Syntheses of Galbulimima Alkaloids

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Abstract: The bark of the rain forest tree *Galbulimima belgraveana* has been identified as a rich source of fascinating natural products and so far 28 unique alkaloids have been isolated. The chemical interest in Galbulimima alkaloids started with the discovery of the promising biological activities of himbacine. Fifteen years after the first total synthesis of himbacine, this class of natural product still inspires, with the structurally more complex congeners himandrine, himgaline, and G.B. 13 as highly challenging synthetic targets. This review article summarizes and discusses all syntheses of Galbulimima alkaloids published to date.

Key words: Galbulimima alkaloids, natural products, total synthesis, Diels–Alder reaction, heterocycles, fused-ring systems

1 Introduction

The rain forest tree commonly called white magnolia or pigeonberry ash (Figure 1), endemic in Northern Australia and Papua New Guinea, was first botanically described in 1887 by F. Mueller and was originally named *Eupomatia belgraveana*.[1] Ever since this first disclosure, botanists have argued about the correct taxonomic classification and the plant was allocated different synonyms, the most common name being *Himantandra belgraveana*.[2,3] Today the name *Galbulimima belgraveana* is used and this name has been given as synonym to *Galbulimima baccata* by authors who consider the genus monotypic. Recently, Jessup reported that *Galbulimima belgraveana* is endemic to Papua New Guinea and Indonesia while *Galbulimima baccata* is found in Northern Queensland, Australia.[4] The rain forest tree is categorized as a member of the family Himantandraceae in the order Magnoliales.

Traditional medicine of the native populations of Papua New Guinea, Malaysia, and Northern Australia made use of this rain forest tree. The bark was chewed – often in combination with leaves of *Homalomena* sp. – to induce vision and dream-like states, for divination and religious rites, or it was swallowed to reduce abdominal pains.[5–7]

Figure 1 *Galbulimima baccata*[11]

Powdered bark in combination with wild tobacco and ginger served as natural treatment for hair lice.[7]

In 1948, Webb recorded that the bark of *Galbulimima baccata* is rich in alkaloids and several compounds were isolated.[8] In the following years, a total of 28 alkaloids were revealed, of which 22 were structurally characterized. The newly isolated compounds were either named with the prefix 'him', as the authors were under the impression that the botanically correct name for white magnolia was *Himantandra belgraveana*, or they were given numbers. Based on their structural properties, the Galbulimima alkaloids are subdivided in four classes; the structurally characterized alkaloids (classes I to III) are outlined in Figure 2, and the miscellaneous compounds (class IV) include the alkaloids for which characterization and thus categorization have not yet been achieved. Only recently, Mander published the structures of three Galbulimima alkaloids which had not been characterized previously.[9] While himgrine (**5**) possesses the structural features of a Galbulimima class I alkaloid, G.B. 16 (**24**) is more complex and could be classified as a class III alkaloid despite the missing C9–C20 bond. G.B. 17 (**25**) clearly stands out, as the structure of this natural product is unique among Galbulimima constituents.

Atoms and ring systems are labeled in Figure 2. The numbering for class I alkaloids is consistent throughout the chemical literature with only a few exceptions. There is no uniform system for the atom numbering of class II and class III alkaloids, so we have adopted the method suggested by Ritchie and Taylor.[10]

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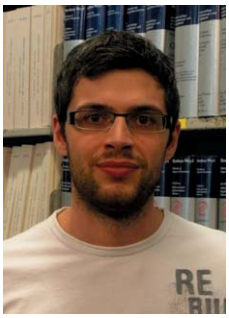
The synthetic interest in Galbulimima alkaloids began with the discovery of their biological properties. Himbacine (**2**) was identified as a potent muscarinic receptor antagonist[12,13] and a possible candidate for the treatment of senile dementia associated with Alzheimer's disease.[14,15] Furthermore, derivatives of himbacine are currently in clinical trial as antithrombotic agents.[16,17] Despite the high potential of himbacine, the biological properties of most other Galbulimima alkaloids remain unexplored.

A characteristic feature of all the Galbulimima alkaloids is a *trans*-decalin system. While the piperidine ring is attached to the decalin moiety via a carbon tether in class I alkaloids, the heterocycle is part of a complex fused-ring system in the class II and class III alkaloids. Although class II and III alkaloids are structurally more complex, the main carbon skeleton remains basically identical for all members of this family of natural products.

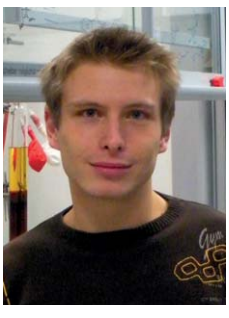
The structure of Galbulimima alkaloids has been intensively studied. Degradation studies revealed the structure of himbacine (**2**)[18,19] before the absolute configuration was determined by X-ray crystal structure analysis.[20] Subsequently, the structure of Galbulimima class II alkaloid himbosine (**7**) was established via X-ray crystal structure analysis of the corresponding hydrobromide[21] and the structures of himandrine (**6**) and himandridine (**8**) were determined by degradation studies and X-ray crystal structure analysis.[22,23] The structurally related Galbulimima class II alkaloids were assigned based on these findings without proof of the absolute configuration.[10,24] Because of the similarity of the carbon skeleton, it was assumed that subtypes of this family of natural products would also share the absolute configuration of the decalin system and the structures of himbadine (**23**), himgaline (**21**) and G.B. 13 (**22**) were assigned accordingly.[25,26] In 2006, Movassaghi[27] corrected the stereochemistry of G.B. 13 from 2*R* to 2*S* and this report also motivated Willis and Mander[28] to reevaluate this group of natural products. After extensive X-ray studies, they were able to prove, unambiguously, that the C2 stereochemistry is *S* in all of these alkaloids. Apart from that, they found the C10 and C15 stereocenters of more complex class II and class III alkaloids to be antipodal to those in himbacine (**2**) and related class I congeners. This highly interesting result is in full agreement with all total synthetic efforts published to date.

Biographical Sketches

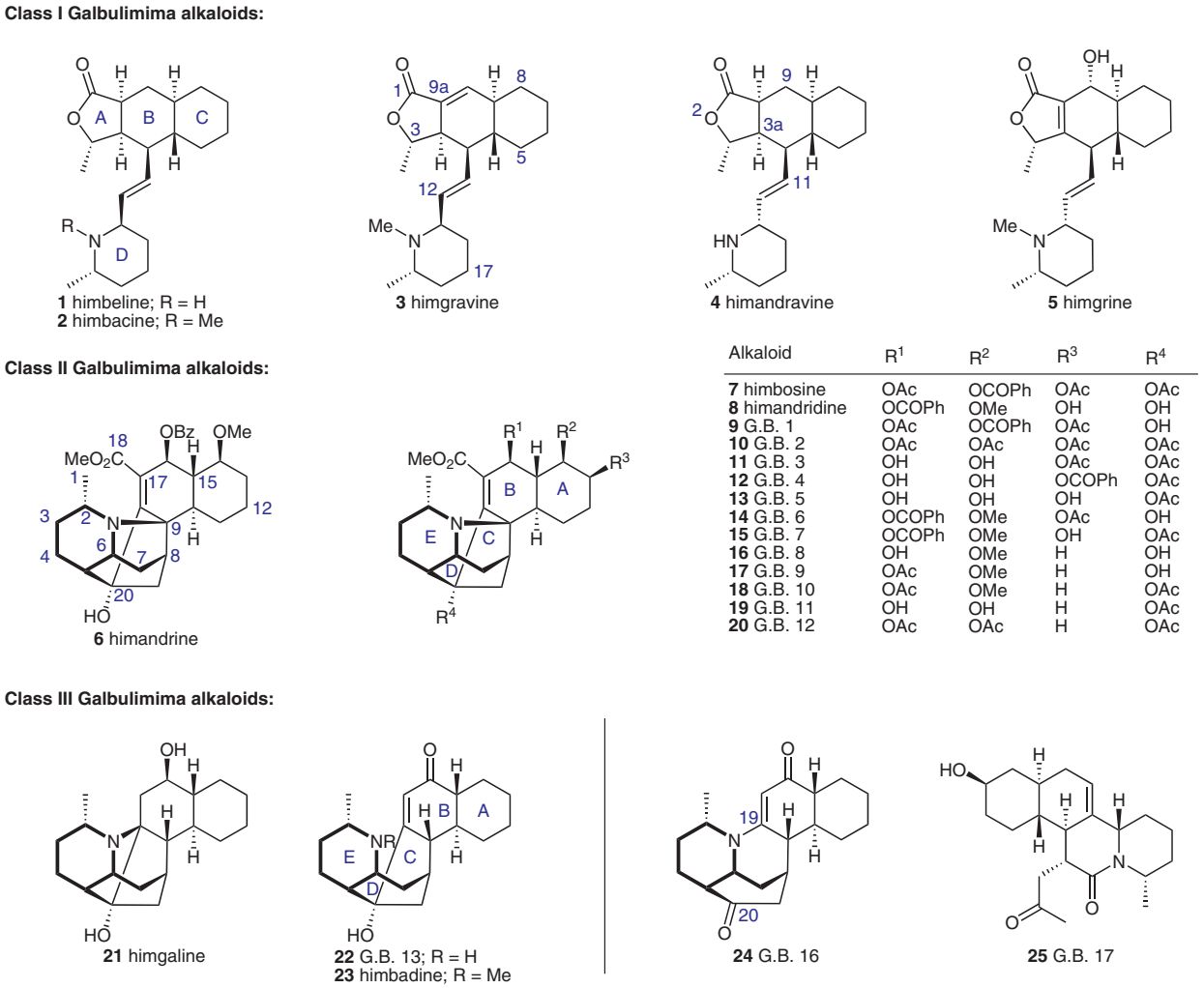
Uwe Rinner studied chemistry at the Technical University in Graz. After graduation he moved to Gainesville, Florida (USA) to pursue graduate studies in the area of total synthesis of Amaryllidaceae constituents with Prof. Hudlicky. In 2003, he received is Ph.D. from the University of Florida and moved to Brock University, Ontario (Canada) for postdoctoral studies. After returning to Austria, Uwe Rinner joined the research group of Prof. Johann Mulzer and was active in the field of diterpene chemistry before he started his own research group in 2007. His current interests include the synthesis of diterpenes and the preparation of other biologically interesting natural products.



Christoph Lentsch was born in 1981 in Zams, Austria. He studied chemistry at the University of Vienna, where he received his M.Sc. in 2006 under the supervision of Prof. Walther Schmid. Currently he is carrying out his Ph.D. studies under the guidance of Prof. Johann Mulzer in the field of natural product total synthesis.



Christian Aichinger was born in 1984 in St. Pölten, Austria. He studied chemistry at the University of Vienna, where he received his M.Sc. in 2008 under the supervision of Prof. Michael Widhalm, working on improved methods to access binaphthyl derivatives. Currently, he is working towards his Ph.D. in the Rinner group, studying the total synthesis of euphosalicin. His research interests include transition-metal-mediated coupling reactions and the synthesis of biologically important natural products and derivatives.



Alkaloid	R^1	R^2	R^3	R^4
7 himbosine	OAc	OCOPh	OAc	OAc
8 himandridine	OCOPh	OMe	OH	OH
9 G.B. 1	OAc	OCOPh	OAc	OH
10 G.B. 2	OAc	OAc	OAc	OAc
11 G.B. 3	OH	OH	OAc	OAc
12 G.B. 4	OH	OH	OCOPh	OAc
13 G.B. 5	OH	OH	OH	OAc
14 G.B. 6	OCOPh	OMe	OAc	OH
15 G.B. 7	OCOPh	OMe	OH	OAc
16 G.B. 8	OH	OMe	H	OH
17 G.B. 9	OAc	OMe	H	OH
18 G.B. 10	OAc	OMe	H	OAc
19 G.B. 11	OH	OH	H	OAc
20 G.B. 12	OAc	OAc	H	OAc

Figure 2 Classification of Galbulimima alkaloids

In a first speculation about the biosynthesis of Galbulimima alkaloids, Taylor and Ritchie[18,26] suggested that these natural products are derived from either nine acetates and one pyruvate unit or ten acetates and a one-carbon unit. Movassaghi[27,29,30] published a hypothetical biogenesis which explains the generation of class II and class III Galbulimima alkaloids. Mander suggested biosynthetic pathways for the formation of G.B. 16 and G.B. 17.[9] Aside from these reports, no further information about the biosynthesis of Galbulimima alkaloids has appeared.

2 Syntheses of Galbulimima Alkaloids

Several syntheses of Galbulimima alkaloids have appeared in the literature over the last few years and these efforts are listed in Table 1. Despite the growing interest in this highly fascinating class of natural products, syntheses of Galbulimima alkaloids have not been summarized previously.

This review article concentrates on total and formal syntheses of members of this interesting class of natural products, and all of the syntheses outlined in Table 1 are discussed within this article. Reports describing the preparation of derivatives or simplified models for biological activity studies are not included. For clarity and better understanding, key steps are depicted in blue color within the schemes.

2.1 Class I Alkaloids

Syntheses of class I alkaloids are discussed in detail below. All synthetic efforts utilize Diels–Alder reactions as the key step to establish the decalin unit of the natural product. As each of the approaches varies by the bonds formed during the cycloaddition step, different strategies for the construction of the Diels–Alder precursors were applied (Scheme 1).

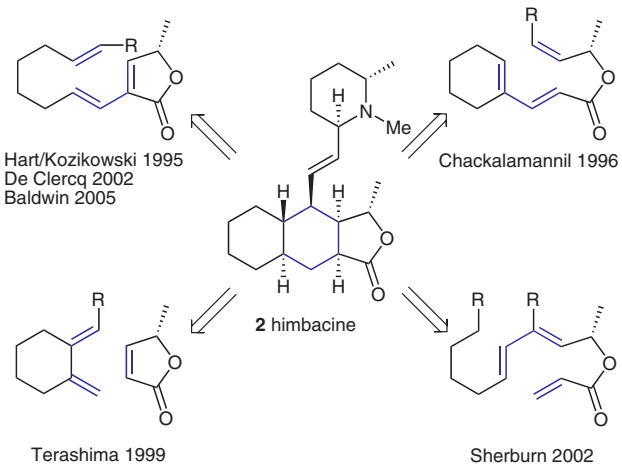
Hart, Kozikowski, 1995 (Himbacine, Himbeline)

In 1995, Hart and Kozikowski[31,42] reported the first total synthesis of himbacine via himbeline, as outlined in Scheme 2. The key step in this synthetic effort is the formation of the *trans*-decalin system by an intramolecular Lewis acid promoted Diels–Alder reaction of thioester **29**.

Table 1 Syntheses of Galbulimima Alkaloids

Alkaloid class	Compound	Author	Publication year	Number of steps	Overall yield
class I	himbacine/himbeline	Hart, Kozikowski[31]	1995	19 (himbeline) 20 (himbacine)	5.4% (himbeline) 3.8% (himbacine)
class I	himbacine/himbeline	Chackalamannil[32]	1996	11 (himbeline) 12 (himbacine)	12.4% (himbeline) 9.7% (himbacine)
class I	himbacine (formal synthesis)	Terashima[33]	1999	18	12.6%
class I	himandravine	Chackalamannil[34]	2001	12	17.0%
class I	himbacine (formal synthesis)	De Clercq[35]	2002	13	6.6%
class I	himbacine (formal synthesis)	Sherburn[36]	2003	26	2.4%
class I	himbacine/himbeline	Baldwin[37]	2005	12 (himbeline) 13 (himbacine)	3.1% (himbeline) 2.3% (himbacine)
class II	himandrine	Movassaghi[29]	2009	28	0.7%
class III	(±)-G.B. 13	Mander[38]	2003	30	0.2%
class III	G.B. 13/himgaline	Chackalamannil[39]	2006	31 (G.B. 13) 33 (himgaline)	0.5% 0.3%
class III	G.B. 13	Movassaghi[27]	2006	19	1.7%
class III	*ent*-G.B. 13/*ent*-himgaline	Evans[40]	2007	31 (*ent*-G.B. 13) 32 (*ent*-himgaline)	1.0% (*ent*-G.B. 13) 0.9% (*ent*-himgaline)
class III	(±)-G.B. 13	Sarpong[41]	2009	18	1.2%

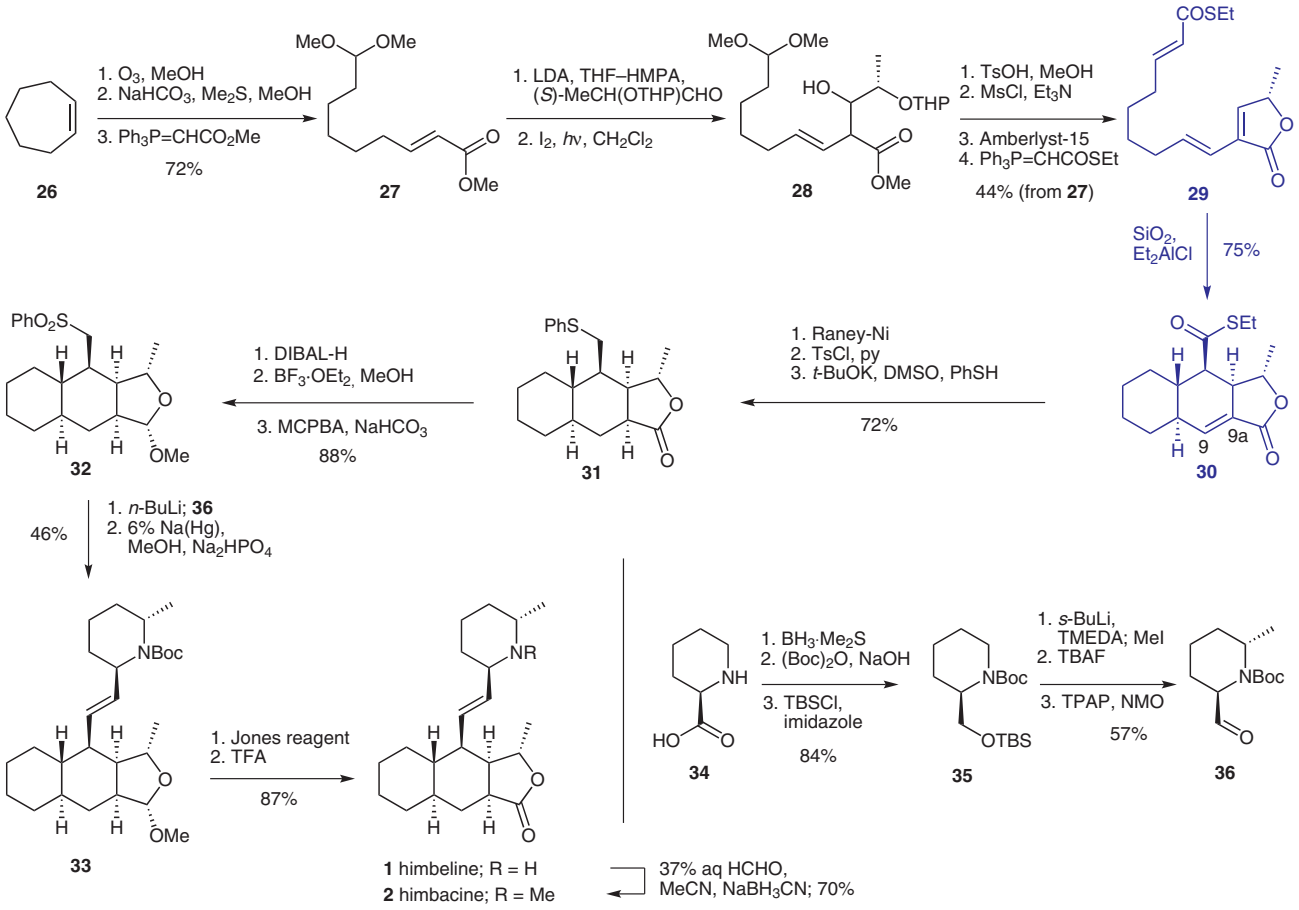
The reaction sequence started with cycloheptene (**26**) which was converted into 7,7-dimethoxyheptanal via ozonolysis in the presence of methanol following a procedure described by Schreiber.[43] Subsequent Wittig olefination gave α,β-unsaturated ester **27** as a 2:1 mixture of geometrical isomers. Deprotonation of this material with lithium diisopropylamide afforded the corresponding enolate, which reacted with O-protected (*S*)-2-hydroxypropanal to give tetrahydropyranyl ether **28**. By exposing alkene **28** to sunlight in the presence of iodine, the ratio of the desired *trans*-isomer could be increased to 32:1. The unsaturated γ-lactone was obtained by cleavage of the acid-labile tetrahydropyran group in methanol and elimination of the hydroxy functionality.



Scheme 1 Different strategies in the syntheses of himbacine (**2**)

Installation of the thioester and formation of the triene was achieved by cleavage of the acetal followed by Wittig olefination. Diels–Alder cyclization of triene **29** under thermal conditions afforded a 3:2 mixture of the desired *endo*-cycloadduct **30** and the corresponding *exo*-derivative. The *endo*/*exo* selectivity could be improved by addition of Lewis acids. The best results (*endo*/*exo* = 20:1) were obtained with a heterogeneous promoter prepared from diethyl aluminum chloride and silica gel.

The synthetic strategy envisaged the introduction of the piperidine ring via Julia–Lythgoe olefination and the following steps were devoted to the installation of the sulfone required for this olefination reaction. Reduction of the thioester with Raney nickel under concomitant stereoselective hydrogenation of the remaining double bond in the decalin system (C9–C9a), and conversion of the primary alcohol into the corresponding tosylate and displacement with thiophenol gave sulfide **31**. In order to circumvent compatibility issues of a deprotonated sulfone and a lactone present in one species, the lactone moiety in **31** was converted into a methyl acetal by reduction with diisobutylaluminum hydride and exposure to boron trifluoride etherate in methanol (the original erroneous stereochemical assignment of the acetal carbon atom[31] was corrected in the full paper published in 1997).[42] Subsequently, sulfur was oxidized by means of *m*-chloroperoxybenzoic acid to afford sulfone **32** in good overall yield. The required coupling partner for the Julia–Lythgoe olefi-

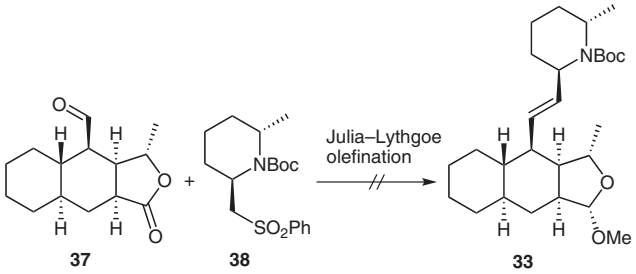


Scheme 2 Hart and Kozikowski's synthesis of himbacine (**2**)

nation reaction – aldehyde **36** – was prepared from commercially available (*R*)-piperidinecarboxylic acid (**34**). Reduction followed by N- and O-protection gave *tert*-butyldimethylsilyl ether **35**. After stereoselective methylation, the silyl ether was removed and oxidation using Ley's protocol[44] completed the reaction sequence to aldehyde **36**.

The first synthesis of himbacine was completed by the coupling of sulfone **32** and aldehyde **36**, which after treatment with sodium-amalgam delivered *trans*-alkene **33**. It is interesting to note that the original synthetic plan devised by Hart and Kozikowski proposed a Julia–Lythgoe olefination between aldehyde **37** and sulfone **38** as shown in Scheme 3. When this protocol failed, the problem was solved by preparing coupling partners with reversed functionalities.

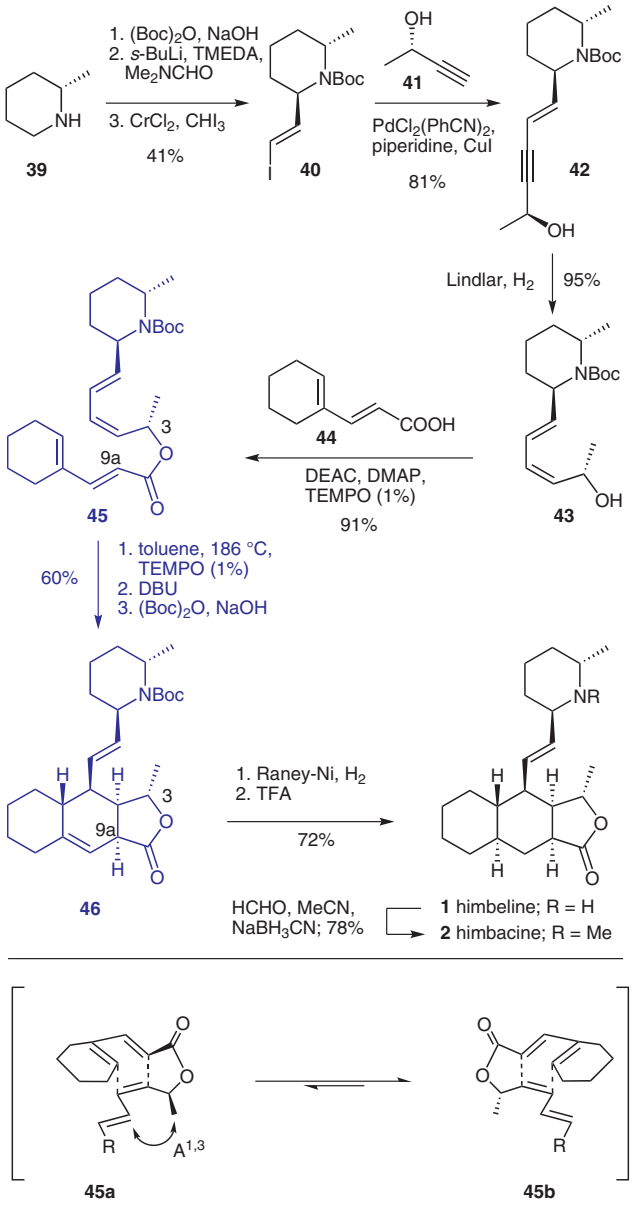
Oxidation of the protected lactol with Jones reagent and cleavage of the Boc group on the piperidine nitrogen afforded himbeline (**1**) which was converted into himbacine (**2**) by N-methylation under reductive alkylation conditions. Overall, himbeline was prepared in 17 steps and 5.4% yield and himbacine was obtained in 18 steps and 3.8% yield.



Scheme 3 Attempted Julia–Lythgoe olefination of aldehyde **37** and sulfone **38**

Chackalamannil, 1996 (Himbacine, Himbeline)

Shortly after the publication of the first synthesis of himbacine by Hart and Kozikowski, Chackalamannil[32] reported his route to the alkaloid. The key step is an intramolecular Diels–Alder reaction of a substrate which bears the complete carbon framework of the natural product as shown in Scheme 4. The stereochemistry of this reaction was controlled by the C3-methyl group attached to the projected γ-lactone. Conformation **45b** is energetically favored, as the methyl group in **45a** adds considerable allylic strain. In this intramolecular cyclization reaction, the piperidinyl-substituted diene system acts as dienophile. The authors suggest that the vinylcyclohexenyl



Scheme 4 Chackalamannil's synthesis of himbacine (**2**)

moiety is more likely to adopt the required cisoid conformation.

Amine **39** was obtained by chiral resolution of commercially available 2-methylpiperidine with L-tartaric acid. Boc-protection of the nitrogen and installation of an aldehyde functionality via treatment of the carbamate with *sec*-butyllithium and addition of dimethylformamide was followed by Takai iodovinylation to afford vinyl iodide **40**.[45] This material was used in a palladium-mediated coupling reaction with (*S*)-but-3-yn-2-ol (**41**) and the triple bond in alkyne **42** was reduced to the corresponding double bond via Lindlar hydrogenation. Esterification of alcohol **43** with acid **44** (accessible in three steps from cyclohexane carbaldehyde)[46] cleanly gave key intermediate **45** which was used in the intramolecular Diels–Alder reaction. As pointed out earlier, this intramolecular process only afforded the *exo*-adduct with a *trans*-fused lactone ring attached to the decalin system. As reaction conditions only afforded partial isomerization to the desired *cis*-fused material, the cycloaddition product was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene, resulting in complete epimerization at C9a. Reprotection of the piperidinyl nitrogen was necessary as the high reaction temperature required for the Diels–Alder reaction also resulted in thermally induced cleavage of the Boc functionality. Stereoselective hydrogenation of the decalin double bond in **46** from the less hindered face of the molecule with Raney nickel and cleavage of the Boc group afforded himbeline (**1**) which was converted into himbacine (**2**) following the reductive alkylation protocol applied by Hart and Kozikowski.[31]

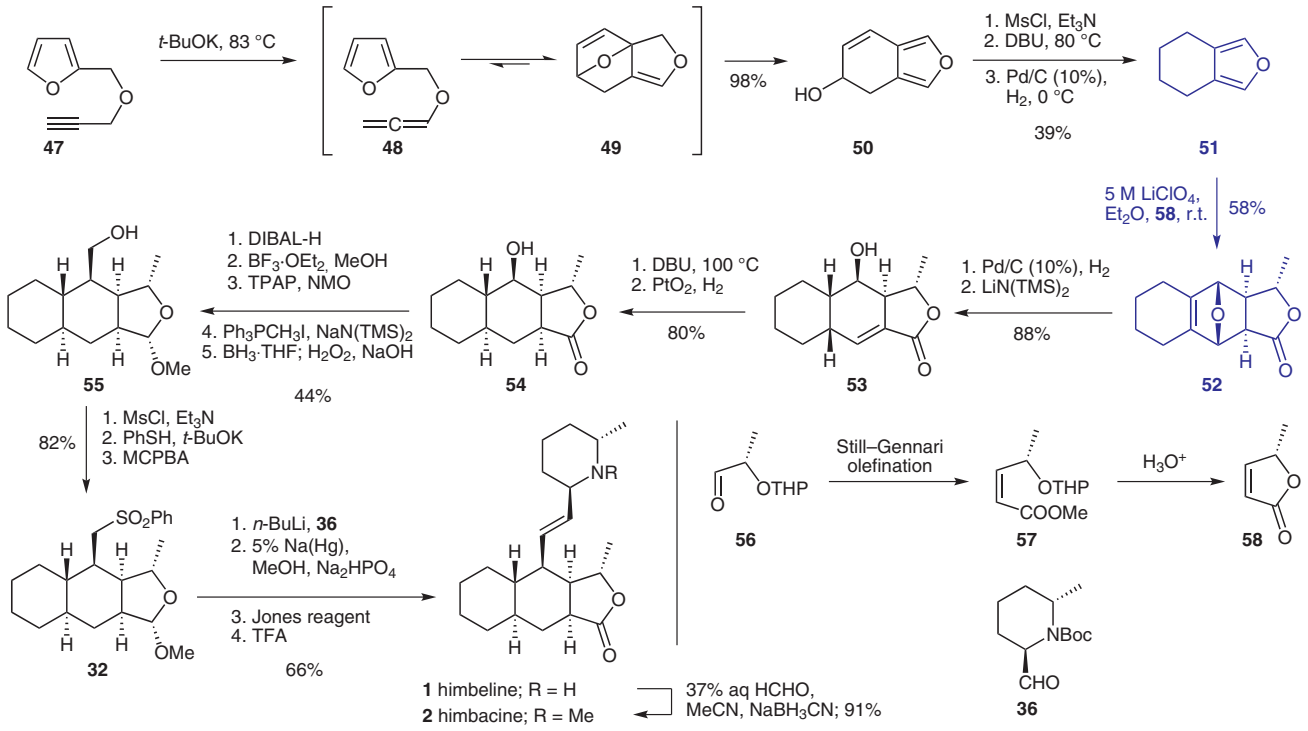
Chackalamannil thus presented a highly efficient route to himbacine and the synthesis is the shortest and highest-yielding process published so far. Only 12 steps (11 from Boc-protected methyl piperidine) were required to elaborate this piperidine alkaloid from inexpensive and readily available starting materials, and the author reported a 9.7% overall yield.

Terashima, 1999 (Himbacine)

In 1999, Terashima and co-workers[14,33] reported a synthesis of himbacine (**2**) based on an intermolecular Diels–Alder reaction of tetrahydroisobenzofuran **51** and chiral butenolide **58** as outlined in Scheme 5.

Following a procedure developed by Kanematsu,[47] **50** was obtained starting from propargyl ether **47** by an intramolecular Diels–Alder reaction and base-catalyzed ring opening sequence of cycloadduct **49**. The hydroxy functionality in **50** was converted into a leaving group and eliminated. Hydrogenation finally delivered the coupling partner for the key cycloaddition reaction. Butenolide **58** was accessible from tetrahydropyranyl-protected (*S*)-2-hydroxypropanal (**56**) by Still–Gennari olefination and acid-catalyzed cyclization in large quantities.[48] Reaction of diene **51** and butenolide **58** in diethyl ether containing lithium perchlorate afforded the *exo*-cycloadduct **52** as sole product. Hydrogenation of the double bond from the sterically less hindered face of the decalin derivative **52** and base-mediated opening of the oxygen bridge gave alkene **53**. Isomerization of the double bond and hydrogenation cleanly afforded alcohol **54**.

Installation of the piperidinyl moiety was accomplished via the Julia–Lythgoe olefination protocol which had already proven successful in the work of Hart and Kozikowski. Therefore, a one-carbon elongation was required, which, after protection of the lactone as methyl acetal, was carried out by oxidation of the secondary alcohol and subsequent Wittig olefination. Hydroboration of the double bond delivered primary alcohol **55** which was converted into sulfone **32**. The synthesis was completed in analogy to Hart and Kozikowski's protocol with significantly higher reported yields.

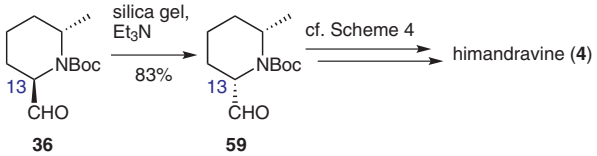


Scheme 5 Terashima's synthesis of himbacine (2)

The natural product was obtained in 18 linear steps with 12.6% overall yield. As several steps of the endgame were adopted from earlier studies, this synthetic effort constitutes a formal synthesis of the natural product. The elegance of the synthesis with a nice intermolecular Diels–Alder key step suffers from the tedious C1 elongation sequence. Terashima also employed the reaction sequence to prepare derivatives of the natural product for further structure–activity relationship studies.

Chackalamannil, 2001 (Himandravine)

As himandravine (**4**) and himbeline (**1**) only differ in the stereochemistry at C13, synthetic routes to himbeline (**1**) can be modified in a way to grant access to himandravine (**4**) as well. In 2001, Chackalamannil[34] reported the first total synthesis of himandravine (**4**) based on results obtained in his earlier work on the epimeric alkaloid. The preparation of **4** was carried out in complete analogy to the synthesis of himbacine (**2**) and the only difference was the epimerization of starting material **36** with triethylamine on silica gel to aldehyde **59** as outlined in Scheme 6. The alkaloid was obtained after 12 synthetic operations (11, if counting from Boc-protected piperidine **36**) in 17.0% yield overall.



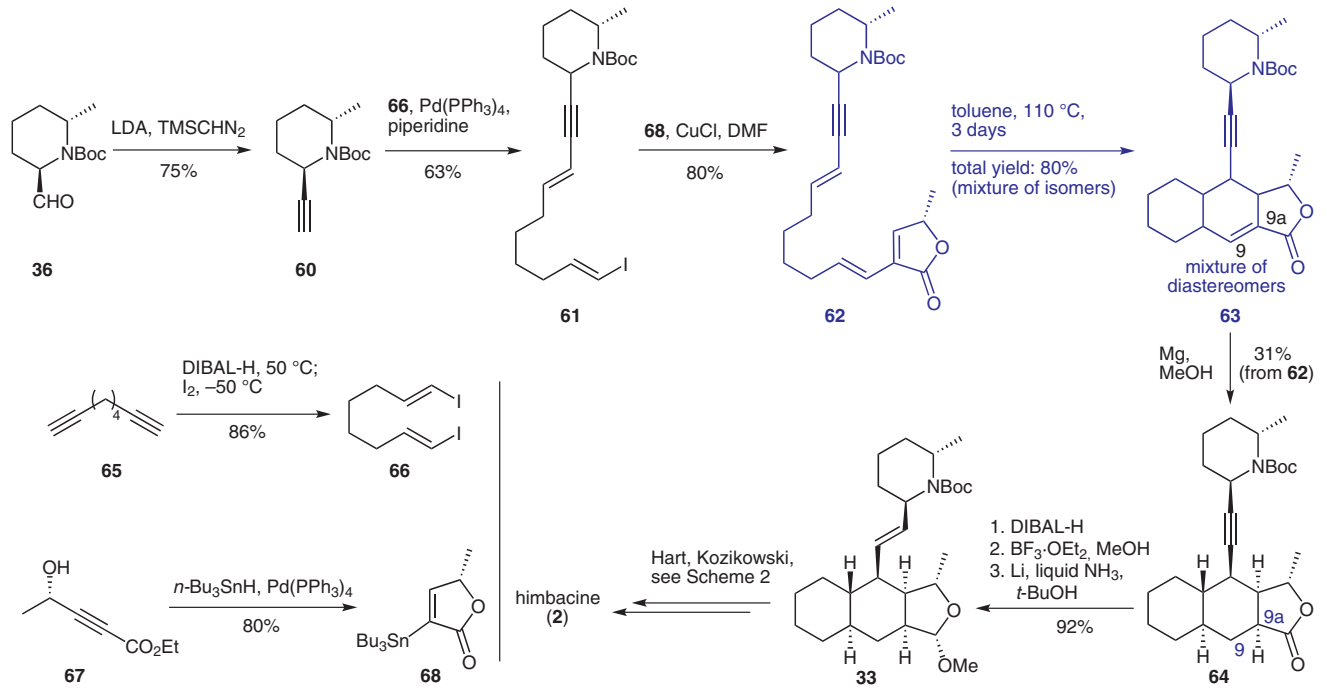
Scheme 6 Epimerization of aldehyde **36** in Chackalamannil's synthesis of himandravine (**4**)

DeClercq, 2002 (Himbacine)

A Diels–Alder strategy similar to that already employed by Hart and Kozikowski[31] in their first total synthesis of himbacine was used by De Clercq[35,49] who presented a formal synthesis of the Galbulimima alkaloid in 2002 (Scheme 7).

Aldehyde **36** was converted into alkyne **60** with deprotonated (trimethylsilyl)diazomethane in good yield and subjected to a Sonogashira coupling reaction with vinyl iodide **66**, easily obtained by *syn*-hydroalumination of commercially available octa-1,7-diyne (**65**). Stille coupling of iodide **61** with stannylated butenolide **68** delivered the precursor for the key cyclization reaction. The cycloaddition was accomplished in refluxing toluene after a reaction time of three days, resulting in a complex mixture of isomers in 80% total yield. The double bond between C9 and C9a in conjugation to the ester functionality was reduced with magnesium in methanol and intermediate **64** was obtained in 31% yield over two steps. De Clercq decided to convert the alkyne into an already known intermediate. Thus, the lactone moiety was reduced and converted into its methyl ketal before the triple bond was reduced under dissolving metal conditions affording alkene **33** in excellent yield. As this material was described in Hart and Kozikowski's synthesis of himbacine, the reduction concludes the formal synthesis of the alkaloid.

De Clercq thus presented an approach towards Galbulimima alkaloids that is highly valuable for obtaining various derivatives for SAR studies. All major isomers isolated after the Diels–Alder/reduction sequence were further converted into himbacine analogues and used in biologi-



Scheme 7 De Clerq's formal synthesis of himbacine (**2**)

cal investigations. However, the low selectivity of the Diels–Alder reaction is a drawback and obstacle for an efficient preparation of himbeline (**1**) and himbacine (**2**).

Sherburn, 2003 (Himbacine)

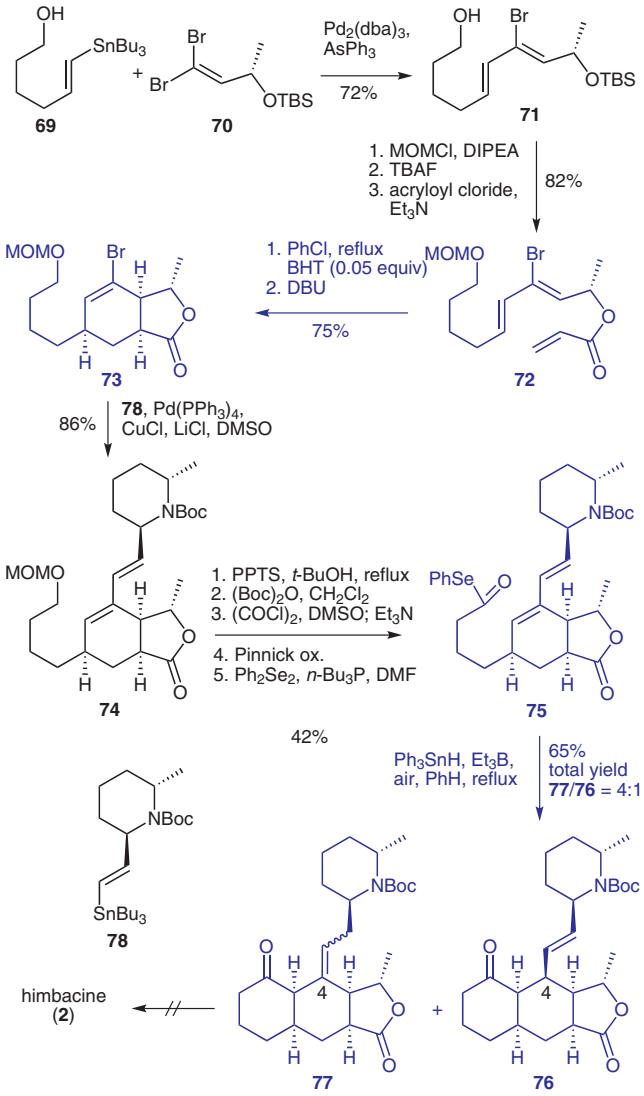
In 2003, Sherburn[36] published a formal synthesis of himbacine (**2**) with an intramolecular Diels–Alder reaction and a radical cyclization as key steps. The alkene moiety formed in the Diels–Alder reaction is utilized as reactive handle for the radical process. The synthesis is outlined in Schemes 8 and 9.

Stille coupling of vinylstannane **69** and dibromide **70**, derived from (*S*)-lactic acid in three steps,[50] afforded diene **71**. Protection of the free hydroxy functionality and cleavage of the silyl ether paved the way for the preparation of Diels–Alder precursor **72** which was obtained after esterification of the primary alcohol with acryloyl chloride. The thermal cycloaddition reaction was carried out in refluxing chlorobenzene and delivered a mixture of *cis*- and *trans*-fused bicyclic reaction products; this mixture was converted into the desired *cis*-fused adduct **73** in quantitative yield by exposure to 1,8-diazabicyclo[5.4.0]undec-7-ene. The piperidinyl side chain was attached by way of a Stille coupling between stannane **78** and the vinyl bromide moiety in **73** and the corresponding *E*-alkene **74** was obtained in high yield.

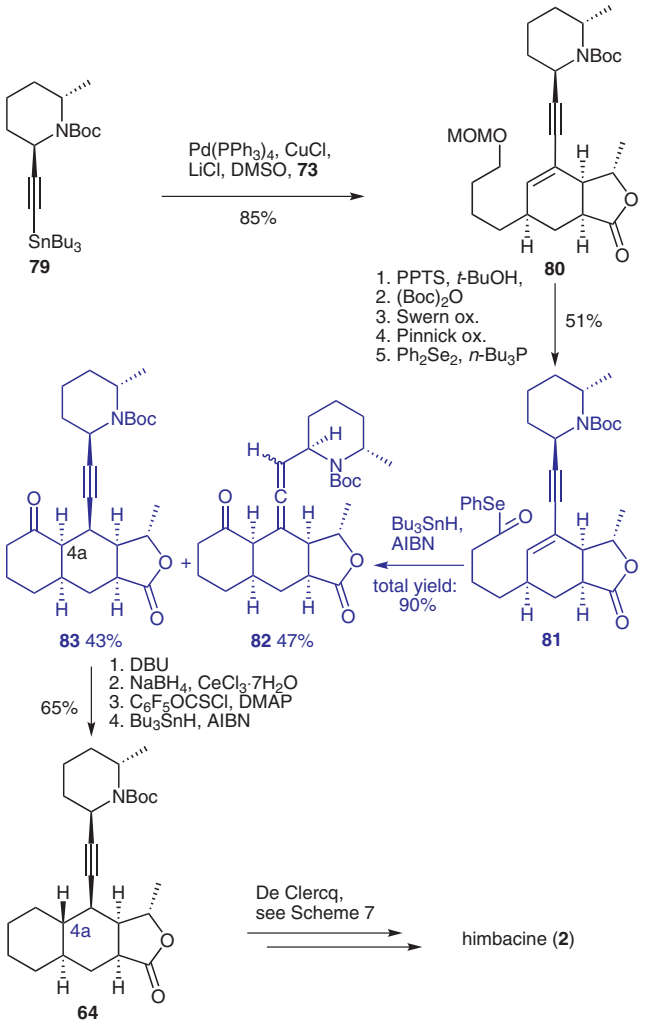
The following steps were devoted to the installation of the selenoate ester required for the radical cyclization. This was achieved by cleavage of the methoxymethyl ether followed by oxidation of the primary alcohol under Swern and Pinnick[51] conditions and exposure of the carboxylic acid to diphenyl diselenide and tributyl phosphine. For the radical cyclization reaction, different reaction conditions and mediators were employed. The desired cyclization product **76** could be isolated without evidence of the C4 epimer, thus indicating the high degree of stereocontrol in this reaction. However, the main product in this key step was identified to be a mixture of *E*- and *Z*-isomers of ketone **77**. As the maximum yield of the desired product did not exceed 13%, the approach was abandoned.

As delocalized propargylic radicals react almost exclusively at the propargylic site, the modified approach asked for the preparation of alkyne **80** which was achieved by coupling of stannane **79** with bromide **73** as outlined in Scheme 9. In analogy to the procedure described above, the methoxymethyl group in **80** was cleaved and the hydroxy functionality was oxidized to the corresponding carboxylic acid by applying Swern and subsequent Pinnick[51] oxidation protocols. Esterification with diphenyl diselenide and tributyl phosphine again proceeded smoothly and selenoate **81** was isolated in 51% overall yield from methoxymethyl ether **80**. All cyclization efforts resulted in approximately 1:1 mixtures of alkyne **83** and allene **82**; the best results were obtained when the reaction was carried out in refluxing benzene with a total yield of 90% and 43% yield of the desired alkyne **83**.

Epimerization of C4a by treatment of ketone **83** with 1,8-diazabicyclo[5.4.0]undec-7-ene was followed by Luche reduction. The Barton–McCombie deoxygenation protocol required installation of a thionocarbonate. Unexpectedly, all attempts to introduce the thionocarbonate failed and when more forcing conditions were applied, the corresponding secondary chloride was obtained. As pointed out by Sherburn, this transformation is unprecedented with thionocarbonates but has been observed with xan-



Scheme 8 Sherburn's first approach towards himbacine (**2**)



Scheme 9 Sherburn's formal synthesis of himbacine (**2**)

thates.[52] As dechlorination proceeds under same reaction conditions as removal of the xanthate or thionocarbonate, the formation of a chloride might have easily been overlooked in previous deoxygenation protocols.

The formal synthesis of himbacine (**2**) was concluded by such a radical dechlorination, resulting in the formation of alkyne **64** which had been reported as intermediate in De Clercq's preparation of the natural product.

Sherburn's synthesis clearly suffered from unexpected problems such as migration of the double bond in the first approach and formation of the allene in the second approach which significantly reduces the overall efficiency of the published formal synthesis. The utilization of both bromines in the starting material for coupling reactions, and the use of the double bond generated in the Diels–Alder reaction for the radical cyclization are worth mentioning. However, the installation of the selenoate ester requires several synthetic operations and preparation of the unfunctionalized six-membered ring is tedious. Counting, 26 operations are necessary to prepare the natural product with a yield of 2.6% overall.

Baldwin, 2005 (Himbacine, Himbeline, Himandravine)

The latest synthetic contribution to class I Galbulimima alkaloids was published by Baldwin in 2005.[37] The approach mimics the assumed biosynthetic pathway and features an intramolecular Diels–Alder reaction similar to the strategies presented by Hart and Kozikowski and by De Clercq accompanied by simultaneous formation of the piperidine ring.

Starting from cycloheptene (**26**), Baldwin repeated the first six steps of Hart and Kozikowski's route to aldehyde **84**. Conversion into α,β-unsaturated aldehyde **86** was effected by reaction with aldimine **85**, as traditional Wittig olefination protocols unexpectedly delivered the desired product only in low yield. Chiral phosphonate **92** was derived from Boc-protected methyl piperidine **90** through ruthenium tetraoxide oxidation and reaction with lithiated dimethyl methylphosphonate. The key cyclization precursor **87** was accessed via Horner–Emmons reaction of aldehyde **86** and phosphonate **92**. Exposure to trifluoro-

acetic acid in dichloromethane, followed by cyanoborohydride reduction, gave the desired tetracycle **88** as an inseparable mixture of C13 epimers. Reprotection of the nitrogen and hydrogenation of the trisubstituted double bond afforded lactones **33** and **89** which were separated by column chromatography. The two diastereomers **33** and **89** were then elaborated into himbacine (**2**; from lactone **33**) and himandravine (**4**; from lactone **89**) as outlined in Scheme 10.

In his effort to improve upon Hart and Kozikowski's synthesis of himbacine, Baldwin presented a highly divergent approach towards all class I Galbulimima alkaloids. The key step not only establishes the decalin system but also delivers the piperidine unit of the natural products. Given that the key Diels–Alder cycloaddition delivers a mixture of epimers, the strategy does not allow the preparation of a single alkaloid in high yield.

2.2 Class II Alkaloids

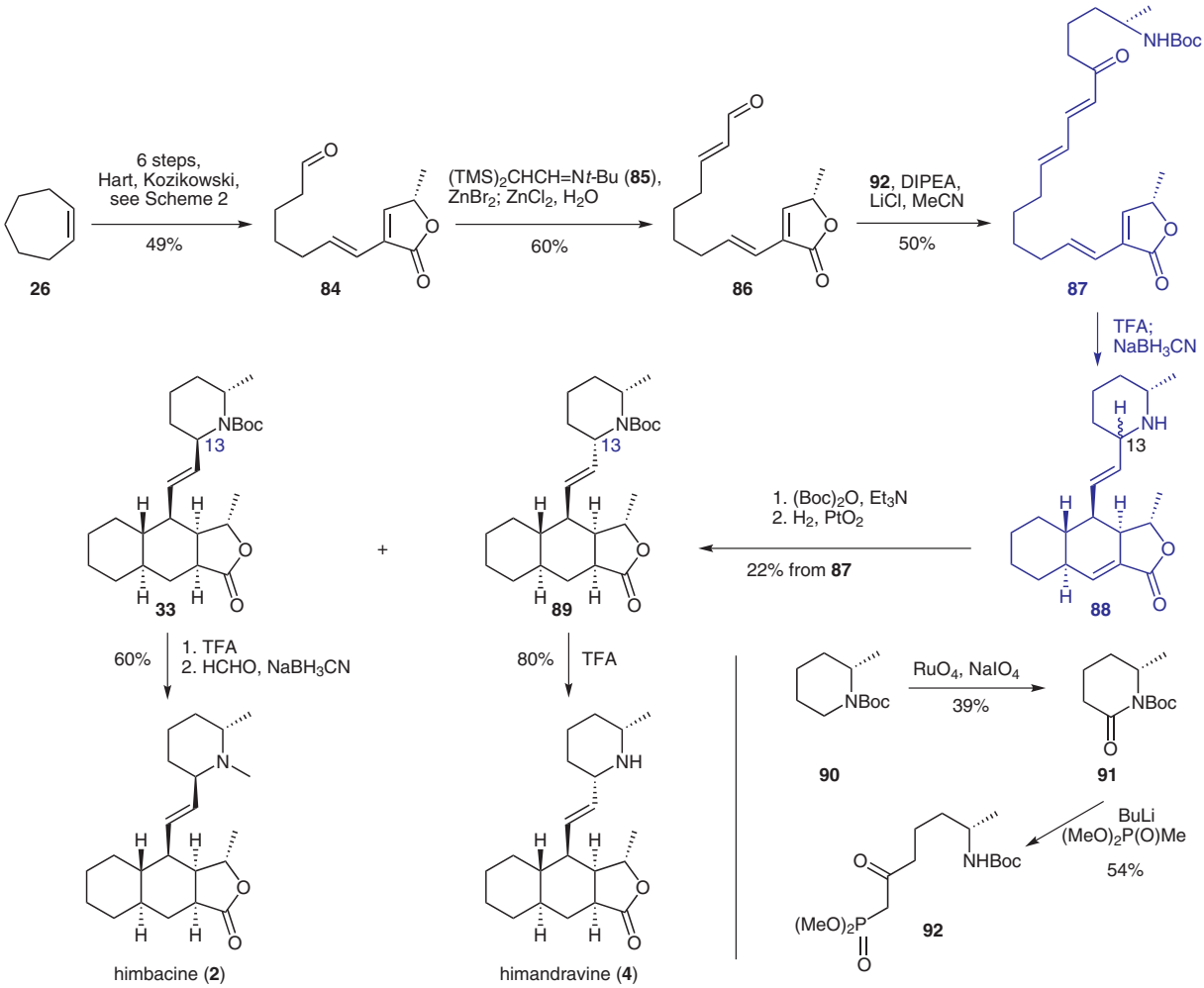
Only one synthesis of a class II Galbulimima alkaloid has been presented to date. The preparation of himandrine, published by Movassaghi in 2009, is described below.

Movassaghi, 2009 (Himandrine)

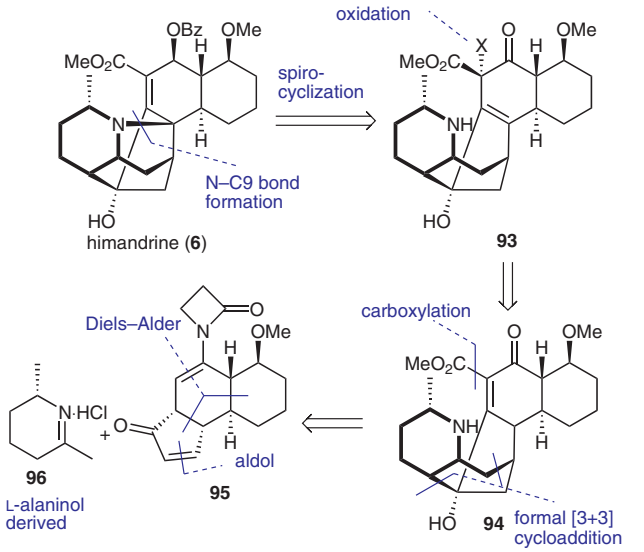
In 2006, Movassaghi reported the synthesis of G.B. 13 which is outlined in the discussion of Galbulimima class III alkaloids (section 2.3). The preparation of himandrine (**6**) can be regarded as a follow-up project to build a structure of higher complexity and is closely related to Movassaghi's earlier work. As similar strategies have been applied, a direct comparison of these two syntheses might be of interest.

The synthesis of the natural product follows the assumed biosynthetic pathway as outlined by Movassaghi.[27] Accordingly, the N–C9 bond is formed at a late stage of the synthesis by spirocyclization of pentacycle **93** that is obtained by oxidation of α,β-unsaturated ester **94** (Scheme 11). The heterocyclic ring is introduced through a formal [3+3]-cycloaddition reaction of tricyclic ketone **95** and alaninol-derived piperidine derivative **96**. The key steps in the preparation of tricyclic ketone **95** are an aldol condensation and a Diels–Alder reaction.

The starting material for this synthesis was obtained via proline-catalyzed α-oxidation of hept-6-enal following the procedure developed by MacMillan.[53] Monosilylation of diol **97**, methylation of the secondary hydroxy group with Meerwein salt and subsequent desilylation delivered



Scheme 10 Baldwin's synthesis of himbacine (**2**) and himandravine (**4**)



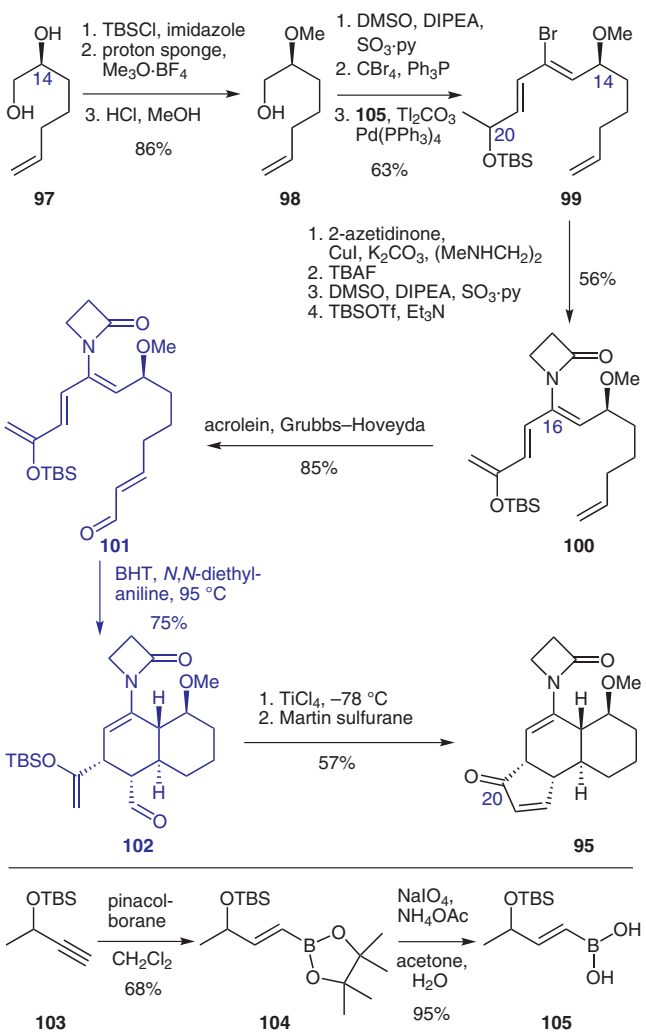
Scheme 11 Retrosynthetic analysis of Movassaghi's synthesis of himandrine (**6**)

alcohol **98** in excellent overall yield (Scheme 12). The hydroxy moiety was oxidized and converted into the corresponding dibromide by means of tetrabromomethane and triphenylphosphine. Suzuki coupling of this material with boronic acid **105** delivered bromide **99**. Next, the 2-azetidinone moiety was introduced; this served as masking functionality for the C16-carbonyl group and simultaneously forced the diene system into the s-*cis* conformation required for the Diels–Alder cycloaddition. Before the key step could be carried out, the silyl ether was converted into the corresponding silyl enol ether **100** by cleavage of the *tert*-butyldimethylsilyl group, oxidation of the alcohol and treatment of the corresponding ketone with *tert*-butyldimethylsilyl triflate in the presence of triethylamine. Terminal alkene **100** was subjected to a ruthenium-catalyzed cross-metathesis reaction with acrolein, and the resulting Diels–Alder precursor **101** was heated to 95 °C in acetonitrile containing butylated hydroxytoluene (BHT) and *N*,*N*-diethylaniline to afford *trans*-decalin **102** in 75% yield via an *endo* transition state. Tricyclic lactone **95** was obtained by titanium tetrachloride promoted Mukaiyama aldol reaction and subsequent exposure to Martin sulfurane.[54]

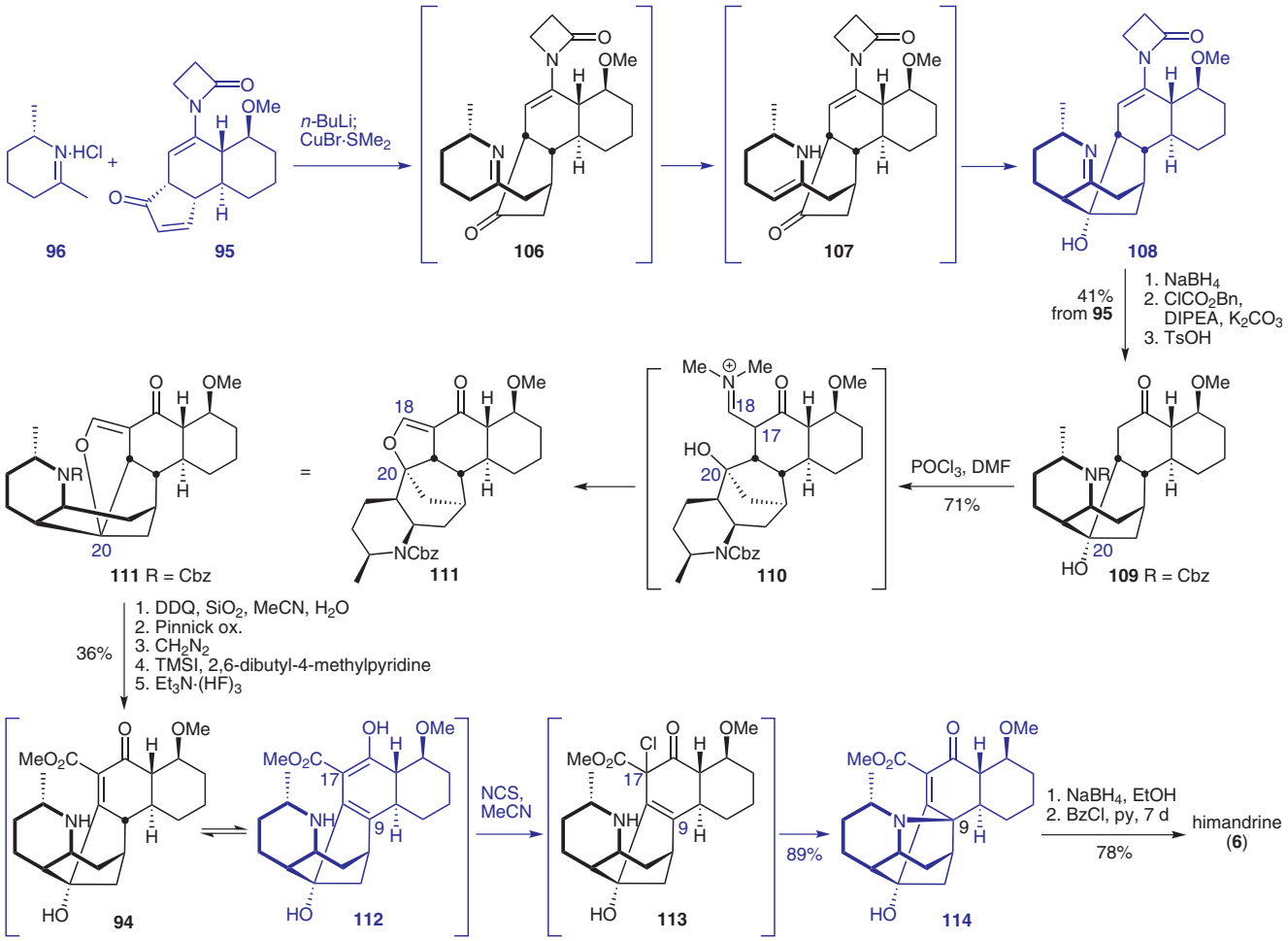
The nitrogen heterocycle was introduced via a formal [3+3]-cycloaddition reaction[30] as shown in Scheme 13. Iminium hydrochloride **96**, readily available from L-alaninol,[27] was lithiated and subjected to a copper-promoted 1,4-addition reaction with pentenone **95**. Iminoketone intermediate **106** tautomerized to enamine **107** which reacted in a subsequent nucleophilic 1,2-addition to yield pentacycle **108**. The reduction of the imino functionality proceeded under complete stereocontrol and the resulting amine was protected as carbamate. Hydrolysis of the *N*-vinyl lactam released the masked ketone (**109**) and paved the way for the introduction of the methoxycarbonyl functionality present in the natural product. After a variety of conditions had been probed, Vilsmeier formylation was found to be the method of choice and vinyl ether **111** was obtained by intramolecular trapping with the hydroxy functionality at C20. The close vicinity of the C20 hydroxy functionality and C18 becomes obvious when the structure is redrawn as shown for Vilsmeier adduct **111**.

Oxidation of vinyl ether **111** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone afforded the α,β-unsaturated aldehyde which was further oxidized to the carboxylic acid. The methyl ester was formed by exposure to diazomethane and the carbamate was cleaved with iodotrimethylsilane.[55] As this protocol also converted the hydroxy functionality at C20 into the trimethylsilyl ether, an additional deprotection step with triethylamine trihydrogen fluoride became necessary to reveal amino keto ester **94** which served as key intermediate for the completion of the synthesis of the natural product.

The key spirocyclization reaction was accomplished by treatment of amino keto ester **94** with *N*-chlorosuccinimide in acetonitrile. Presumably, this highly efficient reaction proceeded via chlorination of dienol **112** at C17 and subsequent intramolecular attack of the nitrogen at C9 with concomitant loss of the chlorine atom. An interesting



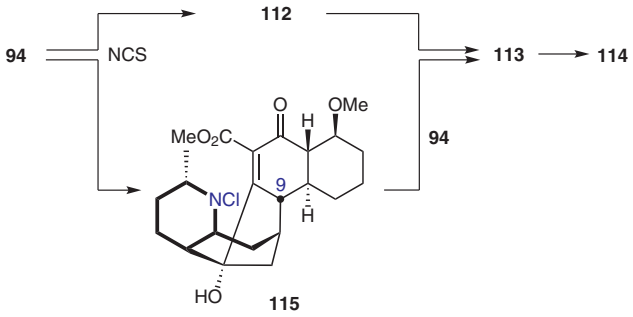
Scheme 12 Movassaghi's synthesis of himandrine (**6**) – part 1



Scheme 13 Movassaghi's synthesis of himandrine (**6**) – part 2

mechanistic insight is shown in Scheme 14. *N*-Chloro pentacycle **115** was formed in small amounts during the course of the cyclization reaction but disappeared after the reaction neared completion. Dissolution of the isolated *N*-chloro compound in acetonitrile did not result in the formation of spirocycle **114** even after prolonged reaction time. However, when small amounts of amino keto ester **94** were added, **114** was obtained. These results suggest that the nitrogen of pentacycle **115** is not basic enough to facilitate deprotonation at C9 and formation of dienol **112** and a stronger base such as **94** is required for the reaction to proceed via a nitrogen-to-chlorine halogen transfer. Reduction of the ketone and benzoylation of the hydroxy functionality concluded the synthesis of the natural product.[56]

Movassaghi thus reported a beautiful synthesis of this highly complex Galbulimima alkaloid. He succeeded in modifying and advancing an already existing protocol (preparation of G.B. 13 as discussed below) and was able to demonstrate that the proposed biosynthetic pathway to Galbulimima alkaloids is plausible. The formal [3+3] cycloaddition and the spirocyclization are clearly highlights of this synthesis.



Scheme 14 Mechanistic considerations on the key spirocyclization

2.3 Class III Alkaloids

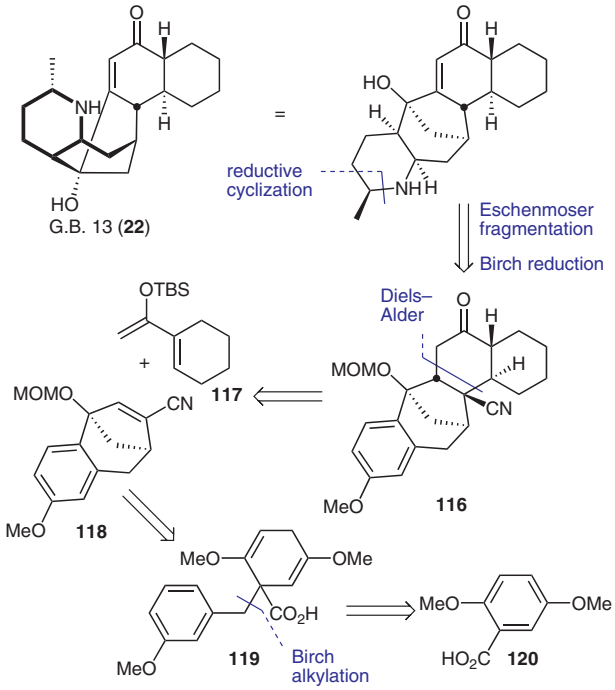
In 2003, Mander[38] reported the first total synthesis of a class III Galbulimima alkaloid with the preparation of G.B. 13. In subsequent years, Movassaghi,[27] Chackalamannil,[39] Evans,[40] and Sarpong[41] contributed to this field with syntheses of G.B. 13 (**22**) and himgaline (**21**).

Diels–Alder reactions are key steps in the construction of the decalin unit in all syntheses of class III Galbulimima alkaloids. However, strategies for the elaboration of the remaining framework vary significantly. The following

section summarizes and discusses synthetic efforts towards G.B. 13 and himgaline.

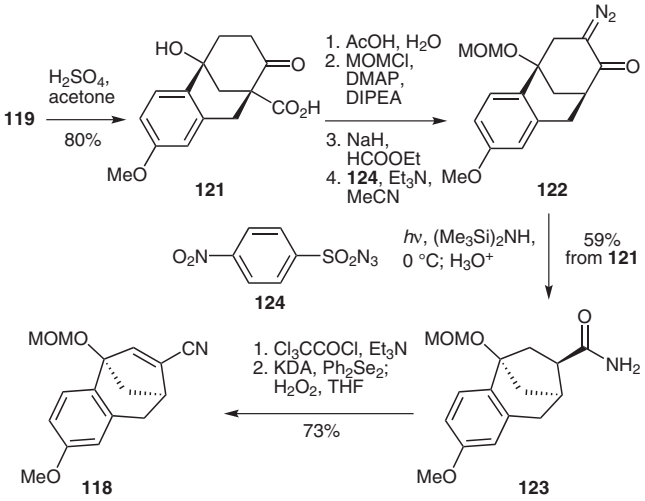
Mander, 2003 [(±)-G.B. 13]

The strategy of the first racemic synthesis of G.B. 13 (**22**), published by Mander in 2003,[38] is shown in Scheme 15. The approach is based on the utilization of tricyclic alkene **118** as dienophile in a Diels–Alder reaction with *tert*-butyldimethylsilyl-protected enol ether **117**. The aromatic portion of cycloadduct **116** is subsequently converted into the nitrogen heterocycle of the natural product. Key intermediate **118** was prepared from acid **119** which can be accessed via reduction of dimethoxy benzoic acid (**120**) with lithium in liquid ammonia and subsequent alkylation of the intermediary dianion.



Scheme 15 Retrosynthetic analysis of Mander's synthesis of (±)-G.B. 13 (**22**)

Dimethoxy benzoic acid **120** was subjected to lithium in liquid ammonia and subsequently alkylated with *m*-methoxybenzyl bromide to afford bis-enol ether **119**[57] which was treated with sulfuric acid in acetone to deliver tricycle **121** in good yield (Scheme 16). Decarboxylation and protection of the tertiary hydroxy functionality as its methoxymethyl ether was followed by diazotation employing a protocol developed by Regitz[58] to furnish diazo ketone **122**. Photolysis in the presence of hexamethyldisilazane resulted in Wolff ring contraction and delivered amide **123** which was dehydrated to the corresponding nitrile by reaction with trichloroacetyl chloride. The alkene moiety was established by deprotonation of the nitrile and trapping of the anion with diphenyl diselenide and a subsequent oxidation and elimination sequence. Starting from



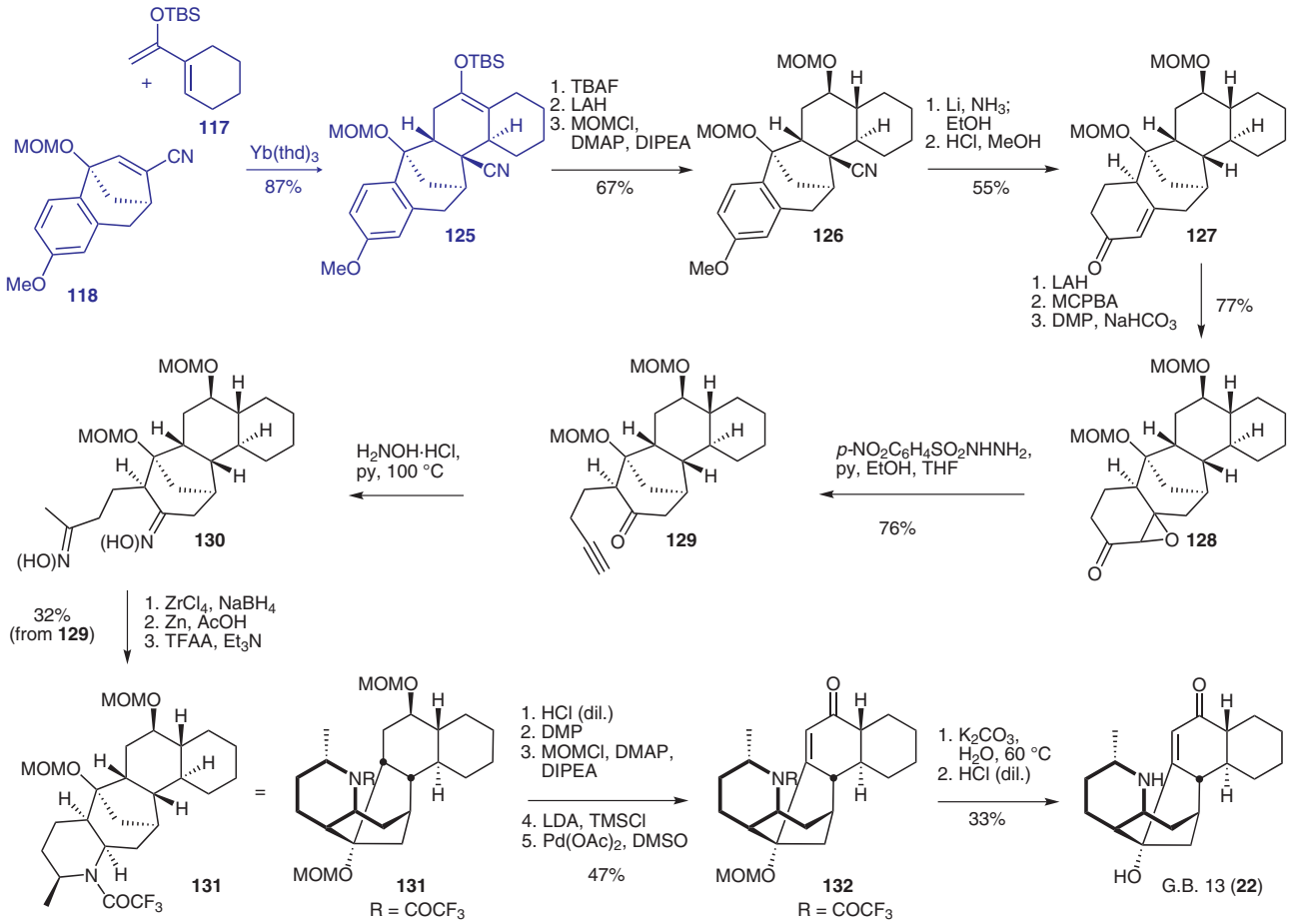
Scheme 16 Mander's synthesis of (±)-G.B. 13 (**22**) – part 1

bis-alkene **119**, key intermediate **118** was prepared in eight steps and 34% yield overall.

Lewis acid catalyzed Diels–Alder cycloaddition of alkene **118** with silyl enol ether **117** delivered the desired *endo*-adduct **125** in excellent 87% yield as outlined in Scheme 17. After hydrolysis of the enol ether, the ketone was reduced and the corresponding hydroxy functionality was protected (**126**). Next, the aromatic portion had to be converted into the piperidine ring. Treatment of nitrile **126** with lithium in ammonia resulted in reductive cleavage of the cyano functionality[59] and subsequent addition of ethanol to the reaction mixture delivered the Birch reduction product. Hydrolysis of the methyl enol ether with a catalytic amount of hydrochloric acid in methanol gave the corresponding enone **127** which was epoxidized to deliver the precursor required for the Eschenmoser fragmentation. As all attempts to directly convert the enone into epoxide **128** failed, the ketone was reduced to the allylic alcohol and reoxidized after successful epoxidation with *m*-chloroperoxybenzoic acid.

When **128** was subjected to traditional Eschenmoser conditions, alkyne **129** was obtained in only low yields. Better results were obtained when *p*-nitrobenzenesulfonylhydrazide was used.

Reductive amination of ketone **129** was unsuccessful. However, treatment of this alkynyl ketone with an excess of hydroxylamine afforded bis-oxime **130**. Such hydroaminations of nonactivated alkynes has long depended on the application of transition-metal catalysis or the use of strong acids. In 1989, Pradhan[60,61] reported the formation of a piperidine ring from alkynyl ketones by reaction with hydroxylamine, and most recently, Mayrargue[62] and Beauchemin[63,64] contributed to this highly interesting field with the development of milder reaction conditions and the presentation of possible mechanisms. Reductive cyclization of bis-oxime **130** was achieved with sodium borohydride and zirconium tetrachloride and the hydroxylamine was reduced by means of zinc and acetic acid before the nitrogen was protected as the trifluoroacetamide



Scheme 17 Mander's synthesis of (±)-G.B. 13 (**22**) – part 2

(**131**). Cleavage of the methoxymethyl ethers was followed by oxidation of the secondary alcohol and reprotection of the tertiary hydroxy functionality. Enolization of the ketone and dehydrosilylation of the intermediary silyl enol ether afforded α,β-unsaturated ketone **132**. The synthesis was completed by cleavage of the oxygen and nitrogen protecting groups to furnish G.B. 13.

Mander thus presented an interesting approach toward the natural product and demonstrated the utility of benzenoid synthons. Problems with the epoxidation of enone **127** as well as the methoxymethyl deprotection/reprotection sequence during the endgame prolonged the synthesis of G.B. 13. Overall, the alkaloid was prepared in an elegant and efficient manner.

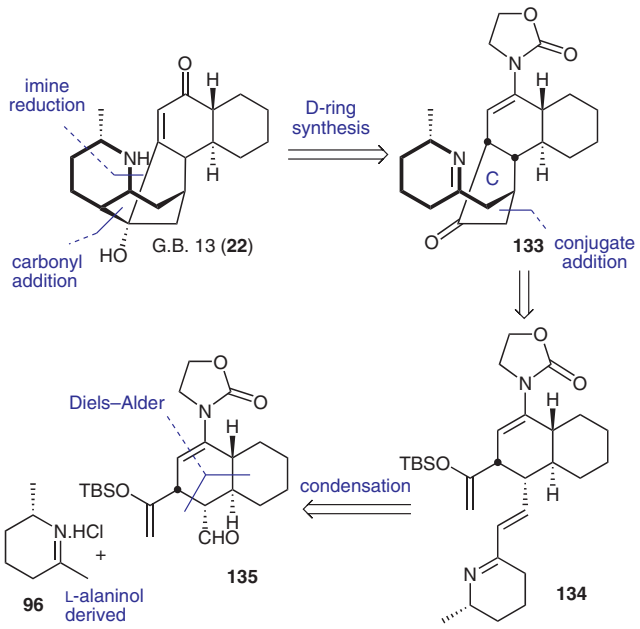
Movassaghi, 2006 (G.B. 13)

The preparation of G.B. 13 and the assignment of the absolute stereochemistry of the natural product was Movassaghi's first contribution[27] to the interesting field of Galbulimima alkaloids. During the course of this synthetic effort, Movassaghi developed strategies that also resulted in the successful preparation of the class II alkaloid himandrine,[29] published in 2009 and discussed above.

The retrosynthetic analysis is outlined in Scheme 18. Disconnection between C5 and C20 simplifies the alkaloid to imine **133** which is accessed by conjugate addition of substrate **134** to build the C ring of the natural product. The piperidine ring can be traced back to L-alaninol-derived imine **96** which is linked to aldehyde **135** via a condensation reaction. The key step in the formation of the decalin system is a Diels–Alder cycloaddition. The decalin unit was prepared as a racemic mixture; however, as piperidine **96** was synthesized in enantiopure form, the absolute configuration of the natural product could be defined.

As outlined in Scheme 19, dibromide **136** was coupled with boronic acid **105** in a Suzuki coupling before the oxazolidin-2-one moiety was attached to deliver triene **137** in excellent yield. This oxazolidin-2-one moiety served as the masking group for a ketone which was installed later in the sequence but also, as noted in Movassaghi's communication describing the synthesis of himandrine,[29] forces the diene into the s-*cis*-configuration required for the key Diels–Alder reaction to establish the decalin core.

The silyl ether in **137** was cleaved, and the hydroxy functionality was oxidized and converted into the corresponding silyl enol ether before the tetraene was subjected to cross-metathesis with acrolein to deliver Diels–Alder precursor **138**. The key cyclization step proceeded smoothly and *trans*-decalin **135** was obtained in good yield with an *endo*/*exo* ratio greater than 20:1. This reaction sequence

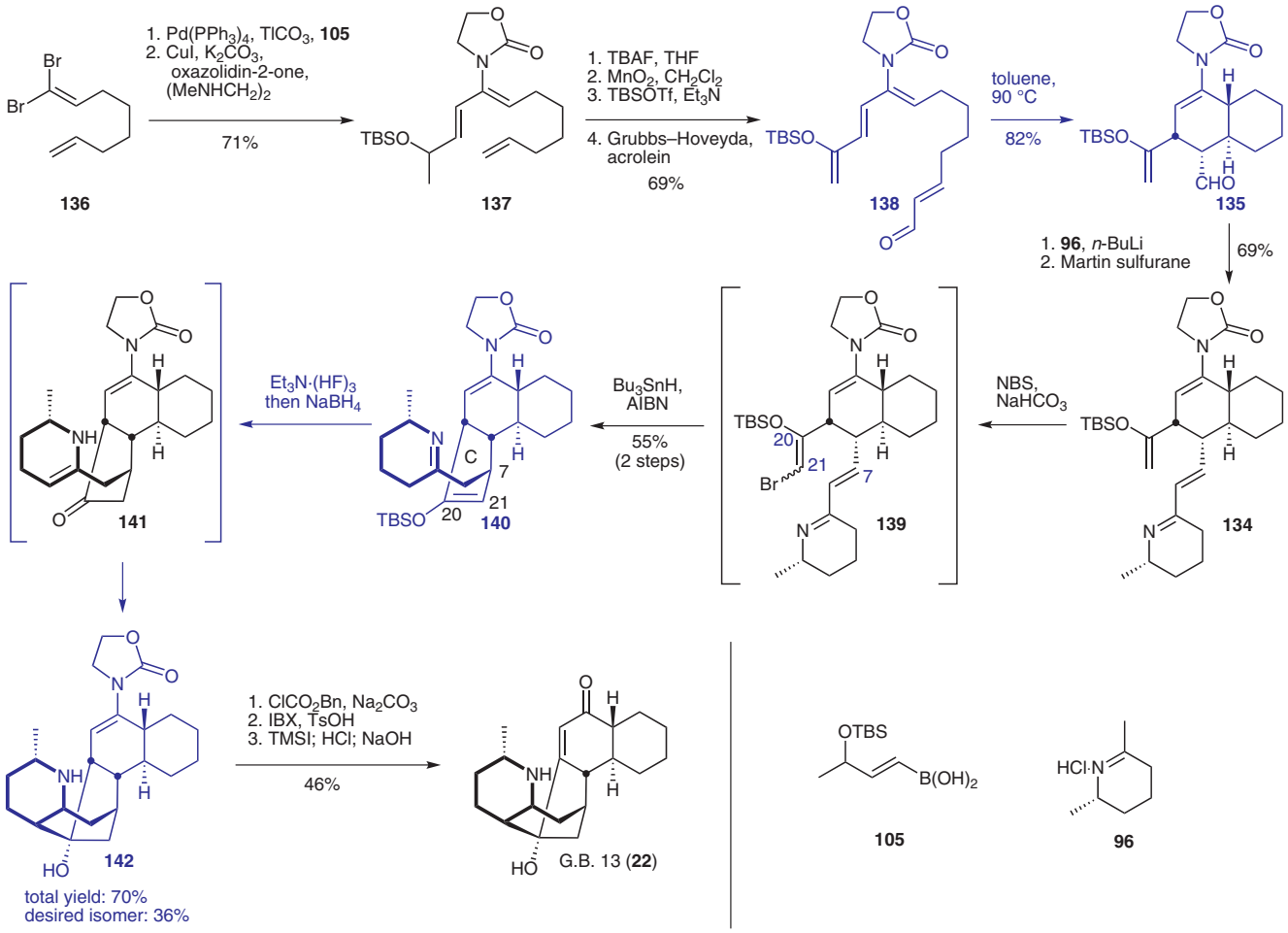


Scheme 18 Retrosynthetic analysis of Movassaghi's synthesis of G.B. 13 (**22**)

was successfully applied to a more complex substrate in the preparation of himandrine (Scheme 12).

Enantiopure iminium hydrochloride **96** was deprotonated and added to racemic aldehyde **135**. Subsequent dehydration using Martin sulfurane afforded *E*-alkene **134** as a mixture of diastereomers (for ease of reading, the undesired isomers are not shown in Scheme 19; the diastereomers were separated after formation of pentacycle **142**). Vinyl bromide **139** was obtained after exposure of silyl enol ether **134** to *N*-bromosuccinimide. Next, the C ring was formed. Heating of crude bromide **139** with tributyltin hydride and 2,2′-azobis(isobutyronitrile) generated a radical at C21 which reacted with C7 in a 5-*exo*-trig cyclization reaction to tetracycle **140**. Silyl enol ether cleavage also triggered a clean cyclization of the enamine onto the newly formed carbonyl functionality. Reduction of the imine intermediate finally produced pentacycle **142**. At this point, the separation of the diastereomers generated four steps earlier was accomplished by flash column chromatography. Subsequently, the enone had to be formed; therefore, the nitrogen was protected as a carbamate and the compound was treated with excess *p*-toluenesulfonic acid and 2-iodoxybenzoic acid (IBX).[65] The synthesis was completed by N-deprotection with iodotrimethylsilane[55] followed by acidic workup.

In summary, Movassaghi presented a highly efficient approach towards G.B. 13 (**22**). As already mentioned, strat-



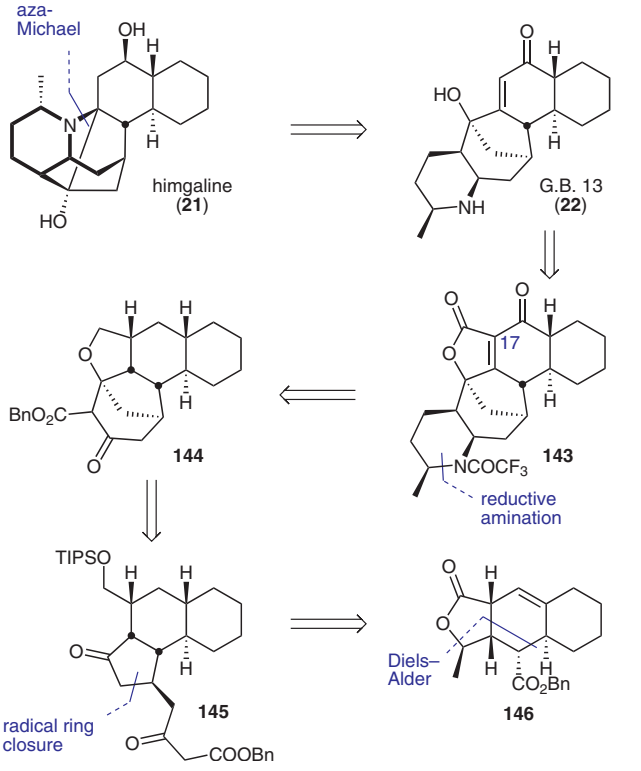
Scheme 19 Movassaghi's synthesis of G.B. 13 (**22**)

egies developed during this synthetic effort were successfully incorporated in the preparation of himandrine three years later.

Chackalamannil, 2006 (Himgaline)

The first synthesis of himgaline (**21**) was reported by Chackalamannil in 2006.[39,66] The alkaloid was obtained from G.B. 13 via an aza-Michael reaction, thus providing proof for Movassaghi's assumption and observation of the ease of interconversion between himgaline and G.B. 13.

Scheme 20 outlines the retrosynthetic analysis. G.B. 13 (**22**) can be obtained from **143** through acid-catalyzed N-deprotection, lactone opening and decarboxylation. Simplification of the piperidine ring and removal of the oxidation around C17 leads back to **144**. Precursor **145** is accessible from **146**, which Chackalamannil had already prepared in an earlier synthetic effort towards Galbulimima class I alkaloids.[16]



Scheme 20 Retrosynthetic analysis of Chackalamannil's synthesis of himgaline (**21**)

As shown in Scheme 21, tetrahydropyranyl-protected (*R*)-but-3-yn-2-ol (**147**) was converted into the pentynoic acid benzyl ester by deprotonation and reaction with benzyl chloroformate. Hydrolysis of the tetrahydropyran and esterification with dienoic acid **44** afforded **148**. After hydrogenation using Lindlar's catalyst, a thermally induced Diels–Alder cycloaddition followed by epimerization to the *cis*-lactone by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene gave decalin **146**. Hydrogenation of the double bond resulted in simultaneous cleavage of the benzyl ester. The acid moiety was converted into the corresponding acid chloride and this functionality was reduced to the aldehyde by reaction with tributyltin hydride in the presence of palladium.[67] The terminal double bond was introduced via Wittig chemistry, delivering alkene **149**.

Next, the C ring of the natural product was prepared. The lactone was reduced and the primary alcohol was selectively protected as a silyl ether before the methyl ketone was formed by oxidation of the secondary alcohol. Ozonolysis of the terminal double bond permitted chain extension to the α,β-unsaturated benzyl ester. α-Bromination of the silyl enol ether at C21 with *N*-bromosuccinimide led to **151**, the precursor for the radical ring-closure reaction.

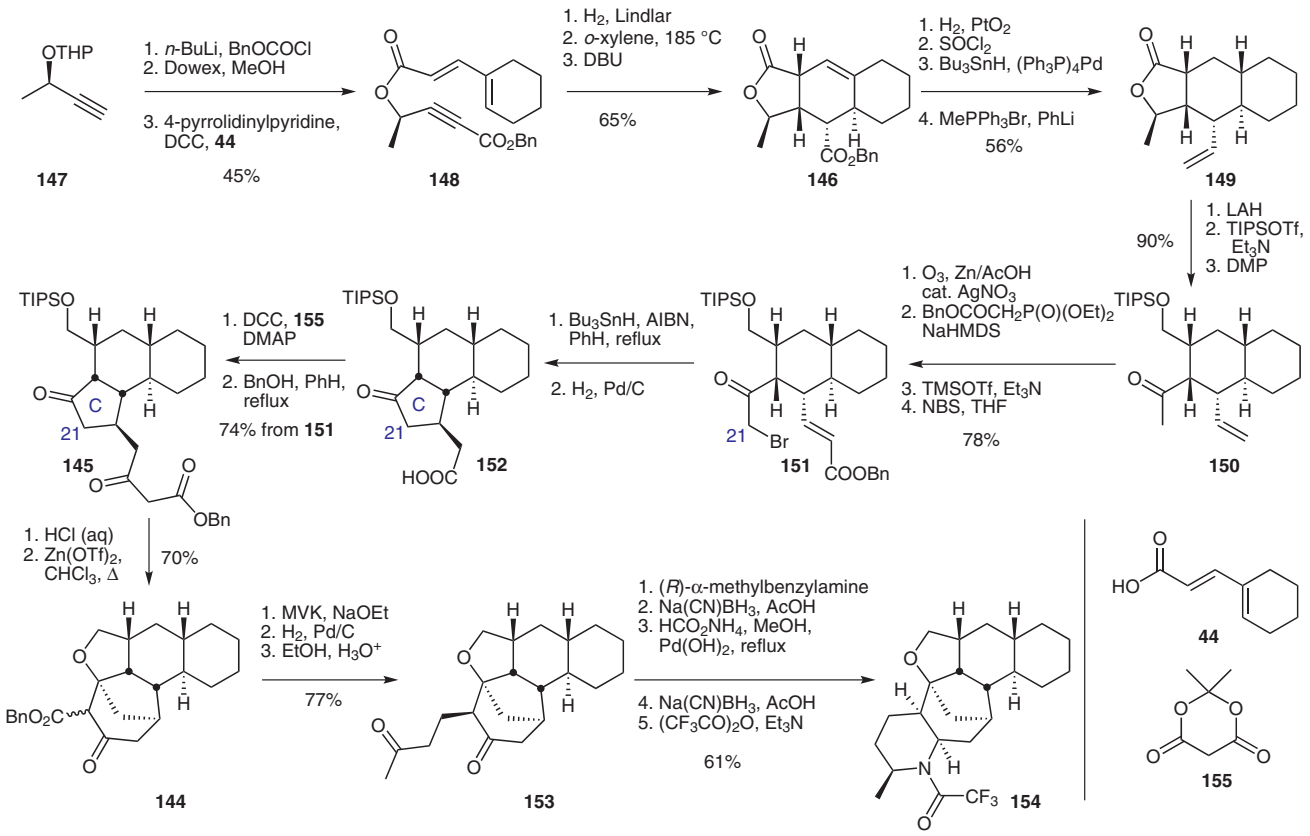
The radical-promoted formation of the C ring proceeded with high diastereoselectivity. Hydrogenation delivered acid **152** which was treated with *N*,*N*′-dicyclohexylcarbodiimide and Meldrum's acid (**155**) and esterified to yield **145**. Cleavage of the silyl ether under acidic conditions was followed by addition of zinc triflate to effect the closure of the D ring.

Diketone **153** was obtained after conjugate addition of β-keto ester **144** to methyl vinyl ketone followed by debenzylation and decarboxylation. Construction of the piperidine ring started with selective reductive amination of **153** with (*R*)-α-methylbenzylamine and sodium cyanoborohydride. Subsequent N-debenzylation by hydrogen transfer and a second cyanoborohydride reduction completed the sequence. Protection of the free amine as a trifluoroacetamide delivered hexacycle **154**.

Scheme 22 shows the continuation of the synthesis. The tetrahydrofuran ring in **154** was oxidized to the corresponding lactone by means of ruthenium tetroxide[68] and the C17–C19 double bond was introduced via formation of the thioether at C17 (α to the ester), and a subsequent oxidation and elimination sequence. With the double bond in place, the stage was set for the introduction of the ketone moiety at C16. Allylic bromination was followed by displacement of the bromine by treatment with silver trifluoroacetate. The intermediary trifluoroacetate was hydrolyzed and the resulting secondary alcohol was oxidized with Dess–Martin periodinane to deliver ketone **143** in good overall yield.

When subjected to 6 M hydrochloric acid in a microwave reactor at 100 °C, ketone **143** afforded G.B. 13 (**22**) in excellent 80% yield. The reaction sequence included cleavage of the trifluoroacetamide, aza-Michael addition onto the conjugated double bond, thermally induced decarboxylation and retro-Michael reaction.

Treatment of G.B. 13 (**22**) with scandium triflate in chloroform and subsequent reduction with sodium borohydride yielded 16-*epi*-himgaline. The problem was solved by the use of an internally coordinated reducing agent: with sodium (triacetoxy)borohydride, himgaline (**21**) was obtained in 60% yield.

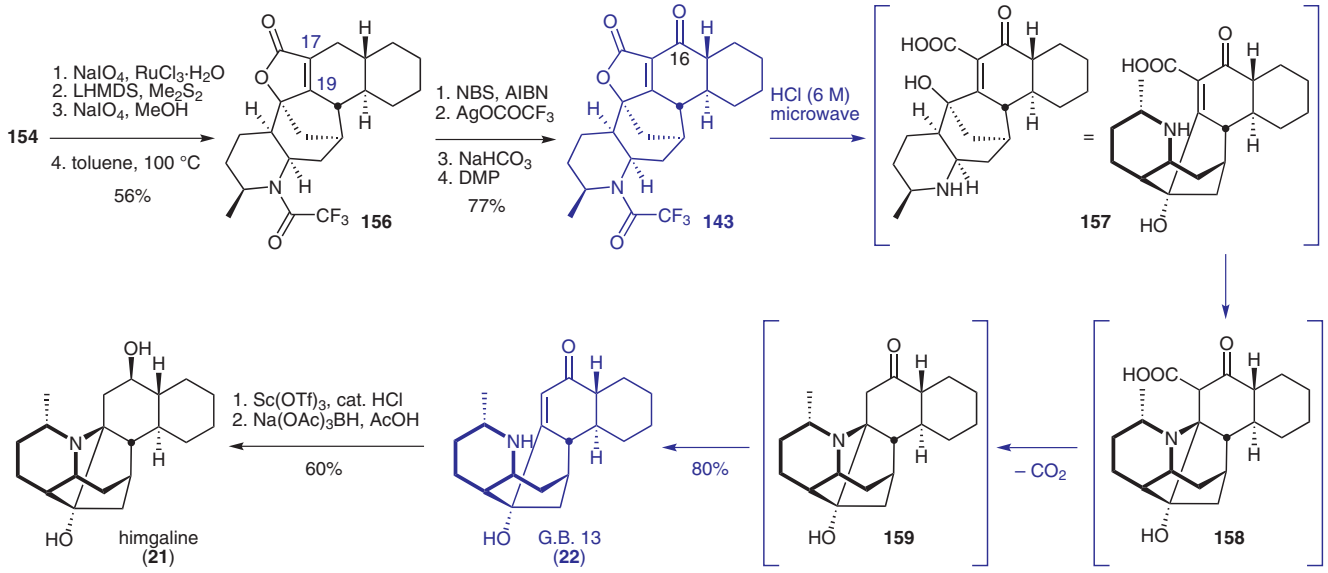


Scheme 21 Chackalamannil's synthesis of himgaline (**21**) – part 1

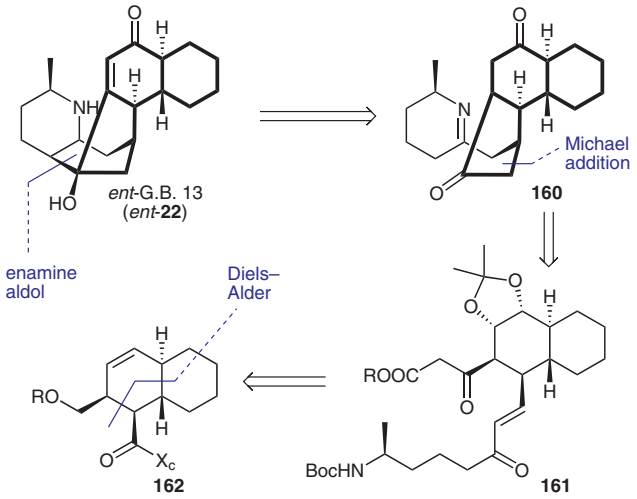
Chackalamannil thereby successfully employed Diels–Alder adduct **146**, used in previous efforts towards derivatives of himbacine (**2**), as the starting point for the stereoselective preparation of G.B. 13 (**22**) and himgaline (**21**). The microwave-promoted reaction sequence leading to G.B. 13 clearly represents the highlight of this work. A drawback, however, is the highly linear synthetic strategy and the oxidation and reduction sequences, especially with regard to the lactone moiety which is eventually removed to afford the natural product. The first preparation of himgaline (**21**) from G.B. 13 (**22**) proves observations by Mander describing the formation of oxohimgaline from G.B. 13 under acidic conditions.[26]

Evans, 2007 (*ent*-G.B. 13, *ent*-Himgaline)

With an auxiliary-controlled, enantioselective Diels–Alder reaction as one of the key steps, Evans reported the



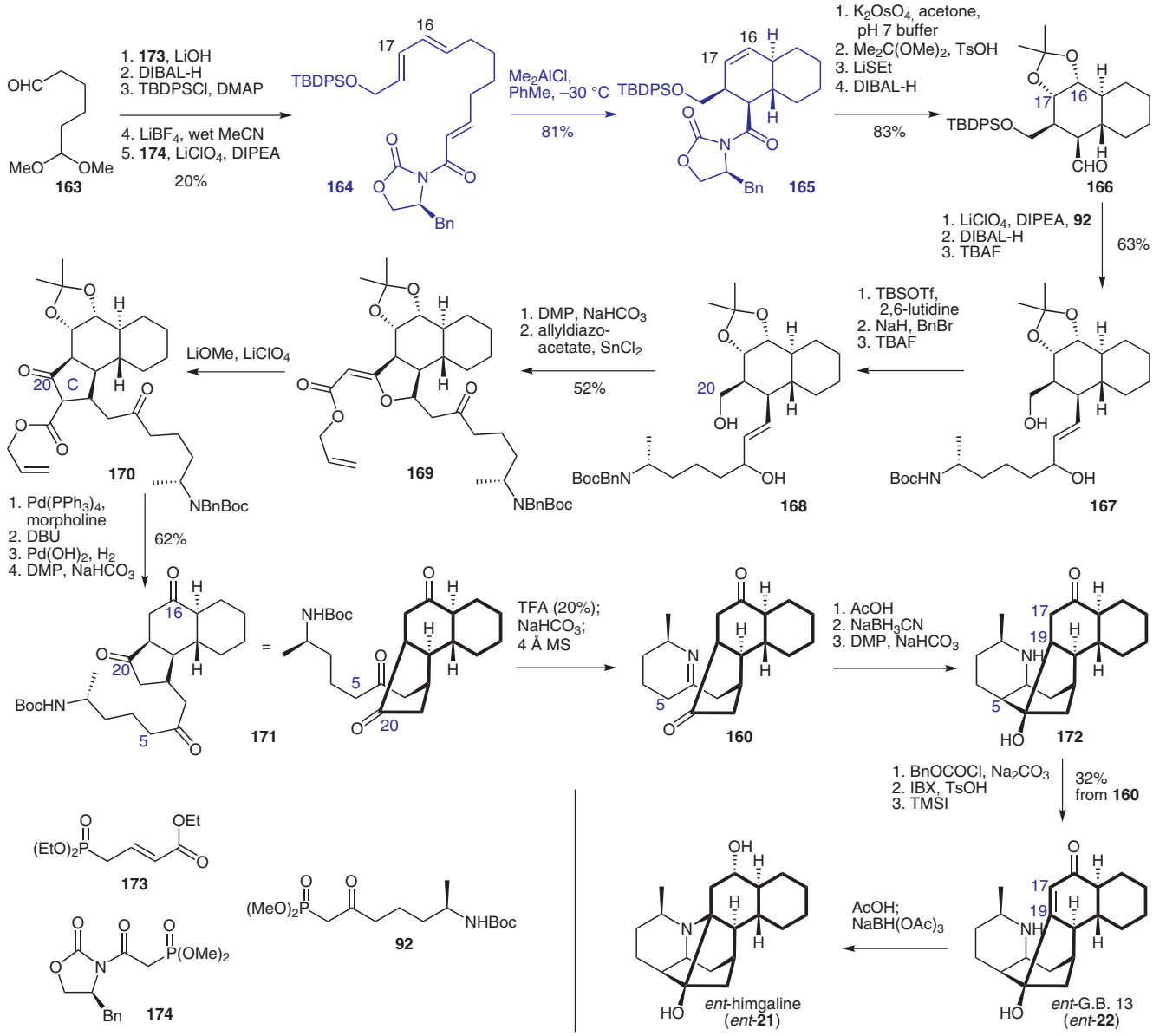
Scheme 22 Chackalamannil's synthesis of himgaline (**21**) – part 2



Scheme 23 Retrosynthetic analysis of Evans' synthesis of *ent*-himgaline (*ent*-**21**) and *ent*-G.B. 13 (*ent*-**22**)

synthesis of *ent*-G.B. 13 and *ent*-himgaline in 2007.[40] As shown in Scheme 23, *ent*-G.B. 13 was simplified to **160**, which should be accessible from decalin **161**. With this disconnection of two rings, the complexity is significantly reduced. Further carbon–carbon bond disconnections of the side-chains and dihydroxylation of the double bond finally lead back to **162**, which is easily obtained through a Diels–Alder reaction of a linear precursor.

Vinylogous Horner–Wadsworth–Emmons olefination of 6,6-dimethoxyhexanal (**163**)[43] with phosphonate **173** was followed by diisobutylaluminum hydride reduction of the ester and subsequent protection of the primary alcohol as a silyl ether (Scheme 24). The chiral auxiliary was installed by reaction of the unmasked aldehyde with oxazolidinone **174** in a second Horner–Wadsworth–Emmons olefination. When treated with dimethylaluminum chloride at –30 °C in toluene, triene **164** cleanly afforded *trans*-decalin **165** as a single diastereomer in good yield.[69]



Scheme 24 Evans' synthesis of *ent*-himgaline (*ent*-**21**) and *ent*-G.B. 13 (*ent*-**22**)

Dihydroxylation of the C16–C17 double bond by reaction with potassium osmate and subsequent protection of the vicinal *cis*-diol afforded aldehyde **166** after removal of the chiral auxiliary.

Horner–Wadsworth–Emmons olefination of **166** with *N*-Boc-protected ketophosphonate **92**[70] was followed by reduction of the ketone functionality and desilylation to afford allylic alcohol **167**. Next, the nitrogen was benzylated after intermediary protection of the two hydroxy functionalities and **168** was obtained in good yield. Both hydroxy groups were oxidized with Dess–Martin periodinane and the keto ester required for the Michael addition was introduced via a Roskamp reaction[71] of the aldehyde. The desired β-keto ester **170** was observed; however, the compound was formed only as minor reaction product and the main product was identified to be enol ester **169**. This observation can easily be explained by conjugate addition of the enol oxygen of the β-keto ester. Fortunately, the process proved to be reversible upon exposure to basic conditions, and the desired Michael adduct was obtained after treatment with a mixture of lithium perchlorate and lithium methoxide.[72] Decarboxylation was achieved by addition of morpholine and $Pd(PPh_3)_4$ and the ketone at C16 was installed by 1,8-diazabicyclo[5.4.0]undec-7-ene promoted elimination of the acetonide to the corresponding allylic alcohol which was hydrogenated with concomitant cleavage of the *N*-benzyl group, and oxidized to afford triketone **171**.

Next, the piperidine ring was to be formed and the required ring-closure reaction proceeded smoothly upon cleavage of the carbamate under acidic conditions, and after dehydration imine **160** was obtained. The stage was set for the intramolecular enamine aldol addition which took place under acidic conditions. Reduction of the iminium functionality with sodium cyanoborohydride also resulted in reduction of the keto functionality and the alcohol had to be reoxidized with Dess–Martin periodinane to deliver intermediate **172**.

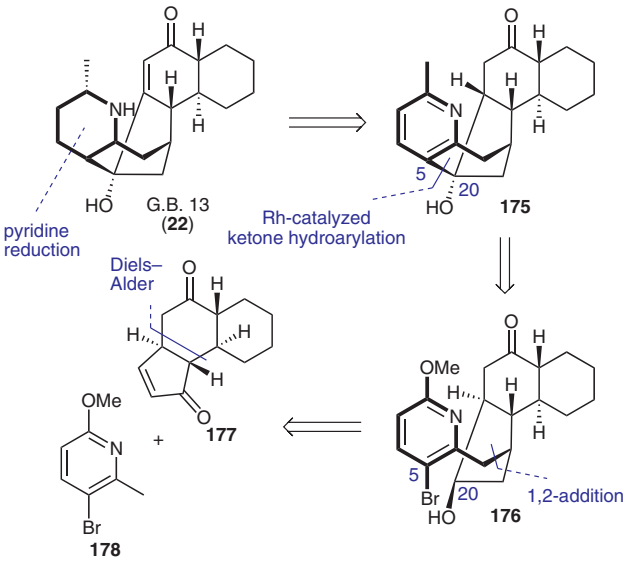
The synthesis of *ent*-G.B. 13 was completed by installation of the C17–C19 double bond which was achieved by protection of the amine as a carbamate, oxidation by means of 2-iodoxybenzoic acid and then deprotection of the nitrogen. The conversion of *ent*-G.B. 13 to *ent*-himgaline proceeded in the same fashion as described by Chackalamannil[39] by exposure to acetic acid and reduction with sodium (triacetoxy)borohydride.

Evans' synthesis of the natural product is another example of the high versatility of chiral oxazolidinone as auxiliary in enantioselective Diels–Alder reactions. The decalin system is prepared in a short synthetic sequence. As the synthesis suffers from several unexpected problems, however, the elaboration of the remaining ring systems required more steps than originally anticipated.

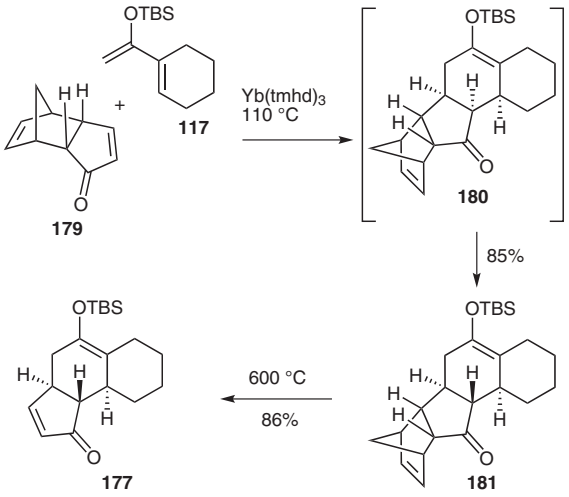
Sarpong, 2009 [(±)-G.B. 13]

The latest and also shortest total synthesis of racemic G.B. 13 (**22**) was published by Sarpong in 2009.[41] The synthesis is based on the utilization of a bromopyridine (**178**) as synthon for the piperidine ring of the natural product (Scheme 25). The piperidine is obtained by hydrogenation of pyridine **175** at a late stage of the synthesis. Disconnection of the C5–C20 bond results in **176** which should be assembled via 1,2-addition of ketone **177** and **178**. The key step in the formation of tricyclic ketone **177** is a Diels–Alder cycloaddition reaction.

An *endo*-selective Lewis acid catalyzed Diels–Alder reaction of silyl enol ether **117** and α,β-unsaturated ketone **179** delivered, after in situ epimerization, cycloadduct **181**.[73] Cyclopentenone **177** was obtained by retro-Diels–Alder reaction effected by flash vacuum pyrolysis in excellent yield (Scheme 26).



Scheme 25 Retrosynthetic analysis of Sarpong's synthesis of (±)-G.B. 13 (**22**)



Scheme 26 Sarpong's synthesis of (±)-G.B. 13 (**22**) – part 1

Next, the pyridine ring was installed (Scheme 27): 1,2-addition of lithiated **178**, available by methylation of commercially available 3-bromo-6-hydroxy-2-picoline,[74] proceeded with complete diastereocontrol, presumably because of the steric influence of the hydrogen at C9, and **182** was obtained after hydrolysis of the silyl enol ether. In order to establish the correct oxygenation pattern, an allylic hydroxy group transposition had to be performed. After standard procedures failed to give the desired product, Larson and Sarpong[41] found that the desired 1,3-transposition was successfully accomplished using Parikh–Doering conditions[75] and **176** was obtained after hydrogenation of the double bond using platinum oxide as catalyst. The hydrogenation reaction proceeded from the α-face with a diastereomeric ratio greater than 95:5 in favor of the desired material. To form the crucial C5–C20 bond, Larson and Sarpong attempted halogen–metal exchange after oxidation to the C20 ketone. As no product could be obtained via this route, the bromine was substituted for a boronic acid ester. After C20 oxidation and epimerization to the *cis*-fused pentanone (yielding **183**), a variety of palladium catalysts were investigated. Unfortunately, those, too, failed to deliver the desired product. When the researchers finally turned to cationic rhodium catalysts, they met with success: $[Rh(cod)(MeCN)_2]^+BF_4$ in the presence of triethylamine gave **184** in 77% yield. According to the authors, this is the first example of an addition of an aryl boron species onto an unactivated ketone using rhodium(I) catalysis.

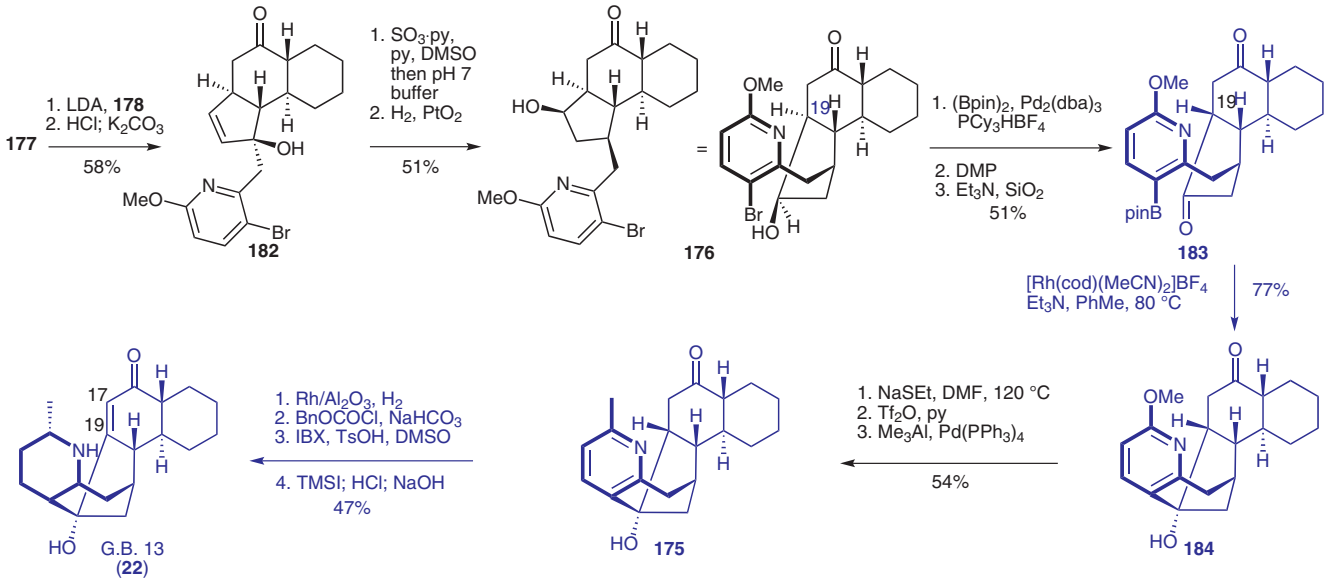
Next, a methyl group was installed at the pyridine ring at C2 instead of the methoxy functionality. This was achieved by cleavage of the methyl ether using sodium ethanethiolate in *N*,*N*-dimethylformamide at 120 °C followed by triflation of the resultant pyridine and cross-coupling via exposure to trimethylaluminum and $Pd(PPh_3)_4$. At this point, the pyridine was hydrogenated to establish the piperidine moiety and the reaction afforded the desired material in good diastereoselectivity from the *exo*-face. The synthesis of the natural product was completed by protection of the nitrogen as a carbamate, installation of the C17–C19 double bond by oxidation with 2-iodoxybenzoic acid, and final cleavage of the carbamate.

Sarpong thus presented a beautiful and concise total synthesis of racemic G.B. 13 and clearly points out the advantage of the hydrogenation of pyridine in the formation of piperidine motifs in the preparation of complex alkaloids. In comparing Sarpong's addition of lithiated pyridine **178** to enone **177** with Movassaghi's annulation chemistry with imine **96**, both authors introduce the same carbon framework with different synthetic strategies. Although the natural product was prepared in racemic form, the synthesis could be modified by starting with an enantioselective Diels–Alder[76] to allow the generation of enantiomerically enriched material. Besides the brevity of this synthetic effort, the rhodium-catalyzed 1,2-addition is well worth mentioning.

3 Conclusion

Although the chemical interest in Galbulimima alkaloids clearly started with, and benefited from, the discovery of the promising biological properties of himbacine, research in this area has also been motivated by the synthetic challenges of these structurally complex and compelling natural products. After the first synthesis of himbacine by Hart and Kozikowski in 1995, Galbulimima class I alkaloids became the main research focus and nearly a full decade had passed before the total synthesis of a class III alkaloid appeared in the literature. Today, several groups have contributed to this field and current research activity centers around the class II and class III alkaloids.

All syntheses utilize Diels–Alder reactions as key steps to establish the decalin system or to generate the cyclohex-



Scheme 27 Sarpong's synthesis of (±)-G.B. 13 (**22**) – part 2

ane-fused γ-lactone. Chiral piperidine derivatives are used in syntheses of Galbulimima class I alkaloids and the stereochemical information of C2 can always be traced back to lactic acid as an inexpensive chiral pool starting material. The approaches differ mainly in the different bonds formed through the key Diels–Alder cycloaddition reaction and the reaction type employed to couple the piperidinoyl side chain to the decalin system.

Syntheses of Galbulimima class II and III alkaloids are more complex as these targets contain a highly fused ring system. Mander was first to publish the preparation of racemic G.B. 13. The conversion of an aromatic moiety into the piperidine ring is interesting and demonstrated the high potential of alkyne functionalization with hydroxylamine for alkaloid synthesis. Chackalamannil utilized fragments prepared during earlier approaches towards Galbulimima class I alkaloids and used well-established reaction sequences to prepare the natural product. Evans' contribution to this field clearly proves the versatility of chiral auxiliaries in enantioselective Diels–Alder reactions. Sarpong and Movassaghi presented highly concise syntheses of Galbulimima alkaloids, and both were also able to develop new synthetic strategies such as the formal [3+3]-cycloaddition reaction (Movassaghi) or the rhodium-catalyzed hydroarylation reaction (Sarpong).

This review article summarizes approximately fifteen years of research on Galbulimima alkaloids and covers this field from the first successful synthesis of himbacine to the preparation of G.B. 13, himandrine, and himgaline. Recent contributions are indicative of the ongoing interest in this area and there is no doubt that further interesting contributions will be made.

Note Added in Proof

After this article was accepted for publication, two syntheses of Galbulimima alkaloids were reported.[77,78]

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