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Total Synthesis of (+)-Galbulimima Alkaloid 13 and (+)-Himgaline

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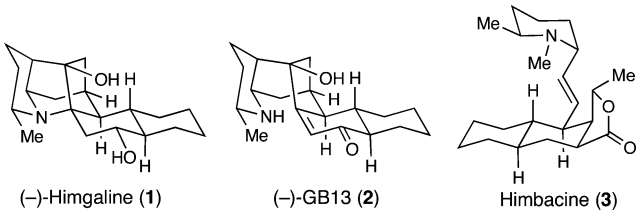
Himgaline (**1**) and galbulimima alkaloid 13 (**2**) (GB13) are two members of a family of complex polycyclic alkaloids isolated from *Galbulimima belgraveana*, a rain forest tree native to Papua New Guinea and northern Australia.[1] Its bark has been used medicinally by Papua New Guinean tribes,[2] and himbacine (**3**) has attracted attention from the medicinal[3] and synthetic[4] community as a result of its potent muscarinic antagonist activity. However, it was the molecular architecture of these structures that attracted our interest as synthesis targets. We wish now to report the synthesis of *ent*-galbulimima alkaloid 13 and *ent*-himgaline.



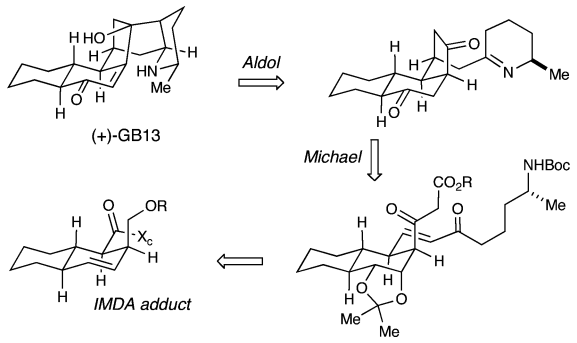
On the basis of Taylor's postulated polyketide-derived biosynthesis of these structures[1c] and informed by Baldwin's biomimetic approach to himbacine,[4d] we initiated a synthesis of *ent*-**1** and *ent*-**2** from a linear precursor. In addition to the racemic total synthesis of GB13 published by Mander prior to the outset of this work,[5a] two total syntheses of GB13 have been recently reported, including one by Movassaghi.[5b] The other synthesis, by Chackalamannil, also reported the successful conversion of GB13 to himgaline.[5c,d]

The synthesis plan is outlined in Scheme 1. We anticipated that himgaline could be accessed from GB13 via conjugate addition of the piperidine nitrogen into the proximal enone and subsequent stereoselective ketone reduction. The GB13 [3.2.1] bicyclooctane core was envisioned to arise from an intramolecular enamine aldol addition, while the cyclopentanone synthon would be formed by a stereoselective intramolecular Michael addition of the illustrated β-ketoester. It was thought that such a Michael precursor could be obtained by elaboration of the illustrated intramolecular Diels–Alder cycloadduct.

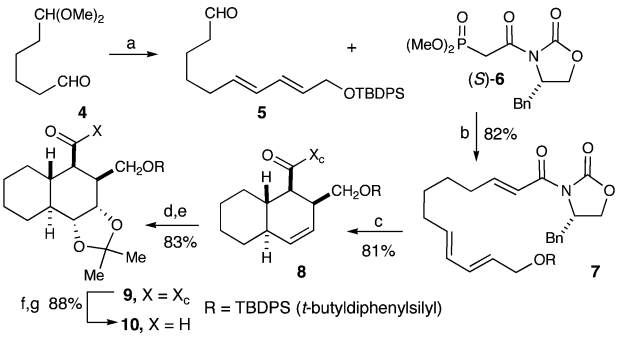
The synthesis began with vinylogous Horner–Wadsworth–Emmons (HWE) olefination[6] of 6,6-dimethoxyhexanal[7] with triethyl 4-phosphonocrotonate. This adduct was elaborated, in a routine series of transformations, to the illustrated diene aldehyde **5** (Scheme 2). Following a second HWE olefination to incorporate the chiral auxiliary,[8] intramolecular Diels–Alder cycloaddition provided *trans*-decalin **8** (81% yield) as a single diastereomer.[9] The necessary decalin oxygenation was installed at this stage by a highly diastereoselective dihydroxylation and acetonide protection to give **9** in good yield. The chiral auxiliary then was converted to the thioester, which was reduced with DIBAL-H to afford aldehyde **10** (88%, two steps).

Elaboration of the *trans*-decalin synthon **10** to both (+)-GB13 and (+)-himgaline is presented in Scheme 3. The HWE olefination of aldehyde **10** using the previously reported (*R*)-β-ketophosphonate **11**[4e] afforded the derived unsaturated ketone **12** (92%). Since attempted deprotection of the silyl ether under a variety of conditions led to irreversible conjugate addition of the liberated

Scheme 1. Proposed Synthesis Plan



Scheme 2. Synthesis of the Functionalized Decalin Subunit[a]



[a] Conditions: (a) See Supporting Information; (b) (*S*)-**6**, $LiClO_4$, *i*-Pr_2NEt, MeCN; (c) Me_2AlCl, PhMe, −30 °C; (d) K_2OsO_4, NMO, acetone/pH 7 buffer; (e) dimethoxypropane, TsOH, acetone; (f) LiSEt, THF, 0 °C; (g) DIBAL-H, PhMe, −90 °C.

alcohol, **12** was reduced (DIBAL-H) and deprotected (TBAF) to afford the illustrated allylic alcohol **13a**, which was then *N*-benzylated.[10] Both alcohols in **13b** could be oxidized with Dess–Martin periodinane,[11] and the resulting aldehyde was selectively engaged in a Roskamp reaction to install the β-ketoester necessary for the planned Michael reaction.[12] Although formation of the β-ketoester could be monitored by ^{1}H NMR spectroscopy, the isolated product was enol ester **14**, derived from conjugate addition of the β-ketoester enol oxygen. This undesired process proved to be reversible under basic conditions: a combination of lithium methoxide and lithium perchlorate, conditions reported to provide chelated β-ketoester anions,[13] was employed to afford the desired Michael adduct **15a** in 62% over three steps. Although **15a** was obtained as a mixture of carboalkoxy diastereomers, decarboxylation with $Pd(PPh_3)_4$ and morpholine revealed the desired cyclopentanone **15b** as a single diastereomer, implying that the Michael reaction had proceeded with high diastereoselection.

The transformation of acetonide **15b** to triketone **16** was carried out in the following manner: DBU-promoted elimination of the acetonide afforded its derived allylic alcohol, which was hydrogenated over $Pd(OH)_2$ on carbon with 9:1 selectivity for the desired [3,2,0] cis ring fusion and concomitant *N*-benzyl cleavage. Oxidation of the secondary alcohol with Dess–Martin periodinane provided triketone **16** in 72% over three steps.

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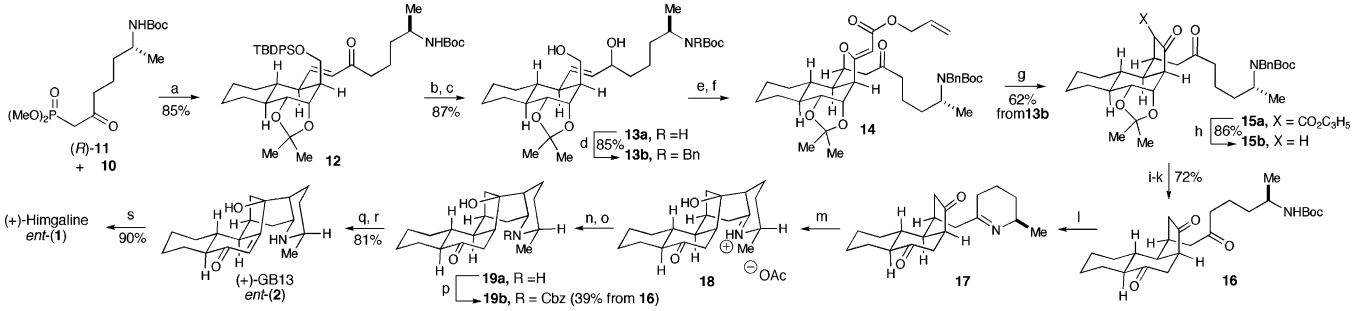
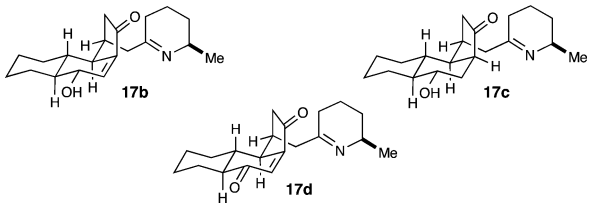
Scheme 3. Himgaline and GB13 Syntheses[a]



[a] Conditions: (a) $LiClO_4$, *i*-Pr_2NEt, MeCN, 50 °C; (b) DIBAL-H, PhMe, −90 °C; (c) TBAF, HOAc, THF; (d) see Supporting Information; (e) DMP, $NaHCO_3$, CH_2Cl_2; (f) allyldiazoacetate, $SnCl_2$; (g) LiOMe, $LiClO_4$, Et_2O, 0−23 °C; (h) $Pd(PPh_3)_4$, morpholine, THF; (i) DBU, PhH; (j) $Pd(OH)_2$, H_2, THF; (k) DMP, $NaHCO_3$, CH_2Cl_2; (l) 20% TFA/CH_2Cl_2, 0 °C, aq $NaHCO_3$ workup; 4 Å MS, PhH; (m) HOAc, THF, 0−23 °C; (n) $NaBH_3CN$, EtOH, 0 °C; (o) DMP, $NaHCO_3$, CH_2Cl_2; (p) benzyl chloroformate, Na_2CO_3, CH_2Cl_2/H_2O, 0−23 °C; (q) IBX, $TsOH\cdot H_2O$, DMSO/PhH, 65 °C; (r) TMSI, CH_2Cl_2, 0 °C; HCl; NaOH, 23 °C; (s) HOAc, MeCN, 30 min; $NaBH(OAc)_3$.

We next turned our attention to the intramolecular enamine aldol addition. To our gratification, after deprotection of the amine under acidic conditions, dehydration to the cyclic imine, and treatment with excess acetic acid in THF, the desired addition took place to give the aldol adduct isolated as its iminium ion **18**. Interestingly, the related structures depicted below failed to undergo the desired aldol addition. Alcohols **17b** and **17c** were inert to a variety of reaction conditions, highlighting the influence of the conformation of the decalin on cyclopentanone reactivity. Enedione **17d** appeared to undergo conjugate addition in preference to the desired 1,2-addition.



Surprisingly, treatment of **18** with $NaBH_3CN$ reduced both the iminium and the carbonyl moieties, even under pH 6 reaction conditions, to give a 2:1 mixture of axial and equatorial alcohol epimers. Oxidation of this mixture with Dess−Martin periodinane provided dihydro-GB13 **19a** without affecting the hindered secondary amine. The amine was then protected using benzyl chloroformate[14] and purified to give the carbamate **19b** in 39% yield over six steps (average yield, 85%). No undesired diastereomers were isolated from this sequence. The necessary unsaturation was then introduced using IBX (90%),[5b,15] and the benzyl carbamate was removed with TMSI to provide *ent*-GB13.[5b] Synthetic GB13 matched a natural sample spectroscopically and gave an optical rotation of similar magnitude but opposite sign (*ent*-**2**, $[\alpha]^{20}_D$ +71.6 (*c* 0.2, $CHCl_3$); **2**, $[\alpha]^{20}_D$ −76 (*c* 1.0, $CHCl_3$)).[1a]

The conversion of (+)-GB13 to (+)-himgaline began with the conjugate addition of the piperidine nitrogen to the pendent enone, which was facile in a variety of acidic media.[1b,5c] Eventually, it was found to be convenient to perform the conjugate addition by stirring (+)-GB13 in a 1:1 mixture of acetic acid and acetonitrile. Subsequent addition of sodium triacetoxyborohydride initiated directed hydride delivery to furnish *ent*-himgaline in 90% yield.[16] Synthetic himgaline was spectroscopically identical to a natural sample and gave an optical rotation of similar magnitude but opposite sign (*ent*-**1**, $[\alpha]^{20}_D$ +80.0 (*c* 0.1, $CHCl_3$); **1**, $[\alpha]^{20}_D$ −84 (*c* 1.0, $CHCl_3$)).[1a]

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Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ^1H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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