Natural Product Synthesis

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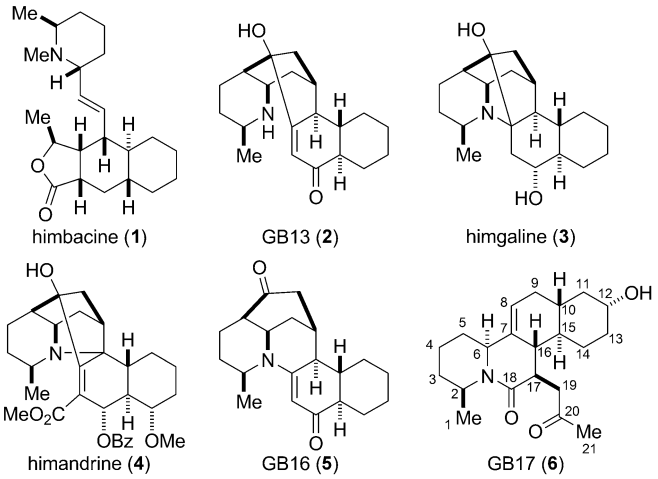
Total Synthesis of the *Galbulimima* Alkaloid (−)-GB17**

*Reed T. Larson, Michael D. Clift, and Regan J. Thomson**

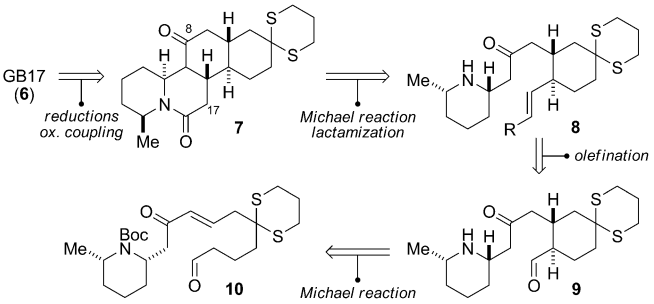
The *Galbulimima* alkaloids are isolated from the bark of rainforest trees belonging to the *Galbulimima* genus that grow in regions of Northern Australia, Papua New Guinea, and Indonesia.[1] Significant structural diversity exists within this alkaloid family,[2] but common to all members is the presence of a piperidine ring and a *trans*-decalin carbocylic core (Scheme 1). Investigations into the biological activity of the *Galbulimima* alkaloids have focused in large part on himbacine (**1**): a potent muscarinic receptor antagonist that might serve as a lead for the development of therapeutic agents to treat Alzheimer's disease.[3] Himbacine-centered research at Schering-Plough led to SCH 530348 (now Vorapaxar at Merck),[4] a promising thrombin receptor agonist. However, the clinical trial of SCH 530348 for the treatment of acute coronary syndrome was halted in 2011 owing to adverse side-effects.



Scheme 1. Selected *Galbulimima* alkaloids.

The combination of fascinating molecular structure and significant therapeutic potential has made the *Galbulimima* alkaloids attractive targets for total synthesis.[5] While early work focused on himbacine (**1**), most recent efforts have been directed at preparing the more complex members of the family. The first synthesis of GB13 (**2**) was reported by Mander and MacLachlan in 2003,[6a] with subsequent reports from the groups of Movassaghi, Chackalamannil, Evans, Sarpong, and Ma.[6b–f] Himgaline (**3**) can be synthesized from GB13 (**2**), as shown by the groups of both Chackalamannil[6c] and Evans.[6d] Movassaghi and co-workers reported the only synthesis of himandrine (**4**) in 2009,[7] while the group of Ma reported the only synthesis of GB16 (**5**) that same year.[8] Our interest was drawn to GB17 (**6**), which was one of 19 new *Galbulimima* alkaloids whose isolation was reported by Taylor and co-workers in 1965.[1a] At that time only an elemental formula was reported; the structure of GB17 was only revealed in 2009 when Mander and co-workers reported an X-ray crystal structure.[2e] GB17 (**6**) possesses an unusual naphthoquinolizinone ring system that is unique amongst the family. We were drawn to the 1,4-dicarbonyl within **6** that we hoped might be formed by oxidative enolate coupling.[9] Herein we report the first enantioselective total synthesis of GB17 (**6**), through a concise and flexible strategy.

Our approach to GB17 (**6**) is outlined in retrosynthetic format in Scheme 2. We envisioned the C8 ketone **7** as a suitable precursor to **6** by way of carbonyl reduction and a late-stage oxidative enolate coupling to install the C17 2-propanone substituent. This allowed for the retrosynthetic clearing of several stereocenters and three of the compound's four rings through application of two intramolecular Michael additions. Thus, we arrived at aldehyde **10** as our first subtarget on the way to GB17 (**6**).



Scheme 2. Retrosynthetic analysis of (−)-GB17.

The conversion of aldehyde **10** into the desired *trans*-cyclohexane **9** required the development of a stereoselective catalyst-controlled intramolecular Michael addition. We therefore conducted an initial model study utilizing readily prepared aldehyde **12** (Scheme 3).[10] Related catalytic intramolecular Michael additions had been reported for the analogous cyclopentanes by the groups of List and Hayashi.[11] A survey of several available organocatalysts revealed that

[*] R. T. Larson, M. D. Clift, Prof. R. J. Thomson
Department of Chemistry, Northwestern University
2145 Sheridan Rd, Evanston, IL 60208 (USA)
E-mail: r-thomson@northwestern.edu

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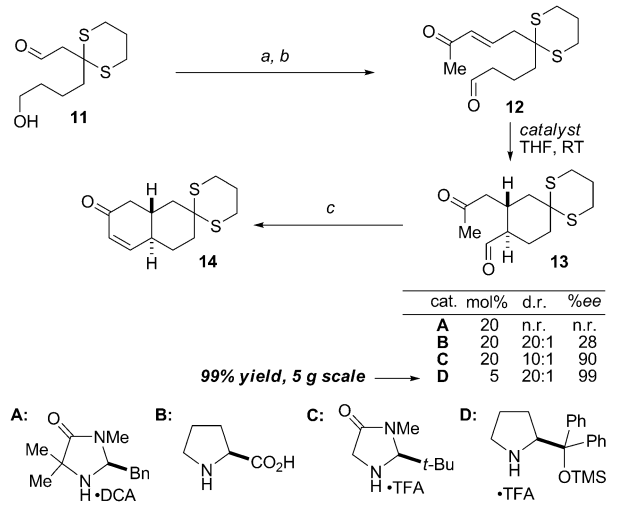
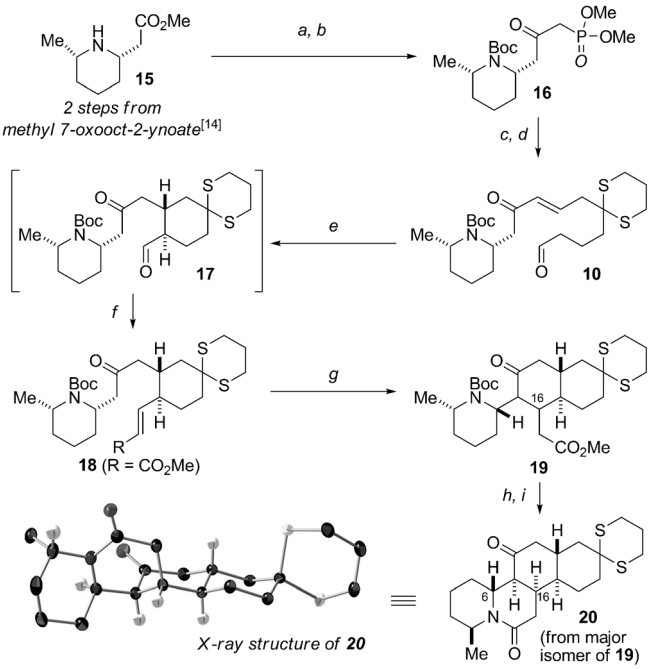


Scheme 3. Model study for the catalyst-controlled Michael addition. a) Dimethyl 2-oxopropylphosphonate (1.3 equiv), LiCl (2.3 equiv), iPr$_2$EtN (1.8 equiv), 91%; b) $(COCl)_2$ (1.6 equiv), $Me_2S(O)$ (4.2 equiv), Et_3N (9.5 equiv), 89%; c) TsOH· H_2O (10 mol%), $MgSO_4$ (2.6 equiv), PhMe, 100°C, 91%. Ts = *p*-toluenesulfonyl, DCA = dichloroacetic acid, TFA = trifluoroacetic acid.

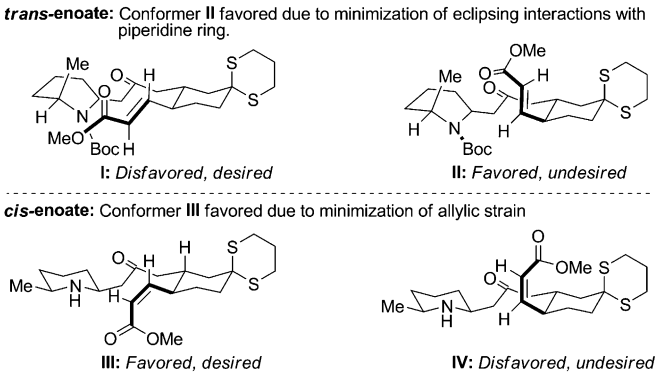


Scheme 4. Synthesis of tetracyclic lactam **20**. a) Dimethyl methylphosphonate (2.1 equiv), *n*-BuLi (2.1 equiv); b) i. $(Boc)_2O$ (3.0 equiv), Et_3N (3.0 equiv), DMAP (9 mol%); ii. K_2CO_3 (1.0 equiv), MeOH, 75% from **15**; c) iPr$_2$EtN (2.0 equiv), LiCl (2.0 equiv), **11** (0.97 equiv), 99%; d) DMP (1.2 equiv), Py (7.0 equiv), 85%; e) cat. **D** (5 mol%), THF, 99%; f) methyl (triphenylphosphoranylidene)acetate (1.3 equiv), THF, reflux, (91% from **10**); g) KOtBu (15 mol%), MeOH, (80% of major isomer); h) CF_3CO_2H; i) Cs_2CO_3 (1.0 equiv), MeOH, reflux, 44% from **19**. Boc = *tert*-butylcarbonyl, Py = pyridine, DMP = Dess–Martin periodinane, TBS = *tert*-butyldimethylsilyl.

the diphenylprolinol derivative **D**[12] provided the highest levels of both diastereo and enantiocontrol for the synthesis of cyclohexane **13** (20:1 d.r., 99% *ee*). We were able to conduct this reaction on a 5 g scale using 5 mol% of **D** to provide essentially quantitative yield of the carbocycle **13**, which could then be converted into the potentially useful decalin synthon **14**.[13] Interestingly, very poor results were obtained during attempts to carry out the intramolecular Michael reaction without the dithiane present, an outcome we interpret as arising from a lack of the favorable Thorpe–Ingold effect[14] that is present in dithiane **12**. In contrast, the corresponding cyclopentane reactions reported by the groups of List and Hayashi[11] do not seem to require such an effect.

With this valuable insight into our proposed catalyst-controlled cyclization, we began our GB17 (**6**) synthesis (Scheme 4). The enantioenriched phosphonate **16** was prepared from known *cis*-piperidine **15**[15] in three steps. Condensation of **16** with the previously prepared aldehyde **11**, under Masamune–Roush conditions[16] followed by oxidation, delivered the desired aldehyde **10** and set the stage for the first of our planned cyclization events. Exposure of aldehyde **10** to 5 mol% of organocatalyst **D** under our previously developed conditions smoothly generated the desired *trans*-substituted cyclohexane in excellent yield (99%). A Wittig reaction of aldehyde **17** gave rise to the *trans*-enoate **18** in high yield (91%) and with greater than 20:1 stereoselectivity. This sequence (**10** to **18**) could be carried out in one pot with no loss in yield or selectivity. At this juncture, we set out to explore conditions to promote the second planned intramolecular Michael addition. Potassium *tert*-butoxide was found to be effective for this reaction, affording the desired decalin ring **19** in high yield and as a 16:2:1:1 mixture of diastereomers. The major isomer could be readily separated (80% yield) and was converted into the tetracyclic lactam **20** by removal of the Boc group and cyclization using Cs_2CO_3 in methanol at reflux. X-ray analysis of a single crystal of **20**[13] revealed that the Michael addition had proceeded with the undesired sense of stereochemistry at C16 and that the C6 position of the piperidine had isomerized. 2D NMR studies indicated that piperidine inversion occurred under the lactamization conditions. Presumably, this isomerization proceeds through an E1cB elimination/conjugate addition sequence of the β-disposed nitrogen; although this discovery was potentially problematic for our synthesis, more pressing was the issue of the C16 stereochemistry.

We had anticipated that the correct C16 stereochemistry would be delivered from **18** by virtue of the enoate adopting a pseudo equatorial conformation **I** (Scheme 5), but this leads to unfavorable interactions with the piperidine ring, making the axial conformer **II** more favorable. Based upon the model proposed in Scheme 5, we hypothesized that the corresponding *cis*-enoate might provide the desired C16 stereochemistry via conformer **III**; the corresponding axial conformer **IV** would now be significantly higher in energy because of severe allylic strain. It also appeared that the carbamate protecting group enforced a 1,3-diaxial relationship between the substituents of the piperidine ring, giving rise to unfavorable steric interactions in the transition state leading to the desired isomer of decalin **19**. Therefore, it appeared to us that

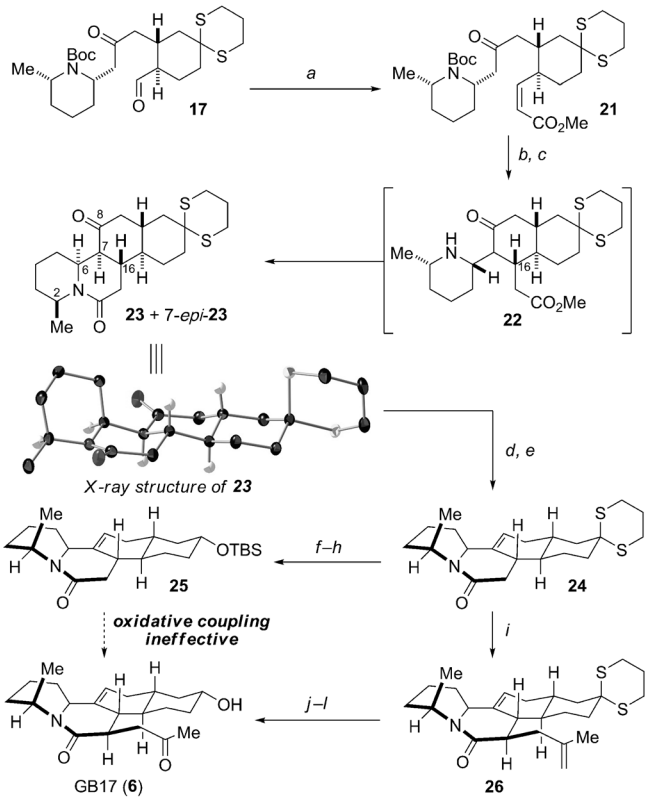


Scheme 5. Models for the intramolecular Michael addition.

a substrate possessing a *cis*-enoate and free piperidine nitrogen would significantly favor the desired stereochemical outcome.

Our modified approach commenced with a Still–Gennari olefination[17] of aldehyde **17** to afford enoate **21** in 80% yield after isolation (Scheme 6). Attempted cyclization of **21** using potassium *tert*-butoxide gave rise to a mixture of stereoisomeric products, with the major product corresponding to the same major isomer obtained from the cyclization of the *trans*-enoate **18**. This result confirmed our suspicions regarding the impact of the Boc-group, and it was therefore removed by treatment with TFA. While exposure of this free piperidine to potassium *tert*-butoxide led to significant decomposition and no desired cyclization products, the use of sodium methoxide in methanol produced a remarkable transformation. Under these conditions, the desired Michael addition proceeded smoothly, and the intermediate ester **22** underwent lactamization in situ to produce a product with the desired tetracyclic framework (**23**). A combined yield of 70% of the desired C16 isomers, differing only at C7, was obtained under these conditions. X-ray crystallographic analysis established the structure of **23**,[13] thereby unambiguously confirming the stereochemistry of the Michael addition (Scheme 6). It therefore appeared that the C16 stereocenter of **23** was set via conformer **III** (Scheme 5) as we had hypothesized, but also that this stereochemistry allowed lactamization of **22** to proceed without isomerization of the C6 piperidine stereocenter.[18]

Our endgame sequence called for conversion of the C8 ketone within **23** and 7-*epi*-**23** into the requisite $\Delta^{7,8}$ alkene. This transformation was readily achieved by generation of the corresponding enol triflate of **23** by the more thermodynamically stable enolate, followed by palladium-catalyzed reduction (80% yield of **24**, two steps).[19] Conversion of *epi*-**23** into the corresponding enol triflate was problematic. Fortunately, we found that *epi*-**23** could be equilibrated upon reexposure to NaOMe to give a 3:2 mixture of **23** and *epi*-**23**, allowing for easy recycling of material. From alkene **24**, installation of the equatorially disposed C12 hydroxy group proceeded first by cleavage of the thioketal,[20] then subsequent reduction of the resulting ketone along the axial vector using sodium borohydride. Protection of the hydroxy group as its *tert*-butyldimethylsilyl (TBS) ether **25** was carried out as a prelude to



Scheme 6. Synthesis of GB17. a) LiCl (2.0 equiv), iPr$_2$EtN (2.0 equiv), methyl 2-[bis(2,2,2-trifluoroethoxy)phosphoryl]ethanoate (1.2 equiv), 80%; b) CF_3CO_2H; c) NaOMe (6.0 equiv), MeOH, 70% **23** and *epi*-**23** from **21**; d) NaHMDS (1.0 equiv), Tf_2NPh (1.1 equiv), 86%; e) $Pd(OAc)_2$ (7 mol%), Ph_3P (14 mol%), HCO_2H (2.0 equiv), Bu_3N (3.0 equiv), 99%; f) Selectfluor (2.5 equiv), 69%; g) $NaBH_4$ (1.5 equiv); h) TBSCl (8.0 equiv), imidazole (16 equiv), DMF, 89% over 2 steps; i) NaHMDS (4.5 equiv), 3-bromo-2-methylprop-1-ene (1.2 equiv), 75% **26** and 13% *epi*-**26**; j) Selectfluor (2.5 equiv), 66%; k) $NaBH_4$ (4.5 equiv), 99%; l) OsO_4 (1.4 mol%), NMO (1.0 equiv); $NaIO_4$ (2.0 equiv), H_2O, 50%. HMDS = hexamethyldisilazide, Tf = trifluoromethanesulfonyl, Selectfluor = 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), NMO = *N*-methylmorpholine *N*-oxide.

installation of the propanone substituent (61% from **24**). Disappointingly, our attempts to utilize oxidative enolate coupling to install the propanone unit were met with difficulties. We did not observe formation of the desired adduct under a variety of conditions,[21] and so made recourse to an alternative strategy. We found alkylation of lactam **24** using NaHMDS and methallyl bromide provided the desired product **26** in 75% yield, along with 13% of the undesired axial epimer. Cleavage of the thioketal (66% yield), followed by reduction using sodium borohydride, installed the requisite equatorial C12 hydroxy group. Lastly, oxidative cleavage of the methallyl group afforded synthetic GB17 (**6**), which was spectroscopically identical to a natural sample (^{1}H NMR, ^{13}C NMR, and HRMS).

Our stereoselective synthesis of the tetracyclic alkaloid GB17 was executed through a route utilizing two intramolecular Michael additions to forge key stereochemical elements. The development of the diphenylprolinol-catalyzed

enantioselective intramolecular Michael addition was crucial to the success of the synthesis, and will likely find further applications for other natural product targets. The second intramolecular Michael addition provided an example of the profound effect enoate geometry can have during a substrate-controlled conjugate addition.[22] Future research on GB17 will focus on exploring its biological activity, which at this time remains unknown.

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[18] When these same conditions (TFA followed by NaOMe) were employed on the *trans*-enoate **18**, the same one-pot double cyclization ensued to deliver an approximate 1:1 ratio of the desired C16 stereoisomer **23** to the undesired isomer **20** in a combined yield of 50%. Interestingly, it appears that piperidine inversion is a prerequisite for lactamization of the incorrect C16 epimer.

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