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

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A Tale of Two Michaels

The first enantioselective total synthesis of (–)-GB17 is reported. Construction of this unique naphthoquinolizinone skeleton was achieved by two stereoselective intramolecular Michael additions. The first of these Michael additions is controlled by the use of a chiral organocatalyst, while the second cyclization is under substrate control and proceeds with concomitant lactam formation.

Keywords

Galbulimima Alkaloids; Natural Product Synthesis; Michael Addition

The *Galbulimima* alkaloids are isolated from the bark of rain forest 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 carbocyclic core (Figure 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] Research at Schering–Plough centered on himbacine led to SCH 530348 (now Vorapaxar at Merck),^[4] a promising thrombin receptor agonist whose clinical trial for treating acute coronary syndrome was halted in 2011 due to adverse side-effects.

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 both Chackalamannil^[6c] and Evans.^[6e] Movassaghi and coworkers 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 coworkers in 1965.^[1a] At that time only an elemental formula was reported – the structure of GB17 was only revealed in 2009 when Mander and coworkers reported an X-ray crystal

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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 1. 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 addition transforms. Thus, we arrived at aldehyde **10** as our first subtarget en route to GB17 (**6**).

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 2).^[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 the diphenylprolinol derivative **D**^[12] provided the highest levels of both diastereo and enantiocontrol for the synthesis of cyclohexane **13** (20:1 dr, 99% ee). This reaction could be conducted on a 5 g scale using 5 mol% of **D** to provide essentially quantitative yield of the carbocycle **13**, which could 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 a favorable Thorpe–Ingold effect that is present in dithiane **12**. In contrast, the corresponding cyclopentane reactions reported by 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 3). The enantioenriched phosphonate **16** was prepared from known *cis*-piperidine **15**^[14] in three steps. Condensation of **16** with the previously prepared aldehyde **11**, under Masamune–Roush conditions^[15] 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 *ent*-**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 >20:1 stereoselectivity. This sequence (i.e., **10** → **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 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 Cs₂CO₃ 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 the piperidine inversion occurred under the conditions required to induce lactamization. This isomerization presumably occurred through an E1cB elimination/conjugate addition sequence of the β-disposed nitrogen, and while 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** (Figure 2), but this leads to unfavorable interactions with the piperidine ring making the axial conformer **II** more favorable. Based upon the model proposed in Figure 2, 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 due to 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 tetracycle **19**. It appeared to us, therefore, that 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^[16] of aldehyde **17** to afford enoate **21** in 80% isolated yield (Scheme 3). 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 the desired tetracyclic framework of GB17 (i.e., **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 confirming the stereochemistry of the Michael addition unambiguously (Scheme 3). It therefore appeared that the C16 stereocenter of **23** was set via conformer **III** (Figure 2) as we had hypothesized, but also that this stereochemistry allowed lactamization of **22** to proceed without isomerization of the C6 piperidine stereocenter.^[17]

Our endgame sequence called for the 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** via the more thermodynamically stable enolate, followed by palladium-catalyzed reduction (80% yield of **24**, two steps).^[18] Conversion of *epi*-**23** into the corresponding enol triflate was problematic. Fortunately, we found that *epi*-**23** could be quantitatively equilibrated upon reexposure to NaOMe to a 3:2 mixture of **23** and *epi*-**23**, allowing for easy recycling of material. From alkene **24**, installation of the equatorially disposed C12 hydroxyl group proceeded first by cleavage of the thioketal,^[19] then subsequent reduction of the thus formed ketone along the axial vector using sodium borohydride. Protection of the hydroxyl group as its TBS ether **25** was carried out as a prelude to 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. Under a variety of conditions^[20] we did not observe formation of the desired adduct, 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%) followed by reduction using sodium borohydride installed the requisite equatorial C12 hydroxyl group. Lastly, oxidative cleavage of the methallyl group afforded synthetic GB17 (**6**) that was spectroscopically identical to a natural sample (¹H-NMR, ¹³C-NMR, 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 to 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.^[21] Future research on GB17 will focus on exploring its biological activity, which at this time remains unknown.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Selected Galbulimima Alkaloids

trans-enoate: Conformer II favored due to minimization of eclipsing interactions with piperidine ring.

I: *Disfavored, desired*

II: *Favored, undesired*

cis-enoate: Conformer III favored due to minimization of allylic strain

III: *Favored, desired*

IV: *Disfavored, undesired*

Figure 2.
Models for the Intramolecular Michael Addition.

Scheme 1.
Retrosynthetic Analysis of (-)-GB17

Scheme 2.

a) Dimethyl 2-oxopropylphosphonate (1.3 equiv), LiCl (2.3 equiv), *i*-Pr₂EtN (1.8 equiv), 91%; b) (COCl)₂ (1.6 equiv), Me₂S(O) (4.2 equiv), Et₃N (9.5 equiv), 89%; c) TsOH•H₂O (10 mol%), MgSO₄ (2.6 equiv), PhMe, 100 °C, 91%. Ts = *p*-toluenesulfonyl. D C A = dichloroacetic acid. TFA = trifluoroacetic acid.

Scheme 3.

a) Dimethyl methylphosphonate (2.1 equiv), *n*-BuLi (2.1 equiv); b) i. (Boc)₂O (3.0 equiv), Et₃N (3.0 equiv), DMAP (9 mol%); ii. K₂CO₃ (1.0 equiv), MeOH, 75% from **15**; c) *i*Pr₂EtN (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) KO*t*-Bu (15 mol%), MeOH, (80% of major isomer); h) CF₃CO₂H; i) Cs₂CO₃ (1.0 equiv), MeOH, reflux, 44% from **19**. Boc = *tert*-butylcarbonyl, Py = pyridine, DMP = Dess–Martin periodinane.

Scheme 4.

a) LiCl (2.0 equiv), *i*Pr₂EtN (2.0 equiv), methyl 2-(bis(2,2,2-trifluoroethoxy)phosphoryl)ethanoate (1.2 equiv), 80%; b) CF₃CO₂H; c) NaOMe (6.0 equiv), MeOH, 70% **23** + epi-**23** from **21**; d) NaHMDS (1.0 equiv), Tf₂NPh (1.1 equiv), 86%; e) Pd(OAc)₂ (7 mol%), Ph₃P (14 mol%), HCO₂H (2.0 equiv), Bu₃N (3.0 equiv), 99%; f) Selectfluor (2.5 equiv), 69%; g) NaBH₄ (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** + 13% epi-**26**; j) f) Selectfluor (2.5 equiv), 66%; k) NaBH₄ (4.5 equiv), 99%; l) OsO₄ (1.4 mol%), NMO (1.0 equiv); NaIO₄ (2.0 equiv), H₂O, 50%. HMDS = hexamethyldisilazide, Tf = trifluoromethanesulfonyl, Selectfluor = 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate), NMO = *N*-methylmorpholine *N*-oxide.