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Studies Towards a Postulated Biomimetic Diels-Alder Reaction for the Synthesis of Himgravine[1]

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Abstract: The possible role of an iminium ion mediated Diels-Alder reaction on the biosynthetic pathway to himgravine is discussed. The results of a preliminary investigation of a related oxycarbenium ion mediated Diels-Alder reaction are reported and are in accord with the stereochemistry of the natural product.

The tetracyclic alkaloid himbacine **1**, isolated in 1956 from the bark of the *Galbulimima Baccata* FM Bail[2], has been the source of considerable medicinal interest, initially as an antispasmodic agent[3] and more recently its ability to bind selectively to M2 and M4 muscarinic receptors[4] has led to discussion of its potential role in the treatment of Alzheimer's disease[5]. Taking into account its occurrence with the related unsaturated compound himgravine **2**, which can be simply converted to **1** by hydrogenation[6], and the stereochemistry of the tricyclic portion of **2** we speculated that an *endo*-selective Diels-Alder reaction may be involved in its biosynthesis[7].

In the light of the recent increased interest in himbacine we considered whether such a Diels-Alder reaction would be possible for the synthesis of **1** and **2**. Careful consideration of the established preference of 2-carboxybutadienes to react with electron deficient olefins[8] led to the suggestion of an iminium ion accelerated Diels-Alder of the type shown in Figure 1. This is in accord with our biosynthetic proposal, as the reductive amination of a ketonic precursor[9] is the likely origin of the C-N bonds of the piperidine ring.

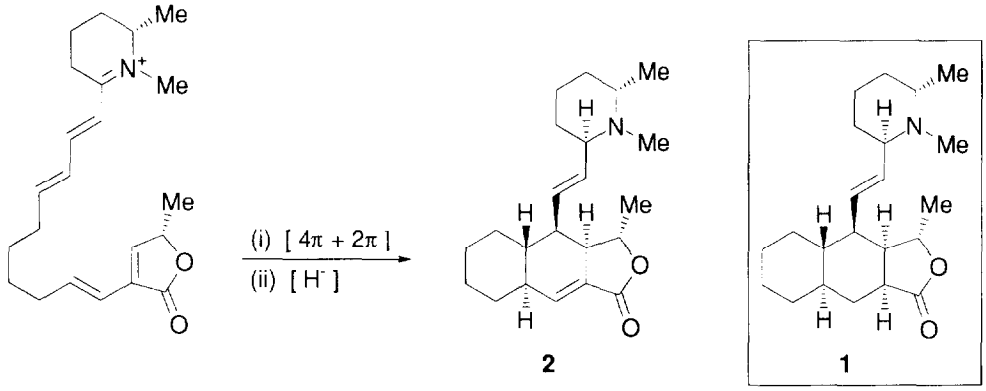
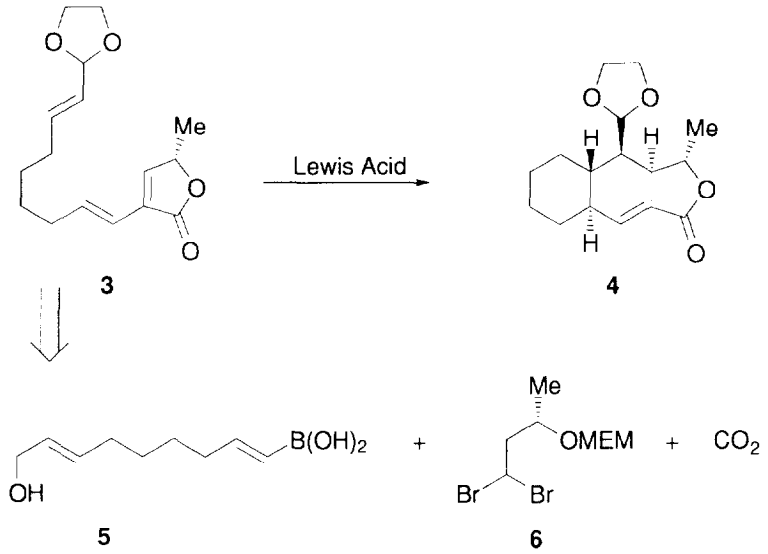
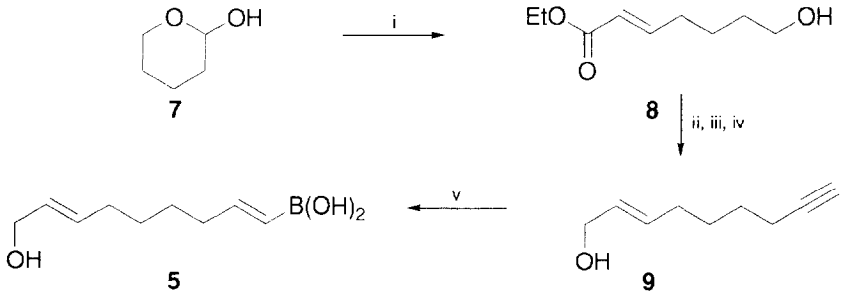


Figure 1

In order to carry out a preliminary evaluation of a Diels-Alder strategy we have carried out an analogous oxycarbenium ion mediated Diels-Alder of **3** to **4**. Consideration of the structure of **3** led to the following key disconnections.



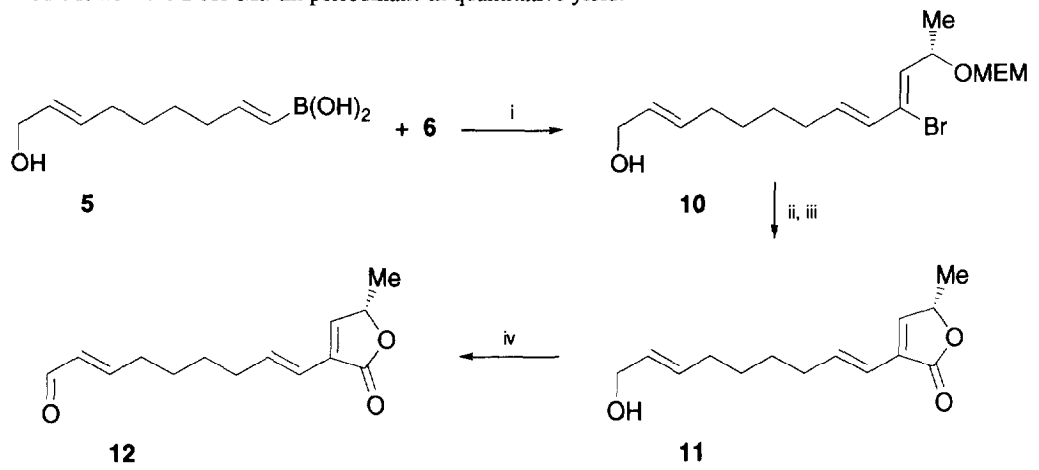
Dibromoolefin **6** was prepared as described by Mahler and Braun[10], while the synthesis of **5** proceeded as shown below. Thus, alcohol **8** was produced by Wittig reaction[11] of 2-hydroxypyran **7** with carboethoxytriphenylphosphorane as a mixture of geometric isomers (10:1; *E*:*Z* ; 89%) which, following tosylation could be separated by careful column chromatography. DIBAL-H reduction of the ester with subsequent displacement of the tosylate by lithium acetylide ethylenediamine complex in DMSO afforded acetylene **9** in 69% yield for the two steps. Hydroboration of **9** with 2.2 equivalents of catechol borane at 80 °C, followed by vigorous shaking with water[12] for 1h then stirring overnight allowed isolation of boronic acid **5** in 63% yield.



Reagents and conditions: **i**. $Ph_3P{=}CHCO_2Et$ (1.05equiv), THF, reflux, 89%, *E*:*Z* 10:1. **ii**. TsCl (3.0equiv), pyridine (2.0equiv), CH_2Cl_2, 86%. **iii**. DIBAL-H (2.2equiv), CH_2Cl_2, -78 °C, 85%. **iv**. LiCCH.eda (2.2equiv), DMSO, 10 °C, 81%. **v**. catechol borane (2.2equiv), 80 °C then H_2O, shake, 63%.

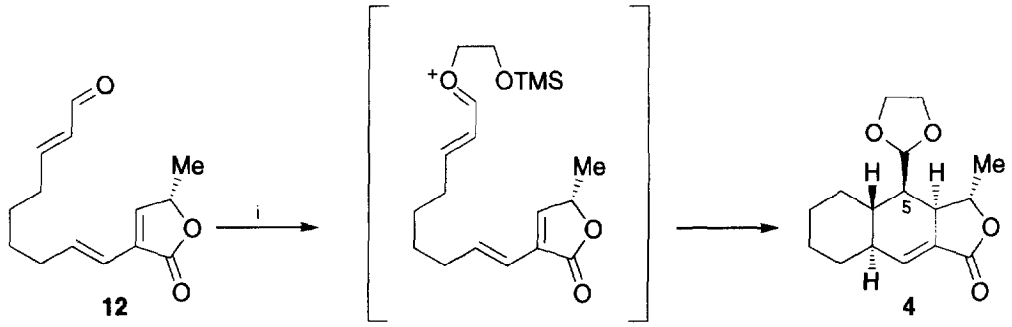
The Suzuki coupling of **5** and **6** could be achieved by refluxing overnight in the presence of $Pd(PPh_3)_4$ (0.1equiv) and K_2CO_3 in THF/MeOH/H_2O in 50% yield. However, use of $Ba(OH)_2$[13] in place of K_2CO_3 gave rise to a dramatic rate acceleration with the reaction being complete in 1h at 20 °C, a yield of 58% being obtained. Following TBDMS protection of the primary alcohol the vinyl bromide was metallated with *sec*-

butyllithium at -78 °C then regiospecifically carboxylated[14] with carbon dioxide. Treatment of the crude acid with pyridinium *para*-toluenesulphonate in ^{t}BuOH effected removal of both protecting groups with concomitant lactonisation to give butenolide **11** in 69% overall yield. Oxidation to the aldehyde **12** was carried out with the Dess-Martin periodinane in quantitative yield.



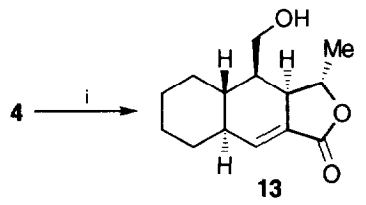
Reagents and conditions: i. $Pd(PPh_3)_4$ (0.25equiv), $Ba(OH)_2$ (3.0equiv), THF/MeOH/H_2O, 20 °C, 1h, 58%..ii. TBDMSCl (2.0equiv), Imidazole (4.0equiv), THF:CH_2Cl_2 4:1, 85%. iii. ^{s}BuLi (2.6equiv), CO_2, THF, -78 °C, then PPTS (10.0equiv), ^{t}BuOH, reflux, 69%. iv. Dess-Martin Reagent (1.2equiv), CH_2Cl_2, 100%.

In order to generate the desired oxycarbenium ion we employed the Gassman methodology[15]. To allow the Diels-Alder reaction to be carried out at the lowest possible temperature we generated the acetal **3** at -78 °C using the Noyori conditions[16]. On warming the reaction mixture to -20 °C cycloaddition was seen to occur over a period of 2h to afford the desired tricycle as a 40:1 ratio of diastereomers in 53% yield[17]. In control experiments the acetal **3** was isolated then resubjected to trimethylsilyl triflate to give **4**, while treatment of the aldehyde **12** with trimethylsilyl triflate gave a 20% yield of the cycloadduct as a mixture of 3 isomers, indicating that it is a cation derived from the acetal which is responsible for the cycloaddition reaction.



Reagents and conditions: i. $TMSOCH_2CH_2OTMS$ (3.0equiv), TMSOTf (1.0equiv), CH_2Cl_2, -78 °C 3h then -20 °C 2h, 53%.

Attempted hydrolytic removal of the acetal was compromised by partial epimerisation at C5 of the aldehyde in the later stages of the reaction. Thus we allowed the hydrolysis reaction to proceed to *ca.* 75% completion then treated the crude mixture with sodium borohydride to obtain the crystalline alcohol **13** without detectable epimerisation. Single crystals of **13** were studied by X-ray crystallography (Figure 2), the resultant structure being in accord with the postulated *endo* selective Diels-Alder reaction.



Reagents and conditions. I. TsOH (3.0equiv), CH_3COCH_3/H_2O, reflux, 5h, then $NaBH_4$ (6.0equiv), EtOH, 60%.

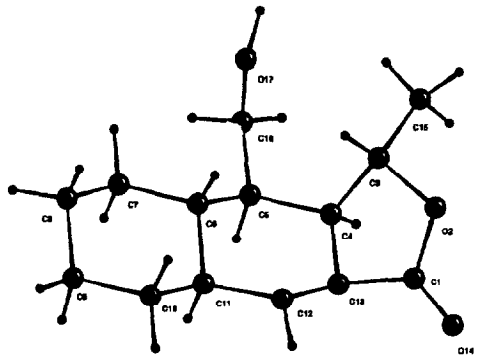


Figure 2

We are currently examining an iminium ion Diels-Alder reaction and alternative methods of constructing the vinyl butenolide.

NOTE ADDED IN PROOF An analogous route to Himbacine has recently been reported; Hart, D. J.; Wu, W-L.; Kozikowski, A. P. *J. Am. Chem. Soc.* **1995**, *117*, 9369.

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17. Due to the small quantities of the minor isomer we were unable to determine its stereochemistry.

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