Synthetic Approaches to C-18 Oxygenated Aspidosperma Alkaloids *via* Organoiron Complexes [1]

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An improved synthesis of the (±)-limaspermine intermediate (3b), starting from tricarbonyl-1—4-η-[4-isopropoxy-1-(2-methoxyethyl)cyclohexa-1,3-diene]iron (2c), is described.

Aspidosperma alkaloids, of general structure (1) are now a well-known class of natural products.[2] Whilst aspidospermine (1a), one of the simpler alkaloids, has been the object of a number of synthetic endeavours,[3] only scant attention [4] has been given to the somewhat greater challenge associated with the preparation of those compounds bearing oxygen functionality at C-18, typified by cylindrocarpinol (1b) and limaspermine (1c). We recently reported [5] a total synthesis of (±)-limaspermine commencing with the cyclohexadiene-$Fe(CO)_3$ complex (2a) which was converted in 16 steps into the *cis*-decahydroquinoline derivative (3b). This compound was then successfully converted into limaspermine, *via* the tricyclic intermediate (4), using standard methodology. Whilst this synthesis was archetypal for the application of functionalised tricarbonylcyclohexadieneiron complexes to target-orientated synthesis of non-trivial natural products, there being five rings and four centres of asymmetry in the target molecules, it was nevertheless inefficient in terms of the number of steps involved, and was by no means competitive with the conventional synthesis of (±)-*N*,*O*-diacetylcyclindrocarpinol described by Saxton's group.[4] Consequently, we decided to investigate a shorter route to the intermediate (3a), based on methodology developed in our laboratories [6] for the conversion of complex (2b) into Stork's aspidospermine intermediate (3c). The results of these studies, in which we employ a complex as the synthetic equivalent of the functionalised 4-substituted cyclohexenone-γ-cation (5), are presented in the present paper. The route which we have developed is now of comparable length to the more conventional synthesis.

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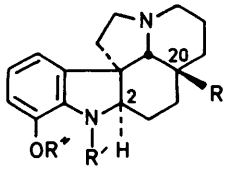
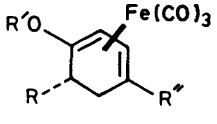
Results and Discussion

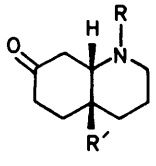
Our plan was to utilise a tricarbonylcyclohexadienyliumiron complex of structure (6) in which the protected hydroxyethyl group was to become the angular C-20 functionalised substituent of limaspermine. Since our previous synthesis [5] proceeded *via* the methyl ether (3b) we decided to make use of this form of protection in the present study. Also, we have previously shown [7] that a 4-methoxy-substituent, as in (6a), is a rather poor directing group in the nucleophile addition step, giving mixtures of compounds arising from addition at C-1 and C-5, but this problem is largely overcome by employing a 4-isopropoxy group.[8] Our immediate target therefore became the dienylium complex (6b). The appropriate aromatic starting material (7a) was readily prepared from 4-hydroxyphenylacetic acid. Reduction of (7a) with diborane proceeded smoothly to give the alcohol (7b), which was converted into the methyl ether (7c) in excellent overall yield. Birch reduction of (7c) afforded the diene (8), and to avoid the formation of mixtures during the complexation step this material was (partially) conjugated using a catalytic amount of toluene-*p*-sulphonic acid at 80 °C. Thus was obtained a mixture of 1,3- and 1,4-dienes, in which the former was preponderant. The complex (2c) was prepared in satisfactory yield by either of two



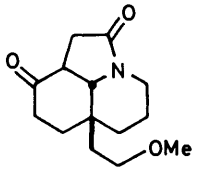
(1) a; R = Et, R′ = COMe, R″ = Me
b; R = CH_2CH_2OH, R′ = H, R″ = Me
c; R = CH_2CH_2OH, R′ = COEt, R″ = H



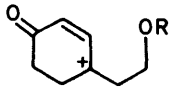
(2) a; R = H, R′ = Me, R″ = $CH_2CH_2CO_2Me$
b; R = H, R′ = Me, R″ = Et
c; R = H, R′ = Pr^i, R″ = CH_2CH_2OMe
d; R = $CH(CO{\cdot}SEt)_2$, R′ = Pr^i, R″ = CH_2CH_2OMe
e; R = $CH(CO_2Me)_2$, R′ = Pr^i, R″ = CH_2CH_2OMe



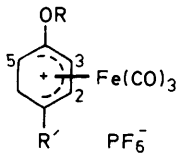
(3) a; R = H, R′ = CH_2CH_2OMe
b; R = $CO{\cdot}CH_2Cl$, R′ = CH_2CH_2OMe
c; R = H, R′ = Et



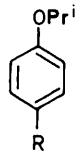
(4)



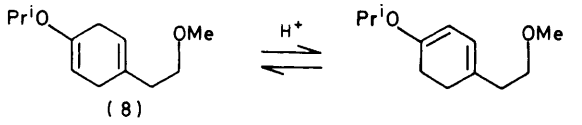
(5)



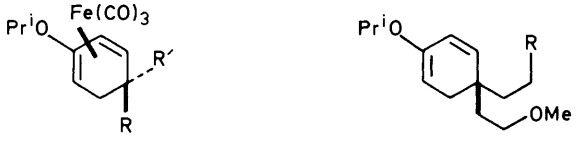
(6) a ; R = Me, R′ = CH_2CH_2OMe
b ; R = Pr^i, R′ = CH_2CH_2OMe
c ; R = Pr^i, R′ = Et
d ; R = Pr^i, R′ = CH_2CH_2OAc



(7) a ; R = CH_2CO_2H
b ; R = CH_2CH_2OH
c ; R = CH_2CH_2OMe



(8)



(9) a ; R = Et, R′ = $CH(CO{\cdot}SEt)_2$
b ; R = Et, R′ = CH_2CH_2OH
c ; R = CH_2CH_2OMe, R′ = $CH(CO_2Me)_2$
d ; R = CH_2CH_2OMe, R′ = CH_2CO_2Me
e ; R = CH_2CH_2OMe, R′ = CH_2CH_2OH
f ; R = CH_2CH_2OMe, R′ = CH_2CH_2OTs
g ; R = CH_2CH_2OMe, R′ = CH_2CH_2CN

(10) a ; R = CN
b ; R = CH_2NH_2

methods: treatment with $Fe(CO)_5$ in di-n-butyl ether at reflux, or reaction with $Fe_2(CO)_9$ in acetone at 30 °C. Treatment of (2c) with triphenylmethylium hexafluorophosphate under the usual conditions led to regiospecific hydride abstraction, despite the presence of the relatively bulky isopropoxy group, to give the desired complex (6b) in good yield. With this crystalline material now in hand we were in a position to examine its reaction with a nucleophile destined to form the D ring of limaspermine. In the absence of any reagent which, to our knowledge, would lead to successful incorporation at C-1 of a terminally functionalised three-carbon atom fragment, it was necessary at this stage to employ our previously devised strategy,[6] introducing a C_2 nucleophile which is homologated with concomitant introduction of the necessary terminal nitrogen atom. Our requirement was therefore to effect the introduction of a nucleophile which could be converted into a hydroxyethyl group. The most obvious choice for this is in fact *S,S′*-diethyl dithiomalonate which is known to lead directly to a hydroxyethyl group on treatment with Raney nickel.[9] Whilst we have previously shown [8] that the related complex (6c) reacts with *S,S′*-diethyl potassiomalonate predominantly at C-1 to give good yields (*ca.* 80%) of the complex (9a) which can be converted in one step into (9b), we were disappointed to learn that complex (6b) gave exclusively the wrong adduct (2d) in this reaction. This profound effect of a relatively remote methyl ether grouping on the reactivity of the dienylium complex is indeed puzzling. We have no evidence to suggest interaction between the ether oxygen and the dienylium system, and we have not pursued the matter further at this stage. Reaction of (6b) with dimethyl sodiomalonate occurred smoothly on a multigram scale to give, after flash chromatography,[10] 67% isolated yield of pure desired complex (9c) and 27% yield of pure undesired complex (2e). Subsequent to this work we found [8,11] that use of dimethyl *potassio*malonate generally gives better regioselectivity under the same conditions, and indeed reaction of (6b) with this nucleophile gave a 9 : 1 mixture of (9c) and (2e) in 78% yield. With the complex (9c) now in hand in reasonable quantities the stage was set for its elaboration to the limaspermine intermediate (3b). Demethoxycarbonylation of (9c) afforded cleanly the monoester (9d) which was reduced in high yield to the alcohol (9e). This was converted into the tosylate (9f) which was then homologated to the nitrile (9g) by treatment with sodium cyanide in HMPA at 55 °C. The nitrile (9g) was thus available in 45% overall yield from the diester (9c). The remaining steps were straightforward. Removal of $Fe(CO)_3$ was accomplished by the now standard method, anhydrous Me_3NO in benzene,[12] to afford the dienol ether (10a) which, being somewhat prone to enol ether hydrolysis, was reduced directly with lithium aluminium hydride to the primary amine (10b). This compound was hydrolysed with concomitant Michael cyclisation to give the *cis*-decahydroquinoline derivative (3a), which was converted into the target *N*-chloroacetyl derivative (3b) using the standard procedure. It may be noted that the hydrolytic instability of the dienol ethers (10a) and (10b) precluded their purification by the usual methods, and crude materials were carried through to the intermediate (3a). In fact, this material was obtained in a state of high purity, as judged by t.l.c. and spectroscopic means. Also, whilst (3a) could be purified for characterisation purposes it was found that losses occurred on chromatography, so that for the purpose of procuring good yields of the chloroacetyl derivative (3b) it was more expedient to convert crude (3a) into (3b) and then purify the latter compound, without losses. Once in hand, the intermediate (3b) proved to be identical in every respect with the compound previously prepared in our laboratory and converted into (±)-limaspermine.[5] By the present route compound (3b) is available in 10 steps and 15% overall yield from the complex (2c), a significant improvement over our earlier synthesis.

A considerable advantage to the use of diene-$Fe(CO)_3$ complexes of type (2c) in the synthesis of natural products lies in the fact that attachment of the tricarbonyliron group to the diene introduces asymmetry into the molecule. Birch and coworkers have shown that similar complexes may be prepared in optically active form by a process of asymmetric induction [13] so that there exists now the real potential for asymmetric synthesis of a wide range of fairly complex natural products.[14]

It may also be noted that the above synthesis offers considerable flexibility with regard to the primary alcohol protecting group employed. Whilst we chose the methyl ether in this work in order to obtain our earlier intermediate (3b) and thereby achieve a formal synthesis of limaspermine, we could in fact use a wide range of protection. Indeed, we have shown during another project that the *acetate* (6d) also reacts with dimethyl potassiomalonate with high regioselectivity for the C-1 terminus,[15] thus demonstrating the flexibility of our approach.

Experimental

I.r. spectra were determined with a Perkin-Elmer 577, mass spectra with A.E.I. MS 12 (organometallics) or MS 30 (organic compounds), and ^1H n.m.r. spectra with Varian EM 390 or Brucker WH 400 (400 MHz) machines. M.p.s are uncorrected. All chromatographic operations and reactions with iron complexes were conducted under an atmosphere of nitrogen or argon. Tetrahydrofuran (THF) and diethyl ether (ether) were freshly distilled from sodium benzophenone under nitrogen; pyridine was distilled from barium oxide.

p-*Isopropoxyphenylacetic Acid* (7a).—*p*-Hydroxyphenylacetic acid (29 g, 0.19 mol) was dissolved in isopropyl alcohol

(150 ml) and isopropyl bromide (37 ml, 0.39 mol) and added to 2M-aqueous sodium hydroxide (220 ml). The bilayer was heated on a steam-bath under reflux for 30 h. The reaction mixture was acidified and extracted with ether in the usual way to give a red solid which was recrystallized from toluene–petroleum to give pure white crystalline *p*-isopropoxyphenylacetic acid (23 g, 62%), m.p. 63—65 °C (lit.,[16] m.p. 87 °C); $\nu_{max.}$ (Nujol mull) 3 500—2 400, 1 700, 1 610, and 1 591 cm^{-1}; δ ($CDCl_3$) 10.3 (1 H, s, exchanges in D_2O, CO_2H), 7.10 (2 H, d, *J* 8 Hz, 2 × ArH), 6.75 (2 H, d, *J* 8 Hz, 2 × ArH), 4.50 (1 H, hept, *J* 6 Hz, $CHMe_2$), 3.60 (2 H, s, CH_2), and 1.40 (6 H, d, *J* 6 Hz, 2 × Me) (Found: C, 67.7; H, 7.2. Calc. for $C_{11}H_{14}O_3$: C, 68.0; H, 7.3%), *m/z* (%) 194 (16), 152 (17), 107 (100), and 77 (39).

2-(p-*Isopropoxyphenyl*)*ethanol* (7b).—Borane in THF (160 ml of a 1M-solution, 0.16 mol) was added during 1 h with occasional ice cooling to a solution of the acid (7a) (22.8 g, 0.12 mol) in THF (200 ml). The mixture was stirred for a further 2 h and then water (100 ml) was added dropwise; after hydrolysis the aqueous fraction was acidified and extracted with ether. The crude oily product was purified by flash chromatography (30% ethyl acetate in petroleum) to give 2-(*p*-isopropoxyphenyl)ethanol as a colourless oil which was homogeneous on t.l.c. (21.2 g, 100%). An analytically pure sample was obtained by distillation (114—115 °C/0.4 mmHg), $\nu_{max.}$ (liquid film) 3 550—3 050, 1 608, and 1 590 cm^{-1}; δ ($CDCl_3$) 7.17 (2 H, d, *J* 9 Hz, 2 × ArH), 6.82 (2 H, d, *J* 9 Hz, 2 × ArH), 4.50 (1 H, hept, *J* 6 Hz, $CHMe_2$), 3.81 (2 H, t, *J* 6 Hz, CH_2OH), 2.78 (2 H, t, *J* 6 Hz, CH_2), 1.80br (1 H, s, CH_2OH), and 1.32 (6 H, d, *J* 6 Hz, 2 × Me); *m/z* (%) 180 (12), 138 (17), and 107 (100) (Found: C, 72.9; H, 8.9. Calc. for $C_{11}H_{16}O_2$: C, 73.3; H, 8.95%).

2-(p-*Isopropoxyphenyl*)*ethyl Methyl Ether* (7c).—The alcohol (7b) (15.1 g, 83.9 mmol) was dissolved in THF (250 ml) and added to sodium hydride (4.7 g of a 50% dispersion in oil, washed with dry pentane) and stirred with ice cooling for 0.5 h. Methyl iodide (45 ml) was added slowly to the stirred suspension with ice cooling. After 4 h more sodium hydride (1.0 g, 50% dispersion) was added. After 19 h the reaction mixture had attained room temperature and a further addition of methyl iodide (10 ml) was made. After 19.5 h water was added dropwise and the aqueous fraction was extracted with ether to give a crude product which was purified by flash chromatography (10% ethyl acetate in petroleum) to give 2-(*p*-isopropoxyphenyl)ethyl methyl ether as a colourless oil which was homogeneous on t.l.c. (15.0 g, 92%). An analytically pure sample was obtained by distillation (92—95 °C/0.5 mmHg), $\nu_{max.}$ (liquid film) 1 608 and 1 590 cm^{-1}; δ ($CDCl_3$) 7.12 (2 H, d, *J* 9 Hz, 2 × ArH), 6.78 (2 H, d, *J* 9 Hz, 2 × ArH), 4.47 (1 H, hept., *J* 6 Hz, $CHMe_2$), 3.52 (2 H, t, *J* 7 Hz, CH_2OMe), 3.33 (3 H, s, OMe), 2.78 (2 H, t, *J* 7 Hz, CH_2), and 1.31 (6 H, d, *J* 6 Hz, 2 × Me); *m/z* (%) 194 (12), 162 (4), 152 (14), 120 (18), and 107 (100) (Found: C, 74.1; H, 9.5. Calc. for $C_{12}H_{18}O_2$: C, 74.2; H, 9.3%).

4-*Isopropoxy*-1-(2-*methoxyethyl*)*cyclohexa*-1,4-*diene* (8).—Liquid ammonia (500 ml) was added to a solution of the aromatic compound (7c) (15 g) in THF (100 ml) and ethanol (30 ml). Lithium metal (10 g) was added in portions during 0.5 h with vigorous stirring and the reaction mixture turned deep blue. After 6.5 h methanol (100 ml) was added dropwise to discharge the blue colour and the ammonia was allowed to evaporate. The white residue was dissolved in water and extracted with ether to give 4-isopropoxy-1-(2-methoxyethyl-cyclohexa-1,4-diene as a colourless oil (14 g, 93%), δ ($CDCl_3$) 5.37br (1 H, s, vinyl-H), 4.60br (1 H, s, vinyl-H), 4.30 (1 H, hept, *J* 6 Hz, $CHMe_2$), 3.50 (2 H, t, *J* 7 Hz, CH_2OMe), 3.41 (3 H, s, OMe), 3.72br (4 H, s, 2 × allyl CH_2), 2.30br (2 H, t, *J* 7 Hz, CH_2CH_2OMe), and 1.36 (6 H, d, *J* 6 Hz, 2 × Me); $\nu_{max.}$ (liquid film) 1 690 and 1 665 cm^{-1}; *m/z* (%) 196 (6), 154 (10), and 107 (100).

Tricarbonyl{1—4-η-4-*isopropoxy*-[1-(2-*methoxyethyl*)-*cyclohexa*-1,3-*diene*]}*iron* (2c).—*Method A. With pentacarbonyliron.* The unconjugated diene (8) was distilled (87—90 °C/0.7 mmHg) to effect partial conjugation of the double bonds. This mixture of 1,4- and 1,3-dienes (32 g) was dissolved in di-n-butyl ether (300 ml) and pentacarbonyliron (90 ml) and heated under reflux in an oil-bath at 125—135 °C with efficient stirring. After 26 h the reaction mixture was cooled, filtered through Celite, and the solvent, together with unchanged pentacarbonyliron, was removed under reduced pressure. The crude product (37 g) contained the unchanged 1,4-diene (8), which was recovered by distillation and repeated flash chromatography (toluene then 8% ethyl acetate in hexane) to give pure (8) (13.7 g) and the desired complex (2c) (10.4 g, 19%. Yield based on recovered starting material 31%).

Method B. With nonacarbonyldi-iron. The unconjugated diene (1.3 g) from the Birch reduction was treated with a catalytic amount of anhydrous toluene-*p*-sulphonic acid under argon at 80 °C for 0.5 h. Sodium hydrogen carbonate solution was added and the product was extracted with ether to give a mixture of the substituted cyclohexa-1,3-diene and cyclohexa-1,4-diene (^1H n.m.r. indicates *ca.* 4 : 1 ratio).

This mixture of dienes was dissolved in acetone (25 ml) and added to nonacarbonyldi-iron (4.2 g). The suspension was stirred at 30 °C for 5.5 h and then filtered through a column of alumina to remove decomposition products. The resulting crude product was further purified by flash chromatography (8% ethyl acetate in petroleum) to give (2c) (1.1 g, 50%) as a yellow oil which would not crystallise but was homogeneous on t.l.c.; $\nu_{max.}$ (liquid film) 2 050 and 1 960 cm^{-1}; δ ($CDCl_3$) 5.07 (1 H, d, *J* 5 Hz, 3-H), 4.93 (1 H, d, *J* 5 Hz, 2-H), 4.07 (1 H, hept, *J* 6 Hz, $CHMe_2$), 3.45 (2 H, m, CH_2OMe), 3.33 (3 H, s, OMe), 2.5—1.5 (6 H, m), 1.17 (3 H, d, *J* 6 Hz, Me), 1.14 (3 H, d, *J* 6 Hz, Me); *m/z* (%) 336 (1), 308 (5), 280 (50), and 250 (100) (Found: C, 54.1; H, 6.1. Calc. for $C_{15}H_{20}FeO_5$: C, 53.6; H, 6.0%).

Tricarbonyl{1—5-η-[4-*isopropoxy*-1-(2-*methoxyethylcyclohexadienylium*]}*iron Hexafluorophosphate* (6b).—Triphenylmethylium hexafluorophosphate (1.40 g, 3.6 mmol) was added to a solution of the complex (2c) (1.01 g, 3.0 mmol), in dichloromethane (100 ml) and the mixture was heated under reflux for 20 min. Water (1 ml) was added and the mixture stirred for a further 20 min at room temperature to hydrolyse unchanged triphenylmethylium hexafluorophosphate. The dried solution was evaporated to give a crude product which was recrystallized (dichloromethane–ether) to give analytically pure (6b) (1.23 g, 85%), $\nu_{max.}$ (Nujol mull) 2 100, 2 050, and 845 cm^{-1}; δ (CD_3CN) 6.80 (1 H, dd, *J* 3, 6 Hz, 3-H), 5.68 (1 H, d, *J* 6 Hz, 2-H), 4.60 (1 H, hept, *J* 6 Hz, $CHMe_2$), 3.90 (1 H, m, 5-H), 3.47 (2 H, t, *J* 6 Hz, CH_2OMe), 3.29 (3 H, s, OMe), 3.02 (1 H, dd, *J* 16, 7 Hz, *endo*-6-H), 2.5—2.1 (3 H, m, *exo*-6-H and CH_2), 1.33 (3 H, d, *J* 6 Hz, Me), 1.28 (3 H, d, *J* 6 Hz, Me) (Found: C, 37.67; H, 3.76. Calc. for $C_{15}H_{19}F_6FeO_5P$: C, 37.53; H, 3.99%).

Tricarbonyl{2—5-η-[S,S′-*diethyl* 2-*isopropoxy*-5-(2-*methoxyethyl*)*cyclohexa*-2,4-*dienyldithiomalonate*]}*iron* (2d).—The salt (6b) (504 mg, 1.05 mmol) was treated with *S,S*-diethyl potassiodithiomalonate [prepared from potassium t-butoxide (132 mg, 1.18 mmol) and *S,S*-diethyl dithiomalonate (0.24 ml, 1.44 mmol)] in THF (30 ml) at room temperature. After

being stirred for 20 min the reaction mixture was poured into brine and the product extracted with ethyl acetate.

The crude product was purified by flash chromatography [10% ethyl acetate in light petroleum (b.p. 60—80 °C)] to give the adduct (2d) (414 mg, 75%), the only organometallic compound isolated; $\nu_{max.}$ (liquid film) 2 045, 1 965, 1 697, and 1 687 cm^{-1}; δ ($CDCl_3$) 5.15 (1 H, d, *J* 5 Hz, 3-H), 4.86 (1 H, d, *J* 5 Hz, 4-H), 3.97 [1 H, d, *J* 5 Hz, C*H*(COSEt)$_2$], 4.0 (1 H, hept, *J* 7 Hz, $CHMe_2$), 3.44 (2 H, t, *J* 7 Hz, CH_2OMe), 3.34 (3 H, s, OMe), 3.2—2.7 (5 H, m, 2 × SCH_2 and *endo*-1-H), 2.2—1.7 (4 H, m), 1.4—1.1 (12 H, m, 4 × Me); *m/z* (%) 526 (2), 498 (2), 470 (1), 442 (40), 386 (100), 250 (60), and 194 (67).

Tricarbonyl{2—5-η-[*dimethyl* 4-*isopropoxy*-1-(2-*methoxyethyl*)*cyclohexa*-2,4-*dienylmalonate*]}*iron*, (9c) *and Tricarbonyl*{2—5-η-[*dimethyl* 2-*isopropoxy*-5-(2-*methoxyethyl*)*cyclohexa*-2,4-*dienylmalonate*]}*iron* (2e).—The salt (6b) (7.00 g, 14.6 mmol) was added to dimethyl sodiomalonate [generated from sodium hydride (1.0 g of a 50% dispersion in oil, washed with hexane, 21 mmol) and dimethyl malonate (2.38 ml, 21 mmol)] in THF (100 ml). After being stirred with ice cooling for 0.5 h the reaction mixture was poured into brine and the product extracted with ether. The two regioisomers were separated by flash chromatography [10% ethyl acetate in light petroleum (b.p. 60—80 °C)] to give (9c) (4.55 g, 67%) and (2e) (1.83 g, 27%). Analytically pure samples were obtained by recrystallisation from pentane: (9c), m.p. 52—53.5 °C. $\nu_{max.}$ (Nujol mull) 2 050, 1 985, 1 755, 1 735, and 1 480 cm^{-1}; δ ($CDCl_3$) 4.98 (1 H, dd, *J* 7, 2 Hz, 3-H), 4.22 (1 H, hept, *J* 6 Hz, $CHMe_2$), 3.74 (3 H, s, CO_2Me), 3.73 (3 H, s, CO_2Me), 3.63 [1 H, s, $CH(CO_2Me)_2$], 3.38 (2 H, t, *J* 6 Hz, CH_2OMe), 3.29 (1 H, obscured m, 5-H), 3.26 (3 H, s, OMe), 2.83 (1 H, d, *J* 7 Hz, 2-H), 2.56 (1 H, dd, *J* 16, 3 Hz, *endo*-6-H), 1.84 (2 H, t, *J* 6 Hz, CH_2), 1.63 (1 H, dd, *J* 16, 3 Hz, *exo*-6-H), 1.36 (3 H, d, *J* 6 Hz, Me), and 1.25 (3 H, d, *J* 6 Hz, Me); *m/z* (%) 466 (1), 438 (1), 410 (1), 382 (19), 322 (10), 250 (19), 194 (13), and 107 (100) (Found: C, 51.6; H, 5.6. Calc. for $C_{20}H_{26}FeO_9$: C, 51.5; H, 5.6%); (2e) m.p. 84—86 °C, $\nu_{max.}$ ($CHCl_3$) 2 040, 1 965, and 1 770—1 730 cm^{-1}; δ ($CDCl_3$) 5.13 (1 H, d, *J* 5 Hz, 3-H), 4.94 (1 H, d, *J* 5 Hz, 4-H), 4.07 (1 H, hept, *J* 6 Hz, $CHMe_2$), 3.76 (3 H, s, CO_2Me), 3.72 (3 H, s, CO_2Me), 3.75 [1 H, obscured, $CH(CO_2Me)_2$] 3.49 (3 H, m, CH_2OMe), 3.36 (3 H, s, OMe), 3.2 (1 H, m, *endo*-1-H), 2.4—1.7 (4 H, m), 1.25 (3 H, d, *J* 6 Hz, Me), and 1.19 (3 H, d, *J* 6 Hz, Me); *m/z* (%) 466 (1), 438 (1), 410 (1), 382 (19), 324 (22), 250 (80), 192 (28), and 107 (100) (Found: C, 51.65; H, 5.52. Calc. for $C_{20}H_{26}FeO_9$: C, 51.5; H, 5.6%).

Reaction of the Salt (6b) *with Dimethyl Potassiomalonate.*—The salt (6b) (446 mg, 0.929 mmol) was treated with dimethyl potassiomalonate [prepared from potassium t-butoxide (129 mg, 1.15 mmol) and dimethyl malonate (162 mg, 1.23 mmol)] in THF (12 ml) at room temperature. After being stirred for 20 min the reaction mixture was poured into brine and the crude product extracted with diethyl ether. The regioisomers were separated as above to give pure (9c) (305 mg, 70%) and (2e) (35 mg, 8%).

Tricarbonyl{2—5-η-[*methyl* 4-*isopropoxy*-1-(2-*methoxyethyl*)*cyclohexa*-2,4-*dienylacetate*]}*iron* (9d).—Potassium cyanide (2 g) was added to a solution of the diester (9c) (3.7 g, 7.9 mmol) in degassed Me_2SO (20 ml) containing 1% of added water. The suspension was heated on a steam-bath for 16 h and then in an oil-bath at 100—120 °C for a further 6 h. The reaction was cooled and added to brine and the aqueous layers were extracted thoroughly with hexane to give a yellow oil (9d) (2 g, 62%), purified by flash chromatography (13% ethyl acetate in hexane); $\nu_{max.}$ (liquid film) 2 050, 1 970, 1 735, and 1 480 cm^{-1}; δ ($CDCl_3$) 4.97 (1 H, dd, *J* 6, 2 Hz, 2-H), 4.21 (1 H, hept, *J* 6 Hz, $CHMe_2$), 3.61 (3 H, s, CO_2Me), 3.36 (2 H, t part obscured, *J* 7 Hz, CH_2OMe), 3.23 (3 H, s, OMe), 3.2 (1 H, m, obscured, 5-H), 2.58 (1 H, d, *J* 6 Hz, 3-H), 2.21 (2 H, s, CH_2CO_2Me), 2.01—1.45 (4 H, m, CH_2 and 2 × 6-H), 1.34 (3 H, d, *J* 6 Hz, Me), and 1.20 (3 H, d, *J* 6 Hz, Me); *m/z* (%) 408 (2), 380 (18), 352 (30), 324 (100), 264 (95), 250 (95), and 107 (95).

Tricarbonyl(2—5-η-{2-[4-*isopropyl*-1-(2-*methoxyethyl*)*cyclohexa*-2,4-*dienyl*]*ethanol*})*iron* (9e).—Di-isobutylaluminium hydride (DIBAL) (8.3 ml of a 25 wt. % solution in toluene) was added to a solution of the ester complex (9d) (2.1 g, 0.51 mmol) in THF (30 ml) at −78 °C. The stirred reaction mixture was allowed to warm to room temperature and after 3 h methanol (30 ml) followed by water (30 ml) was added dropwise with ice cooling. The aqueous component was acidified with dilute hydrochloric acid and extracted with ether to give a crude product which was purified by flash chromatography (70% ethyl acetate in light petroleum) to give the pure alcohol (9e) as a yellow oil homogeneous on t.l.c. (1.57 g, 80%), $\nu_{max.}$ ($CHCl_3$) 3 620, 3 550—2 400, 2 040, and 1 970 cm^{-1}; δ ($CDCl_3$) 5.07 (1 H, dd, *J* 6, 2 Hz, 3-H), 4.30 (1 H, hept, *J* 6 Hz, C*H*Me_2), 3.72 (2 H, t, *J* 7 Hz, CH_2OH), 3.45 (2 H, t, *J* 7 Hz, CH_2OMe), 3.34 (3 H, s, OMe), 3.3 (1 H, m, obscured, 5-H), 2.58 (1 H, d, *J* 6 Hz, 2-H), 2.2br (1 H, exchanges in D_2O, OH), 2.0—1.5 (6 H, m), 1.41 (3 H, d, *J* 6 Hz, Me), and 1.38 (3 H, d, *J* 6 Hz, Me); *m/z* (%) 380 (1), 352 (27), 324 (40), 296 (90), 250 (30), 236 (100), 208 (42), 194 (71), and 107 (55).

Tricarbonyl{2—5-η-[4-*isopropoxy*-1-(2-*methoxyethyl*)*cyclohexa*-2,4-*dienyl*]*ethyltoluene*-p-*sulphonate*}*iron* (9f).—Toluene-*p*-sulphonyl chloride (900 mg, 1.9 equiv.) was added to a solution of the alcohol (9e) (0.925 g, 2.43 mmol) in pyridine (5 ml) and the reaction mixture was set aside at 0 °C for 22 h. Water (1 ml) was added with ice cooling and the mixture was stirred for 0.5 h and then poured into 20% aqueous hydrochloric acid. The product was extracted with ether at 0 °C and the ether fraction was washed with aqueous sodium hydrogen carbonate. The tosylate (9f) was thus obtained as a yellow oil which was homogeneous on t.l.c. but would not crystallise (1.25 g, 96%), $\nu_{max.}$ ($CHCl_3$) 2 045, 1 975, 1 602, 1 362, and 1 174 cm^{-1}; δ ($CDCl_3$) 7.79 (2 H, d, *J* 9 Hz, 2 × ArH), 7.33 (2 H, d, *J* 9 Hz, 2 × ArH), 4.92 (1 H, dd, *J* 7, 2 Hz, 3-H), 4.20 (1 H, hept, *J* 6 Hz, $CHMe_2$), 4.03 (2 H, t, *J* 7 Hz, CH_2OTs), 3.20 (2 H, t, *J* 7 Hz, CH_2OMe), 3.14 (3 H, s, OMe), 3.14 (1 H, m, obscured, 5-H), 2.36 (3 H, s, Ar-Me), 2.30 (1 H, d, *J* 7 Hz, 2-H), 1.80—1.10 (6 H, m), 1.30 (3 H, d, *J* 6 Hz, Me), and 1.16 (3 H, d, *J* 6 Hz, Me); *m/z* (%) 534 (<1), 506 (<1), 478 (<1), 450 (<1), 348 (10), 320 (45), 292 (35), 264 (16), and 208 (100).

Tricarbonyl{2—5-η-[4-*isopropoxy*-1-(2-*methoxyethyl*)*cyclohexa*-2,4-*dienylpropionitrile*]}*iron* (9g).—Sodium cyanide (0.48 g, 3.5 equiv.) was added to a solution of the tosylate (9f) (1.25 g, 2.34 mmol) in hexamethylphosphoric triamide (HMPA) (3 ml) and the suspension was warmed in an oil-bath at 55 °C for 3 h. The reaction mixture was cooled and poured into dilute hydrochloric acid. The product was extracted with ether and purified by crystallisation from pentane and flash chromatography of the mother liquors to give the pure nitrile (9g) (0.855 g, 94%), m.p. 76—77.5 °C; $\nu_{max.}$ ($CHCl_3$) 2 250, 2 050, and 1 971 cm^{-1}; δ ($CDCl_3$) 5.04 (1 H, dd, *J* 6, 2 Hz, 3-H), 4.27 (1 H, hept, *J* 6 Hz, $CHMe_2$), 3.30 (2 H, t, *J* 7 Hz, CH_2OMe), 3.25 (3 H, s, OMe), 3.25 (1 H, m, obscured, 5-H), 2.30 (3 H, m, 2-H and *endo*-6-H and one of CH_2CN),

1.55 (6 H, m), 1.38 (3 H, d, *J* 6 Hz, Me), and 1.23 (3 H, d, *J* 6 Hz, Me); *m/z* (%) 389 (<1), 361 (5), 333 (17), 305 (27), 246 (20), 245 (100), 203 (33), and 107 (25) (Found: C, 55.75; H, 5.7; N, 3.7. Calc. for $C_{15}H_{23}FeNO_5$: C, 55.54; H, 5.96; N, 3.60%).

4aβ-*Methoxyethyl*-cis-*decahydroquinolin*-7-*one* (3a).—The iron complex (9g) (0.508 g, 1.31 mmol) was added to a suspension of anhydrous trimethylamine *N*-oxide (1.5 g) in benzene (20 ml) and stirred in an oil-bath at 46 °C for 3 h. A further addition of anhydrous trimethylamine *N*-oxide (0.8 g) was made and after a total of 4.5 h the reaction mixture was cooled, filtered through Celite, poured into aqueous sodium hydrogen carbonate and extracted with ether to give the *dienol ether*, (10a) (274 mg, 84%); $\nu_{max.}$ (CCl_4) 2 260, 1 655, and 1 605 cm^{-1}. This compound was exceedingly unstable towards traces of acid and was carried through to the next step immediately.

Lithium aluminium hydride (150 mg) was added to a solution of the unstable nitrile (10a) in ether (10 ml). The suspension was stirred with ice cooling for 3.5 h and then aqueous methanol was added dropwise until a white precipitate had formed. The solution was decanted, dried, and evaporated to give the amine, (10b) as a yellow oil [260 mg, 79% from iron complex (9g)], $\nu_{max.}$ (CCl_4) 3 550—3 200, 1 654, and 1 608 cm^{-1}; *m/z* (%) 253 (2), 210 (27), 194 (55), and 59 (100) (Found: M_r, 253.2025. HRMS Calc. for $C_{15}H_{27}NO_2$: M_r, 253.2042). Attempts to characterise and purify this compound led to decomposition, so it was carried through to the next step in crude form.

The aminodienol ether (10b) (250 mg, 0.988 mmol) was dissolved in methanol (10 ml) and added to a stirred solution of oxalic acid (0.6 g) in water (3 ml) at room temperature. After 1 h aqueous sodium hydrogen carbonate was added and the mixture stirred for a further 1 h. The reaction mixture was then poured into aqueous potassium carbonate and the product was thoroughly extracted with chloroform. This gave crude aminoketone (3a) [208 mg, 100% from the dienol ether (10b)] which could be purified by preparative t.l.c. (20% methanol in chloroform); it was found, however, more expedient to chloroacetylate the crude mixture and purify the amide; $\nu_{max.}$ (CCl_4) 2 815, 2 740, and 1 730 cm^{-1}; δ ($CDCl_3$) 3.56 (2 H, t, *J* 7 Hz, CH_2OMe), 3.40 (3 H, s, OMe), and 3.2—1.1 (16 H, m); *m/z* (%) 211 (4), 196 (11), 152 (48), and 96 (100) (Found: M_r, 211.1570. HRMS Calc. for $C_{12}H_{21}NO_2$: M_r, 211.1573).

1-*Chloroacetyl*-4aβ-*methoxyethyl*-cis-*decahydroquinolin*-7-*one* (3b).—The crude amine (3a) (105 mg, 0.498 mmol) was dissolved in benzene (10 ml) and added to a stirred suspension of pyridine (114 μl, 2.8 equiv.) and chloroacetyl chloride (110 μl, 1.8 equiv.) in benzene (5 ml). After 2 h at 5—10 °C water was added and after a further 10 min the reaction mixture was poured into dilute hydrochloric acid. The crude amide was extracted with chloroform and purified by flash chromatography (80% ethyl acetate in light petroleum) to give pure (3b) [100 mg, 70%; 15% overall yield from the complex (2c)] which was identical with the sample in our previous limaspermine synthesis.[5]

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