3-(Z)-*Ethylidene*-1-*methoxycarbonylpiperidin*-4-*yl*]-*acetic Acid* (+)-**14**.—1 mol dm^{-3} NaOH solution (0.85 cm^3, 0.85 mmol) was added to a solution of ester (+)-**13** (216.9 mg, 0.851 mmol) in EtOH (6 cm^3) at 0 °C. After being stirred for 8 h at room temperature, the reaction mixture was concentrated under reduced pressure at below 20 °C. To the resulting residue was added water (10 cm^3) and the solution was acidified with 10% HCl and extracted with CH_2Cl_2. The CH_2Cl_2 phase was dried ($MgSO_4$), and concentrated under reduced pressure. The resulting residue was subjected to column chromatography (silica gel, 6 g; elution with CH_2Cl_2) to afford acid (+)-**14** (191.2 mg, 0.842 mmol) as an oil (Found: M^+, 227.1145. Calc. for $C_{11}H_{17}NO_4$ M, 227.1157); $[\alpha]_D^{26}$ +16.4° (*c* 1.4, MeOH); ν_{max}(neat)/cm^{-1} 1730sh and 1700 (CO); δ_H 1.25–1.45 (2 H, m), 1.69 (3 H, d, *J* 6.6, $=CHMe$), 1.76–1.93 (1 H, m), 2.31–2.46 (1 H, m), 2.56–2.80 (2 H, m), 3.23–3.39 (1 H, m), 3.59–3.72 (1 H, m), 3.70 (3 H, s, OMe), 3.72–3.90 (1 H, m, 6-H^{eq}), 4.42 (1 H, br d, *J* 14.2, 2-H^{eq}) and 5.27 (1 H, q, *J* 6.8, $=CHMe$); *m*/*z* 227 (M^+). These spectral and analytical data were identical with those of an authentic sample.[4]

[(S)-3-(Z)-*Ethylidene*-1-*methoxycarbonylpiperidin*-4-*yl*]-*acetic Acid* (−)-**14**.[5]—As described for the acid (+)-**14**, the ester (−)-**13** (43.5 mg) was transformed into acid (−)-**14** (33.1 mg) (Found: M^+, 227.1153. $C_{11}H_{17}NO_4$ requires M, 227.1157); $[\alpha]_D^{26}$ −14.4° (*c* 0.93, MeOH). The IR (neat) and ^1H NMR spectra of this sample were identical with those of (+)-**14**.

Methyl [(R)-3-(Z)-*Ethylidene*-1-*methoxycarbonylpiperidin*-4-*yl*]*acetate* (+)-**15**.—Diazomethane (5 cm^3; 0.4 mol dm^{-3} solution in ether) was added to a solution of the acid (+)-**14** (43.2 mg, 0.190 mmol) in ether (2 cm^3) at 0 °C. After being kept for 10 min at the same temperature, the mixture was concentrated under reduced pressure. The resulting residue was subjected to column chromatography [silica gel, 2 g; elution with benzene–CH_2Cl_2 (1:1)] to give the methyl ester (+)-**15** (34.6 mg, 0.1435 mmol) as an oil; $[\alpha]_D^{26}$ +15.1° (*c* 1.2, MeOH); ν_{max}(neat)/cm^{-1} 1730 (ester CO) and 1700 (carbamate CO); δ_H 1.29–1.45 (1 H, m, 5-H^{eq}), 1.68 (3 H, d, *J* 6.6, $=CHMe$), 1.70–1.90 (1 H, m, 5-H^{eq}), 2.34 (1 H, dd, *J* 14.9 and 7.6, $CHHCO_2Me$), 2.59 (1 H, dd, *J* 14.9 and 7.1, $CHHCO_2Me$), 2.63–2.83 (1 H, m, 4-H), 3.31 (1 H, ddd, *J* 13.2, 9.3 and 3.9), 3.68 (3 H, s, OMe), 3.69 (3 H, s, OMe), 3.65–3.83 (2 H, m), 4.38 (1 H, br d, *J* 14.4, 2-H^{eq}) and 5.24 (1 H, q, *J* 6.8, $=CHMe$); *m*/*z* 241 (M^+). The ^{13}C NMR spectrum of ester (+)-**15** was identical with that previously reported.[4]

Ethyl {(3R,4R,1′S)-3-[1′-(*Imidazole*-1-*thiocarbonyloxy*)-*ethyl*]-1-*methoxycarbonylpiperidin*-4-*yl*}*acetate* (−)-**18**.—A solution of 1,1′-thiocarbonyldiimidazole (82.4 mg, 0.4487 mmol) was added to a stirred solution of the alcohol (−)-**6** (122.5 mg, 0.449 mmol) in ethylene dichloride (20 cm^3) and the resulting solution was refluxed for 10 h. The reaction mixture was concentrated under reduced pressure to give a residue which was subjected to column chromatography (silica gel, 6 g; elution with $CHCl_3$) to give compound (−)-**18** (168.6 mg, 0.440 mmol) as a yellow oil; $[\alpha]_D^{26}$ −18.5° (*c* 1.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1730 (ester CO) and 1700 (carbamate CO); δ_H 1.24 (3 H, t, *J* 7.1, OCH_2Me), 1.52 (3 H, d, *J* 6.6, $MeCHCS$), 1.7–1.9 (2 H, m), 1.9–2.1 (1 H, m), 2.2–2.4 (1 H, m), 2.63 (1 H, dd, *J* 4.6 and 15.4), 2.8–3.2 (2 H, br), 3.67 (3 H, s, NCO_2Me) 3.8–4.1 (1 H, br), 4.12

(2 H, q, *J* 7.1, OCH_2Me), 5.89 (1 H, br s, CHOC=S), 7.06 (1 H, s, imid. 4-H), 7.61 (1 H, s, imid. 5-H) and 8.32 (1 H, s, imid. 2-H); *m/z* 384 ($M^+ + 1$).

Ethyl [(3R,4R)-3-*Ethyl*-1-*methoxycarbonylpiperidin*-4-*yl*]-*acetate* (+)-**19**.—A solution of the imidazolide (−)-**18** (158.5 mg, 0.413 mmol) in toluene (5 cm^3) was added dropwise to a stirred solution of tributyltin hydride (195.9 mg, 0.673 mmol) in toluene (15 cm^3) under reflux. The mixture was then further heated under reflux for 3 h, after which the solvent was evaporated to give a residue, which was subjected to column chromatography (silica gel, 3 g; elution with CH_2Cl_2) to afford diester (+)-**19** (96.7 mg, 0.376 mmol) as an oil (Found: C, 60.5; H, 9.1; N, 5.4. Calc. for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44%); $[\alpha]_D^{26}$ +39.3° (*c* 1.1, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1730 (ester CO) and 1700 (carbamate CO); δ_H 0.92 (3 H, t, *J* 7.1, $CHCH_2Me$) 1.1–1.25 (3 H, m), 1.26 (3 H, t, *J* 7.1, OCH_2Me), 1.50–1.65 (1 H, m), 1.65–1.73 (2 H, m), 2.07 (1 H, dd, *J* 15.0 and 8.7, $CHHCO_2Et$), 2.56 (1 H, dd, *J* 15.1 and 4.2, $CHHCO_2Et$), 2.75–2.90 (1 H, m), 3.68 (3 H, s, NCO_2Me), 3.9–4.1 (1 H, m, 2-H^{eq}) and 4.13 (2 H, q, *J* 7.1, OCH_2Me); *m/z* 257 (M^+).

Ruthenium Oxide Oxidation of Diester (+)-**19**.—A mixture of a solution of diester (+)-**19** (69.3 mg, 0.269 mmol) in AcOEt (26 cm^3) and 10% aq. $NaIO_4$ (2.6 cm^3) was stirred at room temperature, and ruthenium dioxide hydrate (5 mg) was added. After being stirred for 5 h, the AcOEt layer was separated and, after addition of propan-2-ol (1 cm^3), was kept at room temperature for 3 h. The black precipitate that resulted was removed by filtration, and the filtrate was washed successively with water, 2% aq. $Na_2S_2O_3$, and water, dried ($MgSO_4$), and concentrated under reduced pressure. The resulting residue was subjected to column chromatography [alumina, 5 g; elution with hexane–AcOEt (1:2)]. Early fractions gave *ethyl* [(3R,4R)-3-*ethyl*-2-*oxopiperidin*-4-*yl*]*acetate* (+)-**20** (7.3 mg, 0.034 mmol) as an oil (Found: M^+, 213.1364. $C_{11}H_{19}NO_3$ requires M, 213.1364); $[\alpha]_D^{26}$ +30.1° (*c* 0.325, EtOH); δ_H 0.95 (3 H, t, *J* 7.3, $CHCH_2Me$), 1.27 (3 H, t, *J* 7.3, OCH_2Me), 1.48–1.78 (2 H, m), 1.80–2.05 (2 H, m), 2.05–2.15 (1 H, m), 2.17–2.37 (2 H, m), 2.41–2.63 (1 H, m), 3.22–3.46 (2 H, m, 6-H_2), 4.15 (2 H, q, *J* 7.3, OCH_2Me) and 5.87–6.03 (1 H, br, NH); *m/z* 213 (M^+); later fractions in the above column chromatography yielded ethyl [(4*R*,5*R*)-5-ethyl-2-oxopiperidin-4-yl]acetate (+)-**21**[8] (6.5 mg, 0.0305 mmol) as an oil (Found: M^+, 213.1334. Calc for $C_{11}H_{19}NO_3$: M, 213.1364); $[\alpha]_D^{26}$ +66.7° (*c* 0.15, EtOH); δ_H 0.93 (3 H, t, *J* 7.3, $CHCH_2Me$) 1.26 (3 H, t, *J* 7.1, OCH_2Me), 1.20–1.40 (2 H, m), 1.46–1.70 (1 H, m), 2.07–2.34 (3 H, m), 2.40–2.60 (2 H, m), 2.97–3.07 (1 H, m, 6-H^{ax}), 3.35–3.45 (1 H, m, 6-H^{eq}), 4.15 (2 H, q, *J* 7.1, OCH_2Me) and 5.75–5.90 (1 H, br, NH); *m/z* 213 (M^+). The specific rotation of this sample was identical with that of an authentic sample.

Ethyl [(3R,4R)-3-*Acetylpiperidin*-4-*yl*]*acetate* **24**.—A solution of the benzylamine (−)-**2** (2.32 g, 7.65 mmol) in EtOH (30 cm^3) containing $Pd(OH)_2$ (30 mg) was hydrogenated under hydrogen at room temperature for 11 h. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to afford *compound* **24** (1.58 g, 7.41 mmol) as a yellow oil (Found: M^+, 213.1402. $C_{11}H_{19}NO_3$ requires M, 213.1364). The crude product **24** was used for the next step without purification, and had ν_{max}(neat)/cm^{-1} 1730 (ester CO) and 1710 (CO); δ_H 1.26 (3 H, t, *J* 7.1, CH_2Me), 1.2–1.4 (1 H, m), 1.84 (1 H, dq, *J* 3.2 and 13.4), 2.20 (3 H, s, COMe), 2.1–2.4 (3 H, m), 2.5–2.8 (3 H, m), 3.56 (1 H, br s, NH) and 4.11 (2 H, q, *J* 7.1, OCH_2Me); *m/z* 213 (M^+).

Ethyl [(3R,4R)-3-*Acetyl*-1-(t-*butoxycarbonyl*)*piperidin*-4-*yl*]*acetate* (−)-**25**.—A solution of di-*t*-butyl dicarbonate $(Boc)_2O$ (1.75 g, 8.02 mmol) in ether (10 cm^3) was added to a stirred solution of the product **24** (1.58 g, 7.41 mmol) and pyridine (0.635 g, 8.03 mmol) in ether (30 cm^3) at room temperature. After being stirred for 1 h, the reaction mixture was washed successively with 10% HCl (15 cm^3), 10% aq. NaOH, and brine. The organic phase was dried, and concentrated under reduced pressure to give a yellow oil. Chromatography of the resulting material (silica gel, 100 g; elution with CH_2Cl_2) furnished diester (−)-**25** (2.21 g, 7.05 mmol) as a pale yellow oil (Found: C, 61.2; H, 8.8; N, 4.4. Calc. for $C_{16}H_{27}NO_5$: C, 61.32; H, 8.68; N, 4.47%); $[\alpha]_D^{26}$ −53.2° (*c* 1.10, $CHCl_3$); ν_{max}-(neat)/cm^{-1} 1730 (ester CO) and 1690 (carbamate and ketone CO); δ_H 1.26 (3 H, t, *J* 7.1, OCH_2Me), 1.15–1.34 (1 H, m, 5-H^{eq}), 1.47 (9 H, s, Bu^{t}O), 1.72–1.83 (1 H, m), 2.23 (3 H, s, COMe), 2.09–2.46 (3 H, m), 2.46–2.85 (3 H, m), 4.11 (2 H, q, *J* 7.1, OCH_2Me) and 4.36–4.40 (2 H, br, 2- and 6-H^{eq}); *m/z* 313 (M^+).

t-*Butyl* (4aR,8aR)-*Decahydro*-6,8-*dioxoisoquinoline*-2-*carboxylate* (−)-**26**.—A stirred solution of diisopropylamine (0.704 g, 6.96 mmol) in THF (30 cm^3) at −78 °C was treated with butyllithium (4.46 cm^3; 10% w/v solution in hexane). After 30 min, a solution of the piperidine derivative (−)-**25** (1.82 g, 5.797 mmol) in THF (10 cm^3) was added. After being kept at −78 °C for 1 h, the mixture was allowed to warm to room temperature and was then acidified with 10% HCl at 0 °C, and then the whole was extracted with CH_2Cl_2 (20 cm^3 × 3). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The crude product was subjected to column chromatography (silica gel, 50 g; elution with $CHCl_3$) to give dione (−)-**26** (1.53 g, 5.73 mmol) as a solid, m.p. 141–146 °C (from benzene–hexane) (Found: 63.2; H, 8.0; N, 5.2. Calc. for $C_{14}H_{21}NO_5$: C, 62.90; H, 7.92; N, 5.24%); $[\alpha]_D^{26}$ −75.7° (*c* 1.08, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1680 (CO); δ_H 1.2–1.6 (2 H, m), 1.47 (9 H, s, Bu^{t}O), 1.6–1.8 (1 H, m), 1.8–2.0 (1 H, m), 2.0–2.8 (5 H, m), 3.3–3.6 (1 H, m), 4.1–4.4 (1 H, m), 4.4–4.7 (1 H, m); *m/z* 267 (M^+).

t-*Butyl* (4aR,8aR)-1,2,3,4,4a,5,6,8a-*Octahydroiso*-8-*methoxy*-6-*oxoquinoline*-2-*carboxylate* (+)-**27** *and* t-*Butyl* (4aR,8aR)-1,2,3,4,4a,5,8,8a-*Octahydro*-6-*methoxy*-8-*oxoisoquinoline*-2-carboxylate (−)-**28**.—A catalytic amount of *p*-TsOH (20 mg) was added to a solution of dione (−)-**26** (1.53 g, 5.73 mmol) in dry MeOH (20 cm^3) and the mixture was kept for 20 h at room temperature before being made alkaline with aq. $NaHCO_3$ and concentrated under reduced pressure. The resulting residue was partitioned between water (5 cm^3) and CH_2Cl_2 (5 cm^3). The layers were separated and the aq. layer was extracted with CH_2Cl_2 (30 cm^3 × 3). The combined organic phase was dried ($MgSO_4$), and concentrated under reduced pressure. The residue was subjected to column chromatography (silica gel, 50 g; elution with CH_2Cl_2) to give, in the order of elution, compound (−)-**28** (1.078 g, 3.83 mmol) and its isomer (+)-**27** (0.282 g, 1.00 mmol).

Compound (−)-**28** (Found: M^+, 281.1670. $C_{15}H_{23}NO_4$ requires M, 281.1626); $[\alpha]_D^{26}$ −132.6° (*c* 1.08, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1695 (CO), 1660 and 1610; δ_H 1.30–1.52 (1 H, m, 4-H^{ax}), 1.47 (9 H, s, Bu^{t}O), 1.69–1.85 (1 H, m, 4-H^{eq}), 1.85–2.00 (1, m, 4a-H), 2.05 (1 H, dt, *J* 5.1 and 11.3, 8a-H), 2.28 (1 H, ddd, *J* 1.5, 11.3 and 17.4, 5-H^{ax}), 2.42 (1 H, dd, *J* 4.6 and 17.4, 5-H^{eq}), 2.50–2.70 (2 H, m, 1- and 3-H^{ax}), 3.69 (3 H, s, OMe), 4.21 (1 H, br d, *J* 11.5, 3-H^{eq}), 4.62 (1 H, br d, *J* 11.5, 1-H^{eq}) and 5.35 (1 H, d, *J* 15, 7-H); *m/z* 281 (M^+).

Compound (+)-**27** (Found: C, 64.4; H, 8.4; N, 4.9. Calc. for $C_{15}H_{23}NO_4$: C, 64.03; H, 8.24; N, 4.98%); m.p. 152–155 °C (from Et_2O); $[\alpha]_D^{26}$ +1.00° (*c* 1.09, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1680 (CO), 1650 and 1590; δ_H 1.30–1.53 (1 H, m, 4-H^{ax}), 1.45 (9 H, s, Bu^{t}O), 1.70 (1 H, ddd, *J* 2.6, 5.3 and 13.8, 4-H^{eq}), 1.81–2.00

(1 H, m, 4a-H), 2.12 (1 H, dd, *J* 13.2 and 16.4, 5-H^{ax}), 2.28–2.32 (1 H, m, 8a-H), 2.46 (1 H, dd, *J* 3.7 and 16.4, 5-H^{eq}), 2.62–2.80 (1 H, br t, *J* 12.4, 3-H^{ax}), 3.69 (3 H, s, OMe), 4.08–4.30 (1 H, br, 3-H^{eq}), 4.50–4.85 (1 H, br, 1-H^{eq}) and 5.37 (1 H, d, *J* 1.2, 7-H); *m/z* 281 (M^+).

t-*Butyl* (4aR,8aR)-1,2,3,4,4a,5,6,8a-*Octahydro*-6-*oxoisoquinoline*-2-*carboxylate* (−)-**30**.—DIBAL (4.71 cm^3; 1 mol dm^{-3} solution in hexane) was added dropwise to a solution of enone (−)-**28** (1.20 g, 4.27 mmol) in toluene (10 cm^3) at −78 °C. After being kept at the same temperature for 2 h, the reaction mixture was quenched with saturated aq. NH_4Cl (10 cm^3). After filtration through Celite, the layers were separated and the aq. layer was extracted with benzene (20 cm^3 × 2). The combined organic phase was washed with brine, dried, and concentrated under reduced pressure. The residual oil was subjected to column chromatography (silica gel, 40 g; elution with CH_2Cl_2) to give compound **29** (881 mg, 3.11 mmol) as a mixture of diastereoisomers. This mixture was used for the next step without separation.

A catalytic amount of *p*-TsOH (20 mg) was added to a solution of the alcohol **29** (881 mg, 3.11 mmol) in ether (20 cm^3) at 0 °C and the mixture was kept for 11 h at room temperature, then was made alkaline with saturated aq. $NaHCO_3$. The layers were separated and the aq. phase was extracted with CH_2Cl_2 (15 cm^3 × 2). The combined organic phase was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was subjected to column chromatography (silica gel, 20 g; elution with CH_2Cl_2) to give enone (−)-**30** (774 mg, 3.08 mmol) as crystals, m.p. 106–108 °C (from Et_2O) (Found: C, 67.1; H, 8.35; N, 5.6. Calc. for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.42; N, 5.57%); $[\alpha]_D^{26}$ −55.6° (*c* 1.2, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1690 (CO); δ_H 1.32–1.50 (1 H, m, 4-H^{ax}), 1.47 (9 H, s, Bu^{t}O), 1.62–1.72 (1 H, m, 4-H^{eq}), 1.75–1.95 (1 H, m, 4a-H), 2.14–2.27 (1 H, m, 8a-H), 2.18 (1 H, dd, *J* 13.4 and 16.4, 5-H^{ax}), 2.52 (1 H, dd, *J* 3.7 and 16.4, 5-H^{eq}), 2.42–2.58 (1 H, m, 3-H^{ax}), 2.72 (1 H, br t, *J* 12.3, 1-H^{ax}), 4.10–4.50 (2 H, br, 1- and 3-H^{eq}), 6.05 (1 H, dd, *J* 2.7 and 10.0, 7-H) and 6.69 (1 H, dd, *J* 1.5 and 10.0, 8-H); *m/z* 251 (M^+).

(2)-t-*Butyl* (5)-*Methyl* (4aS,5R,8aR)-1,2,3,4,4a,5,6,8a-*Octahydro*-6-*oxoisoquinoline*-2,5-*dicarboxylate* (+)-**31**.—A stirred solution of diisopropylamine (97.6 mg, 0.965 mmol) in THF (5 cm^3) was treated with butyllithium (0.62 cm^3; 10% w/v in hexane). After 30 min, the mixture was cooled to −78 °C and a solution of ester (−)-**30** (202 mg, 0.804 mmol) was added at the same temperature. The reaction mixture was allowed to warm to 0 °C and was kept at the same temperature for 1 h, then was cooled again at −78 °C, and hexamethylphosphoric triamide (144.0 mg, 0.804 mmol) and methyl cyanoformate (82 mg, 0.965 mmol) were added. After being stirred for 30 min at −78 °C, the reaction mixture was quenched with ice–water. The layers were separated and the aq. layer was extracted with ether (10 cm^3 × 3). The combined organic phase was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was subjected to column chromatography [silica gel, 10 g; elution with benzene–CH_2Cl_2 (1:1)] to give *diester* (+)-**31** (209 mg, 0.676 mmol) as an oil (Found: M^+, 309.1552. $C_{16}H_{23}NO_5$ requires M, 309.1575); $[\alpha]_D^{26}$ +25.3° (*c* 0.7, $CHCl_3$); ν_{max}(KBr)/cm^{-1} 1740 (ester CO) and 1670 (ketone and carbamate CO); δ_H 1.31–1.53 (1 H, m, 4-H^{ax}), 1.47 (9 H, s, Bu^{t}O), 1.53–1.72 (1 H, m, 4-H^{eq}), 2.15–2.38 (2 H, m, 4a- and 8a-H), 2.43–2.85 (2 H, br, 1- and 3-H^{ax}), 3.22 (1 H, d, *J* 12.7, 5-H), 3.79 (3 H, s, OMe), 4.17–4.53 (2 H, br, 1- and 3-H^{eq}), 6.10 (1 H, dd, *J* 2.4 and 10.0, 7-H) and 6.74 (1 H, *J* 10.0, 8-H); *m/z* 309 (M^+).

(2)-t-*Butyl* (5)-*Methyl* (4aS,5R,8aR)-*Decahydro*-6-*oxoisoquinoline*-2,5-*dicarboxylate* (+)-**32**.—A solution of enone (+)-**31** (600 mg, 1.94 mmol) in MeOH (15 cm^3) was catalytically hydrogenated over 5% palladium–carbon under hydrogen at room temperature for 5 h. After separation of the catalyst, MeOH was distilled off under reduced pressure. The resulting residue was subjected to column chromatography [silica gel, 10 g; elution with benzene–CH_2Cl_2 (1:1)] to give keto diester (+)-**32** (429.7 mg, 1.38 mmol) as an oil (Found: C, 62.0; H, 8.1; N, 4.4. Calc. for $C_{16}H_{25}NO_5$: C, 61.71; H, 8.09; N, 4.50%); $[\alpha]_D^{26}$ +15.4° (*c* 1.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1750 (ester CO) and 1690 (ketone CO); δ_H 1.20–1.55 (2 H, m), 1.43 (9 H, s, Bu^{t}O), 1.55–1.77 (2 H, m), 1.85–2.05 (2 H, m), 2.31–2.50 (2 H, m), 2.70 (1 H, br t, *J* 12.0, 3-H^{ax}), 3.15 (1 H, d, *J* 12.0, 5-H), 3.77 (3 H, s, OMe) and 4.05–4.30 (2 H, br, 1- and 3-H^{eq}); *m/z* 311 (M^+).

Procedure for Reduction of the Ketone (+)-**32**.—A. *With sodium borohydride*. The ketone (+)-**32** (19 mg, 0.061 mmol) was dissolved in MeOH (2 cm^3), the solution was taken to −15 °C, and then sodium borohydride (2.3 mg, 0.061 mmol) was added. The reaction mixture was stirred for 1.5 h and then concentrated under reduced pressure to dryness. The residue was partitioned between CH_2Cl_2 (10 cm^3) and water (5 cm^3), and the aq. layer was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was subjected to column chromatography (silica gel, 1 g; elution with CH_2Cl_2) to give, in order of elution, (2)-*t*-butyl (5)-methyl (4a*S*,5*R*,6*S*,8a*R*)-decahydro-6-hydroxyisoquinoline-2,5-dicarboxylate (+)-**33** (5.9 mg, 0.019 mmol) as an oil (Found: C, 61.0; H, 8.7; N, 4.5. Calc. for $C_{16}H_{27}NO_5$: C, 61.32; H, 8.68; N, 4.47%) and (2)-t-*butyl* (5)-*methyl* (4aS,5R,6R,8aR)-*decahydro*-6-*hydroxyisoquinoline*-2,5-*dicarboxylate* (+)-**34** (13.0 mg, 0.042 mmol) as an oil (Found: M^+, 313.1926. $C_{16}H_{27}NO_5$ requires M, 313.1888).

Compound (+)-**33**: $[\alpha]_D^{26}$ +39.4° (*c* 1.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1740 (ester CO) and 1690 (carbamate CO); δ_H 1.45 (9 H, s, Bu^{t}O), 1.75–2.07 (2 H, m, 4a- and 8a-H), 2.24 (1 H, dd, *J* 2.0 and 1.0, 5-H), 2.41 (1 H, br t, *J* 11.1, 3-H^{ax}), 2.70 (1 H, br t, *J* 12.4, 1-H^{ax}), 3.28 (1 H, br s, OH), 3.73 (3 H, s, OMe) and 3.85–4.30 (3 H, br, 1- and 3-H^{eq}, and 6-H); *m/z* 313 (M^+).

Compound (+)-**34**: $[\alpha]_D^{26}$ +19.0° (*c* 1.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1734 (ester CO) and 1690 (carbamate CO); δ_H 1.38 (9 H, s, Bu^{t}O), 2.03 (1 H, dd, *J* 10.4 and 10.3, 5-H), 2.1–2.35 (1 H, m, 3-H^{ax}), 2.4–2.7 (1 H, m, 1-H^{ax}), 3.77 (1 H, ddd, *J* 4.5, 10.2 and 11.5, C*H*OH) and 3.85–4.20 (2 H, m, 1- and 3-H^{eq}); *m/z* 313 (M^+).

B. *With zinc borohydride*. Zinc borohydride (0.403 cm^3; 0.13 mol dm^{-3} solution in ether) was added dropwise to a solution of ketone (+)-**32** (16.3 mg, 0.052 mmol) in ether (5 cm^3) during 5 min at −78 °C. After being stirred for 1 h, the reaction mixture was quenched by addition of saturated aq. NH_4Cl. The layers were separated and the aq. layer was extracted with CH_2Cl_2. The combined organic phase was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was subjected to column chromatography (silica gel, 1 g; elution with CH_2Cl_2) to give, in the order of elution, compound (+)-**33** (2.6 mg, 0.0083 mmol) and compound (+)-**34** (13.8 mg, 0.044 mmol).

C. *With L-Selectride*. L-Selectride (0.799 cm^3; 1.0 mol dm^{-3} solution in THF) was added dropwise to a solution of ketone (+)-**32** (206.1 mg, 0.66 mmol) in THF (10 cm^3) during 5 min at −78 °C. After being kept at the same temperature for 1.5 h, the reaction mixture was quenched with saturated aq. NH_4Cl. The layers were separated and the aq. phase was extracted with ether (15 cm^3 × 2). The combined organic phase was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was subjected to column chromatography (silica gel, 15 g; elution with CH_2Cl_2) to give compound (+)-**33** (151.5 mg, 0.483 mmol) as a single product.

Methyl (4aS,5R,6S,8aR)-6-(t-*Butyldimethylsiloxy*)*decahydroisoquinoline*-5-*carboxylate* (+)-**35**.—TBSOTf (202.9 mg, 0.768 mmol) was added dropwise to a solution of the alcohol (+)-**33** (80.2 mg, 0.256 mmol) and 2,6-lutidine (2,6-dimethylpyridine) (109.7 mg, 1.024 mmol) in dry CH_2Cl_2 (1 cm^3) at room temperature. After the mixture had been stirred for 20 min, saturated aq. NH_4Cl (2 cm^3) was added. The layers were separated and the aq. layer was extracted with ether (10 cm^3 × 3). The combined organic phase was washed with brine, dried (K_2CO_3), and concentrated under reduced pressure. The residue was subjected to column chromatography [silica gel, 3 g; elution with $CHCl_3$–isopropylamine, (49:1)] to give *ester* (+)-**35** (76.1 mg, 0.232 mmol) as an oil (Found: M^+, 327.2223. $C_{17}H_{33}NO_3Si$ requires M, 327.2228); $[\alpha]_D^{26}$ +54.9° (*c* 1.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 1740 (CO); δ_H 0.05 (3 H, s, SiMe), 0.06 (3 H, s, SiMe), 0.92 (9 H, s, Bu^t), 1.00–1.70 (6 H, m), 1.70–2.05 (2 H, m), 2.13–2.50 (3 H, m), 2.72–2.97 (1 H, m), 2.99 (1 H, dd, *J* 3.2 and 12.6), 3.12 (1 H, br d, *J* 12.6), 3.69 (3 H, s, OMe) and 4.34 (1 H, br s, CHOSi); *m*/*z* 327 (M^+).

O-(t-*Butyldimethylsilyl*)-2,3-*seco-yohimbine* (+)-**36**.—A mixture of tryptophyl bromide (40.6 mg, 0.181 mmol), compound (+)-**35** (49.4 mg, 0.151 mmol), K_2CO_3 (25 mg, 0.181 mmol), and acetonitrile (2 cm^3) was heated at reflux for 10 h. After evaporation of the solvent under reduced pressure, the residue was partitioned between water (2 cm^3) and CH_2Cl_2 (10 cm^3). The layers were separated and the aq. layer was extracted with CH_2Cl_2 (10 cm^3 × 3). The combined organic phase was washed with brine, dried (K_2CO_3), and condensed under reduced pressure. Chromatography of the resulting oil [silica gel, 8 g; elution with $CHCl_3$–MeOH, (50:1)] gave *compound* (+)-**36** (61.7 mg, 0.131 mmol) as a pale yellow oil (Found: M^+, 470.2979. $C_{27}H_{42}N_2O_3Si$ requires M, 470.2962); $[\alpha]_D^{26}$ +35.1° (*c* 1.0, $CHCl_3$); ν_{max}(neat)/cm^{-1} 3400 (NH) and 1740 (CO); δ_H −0.04 (3 H, s, SiMe), 0.02 (3 H, s, SiMe), 0.88 (9 H, s, Bu^t), 1.1–1.6 (4 H, m), 1.7–2.0 (4 H, m), 2.1–2.4 (3 H, m), 2.65–2.80 (2 H, m), 2.9–3.05 (3 H, m), 3.11 (1 H, br d, *J* 3.1), 3.66 (3 H, s, OMe), 4.32 (1 H, br s, CHOSi), 7.01 (1 H, br s, 2-H), 7.05–7.25 (2 H, m, ArH), 7.34 (1 H, d, *J* 8.1, ArH), 7.61 (1 H, d, *J* 7.8) and 8.15 (1 H, br s, NH); *m*/*z* 470 (M^+).

2,3-*Seco-yohimbine* (+)-**37**.—Hydrofluoric acid (50 mm^3; 47% solution) was added to a solution of the siloxane (+)-**36** (18.7 mg, 0.04 mmol) in acetonitrile (1 cm^3) at 0 °C. After being stirred for 13 h at room temperature, the reaction mixture was made alkaline with saturated aq. $NaHCO_3$. The layers were separated and the aq. layer was extracted with CH_2Cl_2 (2 cm^3 × 4). The combined organic phase was washed with brine, dried (K_2CO_3), and concentrated under reduced pressure. The residue was subjected to column chromatography [silica gel, 1 g; elution with $CHCl_3$–MeOH (50:1)] to give compound (+)-**37** (12.4 mg, 0.035 mmol) as needles, m.p. 116–118 °C (from $CHCl_3$) (lit.,[19] 117–118 °C); $[\alpha]_D^{26}$ +43.8° (*c* 1.1, MeOH) {lit.,[19] $[\alpha]_D^{26}$ +48.3° (MeOH)}; *m*/*z* 356 (M^+); δ_H (*inter alia*) 3.74 (3 H, s, CO_2Me), 4.18 (1 H, br, 17-H) and 7.02 (1 H, d, *J* 2.0, 2-H). The IR (KBr) and ^1H NMR spectral data, and specific rotation of this sample, were identical with those of an authentic sample derived from natural yohimbine.

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