A New Strategy for the Synthesis of Himbacine

Mike Casey,* Robert McCarthy

School of Chemistry and Chemical Biology, University College Dublin, Dublin 4, Ireland
Fax +353(1)7181178; E-mail: mike.casey@ucd.ie

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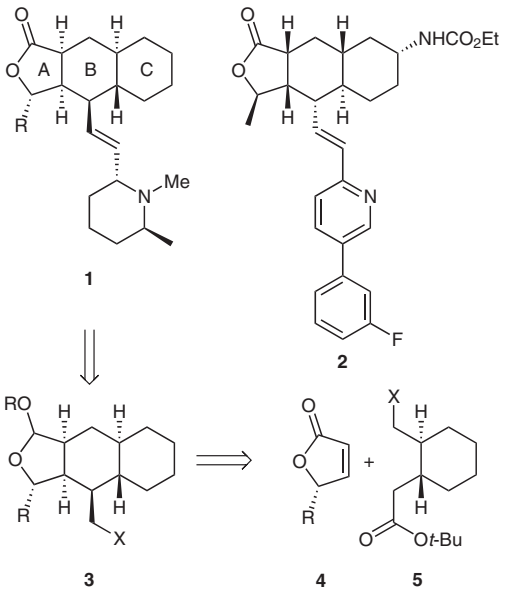
Abstract: A new strategy for the assembly of himbacine and analogues, which display potent biological activity, is described. A four-step route to a key intermediate has been developed, in which the key step is a highly diastereoselective Michael–Dieckmann domino reaction. Use of an enantioenriched Michael acceptor, readily obtained by an asymmetric dihydroxylation reaction, allowed kinetic resolution of the Michael donor, which was itself prepared by a domino reaction.

Key words: alkaloids, domino reactions, kinetic resolution, Michael additions, stereoselective synthesis

Himbacine **1** (R = Me), a natural product isolated from a species of magnolia trees,[1] is a potent, subtype-selective muscarinic receptor (M_2) antagonist, and is regarded as a promising lead in the development of treatments for neurodegenerative disorders such as Alzheimer's disease.[2] A number of himbacine analogues show related activity and it is notable that normethyl himbacine **1** (R = H) is a more potent M_2 receptor antagonist than himbacine itself.[3] Moreover, a major effort by Chackalamannil et al. resulted in the discovery that several series of analogues of the enantiomer of himbacine, in which the piperidine ring is replaced by an aromatic ring and the C-ring is modified, are nanomolar inhibitors of thrombin receptor, potentially useful for the treatment of disorders such as arterial thrombosis, atherosclerosis and restenosis.[4] The most promising lead in the series, SCH 530348 (Vorapaxar) **2** is an orally active thrombin receptor antagonist with potent antiplatelet activity.[4d]

Beginning with the work of Hart, Kozikowski and coworkers in 1995, a number of syntheses of himbacine, and of analogues, have been reported.[5] Remarkably, all of these syntheses utilise a Diels–Alder reaction for construction of the stereochemically complex decalin segment. While the Diels–Alder strategy has proven to be extremely effective and versatile, we decided to explore a different approach. Our retrosynthetic analysis (Scheme 1) envisaged the coupling of a tricyclic intermediate of type **3** with a piperidine fragment, as in earlier syntheses. Analysis of intermediate **3** suggested that it could be obtained by a Michael-Initiated Ring Closure (MIRC) reaction involving a *trans* disubstituted cyclohexane **5** and a butenolide **4**. We hoped that this approach would provide a short route to the key intermediate **3** and that it would be possible to use it to make novel analogues that would not be readily accessible by the Diel–Alder routes. We now report preliminary results that demonstrate the viability of this strategy.



Scheme 1 Retrosynthetic analysis

Our first objective was to test the feasibility of the key MIRC reaction, and, in particular, to determine the diastereoselectivity of the Michael reaction. The racemic cyclohexane diester **7** was prepared using the method of Yamaguchi et al.,[6] again using a MIRC reaction (Scheme 2). Reaction of an excess of the lithium enolate formed from *tert*-butyl acetate, with the readily accessible ω-iodo enoate **6**,[7] and addition of potassium *tert*-butoxide to induce cyclisation, gave the *trans* disubstituted cyclohexane **7** in 70% yield with complete *trans* diastereoselectivity.

The crucial MIRC reaction was then attempted using the unsubstituted furanone, suitable for the synthesis of normethyl himbacine **1** (R = H). Regioselective deprotonation of diester **7** using LTMP, addition of furanone and warming in the presence of potassium *tert*-butoxide to induce an in situ intramolecular Claisen condensation gave the desired tricyclic lactones **8** and **9** and a small amount uncyclised triester **10** along with some unreacted starting material.

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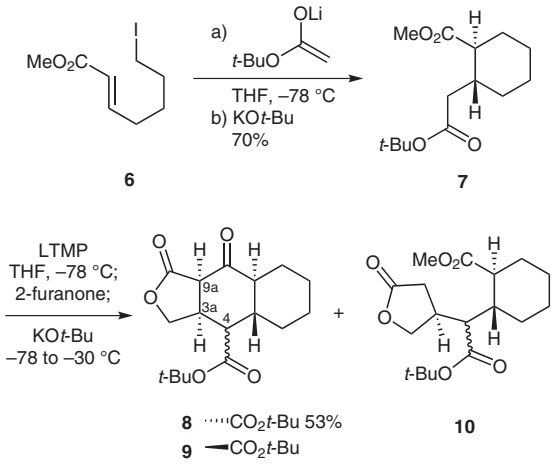


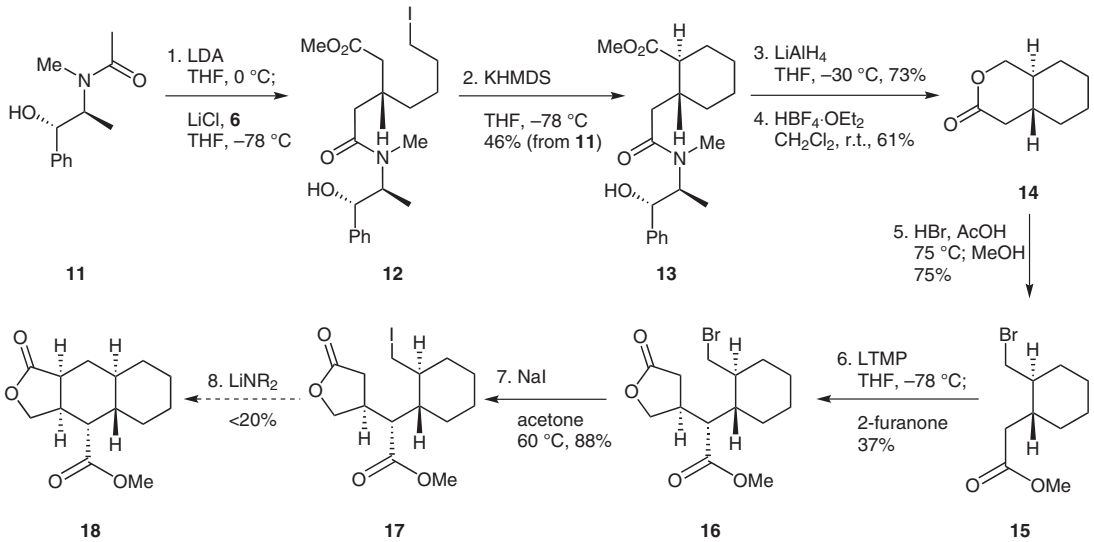
Scheme 2 Double MIRC sequence

The reaction produced two diastereoisomers of the product, **8** and **9**, and careful analysis of the ^{1}H NMR spectra, supported by molecular mechanics calculations, clearly showed that both had the desired relative configuration at the fused lactone ring and that they were epimeric at C-4, α to the *tert*-butyl ester. Chromatography yielded the major isomer **8** (53% yield, 63% based on unrecovered starter), the tricycle with the incorrect configuration at C-4, which is potentially epimerisable. The minor diastereomer **9** and the triester **10** together constituted less than 25% of the mixture, but were not obtained in pure form.

The good stereoselectivity in the formation of three chirality centres in the Michael–Dieckmann domino reaction is notable. The stereochemical outcome at C-4, relative to the existing centres on the cyclohexane, is in accord with results in related systems.[8] Good diastereoselectivity α and β to the carbonyl of the nucleophilic component is often observed in Michael reactions of ester enolates,[6,8] and may be ascribed to the involvement of a well-ordered cyclic transition state. However, the addition of simple α-substituted lithium enolates to butenolides does not appear to have been reported previously, so we were gratified to find excellent stereoselectivity for the desired relative configuration at C-3a. Formation of the *cis* configuration at carbons 3a and 9a, in the Dieckmann step, is inevitable in this case because the methylene of the lactone is axial on a *trans*-decalin system.

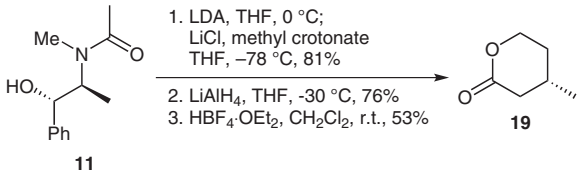
Having demonstrated the feasibility of the method for tricycle formation, we turned to an asymmetric synthesis of a MIRC precursor of type **5**. A chiral auxiliary approach was adopted in this first study. Although a number of chiral auxiliaries have given good results in asymmetric Michael reactions,[8a,9,10] we were only able to locate one example involving α-unsubstituted acetate derivatives.[11] Following the precedent for phenylacetate analogues,[10] we investigated the use of pseudoephedrine as a chiral auxiliary (Scheme 3). Conjugate addition of amide **11** was successful only when an excess of lithium chloride was added,[12] and even then it gave adduct **12** in moderate yield, accompanied by cyclisation product **13** (Scheme 3). The presence of amide rotamers made analysis of the diastereomer ratio by NMR more difficult, but we were unable to detect any other stereoisomers so it is clear that the chiral auxiliary was very effective. Attempts to induce complete ring closure of the enolate from the Michael reaction in situ were unsuccessful, but treatment of the Michael reaction product with KHMDS provided the *trans* disubstituted cyclohexane **13** as a single stereoisomer, in 46% overall yield.

Selective reduction of the ester group (73%) and treatment of the resulting hydroxy amide with acid resulted in cleavage of the auxiliary to yield lactone **14** (61%). The absolute stereochemistry of the bicyclic lactone **14** was assigned by analogy with that of the lactone **19** obtained from methyl crotonate in the same way (Scheme 4). The specific rotation of lactone **19** {$[\alpha]_D$ –22.0 (c = 0.5, $CHCl_3$)} was in good agreement with the value reported for (*S*)-**19** {$[\alpha]_D$ –26.2 (c = 0.83, $CHCl_3$)}.[13] This stereo-



Scheme 3

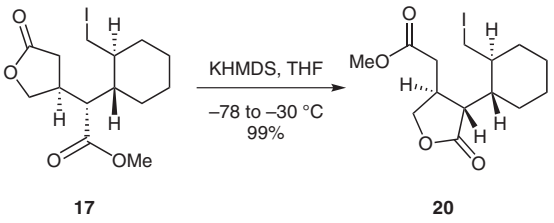
chemical outcome is the same as that found in reactions of phenylacetamides derived from the pseudoephedrine auxiliary.[10] Ring opening of the lactone **14** with HBr, and in situ methyl ester formation,[14] then gave the desired MIRC precursor **15** in 75% yield.



Scheme 4

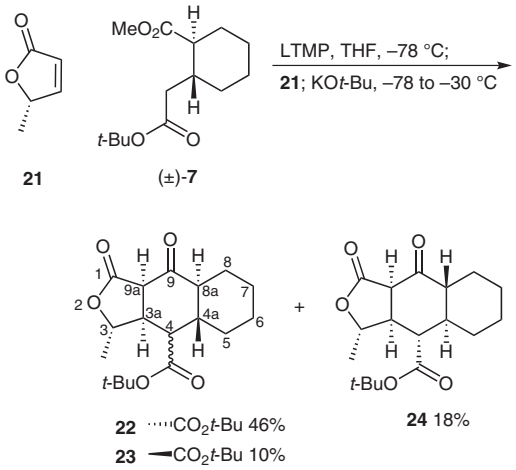
Michael reaction with furanone yielded the conjugate adduct **16** in just 37% yield, but with high diastereoselectivity as before. Conversion of the bromo lactone into the iodo analogue **17** was efficient (88%; Scheme 3), but attempts to effect cyclisation yielded the desired tricyclic product **18** in low yields, together with unreacted starting material and a rearranged product (see below). It would appear that the intramolecular enolate alkylation reaction was very much slower than the Dieckmann reaction used in our initial studies.

During the work described above, it was apparent that compounds **16** and **17** were contaminated with small amounts of closely related materials. The structures of the contaminants were revealed in the course of the attempts to cyclise iodo lactone **17**. Use of potassium bases, in an effort to increase the reactivity of the enolate, produced a clean reaction, but the product was the rearranged lactone **20** (Scheme 5). The structures of both lactones were unambiguously determined by NMR spectroscopy using HMBC experiments. A possible pathway for this rearrangement is fragmentation of the initially formed enolate to give an alkoxy ketene, followed by cyclisation to give the alternative lactone, with release of methoxide, which then intercepts the ketene. Presumably, these reactions are reversible and formation of the rearranged product **20** is thermodynamically favoured.



Scheme 5

We then returned to the Michael–Dieckmann domino reaction, but using an enantioenriched substituted furanone **21** (70% ee), which was prepared in two steps, using asymmetric dihydroxylation (Scheme 6).[15] We used racemic diester **7** in the hope that kinetic resolution might be achieved in the reaction with the enantioenriched Michael acceptor. Addition of two equivalents of racemic diester **7** to enantioenriched butenolide **21**, followed by in situ Dieckmann reaction, gave tricyclic product **22** (46%),[16] along with two minor diastereoisomers **23** (10%) and **24** (18%). The three diastereomeric products were separated by flash chromatography and the structure of the major product **22** was confirmed by X-ray crystallography.[17] Its relative stereochemistry is that expected for addition *trans* to the methyl substituent on the furanone, with the same stereochemical preference relative to the chirality centres on the cyclohexane as observed previously. Although there was only a threefold difference in the reactivity of the enantiomers of diester **7**, the ease of preparation of the enantioenriched lactone **21** and the brevity of the route (the longest linear sequence is four steps), make this a very practical synthetic strategy.



Scheme 6

The necessity to invert the configuration at C-4 in intermediate **22** is not expected to cause problems. In order to effect this epimerisation the ketone will be removed and the lactone protected as an acetal.[5b,d,e] Formation of the enolate anion of the *tert*-butyl ester, followed by kinetically controlled protonation of the 'bottom' face of the enolate, *trans* to the fused five-membered ring, will then result in the correct configuration at C-4. Work on the hydroboration of 4-methylene derivatives by Takadoi and Tereshima[5d] supports the belief that protonation will occur from the bottom face, as required.

In conclusion, the combination of two MIRC-type domino reactions leads to a short enantioselective route to tricyclic lactones **22** and **23**, which have the correct stereochemistry and functionality to be useful intermediates for the synthesis of himbacine. The high diastereoselectivity of the Michael reactions with butenolides, and the demonstration that pseudoephedrine is an excellent chiral auxiliary for Michael reactions of acetate, are other noteworthy aspects of this work, that may have wider implications. Efforts to complete the synthesis of himbacine, and of novel analogues, are underway.

Acknowledgment

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(16) Data for compound **22**: white solid; mp 144–146 °C; $[\alpha]_D^{23}$ –6.0 (*c* = 0.85, $CHCl_3$). IR (KBr): 2980, 2924, 2831, 1780, 1719, 1702, 1408, 1334, 1280, 1210, 1160, 1012 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 4.27 (1 H, dq, *J* = 10.3, 5.9 Hz, C^3H), 3.80 (1 H, d, *J* = 8.6 Hz, $C^{9a}H$), 2.66–2.77 (2 H, m, $C^{8a}H$, $C^{3a}H$), 2.54 (1 H, app d, *J* = 4.6 Hz, C^4H), 2.03 (1 H, m, C^8H*H*), 1.77–1.87 (4 H, m, $C^{4a}H$, C^5H*H*, C^6H*H*, C^7H*H*), 1.54 [9 H, s, $C(CH_3)_3$], 1.45 (3 H, d, *J* = 5.9 Hz, C^3HCH_3), 1.34–1.40 (1 H, m, C^5*H*H), 1.26–1.34 (1 H, m, C^8*H*H), 1.15–1.26 (2 H, m, C^6*H*H, C^7*H*H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 203.7 (C^9=O), 171.9 (OC=O), 170.9 (OC=O), 82.4 [*C*$(CH_3)_3$], 77.5 (C^3H), 54.4 ($C^{9a}H$), 48.3 ($C^{3a}H$), 48.0 ($C^{8a}H$), 44.1 (C^4H), 41.0 ($C^{4a}H$), 31.3 (C^5H_2), 28.2 [C(*C*$H_3)_3$], 25.6 (C^7H_2), 25.4 (C^8H_2), 25.0 (C^6H_2), 19.0 [C^3H(*C*H_3)]. HRMS (ESI): *m*/*z* [M^+ + H] calcd for $C_{18}H_{27}O_5$: 323.1858; found: 323.1847.
(17) CCDC 711490 contains the crystallographic data for compound **22**. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallograpic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 (1223)336033; or deposit@ccdc.cam.ac.uk].