Natural Products

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# A Convergent Route to the *Galbulimima* Alkaloids (−)-GB 13 and (+)-GB 16**

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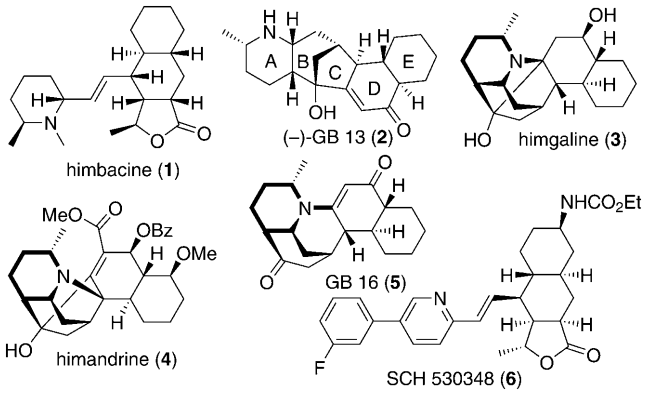
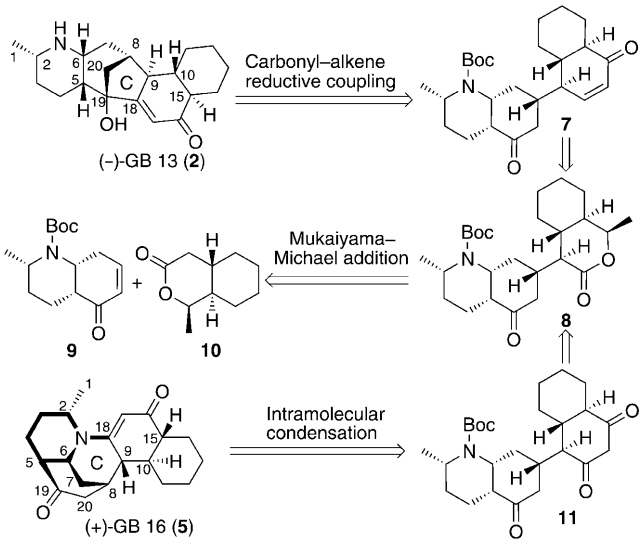
GB alkaloids are a growing family of natural products that were isolated from the bark of *Galbulimima belgraveana*, which include himbacine (**1**),[1] (−)-GB 13, (**2**),[2] himgaline (**3**),[2] himandrine (**4**)[2] and (+)-GB 16 (**5**)[3] (Scheme 1).




***Scheme 1.*** Structures of *galbulimima* alkaloids and their analogue.

These alkaloids have received much attention from the pharmaceutical industry, mainly because the *Galbulimima belgraveana* bark has been used as a medicinal substance and himbacine (**1**) displays potent muscarinic antagonist activity.[4] Based on intensive structure-activity relationship (SAR) studies of himbacine, an exceptionally potent series of thrombin receptor antagonists have been discovered. One of these compounds (SCH 530348, **6**) is now in phase III clinical trials for treatment of acute coronary syndrome.[4a] Meanwhile, the fascinating structures of these alkaloids have attracted much interest in the orgainc synthesis community. As a consequence a number of total syntheses of himbacine,[5] five of GB 13,[6] two of himgaline[6c,d] and one of himandrine[7] have been disclosed. A biomimetic transformation of (−)-GB 13 into (+)-GB 16 was reported.[3] However, more convergent and efficient routes to these alkaloids are still required to facilitate their SAR studies.

In the previous reports, formation of the D ring,[6a] B ring,[6b,d,e] or A ring[6c] was set up at a late stage to complete the total synthesis of GB 13. Apparently, if formation of the C-ring of GB 13 could be conducted at the late stage, this molecule would be disconnected into two equally complex fragments, thereby offering a more convergent approach to the natural product. With this idea in mind, we started our retrosynthetic analysis for (−)-GB 13 (**2**). As shown in Scheme 2, we envisioned that the C ring of **2** could be




***Scheme 2.*** Retrosynthetic analysis for (−)-GB 13 and (+)-GB 16. Boc = *tert*-butoxycarbonyl.

installed by a carbonyl–alkene reductive coupling of intermediate **7** mediated by $SmI_2$.[8,9] If this transformation worked well we would be able to disconnect the pentacyclic skeleton of **2** into two less complicated bicyclic intermediates **9** and **10**, which could be connected to each other by a Mukaiyama–Michael addition.[10] This approach could also provide an opportunity to synthesize (+)-GB 16 (**5**) because it would be possible to convert the lactone **8** into 1,3-diketone **11**, which could undergo an intramolecular condensation between its secondary amine moiety and its 1,3-diketone to set up the C ring of (+)-GB 16. In the following investigations, we realized that our strategy offered a very convergent synthesis of (−)-GB 13 and (+)-GB 16, allowing for a 19-step total synthesis of the former alkaloid beginning from commercially available material, and the first total synthesis of the latter alkaloid. Herein, we disclose our results.

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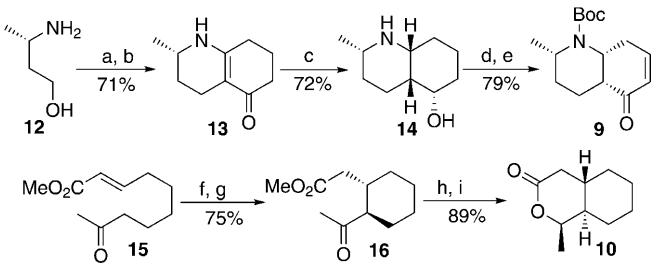
Our synthesis started from the preparation of the two required partners for the Mukaiyama–Michael addition. As shown in Scheme 3, condensation of commercially available

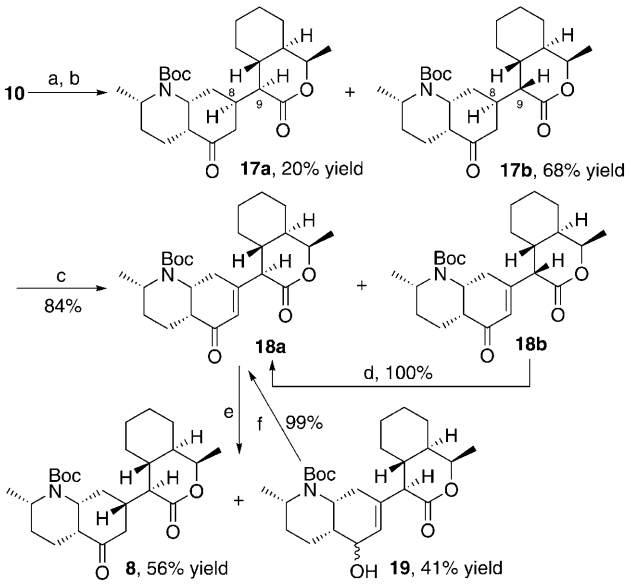



***Scheme 3.*** Reagents and conditions: a) 1,3-cyclohexanedione, M.S. (4 Å), THF, reflux; b) $CBr_4$, $Ph_3P$, $CH_3CN$, RT; then *i*$PrNEt_2$, reflux; c) Pt/C, $H_2$ (80 atm), AcOH, 40 °C; d) $(Boc)_2O$, NaOH, benzene/THF/$H_2O$ (2:1:1), reflux; e) IBX, DMSO, 65 °C; f) (*S*)-1-phenylethylamine, M.S. (4 Å), $MgSO_4$, THF, RT; g) KOH, MeOH, reflux, acid workup; then $CH_2N_2$, $Et_2O$, 91 % *ee*; h) $NaBH_4$, MeOH, −78 °C; i) $TsOH{\cdot}H_2O$, $CH_2Cl_2$, reflux. DMSO = dimethyl sulfoxide, IBX = 2-iodoxybenzoic acid, M.S. = molecular seives, THF = tetrahydrofuran, Ts = 4-toluenesulfonyl.

(*S*)-3-aminobutan-1-ol (**12**) with 1,3-cyclohexanedione followed by treatment with $CBr_4/Ph_3P$ and substitutive cyclization mediated by $Et_3N$ afforded bicyclic enamine **13**.[11] The next step was a stereoselective hydrogenation of the C=C bond of **13**. On the basis of our previous observations,[11a] we anticipated that the methyl group would shield the α face of the enamine **13**, thus directing the hydrogenation to the desired β face to form the reduction product **14**. Accordingly, hydrogenation of **13** catalyzed by Pt/C was conducted in HOAc at 40 °C and afforded **14** in 72 % yield, together with its *trans* isomer in 14 % yield. Protection of **14** with $(Boc)_2O$ and subsequent oxidation with IBX[12] delivered the desired enone **9**. In a parallel procedure, γ-keto ester **16** was assembled from olefin **15**[13a] by applying a known method.[13] Diastereoselective reduction of the keto moiety in **16** with $NaBH_4$ at −78 °C and subsequent cyclization under acidic conditions provided the lactone **10**.

The addition of silyl enol ether generated from the lactone **10** onto the enone **9** was achieved under $TiCl_4$ catalysis at −78 °C,[10] and afforded Michael adducts **17** as a diastereomeric mixture in a ratio of about 3.5:1 (Scheme 4). As predicted, the nucleophilic agent favored addition on the enone **9** from the *Re* face to give the products with *R* configuration at the newly generated stereocenter at C8, which was confirmed by X-ray crystal structural analysis of **17b**.[14] Because this configuration was not matching the one of the target molecule, we planned to invert it through an oxidation/reduction approach.

Accordingly, exposure of the mixture of **17a** and **17b** to IBX in DMSO at 70 °C produced a mixture of enone **18a** and its C9 epimer **18b**. Treatment of this mixture with DBU in methylene chloride gave the thermodynamically more stable **18a** as a single product with 84 % yield. Hydrogenation of **18a** afforded the reduced ketone **8** that has the desired configuration at both the C8- and C9-position together with alcohol **19**. Because **19** could be transferred into **18a** by Dess–Martin



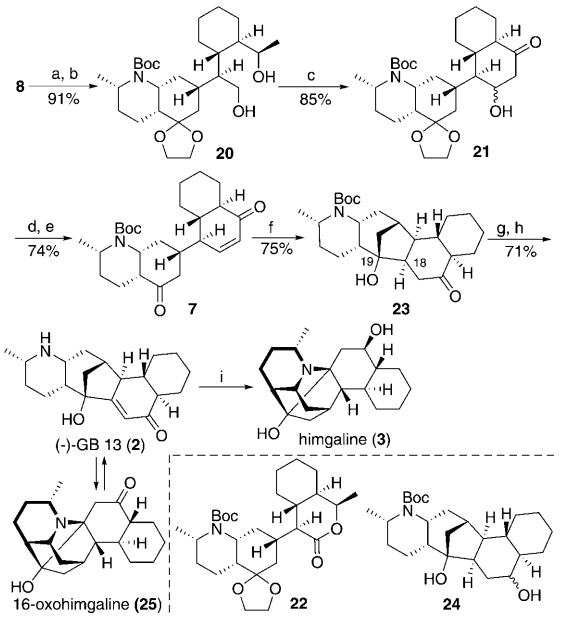

***Scheme 4.*** Reagents and conditions: a) LDA, TMSCl, THF, −78 °C; b) **9**, $TiCl_4$, $CH_2Cl_2$, −78 °C; c) IBX, DMSO, 70 °C; d) DBU, $CH_2Cl_2$, RT; e) Pd/C, $H_2$, *i*PrOH; f) DMP, $NaHCO_3$, $CH_2Cl_2$. DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, DMP = Dess–Martin periodinane, LDA = lithium diisopropylamide, TMS = trimethylsilyl.

oxidation, we were able to obtain the ketone **8** in 80 % combined yield after two cycles.

Next, we turned our attention to the transformation of the lactone moiety in **8** into the desired enone unit. Protection of the ketone **8** with ethylene glycol and subsequent LAH reduction gave rise to diol **20** in 91 % yield (Scheme 5). For obtaining the required β-hydroxy ketone **21** via oxidation of the diol **20** and subsequent intramolecular aldol reaction, we initially utilized Dess–Martin periodinane as the oxidating agent. In this case **21** was isolated in 35–50 % yield, but lactone **22** was formed as a side product. Changing the oxidating agent to PCC or TPAP/NMO gave similar results. The lactone **22** is probably formed through a cascade oxidation/hemiketalization/oxidation process.[15] Inspired by work of Boger et al.,[16] we found that if DBU was used as a base instead TEA or DIPEA, Swern oxidation of diol **20** provided **21** with 85 % yield without any traces of **22**. This result further demonstrated that the cascade oxidation/hemiketalization/oxidation process could be inhibited by using DBU as a base in Swern oxidation. Dehydration of **21** through its trifluoroacetyl ester afforded an enone, which was treated with PTSA in wet acetone to selectively remove the ketal protecting group, thus producing the desired enone **7** in 74 % yield.

With the enone **7** in hand, the stage was set for the crucial carbonyl–alkene reductive coupling mediated by $SmI_2$. To our surprise, the initial attempts under the typical reaction conditions ($SmI_2$/HMPA/*t*BuOH,[17a] $SmI_2$/HMPA,[17b] or $SmI_2$/MeOH,[17c] −78-0 °C) all failed to give any desired cyclization products and only simple reduction products were isolated. After careful screening various reaction conditions, we were pleased to discover that by adding the enone **7** slowly to a solution of $SmI_2$ in THF at reflux in the absence of any

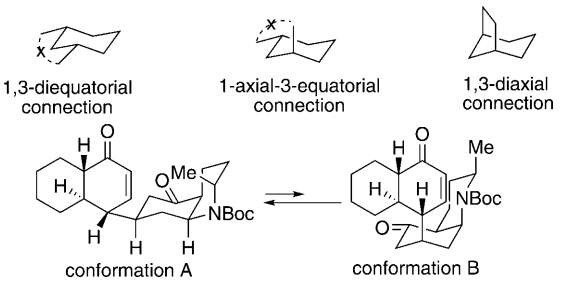



***Scheme 5.*** Reagents and conditions: a) glycol, $TsOH\cdot H_2O$, toluene, Dean–Stark; b) $LiAlH_4$, THF, 0 °C to RT; c) $(CF_3CO)_2O$, DMSO, DBU, $CH_2Cl_2$, −78 °C to RT; d) $(CF_3CO)_2O$, $Et_3N$, $CH_2Cl_2$, RT; e) $TsOH\cdot H_2O$, acetone, $H_2O$, reflux, 4 days; f) $SmI_2$, THF, reflux, then Dess–Martin oxidation; g) IBX, DMSO, 70 °C; h) $CF_3CO_2H$, $CH_2Cl_2$; then NaOH; i) HOAc, $CH_3CN$; then $NaBH(OAc)_3$.

additives,[18] the desired reductive coupling product **23** could be isolated in 45–65 % yields, together with the over-reduced product **24**. Further attempts revealed that a satisfactory yield (75 %) for **23** could be obtained by reductive cyclization mediated by $SmI_2$ and subsequent oxidation of the mixture of the cyclization products with Dess–Martin periodinane.

Our reductive cyclization results could be rationalized by conformation analysis as shown in Scheme 6. During this process, a [3.2.1]bicyclic core structure is created. Among the three possibilities to form a [3.2.1]bicyclic core, only a 1,3-diaxial connection is favored. Thus, only conformation **B** is suitable for carbonyl–alkene reductive coupling mediated by $SmI_2$. Consequently, heating the reaction mixture was required to obtain the thermodynamically less stable conformation **B**.

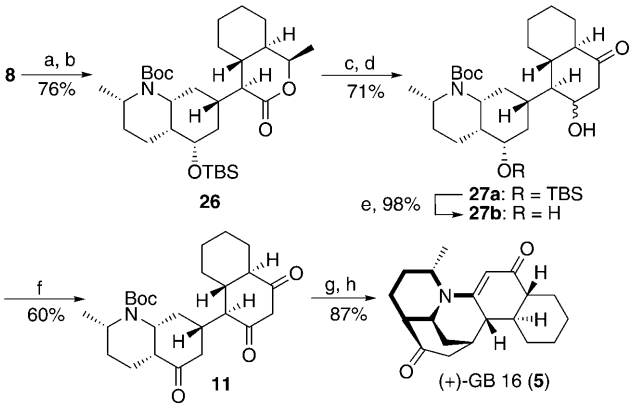
Dehydrogenation of the ketone **23** with IBX afforded N-Boc-protected (−)-GB 13, which was treated with TFA and then subjected to aqueous workup and provided (−)-GB 13




***Scheme 6.*** The favored conformation for carbonyl–alkene reductive coupling of the enone **7**.

(**2**) in 71 % yield. Owing to the known balance between GB 13 and 16-oxahimgaline (**25**), our synthetic **2** contained about 25 % 16-oxohimgaline in $C_6D_6$, which is consistent with the observation of Evans[6d] (containing 10 % of 16-oxohimgaline) and Sarpong[6e] (containing 30 % of 16-oxohimgaline). To further confirm our synthetic result, we converted this mixture into (−)-himgaline (**3**) by treatment with acetic acid and subsequent reduction with $NaBH(OAc)_3$. The analytical data for synthetic **3** were in agreement with those of natural himgaline.

To synthesize (+)-GB 16, we initially employed β-hydroxy ketone **21** as an advanced intermediate. However, after its oxidation to the corresponding 1,3-diketone, cleavage of the ketal protecting group was found to be quite difficult. This problem led us to continue our synthesis using lactone **8**. At this stage we decided to reduce the ketone group of **8** and then protect the resulting hydroxy group with an easily removable silyl ether. Consequently, reduction of **8** with $NaBH_4$ at −78 °C and subsequent treatment with TBSCl in DMF provided **26** in 76 % yield (Scheme 7). Reduction with LAH




***Scheme 7.*** Reagents and conditions: a) $NaBH_4$, MeOH/THF (1:1), −78 °C; b) TBSCl, imidazole, DMAP, DMF, RT; c) $LiAlH_4$, THF, RT; d) $(CF_3CO)_2O$, DMSO, DBU, $CH_2Cl_2$, −78 °C to RT; e) HF, $CH_3CN$, −20 °C; f) PCC, $CH_2Cl_2$, RT; g) $CF_3CO_2H$, $CH_2Cl_2$, RT; h) toluene, NaOAc, Dean–Stark. DMF = *N*,*N*-dimethylformamide, PCC = pyridinium chlorochromate.

of the lactone **26** to the corresponding diol, which was subjected to Swern oxidation and subsequent intramolecular aldol reaction provided β-hydroxy ketone **27a** in 71 % yield. Treatment of **27a** with aqueous HF in acetonitrile afforded diol **27b**, which was then oxidazed with PCC and provided ketone **11**. Removal of the Boc group with TFA and subsequent heating of the free amine in toluene delivered (+)-GB 16 (**5**) in 87 % yield. The analytical data of synthetic **5** are identical with those reported for natural (+)-GB 16.[3] Its structure was further confirmed by X-ray crystal structure analysis.[14]

In conclusion, we have developed a novel and convergent route for the asymmetric synthesis of alkaloid (−)-GB 13. This protocol allows for the assembly of the target molecule in 19 linear steps (overall yield of 6.1 %) from commercially available starting material. The key steps include the connection of two bicyclic parts through a Mukaiyama–Michael

addition and formation of the C ring by a carbonyl–alkene reductive coupling mediated by $SmI_2$. Using an advanced intermediate from our (−)-GB 13 synthesis as a starting material, we achieved the first total synthesis of (+)-GB 16—a newly isolated member of the gabulimima alkaloid family. The synthesis of other *galbulimima* alkaloids based on this strategy and SAR studies of these compounds are currently under way.

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