Asymmetric synthesis of alkaloid (−)-(2*S*,4*S*) SS 20846 A and its C-4 epimer

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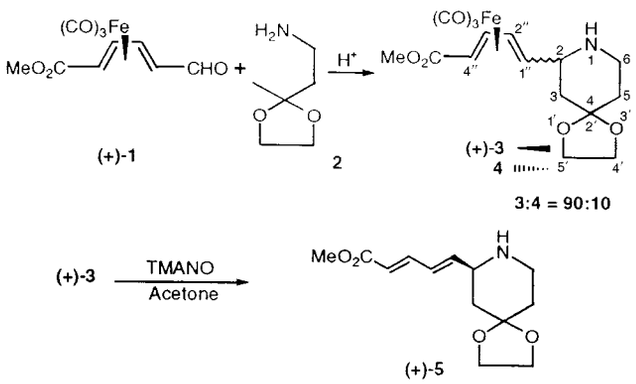
A diastereoselective intramolecular Mannich reaction using planar chiral iron dienal complexes is employed to prepare optically pure 2,4-disubstituted piperidines. This methodology is applied to the synthesis of natural alkaloids (−)-**6** and (−)-**7**.

Introduction

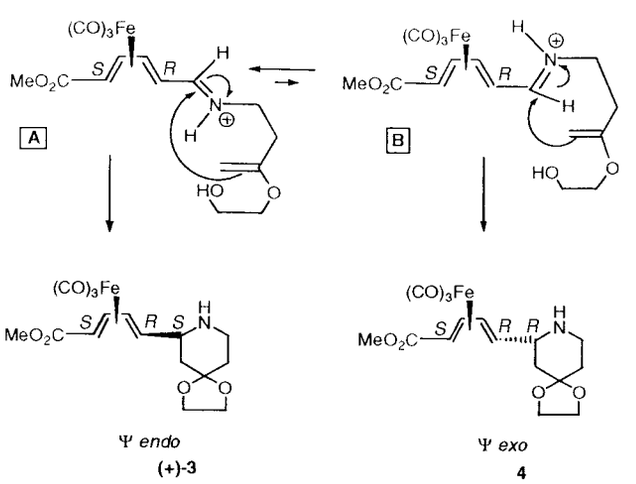
Many natural compounds and drugs contain the piperidine ring system as a structural element. As this class of products exhibits pharmacological properties,[1] the elaboration of versatile flexible regio- and stereoselective syntheses of chiral piperidines is therefore of major interest to organic chemists.[2] Among them, 2-alkyl-4-piperidones constitute an important class of synthetic intermediates[3] which have been extensively used in the preparation of biologically active materials.[4] Several methodologies for their enantioselective synthesis have been developed so far.[5] However, limitations of some of these methods include a lack of generality and/or low diastereoselectivity, even if some syntheses using Diels–Alder methodology have recently proved their efficiency.[6] In our ongoing work devoted to the stereoselective synthesis of polysubstituted piperidines, we are involved in the development of enantioselective cyclization methods that exploit organometallic complex-mediated reactions to create the piperidine ring. Indeed, the use of organometallic complexes in asymmetric synthesis arose since these compounds could be obtained in optically pure form and could therefore serve as chiral inductors.[7] Among them, organoiron complexes have been extensively used.[8] Therefore, we have defined a stereoselective cyclization method in which the piperidine ring is formed through an intramolecular Mannich type reaction,[9] using planar chiral (η^4-dienal) $Fe(CO)_3$ complexes.[10] In our approach, the $Fe(CO)_3$ unit serves as a protecting and directing group for the formation of the C-2 chiral centre. Preliminary experiments[10] were realised with readily available optically pure complex **1**.[11] Thus, reaction of **1** and amine **2**[12] in anhydrous methylene chloride, in the presence of 4 Å molecular sieves as drying agent, led quantitatively to the transient imine which was directly treated with toluene-*p*-sulfonic acid (2 equiv.) in methylene chloride–toluene (1 : 1) at 70 °C. Purification of the reaction mixture by column chromatography furnished a 9 : 1 ratio of separated protected 2-substituted-4-piperidones **3** and **4** in a 75% overall yield (Scheme 1).[10]

The stereochemistry of diastereomeric piperidines **3** and **4** (Ψ *endo* and Ψ *exo* respectively)[13] has been deduced from comparisons of their relative R_f values[14] and by analogy with the reactivity of such complexes **1** towards nucleophiles.[15] In an acidic medium, the transoid iminium complex **A** is more stable than the cisoid complex **B**; as the intramolecular cyclization of the enol ether on the intermediate iminium ion always occurs



Scheme 1

anti to the bulky $Fe(CO)_3$ group, we can then assume that, in the Ψ *endo* series, the absolute configuration of the newly created C-2 centre is (*S*) (Scheme 2).



Scheme 2

Decomplexation of the major isomer **3** with anhydrous trimethylamine *N*-oxide (TMANO)[16] led to the optically active piperidine **5** (Scheme 1). As both enantiomers of starting complex **1** are available,[11] from a synthetic standpoint, the isomeric

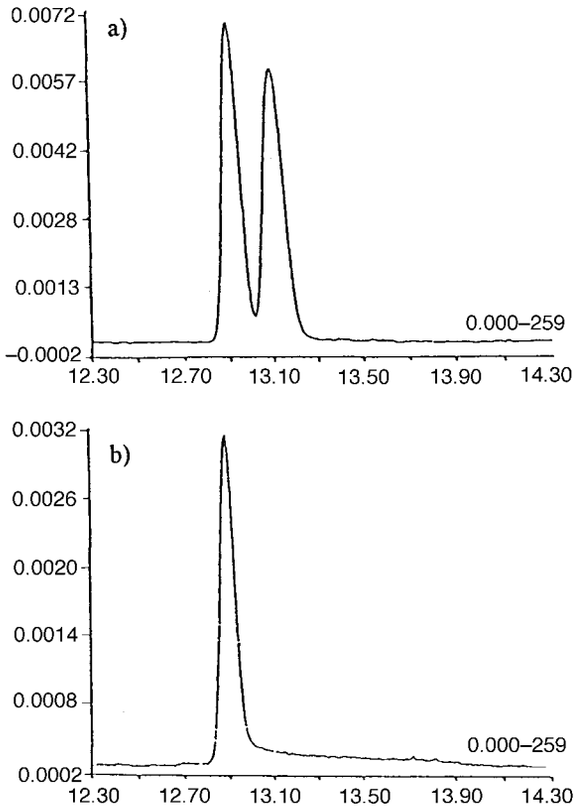
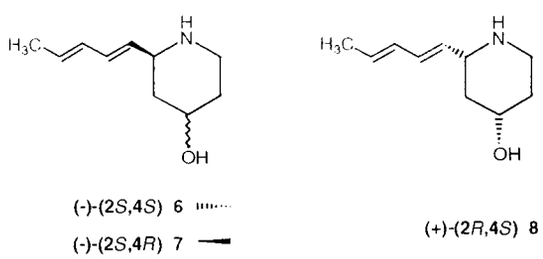


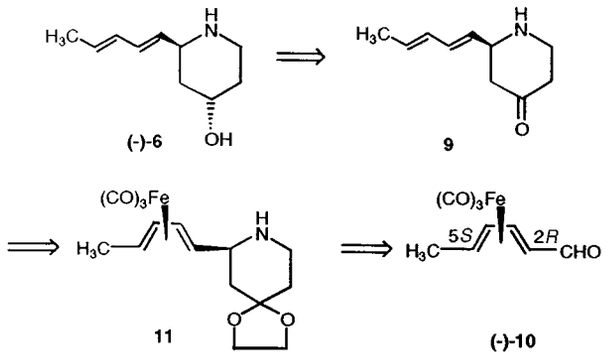
Fig. 1 Chiral capillary electrophoresis of product **5**. a) racemate, b) (+)-enantiomer.

(*R*)-series could be conveniently prepared from the other enantiomer of the starting complex. Next was the confirmation of the predicted absolute configuration of the C-2 centre together with an evaluation of the enantiomeric excess. For amines, the method of choice for simultaneous determination of ee and absolute configuration involves studying the Mosher's ester derivatives, by both ^{1}H and ^{19}F NMR spectroscopy. However, the hindered rotation of the amide bond was responsible for too much complexity in the spectral analysis and we decided to abandon such a strategy.[17] The enantiomeric excess was obtained by the use of a novel chiral capillary electrophoresis method[18] which showed that piperidine **5** was optically pure (Fig. 1).

To confirm our postulated mechanism, we decided to apply our methodology to the synthesis of natural compounds of similar framework and known stereochemistry. We turned our attention to the alkaloid SS 20846 A **6**,[19] a proposed intermediate in the biosynthesis of the potent antimicrobial agent streptazolin,[20] which was isolated from a *Streptomyces* strain,[21] together with its epimers **7** and **8**.



A retrosynthetic analysis of the target molecule is presented in Scheme 3: compound **6** was expected to arise *via* the selective reduction of the carbonyl group of 4-piperidone **9** which should be easily prepared from chiral complex **10**[22] *via* deacetalization and decomplexation of piperidine **11**. According to this, and knowing the absolute configuration of compound **6**, namely (2*S*,4*S*), we needed to use complex (2*R*,5*S*)-(−)-**10**.



Scheme 3

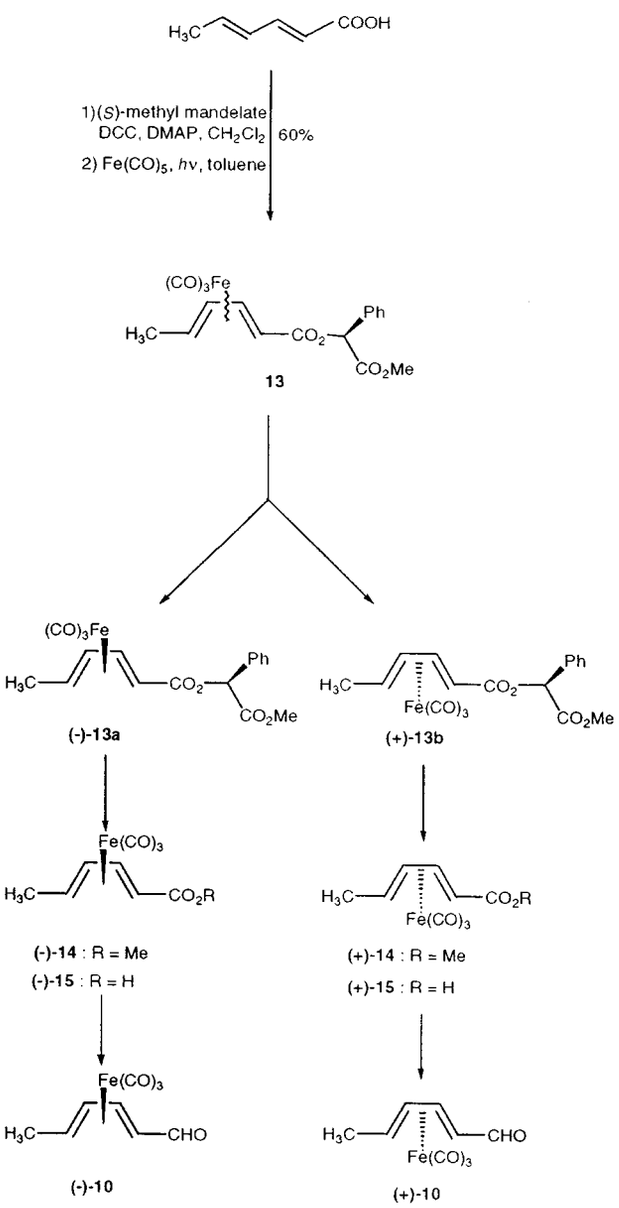
Furthermore, this synthetic approach could give access to the C-2 epimers, starting from the enantiomeric complex (+)-**10**, and to C-4 epimers by stereoselective reduction[23] of the ketone function of **9**.

Results and discussion

According to the retrosynthetic scheme, piperidine **11** is the key intermediate in the synthesis of **6**. However, first attempts to deprotect the ketone of **11** proved to be rather difficult. Standard experimental conditions which have been previously described[24] were not successful in this case.[25] Use of more drastic conditions led to extensive decomposition and/or racemisation of the starting material.[26] Thus we changed the ketone protecting group. As cyclic acetals are needed for the ring closure, we decided to use the higher homologue to effect efficiently the ring closure. Moreover, it has been shown that use of a dioxane rather than a dioxolane group allows deprotection under rather mild conditions.[27] Starting amine **12** was easily prepared using standard methods.[12] Preparation of enantiopure aldehyde complexes (+)-**10** and (−)-**10** through chromatographic separation of the preformed diastereomers has been described.[22] However, the weak difference in polarity usually observed between diastereomers ($\Delta R_f \approx 0.04$) implies a rather difficult separation which is not useful for large scale work. We found that the use of (*S*)-methyl mandelate as a chiral derivatizing agent in place of (*S*)-ethyl lactate[22c] or (*S*)-octan-2-ol[22b] allowed a facile ($\Delta R_f = 0.12$) large scale preparation of homochiral $Fe(CO)_3$-sorbic acid derivatives. Thus, diester complexes **13** were prepared in 60% yield from sorbic acid using conventional procedures (Scheme 4).

Chromatographic separation followed by saponification and reduction[22c] gave both enantiopure complexed aldehydes (+)-**10** and (−)-**10**. Reaction of chiral complex (−)-**10** with amine **12** in anhydrous methylene chloride, followed by acidic treatment, furnished 68% of a 9:1 mixture of piperidines **16** and **17**, separated by column chromatography (Scheme 5). Decomplexation of major isomer (−)-**16** was realised by using anhydrous trimethylamine *N*-oxide (TMANO) in acetone, leading to piperidine **18** in 75% yield. However, all attempts to deprotect the ketone function furnished complex mixtures from which the desired piperidone **9** was only obtained in poor yield (<20%) (Scheme 5).

Considering these disappointing results, we turned our attention to the protection of the amino group in order to get more stable products. It has been shown that a ketone function protected by a dioxane in the *N*-carbamoyl piperidone series was more rapidly regenerated and under milder conditions[28] than in the parent compounds with a free amino group. Choice of the *N*-protecting group is crucial to this strategy since it must not interfere with the ketone deprotection. We therefore selected *N*-Fmoc derivatives since regeneration of the amino function occurs in basic medium. Moreover, the introduction of



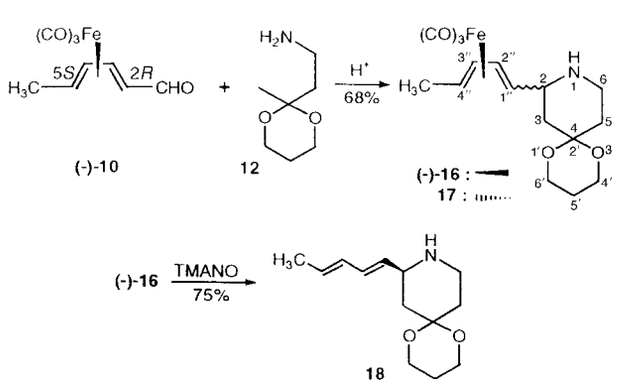
Scheme 4

a carbamate group upon a 2-substituted piperidine induces inversion of the ring conformation to minimise $A^{1,3}$ strain.[29] For this reason, the related *N*-acyl piperidines are alkylated axially at C-2.[30] Confirmation that this happens was obtained by conformational searching (Monte-Carlo sampling method) on compound **19** (Fig. 2) using the Batchmin program within the MM2 force field of the Macromodel package.[31] Reoptimization of the geometry such obtained was then realised by the MOPAC AM1 semi-empirical quantum program[32] and showed that conformers with axial diene substituents are significantly lower in energy and also that the amide carbonyl orientation could be neglected. Considering this result, reduction of the ketone function of *N*-Fmoc derivatives by L-Selectride® reagent, prone to give equatorial attacks on cyclohexanones,[23] should lead predominantly to the 2,4-*cis* isomer (intermediate of **7**) whereas reduction of the free piperidone should yield the 2,4-*trans* isomer (precursor of **6**). Finally, we decided to introduce the organometallic moiety until the end of the synthesis, firstly to aid purification and secondly to use the bulky iron moiety to increase the stereoselectivity of the reduction of the carbonyl group.

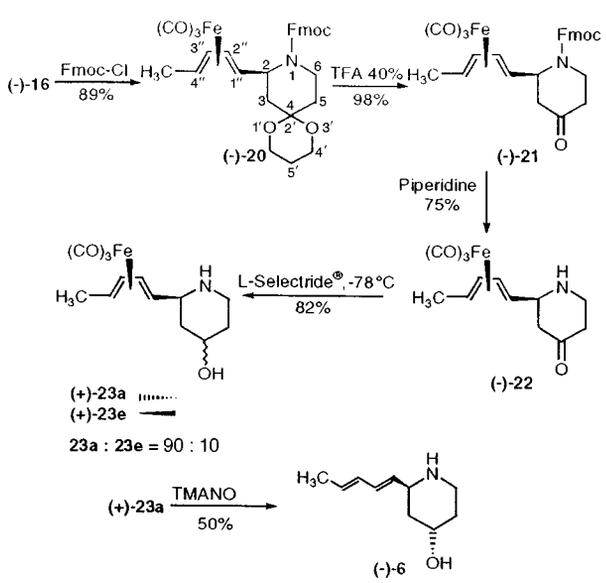
Thus, treatment of piperidine (−)-**16** with Fmoc-Cl in the presence of Hünig's base led to compound (−)-**20** in 89% yield (Scheme 6). Cleavage of the dioxane appendage was then cleanly realised using a 40% TFA solution for 15 hours and furnished the desired piperidone (−)-**21** in 96% yield. Compound **21** was first *N*-deprotected using a solution of piperidine in THF to give (−)-**22**, which was stereoselectively reduced with L-Selectride® at low temperature (*trans*:*cis* = 9:1) to afford after flash chromatography the expected axial piperidinol (+)-**23a** in a 60% overall yield (Scheme 6).

Decomplexation of (+)-**23a** with TMANO in anhydrous acetone led to (2*S*,4*S*) alkaloid SS 20846 A (−)-**6**. The optical rotation and chiral capillary electrophoretic analysis,[33] a useful and efficient method in this series, confirmed that synthetic **6** was optically pure {$[a]_D^{25}$ −20, *c* 1.4 in $CHCl_3$} {lit.,[19] $[a]_D$ −15.2}. On the other hand, reduction of *N*-protected piperidone (−)-**21** by L-Selectride® under the same conditions (Scheme 7) led, as predicted, to a mixture of diastereoisomers **24a** and **24e** (*cis*:*trans* = 95:5) which were separated by column chromatography, the major isomer bearing the hydroxy group in the axial position (*vide supra*). Disappearance of allylic strain after *N*-deprotection induced ring inversion and produced the equatorial piperidinol (+)-**23e**, in a 75% yield (Scheme 7).

Decomplexation of (+)-**23e** with TMANO gave, in 60% yield, optically pure[18] (−)-(2*S*,4*R*)-**7**, as proven by chiral capillary electrophoresis,[33] {$[a]_D^{25}$ −37 (*c* 1 in $CHCl_3$) (lit.,[19] $[a]_D$ −13)}. Anyway, considering the difference between the optical rotation values, we wished to confirm our result through the synthesis of (2*R*,4*S*)-**8**, enantiomer of the natural alkaloid (−)-**7**. Starting from dienal complex (+)-**10**, we obtained (+)-**8** by the same pathway which had an optical rotation {$[a]_D^{25}$ +39 (*c* 1 in $CHCl_3$)} in close agreement with that observed for our synthetic (−)-**7**.



Scheme 5



Scheme 6

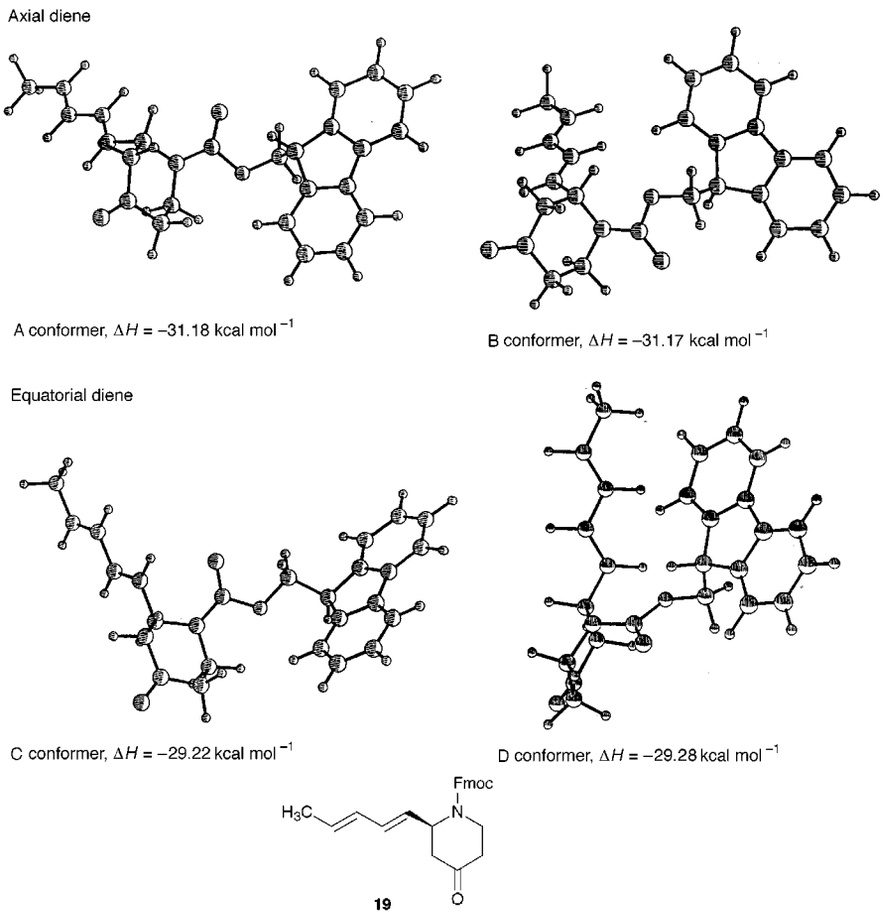
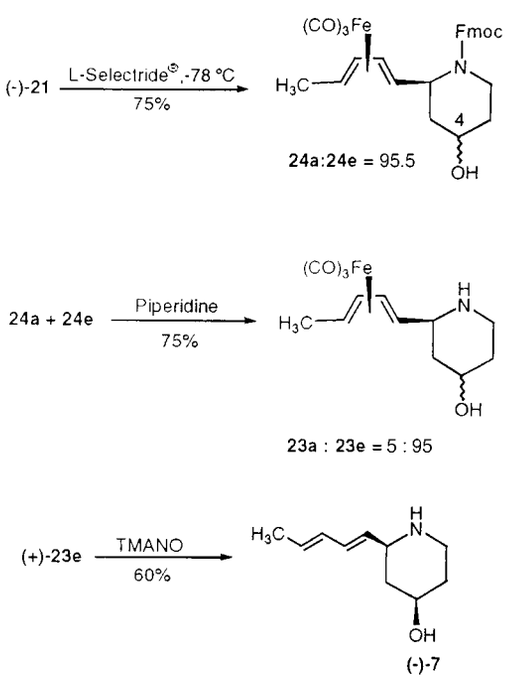


Fig. 2 Conformational analysis of compound **19**.



Scheme 7

Conclusions

We have described the enantioselective preparation of 2,4-substituted piperidines *via* a diastereoselective intramolecular Mannich reaction using planar chiral iron dienal complexes. Using this methodology, enantiomerically pure natural alkaloids SS 20846 A (−)-**6** and its C-4 epimer (−)-**7** have been prepared. Elucidation of the cyclisation mechanism now allows the prediction of the absolute configuration of the newly created C-2 centre. Synthetic applications of this reaction, especially for the enantioselective preparation of more substituted piperidines of biological interest, are currently in progress.

Experimental

General

Melting points are uncorrected. ^{1}H and ^{13}C spectra were measured at 400.13 and 100.61 MHz respectively; chemical shifts are reported in ppm relative to $SiMe_4$. *J* Values are given in Hz. Infrared spectra were recorded on a FTIR spectrometer. Electron impact (EI) mass spectra were obtained at 70 eV. Fast atom bombardment (FAB) mass spectra were obtained from the Centre Régional de Mesures Physiques, Université de Rennes. Optical rotations were measured at 589 nm. Column and flash column chromatography were carried out on silica gel (70–230 mesh and 230–400 mesh respectively). Solvents were dried and freshly distilled following the usual procedures. All reactions were carried out under argon. Product solutions were dried over Na_2SO_4 prior to evaporation of the solvents under reduced pressure on a rotary evaporator.

Tricarbonyl[methoxycarbonyl(phenyl)methyl (2,3,4,5-η)-hexa-2,4-dienoate]iron 13

To a stirred solution of sorbic acid (2 g, 17.8 mmol) and (*S*)-methyl mandelate (3.5 g, 21.1 mmol) in CH_2Cl_2 (80 ml) was added at 0 °C, DCC (3.96 g, 19.2 mmol) and DMAP (15 mg). The resulting mixture was stirred at room temperature for 14 h, before filtration in order to remove the dicyclohexylurea formed. The organic layer, washed successively with 1 M aque-

ous HCl, saturated aqueous $NaHCO_3$ and brine, was dried and evaporated. The crude product was chromatographed (ethyl acetate–cyclohexane, 1:6) to give methoxycarbonyl(phenyl)-methyl hexa-2,4-dienoate (3.0 g, 65%); R_f 0.4 (ethyl acetate–cyclohexane, 1:4); $\delta_H(CDCl_3)$ 7.53–7.49 (2H, m), 7.43–7.33 (4H, m), 6.26–6.14 (2H, m), 6.01 (1H, s), 5.91 (1H, d, *J* 15.5), 3.73 (3H, s), 1.90 (3H, d, *J* 7); $\delta_C(CDCl_3)$ 169.6, 169.5, 146.8, 140.6, 134.1, 129.8, 129.3, 128.9, 127.7, 117.7, 74.3, 52.7, 18.8.

To a degassed solution (argon, 30 min) of methoxycarbonyl(phenyl)methyl hexa-2,4-dienoate (2.7 g, 10.4 mmol) in toluene (100 ml), prepared in a pyrex vessel, was added $Fe(CO)_5$ (2.8 ml, 20.7 mmol). The resulting solution was stirred and irradiated with a medium pressure mercury lamp (400 W) for 12 hours. After filtration the solvent was evaporated. Chromatography on silica gel (diethyl ether–cyclohexane, 1:2) yielded the *diastereomeric complexes* **13a** (1.48 g, 36%) and **13b** (1.35 g, 32%) as orange oils.

(−)-(2*S*,5*S*,1′*S*) 13a. R_f 0.35 (Et_2O-cyclohexane, 1:4); $[a]_D^{25}$ −21 (*c* 1 in acetone); $\nu_{max}(CHCl_3)/cm^{-1}$ 3020, 2061, 1998, 1753, 1710; $\delta_H(CDCl_3)$ 7.50–7.37 (5H, m, *Ph*), 5.93 (1H, s, 1′-H), 5.80 (1H, dd, *J* 5.5 and 8.0, 3-H), 5.23 (1H, dd, *J* 5.5 and 8.0, 4-H), 3.72 (3H, s, CO_2*Me*), 1.55–1.45 (4H, m, 5-H and 5-*Me*), 1.13 (1H, d, *J* 8, 2-H); $\delta_C(CDCl_3)$ 171.6, 169.2, 133.9, 129.0, 128.6, 127.4, 88.4, 82.8, 74.3, 59.2, 52.4, 44.5, 19.0 [Found (FAB): 401.0357. $C_{18}H_{17}O_7Fe{\cdot}H^+$ requires 401.0324].

(+)-(2*S*,5*R*,1′*S*) 13b. R_f 0.47 (Et_2O–cyclohexane 1:4); $[a]_D^{25}$ 94.5 (*c* 1 in acetone); $\delta_H(CDCl_3)$ 7.50–7.30 (5H, m, *Ph*), 5.88 (1H, s, 1′-H), 5.82 (1H, dd, *J* 5.0 and 8.0, 3-H), 5.23 (1H, dd, *J* 5.0 and 8.0, 4-H), 3.70 (3H, s, CO_2*Me*), 1.58–1.48 (4H, m, 5-H and 5-*Me*), 0.99 (1H, d, *J* 8.0, 2-H); $\delta_C(CDCl_3)$ 171.8, 169.3, 133.9, 129.3, 128.8, 127.8, 88.7, 82.5, 74.6, 59.1, 52.6, 44.5, 19.3; *m*/*z* (EI) 344 ($M^+ - 2CO$, 54), 316 ($M^+ - 3CO$, 70), 284 (17), 198 (18), 118 (100), 95 (38).

(−)-Tricarbonyl[(2*R*,5*S*)-methyl (2,3,4,5-η)-hexa-2,4-dienoate]iron 14

To a stirred solution of diester (−)-**13a** (2.16 g, 5.54 mmol) in methanol (15 ml) was added KOH (4.9 ml of a 0.5 M methanol solution). The resulting mixture was stirred at room temperature for 1 h before addition of diethyl ether (20 ml) and aqueous HCl (10 ml of a 0.5 M solution). After separation, the aqueous layer was extracted with diethyl ether (2 × 20 ml). The combined organic extracts were washed with brine, dried and evaporated. Product purification was achieved by chromatography (ethyl acetate–cyclohexane, 1:6), giving *ester* (−)-**14** (1.14 g, 79%) as an orange oil; R_f 0.6 (ethyl acetate–cyclohexane, 1:4); $[a]_D^{25}$ −208 (*c* 1 in acetone) {lit.,[22c] $[a]_D^{25}$ −205 (*c* 0.25 in acetone)}. Spectral data are identical with those reported.[34]

(+)-Tricarbonyl[(2*S*,5*R*)-methyl (2,3,4,5-η)-hexa-2,4-dienoate]iron 14. Following the same procedure, (+)-**14** was prepared in 77% yield from (+)-**13b** {$[a]_D^{25}$ +225 (*c* 1 in acetone); lit.,[22c] $[a]_D^{25}$ +205 (*c* 0.39 in acetone)}.

(−)-Tricarbonyl[(2*R*,5*S*)-(2,3,4,5-η)-hexa-2,4-dienoic acid]iron 15

To a stirred solution of complex (−)-**14** (1.14 g, 4.28 mmol) in ethanol (7.5 ml) was added KOH (15 ml of a 0.5 M solution in ethanol–water, 1:1). The solution was stirred at room temperature for 5 h, then diethyl ether (30 ml) and water (15 ml) were added. After separation, the aqueous layer was acidified (1 M HCl) until pH 2 and was extracted with diethyl ether (3 × 20 ml). The combined organic extracts were washed with brine, dried and evaporated to give pure *acid* (−)-**15** (0.91 g, 83%); R_f 0.3 (ethyl acetate–cyclohexane, 1:4) {$[a]_D^{25}$ −202 (*c* 1 in acetone); lit.,[22b] $[a]_D^{25}$ −205 (*c* 0.5 in acetone)}. Spectral data are identical with those reported.[34]

(+)-Tricarbonyl[(2*S*,5*R*)-(2,3,4,5-η)-hexa-2,4-dienoic acid]iron 15. Following the same procedure, (+)-**15** was prepared in 84% yield from (+)-**14** {$[a]_D^{25}$ 203 (*c* 1 in acetone); lit.,[22b] $[a]_D^{25}$ 210 (*c* 0.5 in acetone)}.

(+)-Tricarbonyl[(2*R*,5*S*)-(2,3,4,5-η)-hexa-2,4-dienal]iron 10

To a stirred solution of acid (+)-**15** (0.58 g, 2.3 mmol) in CH_2Cl_2 (20 ml) was added at 20 °C oxalyl chloride (470 µl, 4.6 mmol). After 2 h, CH_2Cl_2 and excess oxalyl chloride were removed *in vacuo* and the residue was diluted with acetone (15 ml). The resulting mixture was transferred under argon to a stirred suspension of triphenylphosphine (1.2 g, 4.6 mmol) and triphenylphosphine–copper borohydride (1.5 g, 2.5 mmol) in acetone (25 ml). The mixture was stirred for 2 h, then filtered. Concentration followed by chromatography (Et_2O–cyclohexane, 1:6) afforded pure *aldehyde* (+)-**10** (0.35 g, 64%) as an orange solid, mp 21 °C; R_f 0.4 (ethyl acetate–cyclohexane, 1:4) {$[a]_D^{25}$ 115 (*c* 1 in $CHCl_3$); lit.,[22a] $[a]_D^{25}$ 110 (*c* 1 in $CHCl_3$)}; ν_{max}(KBr)/cm^{-1} 2053, 1982, 1682; $\delta_H(CDCl_3)$ 9.26 (1H, d, *J* 5.0, C*HO*), 5.78 (1H, dd, *J* 5.0 and 8.0, 2-H), 5.30 (1H, dd, *J* 5.0 and 8.5, 3-H), 1.75–1.67 (1H, m, 4-H), 1.52 (3H, d, *J* 6.0, *Me*), 1.27 (1H, dd, *J* 5.0 and 8.5, 1-H); $\delta_C(CDCl_3)$ 196.1, 88.3, 82.9, 59.1, 46.2, 19.2; *m*/*z* (EI) 236 ($M^{+\bullet}$, 6%), 208 ($M^{+\bullet} - CO$, 30), 180 ($M^{+\bullet} - 2CO$, 54), 152 ($M^{+\bullet} - 3CO$, 66), 81 (68), 56 (100). 2,4-Dinitrophenylhydrazone derivative, mp 190–192 °C (decomp.) [lit.,[35] 192–193 °C (decomp.)].

(−)-Tricarbonyl[(2*S*,5*R*)-(2,3,4,5-η)-hexa-2,4-dienal]iron 10. Following the same procedure, (−)-**10** was prepared in 65% yield from (−)-**15** {$[a]_D^{25}$ −115 (*c* 1 in $CHCl_3$); lit.,[22a] $[a]_D^{25}$ −110 (*c* 1 in $CHCl_3$)}.

Intramolecular Mannich type cyclisation, general procedure

To a stirred solution of dienal $Fe(CO)_3$ complex (4 mmol) in CH_2Cl_2 (20 ml), was added $MgSO_4$ (1 g) followed by a solution of protected aminobutanone (1 equiv.) in CH_2Cl_2 (2 ml). The resulting solution was heated at reflux for 3 h, then cooled at room temperature and transferred *via* a cannula to a solution of dry toluene-*p*-sulfonic acid (2 equiv.) in CH_2Cl_2 (20 ml). The mixture was heated at 70 °C for 4 h. After being cooled to room temperature, saturated aqueous $NaHCO_3$ (15 ml) was added and the protected piperidone was extracted with CH_2Cl_2 (2 × 20 ml). The combined organic extracts were dried, filtered and evaporated. The residue was then purified by column chromatography using ethyl acetate as eluent.

Reaction with dienal $Fe(CO)_3$ complex (+)-1

Following the general procedure, complex (+)-**1** (0.8 g, 2.83 mmol) and aminobutanone **2** (0.37 g, 2.83 mmol) gave an oily residue which, after chromatography, furnished the two *piperidones* Ψ *endo*-(+)-**3** (0.820 g, 72%) and Ψ *exo*-**4** (0.090 g, 8%).

(+)-Tricarbonyl[(1″*R*,4″*S*)-(1″,2″,3″,4″-η)-1″-{(2*S*)-1-aza-1′,3′-dioxaspiro[4.5]decan-2-yl}-4″-methoxycarbonylbutadienyl]iron 3†

Yellow oil; $[a]_D^{25}$ 154 (*c* 1 in MeOH); ν_{max}(KBr)/cm^{-1} 2940, 2063, 2005, 1720; $\delta_H(CDCl_3)$ 5.87 (1H, dd, *J* 5.0 and 8.0, 3″-H), 5.35 (1H, dd, *J* 5.0 and 9.0, 2″-H), 3.95 (4H, m, 4′ and 5′-H2), 3.65 (3H, s, CO_2*Me*), 3.11 (1H, ddd, *J* 3.0, 3.5 and 12.0, 6-H^{eq}), 2.81 (1H, m, 6-H^{ax}), 2.54 (1H, ddd, *J* 2.5, 8.0 and 12.5, 2-H), 1.84

† The numbering in the name and spectral data for this compound follows that shown in Scheme 1 and does not reflect the IUPAC numbering system.

(1H, m, 3-H^{eq}), 1.66 (2H, m, 5-H$_2$), 1.56 (1H, dd, *J* 11.5 and 12.5, 3-H^{ax}), 1.30 (1H, dd, *J* 8.0 and 9.0, 1″-H), 1.01 (1H, d, *J* 8.0, 4″-H); δ_C($CDCl_3$) 172.3, 107.3, 84.9, 84.1, 69.0, 64.4, 64.3, 58.7, 51.7, 46.4, 44.8, 44.1, 34.8 [Found (IE): $M^+ - CO$, 365.0559. $C_{15}H_{19}O_6NFe$ ($M^+ - CO$) requires 365.0562].

Tricarbonyl[(1″*R*,4″*S*)-(1″,2″,3″,4″-η)-1″-{(2*R*)-1-aza-1′,3′-dioxaspiro[4.5]decan-2-yl}-4″-methoxycarbonylbutadienyl]iron 4†

Yellow oil; δ_H($CDCl_3$) 5.85 (1H, dd, *J* 5.0 and 9.0, 3″-H), 5.40 (1H, dd, *J* 5.0 and 9.0, 2″-H), 4.10–3.90 (4H, m, 4′ and 5′-H$_2$), 3.65 (3H, s, CO_2*Me*), 3.10 (1H, m, 6-H^{eq}), 2.90 (1H, m, 6-H^{ax}), 2.58 (1H, ddd, *J* 4.0, 11.0 and 11.0, 2-H) 1.85 (1H, dd, *J* 4.0 and 14.0, 3-H^{eq}), 1.60 (2H, m, 5-H$_2$), 1.50 (1H, dd, *J* 11.0 and 14.0, 3-H^{ax}), 1.25 (1H, dd, *J* 9.5 and 11.0, 1′-H), 1.05 (1H, d, *J* 9.5, 4″-H); δ_C($CDCl_3$) 172.0, 107.3, 85.3, 84.3, 66.5, 64.4, 64.3, 58.4, 51.8, 48.4, 44.0, 43.1, 35.3 [Found (IE): $M^+ - 2CO$, 337.0604. $C_{14}H_{19}O_5NFe$ ($M^+ - 2CO$) requires 337.0612].

Intramolecular Mannich type cyclization with complex 10

Following the general procedure complex (−)-**10** (0.80 g, 3.39 mmol) and aminobutanone **12** (0.492 g, 3.39 mmol) gave after chromatography *piperidone* Ψ-*endo*-(−)-**16** (0.755 g, 61%) and *diastereoisomer* Ψ-*exo*-**17** (0.065g, 5%) as yellow oils.

(−)-Tricarbonyl[(1″*S*,4″*R*)-(1″,2″,3″,4″-η)-1″-{(2*R*)-1-aza-1′,3′-dioxaspiro[5.5]undecan-2-yl}pentadienyl]iron 16.‡ R_f 0.45 (ethyl acetate–methanol, 5:1); $[a]_D^{25}$ −3 (*c* 1 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2956, 2042, 1975; δ_H($CDCl_3$) 5.16–5.06 (2H, m, 2″-H and 3″-H), 4.00–3.85 (4H, m, OC*H*$_2$), 3.00 (1H, ddd, *J* 2.5, 5.0 and 11.5, 6-H^{eq}), 2.74 (1H, ddd, *J* 2.5, 11.5 and 12.0, 6-H^{ax}), 2.42 (1H, ddd, *J* 2.5, 9.5 and 11.5, 2-H), 2.31 (1H, m, 5-H^{eq}), 2.19 (1H, ddd, *J* 2.5, 3.0 and 13.0, 3-H^{eq}), 1.87–1.77 (1H, m, 5′-H), 1.68–1.58 (2H, m, 5′-H and N*H*), 1.46 (1H, td, *J* 5.0 and 13.0, 5-H^{ax}), 1.40 (3H, d, *J* 6.5, *Me*), 1.37 (1H, t, *J* 12.0, 3-H^{ax}), 1.16 (1H, m, 4″-H), 0.97 (1H, dd, *J* 8.5 and 9.0, 1″-H); δ_C($CDCl_3$) 96.8, 86.1, 81.4, 67.3, 59.3, 59.1, 58.5, 57.4, 43.8, 42.8, 31.5, 25.6, 19.1; *m*/*z* (EI) 335 ($M^+ - CO$, 9%), 307 (100), 85 (13), 56 (66), 28 (35) [Found (FAB): 364.0847. $C_{16}H_{22}NO_5Fe + H^+$ requires 364.0833].

Following the same procedure, the enantiomeric piperidine (+)-**16** was prepared in 56% yield from (+)-**10**: $[a]_D^{25}$ 3 (*c* 1 in $CHCl_3$).

Tricarbonyl[(1″*S*,4″*R*)-(1″,2″,3″,4″-η)-1″-{(2*S*)-1-aza-1′,3′-dioxaspiro[5.5]undecan-2-yl}pentadienyl]iron 17‡

R_f 0.12 (ethyl acetate–methanol, 5:1); ν_{max}(KBr)/cm^{-1} 2964, 2040, 1971; δ_H($CDCl_3$) 5.22 (1H, dd, *J* 5.0 and 8.5, 2″-H), 5.05 (1H, dd, *J* 4.5 and 9.0, 3″-H), 4.08–3.75 (4H, m, OC*H*$_2$), 2.95 (1H, ddd, *J* 2.5, 4.5 and 12.0, 6-H^{eq}), 2.80 (1H, m, 6-H^{ax}), 2.52 (1H, td, *J* 2.5 and 13.0, 5-H^{eq}), 2.43 (1H, ddd, *J* 3.0, 9.5 and 12.0, 2-H), 2.05 (1H, m, 3-H^{eq}), 1.86–1.60 (2H, m, 5′-H$_2$), 1.48 (1H, td, *J* 11.5 and 13.0, 5-H^{ax}), 1.40 (3H, d, *J* 6.0, *Me*), 1.28 (1H, dd, *J* 11.5 and 13.5, 3-H^{ax}), 1.18 (1H, m, 4″-H), 0.85 (1H, dd, *J* 9.0 and 9.5, 1′-H); δ_C($CDCl_3$) 95.9, 86.4, 83.0, 61.9, 59.3, 59.2, 41.9, 38.6, 33.3, 25.4, 19.2; *m*/*z* (EI) 335 ($M^+ - CO$, 29%), 307 ($M^{+\bullet} - 2$ CO, 100), 279 ($M^{+\bullet} - 3$ CO, 71), 221 (48).

2-(Penta-1″,3″-dienyl)-1-aza-1′,3′-dioxaspiro[5.5]undecane 18‡

To a stirred solution of **16** (0.6 g, 1.6 mmol) in acetone (30 ml) was added at 20 °C trimethylamine N-oxide (TMANO) (1.2 g, 16 mmol). The resulting mixture was refluxed for 15 min, then cooled at room temperature. Water (10 ml) was added, and the solution was extracted with ethyl acetate (3 × 20 ml). The combined organic extracts were washed with water, brine, dried and evaporated. Column chromatography (ethyl acetate–methanol, 5:1) afforded *compound* **18** (0.27 g, 75%) as a colourless oil; R_f 0.2 (ethyl acetate–methanol, 5:1); ν_{max}(KBr)/cm^{-1} 3052, 2965, 1265, 1100; δ_H($CDCl_3$) 6.15 (1H, dd, *J* 10.5 and 15.0, 2″-H), 6.01 (1H, ddd, *J* 1.5, 10.5 and 15.0, 3″-H), 5.66 (1H, td, *J* 7.0 and 15.0, 4″-H), 5.51 (1H, dd, *J* 7.0 and 15.0, 1′-H), 3.95–3.85 (4H, m, OC*H*$_2$), 3.30 (1H, ddd, *J* 2.5, 7.0 and 10.5, 2-H), 2.99 (1H, ddd, *J* 2.5, 4.5 and 12.0, 6-H^{eq}), 2.83 (1H, ddd, *J* 2.5, 12.0 and 13, 6-H^{ax}), 2.30–2.17 (2H, m, 5′-H$_2$), 1.78–1.70 (5H, m, 3-H^{eq}, 5-H^{eq} and *Me*), 1.43 (1H, ddd, *J* 4.5, 13.0 and 13.5, 5-H^{ax}), 1.26 (1H, dd, *J* 11.5 and 13.0, 3-H^{ax}); δ_C($CDCl_3$) 133.0, 131.1, 130.4, 129.4, 96.9, 59.2, 55.0, 42.5, 39.8, 33.3, 25.7, 18.1; *m*/*z* (EI) 223 ($M^{+\bullet}$, 54%), 208 (56), 164 (45), 108 (62), 101 (100), 80 (42).

(−)-Tricarbonyl[(1″*R*,4″*S*)-(1″,2″,3″,4″-η)-1″-{(2*S*)-1-fluoren-9-ylmethoxycarbonyl)-1-aza-1′,3′-dioxaspiro[5.5]undecan-2-yl}-pentadienyl]iron 20§

To a stirred solution of compound (−)-**16** (0.56 g, 1.5 mmol) in dichloromethane (20 ml) was added diisopropylethylamine (280 μl, 1.6 mmol) and FmocCl (0.446 g, 1.7 mmol). After 20 min of stirring, water (5 ml) was added and the resulting mixture was extracted with CH_2Cl_2 (3 × 20 ml). The combined organic extracts were washed with brine and dried. Evaporation of the solvent, followed by column chromatography (ethyl acetate–cyclohexane 1:4) gave *N-protected piperidine* (−)-**20** (0.78 g, 89%) as a yellow solid, mp 68–70 °C (diethyl ether); R_f 0.34 (ethyl acetate–cyclohexane, 1:3); $[a]_D^{25}$ −23 (*c* 1 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2964, 2869, 2040, 1966, 1699; δ_H($CDCl_3$): due to the co-existence of amide rotamers, this compound gave a complex spectrum even at 70 °C; δ_C($CDCl_3$) 154.6, 141.4, 127.6, 127.1, 127.0, 125.1, 119.9, 96.4, 84.5, 82.3, 67.3, 59.4, 47.4, 37.1, 26.9, 25.2, 19.1; *m*/*z* (EI) 501 ($M^+ - 3$ CO, 100%), 307 (34), 221 (20), 178 (69), 98 (25), 56 (17) [Found (FAB): 586.1528. $C_{31}H_{21}NO_7Fe + H^+$ requires *m*/*z* 586.1505].

Following the same procedure, the enantiomer piperidine (+)-**20** was prepared in 90% yield from (+)-**16**; $[a]_D^{25}$ 22.5 (*c* 1 in $CHCl_3$).

(−)-Tricarbonyl[(1′*R*,4′*S*)-(1′,2′,3′,4′-η)-1′-{(2*S*)-1-fluoren-9-ylmethoxycarbonyl)-4-oxopiperidin-2-yl}pentadienyl]iron 21

To a stirred solution of *N*-protected piperidine (−)-**20** (0.390 g, 0.67 mmol) in CH_2Cl_2 (20 ml) was added at 20 °C trifluoroacetic acid (1.5 ml of a 40% aqueous solution, 7.8 mmol). The resulting mixture was stirred for 15 hours before addition of saturated aqueous $NaHCO_3$ until pH 8. After separation, the aqueous layer was extracted with CH_2Cl_2 (2 × 10 ml). The combined organic extracts were washed with brine, dried and concentrated. Product separation was achieved by chromatography (ethyl acetate–cyclohexane, 1:3) to give piperidone (−)-**21** (0.34 g, 96%) as a yellow solid, mp 52–54 °C (diethyl ether); R_f 0.27 (ethyl acetate–cyclohexane, 1:3); $[a]_D^{25}$ −23 (*c* 1 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2046, 1976, 1700; δ_H($CDCl_3$): due to the co-existence of amide rotamers, this compound gave a complex ^{1}H NMR spectrum even at 70 °C; δ_C($CDCl_3$) 206.9, 127.2, 124.9, 120.0, 86.1, 82.0, 67.0, 59.8, 58.4, 56.8, 48.2, 47.6, 40.8, 39.2, 27.0, 19.1; *m*/*z* (EI) 443 (34%), 168 (24), 84 (42), 57 (87), 28 (100) [Found (FAB): 528.1505. $C_{28}H_{27}NO_6Fe + H^+$ requires 528.1110].

Following the same procedure the enantiomeric piperidone (+)-**21** was prepared in 94% yield from (+)-**20**. $[a]_D^{25}$ 21 (*c* 1 in $CHCl_3$).

‡ The numbering in the name and spectral data for this compound follows that shown in Scheme 5 and does not reflect the IUPAC numbering system.

§ The numbering in the name and spectral data for this compound follows that shown in Scheme 6 and does not reflect the IUPAC numbering system.

(−)-Tricarbonyl{(1′*R*,4′*S*)-(1′,2′,3′,4′-η)-1′-[(2*S*)-4-oxopiperidin-2-yl]pentadienyl}iron 22

To a stirred solution of piperidine (−)-**21** (0.123 g, 0.23 mmol) in THF (15 ml) was added at room temperature piperidine (600 µl, 6 mmol). Stirring for 1 hour followed by concentration under reduced pressure then column chromatography (ethyl acetate) gave *complexed piperidone* (−)-**22** (0.054 g, 75%) as a yellow solid, mp 91–92 °C (diethyl ether); R_f 0.40 (ethyl acetate); $[\alpha]_D^{25}$ −84 (*c* 0.95 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 2052, 1960, 1725; δ_H($CDCl_3$) 5.14–5.05 (2H, m, 2′-H and 3′-H), 3.42 (1H, ddd, *J* 2.0, 6.0 and 11.0, 6-H^{eq}), 2.85 (1H, ddd, *J* 3.0, 12.0 and 12.5, 6-H^{ax}), 2.53–2.42 (3H, m, 2-H, and 5-H_2), 2.35–2.27 (2H, m, 3-H_2), 1.42 (3H, d, *J* 6.5, *Me*), 1.28–1.17 (1H, m, 4′-H), 0.97 (1H, dd, *J* 8.0 and 8.5, 1′-H); δ_C($CDCl_3$) 207.9, 86.6, 81.0, 65.2, 62.0, 59.1, 51.6, 45.8, 41.6, 19.2; *m*/*z* (EI) 306 (M + H$^+$, 98%), 277 (22), 249 (41), 221 (100), 164 (25), 136 (16); [Found (FAB): 306.0441. $C_{13}H_{15}NO_4Fe$ + H$^+$ requires 306.0429].

General procedure for the L-Selectride® reduction of 4-piperidone Fe(CO)$_3$ complexes

To a cold (−78 °C) stirred solution of 4-piperidone Fe(CO)$_3$ complex (0.3 mmol) in THF (20 ml) was added dropwise L-Selectride® (330 µl of a 1 M solution in THF). After 10 min of stirring at −78 °C, methanol (1 ml) was added and the resulting solution was allowed to warm to room temperature. Evaporation of the solvent under reduced pressure followed by column chromatography gave the pure corresponding 4-piperidinol Fe(CO)$_3$ complexes.

Reduction of 4-piperidone Fe(CO)$_3$ complex (−)-22

Following the general procedure, starting from piperidone (−)-**22** (0.097 g, 0.32 mmol), *piperidinols* (+)-**23a** (0.070 g, 73%) and (+)-**23e** (0.008 g, 9%) were obtained as yellow solids.

(+)-Tricarbonyl{(1′*R*,4′*S*)-(1′,2′,3′,4′-η)-1′-[(2*S*,4*S*)-4-hydroxypiperidin-2-yl]pentadienyl}iron 23a. Mp 136–139 °C (decomp.) (diethyl ether); R_f 0.10 (ethyl acetate–methanol, 5:1); $[\alpha]_D^{25}$ 4 (*c* 3 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3488, 3158, 2920, 2040, 1980, 1934, 1417; δ_H($CDCl_3$) 5.13–5.05 (2H, m, 2′-H and 3′-H), 4.13 (1H, m, 4-H), 3.01 (1H, ddd, *J* 2.5, 12.0 and 12.5, 6-H^{eq}), 2.91 (1H, ddd, *J* 2.5, 5.0 and 12.0, 6-H^{ax}), 2.61 (1H, ddd, *J* 2.5, 9.0 and 11.5, 2-H), 1.86–1.67 (4H, m, 5-H^{ax}, 3-H^{eq}, N*H* and O*H*), 1.61 (1H, ddd, *J* 2.5, 5.0 and 11.5, 5-H^{eq}), 1.54 (1H, ddd, *J* 2.5, 11.0 and 13.5, 3-H^{ax}), 1.40 (3H, d, *J* 6.1, *Me*), 1.17–1.15 (1H, m, 4′-H), 0.99 (1H, dd, *J* 8.0 and 9.0, 1′-H); δ_C($CDCl_3$) 86.1, 81.5, 68.0, 65.1, 58.5, 55.3, 42.5, 41.2, 32.7, 19.2; *m*/*z* (EI) 308 (M + H$^+$, 100%), 290 (11), 251 (24), 224 (75) [Found (FAB): 308.0586. $C_{13}H_{17}NO_4Fe$ + H$^+$ requires 308.0585].

(+)-Tricarbonyl{(1′*R*,4′*S*)-(1′,2′,3′,4′-η)-1′-[(2*S*,4*R*)-4-hydroxypiperidin-2-yl]pentadienyl}iron 23e. Mp 150–151 °C (diethyl ether); R_f 0.20 (ethyl acetate–methanol, 5:1); $[\alpha]_D^{25}$ 18 (*c* 1 in $CHCl_3$); δ_H($CDCl_3$) 5.13–5.10 (2H, m, 2′-H and 3′-H), 3.62 (1H, m, 4-H), 3.15 (1H, ddd, *J* 2.5, 4.0 and 12.0, 6-H^{eq}), 2.60 (1H, ddd, *J* 2.5, 12.0 and 12.5, 6-H^{ax}), 2.22 (1H, ddd, *J* 2.5, 8.5 and 11.0, 2-H), 2.05 (1H, ddd, *J* 2.5, 5.0 and 14.0, 3-H^{eq}), 1.92 (1H, m, 5-H^{eq}), 1.36 (4H, m, 5-H^{ax} and *Me*), 1.27 (1H, ddd, *J* 11.0, 12.0 and 12.0, 3-H^{ax}), 1.18 (1H, m, 4′-H), 1.01 (1H, m, 1′-H); δ_C($CDCl_3$) 86.2, 81.2, 67.0, 61.3, 59.9, 58.7, 45.1, 44.9, 35.1, 19.2.

Reduction of 4-piperidone Fe(CO)$_3$ complex (−)-21

Following the general procedure, reduction of piperidone (−)-**21** (0.160 g, 0.3 mmol) gave a mixture of diastereomeric *piperidinols* **24a** and **24e** which were directly involved in the *N*-deprotection step to give after chromatography (ethyl acetate–methanol, 5:1) the *4-piperidinols* **23a** (0.004 g, 4%) and **23e** (0.070 g, 76%).

Following the same procedure, enantiomeric piperidinol (−)-**23e** was prepared in 57% yield from (+)-**21**. Spectral data were identical with those reported for its enantiomer. $[\alpha]_D^{25}$ −20 (*c* 1 in $CHCl_3$).

(−)-(2*S*,4*S*) Alkaloid SS 20846 A 6

Following the decomplexation procedure given for the preparation of piperidine **18**, piperidinol complex (+)-**23a** (0.067 g, 0.218 mmol) afforded after column chromatography (ethyl acetate–triethylamine, 20:1) the *title compound* **6** (0.018 g, 50%) as a colorless oil; R_f 0.10 (ethyl acetate–methanol, 1:1); $[\alpha]_D^{25}$ −20 (*c* 1.4 in $CHCl_3$) {lit.,[21] $[\alpha]_D^{25}$ −15.2 (*c* 0.53 in $CHCl_3$)}; δ_H($CDCl_3$) 6.15 (1H, dd, *J* 10.5 and 15.0, 2′-H), 6.03 (1H, ddd, *J* 1.5, 10.0 and 13.5, 3′-H), 5.72–5.62 (1H, m, 4′-H), 5.52 (1H, dd, *J* 7.0 and 15.0, 1′-H), 4.15–4.17 (1H, m, 4-H), 3.56 (1H, ddd, *J* 3.0, 7.0 and 10.5, 2-H), 3.09 (1H, td, *J* 3.0 and 12.0, 6-H^{ax}), 2.89 (1H, ddd, *J* 3.0, 3.5 and 12.0, 6-H^{eq}), 1.76 (5H, m, 3-H_2 and *Me*), 1.67–1.54 (4H, m, 5-H_2, N*H* and O*H*); δ_C($CDCl_3$) 132.1, 130.9, 129.5, 64.2, 52.6, 40.0, 38.9, 32.2, 18.0 [Found: (EI) 167.1319. $C_{10}H_{17}NO$ requires 167.1310].

(−)-(2*S*,4*R*)-2-Penta-1′,3′-dienylpiperidin-4-ol *(4-epi-SS 20846 A)* 7

Following the same decomplexation procedure, starting from piperidinol (+)-**23e** (0.083 g, 0.27 mmol), *piperidinol* (−)-**7** (0.026 g, 60%) was obtained as a white solid after chromatography (ethyl acetate–triethylamine, 20:1), mp 67–68 °C (diethyl ether); R_f 0.15 (ethyl acetate–methanol, 1:1); $[\alpha]_D^{25}$ −37 (*c* 1 in $CHCl_3$); δ_H($CDCl_3$) 6.14 (1H, dd, *J* 10.5 and 15.0, 2′-H), 6.03 (1H, ddd, *J* 1.5, 10.5 and 15.0, 3′-H), 5.68 (1H, m, 4′-H), 5.54 (1H, dd, *J* 6.5 and 15.0, 1′-H), 3.68 (1H, tt, *J* 4.5 and 11.0, 4-H), 3.18–3.10 (2H, m, 2-H and 6-H^{eq}), 2.68 (1H, td, *J* 2.5 and 12.5, 6-H^{ax}), 1.97 (2H, m, 5-H^{eq} and 3-H^{eq}), 1.75 (3H, dd, *J* 1.0 and 7.0, *Me*), 1.60 (2H, m, N*H* and O*H*), 1.36 (1H, m, 5-H^{ax}), 1.21 (1H, ddd, *J* 11.0, 11.5 and 12.0, 3-H^{ax}); δ_C($CDCl_3$) 132.7, 131.1, 130.3, 129.5, 69.0, 57.3, 44.5, 42.2, 35.5, 18.1; *m*/*z* (EI) 167 (M$^+$, 70%), 152 (67), 113 (78), 108 (76), 94 (54), 80 (100), 67 (35) [Found (EI): 167.1319. $C_{10}H_{17}NO$ requires 167.1310].

Following the same procedure, enantiomeric *piperidin-4-ol* (+)-**8** was prepared in 60% yield from (−)-**23a**; $[\alpha]_D^{25}$ 39 (*c* 1 in $CHCl_3$). Other structural data are identical with those reported for compound (−)-**7**.

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