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Stereoselectivity in the organoiron-mediated synthesis of (±)-mesembrine

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Abstract

The preparation and structural characterisation of a 1-aryl-substituted electrophilic η^5-cyclohexadienyliron complex with the correct functionalisation as a 'C_{12} building block' for the synthesis of (±)-mesembrine establishes the accessibility of a flattened conformation to allow nucleophile addition *ipso* to the arene. The chirality relay in quaternary centre formation by nucleophile addition has been confirmed, and the product has been converted into the *Sceletium* alkaloid mesembrine.

Keywords: Asymmetric synthesis; Organometallic electrophiles; Tricarbonyliron; Mesembrine

The *Sceletium* alkaloid mesembrine (**1**)[1] is a naturally occurring serotonin uptake inhibitor[2] with a suitable structure to illustrate the utility of aryl-substituted[3] cyclohexadienyliron complexes as central 'C_{12} building blocks'[4] in alkaloid synthesis (Fig. 1). The key structural feature of mesembrine is a saturated pyrrolidine ring fused to a cyclohexanone, with an aryl substituent directly attached to a quaternary centre at the ring fusion. This type of quaternary centre has attracted considerable attention as a synthetic target as it is common in a wide range of alkaloids, particularly *Amaryllidaceae* alkaloids[5] such as crinine[6,7] and maritidine[8,9] which have more complex polycyclic structures. Recently, considerable advances[10] have been made to gain efficient access to structures of this type, which have important biological activity[2,7,9,11] and a suitable size and basicity to inspire the design of biomimetic pharmacophores.[12]

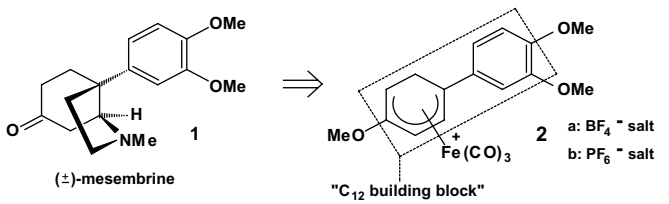

Fig. 1. Illustration of an example of arylcyclohexadienyliron electrophiles as C_{12} building blocks in alkaloid synthesis.

We have described[3] a generally applicable method to prepare synthetically important[13] electrophilic 1-aryl-substituted η^5-cyclohexadienyliron complexes from the 1,4-dimethoxycyclohexadienyliron complex **3** and have used the method to gain access to the 3′,4′-methylenedioxy-substituted example **4**,[3] which has the correct substitution pattern for use as a C_{12} building block for crinine (Scheme 1). A similar approach with a 2′,3′-diether (electrophile **5**) has been used successfully[14] in our formal total synthesis of lycoramine. We describe here, the preparation of **2** and its use in a four-step[15] synthesis of (±)-mesembrine (six steps from **3**; nine steps from 1,4-dimethoxybenzene).

The preparation of the chiral electrophile **2** from its prochiral precursor tricarbonyl(η^4-1,4-dimethoxycyclohexadiene)iron(0)[3,16,17] is an important example of the induction of asymmetry in multihapto complexes[18] and enantioselective

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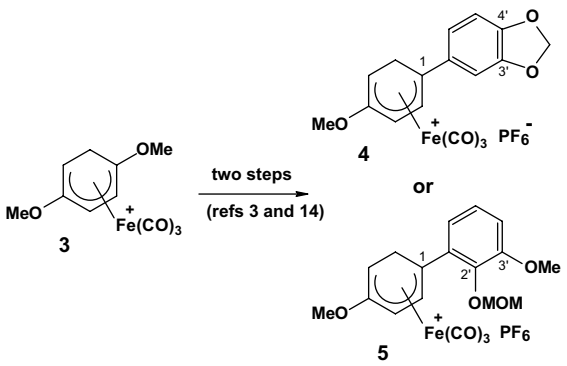
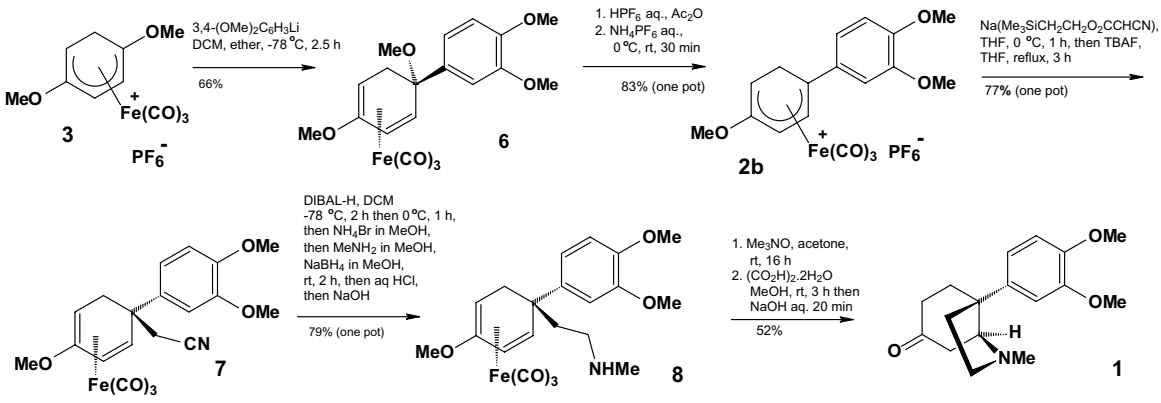


Scheme 1. Examples of the preparation of 1-aryl-4-methoxycyclohexadienyliron electrophiles.

methods for hydride abstraction have been employed[19] in this step, using chiral analogues[20] of triphenylcarbenium ion reagents. Starting from **2**, the electrophilicity introduced into the ligand by the $[Fe(CO)_3]^+$ group is used in both the C-C bond formation steps that establish the chiral quaternary centre of the target structures. The sense of asymmetric induction depends on the order of the nucleophile addition reactions, and our short synthesis of (±)-mesembrine from **2** was undertaken in the racemic series to prove the relative stereochemistry of malononitrile enolate addition[3,4,14,17] to arylcyclohexadienyliron(1) complexes (i.e., introduction of the arene first, and the CH_2CN moiety second). The *exo*-stereochemistry of the CH_2CN substituent in the product[21] has been proved in this work, and crystallographic characterisation of both the electrophile and the malononitrile adduct are described.

The conditions and solvents used with aryllithium reagents in reactions of the type shown in Scheme 1 have been found to be crucial to obtain high yields, since competing addition at CO ligands is possible.[22] Our synthesis of (±)-mesembrine (Scheme 2) thus began with optimisation of the preparation[23] of 3,4-dimethoxyphenyllithium from 4-bromoveratrole, to check the compatibility with the solvent used, and the requirements of the organoiron-mediated step. The efficiency of lithium/bromine exchange was determined by trapping with trimethylsilyl chloride. When the reaction was performed with *n*-butyllithium in diethyl ether at −30 °C,[24] the corresponding arylsilane was obtained in >77% yield. To prepare **6** (Scheme 2), after 10 min to complete the lithium/bromine exchange of 3,4-dimethoxybromobenzene, the reaction mixture was cooled to −78 °C and **3** was added in solution in dichloromethane.[25] Product **6** was obtained in 66% yield and converted into **2a** (55% yield) by reaction[26] with triphenylcarbenium tetrafluoroborate in dichloromethane. The alternative acid-mediated procedure[27] proved more efficient in this case, and using hexafluorophosphoric acid in acetic anhydride afforded **2b** in over 80% yield. The enolate was generated from 2-trimethylsilylethyl cyanoethanoate by our standard method[3,17] and after addition to **2b**, the reaction was quenched with TBAF and heated at reflux for 3 h to effect an in situ desilylation/dealkoxylation/decarboxylation of the intermediate, giving access to the cyanomethyl adduct **7** in 77% yield in a single step.[15] Product **7** was crystallised from diethyl ether, and the relative stereochemistry of nucleophile addition to **2b** was proved by X-ray crystallography (Fig. 2b). The expected *exo* addition of the malononitrile was thus confirmed. Reduction with DIBAL in dichloromethane/diethyl ether was followed by the addition of ammonium bromide and methylamine in methanol, and then sodium borohydride (added in three portions as a solid) to allow direct access[15] to the secondary amine **8**, which was isolated in 79% yield. Decomplexation with anhydrous trimethylamine N-oxide[28] in acetone followed by quenching with oxalic acid (3 h at room temperature) and a basic work up afforded (±)-mesembrine (**1**) in 52% yield.[29]

The electrophilic C_{12} building block was crystallised from acetone by a two-well diffusion procedure (diethyl ether in the outer well). The structure (Fig. 2a) shows the expected orientation of the tricarbonyliron group, which has one CO ligand lying under the CH_2 of the cyclohexadienyl ring. The CH_2 group [C(6)] is also bent away from the principal plane of the haptile part of the ligand [C(1)–C(5)] in the normal way. Importantly, in the solid state structure, the dihedral angle between the plane of the arene and the dienyl ligand is relatively small (+39°),



Scheme 2. Organoiron-mediated synthesis of (±)-mesembrine.

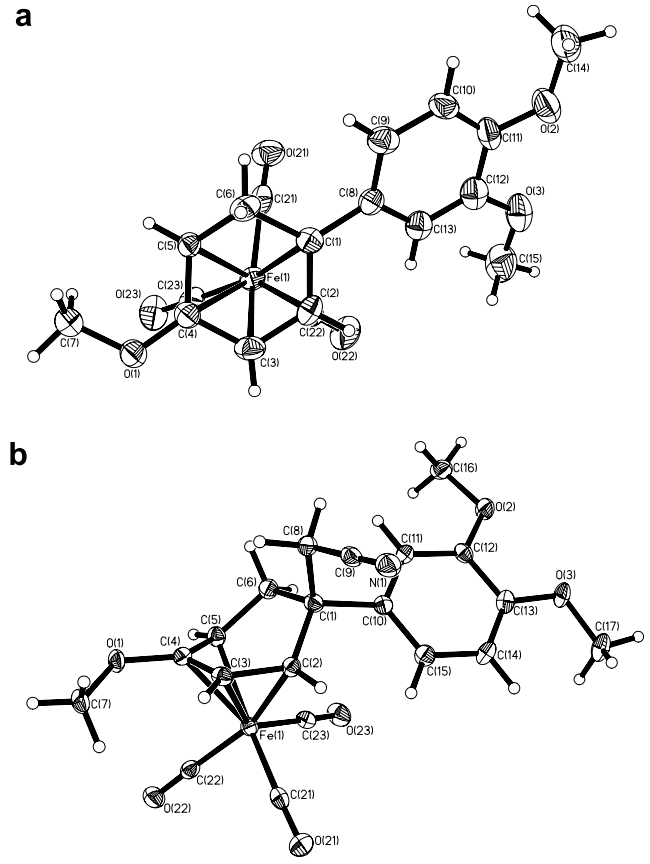


Fig. 2. ORTEP drawings of the organometallic electrophile in **2b** (a) and the adduct **7** (b).

corresponding to the conformation needed to allow access of the malononitrile enolate to the *ipso*[30] electrophilic centre [C(1)]. The C(1)–C(8) bond length (1.479 Å) is consistent with significant π overlap between the arene and dienyl sections of the ligand, and it is proposed that the electron-rich nature of the aryl ether helps promote the flattening of the structure by promoting electron donation from the arene.

In conclusion, we have completed a short synthesis of (±)-mesembrine from the 1,4-dimethoxy salt **3** by a reaction sequence that makes multiple use of the metal, and have proved that chirality relay from the η^5-1-arylcyclohexadienyliron complex **2** promotes exclusive *exo* addition of the second nucleophile in the sequence. Complex **2** adopts a flattened conformation in solution to a sufficient extent to allow efficient nucleophilic addition *ipso* to the arene, and a solid state model for this conformation has been defined. Transfer of electron density from the aromatic ring to the cationic dienyliron moiety helps favour the required flattened structure despite free rotation of the arene. The naturally occurring oxidation patterns of the arenes of *Sceletium* and *Amaryllidaceae* alkaloids are thus shown to be advantageous in synthetic routes based on the organoiron C_{12} building block[3,4] approach. Work is in progress towards the more advanced targets crinine[3] and maritidine[32] based on these methods.

Crystal data:

Compound **2b**: $C_{19.75}H_{21}F_6FeO_{6.5}P$, 563.19 g mol^{-1}, $F(000)$ 2292, D_c 1.620 g cm^{-3}, μ(Mo-Kα) 0.808 mm^{-1}, monoclinic, $C2/c$,a 23.652(3), b 13.9637(15), c 14.4029 (15) Å, β 103.940(2)°, V 4616.8(8) Å^3, T 100 K; 9868 data, 4251 unique, R_{int} 0.0486, 317 parameters, wR_2 0.0949, S 0.995, R_1 (2317 with $I > 2\sigma(I)$) 0.0518, max. diff. peak/hole +0.53/−0.60 e Å^{-3}.

Compound **7**: $C_{20}H_{19}FeNO_6$, 425.21 g mol^{-1}, $F(000)$ 880, D_c 1.480 g cm^{-3}, μ(Mo-Kα) 0.827 mm^{-1}, monoclinic, $P2_1/c$,a 8.9196(13), b 26.161(4), c 9.2714(14) Å, β 118.070(2)°, V 1908.9(5) Å^3, T 100 K; 8101 data, 4199 unique, R_{int} 0.0291, 264 parameters, wR_2 0.0857, S 0.990, R_1 (3269 with $I > 2\sigma(I)$) 0.0402, max. diff. peak/hole +0.63/−0.32 e Å^{-3}.

Supplementary data

Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Nos. CCDC 661648 and 661649. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK: http://www.ccdc.cam.ac.uk/cgi-bin/catreq.cgi, e-mail: data_request@ccdc.cam.ac.uk, or fax: +44 1223 336033.

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