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Diastereoselective Synthesis of a Highly Functionalized Angularly Substituted *cis*-Perhydroisoquinoline-3,6-dione via Organoiron

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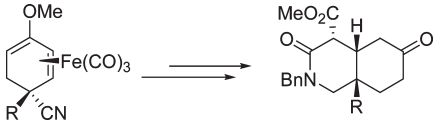

Nitrile addition to cyclohexadienyium-$Fe(CO)_3$ perchlorate salt provides an efficient entry into the angularly substituted cis-fused perhydroisoquinoline ring system. The key steps in the assembly of the angularly substituted *cis*-octahydroisoquinoline ring are the transformation of the nitrile to an *N*-(benzylmethylencie)amino group and a diastereoselective intramolecular Michael reaction to form the bicyclic ring.

Introduction

The *cis*-perhydroisoquinolines are a common scaffold found in a wide array of biologically active natural products[1] such as morphine,[2] Xestocyclamine A,[3] manzamine A,[4] madangamine[5] alkaloids, and pharmaceuticals.[6] To date, numerous strategies have been developed for the construction of the perhydroisoquinoline core which include, intra- and intermolecular Diels−Alder,[7] ionic,[8] radical,[9] photochemical ring cyclizations,[10] ring closing metathesis,[11] and tandem ring-opening and closing.[12] Although the construction of the *cis*-perhydroisoquinoline core has been the primary goal in most of these syntheses, the introduction of an extra angular substitution remains one of the most challenging tasks, and is present in the manzamine family of marine alkaloids. Thus, although several synthetic studies on this family of alkaloids have been published, only three total syntheses have been reported to date.[13,14] Also, the lengthy total synthesis reported for manzamine has also led to the search for a more simplified scaffold, but with the *cis*-perhydroisoquinoline core structure intact.[15] This has prompted us to develop a new pathway for the synthesis of angularly substituted *cis*-perhydroisoquinoline scaffolds. To the best of our knowledge, only a limited number of approaches for the preparation of the important *cis*-perhydroisoquinoline-3,6-diones

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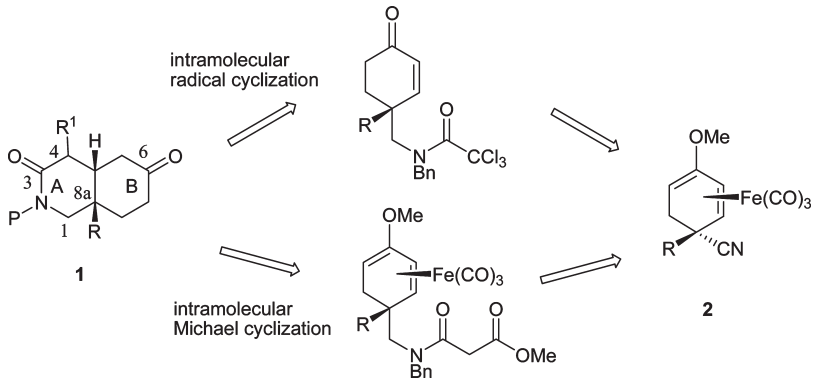
SCHEME 1. Retrosynthesis of *cis*-Perhydroisoquinoline 1



that are highly functionalized, but generally without an angular substitution at C-(8a), have been published: the intramolecular Diels−Alder reaction,[16] intramolecular radical cyclization,[9b] and the intramolecular Michael reaction.[17] We report herein a convenient organoiron-mediated synthetic pathway that utilizes an intramolecular radical/or Michael reaction for the synthesis of a highly functionalized angular *cis*-perhydroisoquinoline-3,6-dione **1** at C-(8a), an intermediate that holds considerable potential for elaboration toward natural products and pharmaceuticals. More importantly, we have also explored the construction of different angular C-(8a) substituents to show the flexibility of our method.

The tricarbonyliron complexes of cyclic and acyclic dienes have been widely used as a temporary moiety for the high level of chemo-, regio-, and stereocontrol in organic synthesis.[18−21] Our laboratory has developed the use of the cyclohexadienylium-Fe(CO)$_3$ perchlorate salt[22] in place of the hexafluorophosphate salt[23] for the successful TMS-CN addition reaction, and this has led to the construction of a cyano-substitued quaternary center. This cyano-substitued iron complex has been further transformed into 1-oxo-2-azaspiro[5.5]undecane,[24] which is an important intermediate in the synthesis of biologically active *Nitraria* alkaloids.[25] Recently, we have further extended the nitrile addition methodology to successfully synthesize the tricyclic spirooxaquinolizidinone ring of Upenamide.[26] On the basis of this strategy, we envisioned that the *cis*-perhydroisoquinoline-3,6-diones **1** can be elaborated from the iron complex **2** via two key steps: (1) the nitrile addition to construct the C-(8a) quaternary center of **1** and (2) elaboration of the nitrile group to undergo the intramolecular radical/or Michael reaction for the consecutive formation of the *cis*-perhydroisoquinoline ring. The proposed retrosynthesis analysis is depicted in Scheme 1.

Results and Discussion

To first investigate the potentiality of our strategy, we chose to synthesize the methyl-substituted angular *cis*-perhydroisoquinoline ring **1** (R = CH_3) by using an intramolecular radical reaction of the N-tethered acetamide to the cyclohexenone ring as outlined in Scheme 1. Our synthesis starts from the organoiron complex **2** (R = CH_3), a known intermediate prepared previously in our laboratory.[22] The resulting cyano-adduct **2** must be transformed into the methylene-amine group for elaboration to the *cis*-perhydroisoquinoline ring. Reduction of the cyano group in complex **2** with DIBAL successfully afforded the aldehyde complex **3** in near-quantitative yield. Treatment of **3** under standard reductive amination conditions afforded the corresponding benzylamine complex **4** in 92% yield after two steps. With the successful synthesis of compound **4**, we next centered on the installation of the *cis*-perhydroisoquinoline core skeleton utilizing an intramolecular radical reaction of a nitrogen-tethered trichloroacetamide onto cyclohexenone as developed by Bonjoch.[9b] Thus, the resulting complex **4** was reacted with trichloroacetyl chloride to afford the *N*-trichloroacetamide complex **5** in 71% yield. The tricarbonyliron group was removed with trimethylamine *N*-oxide, and the resulting enol ether was hydrolyzed to give cyclohexenone **6** in 80% overall yield, the key intermediate for the synthesis of the *cis*-perhydroisoquinoline core skeleton, **1**. Treatment of **6** with AIBN and Bu_3SnH in refluxing benzene as reported[9b] afforded trace amounts of the bicyclic product **7** (Scheme 2),

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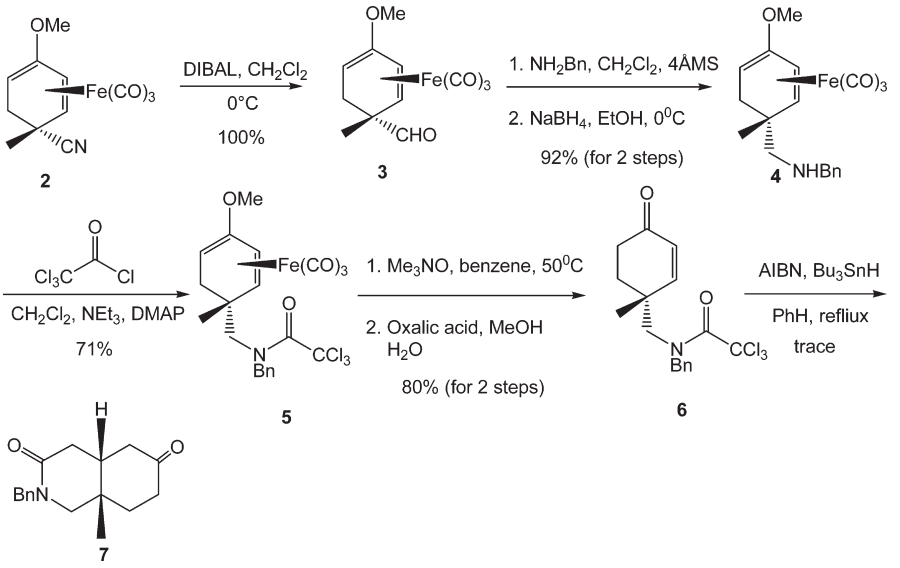
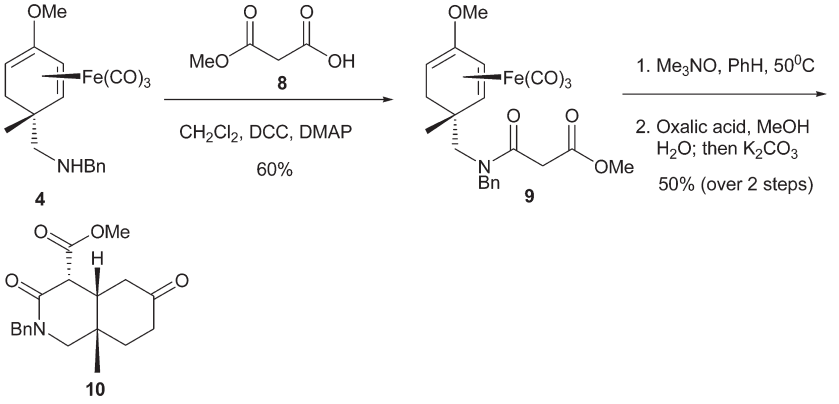
SCHEME 2. Construction of the *cis*-Perhydroisoquinoline Ring via an Intramolecular Radical Reaction



SCHEME 3. Synthesis of the *cis*-Perhydroisoquinoline Ring via Intramolecular Michael Addition



detected in the crude ^{1}H NMR, and several attempts to purify the product proved difficult. It is rather unfortunate that our attempt to induce the analogous intramolecular radical reaction failed to give satisfactory yield of an angular-substituted *cis*-perhydroisoquinoline core skeleton.

The next planned strategy for the formation of the bicyclic ring of the *cis*-perhydroisoquinoline-3,6-dione is to employ an intramolecular Michael reaction of a nitrogen-tethered malonic acid derivative onto cyclohexenone following the protocol of Stork.[17] Accordingly, the secondary amine of complex **4** was condensed with malonic acid monomethyl ester **8** with use of DCC to afford the amide **9** in 60% yield. Decomplexation with Me_3NO afforded the enol ether, which on hydrolysis to the enone with oxalic acid followed by neutralization with potassium carbonate was found to undergo an in situ Michael addition to give **10** as a single isomer, albeit in a 50% moderate isolated yield (Scheme 3). A one-pot procedure for converting complex **9** to **10** can be realized by the use of cerium ammonium nitrate (CAN) to remove the $Fe(CO)_3$ moiety, but with only a slight improvement in the overall yield.

The stereochemistry of compound **10** was established unequivocally from the NOESY ^{1}H NMR experiment. The NOESY ^{1}H NMR showed interaction between the ring angular hydrogen and methyl group illustrating their cis relationship. Furthermore, we also observed interaction between the angular-H and the α-carbonyl-H in the NOESY ^{1}H NMR, establishing their cis relationship as shown in Figure 1. Thus, the intramolecular Michael reaction to the cyclohexenone took place with high diastereoselectivity.

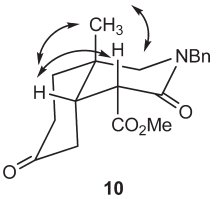
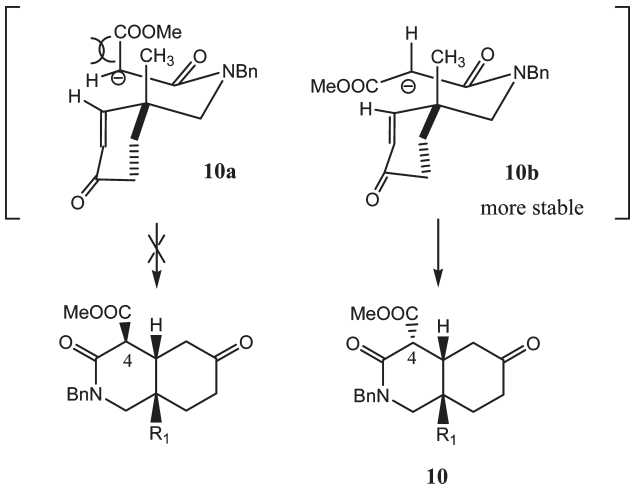


FIGURE 1. NOE correlation of **10**.

In contrast, Bonjoch has reported that a mixture of epimers at C(4) are formed when performing the intramolecular Michael reaction without an angular substitution (R_1 = H).[8c] The high diastereoselectivity in our case might be rationalized to the steric hindrance in the presence of an angular alkyl-substitution (R_1 = CH_3). The transition states for the formation of compound **10** and its diastereomer are outlined in Scheme 4. During cyclization, the transition state

SCHEME 4. Proposed Diastereoselectivity of the Intramolecular Michael Reaction



10a will have an unfavorable 1,3-diaxial interaction between the ester group and the methyl group, hence this diastereomer was not obtained. On the other hand, the more stable transition state with the ester group at the equatorial position, **10b**, undergoes the intramolecular cyclization readily to afford **10**.

With our success in forming the core scaffold **10**, the next goal is to install a suitable angular side chain toward a synthesis of the manzamine family of alkaloids. The proposed plan involves the elaboration of the organoiron complex **11** synthesized previously in our laboratory.[24,26] At this stage, we needed to replace the acetate protecting group in **11** with a *tert*-butyldimethylsilyl (TBDMS) group that is stable to hydride reduction during the next step The acetate was hydrolyzed and protected as the TBDMS ether without decomposition of the iron complex. To our delight, as shown in Scheme 5, the complex **11** can be transformed readily to the key intermediate **14**, analogous to that outlined for the conversion of **3** to **9**. Decomplexation of **14** with CAN in this case gave rise to a much messier mixture of products, probably due to the presence of the hydroxy group. Thus, a two-step protocol was used, decomplexation with Me_3NO, followed by hydrolysis of the enol ether to the enone. This gave a moderate yield of **15** (30% for 2 steps), with the simultaneous removal of the TBS protecting group. The NOESY ^{1}H NMR of **15** also showed interaction between the angular H and CH_2 group, together with the α-carbonyl-H. Here again, the intramolecular Michael reaction proceeded with high diastereoselectivity for the synthesis of **15**.

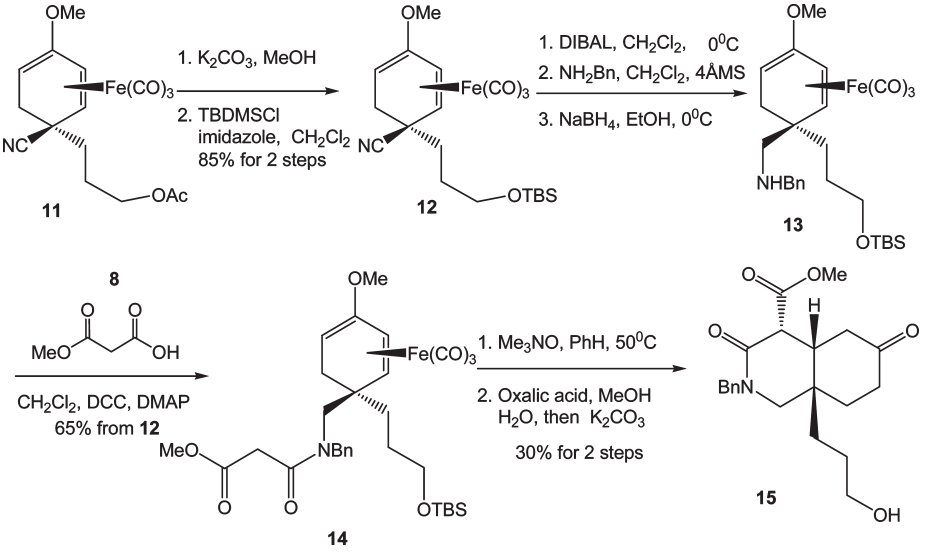
Conclusion

In summary, we have described a convenient strategy for the synthesis of *cis*-perhydroisoquinoline-3,6-dione derivative having angular substitutions. The key element in this approach includes a cyanide group addition to tircarbonylcyclohexadienylium salt, followed by elaboration of the cyano group to a 4,4-disubstituted cyclohexenone. Formation of the *cis*-perhydroisoquinoline core skeleton was accomplished by a highly diastereoselective intramolecular Michael reaction onto the cyclohexenone, establishing three stereogenic centers in a single step. We believe that the availability of compounds such as **10** and **15** will allow them to serve as useful intermediates for synthesis of natural and un-natural products.

Experimental Section

Tricarbonyl{2-5-*η*-[1-*N*-benzyl-2,2,2-trichloro-*N*-(4-methoxy-1-methylcyclohexa-2,4-dienylmethyl)acetamide]}iron (5). To a solution of the complex **2** (370 mg, 1.28 mmol) in CH_2Cl_2 (15 mL) was slowly added DIBAL (20% in toluene, 1.82 mL, 2.56 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After the reaction was completed, 1 M aqueous HCl was added and the reaction mixture was filtered with Celite. To the mixture was added CH_2Cl_2, then the mixture was washed with saturated aqueous $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4 and evaporated to give aldehyde complex **3** as an orange oil, suitable for use in the next reaction. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.00 (s, 1H, −CHO), 5.09 (dd, J = 6.2, 2.6 Hz, 1H, 3-H), 3.61 (s, 3H, −OMe), 3.42 (m, 1H, 5-H), 2.24 (d, J = 6.2 Hz, 1H, 2-H), 2.14 (dd, J = 15.2, 2.6 Hz, 1H, *endo*-6-H), 1.49 (dd, J = 15.2, 2.6 Hz, 1H, *exo*-6-H), 1.06 (s, 3H, CH_3); mass (FAB) m/z 292 (M^+), 264 ($M^+ - CO$), 236 ($M^+ - 2CO$), 208 ($M^+ - 3CO$).

SCHEME 5. Synthesis of the *cis*-Perhydroisoquinoline-3,6-dione 15 via Intramolecular Michael Reaction



To a solution of complex **3** (0.58 g, 2.0 mmol) and benzylamine (0.4 mL, 3.67 mmol) in CH_2Cl_2 (20 mL) was added 4 Å molecular sieve (2.0 g) and then the solution was stirred at room temperature overnight. The reaction mixture was filtered with Celite and washed with CH_2Cl_2. The solution was evaporated to dryness in vacuo to afford the crude imine complex. Thereupon the crude was dissolved in ethanol (10 mL) and $NaBH_4$ (0.20 g, 2.5 mmol) was added in portions under cooling in the ice bath. After complete addition, the reaction mixture was allowed to continue stirring for 3 h. Water was added at 0 °C to destroy the excess $NaBH_4$, then the solution was evaporated to dryness and extracted with CH_2Cl_2. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated to give amine complex **4** (0.70 g, 92% over 3 steps) as an orange oil, suitable for use in the next reaction. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.33−7.26 (m, 5H, Ph), 5.01 (dd, J = 6.2, 2.0 Hz, 1H, 3-H), 3.79 (d, J = 12.0 Hz, 1H, $-CH_2Ph$), 3.60 (d, J = 12.0 Hz, 1H, $-CH_2Ph$), 3.58 (s, 3H, −OMe), 3.26 (m, 1H, 5-H), 2.47 (d, J = 6.2 Hz, 1H, 2-H), 2.16 (m, 2H, $-CH_2NHBn$), 1.74 (dd, J = 16.0, 2 Hz, 1H, *endo*-6-H), 1.47 (dd, J = 16.0, 2.0 Hz, 1H, *exo*-6-H), 1.00 (s, 3H, CH_3); mass (FAB) m/z 384 (M^+), 355 ($M^+ - CO$), 327 ($M^+ - 2CO$), 299 ($M^+ - 3CO$).

To a solution of the amine complex **4** (0.70 g, 1.83 mmol), triethylamine (0.50 mL, 3.66 mmol), and a catalytic amount of 4-dimethylaminopyridine (DMAP) in CH_2Cl_2 (20 mL) was slowly added trichloroacetyl chloride (0.28 mL, 2.75 mmol) at 0 °C. After the addition was complete, the reaction mixture was allowed to continue stirring at room temperature overnight. To the reaction mixture was added CH_2Cl_2, then the mixture was washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried over Na_2SO_4, the solvent was evaporated, and the product was purified by chromatography (hexane:EA = 10:1) to give complex **5** as an orange oil (0.69 g, 71%). R_f 0.60 (hexane:EA = 10:1); IR (CH_2Cl_2) 2046, 1971, 1680 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39−7.15 (m, 5H, Ph), 5.21 (d, J = 17.0 Hz, 1H, $-CH_2Ph$), 5.08 (dd, J = 6.5, 2.5 Hz, 1H, 3-H), 5.01 (d, J = 17.0 Hz, 1H, $-CH_2Ph$), 3.61 (s, 3H, −OMe), 3.35 (d, J = 13.0 Hz, 1H, $-CH_2NCO-$), 3.28 (m, 1H, 5-H), 3.07(d, J = 13.0 Hz, 1H, $-CH_2NCO-$), 2.43 (d, J = 6.5 Hz, 1H, 2-H), 1.82 (dd, J = 15.0, 2.5 Hz, 1H, *endo*-6-H), 1.56 (dd, J = 15.0, 2.5 Hz, 1H, *exo*-6-H), 1.06 (s, 3H, $-CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.1 (CO), 162.1 ($-CON-$), 139.9 (4-C), 135.4 (Ph-1-C), 128.9 (Ph-2-C), 127.8 (Ph-3-C), 126.8 (Ph-4-C), 93.6 ($-CCl_3$), 65.5 (3-C), 59.9 (5-C), 59.0 ($-CH_2Ph$), 54.7 ($-CH_2N-$), 54.4 (−OMe), 53.2 (2-C), 40.8 (6-C), 40.7 (1-C), 27.8 ($-CH_3$); mass (FAB) m/z 528 $(M + H)^+$, 499 ($M^+ - CO$), 472 ($M^+ - 2CO$), 443 ($M^+ - 3CO$); HRMS (FAB) calcd for $C_{21}H_{21}Cl_3NO_5Fe$ (M^+) 527.9835, found 527.9845. Anal. Calcd for $C_{21}H_{20}Cl_3NO_5Fe$: C, 47.86; H, 3.83; N, 2.66. Found: C, 48.02; H, 3.89; N, 2.67.

***N*-Benzyl-2,2,2-trichloro-*N*-(1-methyl-4-oxo-cyclohex-2-enylmethyl)acetamide (6).** The complex **5** (0.69 g, 1.31 mmol) was added to a stirred suspension of anhydrous trimethylamine *N*-oxide (0.98 g, 13.1 mmol) in dry benzene (30 mL) at 50 °C. Stirring was continued for 2.5 h after which the precipitate was removed by filtration of the cooled mixture through Celite. To the solution was added water, then the mixture was extracted with ether. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated to afford the crude dienol ether quantitatively. The crude dienol ether was immediately dissolved in MeOH (3 mL) and treated with oxalic acid (120 mg, 1.31 mmol) in water (2 mL) at room temperature for 1 h. To the reaction mixture was added solid $NaHCO_3$, then the mixture was extracted with ethyl acetate, dried over Na_2SO_4, and evaporated to give the desired compound (0.39 g, 80%) as a pale yellow oil. R_f: 0.64 (CH_2Cl_2); IR (CH_2Cl_2) 1677 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 (m, 3H, Ph-2H and 4-H), 7.18 (d, J = 7.0 Hz, 1H, Ph-3H), 6.69 (d, J = 10.0 Hz, 1H, 2-H), 5.94 (d, J = 10.0 Hz, 1H, 3-H), 5.14 (d, J = 17.0 Hz, 1H, $-CH_2Ph$), 5.05 (d, J = 17.0 Hz, 1H, $-CH_2Ph$), 3.57 (d, J = 11.0 Hz, 1H, $-CH_2NCO-$), 3.45 (d, J = 11.0 Hz, 1H, $-CH_2NCO-$), 3.28 (m, 1H, 5-H), 2.49 (m, 2H, 5-H), 2.08 (m, 1H, 6-H), 1.88−1.83 (m, 1H, 6-H), 1.21 (s, 3H, $-CH_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.6 ($-CO-$), 162.4 ($-CON-$), 155.9 (2-C), 134.9 (Ph-1-C), 129.1 (Ph-2-C), 128.4 (Ph-3-C), 128.1 (3-C), 126.8 (Ph-4-C), 93.1 ($-CCl3$), 55.1 ($-CH_2Ph$), 54.6 ($-CH_2N-$), 39.2 (1-C), 33.9 (5-C), 32.2 (6-C), 24.5 ($-CH_3$); mass (FAB) m/z 376 ($M + H^+$ for $C_{17}H_{18}{}^{79}Cl_2{}^{81}Cl_2NO_2$), 374 ($M + H^+$ for $C_{17}H_{18}{}^{79}Cl_3NO_2$); HRMS (FAB) calcd for $C_{17}H_{19}Cl_3NO_2$ (M^+) 374.0481, found 374.0491. Anal. Calcd for $C_{17}H_{18}Cl_3NO_2$: C, 54.49; H, 4.84; N, 3.74. Found: C, 54.76; H, 4.95; N, 3.72.

Tricarbonyl{2-5-η-1-[*N*-benzyl-*N*-(4-methoxy-1-methylcyclohexa-2,4-dienylmethyl)malonamic acid methyl ester]}iron (9). Complex **4** (0.38 g, 1.0 mmol), monomalonic acid (0.54 g, 3.0 mmol), and 4-dimethylaminopyridine (0.37 g, 3.0 mmol) were dissolved in CH_2Cl_2 (20 mL). A solution of dicyclohexylcarbodiimde (0.62 g, 3.0 mmol) in CH_2Cl_2 (10 mL) was slowly added to the reaction mixture, afterward the mixture was allowed to continue stirring at room temperature overnight. After the precipitate was filtered, the reaction mixture was washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried over Na_2SO_4, the solvent was evaporated, and product was purified by chromatography (hexane:EA = 5:1) to give complex **9** as an orange oil (0.29 g, 60%). R_f 0.18 (hexane:EA = 5:1); IR (CH_2Cl_2) 2047, 1972, 1746, 1650 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.08 (m, 5H, Ph), 5.13 (dd, J = 6.4, 2.4 Hz, 1H, 3-H), 4.64 (m, 2H, $-CH_2Ph$), 3.70 (s, 3H, $-CO_2Me$), 3.63 (s, 3H, −OMe), 3.53 (s, 2H, $-COCH_2CO-$), 3.41 (d, J = 13.2 Hz, 1H, $-CH_2NCO-$), 3.28 (m, 1H, 5-H), 3.11 (d, J = 13.2 Hz, 1H, $-CH_2NCO-$), 2.42 (d, J = 6.4 Hz, 1H, 2-H), 1.94 (dd, J = 15.0, 2.4 Hz, 1H, *endo*-6-H), 1.56 (dd, J = 15.0, 2.4 Hz, 1H, *exo*-6-H), 1.05 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.6 (CO), 168.3 ($-CO_2Me$), 168.1 ($-CON-$), 140.3 (4-C), 136.5 (Ph-1-C), 128.9 (Ph-2-C), 127.8 (Ph-3-C), 126.0 (Ph-4-C), 66.1 (3-C), 60.4 (5-C), 59.2 ($-CH_2Ph$), 54.8 (−OMe), 54.7 ($-CH_2N-$), 53.6 (2-C), 52.7 ($-CO_2CH_3$), 41.8 ($-COCH_2CO-$), 40.8 (6-C), 40.7 (1-C), 28.1 ($-CH_3$); mass (FAB) m/z 484 $(M + H)^+$, 455 ($M^+ - CO$), 399 ($M^+ - 3CO$); HRMS (FAB) calcd for $C_{23}H_{26}NO_7Fe$ (M^+) 484.1060, found 484.1061.

2-Benzyl-8a-methyl-3,6-dioxodecahydroisoquinoline-4-carboxylic Acid Methyl Ester (10). Complex **9** (48.4 mg, 0.1 mmol) was added to a stirred suspension of anhydrous trimethylamine *N*-oxide (111 mg, 1.0 mmol) in dry benzene (15 mL) at 50 °C. Stirring was continued for 2.5 h after which the precipitate was removed by filtration of the cooled mixture through Celite. Water was added to the solution, then extracted with ether. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated to afford the crude dienol ether quantitatively. The crude dienol ether was immediately dissolved in MeOH (3 mL) and treated with oxalic acid (9.0 mg, 0.1 mmol) in water (2 mL) at room temperature for 1 h. Solid K_2CO_3 was added to the reaction mixture and extracted with ethyl acetate, then the product was dried over Na_2SO_4 and the solvent was evaporated. The reaction mixture was purified by preparative TLC (CH_2Cl_2) to give the product **10** as a colorless oil (16.5 mg, 50% over two steps). R_f 0.3 (CH_2Cl_2); IR (CH_2Cl_2) 1746, 1719, 1653 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (m, 5H, Ph), 4.77 (d, J = 14.6 Hz, 1H, $-CH_2Ph$), 4.38 (d, J = 14.6 Hz, 1H, $-CH_2Ph$), 3.80 (s, 3H, $-CO_2Me$), 3.22 (d, J = 12.8 Hz, 1H, $-COCH_2CO-$), 3.19 (d, J = 10.8 Hz, 1H, $-CH_2NCO-$), 2.97 (d, J = 10.8 Hz, 1H, $-CH_2NCO-$), 2.59 (m, 2H, Ha + 5-H), 2.37 (m, 2H, 5-H + 7-H), 2.14 (d, J = 12.0 Hz, 1H, 7-H), 1.89 (m, 1H, 8-H), 1.44 (m, 1H, 8-H), 1.19 (s, 3H, $-CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.0 ($-CO-$), 171.0 ($-CON-$), 165.3 ($-CO_2Me$), 136.4 (Ph-1-C), 129.0 (Ph-2-C), 128.5 (Ph-3-C),

128.0 (Ph-4-C), 56.9 ($-CH_2Ph$), 53.1 ($-CO_2CH_3$), 52.6 ($-COCH_2CO-$), 50.6 ($-CH_2NCO-$), 42.4 (−CH), 41.9 (5-C), 36.8 (7-C), 32.3 (8a-C), 30.5 (8-C), 23.8 ($-CH_3$); mass (FAB) m/z 330 $(M + H)^+$, 298 $(M^+ - OMe)$; HRMS (EI) calcd for $C_{19}H_{23}NO_4$ (M^+) 329.1627, found 329.1629.

Tricarbonyl[2-5-η-1-[3-(*tert*-butyldimethylsilanyloxy)propyl]-4-methoxycyclohexa-2,4-dienecarbonitrile(1-cyano-4-methoxycyclohexa-2,4-dienyl)propane]iron (12). To a solution of complex **11** (375 mg, 1 mmol) in dry MeOH (10 mL) was added K_2CO_3 (200 mg, 1.5 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. After the reaction was completed, 1 M aqueous HCl was added and the reaction mixture was diluted with CH_2Cl_2. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and evaporated to give alcohol complex, suitable for use in the next reaction.

To the solution of alcohol complex, imidazole (140 mg, 2 mmol) in CH_2Cl_2 (20 mL), was added TBSCl (180 mg, 1.2 mmol) at 0 °C. The reaction mixture was stirred at room temperature overnight. Aqueous HCl (1 M) was added and the reaction mixture was diluted with CH_2Cl_2. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4, and evaporated. The product was purified by column chromatography (hexane:EA = 10:1) to give complex **12** as an orange oil (0.38 g, 85% over 2 steps). R_f 0.45 (hexane:EA = 10:1); IR (CH_2Cl_2) 2225, 2059, 1983 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.16 (dd, J = 6.5, 2.0 Hz, 1H, 3-H), 3.67 (s, 3H, −OMe), 3.63 (t, J = 5.0 Hz, 2H, $-CH_2OTBS$), 3.46 (m, 1H, 5-H), 2.61 (d, J = 6.5 Hz, 1H, 2-H), 2.34 (dd, J = 15.0, 3.0 Hz, 1H, *endo*-6-H), 1.73 (dd, J = 15.0, 3.0 Hz, 1H, *exo*-6-H), 1.60 (m, 4H, 2× $-CH_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.6 (CO), 141.2 (4-C), 124.9 (CN), 63.8 (3-C), 62.2 ($-CH_2OTBS$), 54.7 (−OMe), 53.6 (5-C), 53.0 (2-C), 40.6 (6-C), 36.9 (1-C), 36.4 ($-CH_2$), 28.3 ($-CH_2$), 25.8 ($-C(CH_3)_3$), 18.2 ($-C(CH_3)_3$), −5.4 ($-Si(CH_3)_2$); mass (FAB) m/z 448 $(M + H)^+$, 421 $(M^+ - CN)$, 419 $(M^+ - CO)$, 393 $(M^+ - 2CO)$, 363 $(M^+ - 3CO)$; HRMS (FAB) calcd for $C_{20}H_{30}NO_5SiFe$ (M^+) 448.1244, found 448.1247.

Tricarbonyl{2-5-η-1-[3-*N*-benzyl-*N*-{1-[3-(*tert*-butyldimethylsilanyloxy)propyl]-4-methoxycyclohexa-2,4-dienylmethyl}malonamic acid methyl ester]}iron (14). To a solution of the complex **12** (380 mg, 0.85 mmol) in CH_2Cl_2 (15 mL) was slowly added DIBAL (20% in toluene, 1.20 mL, 1.70 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. After the reaction was completed, 1 M aqueous HCl was added and the reaction mixture was filtered with Celite. To the mixture was added CH_2Cl_2, then the solution was washed with saturated aqueous $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4 and evaporated to give aldehyde complex (383 mg, quantitative yield) as an orange oil, suitable for use in the next reaction.

To a solution of aldehyde complex (383 mg, 0.85 mmol) and benzylamine (0.16 mL, 1.45 mmol) in CH_2Cl_2 (20 mL) was added 4 Å molecular sieve (2.0 g) and then the solution was stirred at room temperature overnight. The reaction mixture was filtered with Celite and washed with CH_2Cl_2. The solution was evaporated to dryness in vacuo to afford the crude imine complex. Thereupon the crude was dissolved in ethanol (10 mL) and $NaBH_4$ (103 mg, 1.28 mmol) was added in portions under cooling in the ice bath. After complete addition, the reaction mixture was stirred for 3 h. Water was added at 0 °C to destroy the excess $NaBH_4$, the solution was evaporated to dryness, and the product was extracted with CH_2Cl_2. The organic phase was washed with brine, dried over Na_2SO_4, and evaporated to give amine complex (458 mg, quantitative yield) as an orange oil, suitable for use in the next reaction.

The amine complex (458 mg, 0.85 mmol), monomalonic acid (458 mg, 2.54 mmol), and 4-dimethylaminopyridine (314 mg, 2.54 mmol) were dissolved in CH_2Cl_2 (20 mL). A solution of dicyclohexaylcarbodiimde (525 mg, 2.54 mmol) in CH_2Cl_2 (10 mL) was slowly added to the reaction mixture, then the mixture was stirred at room temperature overnight. After the precipitate was filtered, the reaction mixture was washed with 1 M aqueous HCl, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried over Na_2SO_4, the solvent was evaporated, and the product was purified by chromatography (hexane:EA = 5:1) to give complex **14** as an orange oil (353 mg, 65% over 3 steps). R_f 0.15 (hexane:EA = 5:1); IR (CH_2Cl_2) 2046, 1968, 1744, 1644 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.30−7.29 (m, 4H, Ph-2H + Ph-3H), 7.09 (d, J = 7.2 Hz, 1H, Ph-4H), 5.20 (dd, J = 6.8, 2.8 Hz, 1H, 3-H), 4.62 (s, 2H, $-CH_2Bn$), 3.73 (s, 3H, $-CO_2CH_3$), 3.68 (s, 3H, −OMe), 3.57 (m, 2H, $-CH_2OTBS$), 3.42−3.38 (m, 3H, $-CO_2CH_2CO-$ + $-CH_2NCO-$), 3.30 (m, 1H, 5-H), 3.18 (d, J = 14.0 Hz, 1H, $-CH_2NCO-$), 2.42 (d, J = 6.8 Hz, 1H, 2-H), 1.80 (dd, J = 15.2, 2.8 Hz, 1H, *endo*-6-H), 1.59 (dd, J = 15.2, 2.8 Hz, 1H, *exo*-6-H), 1.50−1.25 (m, 4H, 2× $-CH_2$), 0.89 (s, 9H, $-SiC(CH_3)_3$), 0.05 (s, 6H, 2× $-SiCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.6 (CO), 168.3 ($-CO_2Me$), 168.2 ($-CON-$), 140.3 (4-C), 136.4 (Ph-1-C), 129.4 (Ph-2-C), 128.0 (Ph-3-C), 126.0 (Ph-4-C), 66.6 (3-C), 62.2 ($-CH_2OTBS$), 58.6 (5-C), 55.0 ($-CH_2Ph$), 54.8 (−OMe), 53.5 (2-C), 53.4 ($-CH_2N-$), 52.7 ($-CO_2CH_3$), 42.9 ($-COCH_2CO-$), 41.9 (1-C), 39.4 ($-CH_2CH_2OTBS$), 37.2 (6-C), 27.2 ($-CH_2$), 26.2 ($-C(CH_3)_3$), 18.6 ($-C(CH_3)_3$), −5.09 ($-Si(CH_3)_2$); mass (FAB) m/z 642 $(M + H)^+$, 557 $(M^+ - 3CO)$; HRMS (FAB) calcd for $C_{31}H_{44}NO_8SiFe$ $(M + H)^+$ 642.2187, found 642.2183.

2-Benzyl-8a-(3-hydroxypropyl)-3,6-dioxodecahydroisoquinoline-4-carboxylic Acid Methyl Ester (15). The complex **14** (64.1 mg, 0.10 mmol) was added to a stirred suspension of anhydrous trimethylamine *N*-oxide (111 mg, 1.0 mmol) in dry benzene (15 mL) at 50 °C. Stirring was continued for 2.5 h after which the precipitate was removed by filtration of the cooled mixture through Celite. Water was added to the solution, then it was extracted with ether. The combined organic layer was washed with brine, dried over Na_2SO_4, and evaporated to afford the crude dienol ether quantitatively. The crude dienol ether was immediately dissolved in MeOH (3 mL) and treated with oxalic acid (9.0 mg, 0.1 mmol) in water (2 mL) at room temperature for 1 h. To the reaction mixture was added solid K_2CO_3, which extracted with ethyl acetate, then the soluton was dried over Na_2SO_4 and the solvent evaporated. The reaction mixture was purified by column chromatography (hexane:EA = 1:3) to give the product (11 mg, 30%). R_f 0.71 (CH_2Cl_2:MeOH = 20:1); IR (CH_2Cl_2) 3490, 1746, 1719, 1653 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.33−7.23 (m, 5H, Ph), 4.69 (d, J = 14.5 Hz, 1H, $-CH_2Ph$), 4.43 (d, J = 14.5 Hz, 1H, $-CH_2Ph$), 3.79 (s, 3H, $-CO_2Me$), 3.57 (t, J = 6.2 Hz, 2H, $-CH_2OH$), 3.23 (d, J = 12.8 Hz, 1H, $-COCH_2CO-$), 3.20 (d, J = 10.8 Hz, 1H, $-CH_2NCO-$), 2.99 (d, J = 10.8 Hz, 1H, $-CH_2NCO-$), 2.58 (m, 2H, Ha + 5-H), 2.35 (m, 2H, 5-H + 7-H), 2.14 (dd, J = 18.2, 6.0 Hz, 1H, 7-H), 1.81−1.31 (m, 7H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.9 ($-CO-$), 170.5 ($-CON-$), 165.4 ($-CO_2Me$), 136.2 (Ph-1-C), 128.8 (Ph-2-C), 128.4 (Ph-3-C), 127.9 (Ph-4-C), 62.5 ($-CH_2OH$), 53.7 ($-CH_2Ph$), 52.9 ($-CO_2CH_3$), 52.5 ($-COCH_2CO-$), 50.5 ($-CH_2NCO-$), 41.4 (−CH), 40.9 (5-C), 36.0 (7-C), 34.5 ($-CH_2CH_2OH$), 32.1 (8a-C), 27.5 (8-C), 26.0 ($-CH_2CH_2-CH_2OH$); mass (FAB) m/z 374 $(M + H)^+$; HRMS (EI) calcd for $C_{21}H_{27}NO_5$ $(M + Na)^+$ 396.1787, found 396.1782.

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Supporting Information Available: NMR spectra of compounds **3**, **4**, **5**, **6**, **9**, **10**, **12**, **14**, and **15** and NOESY ^1H data of compounds **10** and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.