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Synthesis of the Himandrine Skeleton

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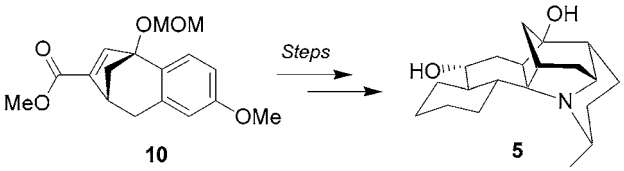
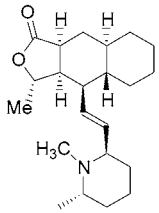
ABSTRACT



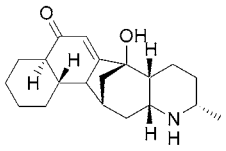
10 **5**

The hexacyclic himandrine skeleton 5, which is present in the most complex alkaloids of the tropical rain forest tree *Galbulimima belgraveana*, has been prepared for the first time. The synthesis begins from the known [3.2.1]benzobicyclooctene intermediate 10. Key steps include a Diels–Alder cycloaddition, Curtius rearrangement, Birch reduction, an intramolecular nucleophilic amination, and a palladium-mediated alkene amination.

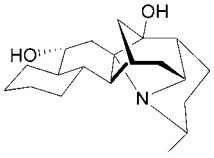
Galbulimima belgraveana is a tropical rainforest tree endemic to Papua New Guinea and Northern Queensland, Australia, and the sole remaining species of the relic family Himantandraceae. The bark has yielded a unique group of 28 anticholinergic[1] alkaloids that may be divided into four distinct classes, typified by himbacine (**1**), GB 13 (**2**), himgaline (**3**) and himandrine (**4**).[2]



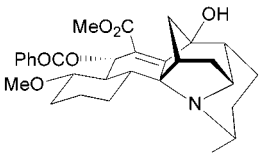
himbacine (**1**)



GB 13 (**2**)

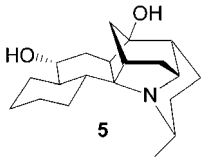


himgaline (**3**)



himandrine (**4**)

Himbacine (**1**), a potent muscarinic antagonist, and its congeners have been the focus of considerable synthetic interest and have been prepared by a number of approaches,[3] while the total synthesis of (±)-GB 13 (from which himgaline (**3**) may be prepared by conjugate addition of the nitrogen atom to the enone moiety) was disclosed by us last year.[4] We now report the successful assembly of the hexacyclic amine **5**, which may serve either as an advanced intermediate or as a model for the construction of the alkaloids of the himandrine group (15 in number).



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The pivotal reaction in the construction of GB 13 (**2**) had been the [4+2] cycloaddition of the unsaturated nitrile **6** and diene **7**, Scheme 1. The nitrile substituent in the adduct **8** was subsequently deleted, but for the present objective we identified an opportunity to attach an amino substituent to the decalin moiety.

Whereas the himgaline (**3**) skeleton is readily accessible from GB 13 (**2**), the closely related skeleton of himandrine

(1) Collins, D. J.; Culvenor, C. C. J.; Lamberton, J. A.; Loder, J. W.; Price, J. R. *Plants for medicines: a chemical and pharmacological survey of plants in the Australian region*; CSIRO Publications: Melbourne, Australia, 1990.

(2) The absolute stereochemistry of **4** has been assumed to be antipodal to this structure. A recent X-ray structure of himandrine hydrobromide has established that the correct configuration is as shown (A. C. Willis, unpublished results).

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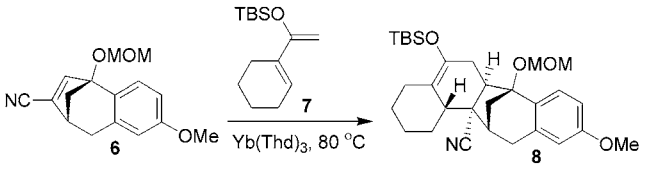
Scheme 1. Endo Diels−Alder Cycloaddition Used during the Synthesis of GB 13



(**4**) is considerably more strained and so we believed that it would be essential to attach the nitrogen atom to the decalin moiety at an earlier stage. Thus, it was envisaged that the ester analogue of nitrile **6** would, after hydrolysis, give a carboxylic acid that could be converted to an isocyanate via a Curtius rearrangement. Subsequently, a Birch reduction could be expected to liberate the latent functionality required to elaborate the remaining rings as outlined in Figure 1 and rendered to practice in Schemes 2−4.

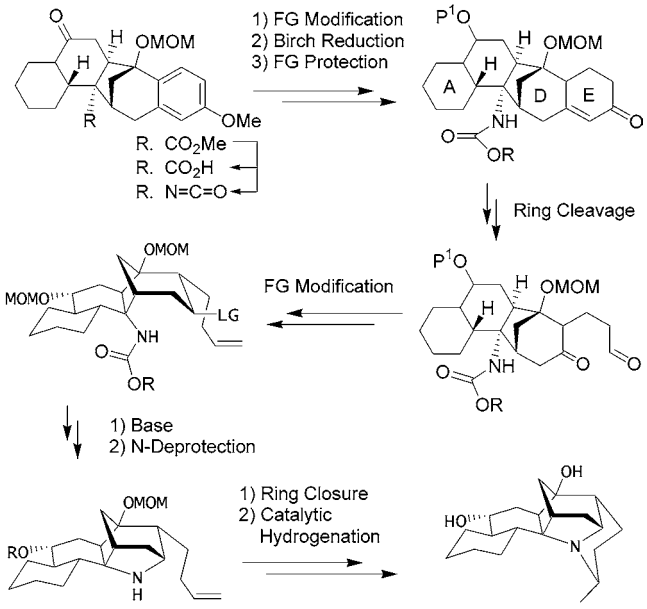


Figure 1. Synthetic plan.

Similarly to the synthesis of GB 13 (**2**), diazoketone **9** was submitted to a photo-Wolff rearrangement, but this time in the presence of methanol, affording a ring-contracted methyl ester. The α,β-unsaturated derivative **10** was synthesized by selenation of the derived trimethylsilylketene acetal,[5] followed by oxidation of the resulting selenide with MCPBA in DCM at −78 °C.

Cycloaddition of the unsaturated ester and diene **7**[6] followed by enol ether hydrolysis furnished **11** as a single diastereomer in fair yield (ca. 65%) along with recovered **10** (ca. 25%). The stereoselectivity in the cycloaddition was presumed to have arisen from an endo transition state with the diene approaching the more exposed upper face of the dienophile, as was established for the corresponding nitrile **8**.[4]

The ester carbonyl function of **11** lying on the hindered concave face of the molecule is resistant to aqueous alkaline hydrolysis, but conversion to the carboxylic acid **12** was accomplished in excellent yield by thiolate-mediated cleavage,[7] which was accompanied by isomerization to the desired *trans*-decalone structure. Next, the acyl azide was made in a one-pot synthesis in good yield. The protocol that we used had been reported to afford carbamoyl azides,[8] but in this case the different outcome is presumably due to steric hindrance. Heating the acyl azide in toluene at reflux furnished the corresponding isocyanate in quantitative yield, reaction progress being monitored by the disappearance of ν_{as}(N═N═N) at 2135 cm^{-1} and the appearance of ν_{as}(N═C═O) at 2266 cm^{-1} in IR spectra. Stirring the isocyanate overnight in methanol containing a catalytic amount of sodium methoxide afforded the methyl carbamate **13**.

With the protected amine function in place, we were now in a position to attempt the critical dissolving metal reduction of the anisole moiety. The Birch reduction not only reduced the aromatic ring, but also reduced the decalone functionality with complete diastereoselectivity, while the carbamate moiety remained intact. Hydrolysis of the resultant methyl enol ether was carried out in a one-pot procedure after evaporation of ammonia to give the derived β,γ-enone-secondary alcohol, which was protected as a MOM ether, and isomerized to the α,β-unsaturated ketone **14** under acidic conditions in moderate yield.

We had planned to subject the epoxide derived from ketone **14** to an Eschenmoser fragmentation,[9] as reported for the synthesis of alkaloid GB 13,[4] but when this approach failed we resorted to the multistep procedure outlined in Scheme 3. Oxidative cleavage of the E ring was accomplished in a three-step sequence that began with the selective 1,2 reduction[10] of **14** with 9-BBN in THF, giving a mixture of diastereomeric allylic alcohols. Catalytic dihydroxylation[11] in this case failed, but oxidation with a stoichiometric quantity of osmium tetroxide gave the isomeric triol **15** in

(3) (a) Wong, L. S. M.; Sherburn, M. S. *Org. Lett.* **2003**, *5*, 3603−3606. (b) Takadoi, M.; Katoh, T.; Ishiwata, A.; Terashima, S. *Tetrahedron* **2002**, *58*, 9903−9923. (c) Takadoi, M.; Terashima, S. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2871−2873. (d) Hofman, S.; Gao, L.-J.; Van Dingenen, H.; Hosten, N. G. C.; Van Haver, D.; De Clercq, P. J.; Milanesio, M.; Viterbo, D. *Eur. J. Org. Chem.* **2001**, 2851−2860. (e) Chackalamannil, S.; Davies, R. J.; Wang, Y.; Asberom, T.; Doller, D.; Wong, J.; Leone, D.; McPhail, A. T. *J. Org. Chem.* **1999**, *64*, 1932−1940. (f) Hofman, S.; De Baecke, G.; Kenda, B.; De Clercq, P. J. *Synthesis* **1998**, 479−489. (g) Hart, D. J.; Li, J.; Wu, W.-L.; Kozikowski, A. P. *J. Org. Chem.* **1997**, *62*, 5023−5033. (h) Chackalamannil, S.; Davies, R. J.; Asberom, T.; Doller, D.; Leone, D. *J. Am. Chem. Soc.* **1996**, *118*, 9812−9813. (i) De Baecke, G.; De Clercq, P. J. *Tetrahedron Lett.* **1995**, *36*, 7515−7518.

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(6) Ireland, R. E.; Thompson, W. J.; Mandel, N. S.; Mandel, G. S. *J. Org. Chem.* **1979**, *44*, 3583−3585.

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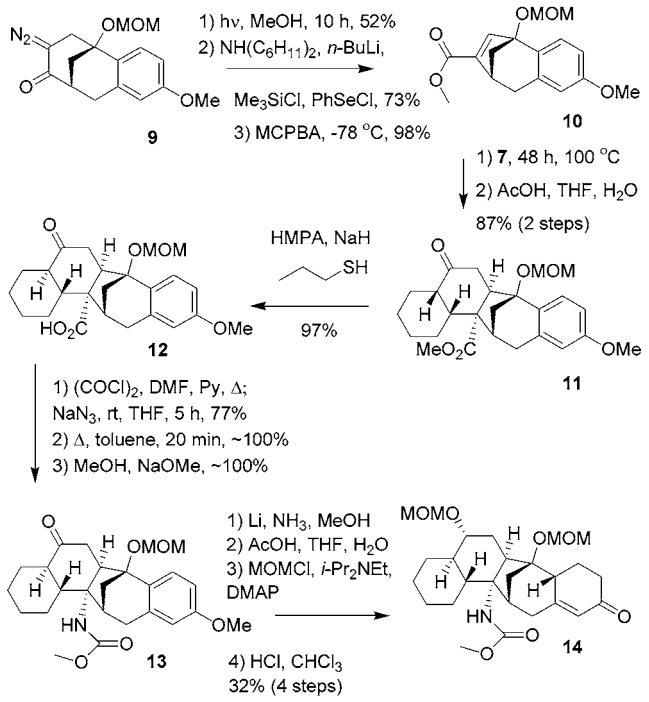
(8) Affandi, H.; Bayquen, A. V.; Read, R. W. *Tetrahedron Lett.* **1994**, *35*, 2729−2732.

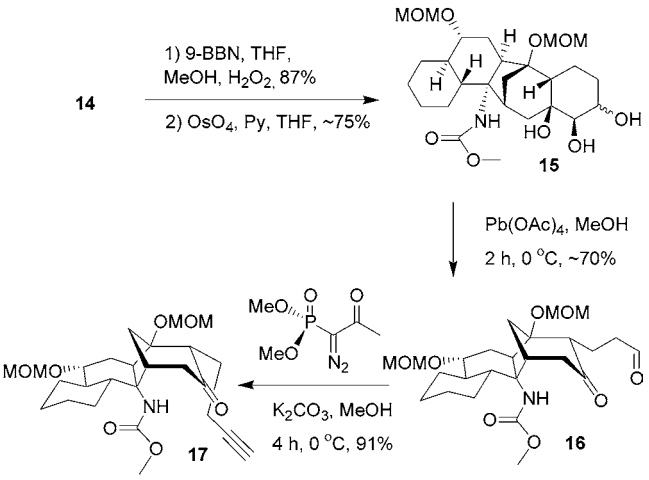
(9) Eschenmoser, A.; Felix, D.; Ohloff, G. *Helv. Chim. Acta* **1967**, 708−713.

(10) Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 1197−1201.

Scheme 2. Synthesis of Pentacyclic Carbamate Intermediate



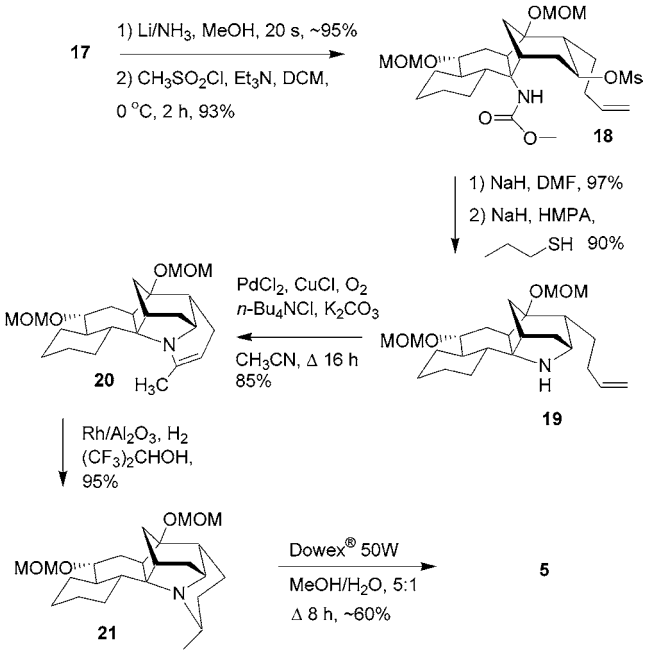
Scheme 3. Ring Cleavage and Homologation



fair yield. Ring cleavage of the triol gave the keto-aldehyde **16**, which was immediately converted into the corresponding alkyne[12] containing all of the requisite carbon atoms to construct the remaining fused pyrrolidine and piperidine rings. Purification of **17** after four steps gave an acceptable yield of ca. 45%.

We envisaged that the equatorial sulfonate ester **18** derived from ketone **17** would serve as a suitable leaving group in an intramolecular S_N2-like amination, but unfortunately all attempts to reduce the ketone with metal hydrides gave predominantly the undesired axial epimer. However, dissolving metal reduction of ketone **17** proceeded in excellent yield to give the desired β-carbinol as a single diastereomer (Scheme 4).[13] Concomitant reduction of the alkyne group

Scheme 4. Pyrrolidine and Piperidine Ring Closure



to give the terminal alkene is unavoidable under these conditions, while the use of methanol as the proton source is necessary to avoid transesterification of the carbamate group. Ring closure to form the pyrrolidine moiety was accomplished in excellent yield in a two-step sequence by conversion of the alcohol to its methanesulfonate ester followed by treatment with sodium hydride in DMF. Hydroxide-mediated methyl carbamate deprotection is notoriously difficult,[14] and predictably failed to give useful yields. However, nucleophilic cleavage under thiolate-mediated conditions[7] gave the carbamic acid and thence the free amine **19** in almost quantitative yield.

With five of the six rings of the target now completed, we were in a position to attempt the final ring closure. Our strategy hinged on the idea that we might be able to aminate the double bond of **19** in an oxidative Wacker-like process to give an enamine, which could then be hydrogenated. We expected to obtain a significant facial bias for the reduction in favor of our target compound due to the steric shielding of the endo face of the alkene. Traditional methods of oxidative amination[15] which call for the use of $PdCl_2$, CuCl, and O_2 in the presence of HCl failed to give acceptable

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(15) Pugin, B.; Venanzi, L. M. *J. Am. Chem. Soc.* **1983**, *105*, 6877−6881.

yields, while prolonged heating in the presence of stoichiometric quantities of $PdCl_2$ also gave poor yields of enamine **20** (ca. 20%). However, a reagent combination for the oxidative amination with *n*-Bu_4NCl, K_2CO_3, CuCl, O_2, and 20 mol % of $PdCl_2$ in acetonitrile was eventually found to give an excellent yield of the desired enamine **20**. Similar reagent combinations have been used by Jeffery[16] to effect Heck-type reactions.

Given the bridgehead nature of the amine function in **20**, the classical hydride reduction of a protonated iminium species was not an available option and unfortunately hydrogenation proved to be much more difficult than expected. Several catalyst systems were tried, and whereas palladium on carbon at 70 psi of H_2 gave a low yield of an *endo*- and *exo*-methyl epimeric mixture, the attempted reduction over platinum or iridium catalysts did not yield any reduced product at all. However, an unusual catalyst/solvent combination, namely Rh−Al_2O_3 in 1,1,1,3,3,3-hexafluoro-2-propanol,[17] was found to give a near-quantitative yield of the saturated product as a 5:1 mixture of epimers in favor of the desired *endo*-methyl diastereomer **21**.

Acid-catalyzed removal of the MOM protecting groups was carried out following a mild procedure[18] and gave the tertiary amine diol **5** as a white solid. Confirmation of the relative stereochemistry was deduced from 2D nOe NMR spectra, the two most significant correlations being illustrated in Figure 2.

Future work will be directed toward the elaboration of the decalin ring system to introduce the unsaturated methyl ester and various carbinol substituents, thereby giving access to the alkaloids of the himandrine (**4**) type. We also plan to modify the general strategy to achieve an enantioselective preparation of **5** as mentioned in our previous paper.[4]

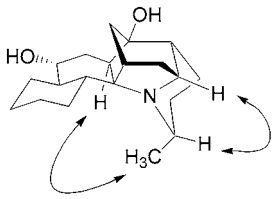

Figure 2. Significant nOe correlations.

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Supporting Information Available: Experimental procedures with full characterization for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.g.

OL036308N

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