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Total Synthesis and Absolute Stereochemical Assignment of (+)- and (−)-Galbulimima Alkaloid 13

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The galbulimima alkaloids are a family of structurally fascinating polycyclic compounds isolated from the bark of *Galbulimima belgraveana*, a tree native to northern Australia and Papua New Guinea (Figure 1).[1] The biological activity[2] of himbacine (**1**), a potential treatment for Alzheimer's disease, has prompted several inventive syntheses of **1**[3] and an intriguing recent synthesis of (±)-galbulimima alkaloid 13 (GB 13, **2**).[4] Herein we describe the total synthesis of both (+)- and (−)-GB 13 (**2**), allowing revision of their absolute stereochemical assignment.

A compelling hypothesis by Mander, Ritchie, and Taylor in 1967 linked various galbulimima alkaloids to a common polyacetate-derived precursor.[1d] Inspired by this theory, intrigued by the unique structure of these alkaloids, and given the paucity of studies directed at complex members possessing the fused CDE-ring system (i.e., **2** and **3**, Figure 1), we initiated our studies in this area. Guided by our original biosynthetic hypothesis, we envisioned a strategic C5−C20 bond disconnection to greatly simplify the structure of **2** to the tetracyclic precursor **4** (Scheme 1). We expected to obtain the imino ketone **4** from the unsaturated imine **5**, in turn, prepared by condensation of the iminium chloride **6** with aldehyde **7**. Given the uncertainty in the absolute stereochemistry of natural (−)-GB 13 (**2**), the coupling of the readily available (+)- or (−)-iminium chloride **6** with (±)-aldehyde **7** provided an expedient route to both enantiomers of advanced intermediates and alkaloid **2**.

An efficient synthesis of *trans*-decalin aldehyde **7** is outlined in Scheme 2. Suzuki cross-coupling[5] of readily available dibromide **8**[6] and vinyl boronic acid **9**[6] using thallium carbonate[5c] provided *cis*-vinyl bromide[7] **10** in 75% yield. Subsequent copper-catalyzed coupling of bromodiene **10** with oxazolidin-2-one afforded the desired triene **11** in excellent yield[8] and proved to be an effective strategy for masking the C16 carbonyl. Conversion of the C20 silyl ether of triene **11** to the C20 silyl enol ether gave tetraene **12** (Scheme 2). Selective functionalization of the C9−C10 alkene of **12** to the corresponding unsaturated aldehyde **13** (C9 *E*:*Z*, >20:1) was achieved via an olefin cross-metathesis reaction with acrolein using the 4,5-dihydroIMesCl$_2$Ru═CH(*o*-^{i}PrO)Ph[9] catalyst. Heating a solution of tetraenal **13** in toluene at 90 °C afforded the desired *trans*-decalin aldehyde **7** in good yield (82%, >20:1, *endo*:*exo*).

Deprotonation of the (−)-iminium chloride **6** (>99% ee, Scheme 1)[6] with ^{n}butyllithium gave the corresponding lithiated enamine,[10] which upon addition to a cold solution of aldehyde **7** provided the corresponding *β*-hydroxy imines in 85% yield. Dehydration using the Martin sulfurane reagent[11] afforded the desired (7*E*)-α,*β*-unsaturated imine **5** (Scheme 3) and the corresponding 2-*epi*-enantiomer (not shown in Scheme 3) as an equal mixture of inseparable diastereomers in 81% yield. The diastereomers were chromatographically separated after the next two steps.

Diastereoselective introduction of the C21−C8 bond in tetracycle **16** was accomplished via a 5-*exo*-trig vinyl radical cyclization.[12] Conversion of silyl enol ether **5** to the vinyl bromide **14** (Scheme 3, ∼1:1.5 mixture of C20 olefin isomers), followed by heating of the crude vinyl bromide **14** with excess tributyltin hydride and AIBN, provided the desired tetracycle **16** along with the C2-*epi*-enantiomer[6] in 55% yield. Treatment of enol ether **16** with triethylamine trihydrofluoride resulted in C5−C6 enamine addition to the unmasked C20 carbonyl, directly providing the corresponding pentacyclic imine. Removal of the volatiles under reduced pressure and introduction of sodium borohydride resulted in diastereoselective C6 imine reduction, affording the corresponding stable pentacyclic amine in a one-pot process (Scheme 3). Optically active pentacyclic amine (−)-**18** (36%) and the corresponding 2-*epi*-enantiomer, amine (+)-**19** (34%), were readily separated by flash

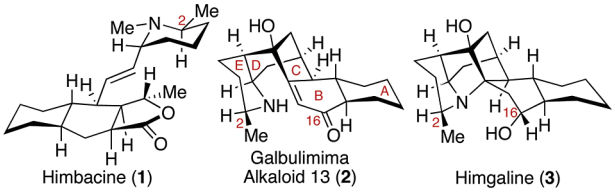
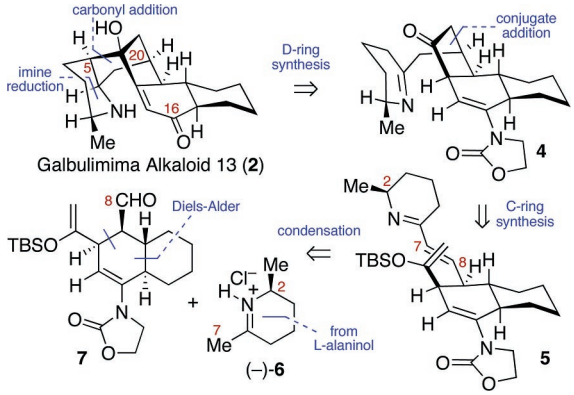
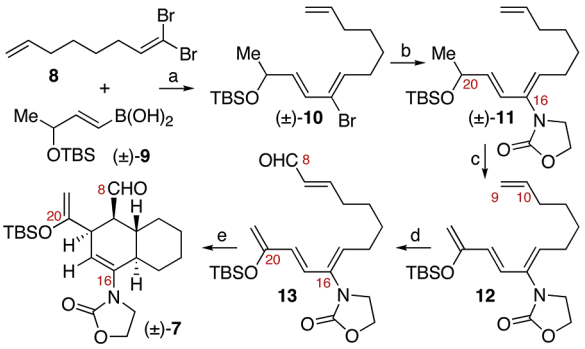


Figure 1. Representative galbulimima alkaloids.[1a]

Scheme 1. Retrosynthetic Analysis of (−)-Galbulimima Alkaloid 13



Scheme 2. Diastereoselective Synthesis of (±)-Aldehyde **7**[a]



[a] Conditions: (a) Pd(PPh$_3$)$_4$, Tl$_2$CO$_3$, THF, H$_2$O, 23 °C, 75%; (b) CuI, K$_2$CO$_3$, oxazolidin-2-one, (MeNHCH$_2$)$_2$, toluene, 110 °C, 95%; (c) (1) TBAF, THF, 95%; (2) MnO$_2$, CH$_2$Cl$_2$, 92%; (3) TBSOTf, Et$_3$N, CH$_2$Cl$_2$, −78 °C, 93%; (d) 4,5-dihydroIMesCl$_2$Ru═CH(*o*-^{i}PrO)Ph (10 mol %), acrolein, CH$_2$Cl$_2$, 23 °C, 85%; (e) toluene, 90 °C, 82%, (≥20:1, *endo*:*exo*).

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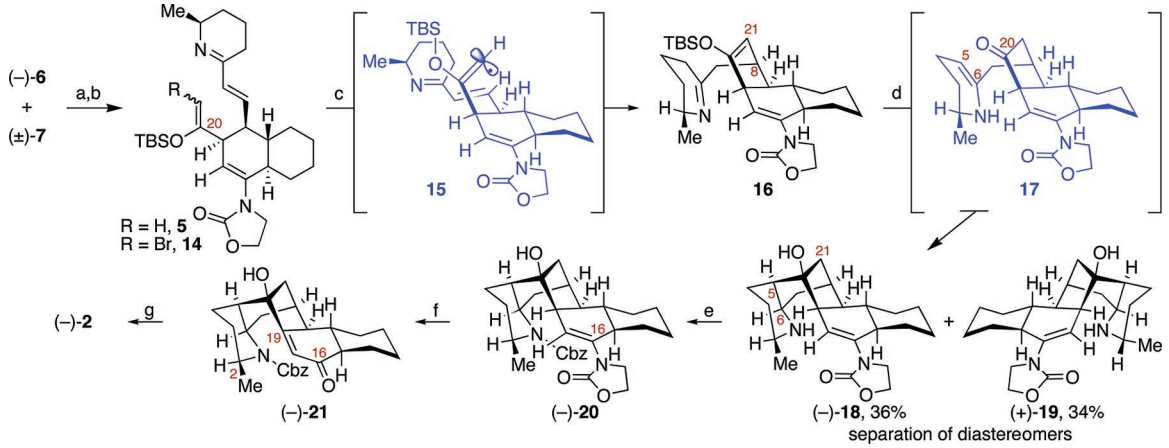
Scheme 3. Concise Synthesis of (−)-Galbulimima Alkaloid 13 (**2**)[a]



[a] Conditions: (a) ^{n}BuLi, THF, −78 °C, 5 min, 85%; (b) Martin sulfurane, benzene, 23 °C, 81%; (c) NBS, $NaHCO_3$, THF, 0 °C; $^{n}Bu_3SnH$, AIBN, benzene, 60 → 90 °C, 55% (two steps); (d) $Et_3N{\cdot}(HF)_3$, THF, 23 °C; $NaBH_4$, EtOH, 0 °C, 70% (two steps); (e) $ClCO_2Bn$, Na_2CO_3, H_2O, CH_2Cl_2, 65%; (f) IBX, $TsOH{\cdot}H_2O$, benzene, DMSO, 65 °C, 10 h, 80%; (g) TMSI, CH_2Cl_2, 0 °C; HCl; NaOH, 23 °C, 89%. For brevity, the corresponding *ent*-2-*epi*-isomer of compounds **5** and **14**−**17** is not shown.[6]

column chromatography. Remarkably, formation of the C8 stereocenter during the radical cyclization as well as the introduction of the three contiguous stereocenters (C20, C5, and C6) in the conversion of silyl enol ether **16** to pentacyclic amine (−)-**18** occurs with a high level of diastereoselection. To date, no other diastereomers have been detected.

Introduction of the enone was accomplished by treatment of *N*-vinyl carbamate (−)-**20** with excess *p*-$TsOH{\cdot}H_2O$ and IBX in benzene/DMSO at 65 °C for 10 h to provide carbamate (−)-**21** in 80% yield.[13] Subsequent deprotection of (−)-*N*-Cbz GB 13 (**21**) with trimethylsilyl iodide (TMSI)[14] followed by an aqueous workup provided synthetic GB 13 (**2**) in 89% yield (Scheme 3). All spectroscopic data for our enantiomerically enriched (−)-**2** matched literature data.[1,4a] The sign of rotation for our synthetic **2** ($[\alpha]^{22}_D = -64$ (*c* 0.06, $CHCl_3$)), was consistent with that reported for the natural enantiomer ($[\alpha] = -84$ ($CHCl_3$)[1b]),[6] unambiguously securing the absolute stereochemistry. Synthesis of (+)-GB 13 (*ent*-**2**, $[\alpha]^{22}_D = +66$ (*c* 0.07, $CHCl_3$)) using (+)-**6** (>99% ee) via the route described above confirmed our absolute stereochemical assignment.[6] Interestingly, intramolecular amine conjugate addition at C19 was observed upon N-deprotection of **21** and acidic treatment. This conjugate addition was subject to reversion on mild base treatment (1 N $NaOH_{aq}$, 1 h).[15] This facile cyclization supports the hypothesis for the biosynthesis of himgaline (**3**) via sequential conjugate addition and carbonyl reduction of **2**.[1c,6]

We describe the first total synthesis of (+)- and (−)-GB 13 (**2**). The absolute stereochemistry of natural (−)-**2** is revised to 2*S*. Noteworthy features of this chemistry include a vinyl radical cyclization strategy to secure the C-ring and the successful execution of our biomimetically inspired strategy for introduction of the CDE-ring system in **2** (**16** → **18**, Scheme 3). Current efforts are directed toward the synthesis of other members of this intriguing family of natural alkaloids.

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Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ^{1}H 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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