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The Total Synthesis of the Galbulimima Alkaloid GB 13

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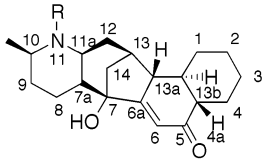
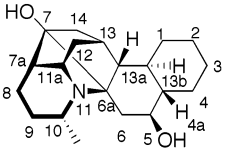
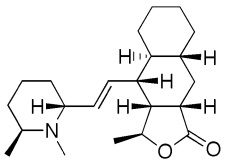
Structures **1**−**4** are representative of a family of 28 unusual alkaloids isolated from the bark of the Northern Australia and Papua New Guinea rain forest tree, *Galbulimima belgraveana*,[1−3] the sole surviving species from the relic family Himantandraceae. The bark of *G. belgraveana* was used as a medicinal substance by some Papua New Guinean tribes for a variety of purposes.[4] Considerable interest is presently centered on himbacine (**3**), a potent muscarinic antagonist and a lead compound in the search for drugs to treat Alzheimer's disease. As a consequence three total syntheses have been completed recently. [5]



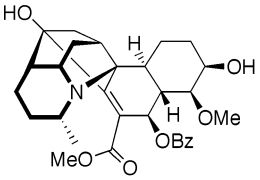
R= H alkaloid G.B.13 **1**
R= Ac **1a**



himgaline **2**



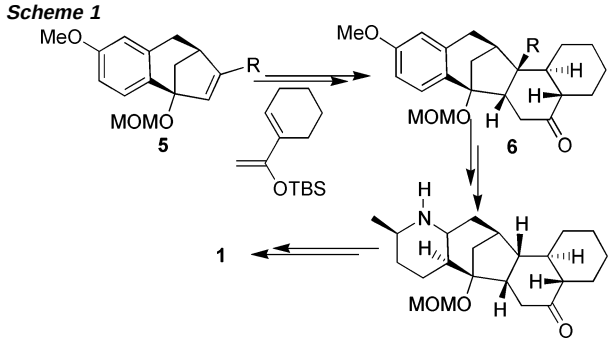
himbacine **3**



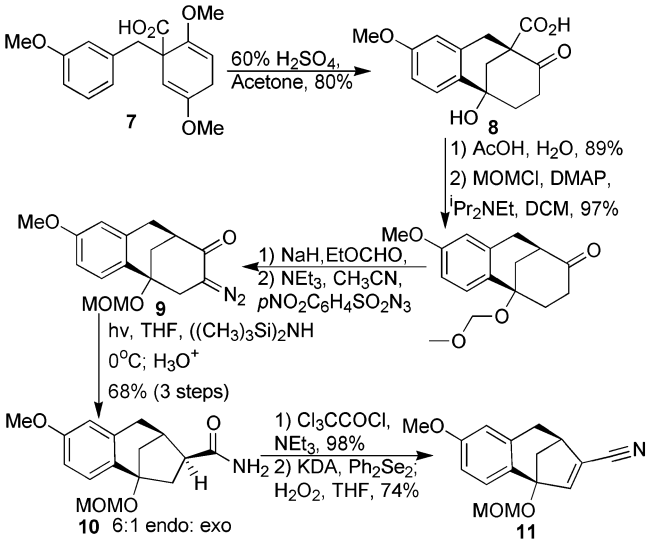
himandridine **4**

Our own interests have been concerned with the assembly of the more complex alkaloids from this series, exemplified by **1**, **2**, and **4**, and in this communication we describe the first total synthesis of (±)-alkaloid GB 13 (**1**) by a strategy that should also allow access to **2** and **4** as well. Our approach is outlined in Scheme 1 and is based on the annelation of the tricyclic intermediate **5**, with subsequent elaboration of the benzenoid moiety in the adduct **6** to afford the piperidine ring of the target structure.

Scheme 1



Scheme 2



A suitable analogue of **5** could be readily assembled following the route outlined in Scheme 2. Thus, 2-(3-methoxybenzyl)-1,3-dienol ether **7** could be synthesized in excellent yield and on a large scale as reported previously.[6]

This material could be cyclized to the [3.3.1]bicyclononane **8** by treatment with 60% v/v aqueous sulfuric acid at 0 °C. After decarboxylation and protection of the hydroxyl as its MOM ether, a Wolff ring contraction to a suitable analogue of **5** was explored. The required diazoketone **9** was synthesized using the two-step Regitz procedure[7] and then subjected to photolysis in the presence of hexamethyldisilazane to give amide **10** after an acidic workup. Amide **10** could be dehydrated to the corresponding nitrile in high yield by treatment with trichloroacetyl chloride. This nitrile was resistant to deprotonation with most common bases, but potassium diisopropyl amide was effective.[8] Trapping of the anion with diphenyl diselenide gave the corresponding α-phenylseleno nitrile, which, after oxidation and elimination, gave alkene **11**.

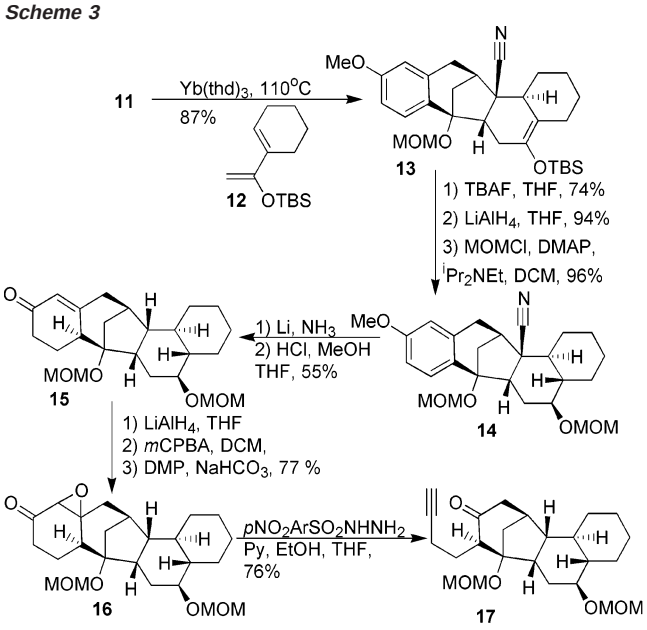
Alkene **11** was a suitable dienophile for a Diels−Alder reaction with diene **12**, as shown in Scheme 3. The desired reaction leading to the *endo* adduct was most effectively catalyzed by ytterbium tris(2,2,6,6-tetramethyl-3,5-heptane-dionate). Hydrolysis of the resulting silyl enol ether **13** and reduction of the ketone and protection of the corresponding alcohol as its MOM ether gave material suitable for the synthesis of the piperidine ring found in alkaloid GB 13 (**1**).

Treatment of compound **14** with lithium metal in ammonia for 2 h resulted in quantitative reductive decyanation of the superfluous cyano group on C6a,[9] and then addition of ethanol resulted in Birch reduction of the aromatic ring. The resulting methyl enol ether was converted to enone **15**[10] by treatment with a catalytic amount of 10 M HCl in methanol.

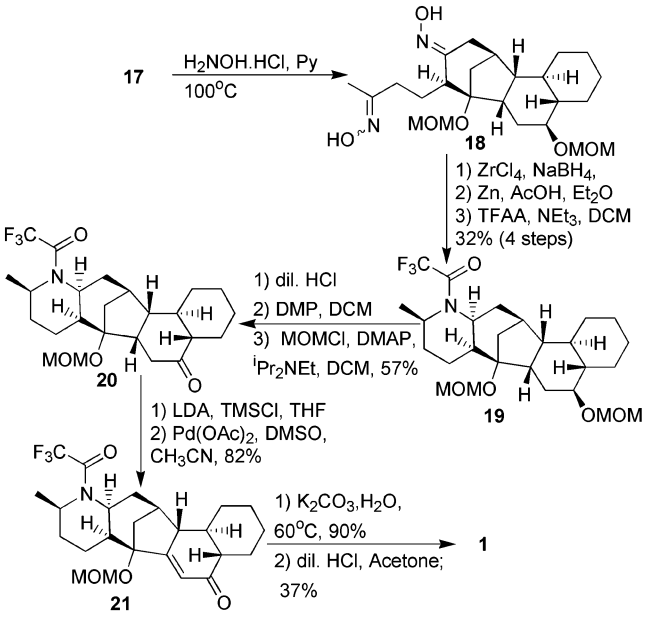
An Eschenmoser fragmentation was planned next, but enone **15** proved to be resistant to direct epoxidation; however, a sequence involving reduction to the allylic alcohol, epoxidation, and then oxidation gave the epoxy ketone **16** in good yield. Treatment of the epoxy ketone under traditional Eschenmoser fragmentation conditions gave only low yields of the desired alkynyl ketone **17**,[11] but this result could be improved significantly by the use of the

10.1021/ja029725o CCC: $25.00

Scheme 3



Scheme 4



p-nitrobenzenesulfonylhydrazide in place of toluenesulfonylhydrazide.

An attempt at a reductive amination of compound **17** was unsuccessful, but treatment of the alkynyl ketone with an excess of hydroxylamine in pyridine gave the bis-oxime **18**,[12] as shown in Scheme 4. A reductive cyclization was effected on this bis-oxime by treatment with zirconium tetrachloride and sodium borohydride to give an *N*-hydroxypiperidine compound.[13] NOE experiments on the *N*-acetoxy derivative confirmed that the major product from this reaction had the desired all-*cis*-piperidine ring stereochemistry required for the synthesis of alkaloid GB 13. Reduction of the hydroxylamine and protection of the resulting amine as its trifluoroacetamide gave the desired compound **19** as the major product.

Heating with dilute hydrochloric acid effected deprotection of the two MOM ether functions, and the C5 hydroxyl group could then be oxidized by treatment with Dess−Martin periodinane, and the 7-hydroxy group was reprotected as its MOM ether. Enolization of the ketone **20**, with subsequent trapping of the enolate with TMSCl, gave the 5,6-silyl enol ether, which could be subjected to Saegusa dehydrosilylation conditions[14] to give the protected (±)-GB 13 derivative **21**.

Gentle heating with aqueous potassium carbonate effected removal of the trifluoroacetamide protecting group, and then warmingwith dilute hydrochloric acid resulted in removal of the MOM ether function. The material from this sequence gave ^{1}H and ^{13}C NMR and mass spectral data matching those of naturally occurring GB 13 (**1**).

This communication has described the first total synthesis of (±)-alkaloid GB 13[15] and provides yet another example of the utility of benzenoid synthons for the synthesis of complex polycyclic natural products.[16] A special feature of this synthetic strategy is the use of the nitrile function for activation and regiocontrol in the Diels−Alder reaction, followed by its efficient removal using dissolving metal conditions. This work also lays a foundation for the preparation of himgaline (**2**)[17] and himandridine (**4**) and its analogues by a modification of this synthetic sequence.[18]

Acknowledgment. We are grateful to Professor W. C. Taylor for an authentic sample of GB 13.

Supporting Information Available: Experimental procedures and characterization data for all novel compounds reported (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Intramolecular Michael addition of the nitrogen to the enone, followed by reduction of the ketone should lead to himgaline **2** (cf. refs 3d and 3e).
(18) By employing the equivalent ester analogous to the nitrile **11**, we envisage a subsequent Curtius rearrangement to establish the N−C6a bond in a precursor to **4**.

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