Efficient Chiral Induction by Diene Iron-Tricarbonyl Moiety. IV.[1]: Asymmetric Total Synthesis of a Piperidine Alkaloid, SS20846A

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Received June 2, 1997; accepted August 8, 1997

By $LiClO_4$-catalyzed cycloaddition with Danishefsky's diene 5, an optically active 1-azatriene $Fe(CO)_3$ complex was converted into the 2-substituted dehydropiperidinone 8, from which a piperidine alkaloid 1 (SS20846A) was synthesized in an enantiomerically pure form *via* successive reduction and removal of the protecting groups. Although the reduction of the ketone 3 proceeded with *cis*-selectivity even with a hindered reducing agent, the desired *trans*-alcohol 4 could be obtained by the reaction with sodium borohydride in the presence of cerium(III) chloride. The *cis*-selective reduction of 3 originates from the equatorial attack of a hydride on conformer A, in which the diene $Fe(CO)_3$ moiety is axially oriented due to the severe steric hindrance with the *p*-methoxyphenyl (PMP) group on the nitrogen atom. However, the cerium salt reverses the stereoselectivity of the hydride reduction of 3.

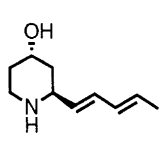
Key words piperidine alkaloid; iron-tricarbonyl complex; [4+2] type cycloaddition; SS20846A; hydride reduction; cerium(III) chloride

Heterocyclic compounds containing the piperidine ring system have attracted much interest by virtue of their varied and clinically useful biological actions. SS20846A (**1**) was first isolated from *Streptomyces* sp. S20846 in 1986 as a piperidine alkaloid which possesses a restrictive action upon the digestive system.[2] Later, **1** was proposed to be a biosynthetic intermediate of streptazolin, which has strong antimicrobial activity[3] (Fig. 1). Though **1** appears to be a novel lead compound for agents with anticonvulsant activity, it has not been synthesized, and its absolute stereochemistry is still unknown. We, therefore, decided to synthesize **1** starting from a chiral dienal $Fe(CO)_3$ complex **2**[4] with the aim of determining the absolute stereochemistry. Our retrosynthetic analysis is shown in Chart 1. The 4-piperidinone skeleton could be constructed by a [4+2] type cycloaddition of a 1-azatriene $Fe(CO)_3$ complex derived from **2** with 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene (Danishefsky's diene) **5**. The cycloaddition had been developed in our laboratory and demonstrated to proceed with high stereoselectivity and a predictable stereochemical course.[5a,b] The successive reductions of the 4-piperidinone would provide the 4α-alcohol **4**, from which the two protecting groups can be removed by oxidative treatment to give the desired product **1**. After examination of the synthetic route, we found that the hydride reduction of **3** tends to afford the 4β-alcohol **9**, but not the desired product **4**. However, the reaction with sodium borohydride in the presence of cerium(III) chloride gave **4** as a major product. We have already described the first asymmetric synthesis of **1** in a previous communication.[5b] The report details the asymmetric synthesis of **1** and determination of its absolute stereochemistry, along with some results concerning the reduction of **3** to the *trans*-alcohol **4**.

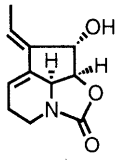
Results and Discussion

Although the chiral non-racemic dienal complex (2*R*)-**2** has been prepared by several groups,[4] these methods are not convenient for a large-scale preparation. Therefore, we first started to develop a more efficient route to (2*R*)-**2**. For this purpose, we chose a known compound **6**[6] as a chiral starting material. Hydrolysis of the ester **6** with a 4 M KOH solution in refluxing ethanol gave the corresponding carboxylic acid **7**,[7] which was converted into **2** by sequential chlorination and reduction with $(PPh_3)_2$-$CuBH_4$.[8] From our previous report,[5] it was clear that a PMP (*p*-methoxyphenyl)imine was the best choice for the next cyclization in terms of diastereoselectivity and ease of removal. Then, **2** was condensed with *p*-anisidine and reaction of the corresponding imine complex with **5** in methylene chloride in the presence of an equivalent amount of $LiClO_4$ at room temperature gave the dehydropiperidinone (6*S*,1′*R*)-**8** in 84% yield with high diastereoselectivity.

Having the requisite cycloadduct **8** in hand, we next examined the transformation of **8** into the natural product

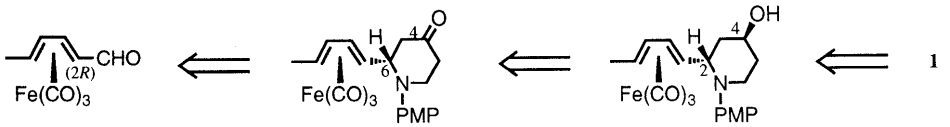


SS20846A (**1**)



Streptazolin

Fig. 1



2 **3** (PMP = p-methoxyphenyl) **4**

Chart 1

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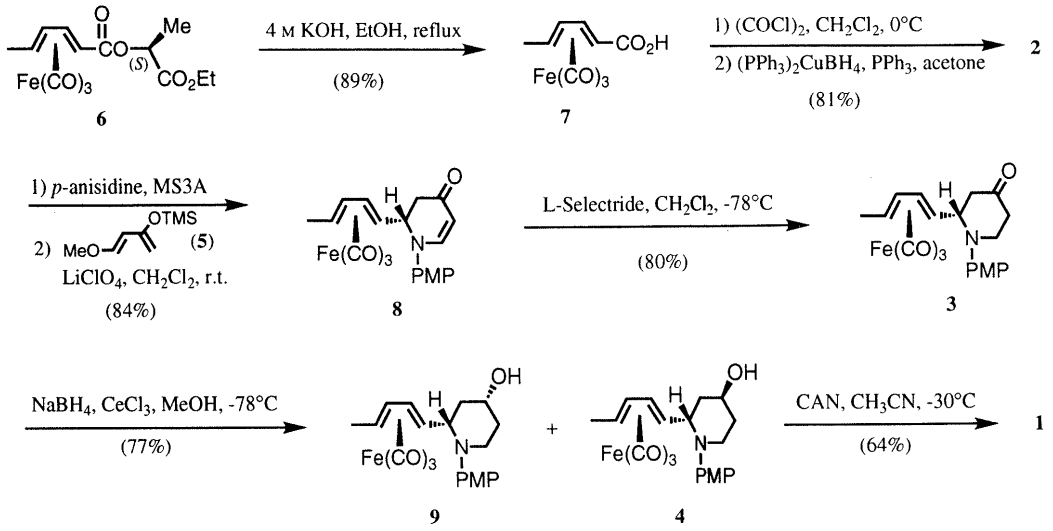

Chart 2

Table 1. Reduction of the 4-Piperidinone **3** with Several Reducing Agents

Entry	Reaction conditions	Yield (%)	Ratio (**4**/**9**)
1	L-Selectride, THF, −78 °C	92	11/89[a]
2	DIBAL-H, CH_2Cl_2, −78 °C	81	39/61[b]
3	$NaBH_4$, MeOH, 0 °C	83	29/71[b]
4	$NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, −78 °C	77	70/30[a]

a) These values were calculated from the isolated yields. *b*) These values were determined by measuring ^{1}H-NMR spectra of the mixture of **4** and **9**.

1. Although the conjugate reduction of **8** with L-Selectride proceeded smoothly to give rise to the saturated ketone **3** in 80% yield, the following 1,2-hydride reduction of **3** was troublesome. In the expectation of predominant production of the 2,4-*trans*-adduct **4**, generated from the equatorial attack of a hydride on a chair-like conformer,[9a,b] **3** was treated with L-Selectride at −78 °C. However, the 2,4-*cis*-adduct **9** was obtained in 82% yield as a major product along with a 10% yield of **4** (Table 1, entry 1). From a nuclear Overhauser effect (NOE) experiment on the ketone **3**, it was found that the diene $Fe(CO)_3$ moiety of **3** is axially located in the preferred conformer A to avoid severe interaction with the protecting group (PMP) on the nitrogen (Fig. 2). Therefore, the hydride would attack the ketone of **3** predominantly from the β-site of conformer A due to the 1,3-diaxial interaction with the diene $Fe(CO)_3$ complex on C2 to give the *cis*-adduct **9**. Table 1 shows that **9** was always a major product, irrespective of the reducing reagent employed. Even using less hindered reagents such as diisobutylaluminum hydride (DIBAL-H) and sodium borohydride (entries 2, 3), there were only marginal increases in the yield of **4** and we could not reverse the ratio of **4**/**9**. After many experiments, we finally found that reduction of **3** with sodium borohydride in methanol in the presence of cerium(III) chloride[9c] afforded the desired *trans*-adduct 4 as a major product (total 77% yield, **4**/**9**=70/30) (entry 4). Though the role of $CeCl_3$ in reversing the ratio of **4**/**9** is not clear, it is assumed that the coordination of cerium salts to the ketone and/or amine groups at the less hindered site, that is

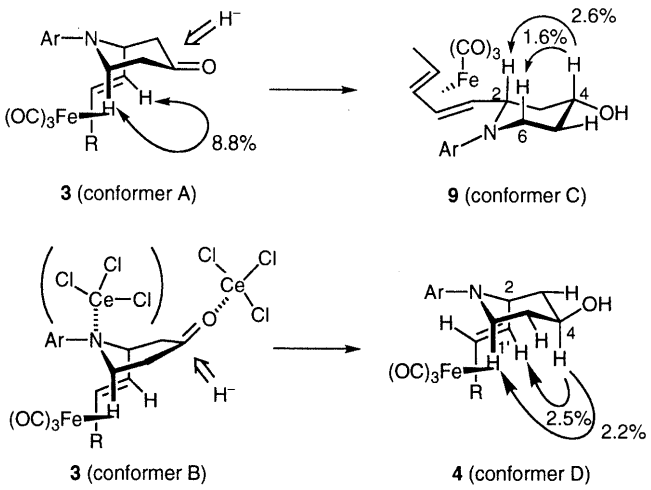

Fig. 2. Plausible Mechanism of the Reduction of **3** to **4** and **9** and the Results of NOE Experiments

the upper side, obliges the hydride to change its reaction trajectory from downward to upward (Fig. 2 B).

The relative stereochemistries of **4** and **9** were determined from NOE experiments (500 MHz ^{1}H-NMR). The observation of NOE enhancement between C4-H and C1′-H in **4** indicates that the hydroxyl group at C4 is located *trans* to the diene $Fe(CO)_3$ group at C2, that is, **4** is a (2*S*,4*S*,1′*R*)-adduct (Fig. 2 D). On the other hand, the observation of NOE enhancement between C4-H and C2-H in **9** indicates that the hydroxyl group at C4 is located *cis* to the diene $Fe(CO)_3$ group at C2, that is **9** is a (2*S*,4*R*,1′*R*)-adduct (Fig. 2 C).

Finally, simultaneous removal of the protecting groups [PMP, $Fe(CO)_3$] was accomplished by treatment of the *trans*-adduct **4** with ceric(IV) ammonium nitrate (CAN)[10] in acetonitrile to give a synthetic natural product (SS20846A) in a chiral form (2*S*,4*S*). Judging from the spectral data, the synthetic sample is identical to the natural product.[1,2] Furthermore, the specific rotation of **1**, $[\alpha]_D^{24}$ −15.2° (c=0.53, $CHCl_3$) [lit. $[\alpha]_D^{20}$ −15° (c=1.00, $CHCl_3$)[2b]], confirms that our synthetic sample has the same absolute configuration as the natural product.

These results indicate that the natural SS20846A has (2*S*,4*S*)-configuration.

We have succeeded in the first asymmetric synthesis of SS20846A in an enantiomerically pure form by using 1) a highly stereoselective [4+2] type cycloaddition of the PMP-imine $Fe(CO)_3$ complex with Danishefsky's diene **5** in the presence of $LiClO_4$ and 2) a $CeCl_3$-mediated hydride reduction of the *N*-substituted 4-piperidinone **3** to the desired 2,4-*trans*-alcohol **4**.

Experimental

All melting points were determined with a Yanagimoto MP-21 melting point apparatus and are uncorrected. Optical rotations were measured using a JASCO DIP-360 digital polarimeter. IR spectra were measured with a Horiba FT-210 IR spectrometer using a neat sample on KBr powder by the diffuse reflection measurement method. ^{1}H-NMR spectra were measured with a JEOL JNM-GX500 spectrometer (500 MHz). ^{13}C-NMR spectra were measured with a Varian VXR-200 spectrometer (50 MHz). All signals are expressed as ppm downfield from tetramethylsilane used as an internal standard (δ value). The following abbreviations are used: singlet (s), doublet (d), triplet (t), multiplet (m), broad (br). Mass spectra were taken with a Shimadzu QP-1000 mass spectrometer. High-resolution mass spectra (HR-MS) were measured with a JEOL JMS-D300 spectrometer. Unless otherwise noted, all reactions were performed in anhydrous solvents. Merck Kieselgel 60 was used as an adsorbent for column chromatography. All extracts were dried over anhydrous $MgSO_4$.

(2*R*,5*S*)-Tricarbonyl[2-5-η-(2*E*,4*E*)-2,4-hexadienal]iron (2) A 4 M aqueous solution of potassium hydroxide (3 ml) was added to a solution of **6** (430 mg, 1.22 mmol), prepared according to the reported procedure,[6] in ethanol (12 ml), and the mixture was refluxed for 2 h. After acidification with 10% HCl solution at 0 °C, the mixture was extracted with dichloromethane three times and the combined extracts were dried and concentrated *in vacuo*. The residue was purified by SiO_2 column chromatography with $CHCl_3$/MeOH = 15/1 to give the carboxylic acid **7** (273 mg, 89%). Oxalyl chloride (167 μl, 1.90 mmol) was added to a solution of **7** (239 mg, 0.948 mmol) in CH_2Cl_2 (4 ml) at 0 °C under a nitrogen atmosphere. After having been stirred at room temperature for 2 h, the mixture was concentrated *in vacuo* to give an oily residue. A solution of the crude residue in acetone (3 ml) was added to a mixture of $(PPh_3)_2CuBH_4$ (865 mg, 1.42 mmol), PPh_3 (7.45 mg, 2.84 mmol), and acetone (10 ml) at room temperature and the whole was stirred for 1 h. It was filtered through a pad of Celite, and the filtrate was concentrated *in vacuo*. The residue was purified by SiO_2 column chromatography with AcOEt/hexane = 1/10 to give the aldehyde **2** (182 mg, 81%) as a yellow oil. $[\alpha]_D^{22}$ −112° (c = 0.770, $CHCl_3$); lit. $[\alpha]_D$ −112° (c = 1.0, $CHCl_3$).[1] ^{1}H-NMR ($CDCl_3$) δ: 1.26 (dd, 1H, J = 4.3, 8.5 Hz, C2-H), 1.51 (d, 3H, J = 6.1 Hz, C6-Me), 1.70 (qd, 1H, J = 6.1, 8.5 Hz, C5-H), 5.29, (dd, 1H, J = 4.9, 8.5 Hz, C4-H), 5.76 (dd, 1H, J = 4.9, 8.5 Hz, C3-H), 9.26 (d, 1H, J = 4.3 Hz, C1-H). IR (KBr): 2069 (CO), 1992 (CO), 1979 (CO), 1676 (C=O), 1657 (C=O) cm^{-1}. MS m/z (%): 236 (M^+, 43), 180 (49), 179 (29), 152 (100), 151 (56), 148 (46).

(6*S*,1′*R*,4′*S*)-Tricarbonyl[1′-4′-η-(1′*E*,3′*E*)-2,3-didehydro-1-*p*-methoxyphenyl-6-(1′,3′-pentadienyl)piperidin-4-one]iron (8) A mixture of **2** (892 mg, 3.78 mmol), *p*-anisidine (466 mg, 3.78 mmol), 3A molecular sieves (MS 3A) (900 mg), and dry benzene (20 ml) was stirred at room temperature for 2 h. Concentration of the reaction mixture *in vacuo* gave the desired product (361 mg). ^{1}H-NMR ($CDCl_3$) δ: 1.49 (d, 3H, J = 6.0 Hz, C5-Me), 1.59 (m, 1H, C5-H), 1.79 (dd, 1H, J = 7.6, 8.4 Hz, C2-H), 3.80 (s, 3H, OMe), 5.23 (dd, 1H, J = 4.9, 9.0 Hz, C4-H), 5.69 (dd, 1H, J = 4.9, 8.4 Hz, C3-H), 6.86 (d, 2H, J = 9.0 Hz, Ar-H), 7.03 (d, 2H, J = 9.0 Hz, Ar-H), 7.62 (d, 1H, J = 7.6 Hz, ArN=C<u>H</u>). IR (KBr): 2029 (CO), 1952 (CO), 1618, 1508, 1273, 1244, 1038 cm^{-1}. MS m/z (%): 341 (M^+, 1.0), 313 (52), 200 (100). Lithium perchlorate (403 mg, 3.79 mmol) was added to a solution of the imine (1.29 g, 3.78 mmol) and **5** (1.30 g, 7.57 mmol) in CH_2Cl_2 (20 ml) at room temperature and the resulting suspension was stirred at room temperature for 8 h. The reaction was quenched with aqueous $NaHCO_3$ solution, and the mixture was extracted with CH_2Cl_2. The extract was washed with water and brine, dried, and then concentrated *in vacuo*. The residue was chromatographed (hexane/AcOEt = 1/1) to give **8** as a sole product (1.30 g, 84%). A yellow oil. $[\alpha]_D^{21}$ +16.2° (c = 2.75, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.09 (qd, 1H, J = 6.8, 8.6 Hz, C4′-H), 1.24 (dd, 1H, J = 6.8, 7.7 Hz, C1′-H), 1.36 (d, 3H, J = 6.8 Hz, C4′-Me), 2.58 (br , 1H, J = 16.2 Hz, C5-Ha), 3.08 (dd, 1H, J = 6.0, 16.2 Hz, C5-Hb), 3.84 (s, 3H, OMe), 4.08 (br dd, 1H, J = 6.0, 6.8 Hz, C6-H), 5.07 (m, 2H, C2′-H, C3′-H), 5.12 (d, 1H, J = 7.7 Hz, C3-H), 6.95 (m, 2H, Ar-H), 7.17 (m, 2H, Ar-H), 7.30 (dd, 1H, J = 1.7, 7.7 Hz, C2-H). ^{13}C-NMR ($CDCl_3$) δ: 18.8 (C4′-Me), 42.5 (C5), 55.5 (OMe), 56.9 (C4′), 58.8 (C1′), 61.4 (C6), 80.5 (C2′), 85.8 (C3′), 100.1 (C3), 114.8 (C2), 123.0 (ArC), 137.2 (ArC), 148.8 (ArC), 157.4 (ArC), 190.2 (C4), 211.5 (CO). IR (KBr): 2040 (CO), 1965 (CO), 1643 (C=O), 1579, 1510, 1247, 1036 cm^{-1}. MS m/z (%): 409 (M^+, 0.1), 382 (1.8), 354 (19.1), 326 (100). *Anal.* Calcd for $C_{20}H_{19}FeNO_5$: C, 58.70; H, 4.68; N, 3.42. Found: C, 58.78; H, 4.77; N, 3.34.

(2*S*,1′*R*,4′*S*)-Tricarbonyl[1′-4′-η-(1′*E*,3′*E*)-1-*p*-methoxyphenyl-2-(1′,3′-pentadienyl)piperidin-4-one]iron (3) A 1 M solution of L-Selectride in tetrahydrofuran (THF) (1.47 ml) was added to a stirred solution of **8** (400 mg, 0.978 mmol) in CH_2Cl_2 (10 ml) at −78 °C under a nitrogen atmosphere and the whole was stirred for 1 h. The mixture was quenched with a saturated $NaHCO_3$ solution and extracted with CH_2Cl_2 three times. The combined extracts were washed with water and brine, dried, and then concentrated *in vacuo*. The residue was purified by SiO_2 column chromatography with hexane/AcOEt = 3/1 to give **3** (322 mg, 80%) as a yellow oil: $[\alpha]_D^{20}$ −48.9° (c = 0.741, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.90 (dd, 1H, J = 7.7, 8.6 Hz, C1′-H), 1.11 (qd, 1H, J = 6.0, 8.6 Hz, C4′-H), 1.37 (d, 3H, J = 6.0 Hz, C4′-Me), 2.33 (dd, 1H, J = 3.4, 14.5 Hz, C5-H_{eq}), 2.47 (br d, 1H, J = 13.7 Hz, C3-H_{eq}), 2.58 (ddd, 1H, J = 6.8, 12.0, 14.5 Hz, C5-H_{ax}), 2.80 (dd, 1H, J = 6.0, 13.7 Hz, C3-H_{ax}), 3.51 (ddd, 1H, J = 3.4, 12.0, 13.7 Hz, C6-H_{ax}), 3.7—3.9 (m, 1H, C6-H_{eq}), 3.78 (s, 3H, OMe), 4.01 (dd, 1H, J = 6.0, 7.7 Hz, C2-H), 5.01 (dd, 1H, J = 5.1, 8.6 Hz, C3′-H), 5.10 (dd, 1H, J = 5.1, 8.6 Hz, C2′-H), 6.86 (d, 2H, J = 9.2 Hz, Ar-3″H), 6.94 (d, 2H, J = 9.2 Hz, Ar-2″H). ^{13}C-NMR ($CDCl_3$) δ: 18.8 (C5′), 39.9 (C5), 43.7 (C6), 46.0 (C3), 55.4 (OMe), 58.1 (C4′), 60.6 (C1′), 61.5 (C2), 81.6 (C2′), 85.4 (C3′), 114.6 (ArC), 117.8 (ArC), 142.0 (ArC), 153.5 (ArC), 208.1 (C4), 211.6 (CO). IR (KBr): 2040 (CO), 1971 (CO), 1713 (C=O), 1512, 1261, 1248, 1036 cm^{-1}. MS m/z (%): 411 (M^+, 3.1), 328 (21), 327 (100). *Anal.* Calcd for $C_{20}H_{21}FeNO_5$: C, 58.41; H, 5.15; N, 3.41 Found: C, 58.30; H, 5.16; N, 3.35.

(2*S*,4*S*,1′*R*,4′*S*)-Tricarbonyl[1′-4′-η-(1′*E*,3′*E*)-1-*p*-methoxyphenyl-2-(1′,3′-pentadienyl)piperidin-4-ol]iron (4) and (2*S*,4*R*,1′*R*,4′*S*)-Tricarbonyl[1′-4′-η-(1′*E*,3′*E*)-1-*p*-methoxyphenyl-2-(1′,3′-pentadienyl)piperidin-4-ol]iron (9) (Table 1, Entry 1): A 1 M solution of L-Selectride in THF (1.47 ml) was added to a stirred solution of **3** (32.0 mg, 0.0778 mmol) in CH_2Cl_2 (2 ml) at −78 °C under a nitrogen atmosphere and the whole was stirred for 1 h. The mixture was quenched with a saturated $NaHCO_3$ solution at 0 °C, and extracted with CH_2Cl_2 three times. The combined extracts were washed with water and brine, dried, and then concentrated *in vacuo*. The residue was purified by SiO_2 column chromatography with hexane/AcOEt = 3/1 to give **4** (3.2 mg, 10%) and **9** (26.3 mg, 82%).

(Entry 2): A 1.0 M solution of DIBAL-H in toluene (41 μl) was added to a stirred solution of **3** (8.4 mg, 0.0204 mmol) in CH_2Cl_2 (1 ml) at −78 °C under a nitrogen atmosphere and the whole was stirred for 1 h. After having been quenched with a saturated NH_4Cl solution, the mixture was filtered through a pad of Celite and washed with CH_2Cl_2. The combined extracts were washed with water and brine, dried, and then concentrated *in vacuo*. The residue was purified by SiO_2 column chromatography with hexane/AcOEt = 1/1 to give a mixture of **4** and **9** (6.8 mg, 81%). The ratio of **4**/**9** was determined from the 500 MHz NMR spectrum.

(Entry 3): A stirred solution of **3** (7.7 mg, 0.0187 mmol) in methanol (1 ml) was treated with $NaBH_4$ at 0 °C, and the whole was stirred for 30 min. The mixture was quenched with water, and extracted with AcOEt. The extract was washed with water and brine, dried, and then concentrated *in vacuo*. The residue was purified by SiO_2 column chromatography with hexane/AcOEt = 1/1 to give a mixture of **4** and **9** (6.4 mg, 83%). The ratio of **4**/**9** was determined from the 500 MHz NMR spectrum.

(Entry 4): A mixture of the ketone **3** (167 mg, 0.406 mmol), $CeCl_3 \cdot 7H_2O$ (454 mg, 1.22 mmol), and methanol (4 ml) was treated with $NaBH_4$ (15.3 mg, 0.406 mmol) at −78 °C. The whole was quenched with water at 0 °C and extracted with CH_2Cl_2 three times. The combined extracts were washed with water and brine, dried, and then concentrated *in vacuo*. The residue was purified by SiO_2 column chromatography with hexane/AcOEt = 5/1 to give **4** (90.4 mg, 54%) and **9** (38.8 mg, 23%). **4**: A yellow oil. $[\alpha]_D^{21}$ +24.8° (c = 0.802, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.97

(qd, 1H, J=6.3, 8.5 Hz, C4′-H), 1.04 (dd, 1H, J=6.0, 9.4 Hz, C1′-H), 1.34 (d, 3H, J=6.3 Hz, C4′-Me), 1.55 (dddd, 1H, J=4.3, 10.3, 11.1, 11.1 Hz, C5-H_{ax}), 1.5—1.7 (br s, 1H), 1.79 (ddd, 1H, J=5.1, 12.8, 12.8 Hz, C3-H_{ax}), 1.94 (br d, 1H, J=10.3 Hz, C5-H_{eq}), 2.09 (br d, 1H, J=12.8 Hz, C3-H_{eq}), 3.08 (ddd, 1H, J=2.6, 11.1, 12.8 Hz, C6-H_{ax}), 3.38 (br d, 1H, J=12.8 Hz, C6-H_{eq}), 3.78 (s, 3H, OMe), 3.87 (br dd, 1H, J=5.1, 6.0 Hz, C2-H), 4.00 (m, 1H, C4-H), 4.99 (dd, 1H, J=5.1, 8.5 Hz, C3′-H), 5.12 (dd, 1H, J=5.1, 9.4 Hz, C2′-H), 6.85 (m, 4H, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 18.8 (C4′-Me), 33.9 (C5), 38.7 (C3), 42.6 (C6), 55.4 (OMe), 57.3 (C4′), 59.0 (C2), 60.6 (C1′), 64.8 (C4), 81.3 (C2′), 84.3 (C3′), 114.4 (ArC), 118.6 (ArC), 143.4 (ArC), 153.1 (ArC), 211.8 (CO). IR (KBr): 3300 (OH), 2945, 2038 (CO), 1975 (CO), 1510, 1246, 1039 cm^{-1}. MS m/z (%): 413 (M^+, 5.6), 329 (100), 273 (10), 235 (24). HR-MS Calcd for $C_{20}H_{23}FeNO_5$: 413.0923. Found: 413.0912. **9**: A yellow oil. $[\alpha]_D^{22}$ +8.05° (c=1.10, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (qd, 1H, J=5.5, 8.6 Hz, C4′-H), 1.15 (dd, 1H, J=5.1, 8.6 Hz, C1′-H), 1.29 (d, 3H, J=5.5 Hz, C4′-Me), 1.5—1.7 (m, 3H, C3-H_{ax}, C5-H_{ax}, OH), 1.88 (m, 1H, C5-H_{eq}), 2.19 (br d, 1H, J=12.2 Hz, C3-H_{eq}), 2.85 (br dd, 1H, J=12.2 Hz, C6-H_{ax}), 3.20 (m, 2H, C2-H, C6-H_{eq}), 3.80 (s, 3H, OMe), 3.86 (m, 1H, C4-H), 4.94 (dd, 1H, J=4.9, 8.6 Hz, C3′-H), 5.09 (dd, 1H, J=4.9, 8.6 Hz, C2′-H), 6.87 (d, 2H, J=8.5 Hz, Ar-H), 7.03 (d, 2H, J=8.5 Hz, Ar-H). ^{13}C-NMR ($CDCl_3$) δ: 18.8 (C4′-Me), 33.9 (C5), 40.7 (C3), 51.2 (C6), 55.4 (OMe), 57.5 (C4′), 59.1 (C2), 64.5 (C1′), 67.8 (C4), 80.5 (C2′), 84.3 (C3′), 114.5 (ArC), 124.0 (ArC), 144.1 (ArC), 155.8 (ArC), 212.1 (CO). IR (KBr): 3394 (OH), 2931, 2038 (CO), 1969 (CO), 1510, 1443, 1246, 1039 cm^{-1}. MS m/z (%): 413 (M^+, 8.8), 357 (16), 329 (100), 273 (31), 255 (17), 235 (41). HR-MS Calcd for $C_{20}H_{23}FeNO_5$: 413.0922. Found: 413.0914.

(2*S*,4*S*)-(1′*E*,3′*E*)-1′,3′-pentadienylpiperidin-4-ol (SS20846A) CAN (3.98 g, 7.26 mmol) was added slowly to a solution of **4** (300 mg, 0.726 mmol) in CH_3CN (7 ml) at −30 °C. The mixture was stirred for 30 min, quenched with a 2 N NaOH solution and extracted with AcOEt three times. The combined extracts were washed with brine, dried, and then concentrated *in vacuo*. The residue was purified by SiO_2 column chromatography with MeOH/CH_2Cl_2/28% NH_4OH=15/90/2 to give **1** (77.7 mg, 64%) as a brownish oil. $[\alpha]_D^{24}$ −15.2° (c=0.53, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.57 (ddd, 1H, J=2.6, 11.1, 13.7 Hz, C3-H_{ax}), 1.63 (br d, 1H, J=14.5 Hz, C5-H), 1.65—1.80 (m, 2H, C3-H_{eq}, C5-H), 1.73 (d, 3H, J=6.8 Hz, C4′-Me), 1.9—2.2 (br s, 2H, OH, NH), 2.88 (br d, 1H, J=12.0 Hz, C6-H_{eq}), 3.09 (ddd, 1H, J=2.6, 12.0, 12.0 Hz, C6-H_{ax}), 3.57 (br dd, 1H, J=6.8, 11.1 Hz, C2-H), 4.16 (br dd, 1H, J=2.6, 3.4 Hz, C4-H), 5.52 (dd, 1H, J=6.8, 15.4 Hz, C1′-H), 5.66 (qd, 1H, J=6.8, 14.5 Hz, C4′-H), 6.02 (dd, 1H, J=10.3, 15.4 Hz, C2′-H), 6.15 (dd, 1H, J=10.3, 14.5 Hz, C3′-H). ^{13}C-NMR ($CDCl_3$) δ: 18.0 (C4′-Me), 32.9 (C5), 39.5 (C3), 40.4 (C6), 52.6 (C2), 64.6 (C4), 129.1 (C4′), 130.3 (C2′), 131.1 (C3′), 133.3 (C1′). IR (KBr): 3317 (OH), 2939, 2918, 1672, 1421, 1383 cm^{-1}. MS m/z (%): 167 (M^+, 100), 152 (77), 150 (41), 137 (27), 113 (100). HR-MS Calcd for $C_{10}H_{17}NO$: 167.1308. Found: 167.1303.

Acknowledgments This work was supported by a Grant-in-Aid for Scientific Research on the Priority Area of Reactive Organometallics (No. 05236101) from the Ministry of Education, Science and Culture, Japan.

References and Notes

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