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Total Synthesis of Alkaloid (±)-G. B. 13 Using a Rh(I)-Catalyzed Ketone Hydroarylation and Late-Stage Pyridine Reduction

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The *Galbulimima* alkaloids encompass 28 structurally intricate natural products isolated from the tree *Galbulimima belgraveana*, which is native to the rain forests of Northern Australia and Papua New Guinea.[1] The discovery that himbacine (**1**, Figure 1) acts as a muscarinic antagonist[2] and related structures as antithrombotic agents[3] has led to pronounced interest in the *Galbulimima* alkaloids as potential pharmacological agents. Because of their biological activity and inspiring architecture, these natural products have garnered considerable interest from the synthetic community. A number of syntheses of himbacine (**1**) have been reported,[4] and more recently, the groups of Mander,[5] Movassaghi,[6] Chackalamannil,[7] and Evans[8] have completed syntheses of alkaloid G. B. 13 (**2**). Furthermore, two of these groups[7,8] have demonstrated that **2** is readily converted to himgaline (**3**). We report herein a concise total synthesis of alkaloid G. B. 13, which is enabled by a late-stage introduction of the piperidine moiety from a pyridine precursor and an unprecedented 1,2-addition of an aryl boronic ester into a ketone group.

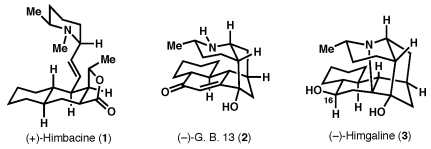
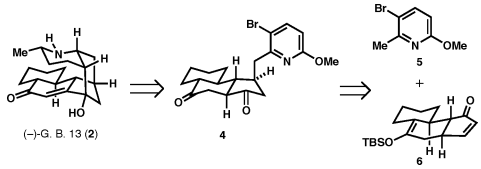


Figure 1. Selected *Galbulimima* alkaloids.

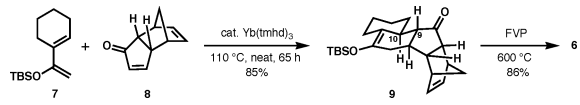
Retrosynthetically, we envisioned that the pentacyclic framework of **2** (Scheme 1) could arise from a late-stage manipulation of bromopyridine **4**. In view of the stereochemical and structural complexity of **2**, this powerful disconnection of the natural product presented an opportunity to highlight the utility of a substituted pyridine as a surrogate for a piperidine moiety. Aryl bromide **4** could, in turn, arise from the coupling of bromomethoxypicoline **5**[9] and cyclopentenone **6**.

Scheme 1



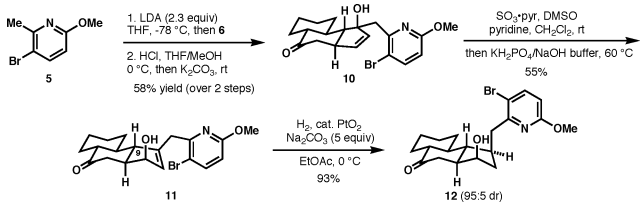
Our synthesis commenced with the Yb(tmhd)$_3$-catalyzed Diels–Alder reaction[10] of silyloxydiene **7** (Scheme 2) and dienone **8**.[11] Presumably, this reaction proceeds via an *endo*-selective cycloaddition[12,13] followed by in situ epimerization to yield **9** (in 85% yield), which possesses the requisite *anti*-stereochemical relationship between C-9 and C-10. At this stage, a retro Diels–Alder reaction was effected using flash vacuum pyrolysis (FVP) conditions to unmask cyclopentenone **6** in 86% yield. The FVP reaction could be performed routinely on multigram scale.

Scheme 2



With a robust route to cyclopentenone **6** secured, we next explored the coupling of **6** to bromomethoxypicoline **5** (Scheme 3). Diastereocontrolled[14] 1,2-addition of the lithioanion of **5** into **6** was readily achieved and was followed by hydrolysis of the silyl enol ether to provide tertiary allylic alcohol **10**. The constitution and stereochemistry of **10** was confirmed by X-ray analysis (see Figure 2). At this stage, our intention was to perform an allylic hydroxy group transposition or oxidative transposition[15] to establish the appropriate oxygenation pattern about the five-membered ring. The use of standard reagents such as IBX[16] or Osborn's rhenium oxo catalysts[17,18] returned only the starting material. Furthermore, careful optimization of Dauben's PCC conditions[19] provided insuperably low yields of the transposed enone product. With regard to the Dauben oxidation, chromium reagents have been noted to have deleterious effects on nitrogen-containing compounds,[20] such as pyridine-containing substrate **10**. Altogether, a variety of factors may contribute to the obstinacy of the allylic alcohol transposition, including the conformational rigidity of **10** and the steric encumberance about the tertiary hydroxyl group.

Scheme 3



After exploring numerous possibilities, it was discovered that the desired 1,3-allylic alcohol transposition of **10** could be accomplished using modified Parikh–Doering Swern conditions[21] to give **11** in 55% yield.[22] Selective hydrogenation of **11** could be achieved without competing hydrogenolysis of the C–Br bond or allylic hydroxy group by using Adams' catalyst in the presence of Na_2CO_3. This reaction proceeded with high levels of diastereocontrol whereby the hydrogenation occurred on the α-face, presumably directed away from the angular hydrogen at C-9. Structural characterization of **12** was confirmed by X-ray analysis of the corresponding nitrobenzoate (see **12a**, Figure 2).

Alcohol **12** was readily oxidized using Dess–Martin periodinane (DMP) to afford the corresponding ketone (**4**). Attempted 1,2-

addition via halogen−metal exchange of the aryl bromide, however, was unsuccessful. Encouraged by the precedent set by Lu,[23] we began to investigate achieving the desired 1,2-addition from an aryl boronic acid using a cationic palladium catalyst. Accordingly, installation of a boronic ester group proceeded in good yield from **12** using standard cross-coupling conditions[24] to afford **13**, which was readily oxidized and equilibrated to the cis [6−5] ring fusion to provide dione **14** (Scheme 4). However, conversion of this boronic ester to the corresponding boronic acid[25] and subsequent exposure to $[Pd(dppp)(H_2O)_2]^{2+}(^{-}OTf)_2$ led only to deborylation.

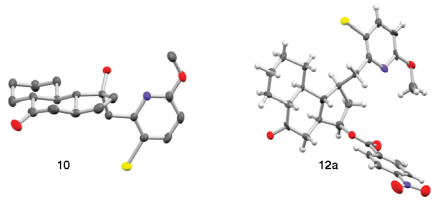
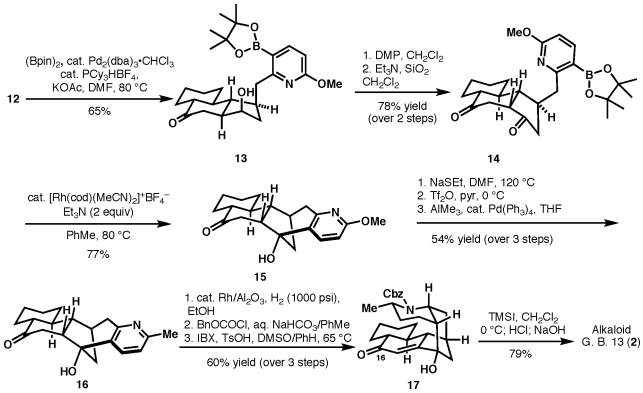


Figure 2. ORTEP representations of **10** (hydrogens omitted for clarity) and nitrobenzoate **12a**.

We then considered the possibility of effecting this transformation using rhodium catalysis. After a screen of conditions, we were delighted to find that treatment of pinacolboronic ester **14** with the cationic catalyst $[Rh(cod)(MeCN)_2]^{+}BF_4^{-}$ in the presence of Et_3N in toluene efficiently executed the 1,2-addition to provide pentacycle **15** in 77% yield. To the best of our knowledge, this is the first example of the addition of an aryl boron species into an unactivated ketone using Rh(I) catalysis.

Installation of the pyridinyl methyl group resident in **16** was accomplished in 54% overall yield through a three-step sequence, which involved cleavage of the methyl ether of methoxypyridine **15**, followed by triflation of the resultant pyridone, and methyl cross-coupling using the Hirota conditions.[26] Hydrogenation of the pyridine ring of pentacycle **16** proceeded with good diastereocontrol (~8:1 dr) from the *exo* face of the molecule and was accompanied by an inconsequential partial reduction of the ketone group. Following selective Cbz protection of the piperidine nitrogen, treatment of the secondary alcohol/ketone mixture with excess IBX[6,27] afforded the corresponding enone (**17**). Removal of the Cbz group using previously established conditions[6] gave alkaloid G. B. 13 (**2**).[28]

Scheme 4



In summary, a concise total synthesis of alkaloid (±)-G. B. 13 has been achieved in 17 total steps from diene **7** and dienone **8**. Key to the completion of the synthesis was a 1,3-allylic alcohol transposition under modified Parikh−Doering conditions in addition to an unprecedented Rh(I)-catalyzed ketone hydroarylation reaction. Because the preparation of **8** in enantioenriched form is known,[29] our strategy should be readily rendered enantioselective. These efforts, as well as the syntheses of related *Galbulimima* alkaloids employing pyridines as piperidine surrogates, are currently underway in our laboratories.

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Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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