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TRANSITION METAL MEDIATED ASYMMETRIC SYNTHESIS, PART 15[1] DIRECTING GROUP COMPETITION IN ORGANOIRON INTERMEDIATES IN THE SYNTHESIS OF (±)-*O*-METHYLJOUBERTIAMINE

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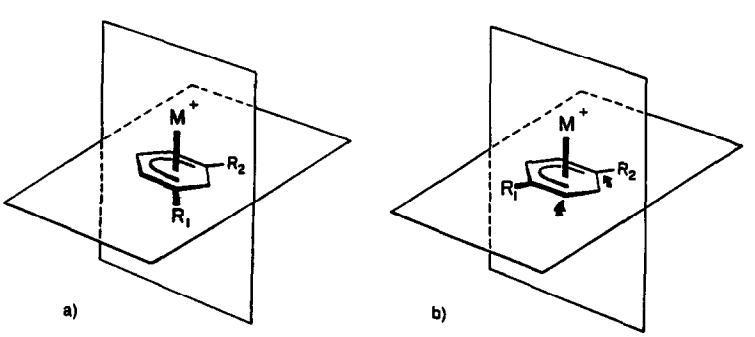
Summary: Directing groups work first in concert and then in competition to control the introduction of aryl and 2-dimethylaminoethyl groups by a sequence of two nucleophile additions to cationic tricarbonyl(η^5-cyclohexadienyl)iron(1+) intermediates in a synthesis of *O*-methyljoubertiamine that employs an iterative approach. This synthesis provides an example of the successful use of directing group competition to effect the reversal of undesired directing effects in target oriented applications of electrophilic π-complexes.

Electrophilic transition metal π-complexes can react with complete stereocontrol[2] but frequently offer several possible pathways which can lead to the formation of mixtures of regioisomers.[3] In the case of η^5-dienyl complexes, attack is precedented at any of the metal-bound carbon atoms,[4] and the widely used cationic η^5-cyclohexadienyl tricarbonyliron complexes represent a special case where C-C bond formation is restricted to the ends of the dienyl system (C-1 and C-5).[5] These complexes are chiral (Fig. 1, a: R_1 / R_2 / H; b: R_1 = or / R_2 / H) and are well suited for use in enantioselective synthesis, since they have been shown in a number of

Figure 1 Potential symmetry planes in η^5-dienyl complexes.

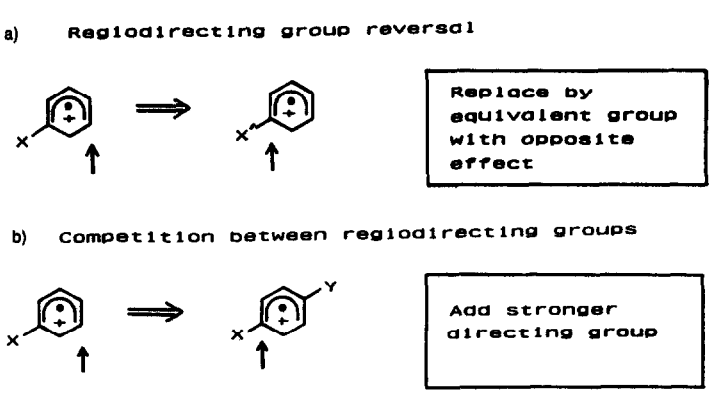


cases to be optically stable,[6] and can be obtained in optically pure form by resolution[7] or induction of asymmetry[8] in the region of planar chirality of the transition metal π-complex. The transition metal exerts

complete control in the diastereoselective addition[2] of nucleophiles to the π-bound ligand, which can thus be elaborated through a series of metal-mediated steps to become incorporated into the target molecule. This ligand can be termed the working ligand (since this is where the action takes place during the synthetic sequence). The other ligands (auxiliary ligands) are important to adjust the reactivity and stability properties of the complexes, and can be varied independently from the working ligand within a series of isoelectronic alternatives to the metal/ligand system.[9] Because the working ligand becomes incorporated into the target molecule, this is an inherently stoichiometric synthetic approach, but can, none-the-less, offer an attractive complementary alternative to the repeated use of asymmetric catalysis in multi-step sequences, provided one essential criterion is met. The metal must be retained on the working ligand to be brought into play at several key steps to impose stereocontrol at each juncture. By carrying the metal through a multi-step reaction sequence in this way, the need to optimise a stereocontrol strategy at each stage is avoided; the same control technology can be employed at each chiral centre, with stable metal/working-ligand attachment serving to anchor the transfer of chirality as the target molecule is built up. Multiple use of the metal to control a series of reactions at the working ligand is an essential objective in the application of electrophilic transition metal complexes in asymmetric synthesis.[10]

When used in chiral form, electrophilic π-complexes of this type must inevitably have an unsymmetrical substitution pattern on the working ligand. In the case of tricarbonyliron complexes, the two reactive termini of the unsymmetrical dienyl unit (e.g. Fig. 1b) will lead to the formation of regioisomeric products. For efficient application in enantioselective synthesis, it is essential to control the regioselectivity of nucleophile addition at the working ligand. The mapping of regiocontrol effects of unsymmetrically placed substituents has been an important objective of our work in Norwich in recent years.[11,12] For the general application of electrophilic π-complexes in synthesis, however, there is a further requirement that goes beyond the simple need for regiocontrol. While powerful regiodirecting groups provide efficient access to a particular set of intermediates, they inevitably preclude access to the alternative regioisomer series. A second essential long-term objective in this field is thus the development of strategies to reverse natural regiodirecting effects of substituents, so opening up selective access to all regioalternative classes of target structures. Two strategies to achieve this objective are currently under investigation in Norwich (Fig. 2). One approach (a) replaces a

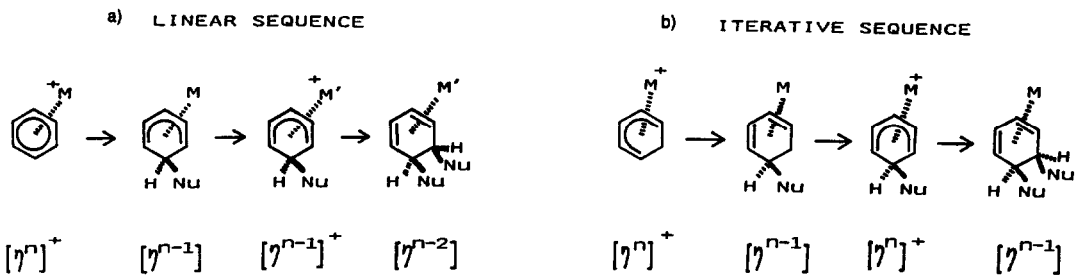
Figure 2 Strategies for reversal of regiocontrol.



directing group X with a functionally equivalent group[13] X' with the opposite directing effect. The first example has been the subject of a recent preliminary communication,[12] but has yet to be applied in target-oriented synthesis. In the alternative strategy (b), regiocontrol groups X and Y are set in opposition to each other on the working ligand, so that control imposed by the stronger directing group Y will reverse the natural

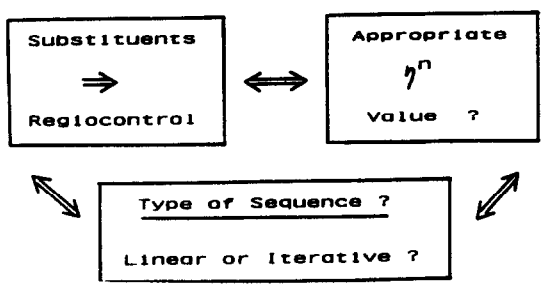
influence of the lesser group. This method lies implicitly behind the control in successful applications[14] of tricarbonyliron groups in the construction of quaternary centres (regiocontrol competition between 4-alkoxy and 1-alkyl substituents), though the systematic ranking of the power of control groups that is needed for the general rational application of this technique is only just beginning.[15] As a step in this direction, we have examined regiocontrol competition in a synthesis of the *Sceletium* alkaloid, *O*-methyljoubertiamine (1). This synthesis makes use of the metal in two C-C bond-formation steps, and has been the subject of a preliminary communication.[16] Although the synthesis has been successful, the synthetic route has been conceived as a model study to establish the practicality of the general approach for application with related but more difficult alkaloid target molecules, many of which will require that the metal controls a third bond-forming step in the closing stages of the route. In this paper, we report full details of our synthesis of *O*-methyljoubertiamine,[17] and the design criteria that apply in the planning of synthetic routes of the type.

Figure 3 Linear and iterative sequences for multiple use of metal π-complexes



In general, two approaches to the multiple utilisation of the working ligand are possible (Fig. 3).[18] The linear approach (a), in which the extent of hapticity of the working ligand decreases with each successive bond formation, and the iterative approach (b), in which η^n cations and η^{n-1} neutral complexes alternate through the reaction sequence. The latter process requires reactivation by return to the initial cationic form, and in our work in the cyclohexadiene/cyclohexadienyl series we have found[19] that the manipulation of leaving groups on the working ligand is particularly effective for this purpose. In linear sequences, several options are available.

Figure 4. Choosing intermediate π-complexes in synthesis design.



In principle, the same metal/ligand system can be employed in a series of reactions at the working ligand in which the charge on the complex varies in each step [dication to cation to neutral, or cation to neutral to anion, etc.], but in most cases it is desirable to reactivate the neutral product arising from nucleophile addition, by replacement[20] of an auxiliary ligand as illustrated in Figure 3a. We have employed this ligand replacement method in studies directed towards the synthesis of tridachiapyrones, and have evaluated dication and

monocation starting materials in a comparison of linear and iterative sequences towards the alkaloid hippeastrine.[21] In general (Fig. 4), in synthesis design with electrophilic π-complexes, a choice must be made between linear and iterative styles of elaboration of the working ligand, though within a given synthesis, the route can combine sections in the iterative mode, and sections that are linear. In enantioselective applications, it is the optimisation of the regiocontrol strategy through a series of steps to meet the demands of elaboration of the working ligand into a section of the target structure, that is the arbiter in the choice between iterative and linear styles at each stage. For *O*-methyljoubertiamine, analysis of these considerations led to the choice of an iterative synthetic plan.

Figure 5. Regiocontrol criteria for the choice of routes to *O*-methyljoubertiamine.

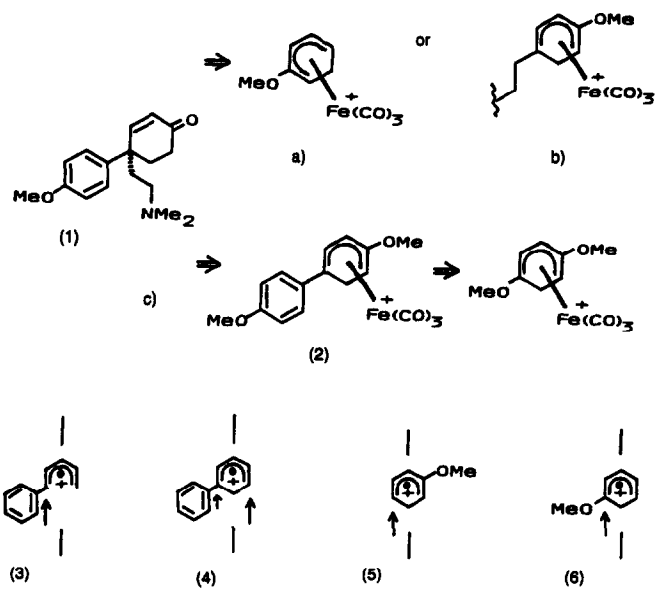


Figure 5 summarises the regiocontrol information that pertains in the selection of tricarbonyliron complexes as intermediates in the synthesis of *O*-methyljoubertiamine (**1**). Three approaches are possible. Alkyl nucleophile addition to an unsubstituted terminus of a dienyl system (a) has provided the original organoiron approach[22] to *O*-methyljoubertiamine. In this route, the working ligand is aromatized after removal of the metal. Alternatively (b), an aryl nucleophile can add to an alkyl-substituted terminus of the dienyl system. An example of this type of process has been reported by Knölker,[23] in a 1,3 difunctionalisation reaction. Because the starting material has two electrophilic centres, the possibility arises that reaction first at the side-chain allows an intramolecular approach by the aromatic ring to the dienyl complex to help overcome steric effects at the substituted terminus.[24] The generallity of the addition of aromatic nucleophiles to form quaternary centres at the junction of aromatic and partially saturated six-membered rings in intermolecular examples remains to be established. The third approach (c) envisages a 1-aryl substituted dienyl complex **2** as an attractive C_{12} precursor to structures of this type.[25] This requires nucleophile addition at the site on the working ligand that carries the aryl group.

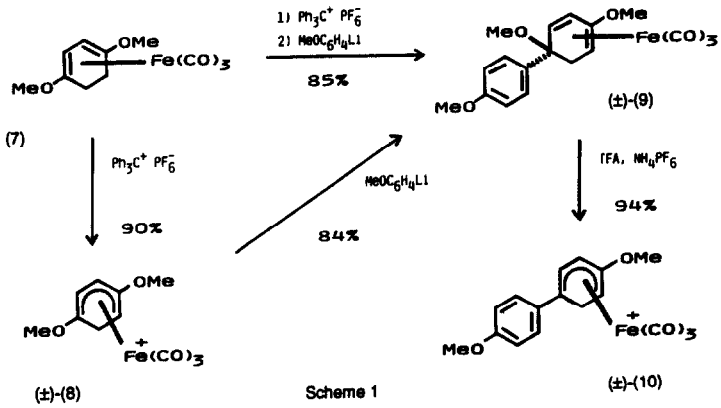
The regiocontrol implications of this approach (c) can now be addressed. While Donaldson has shown[26] that an acyclic 1-phenylpentadienyl complex **3** reacts preferentially at C-1 (ipso attack), our work in the cyclohexadienyl series indicates[15] that in this cyclic case (**4**) the 1-phenyl group is ω-directing (C-5 attack). We have also shown that donor and acceptor groups on the aryl substituent can influence the

regiodirecting power, and that donor (OMe) substitution promotes stronger regiocontrol, while cases with electron withdrawing groups (CF_3) show reduced regioselectivity. This holds both for C-2[27] and C-1[28] aryl substituents on cyclohexadienyl complexes. The nature of the nucleophile is also important for regiocontrol, though effects vary in differing situations. In the C-2 case, a stabilised enolate (malonate) was the most regiocontrolled example, but in the C-1 series this showed poor control, a result that suggests the electronic/orbital effects may be of particular importance in the C-2 case, while steric effects could be more dominant at C-1. From these preliminary studies emerge the two crucial facts needed to guide our synthetic plan. First, for *O*-methyljoubertiamine, the donor substituent on the aromatic ring makes this the most severe test of regiocontrol reversal, since the natural directing effect of the *p*-anisyl substituent is particularly strongly ω. Secondly, it is clear that the use of a stabilised enolate as the nucleophile gives the best chance to promote the minority regioisomer path to become the major pathway, since malonate addition is known to be at least capable of forming the quaternary centre as required at the junction of the two six-membered rings. In the event, a malononitrile nucleophile was selected to introduce a pre-formed C-C-N building block for the two-carbon alkyl substituent, and an easily removed silylalkyl ester protecting group was employed. The known suitability[29] of this group for use in the presence of the tricarbonyliron complex was an important consideration, since the metal must be retained on the working ligand beyond the decarboxylation step, so that it can mask the diene/enone functionality in the ring during hydrogenation of the nitrile substituent. This final requirement appeared reasonable, since tricarbonyliron complexes are known[30] to be resistant to hydrogenation conditions and this form of masking is precedented[31] in other target oriented work. The end-game in the synthesis was also firmly rooted in precedent,[32] since there are many examples of detachment of the metal from methoxydiene complexes and hydrolysis of the enolether to reveal enone functionality. The main features to be determined in our route to *O*-methyljoubertiamine were thus the reversal of regiocontrol of the 1-*p*-anisyl substituent, and the use of the leaving group method[18] for reactivation, following metal-mediated nucleophile addition to build the C_{12} intermediate.

The most extensively applied directing group on tricarbonyliron dienyl complexes is the 2-alkoxy group (e.g. as in **5**).[33] This group is known[34] to attenuate the electrophilicity of the entire complex, but this deactivation effect is far more pronounced at near terminus than at far terminus. Because of the relative placement of the quaternary centre and the ketone functional group in *O*-methyljoubertiamine, it is clear that this molecule suites the iterative mode (Figures 3b and 5) and that deactivation at C-5 by a 4-OMe substituent offers an attractive strategy for regiocontrol reversal. Our successful construction of *O*-methyljoubertiamine by this approach demonstrates the power of the C-4 OMe substituent on the working ligand in the regiocontrol competition, even when put in opposition to the donor-substituted aromatic ring at C-1.

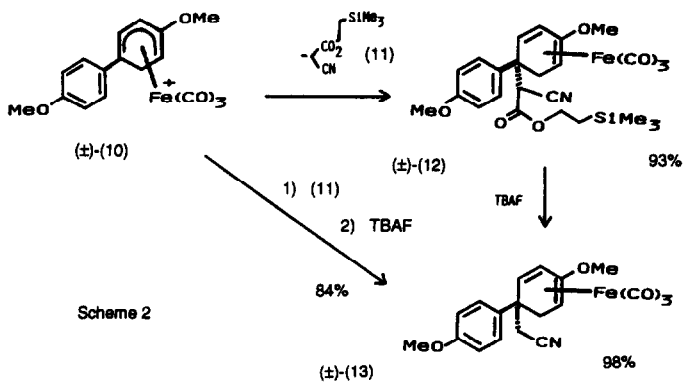
The synthetic route began with the known[35] 1,4-dimethoxy substituted cyclohexadiene complex **7**, a starting material which is prepared easily on a multi-gram scale from 1,4-dimethoxybenzene. This complex is prochiral, so simple hydride abstraction with the normal triphenylcarbenium ion reagent, gives convenient access to the racemic cationic 1,4-dimethoxycyclohexadienyl complex **8**[36] as a single regioisomer in 90% yield. In this cationic intermediate, the two alkoxy directing groups work in concert (Fig. 5, cations **5** and **6**), so regioselective nucleophile addition was anticipated at C-1. Organolithium nucleophiles have been found[12,27] to be the most suitable for use with 1-alkoxy substituted dienyl complexes such as **6** and **8**. The required aryl nucleophile is known, and was prepared by lithiation of 4-iodoanisole, essentially according to the procedure of Schlosser and Ladenberger.[37] It proved important to prepare this reagent in diethyl ether containing the minimum amount of THF to maintain solubility. Addition of an excess of the nucleophile to a solution of **8** in dichloromethane at −78 °C resulted in the formation of the adduct **9** in 84% yield (Scheme 1). Treatment of the product with TFA removed the methoxy leaving group in the expected[15] fashion, and the salt **10** was precipitated from the reaction mixture in 94% yield by the addition of NH_4PF_6. Variations on this reaction sequence have been explored. When 4-bromoanisole was employed in place of the iodoarene, a minor

product arising from competing *o*-metallation of the arene was isolated. The most efficient route used a one-pot procedure in which hydride abstraction from **7** was followed by addition to the reaction mixture of an excess of the aryllithium reagent generated from the iodoarene. In this way, **9** can be obtained from **7** in 85% yield in one step.



Scheme 1

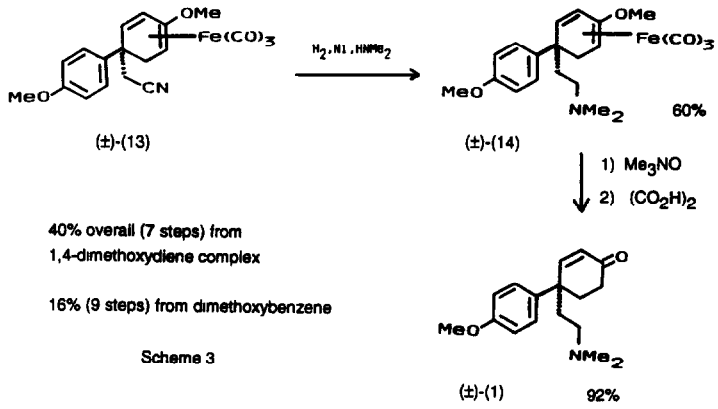
With the salt **10** in hand, it was possible to study the regiocontrol of the crucial second nucleophile addition step (Scheme 2). The required protected malononitrile reagent (2-trimethylsilylethyl cyanoethanoate) was prepared by the literature procedure.[38] Deprotonation was performed with sodium hydride. The 1-aryl substituted dienyl complex was added to a slight excess of the enolate **11** in THF to form the nucleophile addition product **12** as a single regioisomer, in essentially quantitative yield. This complex was produced as the expected 1 : 1 mixture of diastereoisomers at the malononitrile unit (since addition of prochiral nucleophiles to cyclohexadienyl complexes typically lacks control at the centre induced in the nucleophile) but a single



Scheme 2

relative stereochemistry was achieved within the cyclic portion of the working ligand. The lack of stereocontrol in the side-chain was not a problem, since this additional chiral centre is not present in the target molecule, and was to be removed in the decarboxylation step. De-silylation with tetra-*n*-butylammonium fluoride effected de-esterification and decarboxylation in a single procedure to give the anticipated cyanomethyl adduct **13** in 91% yield. The product was shown by ^1H NMR to be a single diastereoisomer, as expected because of the normal[2] completely stereoselective *trans* addition of nucleophiles to tricarbonyliron complexes. Combination of the malononitrile addition and deprotection into a single-step procedure was also examined, but proved to be less efficient than the two step process. In this case it pays to purify the intermediate. Removal of the metal was examined at this stage, since this would afford a known compound[39]

and so confirm that all the preceding steps had been performed correctly. The expected decomplexation product was obtained in 46% yield.

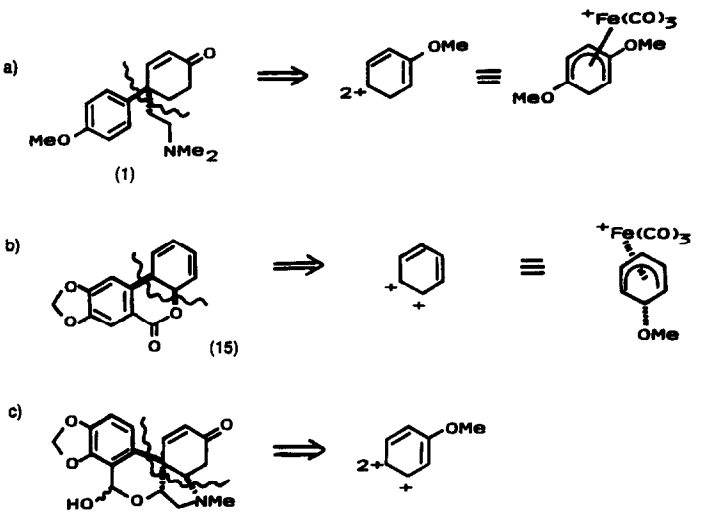


Scheme 3

The closing stages of the synthetic route are illustrated in Scheme 3. An attempt to reduce the nitrile group with DIBAL was unsuccessful, but catalytic hydrogenation performed with hydrogen and excess Raney nickel in the presence[40] of dimethylamine furnished directly the complex **14** in 60% yield.[41] The best results were obtained in a concentrated (*ca.* 5.6 M) solution of dimethylamine in ethanol. Three methods were compared for the removal of the metal. Reaction with either pyridinium chlorochromate (27% yield) or cupric chloride (47% yield) afforded the enone in one step, but the most efficient procedure was the two step method in which demetallation of **14** was performed using anhydrous trimethylamine *N*-oxide in *N,N*-dimethylacetamide. This reaction gave a sample of the crude dienol ether, which was hydrolysed without purification, by reaction with oxalic acid. In this way, *O*-methyljoubertiamine (±)-**1** was obtained in 92% yield from **14**. Our racemic sample from this route gave physical data which were identical to those reported for the natural and synthetic materials[17] (with the exception of optical rotation). Overall, *O*-methyljoubertiamine was obtained in 40% yield[42] in 7 steps from the 1,4-dimethoxydiene complex **7**, or 16% in 10 steps from 1,4-dimethoxybenzene.

This reaction sequence illustrates the importance of the use of regiocontrol information in the planning of synthetic routes employing electrophilic organometallic π-complexes as key intermediates. Two regiocontrol situations have been encountered in this work. In the first nucleophile addition, the two control groups worked in concert to promote regiocontrol. The second case, however, illustrates the success of planning regiocontrol by placing a particularly strong directing group to defeat a weaker one. While it seems reasonable to rely on predictable regiochemistry in cases where directing effects of substituents reinforce each other, the prediction of regiocontrol in cases where groups are in opposition is far less secure. Detailed competition studies employing representative selections of nucleophiles are needed to map the potential of this second situation. This will be one of our objectives in Norwich in the coming years. At present, research teams utilising electrophilic π-complexes must concentrate on cases where unsymmetrically placed substituents act in concert, if the safe realisation of anticipated regiocontrol effects is an essential requirement in a synthetic route. The results reported here also show the feasibility of the iterative approach to the many *Sceletium* and *Amaryllidaceae* alkaloids[43] which contain structural units derived from a 4-aryl-4-alkyl-2-cyclohexen-1-ones. Of particular importance in current target-oriented work in Norwich, are structures which will require a third metal mediated bond-formation. The two nucleophile additions described here in our route to *O*-methyljoubertiamine take place at the same carbon atom on the working ligand. This is an example of 1,1[44] relative regiochemistry (a 1,1-dication equivalent) (Fig. 6a). In our work towards a tricyclic model (**15**)

Figure 6 1,1 and 1,2 dication equivalents



for hippeastrine, we have reported[21] results in the complementary 1,2 regiochemistry series (Fig. 6b). Our future work towards the enantioselective syntheses of *Sceletium* and *Amaryllidaceae* alkaloids (e.g. Fig. 6c) will go further towards achieving the full potential of the multiple use of the tricarbonyliron control group in 6-membered rings, by combining the 1,1 and 1,2 regioisomer patterns to construct two adjacent chiral centres with a sequence of three metal mediated steps. Since the relative stereochemistry between the planar chirality of attachment of the metal control group and the chiral centre resulting from the sequence of two 1,1 nucleophile additions, depends on the order in which these nucleophiles are employed, the complementarity between our regiocontrol reversal approach (alkyl nucleophile addition to an aryl-substituted terminus) and the Knölker methodology[23] (aryl nucleophile addition to an alkyl-substituted terminus) is particularly important. This gives selective access to both possible diastereoisomers of the 1,2 arrangement of chiral centres. When optically pure complexes are employed[6] with these methods, the complete stereoselectivity imparted by the transition metal will be available to control the absolute configuration at each position.[45]

Acknowledgement

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Experimental

General.— All reactions were performed in oven- or flame-dried glassware under an atmosphere of dry, oxygen-free nitrogen. Aryllithium reagents were titrated immediately before use according to the procedure described by Suffert.[46] Low resolution EI mass spectrometry (Kratos MS25 mass spectrometer) and elemental analyses were performed by at the the University of East Anglia by Mr A.W.R Saunders. Other mass spectra were measured at the SERC Mass Spectrometry Centre at University College of Swansea. IR spectra were recorded as a thin film or as a solution in the specified solvent, using a Perkin-Elmer 1720X FT-IR spectrometer. NMR spectra were recorded on Jeol PMX60 (^{1}H, 60 MHz) or Varian EM390 (^{1}H, 90 MHz) spectrometers. High field spectra were recorded by either the spectroscopists of Glaxo Group Research on Bruker AM250 (^{1}H, 250 MHz; ^{13}C, 62.5 MHz) or Varian Unity 400 MHz

(^{1}H, 400 MHz; ^{13}C, 100 MHz) spectrometers, or were measused in Norwich using Jeol EX90 (^{1}H, 90 MHz; ^{13}C, 22.5 MHz) or Jeol GX400 (^{1}H, 400 MHz) spectrometers.

Tricarbonyl[(1,2,3,4-η)-1,4-*dimethoxy*-1,3-*cyclohexadiene*]*iron*(0) (**7**).— This complex was prepared essentially according to the procedure of Birch and co-workers:[35] Lithium/ammonia reduction of 1,4-dimethoxybenzene (100 g) in ethanol gave a mixture (72 g) containing 1,4-dimethoxy-1,4-cyclohexadiene and unreacted aromatic (<10%). Conjugation of a portion (11 g) of this mixture, using Wilkinson's catalyst or tosic acid, gave a mixture (11 g) containing 1,3-diene and 1,4-diene (*ca.* 3 : 1),[47] and aromatic material (<10%). This mixture was heated under reflux with pentacarbonyliron (25 ml) in di-*n*-butyl ether (freshly filtered through basic alumina) at 155–165 °C for 20 h. After the work-up and chromatography, the title complex was obtained as a low melting yellow solid (12.8 g), which ^{1}H NMR analysis showed was contaminated with aromatic material (9%). The yield of the complex (by ^{1}H NMR) was 81% from the 1,3 diene (40% over the three steps from dimethoxybenzene). The product was re-purified in small batches as required.

Tricarbonyl[(1,2,3,4,5-η)-1,4-*dimethoxy*-2,4-*cyclohexadien*-1-*yl*]*iron*(1+) *hexafluorophosphate*(1–) (**8**).— A solution of the 1,4-dimethoxy substituted complex **7** (3.25 g, 11.6 mmol) in dry dichloromethane (5 ml) was added to a solution of triphenylmethylium hexafluorophosphate (5.70 g, 14.7 mmol) in the minimum of dry dichloromethane. The mixture was stirred for 2 h at r.t., and was then poured into ether (800 ml). The yellow precipitate was collected by filtration and dried in a stream of nitrogen, then *in vacuo*, to give the *title salt* (4.45g, 90%) as a yellow powder (Found: C, 31.2; H, 2.6. $C_{11}H_{11}F_6FeO_5P$ requires C, 31.25; H, 2.5%); ν_{max} (CH_3CN) 2 099 and 2 044 cm^{-1} (CO); δ_H (60 MHz; acetone-d_6; TMS) 3.00 (1 H, dm, *J* 16 Hz, 6α-H), 3.43 (1 H, dd, *J* 16 and 6 Hz, 6β-H), 3.92 (3 H, s, 4-OMe), 4.00 (3 H, s, 1-OMe), 4.11 (1 H, m, 5-H), 4.80 (1 H, d, *J* 6 Hz, 2-H), and 6.82 (1 H, dd, *J* 6 and 3 Hz, 3-H).

Reaction of the 1,4-*dimethoxy substituted salt* **8** *with* 4-*methoxyphenyllithium derived from 4-bromoanisole.*— *n*-Butyllithium (2.76 ml of a 1.45 M solution in hexanes, 4.00 mmol) was added to a solution of 4-bromoanisole (748 mg, 4.00 mmol) in dry ether (5 ml) at −78 °C, and the mixture was stirred at that temperature for 10 min, then warmed to r.t. A portion (3.1 ml) of the resulting solution of 4-methoxyphenyllithium was then reacted with a solution of the salt **8** (391 mg, 0.92 mmol) in dry dichloromethane (15 ml) in the usual way. After the work-up, flash chromatography with 5% ethyl acetate in light petroleum as the eluant gave, in order of elution: *tricarbonyl*[(1,2,3,4-η)-2,5β-*dimethoxy*-5α-(4-*methoxyphenyl*)-1,3-*cyclohexadiene*]*iron*(0) **9** (202 mg, 57%) as a viscous yellow oil (Found: C, 56.0; H, 4.7. $C_{18}H_{18}FeO_6$ requires C, 56.1; H, 4.8%); ν_{max} (C_6H_{12}) 2 052, 1 990, 1 988, and 1 973 cm^{-1} (CO); δ_H (250 MHz; $CDCl_3$; TMS) 2.16 (1 H, dd, *J* 14.5 and 3 Hz, 6α-H), 2.21 (1 H, dd, *J* 14.5 and 4 Hz, 6β-H), 2.79 (1 H, d, *J* 7 Hz, 4-H), 3.02 (3 H, s, 5-OMe), 3.39 (1 H, m, 1-H), 3.65 (3 H, s, 2-OMe), 3.79 (3 H, s, 4'-OMe), 5.03 (1 H, dd, *J* 7 and 2.5 Hz, 3-H), 6.83 (2 H, dm, *J* 9 Hz, 3'- and 5'-H), and 7.19 (2 H, dm, *J* 9 Hz, 2'- and 6'-H); *m/z* (EI) 330 (M^+ – 2CO, 0.4%), 302 (2), 270 (5), and 214 (100); *m/z* (FAB) 386 (M^+, 7%), 355 (60), 327 (27), 302 (97), 271 (98), and 215 (100); and *tricarbonyl*[(1,2,3,4-η)-2,5β-*dimethoxy*-5α-(5-*bromo*-2-*methoxyphenyl*)-1,3-*cyclohexadiene*]*iron*(0) (62 mg, 14%) as a pale yellow oil which solidified, m.p. 96.5–98.5 °C; ν_{max} (C_6H_{12}) 2 054, 2 050, 1 992, 1 986, and 1 973 cm^{-1} (CO); δ_H (250 MHz; $CDCl_3$; TMS) 2.21 (1 H, dd, *J* 15 and 4 Hz, 6β-H), 3.34 (1 H, dd, *J* 15 and 2.5 Hz, 6α-H), 2.87 (1 H, d, *J* 7 Hz, 4-H), 3.00 (3 H, s, 5-OMe), 3.31 (1 H, m, 1-H), 3.65 (3 H, s, 2-OMe), 3.77 (3 H, s, 2'-OMe), 5.07 (1 H, dd, *J* 7 and 2.5 Hz, 3-H), 6.72 (1 H, d, *J* 9 Hz, 3'-H), 7.32 (1 H, dd, *J* 9 and 2.5 Hz, 4'-H), and 7.57 (1 H, d, *J* 2.5 Hz, 6'-H); *m/z* (EI) 438/436 (M^+ – CO, 0.2%), 410/408 (0.3), 350/348 (8), 294/292 (84), 214 (22), and 198 (100) [Found *m/z* (EI) M^+ – MeOH, 432.9374. $C_{18}H_{17}BrFeO_6$ requires M^+ – MeOH, 432.9374].

Preparation of 4-*methoxyphenyllithium from* 4-*iodoanisole.*— Based on the procedure described by Schlosser and Ladenberger,[37] *n*-butyllithium (8.33 ml of a 1.20 M solution in hexanes, 10.0 mmol) was added to a solution of 4-iodoanisole (2.69 g, 11.5 mmol) in hexane (20 ml), and the mixture was stirred 20 min at r.t. The white precipitate which formed was allowed to settle, and the supernatant was removed by filtration through the side-arm frit. Hexane (20 ml) was added to the residue, the mixture was stirred for 5 min, and the white solid was once again allowed to settle and the supernatant removed. The residue was then dissolved in dry ether (20 ml) plus the minimum amount of dry THF (<0 7 ml) necessary to give a homogeneous solution. This solution of 4-methoxyphenyllithium was used directly.

Reaction of salt **8** *with* 4-*methoxyphenyllithium derived from 4-iodoanisole.*— The solution of 4-methoxyphenyllithium prepared from 4-iodoanisole (11 5 mmol) and *n*-butyl-lithium (10 mmol) in ether/THF was reacted with a

solution of salt **8** (1.80 g, 4.25 mmol) in dry dichloromethane (80 ml) in the usual way. After the work-up, flash chromatography with 5% ethyl acetate in light petroleum afforded the *product* **9** (1.38 g, 84%) as a viscous yellow oil, identical to that prepared above.

One-pot procedure for the preparation of complex **9** *from complex* **7**.— A solution of the 1,4-dimethoxy substituted complex **7** (868 mg, 3.10 mmol) in dry dichloromethane (15 ml) was added to a solution of triphenylmethylium hexafluorophosphate (1.32 g, 3.41 mmol) in dry dichloromethane (25 ml), and the mixture was stirred at r.t. for 2 h. The mixture was then cooled to −78 °C, and a solution of 4-methoxyphenyllithium [prepared from 4-iodoanisole (11.5 mmol) and *n*-butyllithium (10 mmol) as detailed above] in ether/THF was added at such a rate that the internal temperture of the reaction mixture remained below −60 °C. After the addition of the lithium reagent was complete, the reaction mixture was stirred for 30 min at −78 °C. Saturated aqueous ammonium chloride (30 ml) was then added, and the reaction mixture was warmed to r.t. and poured into a separating funnel charged with ether (100 ml) and water (20 ml). The layers were separated and the aqueous layer was extracted with ether (3 x 30 ml). The combined organic fractions were washed with brine (2 x 30 ml), then dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure to give the crude product. Flash chromatography with 40% dichloromethane in light petroleum as the eluant afforded the *product* (**9**) (1.02 g, 85%), which was identical to that prepared above.

Reaction of complex **9** *with TFA*.— Complex **9** (1.35 g, 3.50 mmol) was stirred with trifluoroacetic acid (TFA) (2.70 ml, 35.0 mmol) for 30 min. Addition of ammonium hexafluorophosphate (1.35 g, 8.28 mmol) afforded *tricarbonyl*-[(1,2,3,4,5-η)-4-*methoxy*-1-(4-*methoxyphenyl*)-2,4-*cyclohexadien*-1-*yl*]*iron*(1+) *hexafluorophosphate*(1−) (**10**) (1.64 g, 94%) as a yellow powder (Found: C, 40.9; H, 3.0. $C_{17}H_{15}F_6FeO_5P$ requires C, 40.8; H, 3.0%); ν_{max} (CH_3CN) 2 103 and 2 054 cm^{-1} (CO); δ_H (250 MHz; acetone-d_6; TMS) 2.87 (1 H, d, *J* 16 Hz, 6α-H), 3.94 (3 H, s, 4'-OMe), 4.03 (1 H, ddd, *J* 16, 6.5, and 1.5 Hz, 6β-H), 4.10 (3 H, s, 4-OMe), 4.53 (1 H, ddd, *J* 6.5, 3, and 1.5 Hz, 5-H), 6.61 (1 H, dm , *J* 6.5 Hz, 2-H), 7.13 (2 H, dm, *J* 9 Hz, 3'- and 5'-H), 7.36 (1 H, dd, *J* 6.5 and 3 Hz, 3-H), and 7.71 (2 H, dm, *J* 9 Hz, 2'- and 6'-H).

2-*Trimethylsilylethyl cyanoethanoate*.— Based on the procedure of Hassner and Alexanian,[38] freshly distilled cyanoethanoic acid (851 mg, 10.0 mmol), DCC (2.27 g, 11.0 mmol), and 4-pyrrolidinopyridine (148 mg, 1.00 mmol) were added in that order to a solution of 2-trimethylsilylethanol (1.30 g, 11.0 mmol) in dry ether (100 ml). The reaction mixture was shaken intermittently during 3 h, and then the urea which had formed was removed by filtration. The filtrate was washed with water (3 x 50 ml), 5% aqueous acetic acid (3 x 50 ml), and water (3 x 50 ml), then dried ($MgSO_4$), filtered, and the solvent was removed under reduced pressure. Hexane (10 ml) was added and the mixture was re-filtered. Removal of the solvent under reduced pressure gave the crude product as a pale yellow oil. Bulb-to-bulb distillation of this crude product afforded the *title compound* (1.62 g, 88%) as a colourless oil, b.p. *ca.* 60–80 °C/0.01 mmHg (Found: C, 52.1; H, 8.35; N, 7.5. $C_8H_{15}NO_2Si$ requires C, 51.9; H, 8.2; N, 7.6%); ν_{max} (film) 2 956 (C-H), 2 358 (CN), and 1 747 cm^{-1} (ester carbonyl); δ_H (60 MHz; $CDCl_3$; TMS) 0.06 (9 H, m, $SiMe_3$), 1.07 (2 H, m, OCH_2CH_2Si), 3.43 (2 H, s, $NCCH_2CO$), and 4.32 (2 H, m, OCH_2CH_2Si).

Tricarbonyl{2'-*trimethylsilylethyl*[(2,3,4,5-η)-4-*methoxy*-1β-(4''-*methoxyphenyl*)-2,4-*cyclohexadien*-1α-*yl*]*cyanoethanoate*}*iron*(0) (**12**).— Sodium hydride (17.2 mg of a 60% dispersion in mineral oil, nominally 0.43 mmol) was washed with hexane (1 ml) and stirred as a suspension in dry THF (1 ml) at 0 °C. A solution of 2-trimethylsilylethyl cyanoethanoate (79 mg, 0.43 mmol) in dry THF (1 ml) was then added, and the mixture was stirred at 0 °C for 5 min to give a colourless solution of the enolate **11**. The salt **10** (195 mg, 0.39 mmol) was then added against nitrogen backpressure, and the reaction mixture was stirred for a further 30 min at 0 °C. The reaction mixture was poured into a separating funnel charged with ether (50 ml) and saturated aqueous sodium hydrogen carbonate (30 ml), and the layers were separated. The organic layer was washed with water and brine, then dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure to give the crude product. Purification by flash chromatography with 15% ethyl acetate in light petroleum as the eluant afforded the *title complex* (195 mg, 93%) (inseparable 1 · 1 mixture of diastereoisomers), as a very viscous yellow oil (Found: C, 55.8; H, 5.7; N, 2.8. $C_{25}H_{29}FeNO_7Si$ requires C, 55.6; H, 5.4; N, 2.6%); ν_{max} (C_6H_{12}) 2 255 (CN), 2 052, 1 979 (CO), and 1 718 cm^{-1} (ester carbonyl); δ_H (250 MHz; $CDCl_3$; $CHCl_3$) −0.04 and 0.02 (9 H, 2 x s, $SiMe_3$), 0.66 and 0.86 (2 H, 2 x m, OCH_2CH_2Si), 2.40 and 2.41 (1 H, 2 x dd, *J* 15.5 and 4 Hz, 6β-H), 2.66 and 2.80 (1 H, 2 x dd, *J* 15.5 and 2.5 Hz, 6α-H), 3.10 and 3.16 (1 H, 2 x d, *J* 7 Hz, 2-H), 3.35 (1 H, m, 5-H), 3.56 and 3.57 (1 H, 2 x s, COCHCN), 3.68 and 3 73 (3 H, 2 x s, 4-OMe), 3 78 and 3.79 (3 H, 2 x s, 4''-OMe), 3 92 and 4 06 (2 H, 2 x m, OCH_2CH_2Si), 5 23 and 5 32 (1 H, 2 x dd, *J* 7 and 2.5 Hz, 3-H), 6 84 and 6.86 (2 H, 2 x d, *J* 9

Hz, 3"- and 5"-H), and 7.20 and 7.23 (2 H, 2 x d, *J* 9 Hz, 2"- and 6"-H); *m/z* (CI) 557 (MNH_4^+, 21%), 357 (40), 203 (67), and 90 (100).

Tricarbonyl[(1,2,3,4-η)-5-*cyanomethyl*-2-*methoxy*-5-(4-*methoxyphenyl*)-1,3-*cyclohexadiene*]*iron*(0) (**13**).— Tetra-n-butylammonium fluoride (TBAF) (0.14 ml of a 1.0 M solution in THF, 0.14 mmol) was added to a solution of complex **12** (70.0 mg, 0.13 mmol) in dry THF (5 ml) under reflux, and reflux was maintained for 2 h. The cooled reaction mixture was then poured into a separating funnel charged with saturated aqueous ammonium chloride (5 ml), water (5 ml) and ether (20 ml), and the layers were separated. The organic layer was washed with water (10 ml) and brine (10 ml), dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure to give the crude product. Purification by flash column chromatography with 30% ethyl acetate in light petroleum as the eluant afforded the *title complex* (50.0 mg, 98%) as a pale yellow viscous oil which solidified, m.p. 124.5–125.5 °C (from ether) (Found: C, 57.6; H, 4.3; N, 3.5. $C_{19}H_{17}FeNO_5$ requires C, 57.75; H, 4.3; N, 3.5%); ν_{max} (C_6H_{12}) 2 054, 2 051, 1 990, 1 985, 1 981, and 1 977 cm^{-1} (CO); ν_{max} ($CHBr_3$) 2 246 cm^{-1} (CN); δ_H (60 MHz; $CDCl_3$; TMS) 2.28 (2 H, m, CH_2CN), 2.53 (2 H, m, 6-H), 3.08 (1 H, d, *J* 7 Hz, 4-H), 3.36 (1 H, m, 1-H), 3.72 (3 H, s, 2-OMe), 3.80 (3 H, s, 4'-OMe), 5.30 (1 H, dd, *J* 7 and 2.5 Hz, 3-H), 6.91 (2 H, dm, *J* 9 Hz, 3'- and 5'-H), and 7.24 (2 H, dm, *J* 9 Hz, 2'- and 6'-H); *m/z* (EI) 367 (M^+ – CO, 1%), 339 (4), 311 (7), 270 (15), 215 (15), 121 (10), 84 (62), and 43 (100)

One-pot procedure for the preparation of complex **13** *from salt* **10**.— Sodium hydride (70.4 mg of a 60% dispersion in mineral oil, nominally 1.76 mmol) was washed with hexane (2 x 1.5 ml) and stirred as a suspension in dry THF (3 ml) at 0 °C. A solution of 2-trimethylsilylethyl cyanoethanoate (326 mg, 1.76 mmol) in dry THF (3 ml) was added and the mixture was stirred for 5 min at 0 °C to give a colourless solution. The salt **10** (800 mg, 1.60 mmol) was added against nitrogen back-pressure, and stirring was continued for 30 min at 0 °C. The reaction mixture was heated to reflux and TBAF (1.76 ml of a 1.0 M solution in THF, 1.76 mmol) was added. Reflux was maintained, and further portions of TBAF were added at 1 h (3.52 mmol) and 3 h (1.76 mmol). After a total reflux time of 5 h, TLC analysis indicated that the reaction was substantially complete, and the cooled reaction mixture was poured into a separating funnel charged with water (30 ml), ether (25 ml), and ethyl acetate (25 ml). The layers were separated and the organic layer was washed with water (2 x 20 ml) and brine (20 ml), then dried ($MgSO_4$) and filtered. Removal of the solvent under reduced pressure gave the crude product, which was purified by flash chromatography with 30% ethyl acetate in light petroleum as the eluant to give the *complex* **13** (530 mg, 84%). This product was identical to that prepared previously.

4-*Cyanomethyl*-4-(4-*methoxyphenyl*)-2-*cyclohexen*-1-*one*.— Complex (**13**) (495 mg, 0.13 mmol) was stirred with pyridinium chlorochromate[48] (155 mg, 0.72 mmol) in dry dichloromethane (5 ml) for 20 h. The reaction mixture was then filtered through a short plug of silica gel with 50% ethyl acetate in light petroleum. Removal of the solvent under reduced pressure, followed by flash chromatography with 40% ethyl acetate in light petroleum as the eluant afforded the *title compound* (14.0 mg, 46%) as colourless crystals, m.p. 108.5–109.5 °C (from ether) (lit.,[39] 107–108 °C).

Attempted reaction of complex **13** *with DIBAL*.— DIBAL (0.28 ml of a 1.0 M solution in hexanes, 0.28 mmol) was added to a solution of complex **13** (100 mg, 0.25 mmol) in dry THF (2 ml) at −78 °C, and the reaction mixture was then stirred at r.t. After 24 h, TLC analysis showed the presence of only starting material, and the reaction was abandoned.

Hydrogenation of the nitrile of complex **13** — (*a*) *Using a palladium*(0) *catalyst*. Complex **13** (100 mg, 0.25 mmol), 10% palladium on carbon (50 mg), and dimethylamine (1 0 ml of a *ca.* 5.6 M solution in ethanol, nominally 5.6 mmol) were stirred together in ethanol (2 ml) at r.t. under an atmosphere of hydrogen. After 24 h, TLC analysis showed the presence of only starting material, and the reaction was abandoned

(b) *Using a nickel*(0) *catalyst*.[40] Complex **13** (248 mg, 0.63 mmol) and Raney nickel (15 drops of a *ca.* 50% slurry in water) were added to methylamine in ethanol (20 ml of a *ca.* 5.6 M solution), and the mixture was stirred at r.t. under an atmosphere of hydrogen until TLC analysis showed that no starting material remained (1 h). The mixture was then filtered through Celite (**CARE!** pyrophoric nickel) and the solvent was removed under reduced pressure to give the crude product. Purification by flash chromatography with 10% diethylamine in ether as the eluant afforded *tricarbonyl*-

{N,N-*dimethyl*-2-[(2,3,4,5-η)-4-*methoxy*-1β-(4-*methoxyphenyl*)-2,4-*cyclohexadien*-1α-*yl*]*ethylamine*}*iron*(0) (**14**) (160 mg, 60%) as a viscous yellow oil which solidified upon prolonged refrigeration, m.p. 74–75 °C (Found: C, 59.2; H, 6.0; N, 3.05. $C_{21}H_{25}FeNO_5$ requires C, 59.0; H, 5.9; N, 3.3%); $\nu_{max.}$ (C_6H_{12}) 2 048, 1 983, and 1 972 cm^{-1} (CO); δ_H (400 MHz; $CDCl_3$; TMS) 1.50–2.03 (4 H, m, CH_2CH_2N), 2.08 (6 H, s, NMe_2), 2.17 (2 H, m, 6-H), 2.97 (1 H, d, *J* 6.7 Hz, 2-H), 3.35 (1 H, m, 5-H), 3.69 (3 H, s, 4-OMe), 3.80 (3 H, s, 4'-OMe), 5.21 (1 H, dd, *J* 6.7 and 2.4 Hz, 3-H), 6.84 (2 H, dm, *J* 8.9 Hz, 3'- and 5'-H), and 7.15 (2 H, dm, *J* 8.9 Hz, 2'- and 6'-H); *m/z* (EI) 399 (M^+ – CO, 3%), 371 (11), 343 (37), 270 (15), 233 (13), and 214 (100).

Demetallation of complex **14**.— (*a*) *Using pyridinium chlorochromate*.[48] Complex **14** (58.0 mg, 0.14 mmol) and pyridinium chlorochromate (173 mg, 0.80 mmol) were stirred together in dry dichloromethane (5 ml) at r.t. for 24 h. The mixture was then poured into a separating funnel charged with 10% aqueous sodium hydroxide (10 ml) and dichloromethane (10 ml). The layers were separated and the organic layer was washed with water (10 ml), then extracted with 1.5 M aqueous hydrochloric acid (10 ml). The acidic extract was made basic by the addition of solid sodium hydroxide and then extracted with dichloromethane (2 x 10 ml). The solvent was removed from these latter extracts under reduced pressure to give the crude product, which was purified by short-path distillation at 0.01 mmHg to give the product, (±)-*O*-methyljoubertiamine (**1**) (10 mg, 27%) as a colourless oil. Data for this compound are reported below.

(*b*) *Using copper*(II) *chloride*.[49] Copper(II) choride (3 ml of a saturated solution in ethanol) was added to a solution of complex **14** (70.0 mg, 0.16 mmol) in ethanol (3 ml), and the reaction mixture was stirred for 2 h at r.t. The mixture was diluted with ethanol (20 ml) and dichloromethane (25 ml), and transferred to a separating funnel. The organic solution was washed liberally with water, saturated aqueous sodium hydrogen carbonate, and brine, and dried ($MgSO_4$) and filtered. Removal of the solvent under reduced pressure gave the crude product. Purification by flash chromatography with 10% diethylamine in ether as the eluant afforded (±)-*O*-methyljoubertiamine (**1**) (21 mg, 47%) as a colourless oil. Data for this compound are reported below.

(*c*) *Using trimethylamine* N-*oxide*.[50] Anhydrous trimethylamine *N*-oxide[51] (300 mg, 3.99 mmol) was added to a solution of complex **14** (98.0 mg, 0.23 mmol) in dimethyl acetamide (DMAC) (5 ml). The reaction mixture was stirred at r.t. for 20 h, then poured into brine (10 ml) and extracted with ether (3 x 10 ml). The combined extracts were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure. The oily residue was warmed gently *in vacuo* to remove residual DMAC, leaving essentially pure enol ether (65.5 mg, 99%) as a colourless oil; δ_H (60 MHz; $CDCl_3$; TMS) 2.08 (4 H, m, CH_2CH_2), 2.16 (6 H, s, NMe_2), 2.54 (2 H, m , 6-H), 3.51 (3 H, s, 4-OMe), 3.80 (3 H, s, 4'-OMe), 4.55 (1 H, br t, *J* 9 Hz, 5-H), 5.95 (2 H, m, 2- and 3-H), 6.85 (2 H, dm, *J* 9 Hz, 3'- and 5'-H), and 7.27 (2 H, dm, *J* 9 Hz, 2'- and 6'-H). The whole of this material was dissolved in methanol (2 ml), and a solution of oxalic acid dihydrate (40 mg, 0.32 mmol) in water (0.5 ml) was added. The mixture was stirred for 21 h, then made basic by the addition of solid potassium hydroxide and extracted with ether (3 x 10 ml). The combined extracts were dried ($MgSO_4$) and filtered, and the solvent was removed under reduced pressure to give chromatographically pure (±)-*O*-methyljoubertiamine {[4-(2-dimethylamino)ethyl]-4-(4-methoxyphenyl)-2-cyclohexen-1-one} (**1**)[17] (58 mg, 93%) as a colourless oil, b.p. *ca.* 100 °C/0.02 mmHg (bulb-to-bulb distillation, 52 mg recovery); R_f 0.46 (10% Et_2NH in Et_2O); ν_{max} (CH_3Br) 1 675 cm^{-1} (C=O); δ_H (60 MHz; $CDCl_3$; TMS) 2.0–2.4 (14 H, m, NMe_2 and 4 x CH_2), 3.80 (3 H, s, OMe), 6.14 (1 H, d, *J* 10 Hz, 2-H), 6.87 (2 H, dm, *J* 9 Hz, 3'- and 5'-H), 7.15 (1 H, d, *J* 10 Hz, 3-H), and 7.20 (2 H, dm, *J* 9 Hz, 2'- and 6'-H) [lit.,[52] δ_H 2.00–2.23 (14 H, m), 3.81 (3 H, s), 6.05 (1 H, d), 6.85 (2 H, d), 7.15 (1 H, d), and 7.22 (2 H, d)]; *m/z* (EI) 273 (M^+, 10%) and 58 (100).

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