Total Synthesis of (±)-Limaspermine and Formal Synthesis of (±)-Aspidospermine using Organoiron Complexes.[1]

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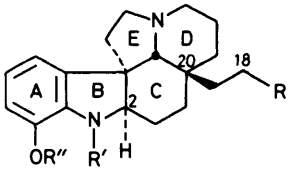
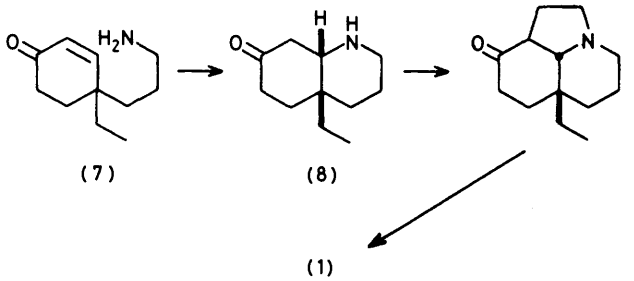
The total synthesis of the C-18 oxygenated aspidosperma alkaloid (±)-limaspermine (3) is described using tricarbonyl{-1—4-η-[1-methoxy1-4-(3-methoxycarbonylpropyl)cyclohexa-1,3-diene}iron (15) as a readily available ring C precursor. A formal synthesis of (±)-aspidospermine (1) from 4-ethylanisole, *via* the organoiron derivative (23) is also described as a model study for an alternative route to the C-18 functionalised alkaloids.

THE Aspidosperma alkaloids, typified by aspidospermine (1), are a widespread class of indole alkaloids,[2] the total synthesis of which has received considerable attention over the past 20 years. Most of the successful approaches employ similar methodology to that described by Stork and Dolfini [3] for aspidospermine synthesis. Thus, a 4,4-disubstituted cyclohexenone of type (7) is allowed to undergo intramolecular Michael reaction to give a *cis*-decahydroquinoline of type (8) which is converted into the alkaloid by successive building on of the E, and of the A and B rings as shown in Scheme 1. Using this approach, Saxton's group [4] have



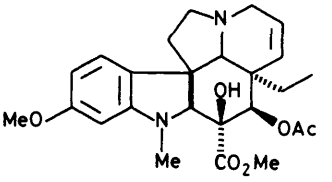
(1) R = H, R' = COMe, R" = Me
(2) R = OH, R' = H, R" = Me
(3) R = OH, R' = COEt, R" = H
(4) R = OMe, R' = H, R" = Me
(5) R = OMe, R' = COEt, R" = Me
(6) R = OH, R' = COEt, R" = Me



(7) (8) (1)

SCHEME 1

synthesised a number of compounds related to cylindrocarpinol (2). Alternative approaches to these C-18 functionalised alkaloids have been described by Ban *et al.*,[5] though considerable difficulty was encountered in producing the *cis*-decahydroquinoline intermediate for an attempted total synthesis of limaspermine (3).[5a] A great variety of alternative approaches both to the Stork intermediate and to the alkaloid system itself have also been reported.[6] More complex alkaloids, such as vindoline (9), a component of the antitumour compound vinblastine,[7] have also been the object of total synthesis.[8] Our ability to synthesise remotely functionalised 4,4-disubstituted cyclohexenones,[9] using tricarbonylcyclohexadienylium iron complexes of type (10), coupled with



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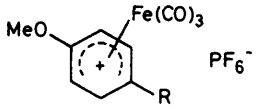
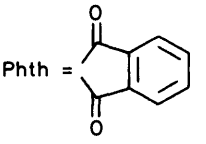


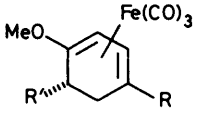
(10) R = general
(11) R = $[CH_2]_3OAc$
(12) R = $[CH_2]_3OTs$
(13) R = $[CH_2]_3NPhth$
(14) R = Et



our desire to establish these organometallic compounds as useful intermediates for the total synthesis of a wide range of natural products, led us to investigate possible routes to the C-18 oxygenated derivatives, and we chose (±)-limaspermine as our initial target. At this stage we were not concerned with the efficiency of our approach, in terms of the number of steps involved, but we were more interested in developing a route employing relatively simple chemical transformations which would illustrate the considerable potential and flexibility of the organoiron complexes. The results of our first approach are described in the present paper. We also describe results of a model study aimed at developing an alternative route and culminating in a synthesis of Stork's aspidospermine intermediate.

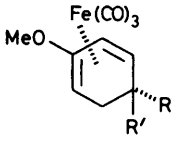
RESULTS AND DISCUSSION

(a) *Total Synthesis of* (±)-*Limaspermine* (3).—The starting point for our synthesis was the ester complex (15), previously prepared in 50% overall yield from *p*-methoxycinnamic acid.[10] Reduction of the ester group to a primary alcohol, whilst not possible in good yield using lithium aluminium hydride, owing to considerable decomposition, was smoothly effected in high yield using di-isobutylaluminium hydride to give the complex (16). At this juncture several alternatives presented themselves for the subsequent strategy. The primary alcohol in complex (16) was destined eventually to become the



(15) R = $CH_2CH_2CO_2Me$, R' = H
(16) R = $[CH_2]_3OH$, R' = H
(17) R = $[CH_2]_3OAc$, R' = H
(18) R = $[CH_2]_3OTs$, R' = H
(19) R = $[CH_2]_3NPhth$, R' = H
(20) R = $[CH_2]_3OAc$, R' = $CH(CO_2Me)_2$
(21) R = $[CH_2]_3OTs$, R' = $CH(CO_2Me)_2$
(22) R = $[CH_2]_3NPhth$, R' = $CH(CO_2Me)_2$
(23) R = Et, R' = H
(24) R = Et, R' = $CH(CO_2Me)_2$

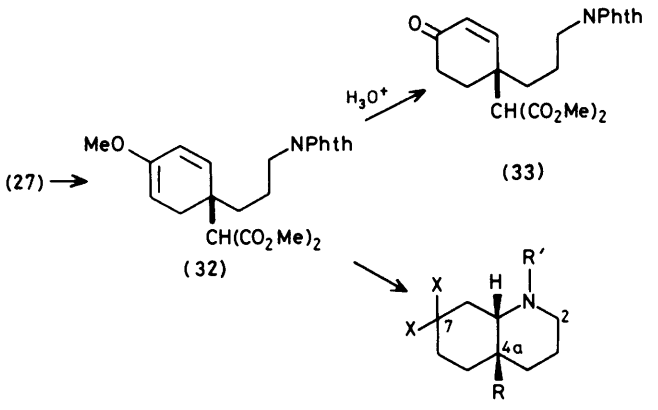
secondary amino-functionality of our projected decahydroquinoline intermediate, and the question arose as to whether to use a protected alcohol, a protected amine, or a direct amine precursor (*e.g.* tosylate) in the dienylium complex to be used in the next steps. Since we were uncertain as to the influence of remote groups on the chemistry of the dienylium system we decided to test all three possibilities. Thus, the alcohol (16) was acetylated to give (17), and also converted into the tosylate (18), in high yield. It was found necessary to destroy the excess of toluene-4-sulphonyl chloride in the latter conversion, *prior* to extraction, since the presence of this reagent during evaporation of solvents caused considerable decomposition of the complex. The tosylate (18) was smoothly converted into the phthalimide complex (19) in 90% yield using the standard procedure. All three complexes (17), (18), and (19) underwent regiospecific hydride abstraction on treatment with triphenylmethylium tetrafluoroborate to give the salts (11), (12), and (13), respectively, which were converted into their hexafluorophosphates for storage. In particular, the phthalimide derivative (13) was obtainable in 77% overall yield from the ester complex (15). We were now in a position to examine the reactions of these salts with a carbon nucleophile destined to become the angular C-20 hydroxyethyl group of limaspermine. Reaction of each with dimethyl sodiomalonate gave mixtures of regioisomers from attack at each dienylium terminus C-1 and C-5. The acetate * complex gave a mixture of compounds (25) and (20) (3.8 : 1, from ^{1}H n.m.r.), the tosylate (12) gave (26) and (21) (1.8 : 1), and the phthalimide (13) gave (27) and (22) (2.8 : 1). Later experiments showed that reaction with dimethyl potassiomalonate proceeded with better regioselectivity [11] giving, for example, compounds (27) and (22) in a ratio of 4.6 : 1. The more advantageous reactivity of complex (13), together with the fact that the product (27) is crystalline and could be isolated pure in 68% yield by crystallisation, indicated



(25) R = $(CH_2)_3OAc$, R' = $CH(CO_2Me)_2$
(26) R = $(CH_2)_3OTs$, R' = $CH(CO_2Me)_2$
(27) R = $(CH_2)_3NPhth$, R' = $CH(CO_2Me)_2$
(28) R = Et, R' = $CH(CO_2Me)_2$
(29) R = Et, R' = CH_2CO_2Me
(30) R = Et, R' = CH_2CH_2OH
(31) R = Et R' = CH_2CH_2CN

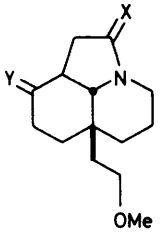
that this was the most convenient precursor. We now had to effect conversion of complex (2) into an appropriate *cis*-decahydroquinoline intermediate and again a number of options presented themselves, according to when we chose to unmask the primary amine and demethoxycarbonylate the *gem* diester. Preliminary trials indicated that demethoxycarbonylation of the diester prior to amine deprotection resulted in a number of problems during the latter step, and the route now described is the one which proved to be the least problematical. Removal of the tricarbonyliron group from compound (27) was smoothly effected using anhydrous trimethylamine *N*-oxide,[12] to give the dienol ether (32) which was obtained as a white solid. The extreme lability of this compound in solution, resulting in considerable hydrolysis to the corresponding cyclohexenone (33), precluded its rigorous purification, but since the crude compound gave a satisfactory combustion analysis, and since we considered it expedient to retain the dienol ether as enone protection during the next step, the crude compound was utilised. Treatment with hydrazine in the usual way liberated the primary amine without affecting the geminal diester or dienol ether and the crude product was immediately subjected to mild acid hydrolysis, followed by base treatment to afford the decahydroquinoline (34) in good overall yield. It was next necessary to demethoxycarbonylate the diester. All attempts to perform this operation on (34) resulted in extremely low yields, and we were forced to protect fully both the amino-function and the ketone to achieve satisfactory results. Whilst this necessarily added four steps to our original synthesis, the dramatic improvement in yields obtained made the diversion worthwhile. Thus, treatment of compound (34) with acetic anhydride in pyridine gave the amide (35) which was acetalised in the usual way to give (36). The *N*-acetyl derivatives, whilst

* Our earlier determinations of regioisomer ratios (ref. 1*b*) are less accurate than those quoted here, which were determined by expansion and multiple integration of ^{1}H n.m.r. spectra of the mixtures.



(34) R = $CH(CO_2Me)_2$; R' = H; X, X = O
(35) R = $CH(CO_2Me)_2$; R' = Ac; X, X = O
(36) R = $CH(CO_2Me)_2$; R' = Ac; X, X = OCH_2CH_2O
(37) R = CH_2CO_2Me; R' = Ac; X, X = OCH_2CH_2O
(38) R = CH_2CH_2OH; R' = Ac; X, X = OCH_2CH_2O
(39) R = CH_2CH_2OMe; R' = Ac; X, X = OCH_2CH_2O
(40) R = CH_2CH_2OMe; R' = H; X, X = OCH_2CH_2O
(41) R = CH_2CH_2OMe; R' = $CO{\cdot}CH_2Cl$; X, X = OCH_2CH_2O
(42) R = CH_2CH_2OMe; R' = $CO{\cdot}CH_2Cl$; X, X = O

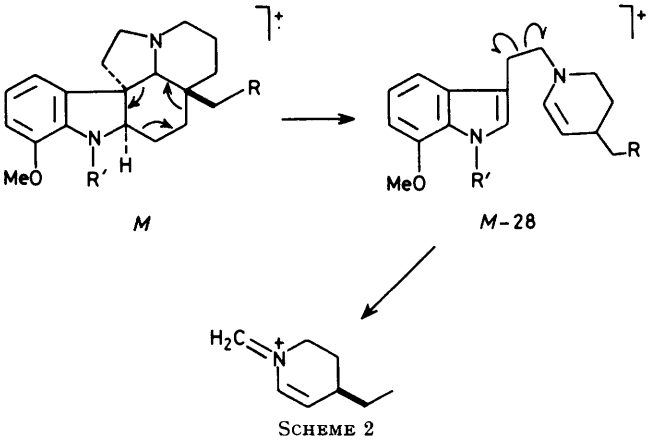
homogeneous according to t.l.c., each indicated the presence of two compounds in their 400 MHz n.m.r. spectra. Since the amine precursor and the products of subsequent deprotection appeared as single compounds, this was undoubtedly due to the well-known amide resonance phenomenon, as a result of which the compounds, whilst analytically pure, did not give sharp melting points. Demethoxycarbonylation of compound (36) now proceeded smoothly to give the monoester (37),



(43) X = O, Y = O
(44) X = O, Y = OCH_2CH_2O
(45) X = H_2, Y = OCH_2CH_2O
(46) X = H_2, Y = O

which was selectively reduced with lithium borohydride to give the primary alcohol (38). It was now necessary to protect the primary alcohol and for this purpose it was converted into the methyl ether (39) since, although this is not a good protecting group in terms of its subsequent removal, it presented itself as the most robust group to withstand the subsequent conversions. We next required to transform the intermediate (39) to the compound (42). This demanded that we replace the *N*-acetyl group with *N*-chloroacetyl, and in the absence of any suitable direct method for this conversion, it was necessary to deprotect the amido-function of (39). Prolonged treatment with boiling aqueous methanolic potassium hydroxide gave only recovered (39), there being no evidence for hydrolysis of the amide. Deprotection was, however, readily achieved in excellent yield using calcium in liquid ammonia,[13] to afford the amine (40) which was readily converted into the chloroacetyl derivative (41), and thence to the ketone derivative (42). We were now assured of a successful alkaloid synthesis, since the remaining steps were identical to those previously employed by others.[3,4] Treatment of compound (42) with base ($KOBu^t$) afforded in 95% yield the crystalline tricyclic derivative (43), which was converted *via* compounds (44) and (45) to the tricyclic aminoketone (46). This compound was converted into *O*-methylcylindrocarpinol (4) in 39% overall yield using the known Fischer indole procedure. The observation that a broad singlet at δ 3.60 corresponding to 2-H in the n.m.r. spectrum of compound (4) became a sharp doublet of doublets upon being shaken with D_2O assured us that (4) had the stereochemistry shown, since this pattern is indicative of the correct aspidosperma alkaloid stereochemistry.[4,5] Reaction of *O*-methylcylindrocarpinol with propionyl chloride–pyridine afforded crystalline *O*,*O*'-dimethyl-limaspermine (5), which now showed the characteristic doublet of doublets for 2-H at δ 4.46.

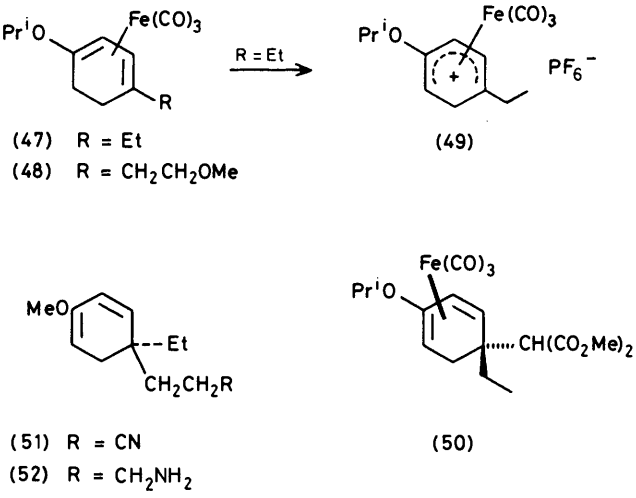
In order to complete a total synthesis of limaspermine (3) it was necessary to remove both the methyl ether groups in compound (5). Two current methods for effecting this transformation are the use of boron tribromide [14] or iodotrimethylsilane.[15] Since at this stage in our synthesis only a small amount of material was at hand, we were able to make only one attempt at each of these two methods and were unable to optimise the procedure. However, the results are useful and instructive for our future work, and we therefore present them here. Treatment of the dimethyl ether (5) with boron tribromide under the recommended conditions resulted in the formation of the monomethyl ether (6) readily characterised from its mass spectrum, which showed the fragmentation characteristic of these alkaloids,[2,16] shown in Scheme 2. This establishes that the aliphatic methyl ether is selectively deprotected by this procedure, albeit in low yield at present, and this will



SCHEME 2

undoubtedly be of use for a future synthesis of, *e.g.* cyclindrocarpinol (2). No other alkaloids, apart from recovered starting material, were obtained in this reaction. Treatment of the dimethyl ether (5) with iodotrimethylsilane resulted in cleavage of *both* methyl ether groups, to afford (±)-limaspermine (3) having spectra (mass i.r., and 400 MHz n.m.r.) comparable with an authentic sample of the natural product, but again in low yield. No other alkaloids, apart from starting material, were evident in appreciable quantities. The final product is, in fact, relatively unstable, appreciable amounts of an impurity becoming evident in the n.m.r. spectrum after 1—2 weeks. We have, in fact, observed the same impurity in samples of the natural product which have been allowed to stand in solution.

(b) *Formal Total Synthesis of* (±)-*Aspidospermine* (1).[17] —Parallel with the above study on limaspermine total synthesis we also undertook a synthesis of the *cis*-decahydroquinoline intermediate used in Stork's approach to aspidospermine. This would be valuable as a model for a shorter route to limaspermine, used to investigate the outcome of certain transformations which would be carried out in the presence of the diene-$Fe(CO)_3$ system, and also to establish methods for controlling the regiochemistry of nucleophile addition to dienylium complexes of type (10). Our starting point was 4-ethylanisole, which was converted into the diene complex (23) by the usual method.[18] Hydride abstraction using triphenylmethylium hexafluorophosphate proceeded regiospecifically to afford the desired dienylium complex (15) in essentially quantitative yield. Reaction of this salt with dimethyl potassiomalonate occurred to give a 5.6 : 1 mixture of regioisomers (28) and (24) in quantitative yield, from which pure compound (28). could be obtained in 78% yield by crystallisation. Subsequent to this work we found[1a] that the isopropoxycyclohexadiene complex (47) also undergoes regiospecific hydride abstraction to give compound (49), and this complex reacts with dimethyl potassiomalonate to give a single crystalline product (50) in 100% yield. This demonstrates that good regiocontrol can now be attained with these types of complex. The present study, however, was carried out using the methoxy-substituted complex (28). Demethoxycarbonylation occurred smoothly using tetramethylammonium acetate in hexamethylphosphoric triamide (HMPA) at elevated temperature to give the monoester (29), which was converted into the primary alcohol (30). Introduction of the requisite extra carbon and nitrogen atoms was readily achieved in greater than 90% yield by conversion of the alcohol (30) into a tosylate and treatment of this with sodium cyanide in HMPA at 60 °C, to give the nitrile (31). This is an excellent means of directly converting primary tosylates into nitriles, which appears to proceed under milder conditions than are generally used in alternative procedures.[19] At this stage removal of the $Fe(CO)_3$ group was effected with trimethylamine *N*-oxide to give the dienol ether (51), and the nitrile was reduced with lithium aluminium hydride, whilst the dienol ether was maintained as enone protection, to give the primary amine (52). Hydrolysis of the dienol ether, followed by basification to effect intramolecular Michael reaction, afforded the *cis*-decahydroquinoline (8) previously used by Stork and Dolfini for the total synthesis of aspidospermine.



Conclusions.—We have developed two flexible approaches to Aspidosperma alkaloid synthesis. Whilst the first synthesis described above involves a larger number of steps due to numerous protection/deprotection operations, it is the first synthesis of a fairly complex natural product using tricarbonylcyclohexadienyliumiron complexes and, indeed, it is the first effective synthesis of (±)-limaspermine. Our second approach offers a rather shorter route to the C-18 functionalised alkaloids, *e.g.* cylindrocarpinol and limaspermine, since we could commence with complex (48) and obtain our intermediate (42) in tens steps as opposed to sixteen steps from complex (15). This route is currently under investigation in our laboratories, as are improvements in the methyl ether deprotection steps. One possible advantage to this approach to organic synthesis is that the attachment of the $Fe(CO)_3$ to a substituted cyclohexadiene introduces asymmetry. Birch and his co-workers[20] have recently shown that diene-$Fe(CO)_3$ complexes may be prepared in optically active form, using an asymmetric induction approach, so that there are now real possibilities for asymmetric synthesis.

EXPERIMENTAL

I.r. spectra were determined with a Perkin Elmer 577, mass spectra with A.E.I. MS12 (organometallics) or MS30 (organic compounds), ^{1}H n.m.r. spectra with Varian EM390 (90 MHz) or Bruker WH 400 (400 MHz) spectrometers. M.p.s are uncorrected. All preparative and chromatographic operations involving iron complexes were conducted under a nitrogen atmosphere. The preparations of complexes (15), (16), (18),[10] (14), (23), and (28) [1] have been detailed elsewhere.

1—4-η-[1-(3-*Acetoxypropyl*)-4-*methoxycyclohexa*-1,3-*diene*]*tricarbonyliron* (17).—A solution of the primary alcohol

complex (16) (493 mg, 1.6 mmol) in pyridine (1.3 ml) was added to a solution of acetic anhydride (0.32 ml, 3.4 mmol) in pyridine (1.0 ml) at 0 °C. After 20 h water (2 ml) was added and the mixture stirred for 1 h. The product was extracted into ether, washed with 5% aqueous HCl and then water until neutral, dried ($MgSO_4$), and evaporated under reduced pressure to give the pure acetate (17) as a yellow oil (506 mg, 1.44 mmol, 90%), $\nu_{max.}$ ($CHCl_3$) 2 040, 1 965, and 1 735 cm^{-1}; δ($CDCl_3$) 5.19 (1 H, d, *J* 5 Hz, 3-H), 4.93 (1 H, d, *J* 5 Hz, 2-H), 4.08 (2 H, m, CH_2OAc), 3.46 (3 H, s, 4-OMe), 2.03 (3 H, s, OAc), and 2.4—1.5 (8 H, m); *m/e* (%) 294 (*M* − 2CO), 266 (50), 264 (100), and 210 (15) (Found: *M* − 2CO, 294.0563. Calc. for $C_{15}H_{18}FeO_6$: 294.0555).

1—5-η-[1-(3-*Acetoxypropyl*)-4-*methoxycyclohexa*-2,4-*dienylium*]*tricarbonyliron Hexafluorophosphate* (11).—Triphenylmethylium tetrafluoroborate (2.1 g, 6.4 mmol) was added to a solution of the acetate (17) (1.354 g, 3.87 mmol) in dichloromethane (15 ml) and heated under reflux for 45 min. The mixture was poured into ether and the tetrafluoroborate salt extracted into water. The aqueous extract was washed with ether and treated with ammonium hexafluorophosphate (1.0 g, 6.13 mmol). The product was filtered off, washed with water, then with ether, and then dried *in vacuo* to give the hexafluorophosphate (11) (1.815 g, 3.67 mmol, 95%), $\nu_{max.}$ (Nujol) 2 105, 2 050, 1 735, 843, and 572 cm^{-1}; δ(CD_3CN) 6.82 (1 H, dd, *J* 6, 2.5 Hz, 3-H), 5.63 (1 H, d, *J* 6 Hz, 2-H), 4.03 (2 H, t, *J* 6 Hz), 3.92 (1 H, m, 5-H) 3.81 (3 H, s, 4-OMe), 2.95 (1 H, dd, *J* 16, 6 Hz, *endo*-6-H), 2.01 (3 H, s, OAc), and 2.43—1.5 (5 H, m) (Found: C, 36.6; H, 3.4. Calc. for $C_{15}H_{17}F_6FeO_6P$: C, 36.5; H, 3.47%).

Tricarbonyl {1—4-η-[1-*methoxy*-4-(3-*phthalimidopropyl*)-*cyclohexa*-1,3-*diene*]}*iron* (1g).—Potassium phthalimide (12.3 g, 66.4 mmol) was added to a solution of the tosylate (18) (27.8 g, 60.1 mmol) in dimethylformamide (DMF) (200 ml) and the resulting suspension was stirred first at room temperature for 18 h and then at 40 °C for 6 h. The mixture was then poured into ethyl acetate and the solution washed successively with brine, dilute aqueous NaOH, water, and then dried ($MgSO_4$) and evaporated under reduced pressure to give the crystalline phthalimide complex (19) (23.6 g, 54.0 mmol, 90%). An analytical sample, obtained by recrystallisation from ether–pentane, had m.p. 113—114 °C; $\nu_{max.}$ ($CHCl_3$) 2 140, 1 965, 1 772, and 1 712 cm^{-1}; δ($CDCl_3$) 7.28 (4 H, m), 5.15 (1 H, d, *J* 5 Hz), 4.96 (1 H, d, *J* 5 Hz), 3.69 (2 H, m, CH_2-N), 3.43 (3 H, s), and 2.6—1.5 (8 H) (Found: C, 57.6; H, 4.55; N, 3.3. Calc. for $C_{21}H_{19}FeNO_6$: C, 57.7; H, 4.38; N, 3.20%).

Tricarbonyl {1—5-η-[2-*methoxy*-5-(3-*phthalimidopropyl*)-*cyclohexa*-2,4-*dienylium*]}*iron Hexafluorophosphate* (13).—Triphenylmethylium tetrafluoroborate (22 g, 67 mmol) was added to a solution of the phthalimide complex (19) (23 g, 53 mmol) in dichloromethane (100 ml) and heated under reflux for 2 h. The solvent was removed under reduced pressure and the solid residue was washed with wet ether and treated with aqueous ammonium hexafluorophosphate (11 g), followed by filtration and aqueous washing, to give the hexafluorophosphate (13) (28.0 g, 48.1 mmol, 88%), $\nu_{max.}$ (Nujol) 2 115, 2 070, 1 769, 1 724, 845, and 564 cm^{-1}; δ(CD_3CN) 7.78 (4 H, s), 6.77 (1 H, d, *J* 6 Hz, 3-H), 5.62 (1 H, d, *J* 6 Hz), 4-H), 3.8 (1 H, m, 1-H), 3.74 (3 H, s), 3.59 (2 H, t, *J* 6 Hz), 2.99 (1 H, dd, *J* 15, 6 Hz, *endo*-6-H), 2.29 (1 H, d, *J* 15 Hz, *exo*-6-H), and 1.5—1.1 (4 H) (Found: C, 43.1; H, 3.25; N, 2.4. Calc. for $C_{21}H_{18}F_6FeNO_6P$: C, 43.4; H, 3.12; N, 2.14%).

1—4-η-[5-(3-*Acetoxypropyl*)-5-(*bismethoxycarbonylmethyl*)-2-*methoxycyclohexa*-1,3-*diene*] *tricarbonyliron* (25) *and* 1—4-η-[1-(3-*Acetoxypropyl*)-5-(*bismethoxycarbonylmethyl*)-4-*methoxycyclohexa*-1,3-*diene*]*tricarbonyliron* (20).—To a stirred solution of dimethyl sodiomalonate, prepared by the addition of dimethyl malonate (38 μl) to sodium hydride (16.8 mg of 50% dispersion in mineral oil) in THF (4 ml), was added the hexafluorophosphate complex (11) (151 mg, 0.305 mmol). Aqueous work-up and ether extraction in the usual way, followed by preparative t.l.c., afforded a mixture of compounds (25) and (20) as an oil (104 mg, 0.22 mmol, 71%). Complex (25), the major product, gave $\nu_{max.}$ ($CHCl_3$) 2 065, 1 950, 1 738sh, 1 728, and 1 488 cm^{-1}; δ($CDCl_3$) 4 95 (1 H, dd, *J* 6.3, 2.4 Hz, 3-H), 3.97 (6 H, 2 × s, 2 × CO_2Me), 3.58 (3 H, s, 2-OMe), 3.43 (1 H, s, malonate), 3.35—3.20 (1 H, m, 1-H), 2.70 (1 H, d, *J* 6.3 Hz, 4-H), 2.47 (1 H, dd, *J* 15, 3 Hz, *endo*-6-H), 1.99 (3 H, s, OAc), and 1.85—1.20 (5 H); *m/e* (%) 480 (1), 452 (0.2), 424 (12), 396 (12), 349 (15), 264 (70), 221 (57), and 148 (100).

1—4-η-[5-*Bismethoxycarbonylmethyl*-2-*methoxy*-5-(3-p-*tolylsulphonyloxypropyl*)*cyclohexa*-1,3-*diene*]*tricarbonyliron* (26) *and* 1—4-η-[5-*Bismethoxycarbonyl*-4-*methoxy*-1-(3-p-*tolylsulphonyloxypropyl*)*cyclohexa*-1,3-*diene*]*tricarbonyliron* (21).—The hexafluorophosphate complex (12) (327 mg, 0.539 mmol) was treated with dimethyl sodiomalonate in the above manner and yielded a mixture of compounds (26) and (21) (1.8 : 1) as a yellow oil (288 mg, 0.486 mmol, 90%). Data for (26): $\nu_{max.}$ ($CHCl_3$) 2 045, 1 975, 1 750, 1 730, 1 600, 1 487, 1 359, and 1 175 cm^{-1}; δ(CCl_4) 7.78 (2 H, d, *J* 9 Hz), 7.33 (2 H, d, *J* 9 Hz), 5.00 (1 H, m, 3-H), 3.93 (2 H, t, *J* 6 Hz), 3.67 (6 H, s, esters), 3.57 (3 H, s), 3.35 (1 H, s), 3.28 (1 H, m, 1-H), 2.67 (4 H, Me and 4-H), and 2.0—0.8 (6 H); *m/e* (%), 420 (1) (*M* − HOTs), 406 (1), 372 (15), 320 (60), 147 (100).

1—4-η-[5-*Bismethoxycarbonylmethyl*-2-*methoxy*-5-(3-*phthalimidopropyl*)*cyclohexa*-1,3-*diene*]*tricarbonyliron* (27). Dimethyl malonate (1.4 ml, 12 mmol) was added dropwise to a stirred solution of potassium t-butoxide (1.153 g, 10.3 mmol) in THF (60 ml). After the mixture had been stirred for 15 min, the reaction vessel was opened, with back-flushing of nitrogen, whilst the complex (13) (4.98 g, 8.57 mmol) was added. Stirring was continued for 0.5 h, after which brine was added, and the product extracted in the usual way with chloroform. Recrystallisation from ether afforded the single complex (27) as a white solid (3.3 g, 5.82 mmol, 68%). An analytical sample, obtained by preparative t.l.c. had m.p. 155.5—156.5 °C, $\nu_{max.}$ ($CHCl_3$) 2 055, 1 950, 1 771, 1 755, 1 732, 1 713, and 1 490 cm^{-1}; δ($CDCl_3$) 7.80 (4 H, m), 4.98 (1 H, dd, *J* 6, 2 Hz, 3-H), 3.7—3.6 (11 H, 2 × CO_2Me, 2-OMe, CH_2N), 3.47 (1 H, s, malonate), 3.27 (1 H, m, 1-H), 2.72 (1 H, d, *J* 6 Hz, 4-H), 2.50 (1 H, dd, *J* 15, 2 Hz, *endo*-6-H), and 1.8—1.3 (5 H) (Found: C, 54.8; H, 4.65; N, 2.5. Calc. for $C_{26}H_{25}FeNO_{10}$: C, 55.0; H, 4.44; N, 2.47%).

Dimethyl [4-*Methoxy*-1-(3-*phthalimidopropyl*)*cyclohexa*-2,4-*dienyl*]*malonate* (32).—The complex (27) (0.999 g, 1.76 mmol) was added to a stirred suspension of anhydrous trimethylamine *N*-oxide (2 g, 26 mmol) in benzene (50 ml) at 50 °C. Stirring was continued for 1.5 h after which the precipitate was removed by filtration of the cooled mixture through Celite; solvent was removed from the filtrate under reduced pressure. The product was extracted into ether, washed with water, and dried (Na_2CO_3) to afford, after removal of solvent, the dienol ether (32) as a white solid which was insufficiently stable to permit recrystallisation

(635 mg, 1.49 mmol, 85%), $\nu_{max.}$ ($CHCl_3$) 1 780—1 735br, 1 655, and 1 610 cm^{-1}; δ($CDCl_3$) 7.77 (4 H, m), 5.73 (2 H, s), 4.48 (1 H, m), 3.66 and 3.62 (each 3 H, s), 3.65 (3 H, m, obscured, CH_2-N, malonate. C*H*), 3.46 (3 H, s), 2.42 (2 H, m), and 1.9—1.5 (4 H, m) (Found: C, 64.9; H, 5.9; N, 3.45. Calc. for $C_{23}H_{25}NO_7$: C, 64.63; H, 5.90; N, 3.28%).

Dimethyl 4-*Oxo*-1-(3-*phthalimidopropyl*)*cyclohex*-2-*enyl*-*malonate* (33).—A solution of the dienol ether (32) (29.6 mg, 0.07 mmol) in methanol (4 ml) was treated with a solution of oxalic acid (180 mg) in water (1 ml) and stirred at room temperature for 40 min. Extraction with ether in the usual way, followed by recrystallisation (benzene–cyclohexane) afforded the enone (33) (25.2 mg, 0.06 mmol, 88%), m.p. 128.5—131.5 °C, $\nu_{max.}$ ($CHCl_3$) 1 772, 1 757, 1 733, 1 714, and 1 675 cm^{-1}; δ($CDCl_3$) 7.85 (4 H, m), 7.13 (1 H, d, *J* 10 Hz), 5.98 (1 H, d, *J* 10 Hz), 3.90—3.40 (9 H, 2 × CO_2Me, CH_2-N, CH, malonate), and 2.6—1.7 (8 H, m) (Found: C, 63.9; H, 5.7; N, 3.55. Calc. for $C_{22}H_{23}NO_7$: C, 63.9; H, 5.61; N, 3.39%).

Dimethyl 7-*Oxo*-cis-*perhydroquinolin*-4a-*ylmalonate* (34).—The solid dienol ether derivative (32) (3.6 g, 8.4 mmol) was added to a solution of hydrazine hydrate (5 ml) in methanol (75 ml) and stirred at 40 °C for 1 h. The reaction mixture was poured into brine containing sodium hydrogen carbonate (200 ml) and thoroughly extracted with chloroform. Removal of solvent under reduced pressure from the extract gave the crude oily amine derivative quantitatively; it was unstable and was immediately hydrolysed as follows. The oil (2.5 g) was dissolved in methanol (120 ml) and stirred whilst a solution of oxalic acid (5.4 g) in water (30 ml) was added. After 1 h the pH was adjusted to 8—9 by addition of sodium hydrogen carbonate, and the mixture was stirred for a further 1 h. The reaction mixture was poured into brine and thoroughly extracted with chloroform. The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give the crude oily amine (34) (2.36 g, 8.3 mmol, 99%). An analytical sample was obtained by preparative t.l.c. (silica gel, 20%) methanol in chloroform) and gave $\nu_{max.}$ 1 760, 1 740, and 1 730 cm^{-1}; δ($CDCl_3$) (400 MHz) 4.16 (1 H, s, malonate), 3.76 (3 H, s), 3.74 (3 H, s), 3.25 (1 H, br s), 3.02 (1 H, m), 2.73—1.4 (11 H), and 1.36 (1 H, s, exch. D_2O) (Found: M^+, 283.1439. Calc. for $C_{14}H_{21}NO_5$: *M*, 283.1419).

Dimethyl 1-*Acetyl*-7-*oxo*-cis-*perhydroquinolin*-4a-*ylmalonate* (35).—The crude amine obtained above (2.36 g, 8.3 mmol) was dissolved in pyridine (20 ml) and cooled to 0 °C. Acetic anhydride (3.8 ml, 40 mmol) and dichloromethane (3 ml) were added to the mixture which was then set aside for 17 h; after this time more acetic anhydride (1 ml, 11 mmol) was added and the mixture was stirred at 30 °C for 1.5 h. The cooled solution was poured into brine, acidified to pH 3 with hydrochloric acid at 0 °C, and thoroughly extracted with chloroform. The crude product was isolated by removal of solvent under reduced pressure, and purified by flash chromatography [21] (8% methanol in ethyl acetate) to give the *N*-acetyl derivative (35) as a white solid, homogeneous on t.l.c. (1.80 g, 5.5 mmol, 67%). An analytical sample was obtained by crystallisation from ether–benzene, m.p. 104—113 °C (n.m.r. shows amide resonance); $\nu_{max.}$ ($CHCl_3$) 1 753, 1 730, and 1 640 cm^{-1}; δ($CDCl_3$, 400 MHz) 5 35 (*ca.* 0.3 H, dd, *J* 12, 5.3 Hz), 4.59 (1 H, dd, *J* 12, 2.7 Hz), 4.04 (0.7 H, s) and 3.93 (0.3 H, s, malonyl CH, rotamers), 3.85, 3.83, 3.82 and 3.80 (6 H, 4 × s, 2 × CO_2Me, rotamers), 2.08, 2.06 (3 H, 2 × s, NAc, rotamers), and 3.2—1.6 (11 H, several m, complex); *m/e* 325, 294, 282, 252, 224, and 152 (Found: C, 58.9; H, 6.9; N, 4.5. Calc. for $C_{16}H_{23}NO_6$: C, 59.07; H, 7.13; N, 4.30%).

Dimethyl 1-*Acetyl*-7,7-*ethylenedioxy*-cis-*perhydroquinolin*-4a-*ylmalonate* (36).—A mixture of the above compound (35) (1.00 g, 3.1 mmol), ethylene glycol (1.8 ml, 32 mmol), toluene-*p*-sulphonic acid (26 mg), and benzene (40 ml) was heated under reflux with a water separator for 18 h. The solvent was removed under reduced pressure and the residue was extracted into chloroform, washed with brine containing sodium hydrogen carbonate, dried (Na_2CO_3), and evaporated to yield the pure acetal (36) (1.14 g, 3.1 mmol, 100%). An analytical sample, obtained by crystallisation from ether had m.p. 105—135 °C (amide resonance), $\nu_{max.}$ (CCl_4) 1 758, 1 735, and 1 650 cm^{-1}; δ($CDCl_3$) 4.4 (1.5 H, m) and 4.0 (1.5 H, m) (C*H*-N-C*H*$_2$), 3.89 (1 H, s, malonate), 3.81 (4 H, s, acetal), 3.63 (3 H, s), 3.60 (3 H, s), 1.98 (3 H, s, NAc), and 2.2—1.1 (10 H); *m/e* (%) 369 (2), 338 (5), 326 (2), 310 (4), 238 (100), and 237 (30) (Found: C, 58.55; H, 7.35; N, 4.02%; Calc. for $C_{18}H_{27}NO_7$: C, 58.52; H, 7.37; N, 3.79%; *M*, 369.1788).

Methyl 1-*Acetyl*-7,7-*ethylenedioxy*-cis-*perhydroquinolin*-4a-*ylacetate* (37). A stirred mixture of the diester (36) (333 mg, 0.90 mmol) and sodium cyanide (100 mg, 2.0 mmol) in dimethyl sulphoxide (15 ml) was heated at 118 °C for 13 h. The cooled mixture was poured into dilute aqueous sodium hydrogen carbonate and extracted with chloroform in the usual way to give the monoester (37) (244 mg, 0.78 mmol, 87%), homogeneous on t.l.c. An analytical sample, obtained by crystallisation from ether, had m.p. 75—79 °C, $\nu_{max.}$ (CCl_4) 1 738, 1 650, 1 110, and 1 100 cm^{-1}; δ (CCl_4) 4.45 (1 H, br d, 8a-H), 3.82 (4 H, s, acetal), 3.7 (1 H, m, equatorial 2-H), 3.56 and 3.52 (3 H, each s, CO_2Me, amide tautomerism), 2.45 and 2.25 (2 H, AB_q, J_{AB} 14 Hz, CH_2CO_2Me), and 1.94 (3 H, s), 2.7—1.2 (11 H); *m/e* (%) 311 (35), 268 (35), 238 (100), and 237 (68) (Found: C, 61.6; H, 7.95; N, 4.75%; M^+, 311.1736. Calc. for $C_{16}H_{25}NO_5$: C, 61.71; H, 8.09; N, 4.50%; M^+, 311.1733).

2-(1-*Acetyl*-7,7-*ethylenedioxy*-cis-*perhydroquinolin*-4a-*yl*)*ethanol* (38).—Lithium borohydride (0.68 g, 31 mmol) was added to a solution of the monoester (37) (1.245 g, 4.00 mmol) in THF (90 ml) and the resulting mixture was stirred at room temperature for 75 h. After this time a further quantity of lithium borohydride (100 mg) was added and the mixture stirred at 38 °C for 14 h. The stirred mixture was cooled in ice whilst water was added, and the product was extracted in the usual way with chloroform. Flash chromatography [21] using 20% methanol–ethyl acetate afforded the pure alcohol (38) (752 mg) and unchanged starting material which was recycled to give more alcohol (total yield: 875 mg, 3.1 mol, 77%). An analytical sample, obtained by crystallisation from ethyl acetate–ether, had m.p. 135—137 °C, $\nu_{max.}$ (CCl_4) 3 410 br, 1 635, and 1 100 cm^{-1}; δ($CDCl_3$) 4.65 (1 H, m, 8a-H), 3.98 (4 H, s), 3.7 (2 H, t, *J* 7 Hz), 4.0—3.3 (2 H, m, 2-H_2), 2.15 (1 H, exch. D_2O), 2.10 (3 H, s), and 2.1—1.2 (12 H); *m/e* (%) 283 (1), 238 (1), 149 (5), 138 (70), 137 (70), 121 (100), and 84 (100) (Found: C, 63.35; H, 8.75; N, 5.05. Calc. for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94%).

1-*Acetyl*-7,7-*ethylenedioxy*-4a-(2-*methoxyethyl*)-cis-*perhydroquinoline* (39).—The alcohol (38) (885 mg, 3.13 mmol) was added to a suspension of sodium hydride (163 mg of 50% dispersion in mineral oil, washed with pentane) in THF (27 ml) and the resulting mixture was stirred at room temperature for 0.5 h. Methyl iodide (2 ml, 32 mmol) was added and stirring was continued for 15 h after which time aqueous

sodium hydrogen carbonate was added with ice cooling. Thorough extraction with chloroform in the usual way yielded the pure white crystalline methyl-ether (39) (926 mg, 3.12 mmol, 99.7%), m.p. 88—93 °C, $\nu_{max.}$ (CCl_4) 1 643 and 1 100 cm^{-1}; δ($CDCl_3$) 4.6 (1 H, m, 8-aH), 3.97 (4 H, s), 3.43 (2 H, t, *J* 7 Hz), 3.33 (3 H, s), 4.0—3.3 (2 H, m, obscured, 2-H_2), 2.09 (3 H, s), and 2.3—1.2 (12 H); *m/e* (%) 297 (70), 254 (100), 252 (90), 210 (60), and 99 (80%) (Found: C, 64.55; H, 9.1; N, 5.0%; M^+, 297.1939. Calc. for $C_{16}H_{27}NO_4$: C, 64.62; H, 9.15; N, 4.71 %; M^+, 297.1940).

7,7-*Ethylenedioxy*-4a-(2-*methoxyethyl*)-cis-*perhydroquinoline* (40).—The amide (39) (451 mg, 1.52 mmol) was dissolved in dimethoxyethane (14 ml) and ethanol (250 μl). This solution was added to refluxing liquid ammonia (120 ml) to give a clear solution. To the stirred solution was added calcium (440 mg, 11 mg-atom) to give a deep blue colouration. After 4 h, excess of calcium was destroyed by dropwise addition of ethanol. In some experiments a further quantity of calcium was required to maintain a deep-blue colour. The ammonia was evaporated and the residues taken up in water and chloroform; 10% aqueous hydrochloric acid was then added dropwise to the stirred mixture until pH 2 was attained. After 30 s the mixture was basified with an excess of aqueous potassium carbonate (to pH 9) and then filtered. The filtrate was extracted with chloroform to give the amine (40) as a colourless oil which could not be crystallised (96% yield), $\nu_{max.}$ ($CHCl_3$) 3 340 and 1 100 cm^{-1}; δ($CDCl_3$) 3.85 (4 H, s), 3.4 (2 H, t, *J* 7 Hz), 3.29 (3 H, s), 2.27 (1 H, exch. D_2O), and 3.2—1.1 (15 H); *m/e* (%) 255 (26), 240 (34), 224 (10), 210 (24), 198 (100), and 99 (26) (Found: M^+, 255.1830. Calc. for $C_{14}H_{25}NO_3$: *M*, 255.1834).

1-*Chloroacetyl*-7,7-*ethylenedioxy*-4a-(2-*methoxyethyl*)-cis-*perhydroquinoline* (41).—Freshly distilled chloroacetyl chloride (119 μl, 1.50 mmol) was added to a solution of pyridine (0.13 ml, 1.6 mmol) in benzene (5 ml) at 10 °C and the mixture was stirred for 10 min. The amine (40) (130 mg, 0.51 mmol) was dissolved in benzene (5 ml) and added to this mixture. After 3.25 h at 10 °C, dilute aqueous HCl was added and the product was immediately extracted with chloroform as above. Purification by preparative t.l.c. (silica gel, 20% methanol in ethyl acetate) afforded the pure white crystalline amide (41) (142 mg, 84%), m.p. 126.5—128 °C (from ether), $\nu_{max.}$ (CCl_4) 1 653 and 1 102; $\nu_{max.}$ ($CHCl_3$) 1 640 and 1 100 cm^{-1}; δ($CDCl_3$) 4.45 (1 H, m), 4.09 (2 H, m, $ClCH_2$-CO), 3.93 (4 H, s), 3.6 (1 H, m, one of 2-H), 3.39 (2 H, t, *J* 7 Hz), 3.28 (3 H, s), and 2.3—1.0 (13 H); *m/e* (%) 333 (3), 331 (10) (Cl isotopes), 296 (100), and 99 (40) (Found: C, 57.75; H, 8.05; N, 4.25. Calc. for $C_{16}H_{26}ClNO_4$: C, 57.91; H, 7.90; N, 4.22%).

1-*Chloroacetyl*-4a-(2-*methoxyethyl*)-7-*oxo*-cis-*perhydroquinoline* (42).—The acetal (41) (359 mg, 1.08 mmol) was dissolved in ethanol (4.5 ml) and 8% aqueous HCl (9 ml) was added. The stirred mixture was heated to 76 °C for 2 h, cooled, poured into brine, and extracted with chloroform to give the ketone (42) (296 mg, 1.03 mmol, 95%) as a chromatographically homogeneous colourless oil which could not be crystallised; $\nu_{max.}$ ($CHCl_3$) 1 720 and 1 648 cm^{-1}; δ($CDCl_3$) 4.6 (1 H, br, m), 4.05 (2 H, s), 3.7 (2 H, br, m), 3.41 (2 H, t, *J* 7 Hz), 3.27 (3 H, s), and 2.5—1.2 (13 H); *m/e* (%) 289 (3), 287 (8), 252 (100), 210 (15), and 83 (18) [Found: $M^+(^{37}Cl)$ = 289.1252. Calc. for $C_{14}H_{22}ClNO_3$: *M*, 289.1246].

6aα-(2-*Methoxyethyl*)-2,9-*dioxo*-9aαH, 9bαH-*perhydropyrrolo*[3,2,1-ij]*quinoline* (43).—Under rigorously dry conditions, a solution of potassium t-butoxide was prepared by dissolving potassium (258 mg) in benzene (4 ml) and t-butyl alcohol (4 ml). A portion of this solution (1.0 ml) was added *via* a syringe to a stirred solution of compound (42) (210 mg, 0.73 mmol) in benzene (20 ml) and t-butyl alcohol (10 ml). After 4.5 h the clear solution had turned slightly opaque, and t.l.c. examination indicated complete reaction. Brine (5 ml) was added, followed by a little 10% aqueous hydrochloric acid, and the organic layer was separated. The resulting aqueous fraction was thoroughly extracted with chloroform. Evaporation of the combined organic fractions, followed by preparative t.l.c. (silica gel, 20% MeOH–EtOAc) gave the pure tricyclic keto lactam (43) as a white solid (183 mg, 0.73 mmol, 100%). An analytical sample was obtained by recrystallisation from ether–benzene, m.p. 123—124.5 °C, $\nu_{max.}$ ($CHCl_3$) 1 712, 1 687, and 1 650 cm^{-1}; δ($CDCl_3$) 4.05 (1 H, br d, *J* 11 Hz), 3.53 (2 H, t, *J* 6 Hz), 3.5 (1 H, m), 3.33 (3 H, s), 3.1—2.7 (2 H, m), and 2.5—0.9 (12 H); *m/e* (%) 251 (12), 236 (1), 206 (2), 193 (34), 191 (18), and 83 (100) (Found: C, 67.05; H, 8.45; N, 5.6. Calc. for $C_{14}H_{21}NO_3$: C, 66.91; H, 8.42; N, 5.57%).

9,9-*Ethylenedioxy*-6aα-(2-*methoxyethyl*)-2-*oxo*-9aαH, 9bαH-*perhydropyrrolo*[3,2,1-ij]*quinoline* (44).—A mixture of the ketone (43) (333 mg, 1.33 mmol), ethylene glycol (0.7 ml, 12 mmol), toluene-*p*-sulphonic acid (14 mg), and benzene (35 ml) was heated under reflux with a water separator for 20 h. The solvent was removed under reduced pressure and the residue extracted with chloroform; the extracts were washed with brine containing sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated to afford the crude acetal (44) as a white solid (391 mg, 1.33 mmol, 100%). An analytical sample, obtained by recrystallisation from ether–benzene, had m.p. 136—138 °C, $\nu_{max.}$ ($CHCl_3$) 1 680 and 1 100 cm^{-1}; δ($CDCl_3$) 3.93 (4 H, br s), 4.0 (1 H, m, obscured), 3.43 (2 H, t, *J* 7 Hz), 3.31 (3 H, s), 3.19 (1 H, m, obscured), and 2.7—1.0 (14 H); *m/e* (%) 295 (15), 249 (7), 237 (5), 195 (5), and 99 (100) (Found: C, 65.25; H, 8.6; N, 4.55. Calc. for $C_{16}H_{25}NO_4$: C, 65.06; H, 8.53; N, 4.74%).

6aα-(2-*Methoxyethyl*)-9-*oxo*-9aαH, 9bαH-*perhydropyrrolo*[3,2,1-ij]*quinoline* (46).—The amide (44) (104.5 mg, 0.354 mmol) was added to a stirred suspension of lithium aluminium hydride (46 mg) in THF (10 ml) at room temperature. After 1.5 h, water and a little ether were added dropwise and the resulting clear supernatant liquid was decanted. The residue was further extracted by decantation with ether. Removal of solvent from the combined dried extracts afforded the intermediate acetal (45) [$\nu_{max.}$ ($CHCl_3$) 2 820, 2 740, 2 680 (Bohlmann bands), and 1 090 cm^{-1}] which was extremely labile and was directly converted into the ketone (46) as follows. The crude product was dissolved in ethanol (2 ml) and 9% aqueous HCl (5 ml) and heated at 90 °C for 1 h. Basification with aqueous sodium hydroxide, followed by chloroform extraction gave a yellow oil, which was purified by preparative t.l.c. to give the tricyclic amino-ketone (46) as a waxy solid (28 mg, 0.12 mmol, 33% overall), $\nu_{max.}$ ($CHCl_3$) 2 810, 2 735, 2 690 (Bohlmann bands), and 1 705 cm^{-1}; δ($CDCl_3$) 3.53 (2 H, t, *J* 7 Hz), 3.36 (3 H, s), and 3.2—1.1 (18 H); *m/e* (%) 237 (45), 236 (63), 222 (23), 207 (5), 206 (10), 192 (15), 181 (19), 179 (52), 178 (55), 154 (15), 151 (33), 150 (30), 136 (30), 135 (20), 134 (25), 123 (30), and 122 (100) (Found: M^+, 237.1737. Calc. for $C_{14}H_{23}NO_2$: *M*, 237.1729).

O-*Methylcylindrocarpinol* (4).—2-Methoxyphenylhydrazine hydrochloride (41.2 mg, 0.24 mmol) was added to a

solution of the above amine (46) (52 mg, 0.22 mmol) in ethanol and the mixture was heated under reflux for 1 h; it was then cooled and added to aqueous potassium carbonate. Extraction with chloroform gave an orange oil which was dissolved in ethyl acetate and passed through a short column of alumina to give the 2-methoxyphenylhydrazone derivative as a yellow oil, $\nu_{max.}$ ($CHCl_3$) 3 390, 2 825—2 795, 2 730, 1 604, and 1 510 cm^{-1}; δ($CDCl_3$) 7.41 (1 H, s, exch D_2O), 7.35—6.65 (4 H, m), 3.81 (3 H, s), 3.47 (2 H, t, *J* 7 Hz), 3.30 (3 H, s), and 3.2—1.0 (18 H). This compound was dissolved in glacial acetic acid (2 ml) and heated at 95 °C for 1 h. Aqueous potassium carbonate was added to basify the cooled mixture, and the crude indolenine was then extracted with dichloromethane (62 mg, 0.18 mmol). This product was not characterised, but was immediately dissolved in THF (5 ml), added to a suspension of lithium aluminium hydride (66 mg) in THF (5 ml), and the mixture stirred at room temperature for 3 h. Dilute aqueous sodium sulphate and a little ether were added dropwise with ice cooling until a precipitate was formed. The supernatant liquid was decanted, dried ($MgSO_4$), and evaporated and the resulting dark oil was purified by preparative t.l.c. (silica gel, 10% methanol–chloroform) to give pure *O*-methylcylindrocarpinol (4) as a colourless oil [29 mg, 0.085 mmol, 39% overall yield from (46)], $\nu_{max.}$ ($CHCl_3$) 3 380 (NH), 2 735, 2 820—2 800 (Bohlmann bands), 1 619, and 1 597 cm^{-1}; δ($CDCl_3$) 6.80—6.50 (3 H, m), 3.77 (3 H, s), 3.60 (1 H, br, sharpens when shaken with D_2O—see Discussion), 3.14 (3 H, s), 3.40—2.90 (4 H, m), and 2.40—1.0 (15 H, and 1 H exch D_2O); *m/e* (%) 342 (95), 314 (25), 269 (50), 182 (10), 174 (10), and 154 (100) (Found: M^+, 342.2299. Calc. for $C_{21}H_{30}N_2O_2$: *M*, 342.2307).

O,O′-*Dimethyl-limaspermine* (5).—Dry pyridine (26 μl, 0.32 mmol) and then freshly distilled propionyl chloride (29 μl, 0.33 mmol) were added to a solution of *O*-methylcylindrocarpinol (29 mg, 0.084 mmol) in benzene (2 ml). The mixture was set aside at 10 °C for 15 h, after which time water (50 μl) was added and the solvent was removed under reduced pressure. Aqueous potassium carbonate was added to the oily residue, and extraction with chloroform in the usual way afforded spectroscopically pure *O,O′*-dimethyl-limaspermine (5) as a white solid (32 mg, 0.08 mmol, 95%). An analytical sample, obtained by recrystallisation from ether-benzene, had m.p. 162—163.5 °C, $\nu_{max.}$ ($CHCl_3$) 2 845, 2 820, 2 795, 2 735 (Bohlmann bands), 1 640, 1 610, and 1 595 cm^{-1}; δ($CDCl_3$) 7.25—6.85 (3 H, m), 4.56 (1 H, dd, *J* 9.2, 6.0 Hz, 2-H), 3.93 (3 H, s), 3.23 (3 H, s), 3.70—3.0 (4 H, m), 2.80—1.0 (17 H), and 1.20 (3 H, t, *J* 7 Hz); *m/e* (%) 399 (27, *M* + 1), 298 (100), 397 (23), 370 (35), 342 (10), 341 (18), 340 (15), and 325 (35) (Found: C, 72.6; H, 8.4; N, 6.8%; M^+, 398.2584. Calc. for $C_{24}H_{34}N_2O_3$: C, 72.33; H, 8.60; N, 7.03%; M^+, 398.2569).

Demethylation of O,O′-*Dimethyl-limaspermine: Synthesis of* (±)-*Limaspermine* (3).—(i) *Using* BBr_3. Boron tribromide (12 μl, 0.124 mmol) was added to a stirred solution of *O,O′*-dimethyl-limaspermine (11.2 mg, 0.028 mmol) in dichloromethane (3 ml) at −78 °C, and the mixture was allowed to warm to room temperature. After 18 h, water was added and the mixture allowed to stand for 0.5 h. The product was extracted with chloroform and subjected to preparative t.l.c.. to yield recovered *O,O′*-dimethyl-limaspermine (*ca* 6 mg) and limaspermine monomethyl ether (*ca*. 2—3 mg) the mass spectrum of which was consistent with structure (6), *m/e* (%) 384 (25%), 356 (15), and 140 100) (see Scheme 2).

(ii) *Using* Me_3SiI: Iodotrimethylsilane (24 μl, 0.17 mmol) was added to a stirred solution of *O,O′*-dimethyl-limaspermine (12 mg, 0.030 mmol) and pyridine (10 μl) in chloroform (2 ml) and the mixture was heated at 60 °C for 21 h. Methanol was added and the solvent was removed under reduced pressure to leave an oil; this was subjected to preparative t.l.c. to give recovered starting material (5.6 mg) and (±)-limaspermine (3) (2—3 mg) which showed i.r., n.m.r., and mass spectra consistent with data reported [16] for the natural product and superimposable upon spectra obtained in our laboratory for a sample of authentic material provided by Professor M. Pinar. With the passage of time both materials formed a single, unidentified impurity.

Tricarbonyl-[1—4-η-(5-*ethyl*-4-*methoxy*-5-*methoxycarbonylmethylcyclohexa*-1,3-*diene*)]*iron* (29).—The crystalline diester complex (28) [19] (2.04 g) and anhydrous tetramethylammonium acetate (5.5 g) were stirred under argon in HMPA (30 ml) at 95 °C for 12 h. The cooled mixture was poured into dilute hydrochloric acid and the product extracted with ether in the usual way. The crude material so obtained was washed through alumina with ether, to remove contaminant $Fe_3(CO)_{12}$ arising from minor decomposition, and chromatographed (silica gel, 10% EtOAc–benzene) to give the pure monoester (29) as a yellow oil (1.0 g, 57%), $\nu_{max.}$ ($CHCl_3$) 2 045, 1 973, 1 727, and 1 487 cm^{-1}; δ($CDCl_3$) 5.06 (1 H, dd, *J* 7, 2.5 Hz), 3.64 (3 H, s), 3.30 (1 H, m), 2.55 (1 H, d, *J* 7 Hz), 2.20 (2 H, s), 1.91 (1 H, dd, *J* 15, 3 Hz), 1.55 (1 H, dd, *J* 15, 3 Hz), 1.43 (2 H, q, *J* 7 Hz), 0.81 (3 H, t, *J* 7 Hz); *m/e* (%) 350 (5), 322 (15), 294 (10), 266 (40), 251 (10), 238 (10), 223 (8), and 192 (100) (Found: C, 51.8; H, 5.45. Calc. for $C_{15}H_{18}FeO_6$: C, 51.45; H, 5.18%).

Tricarbonyl-{1—4-η-[5-*ethyl*-5-(2-*hydroxyethyl*)-2-*methoxycyclohexa*-1,3-*diene*]}*iron* (30).—To a stirred solution of the monoester (29) (757 mg) in THF (10 ml) at 0 °C under N_2 was added dropwise di-isobutylaluminium hydride (6 ml of a 1 M solution in hexane). The mixture was stirred overnight the temperature being allowed to rise to ambient; the mixture was worked up by dropwise addition of methanol (2 ml), water (2 ml), and then ether (50 ml). The filtered solution was dried ($MgSO_4$), evaporated, and chromatographed to give the pure alcohol (30) as a yellow oil (611 mg, 88%), $\nu_{max.}$ ($CHCl_3$) 3 620, 3 450, 2 050, 1 975, and 1 488 cm^{-1}; δ($CDCl_3$) 5.04 (1 H, dd, *J* 7, 2.5 Hz), 3.61 (3 H, s), 3.57 (2 H, t, *J* 7.5 Hz), 3.27 (1 H, m), 2.46 (1 H, d, *J* 7 Hz), 1.8—1.1 (6 H, m, and 1 H exch. D_2O), and 0.75 (3 H, t, *J* 7 Hz); *m/e* (%) 322 (5), 294 (20), 266 (5), 238 (30), and 192 (100) (Found: C, 52.35; H, 5.45. Calc. for $C_{14}H_{18}FeO_5$: C, 52.20; H, 5.63%).

Tricarbonyl-{1—4-η-[5-(2-*cyanoethyl*)-5-*ethyl*-4-*methoxycyclohexa*-1,3-*diene*]}*iron* (31).—The primary alcohol (30) was converted into its toluene-*p*-sulphonate as follows. The alcohol (600 mg) was stirred at 0 °C in dry pyridine (5 ml) whilst toluene-*p*-sulphonyl chloride (500 mg) was added. The mixture was set aside in the refrigerator for 13 h and then stirred at 0 °C whilst water (0.2 ml) was added. After being stirred for a further 0.5 h, the mixture was poured into ice-cold dilute hydrochloric acid and extracted with ether in the usual way to afford the tosylate which crystallised on trituration with pentane, m.p. 45—46.5 °C (0.88 g, 100%), $\nu_{max.}$ ($CHCl_3$) 2 055, 1 980, 1 605, 1 490, 1 365, 1 193, and 1 180 cm^{-1}; δ($CDCl_3$) 7.75 (2 H, d, *J* 8 Hz), 7.31 (2 H, d, *J* 8 Hz), 4.97 (1 H, dd, *J* 7, 2.5 Hz), 3.96 (2 H, t, *J* 7.5 Hz), 3.60 (3 H, s), 3.24 (1 H, m), 2.40 (3 H, s), 2.30 (1 H, d, *J* 7 Hz), 1.7—1.0 (6 H), and 0.65 (3 H, t, *J* 7 Hz); *m/e* (%)

476 (5), 448 (15), 420 (5), and 392 (100) (Found: C, 52.9; H, 5.1. Calc. for $C_{21}H_{24}FeO_7S$: C, 52.95; H, 5.08%). The tosylate (590 mg) and sodium cyanide (75 mg) were stirred under argon atmosphere in HMPA at 60 °C for 2.5 h. The cooled mixture was poured into dilute hydrochloric acid and extracted with ether to afford the pure crystalline nitrile (31), m.p. 72—73 °C, after trituration with ice-cold pentane (0.39 g, 93%), $\nu_{max.}$ ($CHCl_3$) 2 260, 2 055, 1 980, and 1 489 cm^{-1}; δ($CDCl_3$) 5.08 (1 H, dd, *J* 6.5, 2.5 Hz), 3.63 (3 H, s), 3.29 (1 H, m), 2.35 (1 H, d, *J* 6.5 Hz), 2.2 (2 H, m), 1.8—1.3 (4 H, m), 1.29 (2 H, q, *J* 7 Hz), and 0.73 (3 H, t, *J* 7 Hz); *m/e* (%) 331 (10), 303 (20), 275 (10), and 247 (100) (Found: C, 54.3; H, 5.3; N, 4.15. Calc. for $C_{15}H_{17}FeNO_4$: C, 54.41; H, 5.17; N, 4.23%).

3-(1-*Ethyl*-4-*methoxycyclohexa*-2,4-*dienyl*)*propionitrile* (51).—The complex (31) from above (390 mg) was stirred in benzene (15 ml) at 40—50 °C with anhydrous trimethylamine *N*-oxide (1.0 g) for 2 h. The mixture was filtered through Celite, the pad washed with ether, and the combined organic extracts were washed with 5% brine, dried (Na_2CO_3), and evaporated to give the crude, sensitive, dienol ether (51) as a colourless oil which was not further purified (180 mg); $\nu_{max.}$ ($CHCl_3$) 2 260, 1 660, and 1 612 cm^{-1}. For characterisation, a sample of this material was hydrolysed to the corresponding cyclohexenone derivative, as follows. The dienol ether (51) (100 mg) was dissolved in methanol (5 ml) and treated with oxalic acid (300 mg) in water (1.5 ml) at room temperature for 40 min. Aqueous sodium hydrogen carbonate work-up, followed by ether extraction, and preparative t.l.c. (silica gel, 20% ethyl acetate–benzene) afforded 3-(1-ethyl-4-oxocyclohex-2-enyl)-propionitrile as a colourless oil (78 mg, 85%), $\nu_{max.}$ (CCl_4) 2 250, and 1 668 cm^{-1}; δ($CDCl_3$) 6.63 (1 H, d, *J* 10 Hz), 5.91 (1 H, d, *J* 10 Hz), 2.7—1.4 (10 H), and 0.97 (3 H, t, *J* 7 Hz); *m/e* (%) 177 (20), 149 (27), 135 (42), 109 (75), and 107 (100) (Found: M^+, 177.1149. Calc. for $C_{11}H_{15}NO$: *M*, 177.1153).

4a-*Ethyl*-7-*oxo*-cis-*perhydroquinoline* (8).—The crude dienol ether (51) obtained above (78 mg) in dry ether (2 ml) was added to a stirred suspension of lithium aluminium hydride (25 mg) in dry ether (2 ml) at 0 °C. The mixture was stirred for 45 min during which time it was allowed to warm to room temperature; it was then worked up by the addition of a few drops of water. Decantation of the ether layer, followed by evaporation under reduced pressure, afforded the crude, sensitive amine (52) as a colourless oil (78 mg), $\nu_{max.}$ (CCl_4) 3 400—3 200, 1 660, and 1 612 cm^{-1}; δ($CDCl_3$) 5.5 (2 H, m), 4.35 (1 H, br s), 3.57 (3 H, s), 2.6 (2 H, br), 2.17 (2 H), 1.8—1.25 (8 H), and 0.85 (3 H, t, *J* 7 Hz). The crude product was stirred in methanol (5 ml) at room temperature whilst oxalic acid (300 mg) in water (1.5 ml) was added. Stirring was continued for 1 h after which the mixture was made alkaline by addition of aqueous sodium hydrogen carbonate. After 10 min, the mixture was poured into aqueous sodium carbonate and the product extracted thoroughly with chloroform and purified by preparative t.l.c. (silica gel, 15% MeOH–$CHCl_3$) to give the perhydroquinoline (8) (40 mg, 61%), m.p. 46—48 °C (lit.,[3] 47—50 °C). The compound gave a single *N*-acetyl derivative on treatment with acetic anhydride–pyridine, $\nu_{max.}$ ($CHCl_3$), 1 712 and 1 627 cm^{-1}; δ($CDCl_3$) 4.67 (1 H, br t, *J* 12 Hz), 3.7 (1 H, br d, *J* 14 Hz), 3.2—1.2 (13 H), 2.07 (3 H, s), and 0.80 (3 H, t, *J* 7 Hz) (Found: C, 70.45; H, 9.35; N, 6.65. Calc. for $C_{13}H_{21}NO_2$: C, 70.23; H, 9.48; N, 6.27%).

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