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Total Synthesis of (−)-Himgaline

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The rare rain forest tree *Galbulimima belgraveana*, found in Northern Australia and Papua New Guinea, has been the source of several complex alkaloids.[1] Among these, himbacine has attracted considerable synthetic attention due to its promising pharmacological properties.[2] A synthetic analogue of himbacine is currently in clinical trials as an antithrombotic agent.[3]

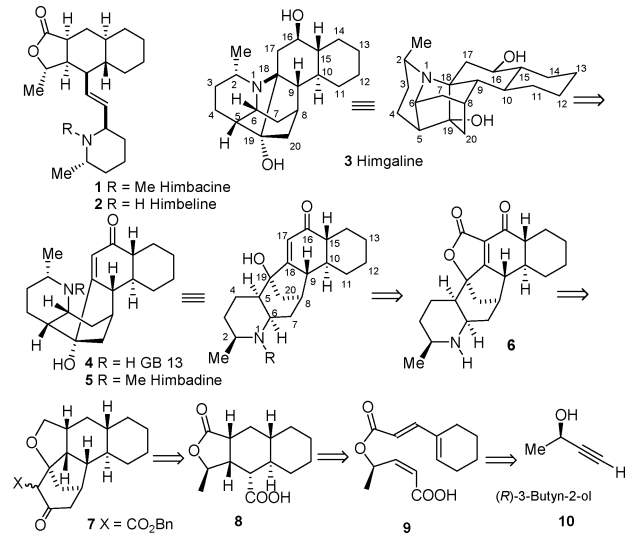
Himgaline (**3**), GB 13 (**4**), and its *N*-methyl derivative himbadine (**5**) are among the congeners of himbacine with even more pronounced structural complexity.[4] The pharmacological properties of these compounds remain unexplored. A common biosynthetic precursor to himbacine (**1**), GB 13 (**4**), himgaline (**3**), and related alkaloids was proposed by Taylor et al. in the early report of isolation of these alkaloids.[4a] The assignment of absolute stereochemistry of himgaline and related alkaloids has been established very recently using X-ray crystallographic analysis.[5] The first total synthesis of racemic GB 13 was reported by Mander's group.[6] Recently, Movassaghi's group has reported the total synthesis of both antipodes of GB 13 and confirmed the absolute stereochemistry.[7] We report here the first total synthesis of (−)-himgaline.

The retrosynthetic analysis presented in Scheme 1 envisions the synthesis of himgaline from GB 13 via an intramolecular aza-Michael reaction, followed by a diastereoselective reduction of the C_{16} ketone. Hexacyclic intermediate **6** was expected to provide GB 13 via a decarboxylative intramolecular aza-Michael reaction, followed by a retro-Michael reaction. Intermediate **6** could be constructed, via the pentacyclic intermediate **7**, from the optically pure tricyclic carboxylic acid **8**. We have previously reported the synthesis of **8** employing a highly diastereoselective intramolecular Diels−Alder reaction of precursor **9**.[3c]

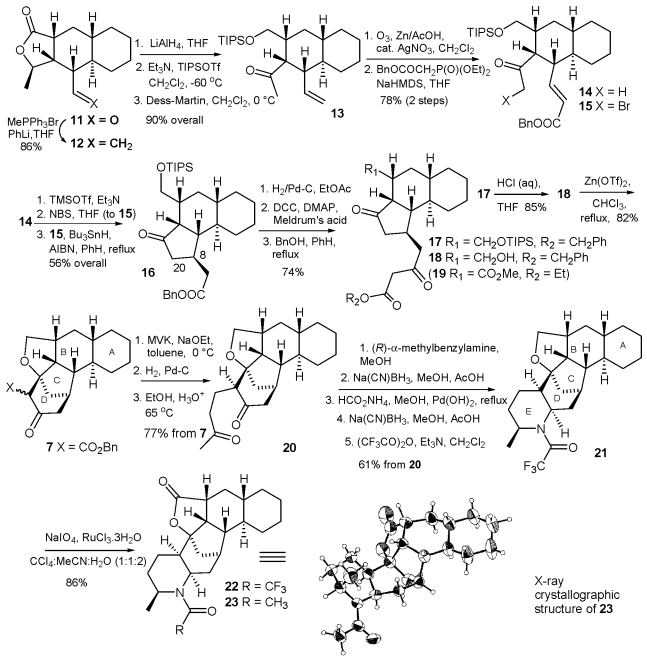
The implementation of the above approach is outlined in Schemes 2 and 3. The previously reported aldehyde **11** was converted to the alkene **12** by Wittig reaction.[3c] Lithium aluminum hydride reduction of the lactone **12**, followed by selective protection of the primary alcohol and subsequent oxidation of the secondary alcohol, gave the methyl ketone **13** in an overall 90% yield. Ozonolysis of the alkene, followed by Emmons−Wadsworth reaction and subsequent α-bromination of the methyl ketone **14**, gave **15**. Under radical conditions, **15** underwent a highly diastereoselective ring closure to give the tricyclic intermediate **16**. The high degree of diastereoselectivity of $C_{20}-C_8$ bond formation, critical to the success of the synthetic plan, is attributed to the preferred conformation of the *trans*-alkene that engenders the required configuration at C_8. It should be mentioned that attempted cyclization of **14** under anionic conditions failed.

The construction of the bicyclo[3.2.1] C−D ring system was achieved via a Lewis acid-catalyzed intramolecular cyclization of

Scheme 1



Scheme 2



β-keto ester **18**.[8] The requisite β-keto ester was prepared from the carboxylic acid derived from **16** via dicyclohexylcarbodiimide-mediated coupling with Meldrum's acid, followed by treatment of the intermediate with benzyl alcohol.

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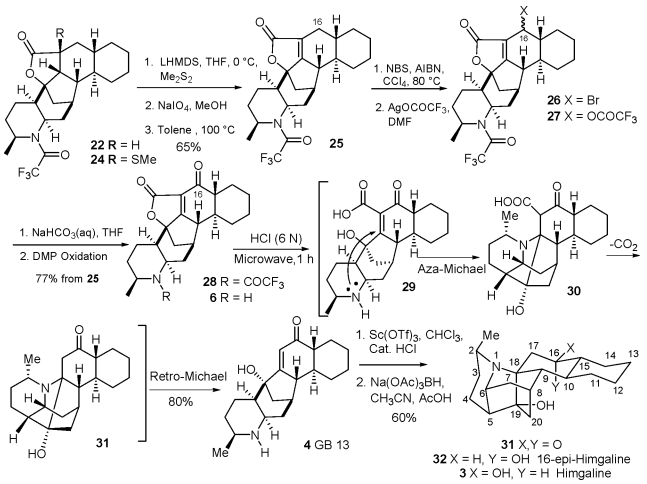
Scheme 3



Next, we turned our attention to the diastereospecific construction of the piperidine E-ring. Toward this end, the β-keto ester **7** was subjected to conjugate addition with methyl vinyl ketone, and the resulting product yielded diketone **20** after debenzylation and decarboxylation. Selective reductive amination of the methyl ketone of **20** with (*R*)-α-methylbenzylamine, followed by *N*-debenzylation and subsequent sodium cyanoborohydride reduction, gave the ring-fused crude piperidine intermediate which was trifluoroacetylated to give an overall 61% yield of **21** as the major diastereomer. Ruthenium oxide-mediated oxidation of the tetrahydrofuran ring system of **21** gave the corresponding γ-lactone **22** in excellent yield.[9] Structural confirmation of crystalline acetamide **23**, initially derived using extensive 2-D NMR experiments, was conclusively established by single-crystal X-ray crystallographic analysis.

Thiomethylation of the enolate derived from lactone **22** gave predominantly the *cis*-substituted thiomethyl ether **24**. Oxidation of sulfide to the corresponding sulfoxide, followed by thermally induced *cis*-elimination, gave predominantly the tetrasubstituted α,β-unsaturated lactone **25**. Allylic bromination of **25**, followed by silver trifluoroacetate-mediated allylic displacement, gave the corresponding acetate **27** as a mixture of diastereomers, which was hydrolyzed and oxidized to the ketone **28** in an overall yield of 77% from **25**.

The decarboxylative unraveling of the lactone to generate GB 13 was predicated on a successful intramolecular aza-Michael reaction of **6**. Treatment of **28** with 1 N sodium hydroxide gave only 10% yield of GB 13. The *N*-deacylated lactone **6** was isolated as the major product. However, when **28** was treated with 6 N HCl in dioxane at 100 °C for 1 h, GB 13 was isolated in 80% yield after basic workup. This result is consistent with the original report that GB 13 cyclizes to oxohimgaline under acidic conditions.[4a] The NMR data of synthetic (−)-GB 13 were identical to those of an authentic natural sample, and the synthetic and natural products showed comparable specific rotation.[4b,6,7,10]

In the final phase of the synthesis, treatment of GB 13 with $Sc(OTf)_3$ in chloroform that contained trace amounts of HCl, followed by sodium borohydride reduction of the crude oxohimgaline (**31**), gave 16-*epi*-himgaline (**32**) as the only product. Heteronuclear multiple-bond correlation correlation studies of **32** confirmed N_1-C_{18} bond formation. However, the C_{16} proton showed only small equatorial coupling with neighboring protons in the ^{1}H NMR, indicating that the axial alcohol was the exclusive product. Use of other standard reducing agents gave similar results. To circumvent this problem, we decided to use an internally coordinated hydride reduction of the C_{16} carbonyl group employing the C_{19} hydroxyl group. When crude oxohimgaline was treated with sodium (triacetoxy)borohydride in acetonitrile, himgaline (**3**) was formed exclusively in 60% yield.[11] The ^{1}H NMR spectrum of synthetic himgaline showed two large diaxial couplings for the C_{16} proton, suggesting the equatorial disposition of the hydroxyl group. Synthetic himgaline showed spectroscopic properties identical to those of natural himgaline and comparable specific rotation.[4b,10]

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Supporting Information Available: Spectral data and procedures for all new compounds, including natural and synthetic himgaline, and 2-D NMR analysis data for **3**, **4**, **25**, and **32**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) Although the exact mechanism of the cyclization of **18** to **7** is unknown, it is likely that the primary alcohol cyclizes into the ketone to give an oxenium ion intermediate which is trapped by the activated ester, since attempted cyclization of ester **19** under basic conditions failed to give the corresponding lactone.

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(10) Specific rotation: **3**, $[\alpha]^{20}_D$ −70.1 (*c* 0.45, $CHCl_3$) [lit.[4b] −76 (*c* 1.0, $CHCl_3$)]; **4**, $[\alpha]^{20}_D$ −80.8 (*c* 0.35, CH_2Cl_2) [lit.[4b] −84 (*c* 1.0, $CHCl_3$)].

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