STRATEGIES IN THE CONSTRUCTION OF CLASS III GALBULIMIMA ALKALOIDS

Reported by Matthew M. Endo April 26, 2011

INTRODUCTION

The galbulimima alkaloids are a growing family of polycyclic compounds isolated from the bark of *Galbulimima belgraveana*. This family of natural products has received attention from the pharmaceutical industry due to recent reports of their bioactivity. Structure activity relationship (SAR) studies of himbacine (**1**), a class I galbulimima alkaloid, have led to the novel thrombin receptor antagonist SCH 530348,[1] which is currently in Phase III clinical trials for acute coronary syndrome. On the other hand, SAR studies are difficult for class II and class III galbulimima alkaloids because they contain highly complex ring systems, making them challenging to synthesize. This seminar will describe the recent efforts towards the synthesis of G.B. 13 (**2**), a class III galbulimima alkaloid, with a specific emphasis on the challenges associated with the construction of the C and D ring system.

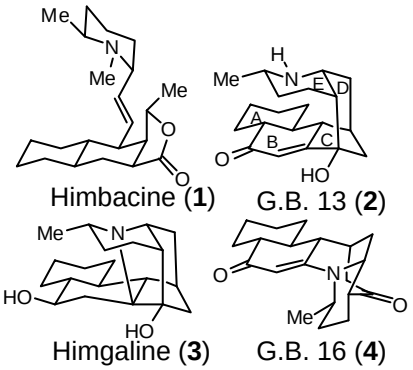

Figure 1. Representative galbulimima alkaloids.

SYNTHESIS OF (+)- AND (−)-G.B. 13 AND [3+3] CYCLOADDITION (MOVASSAGHI)

Movassaghi and co-workers reported the synthesis of G.B. 13 using a "transient-δ-imino ketone" strategy in the construction of the C and D rings.[2] The efficiency of that strategy led to the development of a formal [3+3] cycloaddition, in which a copper-mediated conjugate addition of an iminium chloride to cyclopent-2-enone followed by spontaneous tautomerization and addition to the ketone, allowed for efficient access to a tricyclic imino alcohol.[3] This methodology was then showcased in the synthesis of the class II galbulimima alkaloid himandrine.[4]

SYNTHESIS OF *ENT*-G.B. 13 AND *ENT*-HIMGALINE (EVANS)

In 2007, Evans and coworkers reported the first stereocontrolled synthesis of *ent*-G.B. 13 (**2**) utilizing the chiral auxilliary-controlled, enantioselective Diels-Alder reaction as the key step in the construction of the of the A and B rings.[5] The C and D rings were formed via stereoselective intramolecular Michael addition and an intramolecular enamine aldol, respectively. Evans also demonstrated that *ent*-himgaline (**3**) could be obtained from *ent*-G.B. 13 (**2**) via an aza-Michael reaction.

SYNTHESIS OF (±)-G.B. 13 VIA LATE-STAGE PYRIDINE REDUCTION (SARPONG)

The shortest synthesis (17 total steps) of G.B. 13 was reported by Sarpong and coworkers in 2009.[6] The synthesis utilized the construction of the E ring piperidine moiety via a late-stage pyridine reduction. This transformation enables the use of pyridine surrogates as masks for the piperidine moieties found in all known galbulimima alkaloids. In addition, the pyridine mask can serve as a flexible building block for SAR studies. The late-stage reduction was enabled by the development of an unprecedented Rh(I)-catalyzed hydroarylation of an unactivated ketone to construct the D ring.

CONVERGENT SYNTHESIS OF (−)-G.B. 13 AND (+)-G.B. 16 (MA)

Ma and coworkers recognized that late-stage construction of the C ring would enable access to both G.B. 13 (**2**) and G.B. 16 (**4**) via a common late-stage intermediate.[7] In addition, the late-stage construction of the C ring enabled the AB rings and DE rings to be prepared as separate building blocks and connected via Mukaiyama-Michael addition in a convergent synthesis. This synthesis enables flexibility in the AB ring and DE ring building blocks. The C ring of (−)-G.B. 13 (**2**) was formed via a SmI_2-mediated carbonyl-alkene coupling. The first synthesis of (+)-G.B. 16 (**4**) was completed using an intramolecular condensation in the C ring construction.

SUMMARY

The recent developments in the syntheses of G.B. 13 (**2**) revealed several efficient strategies towards the synthesis of galbulimima alkaloids. The auxilliary-controlled Diels-Alder reaction allows for enantioselective construction of the AB rings. The formal [3+3] cycloaddition and late-stage pyridine reduction provide flexible and efficient access to the CDE rings of class II and III galbulimima alkaloids. The convergent synthesis utilizes AB rings and DE rings as flexible building blocks in the syntheses of G.B. 13 (**2**), G.B. 16 (**4**), and himgaline (**3**). The efficiency and flexibility of each of these strategies could be applied in future SAR studies of G.B. 13 and other class II and III galbulimima alkaloids.

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