Stereoselective Synthesis of Substituted Piperidines – Total Synthesis and Absolute Configurations of (+)- and (–)-Dienomycin C

Isabelle Ripoche,[a] Jean-Louis Canet,[a] Jacques Gelas,[a] and Yves Troin*[a]

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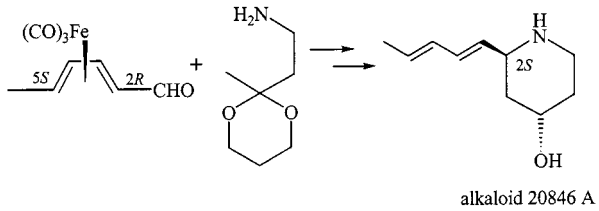
The first total asymmetric synthesis and the attribution of the absolute configurations of (+)-dienomycin C (**1**), an alkaloid isolated from a *Streptomyces* strain, are reported. This compound was prepared in six steps from the enantiopure tricarbonyl(dienal)iron complex (+)-**4** which is easily obtained by separating preformed diastereomers, starting from phenylpentadienoic acid and (*S*)-methyl mandelate.

Introduction

As piperidine alkaloids and synthetic analogues exhibit a large range of biological activities, the elaboration of versatile flexible regio- and stereoselective syntheses of chiral piperidines is of great interest to organic chemists and pharmaceutical research. The intramolecular Mannich-type cyclisation reaction is one of the strategies[1] used for the diastereoselective preparation of functionalised five- or six-membered N-heterocyclic compounds.[2] In this field, the authors have recently described an efficient approach for the construction of the piperidine nucleus, which allows the stereoselective introduction of a dienyl group in the 2-position of the heterocyclic system.[3] Using this methodology, the stereocontrol is obtained by the use of planar chiral tricarbonyl(dienal)iron complexes, which display a directing effect upon the intramolecular cyclisation.[3] This synthetic pathway has been applied to the synthesis of alkaloid SS 20846 A,[4] and through this study it was demonstrated that the use of a tricarbonyl[(2*R*)-dienal]iron complex led primarily to a (2*S*)-alkylated piperidine ring (see Scheme 1).



Scheme 1

The authors now wish to report an extension of this strategy to the enantioselective synthesis of 2,3,4-trisubstituted piperidines, through its application to the first total enantioselective synthesis[5] of (+)- and (−)-dienomycin C (**1**).

(+)-Dienomycin C (**1**)[6a] is an alkaloid, isolated from a *Streptomyces* strain (MC. 67−C1), which shows moderate antibiotic activity against *Mycobacteria*.[6b] This alkaloid is characterised by three consecutive asymmetric centres, and in particular by an axial situation of a hydroxy group at the C-4 position. While the relative configurations of this compound are well established, the absolute configurations of the natural isomer are still undetermined (see Figure 1).

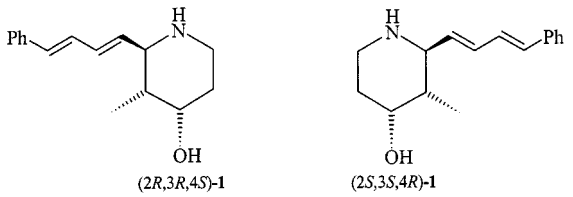


Figure 1

The retrosynthetic analysis proposed for target molecule **1** is presented in Scheme 2. Compound **1** was expected to arise by the stereoselective reduction of the carbonyl group of 4-piperidone **2**, which in turn, could be easily obtained from the chiral complex **4** and the amine **5** by deacetalisation and decomplexation of the piperidine **3**. According to the mechanism proposed,[4] and knowing the absolute configuration of complex **4**, it should, in turn, be possible to determine the absolute configuration of the three stereogenic centres.

Results and Discussion

Since the absolute configurations of (+)-dienomycin C (**1**) were still unknown, the synthesis with both enantiomers of the starting complex was carried out. Preparation of enantiopure aldehyde complexes (+)-**4** and (−)-**4** was conveniently achieved by chromatographic separation of the preformed diastereomers **6a**,**b**, readily available from commercial phenylpentadienoic acid. It was found that the use of (*S*)-methyl mandelate as a chiral derivating agent in place of (*S*)-octan-2-ol, the agent proposed for this separation,[7] allowed a facile (ΔR_f = 0.08 vs. 0.04) large-scale preparation of homochiral $Fe(CO)_3$(phenylpentadienoic acid) derivatives. Thus, the diester complexes **6a**,**b** were prepared

[a] Laboratoire de Chimie des Hétérocycles et des Glucides, Ecole Nationale Supérieure de Chimie de Clermont-Ferrand, Université Blaise Pascal, Ensemble Scientifique des Cézeaux,
B. P. 187, F-63174 Aubière cedex, France
Fax: (internat.) + 33-4/73407008
E-mail: troin@chimtp.univ-bpclermont.fr

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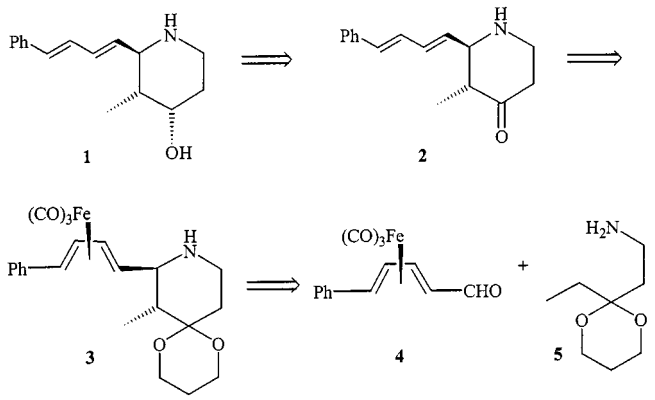


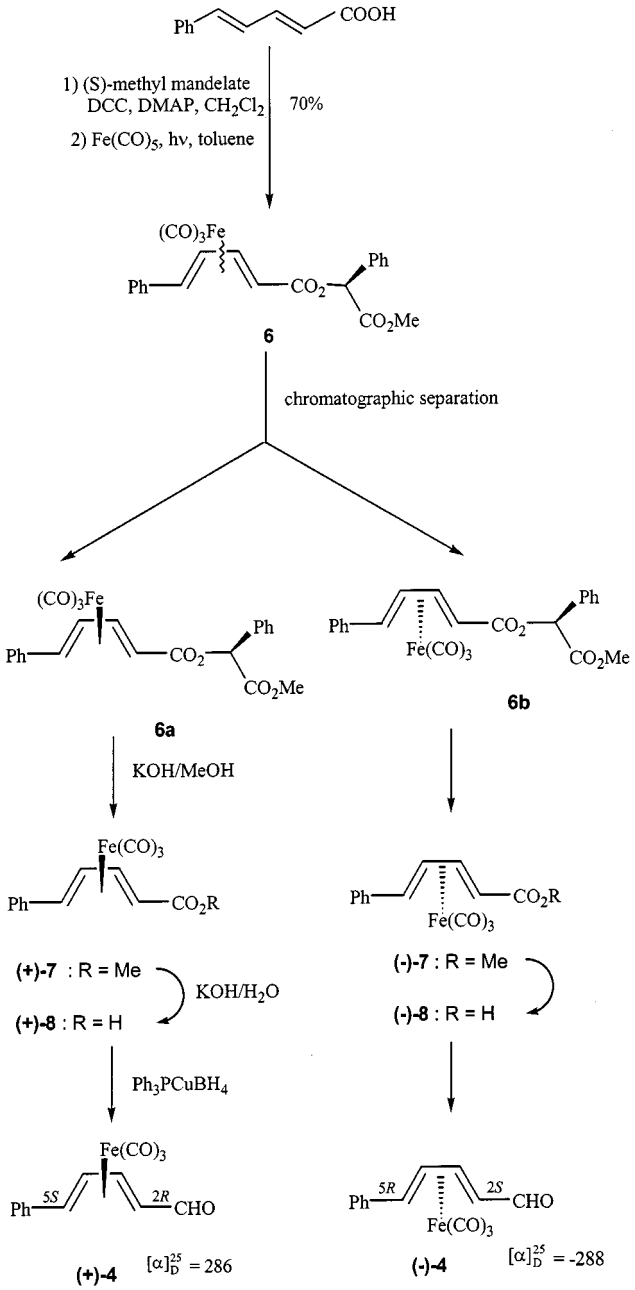
Scheme 2

in 70% yield using conventional procedures. Chromatographic separation followed by saponification, then (triphenylphosphane)copper tetrahydroborate[8] reduction afforded both enantiopure[9] complexed aldehydes (+)-**4** and (−)-**4** (see Scheme 3).

Condensation of (+)-**4** with the amine **5**[10] in anhydrous dichloromethane, in the presence of magnesium sulphate as a drying agent, led quantitatively (TLC control) to the transient imine **9**, which was directly treated with *p*-toluenesulfonic acid (2 equiv.) in dichloromethane/toluene (1:1) at 60°C. Purification of the resulting mixture by column chromatography furnished four stereoisomers, in an overall yield of 70%, two by two corresponding to the Ψ *endo* (**3a**, **b**) and the Ψ *exo* (**10a**, **b**) series[11] (see Scheme 4).

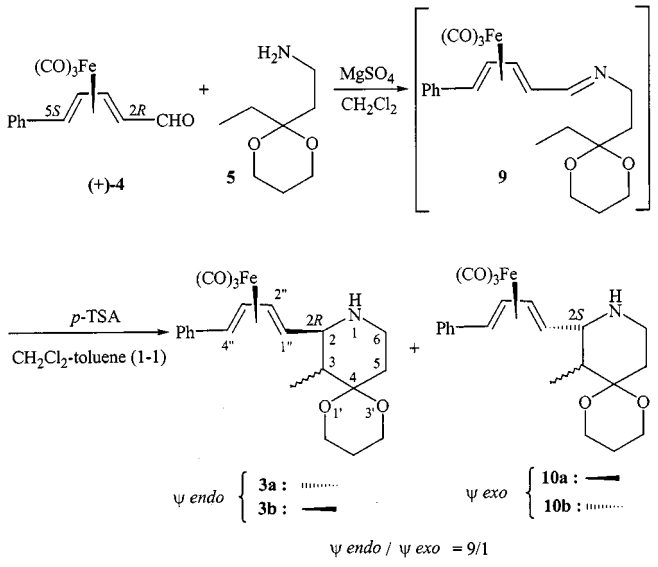
As expected, the Ψ *endo* isomers were the major products[4] in the ratio Ψ *endo*/Ψ *exo* = 9:1. The Ψ *endo* isomers were easily separated, and **3a** and **3b** were obtained in 54% and 9% yields, respectively, while it was not possible to separate the more polar Ψ *exo* isomers (**10a**,**b**: 7% yield). It was then decided to focus attention on compound **3a**, characterised by a *trans*-diaxial relation between 2-H and 3-H, which presents the required stereochemistry for the elaboration of the dienomycin C skeleton. Thus, treatment of piperidine **3a** with Fmoc-Cl in the presence of Hünig's base gave the *N*-protected piperidine[12] **11** in a yield of 91% (see Scheme 5).

Cleavage of the dioxane appendage[13] to furnish the desired piperidone (+)-**12** (85%) was then easily realised using 40% aqueous trifluoroacetic acid. *N*-Deprotection of this compound was realised using piperidine in THF and gave the unstable 4-piperidone (+)-**13** (70%), which was stereoselectively reduced[14] by L-Selectride® to give exclusively the expected axial piperidinol (+)-**14** (70%). Finally, decomplexation of (+)-**14** with anhydrous trimethylamine *N*-oxide (TMANO)[15] gave, in a 60% yield, the optically pure natural isomer (+)-dienomycin C (**1**), as proven by capillary electrophoresis[16] {$[\alpha]_D^{25} = +72$ ($c = 1.5$ in MeOH), ref.[6a] $[\alpha]_D^{25} = +85$}. The structure of the synthetic dienomycin C was unambiguously verified by comparison of ^{1}H-NMR data with those of the natural compound[6a] and synthetic (±)-4-*epi*-dienomycin C. Particularly relevant was the value

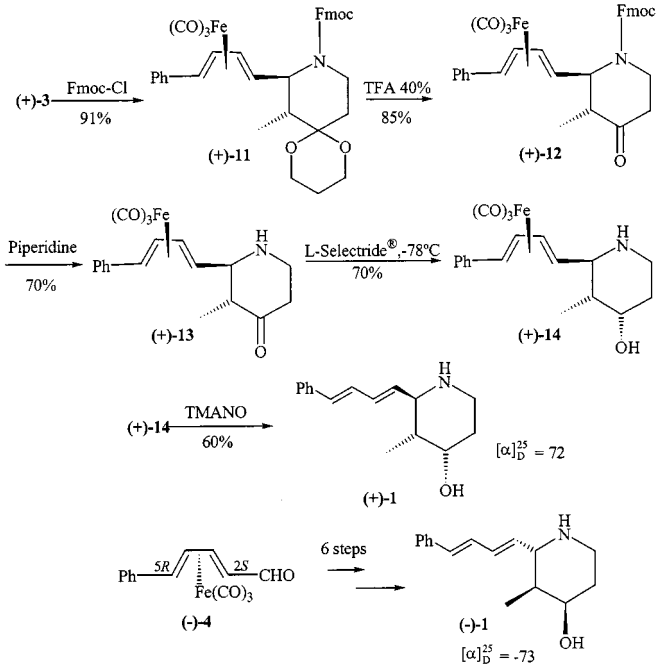


Scheme 3

of the chemical shift of 4-H (δ = 3.94 in the natural compound; δ = 3.27 for its C-4 epimer). Considering the difference between optical rotations values, confirmation of the result through the synthesis of non-natural (−)-dienomycin C (**1**) was desirable. Starting from dienal complex (−)-**4**, enantiopure[16] (−)-**1** was obtained by the same pathway. The optical rotation {$[\alpha]_D^{25} = -73$ ($c = 1.0$ in MeOH)} was in close agreement with that observed for synthetic (+)-**1**. Moreover, since the cyclisation mechanism allows the prediction of a newly created C-2 centre, it is assumed that natural (+)-dienomycin C (**1**), prepared from dienal complex (+)-(2*R*,5*S*)-**4**, presents the (2*R*,3*R*,4*S*) absolute configurations for its three contiguous asymmetric centres.



Scheme 4



Scheme 5

Conclusion

The first enantioselective preparation of the 2,3,4-substituted piperidine alkaloid dienomycin C (**1**) by a diastereoselective intramolecular Mannich reaction using planar (dienal)iron complexes has been described. Moreover, the absolute configuration of the natural compound has been established. The methodology described throughout this synthesis, employing readily available starting materials, could be applied to a wide range of substrates and provides a simple highly enantioselective synthesis of both enantiomers of 2,3,4-trisubstituted piperidines.

Experimental Section

General: M.p.: Uncorrected values. – IR: Perkin–Elmer Paragon 1000 FTIR spectrometer. – ^{1}H and ^{13}C NMR: Bruker AC 400 spectrometer (400.13 and 100.61 MHz, respectively), chemical shifts are reported in ppm relative to TMS as internal standard. – Electron impact (EI) mass spectra: Hewlett Packard 5989 B spectrometer (70 eV). – Fast atom bombardment (FAB) mass measurements: CRMPO (Université de Rennes) with a Varian Mat 311 spectrometer. – Optical rotations: Jasco DIP 370 polarimeter (589 nm). – Column and flash column chromatography: Silica gel (70–230 mesh and 230–400 mesh respectively). – Solvents: Dried and freshly distilled according to usual procedures. – All reactions werecarried out under argon. – Product solutions were dried with Na_2SO_4 prior to evaporation of the solvents under reduced pressure in a rotatory evaporator.

Tricarbonyl[(1*S*)-methoxycarbonyl(phenyl)methyl (2*R*,5*S*)-(2,3,4,5-η)-5-phenylpenta-2,4-dienoate]iron (6a) and Tricarbonyl[(1′*S*)-methoxycarbonyl(phenyl)methyl (2*S*,5*R*)-(2,3,4,5-η)-5-phenylpenta-2,4-dienoate]iron (6b): Dicyclohexylcarbodiimide (DCC) (3.96 g, 19.2 mmol) and DMAP (15 mg) were added to a stirred solution of 5-phenylpenta-2,4-dienoic acid (2.8 g, 16.1 mmol) and (*S*)-methylmandelate (3.5 g, 21.1 mmol) in CH_2Cl_2 (80 mL) at 0°C. The resulting mixture was stirred at room temp. overnight before filtering in order to remove the dicyclohexylurea formed. The filtrate, washed successively with 1 N aqueous HCl, satd. aqueous $NaHCO_3$, and brine, was dried and concentrated. The crude product was chromatographed (Et_2O/cyclohexane, 1:7) to give the methoxycarbonyl(phenyl)methyl 5-phenylpenta-2,4-dienoate (3.90 g, 85%), R_f = 0.5 (Et_2O/cyclohexane, 1:4). – ^{1}H NMR ($CDCl_3$): δ = 7.60–7.30 (m, 11 H), 6.92 (m, 2 H), 6.13 (d, 1 H, J = 15.1), 6.05 (s, 1 H), 3.75, (s, 3 H). – ^{13}C NMR ($CDCl_3$): δ = 166.2, 146.3, 141.5, 136.0, 129.3, 128.9, 127.8, 127.4, 126.1, 119.9, 74.5, 52.7.– $Fe(CO)_5$ (2.8 mL, 20.7 mmol) was added to a degassed solution (argon, 30 min) of methoxycarbonyl(phenyl)methyl 5-phenylpenta-2,4-dienoate (3.7 g, 11.5 mmol) in toluene (150 mL) prepared in a pyrex vessel. The stirred resulting solution was irradiated with a medium-pressure mercury lamp (400 W) for 8 h. After filtration, the solvent was evaporated. Chromatography on silica gel (Et_2O/cyclohexane, 1:9) yielded the diastereomeric complexes **6a** (2.20 g, 41%) and **6b** (2.30 g, 43%) as orange crystals. – **6a**: M.p. 124–125°C. – R_f = 0.43 (Et_2O/cyclohexane, 1:4), – $[\alpha]_D^{25}$ = + 127 (c = 1.0, acetone). – IR ($CHCl_3$): $\tilde{\nu}$ = 3020 cm^{-1}, 2061, 1998, 1753, 1710. – ^{1}H NMR ($CDCl_3$): δ = 7.55–7.15 (m, 12 H), 6.03–5.93 (m, 3 H), 3.75 (s, 3 H), 2.45 (d, 1 H, J = 8.4),1.49 (d, 1 H, J = 6.9). – ^{13}C NMR ($CDCl_3$): δ = 171.7, 169.4, 138.6, 134.1, 129.2, 128.8, 127.9, 127.6, 126.6, 126.4, 82.7, 74.7, 62.9, 52.7, 44.8. – HRMS (FAB); $C_{23}H_{19}FeO_7 \cdot H^+$: calcd. 463.0480; found 463.0478. – **6b**: M.p. 124–125°C. – R_f = 0.51 (Et_2O/cyclohexane, 1:4). – $[\alpha]_D^{25}$ = –156 (c = 1.0, acetone). – ^{1}H NMR ($CDCl_3$): δ = 7.60–7.20 (m, 12 H), 6.05–5.95 (m, 2 H), 5.92 (s, 1 H), 3.75 (s, 3 H), 2.47 (d, 1 H, J = 9.6), 1.44 (d, 1 H, J = 8). – ^{13}C NMR ($CDCl_3$): δ = 171.7, 169.2, 138.9, 133.9, 129.9, 129.3, 128.9, 127.8, 127.2, 126.4, 82.8, 74.7, 62.5, 52.6, 44.7. – IR and HRMS data were identical with those reported for **6a**.

(+)-Tricarbonyl[methyl (2*R*,5*S*)-(2,3,4,5-η)-5-phenylpenta-2,4-dienoate]iron (7): KOH (4.9 mL of a 0.5 M methanol solution) was added to a stirred solution of the diester **6a** (3.60 g, 7.80 mmol) in methanol (25 mL). The resulting mixture was stirred at room temp. for 1 h before addition of ether (30 mL) and aqueous HCl (10 mL, 0.5 M). After separation, the aqueous layer was extracted with ether (2 × 30 mL). The combined organic extracts were washed with brine, dried, and concentrated. Product purification was achieved

by chromatography (AcOEt/cyclohexane, 1:9), giving (+)-**7** (1.14 g, 75%) as an orange solid. − M.p 112−113 °C. − R_f = 0.45 (AcOEt/cyclohexane, 1:6). − $[\alpha]_D^{25}$ = + 120 (*c* = 1.0, acetone). − ^{1}H NMR ($CDCl_3$): δ = 7.30−7.20 (m, 5 H,), 5.98 (m, 2 H, 3-H and 4-H), 3.70 (s, 3 H,), 2.37 (d, 1 H, *J* = 8.5, 5-H), 1.34 (d, 1 H, *J* = 7.5, 2-H). − ^{13}C NMR ($CDCl_3$): δ = 138.7, 129.0, 127.3, 126.4, 83.3, 82.5, 62.6, 51.9, 45.7. − HRMS (FAB); $C_{15}H_{13}FeO_5 \cdot H^+$: calcd. 329.0112; found 329.0125. − According to the same procedure, (−)-**7** was prepared in a yield of 77% from **6b**. − $[\alpha]_D^{25}$ = −125 (*c* = 1.0, acetone).

(+)-Tricarbonyl[(2*R*,5*S*)-(2,3,4,5-η)-5-phenylpenta-2,4-dienoic acid]-iron (8): KOH (15 mL of a 0.5 M solution in ethanol/water, 1:1) was added to a stirred solution of the complex (+)-**7** (1.1 g, 3.35 mmol) in ethanol (7.5 mL). The solution was stirred at room temp. for 5 h, then ether (30 mL) and water (15 mL) were added. After separation, the aqueous layer was acidified (1 N HCl) until pH = 2 and extracted with ether (3 × 20 mL). The combined organic extracts were washed with brine, dried, and concentrated to give pure acid (+)-**8** (0.92 g, 87%) as an orange solid. − M.p 188−189°C (decomp.). − R_f = 0.2 (AcOEt/cyclohexane, 1:3). − $[\alpha]_D^{25}$= +143 (*c* = 1.0, acetone) {ref.[9] $[\alpha]_D^{25}$ = +142 (*c* = 0.5, acetone)}. − ^{1}H NMR ($CDCl_3$): δ = 7.30−7.20 (m, 5 H), 6.00−5.96 (m, 2 H, 3-H and 4-H), 2.50 (m, 1 H, 5-H), 1.29 (d, 1 H, *J* = 7, 2-H). − ^{13}C NMR ($CDCl_3$): δ = 178.2, 138.6, 129.7 128.1, 127.2, 125.2, 83.6, 82.0, 62.2. − According to the same procedure, (−)-**8** was prepared in a yield of 86% from (−)-**7**. − $[\alpha]_D^{25}$ = −142 (*c* = 1, acetone) {(ref.[7] $[\alpha]_D^{25}$ = −139 (*c* = 0.5, acetone)}.

(+)-Tricarbonyl[(2*R*,5*S*)-(2,3,4,5-η)-5-phenylpenta-2,4-dienal]iron (4): Oxalyl chloride (470 μL, 4.6 mmol) was added to a stirred solution of the acid (+)-**8** (0.860 g, 2.74 mmol) in CH_2Cl_2 (20 mL) at 20°C. After 2 h, CH_2Cl_2 and excess of oxalyl chloride were removed in vacuo and the residue diluted with acetone (15 mL). The resulting mixture was transferred under argon to a stirred suspension of triphenylphosphane (1.2 g, 4.6 mmol) and (triphenylphosphane)copper tetrahydroborate (1.5 g, 2.5 mmol) in acetone (25 mL). The mixture was stirred for 2 h and then filtered. Concentration, followed by chromatography (Et_2O/cyclohexane, 1:8), afforded the pure aldehyde (+)-**4** (0.35 g, 70%) as an orange solid. − M.p. 118−119°C. − R_f = 0.45 (AcOEt/cyclohexane, 1:3). − $[\alpha]_D^{25}$ = + 286 (*c* = 1.0, acetone). − ^{1}H NMR ($CDCl_3$): δ = 9.26 (d, 1 H, *J* = 4.8), 7.35−7.20 (m, 5 H), 6.03 (dd, 1 H, *J* = 5.5 and 8, 3-H), 2.63 (d, 1 H, *J* = 9, 5-H), 1.60 (dd, 1 H, *J* = 4.5 and 8, 2-H). − ^{13}C NMR ($CDCl_3$): δ = 196.1, 138.2, 129.7, 129.0, 127.6, 126.5, 83.7, 81.6, 63.7, 54.4. − According to the same procedure, (−)-**4** was prepared in a yield of 70% from (−)-**8**. − $[\alpha]_D^{25}$= −288 (*c* = 0.9, acetone).

Intramolecular Mannich-Type Cyclisation with Complex (+)-(4): $MgSO_4$ (1 g), followed by a solution of protected aminobutanone **5**[10] (0.318 g, 2 mmol) in CH_2Cl_2 (2 mL), was added to a stirred solution of the (dienal)$Fe(CO)_3$ complex (+)-**4** (0.580 g, 1.95 mmol) in CH_2Cl_2 (20 mL). The resulting solution was heated at reflux for 3 h and then cooled at room temp. and transferred via a cannula into a solution of dry *p*-toluenesulfonic acid (0.730 g, 3.8 mmol) in toluene (20 mL). The mixture was heated at 70°C for 4 h. After being cooled to room temp., satd. aqueous $NaHCO_3$ (15 mL) was added and the protected piperidones were extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried, filtered, and concentrated. The residue was then purified by column chromatography (AcOEt) to afford piperidone complexes **3a** (0.463 g, 54%), **3b** (0.077 g, 9%), and an inseparable mixture of compounds **10a** and **10b** (0.060 g, 7%). − **3a**: Orange solid. − M.p 167−168°C (decomp.). − R_f = 0.40 (AcOEt/methanol, 9:1). − $[\alpha]_D^{25}$= + 350 (*c* = 1.0, methanol). − IR (KBr): $\tilde{\nu}$ = 2978 cm^{-1}, 2877, 2063, 1980, 1957. − ^{1}H NMR ($CDCl_3$): δ = 7.30−7.15 (m, 5 H), 5.78 (dd, 1 H, *J* = 5 and 10.5, 3′′-H), 5.34 (dd, 1 H, *J* = 5 and 9.5, 2′′-H), 4.05 (td, 1 H, *J* = 2.5 and 12), 3.93 (td, 1 H, *J* = 2.5 and 12), 3.85−3.78 (m, 2 H), 3.03 (ddd, 1 H, *J* = 3.5, 5 and 12, 6-H_{eq}), 2.80−2.70 (m, 2 H), 2.25 (dd, 1 H, *J* = 9.5 and 10, 2-H), 2.11 (d, 1 H, *J* = 9.5, 4′′-H), 2.08−1.97 (m, 1 H), 1.49 (td, 1 H, *J* = 7 and 10, 3-H), 1.40−1.33 (m, 2 H), 1.28 (dd, 1 H, *J* = 9.5 and 10, 1′′-H), 1.12, (d, 3 H, *J* = 7). − ^{13}C NMR ($CDCl_3$): δ = 139.3, 128.7, 126.8, 126.2, 97.6, 83.4, 79.2, 67.8, 62.8, 62.1, 59.5, 59.3, 47.4, 42.9, 28.2, 25.7, 9.9. − HRMS (FAB); $C_{22}H_{26}FeNO_5 \cdot H^+$: calcd. 440.1160; found 440.1131. − **3b:** R_f = 0.50 (AcOEt/methanol, 9:1). − ^{1}H NMR ($CDCl_3$): δ = 7.30−7.15 (m, 5 H), 5.83 (dd, 1 H, *J* = 5 and 9, 3′′-H), 5.32 (dd, 1 H, *J* = 5 and 9, 2′′-H), 4.05−3.85 (m, 4 H), 2.97 (m, 1 H, 6-H_{eq}), 2.78 (td, 1 H, *J* = 3 and 12, 6-H_{ax}), 2.67 (dd, 1 H, *J* = 3 and 9.5, 2-H), 2.31 (m, 1 H), 2.08−1.97 (m, 1 H), 1.49 (m, 1 H, 3-H), 1.40−1.33 (m, 2 H), 1.28 (dd, 1 H, *J* = 9.5 and 10, 1′′-H), 1.12 (d, 3 H, *J* = 7). − ^{13}C NMR ($CDCl_3$): δ = 139.3, 128.7, 126.8, 126.2, 98.9, 82.0, 79.9, 66.0, 61.4, 60.0, 58.9, 58.8, 42.9, 41.6, 28.0, 25.5, 10.0. − According to the same procedure, (−)-**3a** was prepared in a yield of 54% from (−)-**4**. − $[\alpha]_D^{25}$ = −343 (*c* = 1.0, methanol).

(+)-Tricarbonyl[(1*R*,4*S*)-(1,2,3,4-η)-1-{(2*R*,3*R*)-1-(fluoren-9-ylmethoxycarbonyl)-3-methyl-1,3-dioxa-1-azaspiro[5.5]undecan-2-yl}-4-phenylbutadiene]iron (11): Diisopropylethylamine (115 μL, 0.67 mmol) and FmocCl (0.184 g, 0.71 mmol) were added to a stirred solution of compound **3a** (0.280 g, 0.64 mmol) in dichloromethane (20 mL). After 20 min of stirring, water (5 mL) was added and the resulting mixture 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 (AcOEt/cyclohexane, 1:6) gave *N*-protected piperidone (+)-**11** (0.38 g, 90%) as a yellow solid. − M.p 86−87°C (ether). − R_f = 0.20 (AcOEt/cyclohexane, 1:3). − $[\alpha]_D^{25}$ = + 156 (*c* = 1.0, $CHCl_3$). − IR (KBr): $\tilde{\nu}$ = 3000 cm^{-1}, 2042, 1970, 1698, 1426. − ^{1}H NMR and ^{13}C NMR ($CDCl_3$): Due to the coexistence of amide rotamers, this compound gave complex spectra even at 70°C. − EI MS; *m*/*z* (%): 577 (44), 178 (100), 165 (34), 113 (53), 28 (45). − HRMS (FAB); $C_{37}H_{36}FeNO_7 \cdot H^+$: calcd. 662.1841; found 662.1811. − According to the same procedure, the enantiomeric protected piperidone (−)-**11** was prepared in a yield of 90% from (−)-**3a**. − $[\alpha]_D^{25}$ = −158 (*c* = 1.0, $CHCl_3$).

(+)-Tricarbonyl{(1*R*,4*S*)-(1,2,3,4-η)-1-[(2*R*,3*R*)-1-(fluoren-9-ylmethoxycarbonyl)-3-methyl-4-oxopiperidin-2-yl]-4-phenylbutadiene}iron (12): Trifluoroacetic acid (700 μL of a 40% aqueous solution) was added to a stirred solution of *N*-protected piperidine (+)-**11** (0.300 g, 0.45 mmol) in CH_2Cl_2 (20 mL) at 20°C. The resulting mixture was stirred for 10 h before addition of satd. 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 (AcOEt/cyclohexane, 1:6) to give piperidone (+)-**12** (0.231 g, 85%) as a yellow oil. − R_f = 0.30 (AcOEt/cyclohexane 1:3). − $[\alpha]_D^{25}$ = +156 (*c* = 1.0, methanol). − IR (KBr): $\tilde{\nu}$ = 2970 cm^{-1}, 2044, 1976, 1700, 1451. − ^{1}H NMR ($CDCl_3$): δ = Due to the coexistence of amide rotamers, this compound gave a complex spectrum even at 70 °C. − ^{13}C NMR ($CDCl_3$): δ = 210.8, 144.1, 139.1, 128.8, 127.8, 127.3, 126.9, 126.3, 125.0, 120.0, 82.3, 79.9, 67.0, 62.1, 61.7, 60.0, 47.7, 39.1, 37.1. − HRMS (FAB); $C_{34}H_{30}FeNO_6 \cdot H^+$: calcd. 604.1423; found 604.1413. − According to the same procedure the enantiomeric piperidone (−)-**12** was prepared in a yield of 85% from (−)-**11**. − $[\alpha]_D^{25}$ = −162 (*c* = 1.0, methanol).

(+)-Tricarbonyl{(1*R*,4*S*)-(1,2,3,4-η)-1-[(2*R*,3*R*)-3-methyl-4-oxopiperidin-2-yl]-4-phenylbutadiene}iron (13): Piperidine (2 mL) was added at room temp to a stirred solution of piperidine (+)-**12** (0.290 g, 0.48 mmol) in THF (15 mL). Stirring for 1 h, followed by concentration under reduced pressure and then column chromatography (AcOEt), gave complexed piperidone (+)-**13** (0.128 g, 70%) as a yellow solid. – M.p 106–107°C (Et_2O). – R_f = 0.35 (AcOEt). – $[\alpha]_D^{25}$ = + 343 (*c* = 1.0, methanol). – IR (KBr): $\tilde{\nu} \approx$ 2054 cm^{-1}, 1991, 1718, 1602, 1560. – ^1H NMR ($CDCl_3$): δ = 7.30–7.15 (m, 5 H), 5.84 (dd, 1 H, *J* = 5 and 9.5, 2′-H), 5.31 (dd, 1 H, *J* = 5 and 8.5, 3′-H), 3.46 (m, 1 H, 2-H), 2.91 (ddd, 1 H, *J* = 3, 11.5, and 12.5, 6-H_{ax}), 2.61 (td, 1 H, *J* = 7 and 13, 6-H_{eq}), 2.42–2.34 (m, 2 H), 2.21–2.15 (m, 2 H), 1.34 (dd, 1 H, *J* = 8.5 and 9.5, 1′′-H), 1.19 (d, 3 H, *J* = 7). – ^{13}C NMR ($CDCl_3$): δ = 209.4, 138.9, 128.9, 127.1, 126.3, 82.8, 79.7, 68.5, 65.6, 62.7, 52.8, 46.6, 42.1, 10.8. – HRMS (FAB); $C_{19}H_{20}FeNO_4 \cdot H^+$:calcd. 382.0742; found 382.0743. – According to the same procedure the enantiomeric piperidone (–)-**13** was prepared in a yield of 70% from (–)-**12**. – $[\alpha]_D^{25}$= –341 (*c* = 1.0, methanol).

(+)-Tricarbonyl[(1*R*,4*S*)-(1,2,3,4-η)-1-{(2*R*,3*R*,4*S*)-4-hydroxy-3-methylpiperidin-2-yl}-4-phenylbutadiene]iron (14): L-Selectride® (315 μL of a 1 M solution in THF, 0.315 mmol) was added dropwise to a cold (–78°C) stirred solution of (4-piperidone)$Fe(CO)_3$ complex (+)-**13** (0.084 g, 0.22 mmol) in THF (15 mL). After 10 min of stirring at –78°C, methanol (1 mL) was added and the resulting solution allowed to warm to room temp. Evaporation of the solvent under reduced pressure followed by column chromatography (AcOEt) gave 4-piperidinol (+)-**14** as a yellow oil (0.059 g, 70%). – R_f = 0.30 (AcOEt). – $[\alpha]_D^{25}$ = +360 (*c* = 1.0, methanol). – IR (KBr): $\tilde{\nu}$ = 3427 cm^{-1}, 2040, 1973. – ^1H NMR ($CDCl_3$): δ = 7.30–7.15 (m, 5 H), 5.80 (ddd, 1 H, *J* = 1, 5.5, and 9.5), 5.31 (ddd, 1 H, *J* = 1, 6, and 9.5), 3.94 (m, 1 H, 4-H), 3.03 (dt, 1 H, *J* = 3 and 12, 6-H_{ax}), 2.94 (ddd, 1 H, *J* = 2.5, 5 and 11.5, 6-H_{eq}), 2.33 (t, 1 H *J* = 9.5, 2-H), 2.10 (d, 1 H, *J* = 9.5, 4′-H), 1.90–1.82 (m, 1 H), 1.77 (m, 1 H), 1.55 (m, 1 H), 1.28 (m, 1 H),1.14 (d, 3 H, *J* = 8). – ^{13}C NMR ($CDCl_3$): δ = 139.3, 128.8, 126.8, 126.3, 83.2, 79.2, 69.7, 68.1, 62.1, 60.7, 42.5, 41.2, 33.9, 15.4. – EI MS; *m*/*z* (%): 383 (41), 355 (14), 327 (32), 299 (46), 226 (74), 148(59), 128 (73), 115 (86), 91 (100), 84 (72), 56 (74). – HRMS (FAB); $C_{19}H_{22}FeNO_4 \cdot H^+$: calcd. 384.0898; found 384.0901. – According to the same procedure enantiomeric 4-piperidinol (–)-**14** was prepared in a yield of 68% from (–)-**13**. – $[\alpha]_D^{25}$ = –367 (*c* = 1.0, methanol).

(+)-(2*R*,3*R*,4*S*)-Dienomycin C (1): Anhydrous trimethylamine *N*-oxide (TMANO) (0.087 g, 0.112 mmol) was added at 20°C to a stirred solution of piperidinol (+)-**14** (0.035 g, 0.09 mmol) in anhydrous acetone (10 mL). The resulting mixture was refluxed for 15 min, then cooled to room temp. Water (10 mL) was added, and the solution extracted with AcOEt (3 × 10 mL). The combined organic extracts were washed with water, brine, dried, and concentrated. Column chromatography (AcOEt/methanol, 5:1) afforded compound (+)-**1** (0.013 g, 60%) as a colourless oil. – R_f = 0.25 (AcOEt/methanol, 5:1). – $[\alpha]_D^{25}$ = + 72 (*c* = 1.5, methanol). – IR (KBr): $\tilde{\nu}$ = 3500–3200 cm^{-1}, 3000–2900, 1600, 1500, 1450. – ^1H NMR ($CDCl_3$): δ = 7.42–7.20 (m, 5 H), 6.77 (dd, 1 H, *J* = 10 and 15.5, 9-H), 6.52 (d, 1 H, *J* = 16, 10-H), 6.36 (dd, 1 H, *J* = 10.5 and 15, 8-H), 5.73 (dd, 1 H, *J* = 8 and 15, 7-H), 3.95 (m, 1 H, 4-H), 3.23 (dd, 1 H, *J* = 9 and 9.5, 2-H), 3.11 (m, 1 H, 6-H_{ax}), 2.87 (ddd, 1 H, *J* = 3.5, 4 and 11.5, 6-H_{eq}), 1.84–1.79 (m, 2 H, 5-H_{eq} and 5-H_{ax}), 1.60 (m, 2 H, NH and OH), 1.55 (dq, 1 H, *J* = 3 and 7, 3-H), 0.94 (d, 3 H, *J* = 7); the ^1H NMR spectrum was in good agreement with that reported for the natural compound.[6] – ^{13}C NMR ($CDCl_3$): δ = 137.3, 136.4, 132.2, 132.0, 128.7,128.6, 127.5, 126.4, 69.4, 59.4, 40.6, 40.2, 33.8, 15.1. – EI MS; *m*/*z* (%): 423 (100), 226 (63), 184 (33), 170 (32), 156 (37), 152 (25), 128 (26), 115 (27), 91 (40), 80 (42), 41 (25). – HRMS (FAB); $C_{16}H_{21}NO \cdot H^+$: calcd. 243.1625; found 243.1623. – According to the decomplexation procedure given for the preparation of compound (+)-**1**, enantiomeric dienomycin C (–)-**1** was prepared from piperidinol (–)-**14**. – $[\alpha]_D^{25}$ = –73 (*c* = 1.0, methanol).

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