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Determination of the Absolute Configuration of 3-Pyrrolin-2-ones

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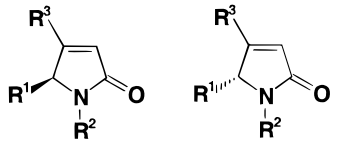
Introduction

Optically active 3-pyrrolin-2-ones have been shown to be important chiral synthons for the preparation of a variety of biologically active compounds. These five-membered ring lactams have successfully been used in routes to various alkaloids[1] and are suitable precursors for unusual γ-amino acids such as statine and its analogues.[2] There are also many examples of pyrrolinone-containing natural products with interesting pharmacological activities. Typical examples are the antitumor alkaloid Jatropham[3] and the platelet aggregation inhibitor PI-091.[4]

The chemistry of these versatile building blocks has been explored by a number of groups. Because of their multifunctional nature, these heterocycles can take part in several stereoselective transformations such as conjugate additions,[5] cycloadditions,[6] acyliminium ion chemistry,[7] and allylic substitutions.[8]

The increasingly frequent use of these compounds as chiral intermediates makes it indispensable to have a fast, universal method for the determination of the absolute configuration. Classical methods to determine the absolute configuration are by chemical correlation or by the introduction of a heavy atom, followed by single-crystal X-ray diffraction. The first method is rather time consuming, and the second is dependent on the availability of crystals suitable for absolute configuration determination. Recently we reported a simple circular dichroic method for determination of the absolute configuration of chiral 2(5*H*)-furanones.[9] These butenolides are of similar reactivity and have structural features comparable to the 3-pyrrolin-2-ones. We have now extended the CD method to the absolute configuration determination of 3-pyrrolin-2-ones.



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Results and Discussion

Synthesis. Several routes to enantiomerically pure 3-pyrrolin-2-ones **1** are reported here, and in this way we obtained 5-alkyl-, 5-acyloxy-, and 5-alkoxypyrrolinones with *N*-alkyl or *N*-acyl groups.

Route 1 is based on amino acids and provides the *N*-Boc-protected 5-methyl pyrrolinone **1** (Scheme 1).[2b] Following the procedure of Jouin[2a] further improved by Ma[2b] (5*S*)-*N*-*tert*-butoxycarbonyl-4-hydroxy-5-methyl-3-pyrrolin-2-one (**11**) was synthesized from *N*-Boc-protected L-alanine and Meldrum's acid. The synthesis of compound **1** was accomplished by first reducing **11** with $NaBH_4$[2b] followed by elimination of the hydroxyl group of **12** via the corresponding mesylate.[10] *N*-Boc-protected 3-pyrrolin-2-one **1** has been synthesized previously[11] but apparently in partly racemized form (identical NMR spectrum but low $[\alpha]_D$ and oil instead of solid). Compound **2** was obtained by methylation of the hydroxy-substituted precursor **11**,[2a] using diazomethane, along with the isomer **13**.

Route 2 starts with a pyrrole or methoxyfuranone and includes an enantioselective enzymatic synthesis step (Scheme 2).[12] *N*-Methylpyrrolinone **3** was synthesized starting with the photooxidation of *N*-methylpyrrole, followed by esterification. Subsequent enzymatic resolution by *Candida antarctica*-mediated transesterification provided enantiopure **3**.[12]

The *N*-acyl derivatives **4** and **5** were synthesized starting from commercially available 5-methoxy-3-furan-2-one and obtained enantiomerically pure by an enzymatic transesterification using the same lipase (*C. antarctica*) as applied in the preparation of **3**. The enzyme specifically converted the (−)-enantiomer to the hydroxy

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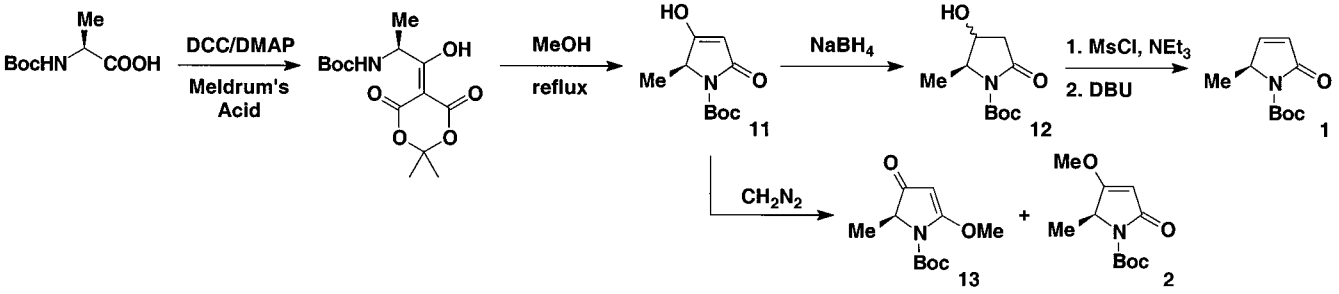
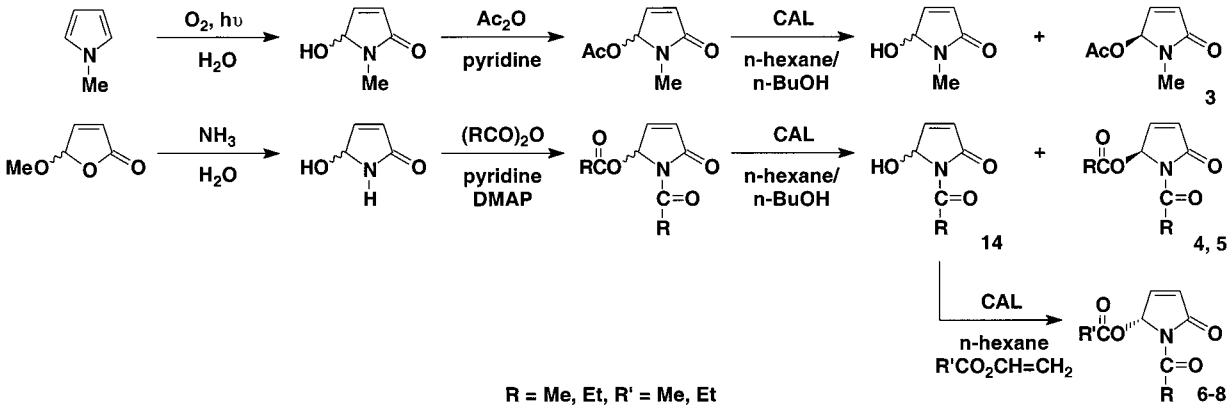
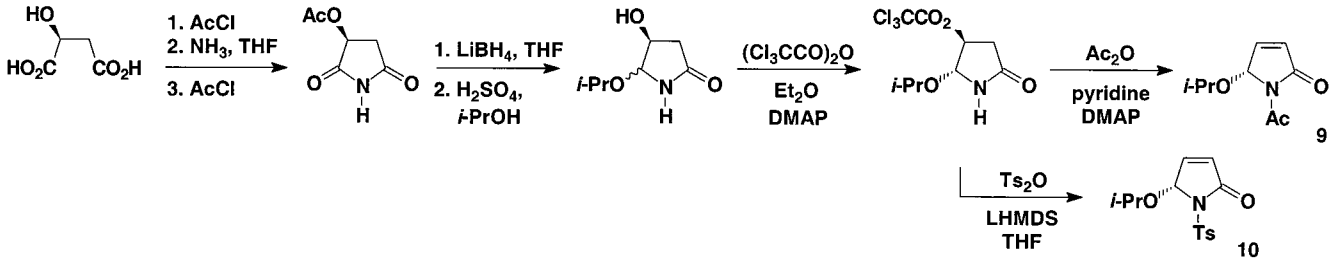
Scheme 1. Synthesis of 3-Pyrrolin-2-ones



Scheme 2. Synthesis of 3-Pyrrolin-2-ones



Scheme 3. Synthesis of 3-Pyrrolin-2-ones

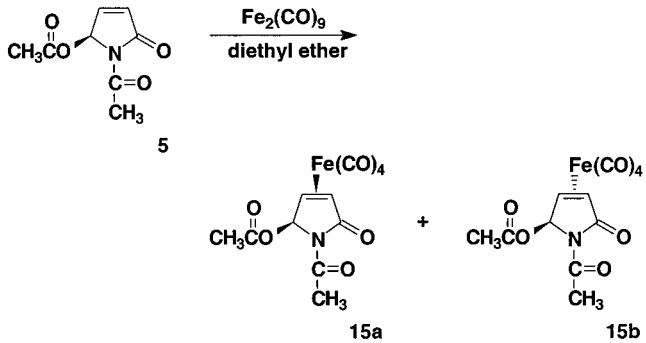


derivative **14**, and the unreactive (+)-enantiomer was obtained in >99% ee. In this way the maximum yield of 50% of enantiopure product in a kinetic resolution was obtained.[12] Compounds **6**−**8** were obtained by the reverse reaction, the enzymatic esterification of hydroxypyrrolinone **14**. In this reaction the (−)-enantiomer of **14** was converted to the (−)-acyloxypyrrolinones **6**−**8**. Because the hydroxypyrrolinone **14** racemized under the reaction conditions, **6**−**8** could be obtained enantiomerically pure in quantitative yield by a dynamic kinetic resolution.[12]

The 5-isopropoxy pyrrolinones **9** and **10** were obtained via a stereoselective synthesis route,[6a,13] starting with (*S*)-malic acid (Scheme 3).

A method to establish independently the absolute configuration of 3-pyrrolin-2-ones is via synthesis and characterization of the corresponding iron tetracarbonyl complexes (Scheme 4). By reaction with $Fe_2(CO)_9$ pyrrolinone, (+)-**5** was converted into a 1:1 mixture of *cis*-(**15a**) and *trans*-(**15b**) $Fe(CO)_4$ complexes (Scheme 4). The lack of π-face selectivity is in contrast with the selectivity observed in our synthesis of iron complexes with isopropoxy-substituted pyrrolinones[13,14] (in which case the cis complex is formed predominantly, probably because of

Scheme 4. Synthesis of Pyrrolinone Iron Tetracarbonyl Complexes



precoordination of iron to the oxygen atom of the isopropoxy group). The isomers were distinguished on the basis of the coupling constants between H(4) and H(5) in the ^{1}H NMR spectra. For the cis complex **15a** a value of 5 Hz was found, whereas for the trans complex **15b** $J <$ 0.5 Hz was observed. As in other pyrrolinone iron tetracarbonyl complexes,[13,14] the C(3)−C(4) bond is elongated from about 1.3 Å for a normal double bond to 1.414 (5) Å in the complex.

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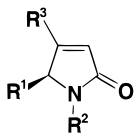
Table 1. CD and UV Data for Chiral 3-Pyrrolin-2-ones (in Acetonitrile)



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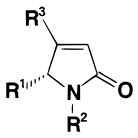

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compound	R^1	R^2	R^3	CD, $\Delta\epsilon$ (nm)/UV, ϵ (nm) α,β unsaturated lactam n−π*	π−π*	other CD bands
1	Me	Boc	H	−0.8 (224)	+7.8 (200)	
				5300 sh (226)	9900 (205)	
2	Me	Boc	MeO	−0.8 (251)	+2.8 (229)	
					12200 (228)	
3	AcO	Me	H	−6 (250)	+25 (198)	
				3400 sh (232)	*a*	
4	EtCOO	EtCO	H	−8.5 (230)	+30.6 (206)	−0.6 (280)
				3600 sh (228)	10500 (203)	
5	AcO	Ac	H	−9.6 (230)	+28.1 (206)	−0.6 (280)[b]
				3900 sh (228)	9600 (205)	
6	AcO	Ac	H	+9.7 (230)	−28.9 (205)	+0.9 (280)
				3600 sh (227)	10100 (203)	
7	AcO	EtCO	H	+9.0 (230)	−30.0 (206)	+0.6 (280)
				3400 sh (228)	9800 (203)	
8	EtCOO	Ac	H	+8.8 (230)	−31.0 (206)	+0.6 (280)
				3400 sh (228)	9500 (204)	
9	i-PrO	Ac	H	+6 (236)	−20 (212)	+1.0 (279)
				2000 sh (235)	*a*	−1.8 (256)
10	i-PrO	Ts	H	+1.8 (271)	−6.0 (233)	
					12100 (229)	

[a] No clear λ_{max} down to 200 nm. [b] Recorded in methanol solution.

The cis-isomer could not be isolated in pure form and was obtained by flash chromatography under nitrogen either as a mixture with the trans-isomer or contaminated with the starting material.

Pure trans-isomer **15b** was isolated by flash chromatography and recrystallized from pentane to give suitable crystals for X-ray crystal structure determination. The crystalline complex is stable to air.

CD Studies. In the case of simple 3-pyrrolin-2-ones bearing no substituents at the olefinic bond, the π−π* Cotton effect is observed at λ_{max} ca. 200 nm. The n−π* Cotton effect is seen at longer wavelength, around 230 nm, where the UV spectrum displays a broad shoulder. CD/UV spectral data of all pyrrolinones investigated are shown in Table 1.

The 3-pyrrolin-2-ones with an oxygen substituent at C(5) generally display much stronger Cotton effects than those substituted with an alkyl group (e.g., compounds **1**, **2**). A methoxy substituent at C(3) shifts the position of the π−π* band to ca. 230 nm (compound **2**), as does tosyl substitution at N(1) (compound **10**).

3-Pyrrolin-2-ones with an imide-type group (R^2 = acyl) display an additional Cotton effect at ca. 280 nm, presumably due to a second n−π* transition. Such double n−π* Cotton effects are observed at ca. 250 nm in saturated imides[15] and result from the transitions involving combinations of the carbonyl n orbitals of opposite symmetry. This Cotton effect is, however, much smaller than the n−π* Cotton effect due to the α,β-unsaturated lactam chromophore.

The absolute configuration of chiral 3-pyrrolin-2-ones is readily determined by the sign of the Cotton effects

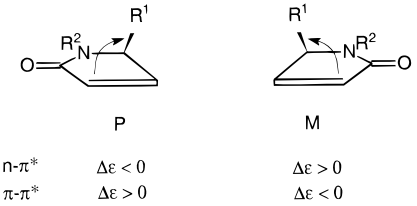

Figure 1. Correlation of the pyrrolinone Cotton effects with absolute configuration.

associated with the α,β-unsaturated lactam chromophore (Figure 1). This is an extension of the configurational rule previously developed for α,β-unsaturated lactones (2(5*H*)-furanones).[9] The extension is justified in view of the planarity of the α,β-unsaturated lactam ring, as demonstrated by the published X-ray data (vide infra),[6a,16] and by the isoelectronic nature of the unsaturated chromophore in 3-pyrrolin-2-ones and in 2(5*H*)-furanones.

The most easy and reliable assignment of absolute configuration is based on the sign of the π−π* Cotton effect (identified by the position of the UV_{max}): positive π−π* Cotton effect is due to *P*-helicity of the C=C−C−R^1 bond system; negative π−π* Cotton effect reflects *M*-helicity of the same bond system. Although no detailed discussion of the observed relationship is offered here, we note that coupling of the π−π* electric dipole transition moment of the planar (conjugated) chromophore with the σ* oscillator of the allylic carbon−carbon or carbon−heteroatom bond is quite a well-established mechanism of generating the rotational power.[17]

Inspection of $[\alpha]_D$ data in the literature for chiral 3-pyrrolin-2-ones[6a,13,16,18] reveals that the sign of $[\alpha]_D$, with apparently no exception, corresponds to the sign of the π−π* α,β-unsaturated lactam CD band: that is, positive $[\alpha]_D$ results from the contribution of the (strong) positive π−π* Cotton effect. Thus the sign of rotation of 3-pyrrolin-2-ones can be used for tentative assignment of its absolute configuration at C(5), but this assignment needs to be confirmed by the measurement of the CD spectrum.

Absolute Configuration by Chemical Correlation and X-ray Analysis. The compounds **1** and **2** were synthesized starting from enantiopure L-alanine and should therefore have the (*S*)-configuration. The synthesis of the pyrrolinones **9** and **10** from enantiopure (*S*)-malic acid could only yield the (*R*)-enantiomer. This correlates with the absolute configuration of the iron tetracarbonyl complex of **10** recently reported by some of us.[13] For the compounds **3**−**8** there is no chemical correlation because these compounds were synthesized from an achiral or racemic starting material. For compound **5** the absolute configuration could be deduced from the crystal structure of the iron tetracarbonyl complex. The synthesis of this complex has been described

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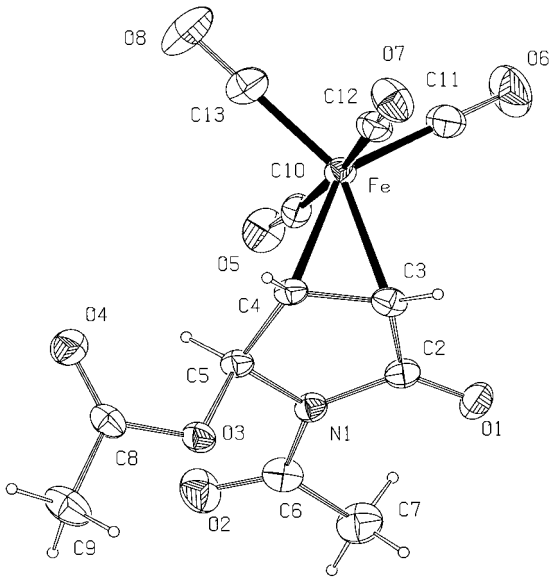

Figure 2. ORTEP drawing (50% probability ellipsoids) of **15b**.

above.The crystal and molecular structure of **15b** is shown in Figure 2. This establishes the trans-relative configuration of the complex as well as the (*S*)-absolute configuration at C(5). From the structure of this complex the absolute configuration at C(5) of the (+)-pyrrolinone **5** that was used can be unequivocally assigned to be *S* in accordance with the assignment according to CD.

Conclusion

By correlation of the sign of CD Cotton effects (Figure 1, Table 1) the absolute configurations of **1**−**10** are established. Since the results from the chemical correlation or X-ray crystal structure determination for a compound in each of the three classes of chiral pyrrolinones correlate perfectly with the absolute configurations determined by the sign of the Cotton effects for all studied pyrrolinones, we can conclude that CD measurement is both a rapid and a reliable method to obtain the absolute configuration of chiral 3-pyrrolin-2-ones.

Experimental Section

General Information. The CD spectra were recorded with a Jobin-Yvon Dichrograph III, and the UV spectra were obtained on a Shimadzu UV 160 spectrophotometer. Optical rotations were determined with a Perkin-Elmer 241 polarimeter. Melting points are uncorrected. Chemical shifts of the ^{1}H NMR and ^{13}C NMR spectra are denoted in δ-units (ppm) relative to $CDCl_3$. The splitting patterns are designated as follows: s (singlet), d (doublet), dd (double doublet), t (triplet), q (quartet), m (multiplet), and br (broad). R_f values were obtained by using TLC on silica gel-coated plastic sheets (Merck silica gel F_{254}). Merck silica gel 60 (230−400 mesh) was used for filtration and for flash chromatography. The solvents were distilled and dried, if necessary, using standard methods. Reagents were used as obtained from Acros Chimica, Aldrich, Fluka, or Merck, unless otherwise stated.

Pyrrolinones **3**−**8**[12] and **9**,[6a] **10**[13] were prepared following reported procedures.

5(*S*)-*N*-*tert*-Butoxycarbonyl-4-hydroxy-5-methyl-3-pyrrolin-2-one (11). 11 was synthesized following the procedure of Jouin[2a] and further improved by Ma.[2b] Compound **11** has mp 122−124 °C; $[\alpha]_D$ +77.8 (c = 1, MeOH). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.51 (d, 3H, J = 6.9 Hz), 1.56 (s, 9H), 3.23 (m, 2H), 4.42 (dq, 1H, J = 6.9, 1.0 Hz), 5.00 (s, 1H). IR (KBr): 3419, 2976, 1718, 1678, 1568 cm^{-1}.

5(*S*)-*N*-*tert*-Butoxycarbonyl-4-hydroxy-5-methylpyrrolidine-2-one (12). The compound has mp 85−87 °C; $[\alpha]_D$ +48 (c = 0.5, MeOH). ^{1}H NMR ($CDCl_3$, 300 MHz), major diastereomer: δ 1.33 (d, 3H, J = 6.5 Hz), 1.53 (s, 9H), 2.24 (br, s, 1H), 2.58 (dd, 1H, J = 17.1, 8.9 Hz), 2.72 (dd, 1H, J = 17.1, 7.5 Hz), 4.25 (dq, 1H, J = 6.5, 6.5 Hz), 4.51 (dd, 1H, J ca. 7.5 Hz). IR (KBr): 3479, 2986, 2931, 1767, 1685 cm^{-1}.

5(*S*)-*N*-*tert*-Butoxycarbonyl-5-methyl-3-pyrrolin-2-one (1). The compound has mp 73−74 °C; $[\alpha]_D$ +145 (c = 1, $CHCl_3$) (lit.[8] colorless oil, $[\alpha]_D$ −9.6, c = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.44 (d, 3H, J = 6.7 Hz), 1.56 (s, 9H), 4.62 (dq, 1H, J = 6.7, 1.8 Hz), 6.07 (dd, 1H, J = 6.1, 1.8 Hz), 7.10 (dd, 1H, J = 6.1, 2.1 Hz). IR (KBr): 3076, 2985, 1765, 1688 cm^{-1}.

5(*S*)-*N*-*tert*-Butoxycarbonyl-4-methoxy-5-methyl-3-pyrrolin-2-one (2). Oil; $[\alpha]_D$ +13.3 (c = 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): 1.47 (d, 3H, J = 6.6 Hz), 1.54 (s, 9H), 3.83 (s, 3H), 4.38 (q, 1H, J = 6.6 Hz), 5.03 (s, 1H). IR (neat): 2960, 2873, 1729 cm^{-1}.

5(*S*)-*N*-*tert*-Butoxycarbonyl-2-methoxy-5-methyl-2-pyrrolin-4-one (13). The compound has mp 62−64 °C; $[\alpha]_D$ −12.7 (c = 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): 1.49 (d, 3H, J = 6.9 Hz), 1.53 (s, 9H), 4.02 (s, 3H), 4.09 (q, 1H, J = 6.9 Hz); 4.86 (s, 1H); IR (KBr): 2932, 2860, 1778, 1630 cm^{-1}.

[5(*S*)-Acetic Acid 1-Acetyl-5-oxo-2,5-dihydro-1*H*-pyrrol-2-yl Ester] Tetracarbonyl Iron (15). To a suspension of (+)-**5** (1.00 g, 5.46 mmol) in diethyl ether (60 mL) was added $Fe_2(CO)_9$ (4.00 g, 11.00 mmol), and the reaction mixture was stirred at room temperature for 20 h. The mixture was filtered over Celite (under an Ar atmosphere, using a connecting filter) and washed with 20 mL of diethyl ether. The dark green solution was concentrated in vacuo, using a rotary evaporator equipped with a nitrogen inlet. The crude product was purified using flash chromatography under nitrogen pressure (pet. ether/CH_2Cl_2/EtOAc 5:5:2). Dry degassed solvents and silica were used, and fractions were maintained under argon. Pure crystalline **15b**, 0.363 g (1.03 mmol, 19%, R_f 0.45), was obtained and recrystallized from pentane to provide light yellow prisms, mp 100 °C (dec). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.12 (s, 3H), 2.43 (s, 3H), 3.68 (d, J = 5.4 Hz, 1H), 3.87 (d, J = 5.1 Hz, 1H), 6.78 (s, 1H). ^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 20.9 (q), 24.6 (q), 43.6 (d), 51.2 (d), 84.2 (d), 205.7 (s). Anal. Calcd for $C_{12}H_9NO_8Fe$: C 41.06, H 2.58, N 3.99, Fe 15.91. Found: C 41.25, H 2.60, N 4.01, Fe 15.70. A mixture of **15b** and **15a** (0.667 g, 1.90 mmol, 35%) was obtained as a yellow solid, and a mixture of 0.382 g of **15a** and **5** (6:4 ratio) was obtained as a light brown solid.

For **15a**: ^{1}H NMR ($CDCl_3$): δ 2.11 (s, 3H), 2.41 (s, 3H), 3.89 (d, J = 5.6 Hz, 1H), 4.26 (dd, J = 5.1 Hz, 1H), 6.89 (d, J = 4.6 Hz, 1H).

Crystal Data for 15b. $C_{12}H_9NO_8Fe$, orthorhombic, space group $P212121$, a = 7.2818(11) Å, b = 10.0953(14) Å, c = 19.1003(17) Å, V = 1404.1(3) Å^3, Z = 4, Mo Kα, λ = 0.710 73 Å, μ = 1.1 mm^{-1}. X-ray data were collected on an Enraf-Nonius CAD4T diffractometer (rotating anode, graphite monochromator, T = 150 K, θ_{max} = 27.5°). The structure was solved with Patterson techniques using DIRDIF96 and refined by full-matrix least-squares on F^2 using SHELXL97 (1918 reflections and 218 parameters). A final difference map showed no significant residual density. Hydrogen atoms of the methyl moieties were refined as rigid rotators riding on their carrier atoms. All other H atoms were located from a difference map and their positions refined. Convergence was reached at R = 0.0365 for 1918 reflections with $I > 2\sigma(I)$ [wR_2 = 0.0890, S = 1.04]. The Flack parameter converged to 0.00(3) for the absolute configuration shown in Figure 2. Full details are available in the Supporting Information.

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Supporting Information Available: Tables of X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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