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The Bromopentadienyl Acrylate Approach to Himbacine

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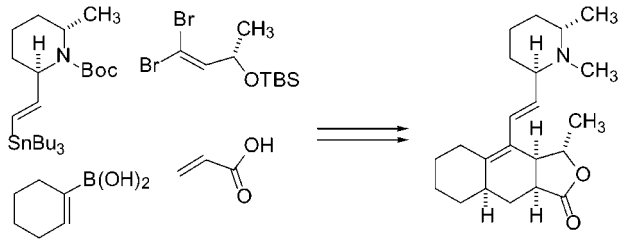
ABSTRACT



The syntheses of 4,4a-didehydrohimbacine and 4,4a-didehydrohimandravine are presented. Key steps include an intramolecular Diels–Alder reaction of a bromopentadienyl acrylate and Suzuki–Miyaura and Stille coupling reactions.

The structures of himbacine (**1**) and himandravine (**2**) (Figure 1) were reported by Pinhey, Ritchie, and Taylor in 1961.[1] These alkaloids were extracted from *Galbulimima baccata*, a species of tree found in Northern Australia and Papua New Guinea. Himbacine was subsequently found to exhibit strong, selective binding to muscarinic receptors of the M_2 subtype.[2] Speculation that selective presynaptic muscarinic receptor antagonists might find application in the treatment of neurodegenerative disorders such as Alzheimer's disease[3] has provoked extensive synthetic efforts toward *Galbulimima* alkaloids by many groups.[4−8]

Reported synthetic work toward himbacine to date involves the construction of ring B by way of a Diels−Alder reaction (Figure 1). Of all possible Diels−Alder-based disconnections that can be applied to the himbacine framework, a ring B

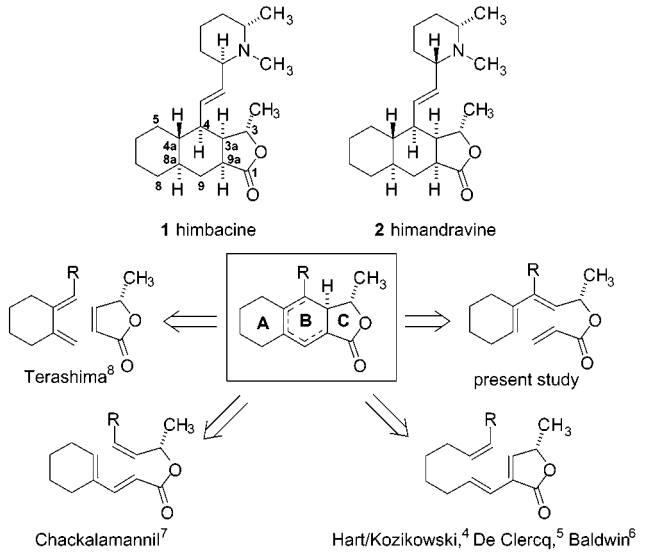


Figure 1. Synthetic approaches to himbacine involving a Diels−Alder reaction to construct the B-ring.

[†] To whom correspondence should be addressed regarding the crystal structure.

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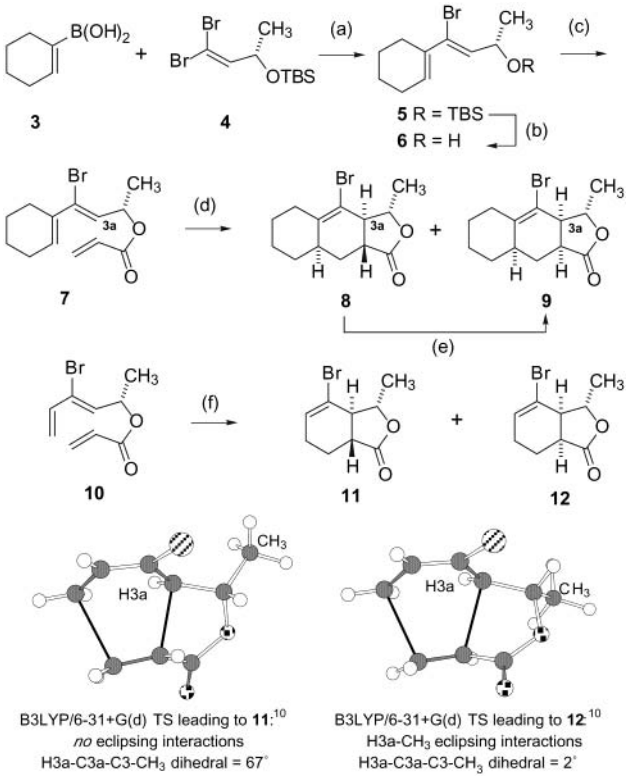
disconnection of 4,4a-didehydrohimbacine appeared to us as the most synthetically attractive, since such a disconnection reveals an intramolecular Diels−Alder (IMDA) reaction involving an acrylate ester derivative of either a [3]-dendralene[9] or a bromodiene. We recently reported the results of a joint synthetic-computational investigation into the feasibility of the latter approach for the preparation of himbacine,[10] and herein we disclose an extension of this work to 4,4a-didehydrohimbacine and 4,4a-didehydrohimandravine.[11] The appearance of a paper by De Clercq and co-workers[12] prompts this preliminary report.

Scheme 1. Synthesis of Bromotricycle **9**[a]

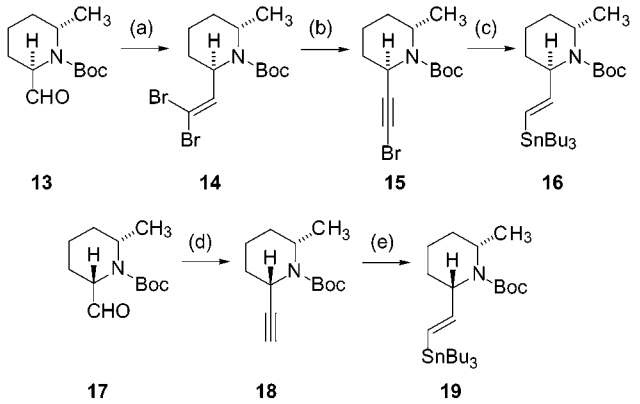


[a] (a) $Pd(PPh_3)_4$ (0.10 equiv), $Ba(OH)_2$ (1.8 equiv), THF−MeOH−H_2O, 25 °C, 15 h, 70%; (b) Bu_4NF (1.5 equiv), THF, 25 °C, 3 h, 94%; (c) CH_2═CHCOCl (1.6 equiv), Et_3N (2.1 equiv), CH_2Cl_2, 25 °C, 0.5 h, 81%; (d) PhCl ($[\mathbf{7}]_{initial}$ = 10 mM), BHT (0.05 equiv), reflux, 112 h, 81%; **8**:**9** = 86:14; (e) DBU (1.1 equiv), CH_2Cl_2, reflux, 16 h, 97%; (f)[10] PhCl ($[\mathbf{10}]_{initial}$ = 10 mM), BHT (0.05 equiv), reflux, 156 h, 83%; **11**:**12** = 81:19.

Our synthesis begins (Scheme 1) with a Suzuki−Miyaura coupling between (*S*)-lactic acid derived dibromoalkene **4**[13] and cyclohexene-1-boronic acid **3**,[14] which, in line with earlier observations by Roush,[15] gave the *Z*-bromodiene **5** in high selectivity. Deprotection of the silyl ether and esterification of the resulting bromodienol with acryloyl chloride gave IMDA precursor **7**. Dilute (10 mM) solutions of **7** in chlorobenzene undergo a highly stereoselective IMDA reaction upon heating to 132 °C for 5 days at ambient pressure to afford two cycloadducts **8** and **9** in an 86:14 ratio. Both cycloadducts possess the C3,C3a-*anti*-stereochemistry required for himbacine. The stereochemical outcome of the IMDA reaction of **7** mirrors that seen with the acyclic precursor **10**.[10] This close similarity in reaction outcome strongly suggests that the same stereocontrolling influences are at play. Thus, π-diastereofacial selectivity in these reactions is dominated by the development of destabilizing ^{1,3}A strain in transition states leading to the unseen C3,C3a-*syn* isomers. Of the two observed C3,C3a-*anti* products, *trans*-fused *exo*-isomer **8** (cf. **11**) is preferred over its *cis*-fused *endo*-congener **9** (cf. **12**) as a result of the presence of a destabilizing eclipsing interaction between the CH_3 group and H3a in the transition state leading to the latter. The major cycloaddition product **8** is readily converted into the required *cis*-fused isomer **9** in essentially quantitative yield on exposure to DBU.[10]

The D-ring-appended vinylstannane side chains required for himbacine and himandravine, **16** and **19**, respectively (Scheme 2), were prepared from the known N-Boc piperidine aldehydes **13**[16] and **17**[7c,16a] through related two- and three-step sequences.[17] In the case of the 2,5-*trans* diastereomer **16**, modified Corey−Fuchs reaction[18] of aldehyde **13** gave

Scheme 2. Synthesis of D-Ring-Appended Vinyl Stannanes[a]



[a] (a) $(Ph_3PCHBr_2)Br$ (2.0 equiv), *t*-BuOK (1.9 equiv), THF, RT, 10 min, 81%; (b) LiHMDS (1.2 equiv), THF, −78 °C − RT, 7 h, 90%; (c) Bu_3SnH (2.2 equiv), Pd_2dba_3 (0.005 equiv), PPh_3 (0.04 equiv), THF, RT, 6 h, 77%; (d) $(Ph_3PCHBr_2)Br$ (2.0 equiv), *t*-BuOK (1.9 equiv), THF, RT, 7 h, then *n*-BuLi (5.0 equiv), −78 °C, 10 min, 78%; (e) Bu_3SnH (1.1 equiv), AIBN (0.05 equiv), PhH, reflux, 11 h, 61%.

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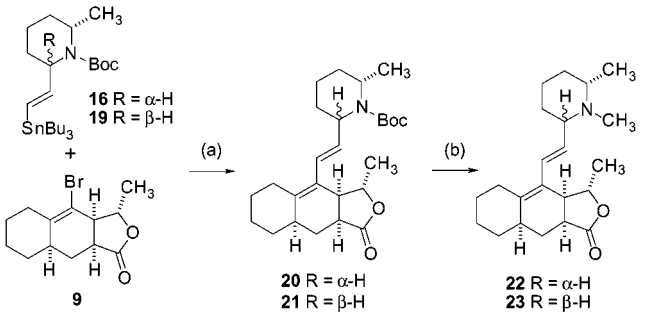
Scheme 3. Synthesis of 4,4a-Didehydrohimbacine **22** and 4,4a-Didehydrohimandravine **23**[a]



[a] (a) $Pd(PPh_3)_4$ (0.20 equiv), CuCl (5.0 equiv). LiCl (6.0 equiv), DMSO, 60 °C, 32 h, 73% for R = α-H; 65% for R = *β*-H; (b) CF_3COOH (80 equiv), CH_2Cl_2, RT, 10 min, then CH_2O (17 equiv), $NaBH_3CN$ (6 equiv), CH_3CN, RT, 16 h, 65% for R = α-H; 60% for R = *β*-H.

the 1,1-dibromoalkene **14**, which was converted to the *E*-vinylstannane **16** via the 1-bromoalkyne **15** according to Pattenden's hydrostannylation−reductive debromination protocol.[19] Interestingly, better yields were obtained in the 2,5-*cis* series by adopting a one-pot Corey−Fuchs reaction−dehydrobromination−debromination sequence[18] (**17** → **18**) followed by radical hydrostannylation (**18** → **19**).

Cuprous chloride accelerated Stille coupling of vinylstannanes **16** and **19** with bromotricycle **9** proceeded in 73% and 65% yields under conditions reported by Corey and coworkers (Scheme 3).[20]

Deprotection and reductive methylation of the tetracyclic products **20** and **21** gave 4,4a-didehydrohimbacine **22** and 4,4a-didehydrohimandravine **23** in overall yields of 65% and 60%, respectively. The structure of the latter was confirmed by single-crystal X-ray analysis (Figure 2).[21]

In summary, a short and modular approach to didehydro analogues of biologically important *Galbulimima* alkaloids has been developed. Current efforts involve the application of this general strategy to the synthesis of himbacine.

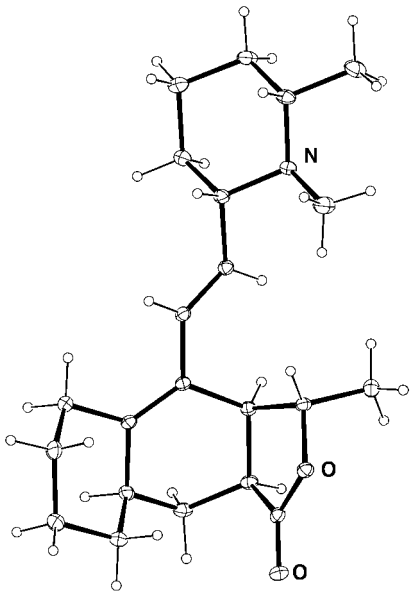


Figure 2. ORTEP diagram of 4,4a-didehydrohimandravine **23**.

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Supporting Information Available: Experimental procedures and product characterization data for key steps (**3** + **4** → **5**; **7** → **8** + **9**; **16** + **9** → **20**; **20** → **22**), ^1H and ^{13}C NMR spectra of all new compounds, and X-ray crystallographic details for 4,4a-didehydrohimandravine **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) See Supporting Information for full details.