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# Switching Regiocontrol in 1-Aryl-substituted Cyclohexadienyliron Complexes in a Formal Total Synthesis of Lycoramine

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***Abstract:*** 1-(o-Alkoxyaryl)cyclohexadienyl tricarbonyliron complexes reverse the regiochemistry of nucleophilic addition compared to that observed for o-(alkoxymethyl)aryl substituted complexes, allowing access to key intermediates in a formal total synthesis of lycoramine.


A feature common to all of the *Amaryllidaceae* alkaloids of the galanthamine and crinine subgroups, which often show pharmaceutically significant biological activity,[1] is a quaternary chiral centre at the junction between aromatic and partially saturated six membered rings. Many of these compounds combine this structural motif with the presence of an aminoalkyl ($CH_2CH_2NRR'$) substituent, which is located at the ring-junction. Versatile methods for the construction of this central feature have been developed, notably those based on aldol cyclisations,[2a,b] the alkylation of enamines,[2b] Pb-mediated electrophilic arylation,[2c] and radical cyclisations.[2d,e] Our approach employs metal-stabilised cyclohexadienyl cations, and attaches both aryl and aminoalkyl groups through a sequence of two carbon-carbon bond formations mediated by electrophillic tricarbonyliron complexes. In the course of this work, general conditions for the combination of aryllithium nucleophiles with 1,4-dialkoxy-substituted tricarbonyl[(1-5-η)-cyclohexadienyl]iron complexes have been identified,[3] and the practicality of the use of these reactions has been established by the synthesis[4] of the simple monocyclic *Amaryllidaceae* alkaloid, *O*-methyljoubertiamine, *via* nucleophile addition to C-1 of a 1-aryl-substituted cyclohexadienyl complex **2**.

In an extension of this approach to more elaborate structures, o-substituted aromatic rings have been introduced to form electrophilic salts of type **4** and **5** (Y = CHO, $CH_2OMe$), but in reactions with nucleophiles[5] we found that the regiochemistry of addition to the dienyl complex was reversed to give exclusively C-5 adducts, an outcome ascribed to steric blocking of C-1 by the o-substituent, which could lie above the terminus of the dienyl moiety. With electron donor substituents (e.g. Y = OR) on the aromatic ring, we expected increased π-overlap between the arene and dienyl regions to flatten the structure, reducing the degree of steric blockade. In this paper we report the first examples of the success of this strategy. This gives access to target molecules of the galanthamine type, in which an ether bridge links the two carbocyclic rings.

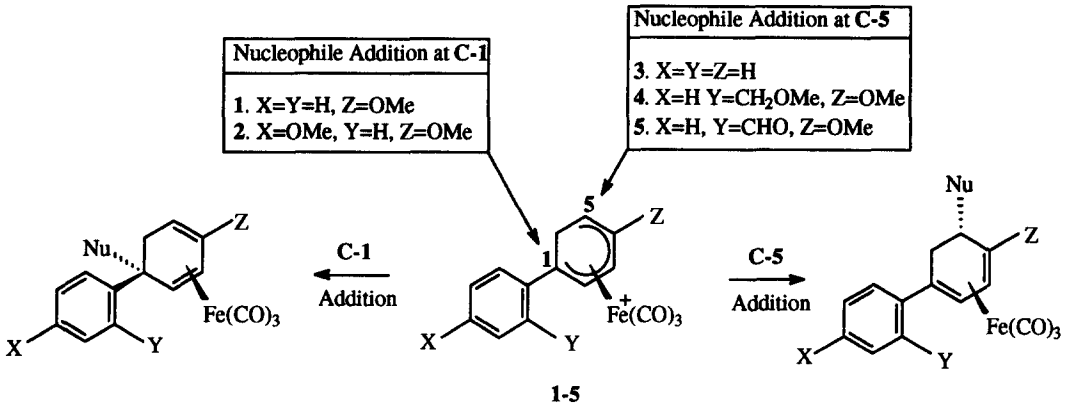
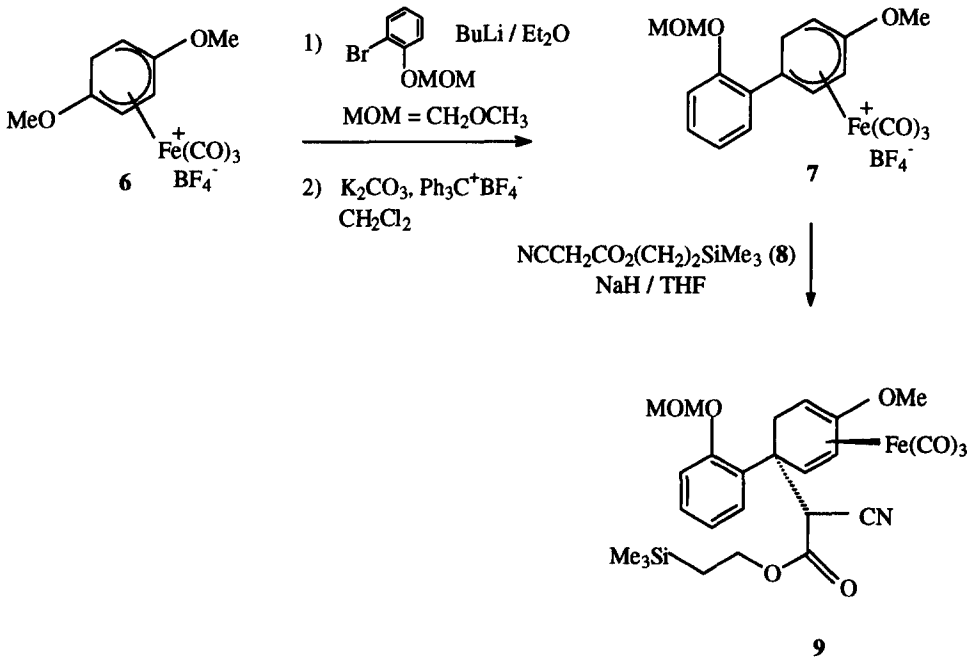



**Figure 1**

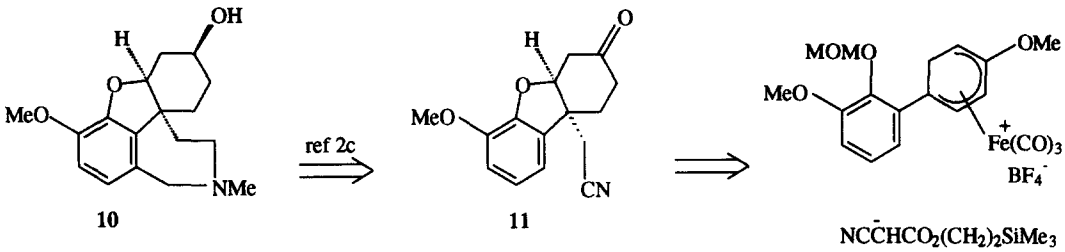
Access to the donor-substituted arylcyclohexadienyl complexes was straightforward (Scheme 1). The lithiated MOM-protected bromoarene (MOM = $CH_2OCH_3$) was reacted with **6**. Subsequent dealkoxylation afforded salt **7**[6] in 55% yield, based on the complex **6**. The silylethyl cyanoacetate ester **8** was selected as the nucleophile to study regiocontrol, since this had proved[4] a convenient precursor to the $CH_2CH_2NMe_2$ portion of *O*-methyljoubertiamine. Reaction of the enolate with **7** at 0°C in THF, afforded the C-1 adduct **9**, the regioisomer needed for target structures of the galanthamine type.




**Scheme 1**

These results indicated that while alkoxyalkyl-substituted aromatic rings block C-1 addition, the presence of alkoxyaryl substituents is compatible with the desired nucleophile approach. In galanthamine-type alkaloids, both types of substitution are present, but as the alkoxyalkyl group can be simply introduced by a Pictet-Spengler reaction,[1,7] an ortho-oxygenated aromatic building block would be sufficient for the

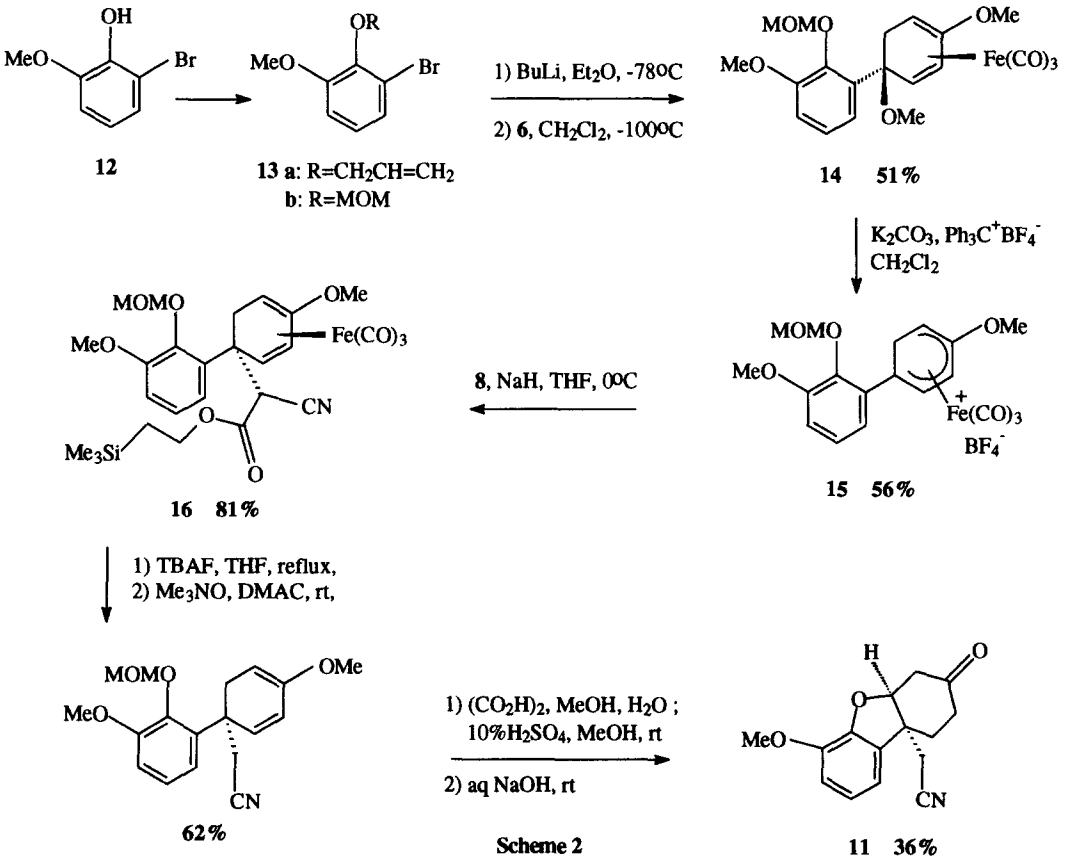
construction of the central dihydrobenzofuran section. This possibility (Figure 2) has now been demonstrated by a formal total synthesis of lycoramine (**10**),[2c] which contains the tetracyclic ring system of galanthamine.




10 11

**Figure 2**

The trisubstituted arene **12** is available from the regioselective bromination of 2-methoxyphenol.[2e] Protection at oxygen with MOMCl (**13b**: 85%) proved more efficient than allylation (**13a**: 38%). The MOM-protected compound was taken on to complete the synthetic route. The aryllithium reagent, formed from **13b**, was cooled to -100°C prior to addition to the cyclohexadienyliron complex in solution in $CH_2Cl_2$ also maintained at -100°C. The use of $CH_2Cl_2$ follows Birch's procedure[8] for organolithium addition to tricarbonyliron complexes, and is crucial for success, though in our case, the reaction must be performed at a lower temperature than that employed by Birch.




**Scheme 2**

In this way, the trimethoxy-MOM-substituted complex **14** was obtained in 51% yield, after separation by column chromatography from tricarbonyl(4-methoxy-2,4-cyclohexadienone)iron(0) (31 %), a typical[3] by-product arising from dealkoxylation of the electrophile. Due to the expected acid-sensitivity of the MOM protecting group, dealkoxylation from **14** to reform the $\eta^5$ bonding mode was effected with $Ph_3C^+BF_4^-$ in the presence of potassium carbonate. The salt **15** proved more unstable than is normal for tricarbonyl(cyclohexadienyl)iron(1+) complexes, and so was isolated in only 56% yield. None the less, efficient addition of the silylethyl-protected nucleophile was possible (81% yield), and afforded only the C-1 regioisomer **16**, which was converted into the cyanomethyl adduct by combined desilylation, dealkoxylation, and decarboxylation effected with fluoride.[4] The metal was removed at this stage (85%)[9] with trimethylamine N-oxide. Hydrolysis of the enol ether with oxalic acid, detachment of the MOM protecting group with sulphuric acid, and cyclisation with aqueous sodium hydroxide, to form the central heterocyclic ring by intramolecular conjugate addition of the phenolate to the enone was achieved in a single step (Scheme 2). Completion of the tricyclic product **11** concludes a formal total synthesis of lycoramine.[2c] Two key features of the galanthamine ring system, the dihydrobenzofuran centre and a nitrogen-substituted alkyl group at the quaternary centre, are present in this product.

**Summary.**

Aryl substituents on tricarbonyl(cyclohexadienyl)iron complexes naturally direct nucleophiles to the C-5 terminus of the dienyl unit.[10] However, in a 1-aryl-4-methoxy-substituted complex, the stronger directing effect of the methoxy group opposes that of the arene, inducing C-1 addition of nucleophiles,[4,11] provided steric effects[5] do not block the approach of the nucleophile at this position. In the case of 1-(o-substituted aryl) substituents with donor groups, flattening of the structure assists reaction at C-1 and allows easy access to products with quaternary centres. This approach is now under investigation with a series of polysubstituted arenes, to afford key intermediates for synthesis of other *Amaryllidaceae* alkaloids.

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