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Electrophilic C_{12} Building Blocks for Alkaloids: Formal Total Synthesis of (±)-Maritidine

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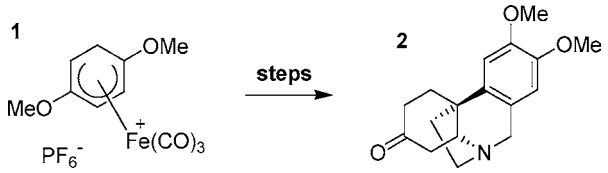
ABSTRACT



Silyl-protected benzyl alcohol derivatives and the salt 1 are used to form *ortho*-substituted C_{12} electrophilic organoiron building blocks which are converted into a spirocyclic cyclohexenone to complete a formal total synthesis of (±)-maritidine (5). The choice of TBDPS protection was shown to be better than TIPS and compatible with *ipso* nucleophile addition to form a quaternary center. The reaction sequence is the first example of a successful application in the synthesis of an arylcyclohexadienyliron complex with an *ortho*-carbon substituent in the position required for *Amaryllidaceae* alkaloids of this type.

Chiral 1-arylcyclohexadienyliron complexes[1] provide electrophilic C_{12} building blocks[2] which react with nucleophiles with complete stereocontrol.[3,4] The C_{12} motif corresponds to the central portion of many alkaloids, particularly, *Sceletium* and *Amaryllidaceae* natural products,[5] which show important biological properties.[6,7] We have recently described a reliable and generally applicable procedure for the preparation (Scheme 1) of suitable[8] 1-arylcyclohexadienyliron complexes from the key 1,4-dimethoxy-substituted intermediate **1**.[1] Because of the powerful control of stereochemistry and the possibility of access to enantiopure **1** by a novel asymmetric hydride abstraction reaction,[9] we have been exploring the scope of synthetic sequences that exploit our organoiron electrophilic C_{12} building blocks in syntheses that make multiple use of the metal.[10]

Groups targeting *Sceletium* and *Amaryllidaceae* natural products have reported many syntheses of mesembrine,[14] galanthamine,[15] lycoramine,[16] and crinine,[17] but the related cytotoxic[18] *Amaryllidaceae* alkaloid maritidine (**5**),[19] which has been found to have significant activity[7] as an inhibitor of [3H]citalopram binding to the rat brain serotonin transporter and shows clastogenic effects, has received much less attention.[20,21]

To develop further our C_{12} electrophile approach (examples already reported include synthesis of *O*-methyl jouber-

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(4) For a general discussion of multihapto electrophiles, see: Stephenson, G. R. In *Handbook of Functionalised Organometallics*; Knochel, P., Ed.; Wiley-VCH: Weinheim, Germany, 2005; pp 569−626.

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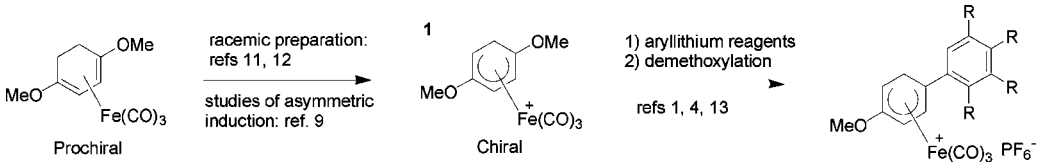
Scheme 1. Introduction of Chirality in the General Procedure to Construct 1-Arylcyclohexadienyliron Electrophiles



tiamine,[12] formal total synthesis of lycoramine,[22] total synthesis of mesembrine[23]), we have chosen maritidine (**5**) as a key strategic target since it requires an *o*-benzylic substituent on the arene. So far, only *ortho*-ether substituents on the arene have been found[22,24] to be compatible with *ipso*[25] addition of nucleophiles, and an *o*-formyl group at this position (which would be useful later in the synthesis in intramolecular reductive amination steps) gave[24] only ω[25] addition products. We describe here, however, the successful applica-

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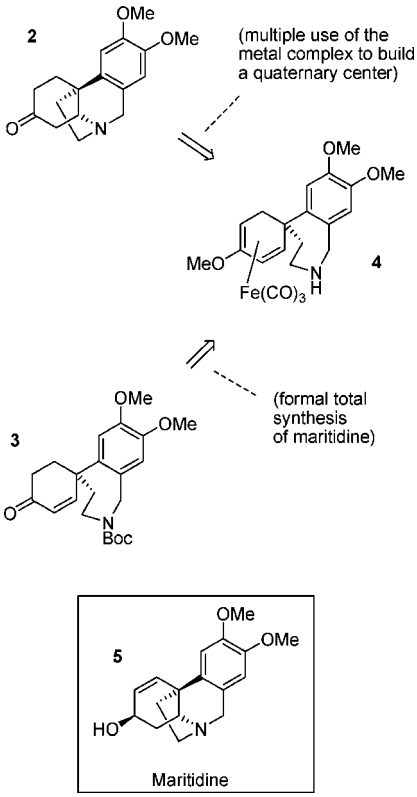
(23) Anson, C. E.; Roe, C.; Sandoe, E. J.; Stephenson, G. R. *Tetrahedron Lett.* **2007**, DOI: 10.1016/j.tetlet.2007.11.137.

(24) Anson, C. E.; Malkov, A. V.; Roe, C.; Sandoe, E. J.; Stephenson, G. R. *Eur. J. Org. Chem.* **2008**, 196−213 (this paper also reports the CH_2-OMe analogue of **9**, but this electrophile gave mixtures of *ipso* and ω products).

(25) For a discussion of *ipso* and ω addition to multihapto π complexes, see ref 4; for the ω directing nature of aryl substituents on cyclohexadienyliron complexes, see ref 1.

tion of the required *ipso* addition, even with bulky silylether-protected benzyl alcohols as the *ortho* substituent on the arene. The product has been taken on to a late-stage tricyclic secondary amine intermediate which is suitable for decomplexation/cyclization to form dihydrooxomaritidine (**2**) (Scheme 2). By conversion to the spirocyclohexenone **3**, this work

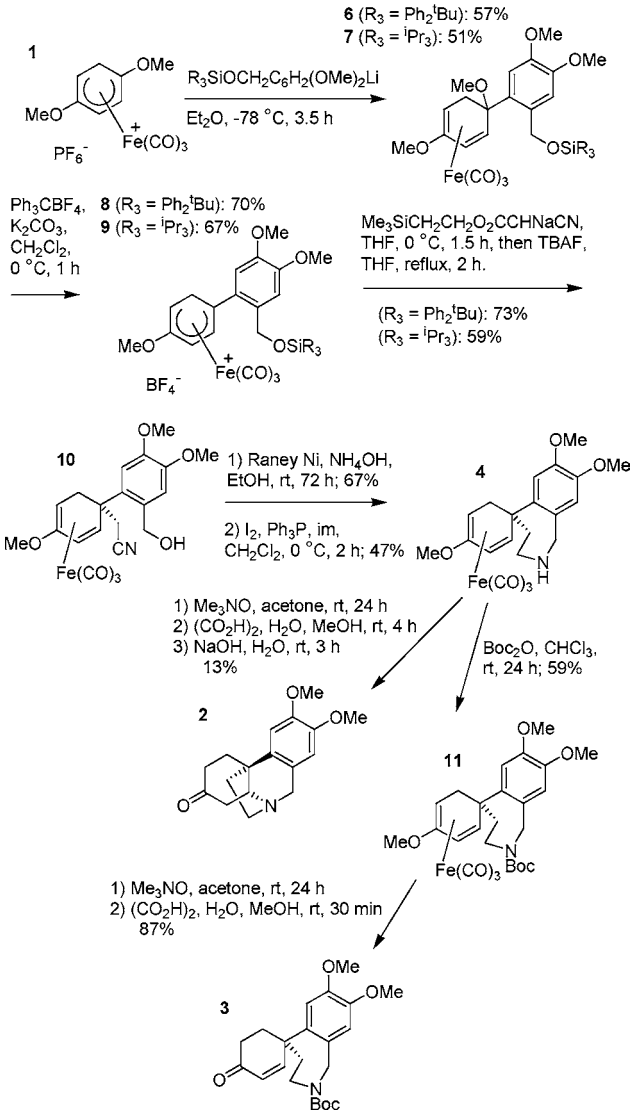
Scheme 2. Retrosynthesis of Dihydrooxomaritidine (**2**) and the Spirocyclohexenone **3**



also constituted a formal total synthesis of (±)-maritidine (**5**) by linking with the excellent concise synthesis of the racemic natural product reported by Bru, Thal, and Guillou.[21]

Our investigation began with a comparison of two silylether derivatives[26] which were easily available from 2-bromo-4,5-dimethoxybenzyl alcohol[27] by standard silylation procedures.[28] The aryllithium reagents were prepared in the normal way using *n*-butyllithium in diethyl ether at −78 °C. Addition to the salt **1** was performed in dichloromethane to give **6** and **7** in 57 and 51% yields, respectively. The conditions used with the acid-sensitive MOM derivatives in our lycoramine work[22] were now employed with **6** and **7** to form the 1-arylcyclohexadienyliron complexes **8** and **9** which were isolated as BF_4^- salts (70 and 67% yields). By the choice of silyl protecting groups, our one-pot malononitrile addition/in situ desilylation/dealkoxylation/decarboxylation procedure[23] can be combined with concurrent deprotection of the benzyl alcohol to give the organonitrile **10** in a single step (for three steps from **1**: $SiPh_2{}^tBu$ series: 29%; Si^iPr_3 series 20%). Reduction of the nitrile (67%) and cyclization (47%) gave **4**. Standard conditions for removal of the tricarbonyliron group and hydrolysis of the enol ether to give the enone were relatively low yielding (13%), but a metal-free product was obtained and identified as dihydrooxomaritidine (**2**) (Scheme 3). Traces of oxomaritidine were

Scheme 3. Organoiron-Mediated Formal Total Synthesis of (±)-Maritidine (**5**)



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also identified in the crude product from this reaction.[29] Boc protection of **4** (59%) afforded a product which was converted far more efficiently (91%) into the spirocyclohexenone, suggesting that the low yield with **2** was a consequence of the presence of the secondary amine. The development of improved isolation procedures may well overcome this problem. The presence of oxomaritidine in the sample obtained from **4** could arise by cyclization of the amine to a dienone, which must have been formed to a small extent in the decomplexation step. Interestingly, careful examination of the spectrum of **3** obtained from **11** again revealed traces of a dienone which could be identified from its ^{1}H NMR data by comparison with the spectrum reported for the pure dienone, which had also been prepared by Bru, Thal, and Guillou.[21] Decomplexation of η^5-3-methoxycyclohexadienyliron complexes to form dienones has been described,[30] but their production has not been observed previously directly from η^4-methoxycyclohexadiene complexes. This anomalous decomplexation process will be examined further in future work since, if the mechanism can be determined, a modified procedure to promote the reaction would lead directly to the dienone from **11**, which is only three steps away from (±)-maritidine (**5**), and if employed with our intermediates for lycoramine[22] would open the way for a synthesis of galanthamine. At the present stage, however, we have established the key features of the metal-mediated part of the route, in which the electrophilicity of the iron complex is used first to introduce the arene, then subsequently to build the quaternary center in an iterative process.[31] The TBDPS group has been shown to be higher yielding than the TIPS alternative and is compatible with the novel deprotection/dealkoxylation/decarboxylation procedure, which is employed for the first time in this work and saves a step.[32] The viability of the synthetic methodology has been established by the formal total synthesis of (±)-maritidine (**5**) and is the first application where an *ortho*-carbon substituent has been present on the 1-arylcyclohexadienyliron complex.[33]

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Supporting Information Available: Detailed experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(29) In the NMR spectrum obtained for the crude product from this reaction, signals corresponding to a trace of oxomaritidine could also be identified, together other minor signals; for the NMR data for authentic oxomaritidine, see ref 21.

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(31) This synthetic route corresponds to an $[\eta^4] \rightarrow [\eta^5]^+ \rightarrow [\eta^4] \rightarrow [\eta^5]^+ \rightarrow [\eta^4]$ iterative process. For definitions of iterative and linear reaction sequences that employ stoichiometric multihapto electrphiles, see refs 4 and 10.

(32) In fact, in the formation of **10**, the concurrent desilylation of the silylether and silylethyl ester occurs in the quench of the malononitrile enolate addition to **8**, so the sequence described in this Letter is two steps shorter than the conventional sequence used in the original *O*-methyljoubertiamine synthesis (ref 12).

(33) This additional carbon atom is often introduced at a late stage in the synthesis, for example, by a Pictet Spengler reaction: (a) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797−1842. For an example employing organoiron complexes, see: (b) Pearson, A. J.; Ham, P.; Ong, C. W.; Perrior, T. R.; Rees, D. C. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1527−1534. Inclusion of this 13th carbon in the initial aryl nucleophile (**6** or **7** in this case) is more efficient because the sequence is more convergent. The 1-arylcyclohexadienyliron complex reported here corresponds, in effect, to a "C_{13} electrophilic building block".