Arene Chromium and Manganese Tricarbonyl Analogs of the PCP Receptor Ligands 5-Methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (MK-801) and 10,5-(Iminomethano)-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene (IDDC)

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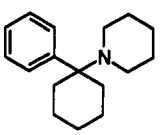
Chromium tricarbonyl complexes of MK-801 (**2**), IDDC (**4**), and 3-Cl-IDDC (**10**) were prepared by arene exchange with benzenechromium tricarbonyl. The resulting complexes retained binding affinity for the PCP receptor, as reflected by IC_{50} values relative to [^{3}H]-**2**. A manganese tricarbonyl analog **28** of **4** was synthesized in which the D ring of **4** was replaced with cyclopentadienylmanganese tricarbonyl. However, **28** showed significantly diminished binding affinity for the PCP receptor, relative to **4**. Attempts to prepare a ferrocene analog of **4** in which the A or D rings were replaced with ferrocene failed, due to a very stable carbocation formed in the last step of the synthetic route; the novel alcohols **25** and **29** were formed instead.

The amino acids glutamate and aspartate are important neurotransmitters at excitatory synapses in the central nervous system.[1] The complex neuronal responses to glutamate appear to be mediated by three major receptor subtypes. These are the NMDA,[2] so named for its prototypical agonist *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), and kainite receptor subtypes. Excessive stimulation of the NMDA receptor by glutamate has been strongly implicated in neuronal death following ischemic or hypoxic insults to the brain, as well as during the course of neurodegenerative disease.[3] There are several ligand-binding sites that modulate the effect of glutamate binding to the NMDA receptor complex,[4] including a noncompetitive site named for the ligand phencyclidine [PCP, (**1**)[5]] which is located within an associated Ca^{2+}/Na^{+} ion channel. Binding of PCP or other high affinity ligands [(+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohexen-5,10-imine, MK-801, (**2**); TCP, (**3**); IDDC, (**4**)] to the PCP site inhibits the excessive inward calcium ion flow that ultimately leads to neuronal cell death upon over-stimulation of the NMDA complex by glutamate.[5] Therefore, potent ligands for the PCP receptor site have potential as neuroprotective agents in the treatment of ischemia.[3]

Much effort has been expended to define pharmacophore models for the PCP receptor site for the purposes of rationalizing structure–activity relationships and the design of more potent ligands.[6] There are several known



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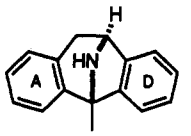

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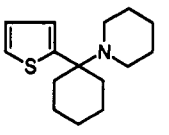

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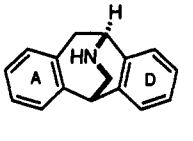

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potent ligands, e.g., **2**[7] and **4**,[8] which share similar three-dimensional shape and placement of hydrogen bonding sites. Within certain ligand families, the receptor is rather intolerant of deviations from the optimal structure, showing a wide range of binding affinities in response to even subtle changes in substitution pattern and ring size.[8,9] As part of our program directed toward the development of novel PCP receptor ligands,[8] we elected to investigate the effect of aromatic ring *face* modification of potent PCP receptor ligands on binding affinity. Investigators have postulated that face-to-face π stacking between aromatic units in systems such as ligand–receptor pairs provides a significant energetic contribution (1–4 kcal/mol) to the nonbonded association.[10] On this basis, it seems reasonable to expect that blocking of potential π-π stacking

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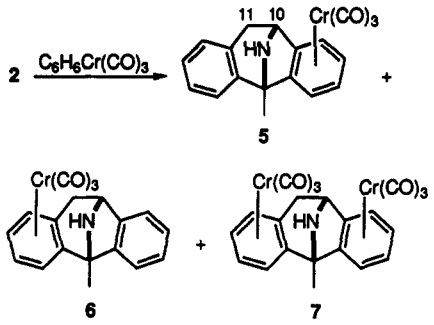
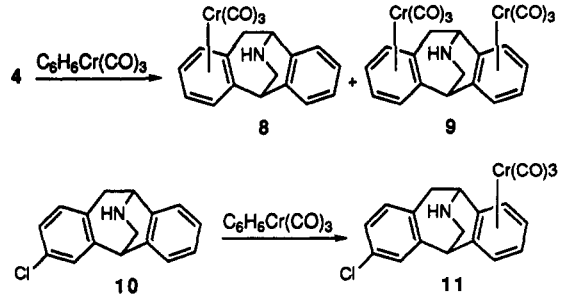
Scheme 1



Scheme 2



could lead to drastically reduced binding affinity, although recent reports[11] indicate that certain other receptors tolerate well chromium tricarbonyl ($Cr(CO)_3$) complexation to ligand aromatic ring faces. Herein we report the preparation of $Cr(CO)_3$ complexes of **2**, **4**, and 3-chloro-IDDC (**10**). We also report the preparation of a cyclopentadienylmanganese tricarbonyl analog of **4**, as well as synthetic approaches to ferrocene analogs of **4**. In vitro binding affinities of these novel ligands for the PCP receptor site are also reported.

Results and Discussion

Chemistry. Chromium tricarbonyl complexes of **2** were prepared by the reaction with $(C_6H_6)Cr(CO)_3$ at 140 °C under argon in degassed diglyme/THF (Scheme 1). The major product was the mono-chromium tricarbonyl complex **5**, which was isolated in pure form by flash chromatography and crystallization from ethanol. Separation of the other mono-complex **6** was only partially successful, as **5** could not be completely removed by crystallization. A 3:1 oily mixture of **6** and **5**, respectively, was obtained. The bis-chromium tricarbonyl complex **7** was isolated in pure form by flash chromatography followed by crystallization from ether.

The structural assignments of complexes **5**–**7** were based on upfield shifts in the NMR spectra induced at the benzylic positions (C-10 and C-11) by $Cr(CO)_3$ complexation. Similar phenomena were observed in $Cr(CO)_3$ complexes of 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene and its 5-hydroxy and 5-oxo derivatives.[12] For **5**, the H-10 resonance (4.45 ppm) in the ^1H NMR spectrum is shifted upfield 0.20 ppm relative to that in **2** (4.65 ppm), while the H-11 resonances remained unchanged. Correspondingly, the H-11 resonances (H_α and H_β) in **6** are shifted upfield by 0.24 ppm relative to **1**, while the H-10 resonance remains unchanged. These data indicate a general shielding effect exerted by arene-bound $Cr(CO)_3$ on benzylic hydrogens that does not extend to homo-benzylic hydrogens.

Inspection of molecular models indicates the likelihood of complexation of the $Cr(CO)_3$ moiety to the exo face of rings A and D (i.e., syn to the imino bridge). Since **2** is curved downward from the imino bridge, there would likely be difficulty in the accommodation of a large $Cr(CO)_3$ group on the endo face(s) of the phenyl rings. Molecular mechanics calculations of the optimized structures using an augmented force field[13] indicated a substantial preference (26 kcal/mol) in **5** for the $Cr(CO)_3$ moiety to be on the exo face of the D ring, as opposed to the endo face. Thus, in **5** the $Cr(CO)_3$ moiety is tentatively assigned as being complexed to the D ring, as depicted in Scheme 1. Correspondingly, **6** has the $Cr(CO)_3$ unit complexed to the exo face of the A ring.

When **4** was treated with $C_6H_6Cr(CO)_3$, only one mono-$Cr(CO)_3$ complex was isolated (**8**, Scheme 2). The resonance corresponding to H-10 in the proton NMR spectrum of **8** is unchanged from that observed in **4**, indicating that the $Cr(CO)_3$ moiety is complexed to the more remote (relative to H-10) A ring. A small amount (ca. 10%) of the bis-complexed **9** was also obtained as a mixture with **8**. When 3-Cl-IDDC (**10**) was subjected to complexation reaction conditions with $C_6H_6Cr(CO)_3$, only the mono-$Cr(CO)_3$ complex **11** was obtained (Scheme 2). The proton NMR spectrum of **11** showed the H-10 signal to be shifted upfield by 0.3 ppm relative to **10**, indicating a shielding effect exerted by the close $Cr(CO)_3$ moiety. Also, the signals corresponding to the ring protons of the shielded phenyl ring (upfield about 1.5 ppm relative to the unshielded ring) integrated to four hydrogens, whereas the unshielded ring signals integrated to three hydrogen atoms. Thus for **11**, the $Cr(CO)_3$ unit is unambiguously assigned as being complexed to the D ring, and most likely syn to the iminomethano bridge. That **2** and **10** prefer $Cr(CO)_3$ complexation to the D ring, while **4** prefers it at the A ring, is illustrative of the subtle nature of structural and electronic effects that governs complexation regiochemistry in these systems. All of the $Cr(CO)_3$ complexed products were stable in the solid state under an inert atmosphere.[14]

In the interest of preparing π-stacked PCP receptor ligands that might be more stable to physiological conditions than $Cr(CO)_3$ complexes, PCP receptor ligands were envisioned in which either ferrocene or cymantrene ($CpMn(CO)_3$) replaced one or both of the benzene rings in **4**. An advantage in beginning with ferrocene or cymantrene is that the metal-complexed ring of the new PCP ligand is defined by the method of synthesis.

Scheme 3 depicts the synthetic effort made toward a ferrocene analog of **4** in which the D ring would be replaced with ferrocene (Ar = Ph, Ar′ = Fc). (Phenylacetyl)-

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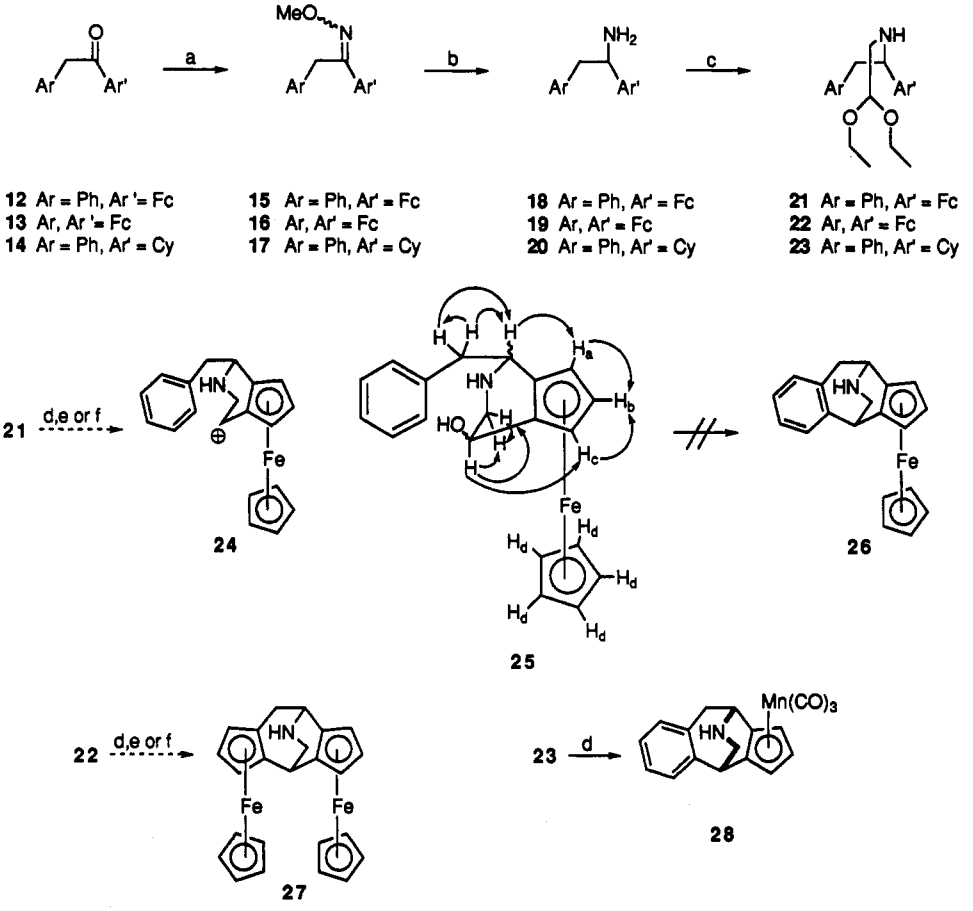
(13) CAChe Molecular Mechanics Augmented Force Field, Tektronix, Inc., Beaverton, OR 97077. "Weak" bonds were designated between Cr° and each of the D ring carbon atoms.

(14) Attempts to form $(CO)_3W$[arene] complexes from $(CO)_3W(CH_3CN)$ and **2** only afforded low yields of $(CO)_5W$-**2**, in which the tungsten was bound to the nitrogen atom of **2**.

Scheme 3[a,b]



[a] Reagents: (a) CH_3ONH_2.HCl, pyr; (b) BH_3·THF; (c) $BrCH_2CH(OEt)_2$, K_2CO_3, DMF; (d) H_2SO_4; (e) $HClO_4$; (f) CF_3SO_3H. [b] Fc = $CpFeC_5H_4$; Cy = $(CO)_3MnC_5H_4$.

ferrocene (**12**)[15] was aminated by conversion to an *E,Z* mixture of *O*-methyl oximes **15**, followed by reduction with borane–THF[16] to the amine **18**. N-Alkylation with bromoacetaldehyde diethylacetal in DMF afforded **21**. Treatment of **21** with strong acid (conditions known to effect cyclization to **4** from the analogous acetal[17]) failed to bring about formation of the desired ferrocenyl-IDDC **26**. Invariably the alcohol **25** was formed, presumably by quench of the ferrocene-stabilized cationic carbon in **24**. Ferrocene is well known for its ability to stabilize α-carbocations,[18] and evidently the carbocation in **24** is too stable for intramolecular attack on the phenyl ring.

The structure of **25** was confirmed by ^1H–^1H COSY experiments (see **25** for the correlations). The 2D spectrum was most helpful in locating all of the Cp hydrogens. Specifically, only three resonances corresponding to Cp hydrogens were seen in the 1D ^1H spectrum, and these integrated as 1:1:5 (4.60, 4.28, 4.09 ppm, respectively). The COSY spectrum on the other hand showed correlation between the large singlet at 4.09 ppm and the signals at 4.60 and 4.28 ppm. Repeating the ^1H 1D experiments with a long delay time (10 s) caused the integration of the large singlet at 4.09 ppm to grow from five to six hydrogen atom units. Clearly, these data indicate that the H_b signal was obscured by the signal corresponding to the unsubstituted Cp hydrogens, H_d.

An attempt was made to synthesize an analog of **4** in which both benzene rings were replaced with ferrocene. The ketone **13**[19] was prepared by reaction of an excess of ferrocene with ferroceneacetic acid[20] in the presence of trifluoroacetic anhydride and aluminum oxide.[21] Preparation of **16**, **19**, and **22** was accomplished using the same procedures as described above. Due to the low polarity difference between ferrocene and **13** and **16**, the excess ferrocene from the first step was carried through the oximation and reduction reactions until it could be easily separated from the amine **19** by column chromatography. N-Alkylation of **19** afforded **22** as described above. However, acidic treatment of **22** failed to bring about double cyclization to the desired diferrocenyl IDDC analog **27**. As was the case with **24** and **25**, only monocyclization was observed. We have tentatively assigned the six-membered ring structure **29** to the resulting alcohol based on NMR and MS data, although formation of the seven-membered ring isomer **30** by cyclization of the carbocation intermediate into the other ferrocene ring could not be ruled out.

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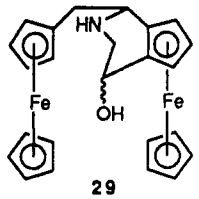

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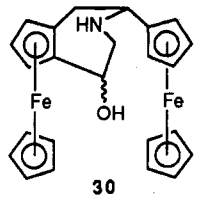

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Replacement of ferrocene with the isosteric cymantrene ($CpMn(CO)_3$) led to a successful synthesis of the π-stacked cyclopentadienyl analog **28** of **4**. Thus, cymantrene was acylated with phenylacetyl chloride to give the known ketone **14**.[22] The rest of the chemistry to the acetal **23** proceeded as described above. Treatment of **23** at room temperature with an excess of triflic or sulfuric acid afforded the cymantryl-IDDC **28** in 34–50% yield. Whereas **21** and **22** failed to undergo the desired double cyclization upon acidic treatment, the successful reaction of **23** to **28** likely stems from the diminished ability of cymantrene to stablize α-carbocations, relative to ferrocene.[23]

The relative stereochemistry of **28**, i.e., the syn- or anti-orientation of the $Mn(CO)_3$ moiety relative to the iminomethano bridge, was investigated by molecular mechanics.[24] A preference worth 6.7 kcal/mol was found for the $Mn(CO)_3$ moiety to be bound to the exo face (syn to the iminomethano bridge) of the A ring, rather than to the endo face in the optimized structures. HPLC analysis indicated the formation of only one diastereomer.

Pharmacology. The PCP receptor binding affinities, relative to [^{3}H]-**2**, were determined as described previously.[25] The results are listed in Table 1.

Remarkably, the IC_{50} values determined for a 2:1 mixture of mono-chromium tricarbonyl ligands **5** and **6** and for the bis-complex **7** indicated that the PCP receptor affinity of these ligands was nearly as good as for the parent compound **2**. Complex **5** was shown to be stable on the in vitro assay time scale to in vitro testing conditions by monitoring its UV spectrum in a buffered aqueous solution. The spectrum maintained its integrity over at least 6 h. Other arene chromium tricarbonyl complexes have also been shown to be stable in buffered aqueous media.[11a,26]

The chromium tricarbonyl complexes **8** and **11** showed IC_{50} values on the same order of magnitude as their uncomplexed counterparts (**4** and **10**, respectively). In contrast, the cymantrene analog **28** of **4** was a poorer ligand for the PCP receptor than **4** itself. Since **5–8**, and **11** were relatively potent ligands, even though bearing an organometallic moiety on an aromatic ring face, and **28** was a relatively poor ligand, it may be that the receptor requires a six-membered D ring. A similar six-membered ring preference by the receptor in the analogous hexahydrofluorenamide family was recently observed.[9] Stability experiments showed that **28** remained intact over the course of several days under binding assay conditions.

Table 1. Inhibition of [^{3}H]-2 Binding to the PCP Receptor

compound	IC_{50}[a]	SEM	n
5[b]	14.6	0.9	3
7	31.9	6.3	3
(±)-**8**	175	39	2
(±)-**11**	165	3.0	2
(±)-**28**	709	93	3
2	4.2	0.5	4
(±)-**4**	52	3	4
(±)-**10**	72	10	4
$Cr(CO)_6$	>10000		

[a] nM. [b] 2:1 mixture of **5** and **6**, respectively.

Summary and Conclusion

Several organometallic compounds were prepared by complexing the chromium tricarbonyl unit to the *exo*-π face(s) of **2**, **4** and **10**, three potent PCP receptor ligands. The receptor affinity of the complexes remained high, leading to the conclusion that aromatic *exo* π_{ligand}-$\pi_{receptor}$ stacking interactions are not critical to the tight binding of **2**, **4** and **10** to the PCP receptor. The poor binding affinity of **28** may be attributed to the fact that the D ring has only five carbon atoms, while all known good ligands of this family have six. Attempts to prepare ferrocenyl and diferrocenyl analogs of **4** failed due to very stable carbocations formed α to ferrocene in the final step of the syntheses.

Experimental Section

General. All reactions were run under a nitrogen or argon atmosphere. Reagents were used as received unless otherwise indicated. Tetrahydrofuran (THF) and ethyl ether were distilled from blue sodium benzophenone ketyl solutions. Liquid chromatography was performed in the flash mode on Davisil silica gel (200-425 mesh), unless otherwise indicated. Analytical thin-layer chromatography was performed on aluminum-backed silica gel 60 F_{254} plates. Preparative thin-layer chromatography was performed on Analtech GF precoated silica gel (1000 μm) glass-backed plates (20 × 20 cm). Melting points are uncorrected. NMR chemical shifts are reported in δ units referenced to residual proton signals of the deuterated solvents. Infrared spectra are recorded in wavenumbers (cm^{-1}), and the intensity of the absorptions are indicated by the letters s (strong), m (medium), and w (weak). Mass spectra were recorded in the electron ionization mode unless otherwise indicated. Microanalyses were performed by Desert Analytics of Tuscon, AZ. Literature procedures were followed in the preparation of racemic **4**,[17] and racemic **10**,[8] and **2**.[27]

Reaction of 2 with $(C_6H_6)Cr(CO)_3$. To a solution of **2** (110.5 mg, 0.50 mmol) in diglyme (1.5 mL, distilled from $LiAlH_4$) and THF (0.2 mL) under argon at room temperature was added benzenechromium tricarbonyl (112.5 mg, 0.55 mmol). The resulting yellow solution was refluxed for 5 h, during which time the color changed to green. The solvent was removed at the water pump, and the residue was purified by flash chromatography. Elution with 1:1 hexanes/ether afforded unreacted $C_6H_6Cr(CO)_3$. Elution with 1:2 hexanes/ether afforded 50 mg of a solid mixture of mono-complexes **5** and **6** (28% yield). Proton NMR indicated a ratio of about 2:1, respectively. Two recrystallizations from ethanol afforded pure **5** as a yellow solid: R_f 0.51 (ether); mp 162–165 °C dec; ^{1}H NMR (acetone-d_6) 1.87 (s, 3H), 2.78 (d, J = 16.8 Hz, 1H), 2.82 (br s, 1H), 3.44 (dd, J = 16.8, 5.4 Hz, 1H), 4.45 (d, J = 5.4 Hz, 1H), 5.34 (t, J = 6.0 Hz, 1H), 5.59 (t, J = 6.0 Hz, 1H), 5.80 (t, J = 6.0 Hz, 1H), 5.91 (d, J = 6.0 Hz, 1H), 7.00–7.36 (m, 4H); MS *m/e* (rel intensity) 357 (M^+, 13), 301 (18), 274 (34), 273 (100), 221 (26), 110 (25), 181 (22), 52 (81); EIHRMS 357.0431 (357.0457 calcd for $C_{19}H_{15}NO_3Cr$). Anal. Calcd for $C_{19}H_{15}NO_3Cr$: C, 63.86; H, 4.23; N, 3.92. Found: C, 64.09; H, 4.09; N, 3.75.

The mother liquors were concentrated and the residue repeatedly recrystallized from methanol/ether to give a mixture

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that contained 6 and 5 in a 3:1 ratio: ^{1}H NMR for 6 (acetone-d_6) 1.88 (s, 3H), 2.54 (d, J = 16.8 Hz, 1H), 2.57 (br s, 1H), 3.26 (dd, J = 16.8, 5.4 Hz, 1H), 4.64 (d, J = 5.4 Hz, 1H), 5.34 (t, J = 6.0 Hz, 1H), 5.59 (t, J = 6.0 Hz, 1H), 5.80 (t, J = 6.0 Hz, 1H), 5.91 (d, J = 6.0 Hz, 1H), 7.00–7.32 (m, 4H).

Further elution with 1:1 hexanes/THF afforded 26 mg of the bis-Cr(CO)$_3$ complex 7 as a yellow solid that was recrystallized from ether (15% yield): mp 188 °C dec; ^{1}H NMR (acetone-d_6) 1.88 (s, 3H), 2.71 (d, J = 16.8 Hz, 1H), 2.81 (br s, 1H), 3.31 (dd, J = 16.8, 5.4 Hz, 1H), 4.42 (d, J = 5.7 Hz, 1H), 5.33–5.39 (m, 3H), 5.65 (t, J = 6.3 Hz, 2H), 5.79 (d, J = 6.3 Hz, 1H), 5.91 (m, 2H); ^{13}C NMR (acetone-d_6) 18.1 (q), 32.7 (t), 56.8 (d), 62.5 (s), 88.3 (d), 89.0 (d), 90.2 (d), 90.3 (d), 90.6 (d), 93.3 (d), 94.5 (d), 94.8 (d), 106.2 (s), 116.3 (s), 118.1 (s), 123.2 (s), 233.6 (s), 233.9 (s); MS m/e (rel intensity) 494 (1.6), 493 (2.2), 438 (6), 437 (8), 382 (10), 381 (14), 354 (13), 353 (18), 326 (23), 325 (32), 274 (56), 273 (100), 271 (31), 222 (17), 221 (47), 220 (33); CIHRMS 493.9800 (493.9788 calcd for $C_{22}H_{16}NO_6Cr_2$). Anal. Calcd for $C_{22}H_{16}NO_6Cr_2$: C, 53.55; H, 3.07; N, 2.84. Found: C, 53.62; H, 2.83; N, 2.82.

Reaction of 4 with (C$_6$H$_6$)Cr(CO)$_3$. A solution of racemic 4 (201 mg, 0.910 mmol) and benzenechromium tricarbonyl (408 mg, 1.90 mmol) in dry diglyme (3.5 mL) and THF (0.4 mL) was heated at 145 °C for 4 h. During this time a green precipitate developed. The solvent was removed at the water pump, and the residue purified by flash chromatography. Elution with 1:1 hexane/ether brought down unreacted benzenechromium tricarbonyl; 100% ether then brought down the mono-Cr(CO)$_3$ complex 8 (65 mg) and a mixture of 8 and bis-Cr(CO)$_3$ complex 9 (117 mg). For pure 8: mp 165 °C dec; ^{1}H NMR 3.04 (d, J = 17.7 Hz, 1H), 3.34–3.53 (m, 3H), 3.83 (d, J = 11.4 Hz, 1H), 4.35 (unresolved t, 1H), 4.92 (d, J = 6.6 Hz, 1H), 4.98 (t, J = 6.3 Hz,1 H), 5.47 (t, J = 6.3 Hz, 1H), 5.61 (d, J = 6.6 Hz, 1H), 7.20-7.25 (m, 4H); EIHRMS 357.0459 (357.0457 calcd for $C_{19}H_{15}NO_3Cr$).

Reaction of 10 with (C$_6$H$_6$)Cr(CO)$_3$. A yellow solution of racemic 10 (230 mg, 0.899 mmol) and benzenechromium tricarbonyl (230 mg, 1.08 mmol) in dry diglyme (2 mL) and THF (0.2 mL) was heated at 145 °C for 5 h. The solvent was removed at the water pump and the residue purified by flash chromatography under argon. Elution with 1:1 hexane/ether brought down unreacted (C$_6$H$_6$)Cr(CO)$_3$; 100% ether then brought down 102 mg (29%) of the mono-Cr(CO)$_3$ complex 11 as a yellow solid: mp 174–176 °C dec; ^{1}H NMR (acetone-d_6) 3.18 (dd, J = 17.7, 3.6 Hz, 1H), 3.45 (dd, J = 13.8, 3.6 Hz, 1H), 3.50 (m, 2H), 3.81 (d, J = 3.6 Hz, 1H), 4.04 (t, J = 3.6 Hz, 1H), 5.51 (dt, J = 24, 3 Hz, 2H), 5.79 (t, J = 7.5 Hz, 2H), 7.14 (dd, J = 18.9, 8.1 Hz, 2H), 7.34 (d, J = 2.1 Hz, 1H); EIHRMS 391.0081 (391.0067 calcd for $C_{19}H_{14}NO_3ClCr$). Anal. Calcd for $C_{19}H_{14}NO_3ClCr$: C, 58.31; H, 3.59; N, 3.58. Found: C, 58.62; H, 3.61; H, 3.40.

1-Ferrocenyl-2-phenyl-1-ethanone *O*-Methyl Oxime (15). To a solution of 12[15] (806 mg, 2.65 mmol) in pyridine (8.5 mL, dried over molecular sieves) was added at room temperature methoxyamine hydrochloride (2.26 g, 27.0 mmol). The resulting solution was stirred at room temperature for 28 h, and then the pyridine was removed in vacuo. The residual solids were stirred with ether (30 mL), followed by filtration. The filtrate was concentrated in vacuo to 766 mg of a dark red-orange solid (87% crude yield), consisting of both geometrical oxime isomers of 15 (R_f 0.50, 0.40, CHCl$_3$). The two isomers were separated by flash chromatography using a hexanes/chloroform elution gradient of 1:0 to 1:1 to 0:1. The less-polar isomer (443 mg) was isolated as orange crystals which were recrystallized from hexanes: R_f (CHCl$_3$) 0.50; mp 95.5–97.0 °C; ^{1}H NMR (CDCl$_3$) 3.97 (s, 3H), 4.02 (s, 2H), 4.06 (s, 5H), 4.29 (s, 2H), 4.56 (s, 2H), 7.3 (m, 5H). Anal. Calcd for $C_{19}H_{19}NOFe$: C, 68.49; H, 5.75; N, 4.20. Found: C, 68.28; H, 5.77; N, 4.15.

The more-polar isomer (174 mg) was isolated as a dark orange oil: R_f 0.40 (CHCl$_3$); ^{1}H NMR (CDCl$_3$) 3.86 (s, 2H), 4.07 (s), 4.08 (s, signals at 4.07 and 4.08 ppm integrate to 7H combined), 4.31 (s, 2H), 4.80 (s, 2H), 7.3 (m, 5H).

1-Amino-1-ferrocenyl-2-phenylethane (18). To a solution of the crude E,Z mixture of 15 (368 mg, 1.11 mmol) in THF (10.0 mL) at 0–5 °C was added borane–tetrahydrofuran solution (1.0 M, 6.0 mL, 6.0 mmol, Aldrich) dropwise over a period of 15 min. The resulting dark red solution was refluxed for 14 h. After cooling the reaction mixture in an ice bath, water (15 mL) was carefully added, followed by 20% NaOH (15 mL). The resulting golden biphasic mixture was refluxed with vigorous magnetic stirring for 12 h. Hexanes were added, and the layers were separated. The aqueous portion was extracted with hexanes (2 × 25 mL). The combined organic portions were dried over potassium carbonate and concentrated in vacuo to an orange oil. Flash chromatography afforded 18 (302 mg, 89%) as a viscous orange-yellow oil: R_f 0.41 (CHCl$_3$); ^{1}H NMR (CDCl$_3$) 1.49 (br s, 2H), 2.63 (dd, J = 13.0, 9.0 Hz, 1H), 2.96 (dd, J = 13.0, 4.5 Hz, 1H), 3.89 (dd, J = 9.0, 4.5 Hz, 1H), 4.03 (s, 2H), 4.10 (s, 5H), 4.18 (s, 2H), 7.3 (m, 5H); ^{13}C NMR (CDCl$_3$) 140.2, 130.3, 129.3, 127.2, 69.2, 68.3, 67.7, 66.3, 53.2, 47.1.

The acetate was formed from glacial acetic acid in ether, recrystallized from hexanes/EtOAc, and isolated as small yellow needles: mp 140–141.5 °C (lit.[28] mp 113 °C). Anal. Calcd for $C_{20}H_{23}NOFe$: C, 65.77; H, 6.35; N, 3.83. Found: C, 65.95; H, 6.22; N, 3.71.

1-[*N*-(2,2-Diethoxyethyl)amino]-1-ferrocenyl-2-phenylethane (21). To a stirred mixture of amine 18 (122 mg, 0.40 mmol) and potassium carbonate (165 mg, 1.19 mmol) in DMF (2 mL, dried over molecular sieves) at 95 °C was added bromoacetaldehyde diethylacetal (133 mg, 0.67 mmol, distilled) as a solution in 2 mL of DMF (four portions over 30 min). Heating was continued for 14 h. The resulting dark red reaction mixture was allowed to cool and then it was poured into 1 N NaOH (20 mL). The resulting mixture was extracted with methylene chloride (4 × 10 mL). The combined extracts were washed with water (1 × 15 mL) and brine and dried over potassium carbonate. The solvent was evaporated, leaving a brown syrup which was purified by flash chromatography on silica gel using hexanes/chloroform (2:1 to 1:1 to 1:2) as eluant. The acetal 21 (118 mg, 70%) was isolated as a yellow-orange oil: R_f 0.67 (ether); ^{1}H NMR (CDCl$_3$) 1.15 (m, 6H), 2.00 (br s, 1H), 2.74 (d, 2H), 2.94 (m, 2H), 3.45 (m, 4H), 3.65 (m, 1H), 3.80 (s, 1H), 4.00 (s, 1H), 4.08 (s, 1H), 4.14 (s, 5H), 4.18 (s, 1H), 4.55 (t, 1H), 7.0–7.3 (m, 5H); EIHRMS 421.1700 (421.1704 calcd for $C_{24}H_{31}NO_2Fe$).

Attempted Cyclization to 26. To neat 21 (40.1 mg, 0.0951 mmol), while being cooled in a dry ice/acetone bath, was added dropwise trifluoromethanesulfonic acid (641 mg, 4.27 mmol) over a period of 5 min. The resulting reaction mixture was allowed to warm to room temperature with the cooling bath with stirring, and then stirred at room temperature for 2 h. Cracked ice (1 g) was added, followed by basification with 1 N NaOH to pH > 10. The resulting cloudy mixture was extracted with methylene chloride (3 × 5 mL). The combined extracts were washed with brine (1 × 10 mL) and dried over sodium sulfate. Evaporation of the solvent left an orange oil which was purified by flash chromatography using 5:95 EtOAc/THF as eluant. The alcohol 25 (22.5 mg, 68%) was isolated as a yellow oil: R_f 0.36 (15% EtOAc/THF); IR (THF) 3582 (m), 3533 (m), 1624 (w); ^{1}H NMR (CDCl$_3$) 2.01 (br s, 2H, exchangeable with D$_2$O), 2.66 (dd, J = 13.5, 9.0 Hz, 1H), 3.03 (dd, J = 13.5, 4.5 Hz, 1H), 3.13 (dd, J = 12.3, 2.1 Hz, 1H), 3.44 (dd, J = 12.3, 1.8 Hz, 1H), 4.09 (s, 6H), 4.19 (d, J = 1.1 Hz, 1H), 4.28 (d, J = 1.3 Hz, 1H), 4.39 (dd, J = 9.0, 4.5 Hz, 1H), 4.60 (t, J = 2.0 Hz, 1H), 7.21–7.36 (m, 5H); ^{13}C NMR (CDCl$_3$) 138.5, 129.4, 128.6, 126.7, 88.4, 85.2, 69.8, 66.5, 65.8, 65.2, 64.2, 56.7, 51.2, 43.6; MS m/e (rel intensity) 347 (M$^+$, 40), 329 (M – H$_2$O, 24), 256 (M – CH$_2$Ph, 100), 238 (M – [H$_2$O + CH$_2$Ph], 62), 118 (M – [H$_2$O + CH$_2$Ph + FeCp], 67), 91 (CH$_2$Ph, 100); EIHRMS 347.0963 (347.0973 calcd for $C_{20}H_{21}NOFe$).

1,2-Diferrocenyl-1-ethanone (13). The method of Benedikt and Schlogl[21] was adapted. To a solution of ferroceneacetic acid[20] (1.00 g, 4.08 mmol) in methylene chloride (125 mL) was added ferrocene (3.74 g, 20.4 mmol) and alumina (15 g, neutral, activity II–III). With stirring, trifluoroacetic anhydride (15.0 mL, 106 mmol) was carefully added over 10 min. The resulting brown-violet suspension was stirred at room temperature overnight. The volatile materials were removed by rotary evaporation, and the residue was extracted with ether (125 mL), which was filtered through Celite. Concentration in vacuo of the filtrate afforded a dark red solid which was taken up in benzene and passed through a column of alumina (neutral, activity I, 35 g). Some of the residual ferrocene was separated from 13 in this manner. The remaining 13–ferrocene mixture (3.62 g of reddish-orange crystals)

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was carried through in the next step without further purification: R_f 0.68, 0.62 (1:1 ether/hexanes) for ferrocene and **13**, respectively.

1,2-Diferrocenyl-1-ethanone *O*-Methyl Oxime (16). To a solution of the mixture (3.62 g) of **13** and ferrocene described directly above in pyridine (11.5 mL, dried over molecular sieves) was added methoxyamine hydrochloride (2.07 g, 24.8 mmol). The resulting red-orange slurry was stirred at room temperature for 20 h. The pyridine was removed in vacuo at 60 °C, and the residual solids were stirred with ether (75 mL). The solids were isolated by filtration and discarded. The filtrate was concentrated in vacuo to give a reddish-orange solid which was taken up in benzene and passed through a column of alumina (neutral, activity I, 35 g) using benzene as eluant. More of the ferrocene was separated from the product **16** in this manner, but there was still ferrocene present in the mixture of oxime geometrical isomers **16**. This mixture (2.79 g, of a deep red crystalline solid) was carried through to the next step without further purification: R_f 0.62, 0.49, 0.42 (5:1 hexanes/EtOAc) for ferrocene and the geometrical isomers of **16**, respectively.

1,2-Diferrocenyl-1-aminoethane (19). To a solution of the oximes **16**/ferrocene mixture (2.79 g) described directly above in 25.0 mL of THF was added borane–tetrahydrofuran complex (15.0 mL, 15.0 mmol, 1.0 M in THF) under nitrogen. The resulting deep red solution was brought to reflux and held there for 15 h. The now yellow-red solution was cooled with an ice bath, and water (37.5 mL) was carefully added, followed by 20% NaOH (37.5 mL). The resulting biphasic solution was refluxed with vigorous magnetic stirring for 12 h, and allowed to cool to room temperature. Hexanes (25 mL) were added, the layers were separated, and the aqueous portion was extracted with hexanes (1 × 25 mL). The combined organic portions were dried over potassium carbonate and concentrated in vacuo. The solid orange residue was purified by column chromatography on alumina (neutral, activity I, 40 g). Elution with benzene brought down ferrocene. The eluant was changed to ether which brought down the amine **19** (919 mg, 55% based on ferroceneacetic acid) as an orange powder: mp 151.0–154.5 °C; R_f 0.58 ($CHCl_3$/Et_2NH 10:1); IR ($CDCl_3$) 3098 (w), 2940 (w), 2850 (w); ^1H NMR ($CDCl_3$) 1.53 (br s, 2H), 2.47 (dd, J = 13.8, 8.7 Hz, 1H), 2.69 (dd, J = 13.8, 4.2 Hz, 1H), 3.65 (dd, J = 8.7, 4.2 Hz, 1H), 3.96–4.21 (m, 18H for the region), 4.10 (s), 4.16 (s); MS *m/e* (rel intensity) 413 (M^+, 19), 396 (10), 214 (100), 200 (39), 186 (20), 147 (16), 121 (51).

The acetate salt was prepared in EtOAc/ether from **19** and acetic acid, and crystallized from hexanes/EtOAc (4:1) as fine orange needles: mp 134–136 °C. Anal. Calcd for $C_{24}H_{27}NO_2Fe_2$: C, 60.92; H, 5.75; N, 2.96. Found: C, 60.86; H, 5.87; N, 2.77.

[*N*-(2,2-Diethoxyethyl)amino]-1,2-diferrocenylethane (22). As for **21**, a mixture of **19** (603.8 mg, 1.462 mmol), potassium carbonate (602 mg, 4.36 mmol), and bromoacetaldehyde diethylacetal (0.576 g, 2.92 mmol) in DMF (15.0 mL) afforded a crude dark brown oil which was purified by flash chromatography on 40 g silica gel using 1:1 hexanes/ethyl acetate as eluant to give **22** (454.3 mg, 59%) as a dark amber syrup: R_f 0.42 (1:1 ethyl acetate/hexanes); IR ($CDCl_3$) 3322 (w), 3098 (m), 2978 (m), 2900 (m), 1451 (m), 1378 (m), 1263 (m), 1227 (m), 1106 (s), 1057 (m); ^1H NMR ($CDCl_3$) 1.23 (q, J = 6.6 Hz, 6H), 2.03 (br s, 1H), 2.61–2.85 (m, 4H), 3.23 (t, J = 6.3 Hz, 1H), 3.51–3.82 (m, 4H), 3.84–4.17 (m, 18H over the region), 4.08 (s), 4.17 (s), 4.64 (t, J = 6.3 Hz, 1H); MS *m/e* (rel intensity) 529 (M^+, 3), 483 (2), 438 (2), 421 (3), 396 (23), 330 (100), 238 (72), 199 (10), 121 (23).

Attempted Cyclization to 27. With cooling by an ice bath, concentrated sulfuric acid (0.120 mL, 2.2 mmol) was added by syringe to neat **22** (41.3 mg, 0.0780 mmol). The resulting dark green syrup was stirred at room temperature overnight. The reaction was quenched by addition of a few pieces of cracked ice and 10% NaOH (6 mL), to pH > 10. The resulting pale brown mixture was extracted with methylene chloride (3 × 5 mL). The combined extracts were washed with brine, dried over sodium sulfate, and concentrated in vacuo to give a light brown residue. This residue was purified by flash chromatography on 4.5 g silica gel using 4:1 THF/ethyl acetate as eluant, to afford the alcohol **29** (20.5 mg, 58%) as a clear, light amber syrup: R_f 0.25 (5:1 THF/ethyl acetate); IR ($CDCl_3$) 3098 (w), 2959 (m), 1602 (w), 1469 (m), 1384 (w), 1106 (m); ^1H NMR ($CDCl_3$) 2.13 (br s, 2H, exchangeable with D_2O), 2.49 (dd, J = 13.9, 8.4 Hz, 1H), 2.75 (dd, 13.9, 4.0 Hz, 1H), 3.10 (dd, J = 12.5, 1.8 Hz, 1H), 3.41 (dd, J = 12.5, 1.2 Hz, 1H), 3.94–4.20 (m, 16H, singlets at 4.06, 4.13, 4.18), 4.24 (d, J = 1.5 Hz, 1H), 4.26 (d, J = 1.8 Hz, 1H), 4.55 (br s, 1H); ^{13}C NMR ($CDCl_3$) 37.7, 50.8, 56.4, 64.2, 65.0, 65.7, 66.4, 67.7, 67.9, 68.8, 69.2, 69.5, 69.8, 84.3, 85.0, 88.1; MS *m/e* (rel intensity) 455 (M^+, 6), 437 (17), 256 (100), 238 (74), 200 (74), 199 (36), 121 (42), 118 (49); EIHRMS 455.0652 (455.0635 calcd for $C_{24}H_{26}NOFe_2$).

When THF that was freshly distilled from sodium was used for the chromatography, the product alcohol **29** was less stable than when untreated THF was used. The product obtained from the "dry" chromatography immediately began to decompose to less-polar material that was difficult to characterize.

[η^5-[2-Phenyl-1-(methoxyimino)ethyl]cyclopentadienyl]manganese Tricarbonyl (17). To a stirred solution of **14**[22] (0.401 g, 1.24 mmol) in pyridine (5.0 mL, dried over molecular sieves) was added methoxyamine hydrochloride (0.167 g, 2.00 mmol). The resulting dull orange slurry was stirred at room temperature for 16 h. The pyridine was removed in vacuo at 50 °C and the resulting heterogeneous mixture was stirred with ether (20 mL), followed by gravity filtration. The isolated solids were rinsed with ether (25 mL). The combined ethereal portions were dried over sodium sulfate and concentrated to afford 416 mg of a golden syrup. This syrup was chromatographed on alumina (20 g, neutral, activity I), using ether as eluant. The syn and anti isomers (1.5:1 ratio from ^1H NMR) were collected together and isolated as a clear golden syrup (356 mg, 82% yield): R_f 0.67, 0.61 (benzene); IR ($CDCl_3$) 2942 (m), 2026 (s), 1940 (s), 1602 (m), 1497 (m), 1454 (m), 1055 (s); ^1H NMR ($CDCl_3$) 3.75 (s, 6H for 4.05–3.75 ppm), 3.88 (s), 4.00 (s), 4.05 (s), 4.67 (2s, 2H), 5.16 (s, 1H), 5.39 (s, 1H), 7.30 (2s, 5H); MS *m/e* (rel intensity) 351 (M^+, 46), 295 (M – 2CO, 25), 267 (M – 3CO, 100), 235 (87).

[η^5-(1-Amino-2-phenylethyl)cyclopentadienyl]manganese Tricarbonyl (20). As for **18**, **17** (0.227 g, 0.646 mmol) was reacted with borane–tetrahydrofuran complex (3.2 mL, 3.2 mmol, 1.0 M), followed by basic hydrolysis. The crude amine was purified by chromatography on alumina (15 g, neutral, activity I) using 20:1 ether–acetonitrile, affording **20** (157.1 mg, 75%) as a clear golden syrup: R_f 0.32 ($CHCl_3$/Et_2NH 25:1); IR (CCl_4) 2020 (s), 1929 (s); ^1H NMR ($CDCl_3$) 1.99 (s, 2H), 2.94 (m, 2H), 4.26 (dd, J = 8.1, 5.4 Hz, 1H), 4.56 (s, 1H), 4.66 (s, 1H), 5.07 (s, 1H), 7.30–7.09 (m, 5H); MS *m/e* (rel intensity) 323 (M^+, 16), 295 (M – CO, 10), 267 (M – 2CO,13), 239 (M – 3CO, 80), 232 (M – CH_2Ph, 20), 222 (82), 91 (CH_2Ph, 100).

The hydrochloride was prepared in ether and crystallized from EtOAc/MeOH as an ivory-colored powder: mp 221–223 °C dec. Anal. Calcd for $C_{16}H_{15}NO_3ClMn$: C, 53.43; H, 4.20; N, 3.89. Found: C, 53.67; H, 4.24; N, 3.81.

[η^5-[1-[*N*-(2,2-Diethoxyethyl)amino]-2-phenylethyl)cyclopentadienyl]manganese Tricarbonyl (23). As for **21**, a mixture of **20** (240 mg, 0.742 mmol), potassium carbonate (130 mg, 0.941 mmol), and bromoacetaldehyde diethylacetal (293 mg, 1.49 mmol) in DMF (4 mL) gave the crude product as a brown syrup, which was purified by flash chromatography using 3:1 hexanes/EtOAc as eluant. Acetal **23** (208 mg, 64%) was isolated as an amber syrup: R_f 0.42 (hex/EtOAc 2:1); IR (CCl_4) 2022 (s), 1939 (s); ^1H NMR ($CDCl_3$) 1.18 (two superimposed triplets, 6H), 1.48 (br s, 1H), 2.86 (m, 4H), 3.51 (m, 4H), 3.63 (m, 1H), 4.57 (d, J = 18 Hz, 3H), 4.82 (s, 1H), 7.2 (m, 5H); MS *m/e* (rel intensity) 355 (M^+ – 3CO, 78), 348 (M^+ – CH_2Ph, 100), 222 (84).

[η^5-Cyclopentadienyl]manganese Tricarbonyl Derivative (28). To neat **23** (69.1 mg, 0.157 mmol) at 0 °C was added concentrated sulfuric acid (154 mg, 1.57 mmol). The resulting dark orange syrup was allowed to warm to room temperature, and then it was stirred for 46 h. Ice (2 g) was added followed by 10% NaOH (5 mL) to pH > 10. The resulting yellow-brown mixture was extracted with methylene chloride (2 × 8 mL). The combined extracts were washed with brine and dried over sodium sulfate. The solvent was evaporated, and the residue was purified by flash chromatography using 1:1 hexanes/EtOAc as eluant. The double cyclization product **28** (27 mg, 50%) was isolated as a clear, pale orange syrup that solidified upon standing: R_f 0.39 (2:1 hexanes/EtOAc); mp 116.0–119.0 °C; IR (CCl_4) 2020 (s), 1934 (s); ^1H NMR 1.82 (br s, 1H), 3.18 (dd, J = 17.3, 2.3 Hz, 1H), 3.36–3.62 (m, 4H), 4.02 (br s, 1H), 4.49 (d, J = 2.4 Hz, 2H), 4.63 (t, J = 2.4 Hz, 1H), 7.11 (m, 4H); ^{13}C NMR ($CDCl_3$) 39.5, 41.7, 48.4, 51.9, 74.1, 75.3, 81.9, 107.7, 110.8, 126.2, 127.1, 127.8, 132.0,

135.5, 142.2, 225.4; MS *m/e* (rel intensity) 347 (M^+, 27), 319 (M - CO, 66), 291 (M - 2CO, 15), 263 (M - 3CO, 100); EIHRMS 347.0350 (347.0354 calcd for $C_{18}H_{14}O_3Mn$).

The hydrochloride was prepared by passing hydrogen chloride through an ethereal solution of **28**, followed by crystallization from methanol/ether to give **28**·HCl as fine, pale brown needles: mp 258–262 °C dec. Anal. Calcd for $C_{18}H_{15}NO_3ClMn·0.5H_2O$: C, 55.05; H, 4.11; N, 3.57. Found: C, 55.36; H, 4.04; N, 3.62.

Stability of 5 and 28 under in Vitro Testing Conditions. Separate solutions of **2** and **5** (10^{-4} M) in nondeoxygenated 1:1 water/methanol (buffered to pH = 7.4 with tris) were monitored by UV spectrophotometry over the wavelength range 200–400 nm. At room temperature, the solution of **5** showed 100% of original absorbance at 265 nm 2 h after solution preparation. At 6.5 h the absorbance had decreased to 97% of its original value; it was 82% at 22 h and 50% at 46 h. The solution of **2** showed no change in the UV spectrum over the same time period (UV max at 227 nm). The same experiment performed on **28**·HCl showed no change in the UV spectrum over 24 h, and >90% of the original absorbances after 1 week.

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Supplementary Material Available: ^1H NMR spectra of **8**, **17**, **21–23**, **25**, and **29** and COSY spectrum of **25** (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.