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The galbulimima alkaloids—a new frontier in alkaloid synthesis

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1. Introduction

Very distinguished work has long been done in the domain of alkaloid synthesis,[1] but recently, a new frontier has been opened up in this classical area through the synthesis of extremely complex members of the galbulimima alkaloids. This review gives an analysis of how the formidable synthetic challenges presented by these substances have been overcome through an impressive mastery of classical reactions supplemented by brilliant innovations, where either need or opportunity presented themselves.

The galbulimima alkaloids[2] were isolated from the bark of the rain forest trees *Galbulimima belgraveana* and *Galbulimima baccata*. The former is found in Papua New Guinea and Indonesia, while the latter occurs in Northern Australia. Of the 30 alkaloids which have been isolated so far, structural assignments have been made to 29.[3,4] All the compounds have been classified[3,4] into the four groups I–IV, as follows: (I) tetracyclic lactones (e.g., himbacine **1**); (II) highly oxygenated hexacyclic esters (e.g., himandrine **5**, $C_{30}H_{37}NO_6$); (III) one hexacyclic and three pentacyclic bases of low oxygen content (e.g., GB 13 **2**, $C_{20}H_{29}NO_2$; GB 16 **4**, $C_{20}H_{27}NO_2$; himgaline **3**, $C_{20}H_{31}NO_2$); and, finally, (IV) several miscellaneous compounds (e.g., GB 17 **6**, $C_{21}H_{31}NO_3$) that do not fit into the other three categories. Fig. 1 shows representative examples of Classes I–IV; the single member of Class IV whose structure has been assigned [(−)-GB 17[4] **6**] has not been synthesized. At present, the number of members in each class is: seven[4b,5] in Class I, 15[3,4] in Class II, four[6] in Class III, and four[4b,7] in the miscellaneous group (Class IV) where they are placed by virtue of their unique structures or the fact that the structures are unknown.

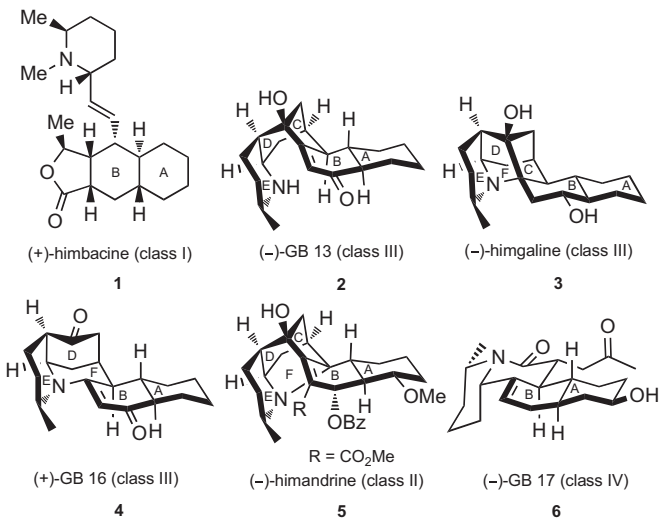


Fig. 1. Representatives of Classes I–IV.

(+)-Himbacine, a member of Class I, is the most important because of its potent muscarinic antagonist activity.[8] The *trans*-decalin substructure present in this molecule is an essential[8a,b,9a] determinant of its selective binding to M2 and M4 muscarinic receptors, and it has served as a lead structure in the field of drug discovery, especially for Alzheimer's disease.[8,9] Consequently, there is an extensive literature on synthetic work related to himbacine and the other Class I alkaloids.[10–13] Most of the other alkaloids do have some interesting biological properties[14] but these do not appear to have been much explored and it is mainly the very complex molecular architecture that has attracted a number of research groups to attempt the total synthesis of several of these alkaloids. Six total syntheses of GB 13 (**2**),[15–21] three of himgaline (**3**),[19–21] and one of himandrine (**5**)[22] have been achieved, along with a synthesis of the hexacyclic himandrine core in racemic form.[23,24] The construction of such intricate structures as **2**–**5** represents the opening of a new frontier in alkaloid synthesis, and, as indicated above, this review will present an analysis of the different strategies that have been developed, together with a discussion of the synthesis of just the *trans*-decalin unit of (+)-himbacine (and not of the whole molecule), as the experience gained with this unit provided a springboard for the synthesis of the more complex alkaloids that have tested the current status of organic synthesis.

2. Synthesis of the ABC tricyclic core of the Class I alkaloid (+)-himbacine

A biosynthetic origin of these alkaloids was first proposed by Ritchie and co-workers[25] in 1967. The proposal was extended to Classes I–III by Baldwin,[11] and later, in more detail, by Movassaghi.[26] A biological Diels–Alder reaction[27] was suggested[11] for the origin of the *trans*-decalin unit—a proposal which is supported by the presence of an endocyclic double bond in another Class I alkaloid, himgravine (**7**, Fig. 2). The intramolecular Diels–Alder reaction (IMDA) was put to good use in the synthesis of the Class I alkaloid (+)-himbacine, and three examples[11–13] of the synthesis of the tricyclic core via diastereoselective IMDA reactions serve to illustrate the possibilities.[10] The retrosynthetic analysis for the three examples is summarized in Scheme 1. Either the *trans*-decalin subunit (rings A and B) or the cis-fused 6/5-ring subunit (rings B and C) can be generated by the Diels–Alder reaction.

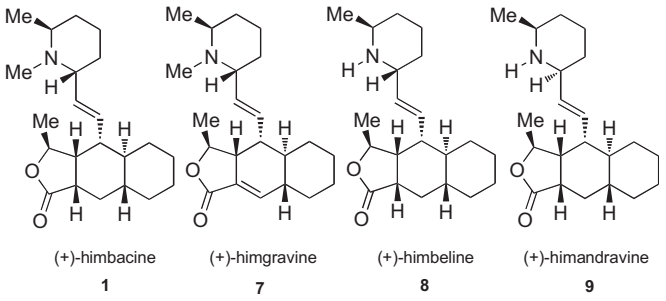
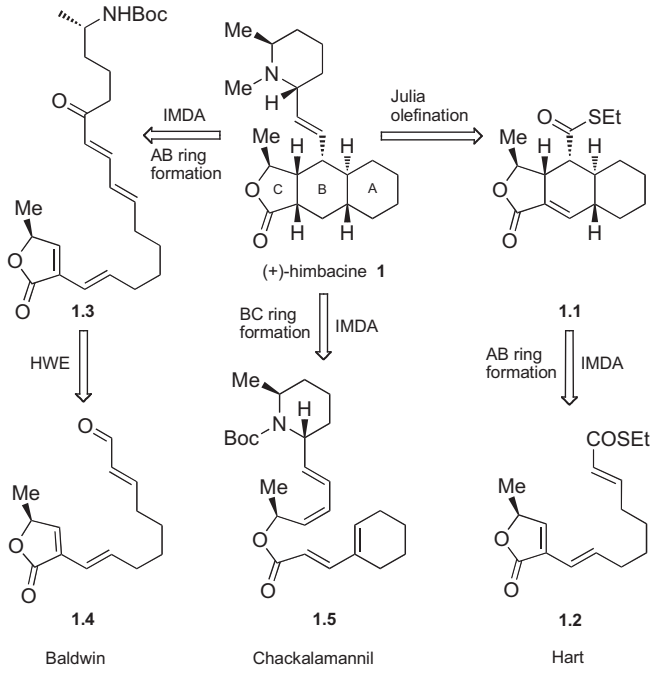


Fig. 2. Representative Class I alkaloids.

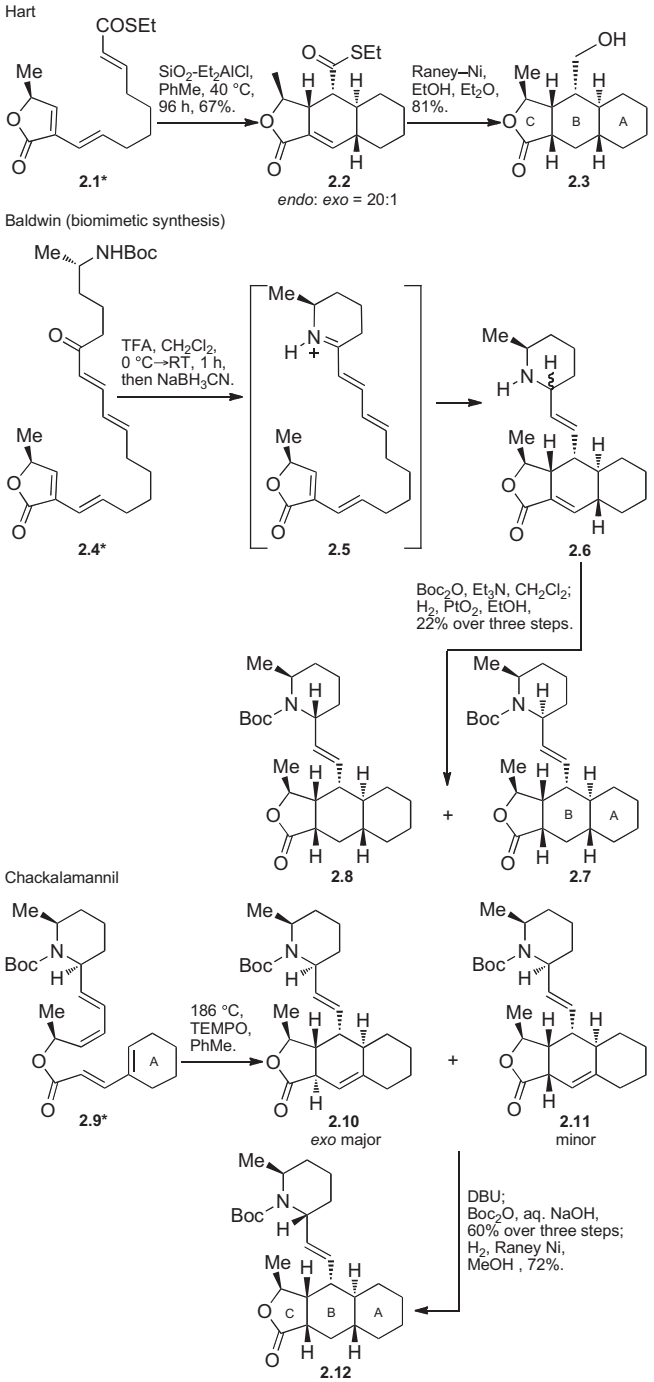
Hart's group reported[12] the first total synthesis of (+)-himbacine, which was accomplished by generating rings A and B using an IMDA process. Starting with the single enantiomer of the thioester **2.1**, the desired *endo*-Diels–Alder product **2.2** was obtained, using SiO_2-supported Et_2AlCl[28] as catalyst. Unsaturated thioesters are not common dienophiles,[29] but in this case the use of a thioester and the special Lewis acid were necessary in order to obtain high diastereocontrol (*endo*/*exo*=20:1). Hydrogenation of the endocyclic double bond in **2.2** occurred from the top face so as to generate the required cis ring fusion between the B and C rings, as in **2.3**. At the same time the thioester unit was reduced to a primary alcohol, setting the stage for attachment of the piperidine unit.

Baldwin's group[11] also used an IMDA reaction, and the route is closely related to their proposed biosynthetic pathway. The iminium ion **2.5** was used as the dienophile and was easily generated in situ by deprotection of the *N*-Boc amine **2.4** under very mild conditions. The product of the Diels–Alder cyclization is itself an iminium ion, and this was reduced to obtain a diastereomeric mixture of amines (**2.6**). The diastereomers were separated after both nitrogen protection (Boc) and selective hydrogenation of the endocyclic double bond (**2.6**→**2.7** and **2.8**).



Scheme 1. Retrosynthetic analysis of (+)-himbacine.

Both the Hart and Baldwin approaches shown in Scheme 2 illustrate the construction of the *trans*-decalin AB-subunit by IMDA reaction, but in the third approach shown in Scheme 2, which was used by the Chackalamannil group,[13] it was the BC rings that were formed by the IMDA reaction. For this route, the Diels–Alder starting material was **2.9**, which already contains the six-membered ring A of the tricyclic core of (+)-himbacine as well as the piperidine subunit. The IMDA reaction, which was carried out under quite harsh conditions, gave a mixture of both the BC *cis*-fused lactone **2.11** and the corresponding trans isomer (**2.10**). Although the latter was the major product, the desired BC cis-geometry was easily accessible by DBU-mediated isomerization. Finally, the *trans*-decalin subunit (as in **2.12**) was completed by stereoselective hydrogenation of the endocyclic double bond, as in the Baldwin synthesis. During the IMDA, some deprotection of the nitrogen occurred, but the Boc group was easily replaced. Once the IMDA strategy had been implemented to reach **2.12**, a few standard manipulations then served to complete the synthesis of (+)-himbacine. As indicted above, a discussion of the remaining steps for these relatively simple Class I alkaloids is not included in this review.



Scheme 2. Synthesis of the tricyclic core of (+)-himbacine. *Single enantiomer. TFA=trifluoroacetic acid, Boc=*tert*-butoxycarbonyl, TEMPO=2,2,6,6-tetramethylpiperidine-1-oxyl, DBU=1,8-diazabicycloundec-7-ene.

3. Analysis of routes to the Class III alkaloids

The alkaloids of Classes II and III are significantly more challenging synthetic targets, as is obvious from a comparison of their structures. The Class II alkaloid himandrine has the most complex architecture and its synthesis represents the present limit of the galbulimima frontier. Not surprisingly, progress was first achieved with the Class III alkaloids, which are structurally similar to those of Class II, but appreciably less complicated. Examination of the structures reveals that, in principle, the Class III alkaloid GB 13 should be convertible into himgaline via an aza-Michael reaction, followed by stereocontrolled reduction of the ring B ketone carbonyl (see Fig. 3, **2**→**3**). In fact, such a synthetic pathway is implicit in the original structural work,[25] during which it was found that hydrogenation of GB 13 in an acidic medium gave 16-*epi*-himgaline (**3a**), the result of sequential aza-Michael closure and reduction of the C(16) carbonyl. In the event, the aza-Michael process was used by the Evans and Adams,[20] Chackalamannil,[19a] and Ma[21] groups in their own total syntheses. An additional relationship among the Class III alkaloids is that (−)-himgaline has been converted[4] into (+)-GB 16 via oxidation of the C(19) hydroxyl and concomitant cleavage of the C(18)–C(19) bond.

A key challenge presented by the Class III alkaloid GB 13 (**2**) is the [3.2.1] bicyclic CD ring system that is cis-fused to the piperidine E ring. Because of the complexity of the structures involved it is convenient to analyze the synthetic approaches to Class III alkaloids **2**–**4** by dealing first of all with routes to the ABC core and then to examine the incorporation of the D, E, and F rings.

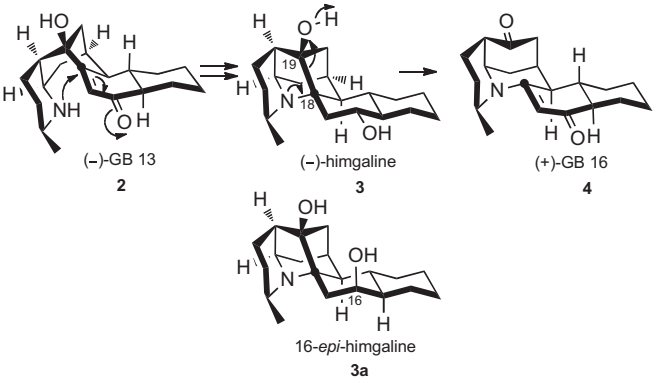


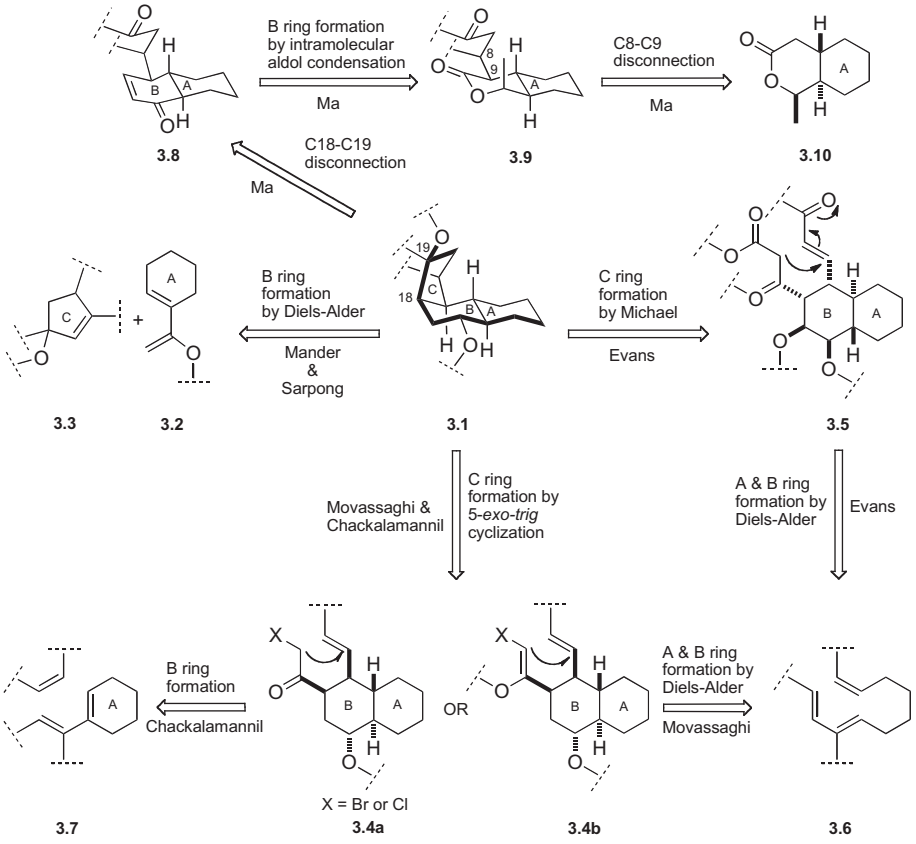
Fig. 3. Interrelationships among three Class III alkaloids.

3.1. Construction of the ABC system of the Class III alkaloids GB 13 and himgaline with some of its associated units

As was already apparent from work on Class I alkaloids, the *trans*-decalin subunit is very effectively made by Diels–Alder reaction, and five different versions of this classical strategy have been applied, as summarized in Scheme 3.

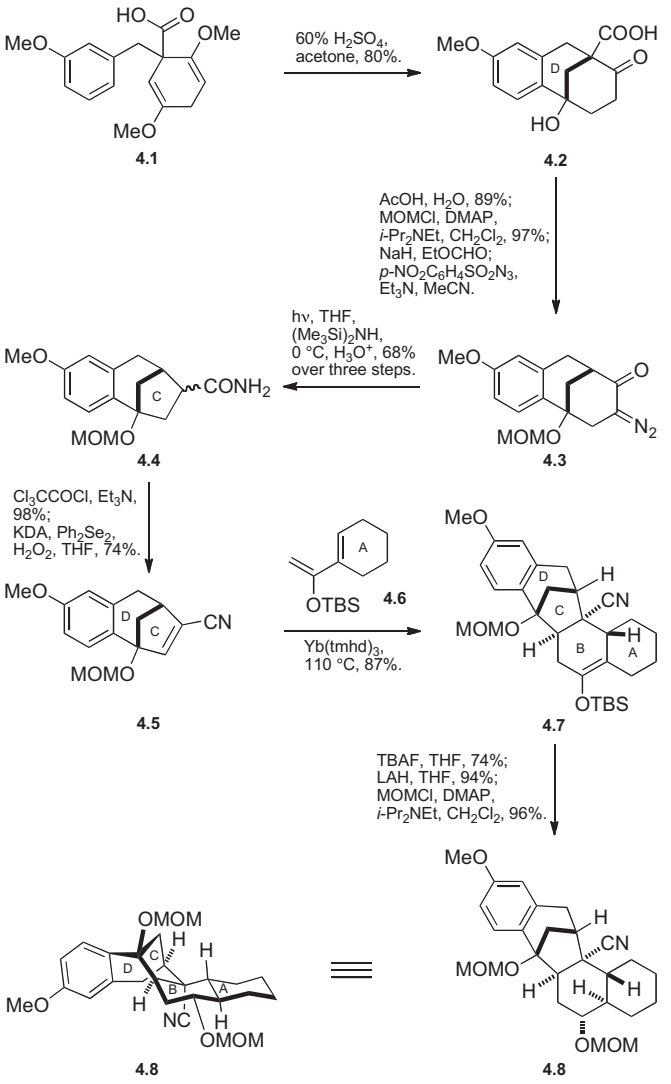
described below. In the event, a 5-*exo*-*trig* radical cyclization of a substructure of type **3.4a** or **3.4b** was used by the groups of Chackalamannil[19a] and Movassaghi,[17] respectively, to form ring C (see **3.4a** or **3.4b** → **3.1**). An intramolecular Michael reaction of a substrate of type **3.5** can also afford the C ring (see **3.5** arrows), a pathway that was used by Evans and Adams.[20] All three research groups judged the bicyclic AB systems **3.4a**, **3.4b**, and **3.5** as being most appropriately dealt with in terms of a Diels–Alder disconnection, and either acyclic intermediates of type **3.6** (Movassaghi[17] and Evans[20]) or a monocyclic intermediate of type **3.7** with ring A already in place (Chackalamannil[19]) were used as the Diels–Alder precursors. The fact that these ideas were eventually reduced to practice, demonstrates that the Diels–Alder process is indeed a reliable method not only for Class I alkaloids but also for the more complex targets of Class III.

A completely different route was designed by Ma's group.[21] His strategy was based on construction of the B and C rings at a very late stage, after forming the D and E rings in a manner that is shown later (in Schemes 16 and 17). Hence a complete discussion of the tricyclic ABC core is not possible in the present section of this review and must be deferred until the early stages of Ma's route have been examined. Only the two key disconnections involved in Ma's formation of ring C are shown in Scheme 3, and these steps will be elaborated further in the discussion corresponding to Schemes 10 and 17. The first of the two key disconnections is cleavage of the



Scheme 3. Retrosynthetic analysis for the ABC rings of Class III alkaloids.

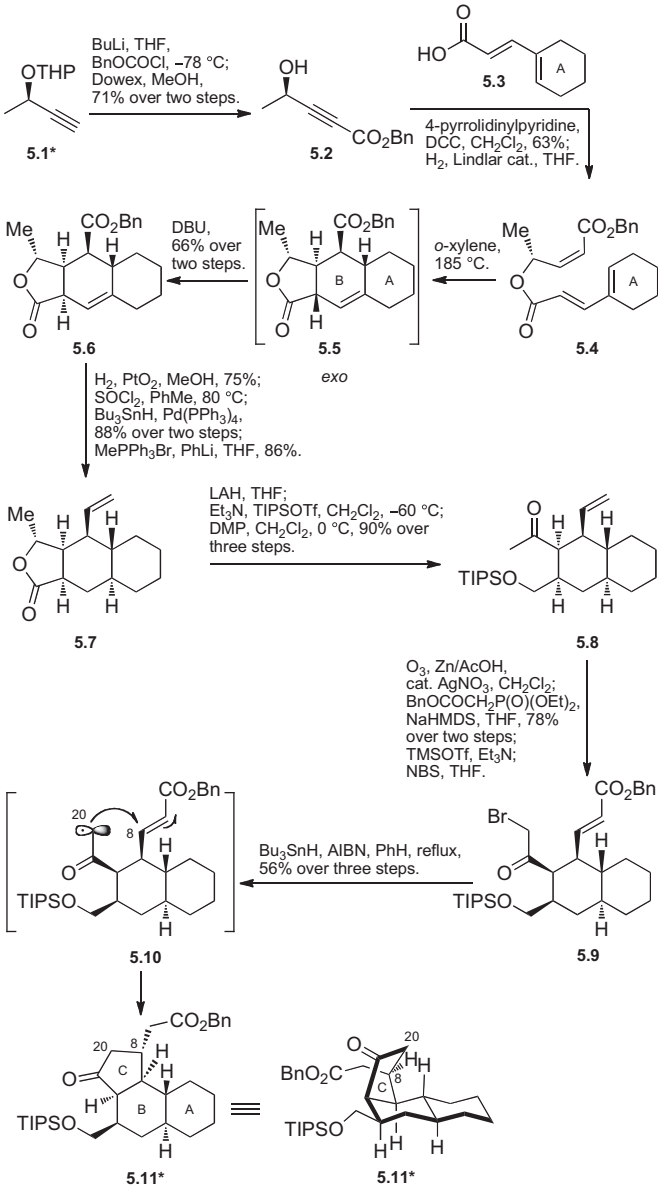
Retrosynthetic disconnection of the B ring of **3.1** gives Diels–Alder precursors where ring A is part of the diene **3.2** and ring C is part of the dienophile **3.3**. This approach was used by Mander[15,16] and by Sarpong and Larson.[18] Alternatively, retrosynthetic disconnection of the five-membered C ring leads to precursors of type **3.4a**, **3.4b**, and **3.5**, which are themselves accessible by Diels–Alder reactions, as C(18)–C(19) bond to give the AB enone system **3.8**, and the B ring was envisioned to come from lactone **3.9**. The second crucial disconnection was of the C(8)–C(9) bond; this simplifies the structure to the bicyclic lactone **3.10** with ring A having the desired trans ring fusion geometry. The notable feature of Ma's route is that no Diels–Alder reaction is involved.



Scheme 4. Mander's approach to the ABCD core of (±)-GB 13. MOM=methoxymethyl, DMAP=4-dimethylaminopyridine, KDA=potassium diisopropylamide, THF=tetrahydrofuran, Htmhd=2,2,6,6-tetramethyl-3,5-heptanedione TBAF=tetra-*n*-butylammonium fluoride, LAH=lithium aluminum hydride.

3.1.1. Construction of the ABCD system—(±)-GB 13 (Mander). The route to racemic GB 13 developed by Mander's group[15,16] was the first total synthesis of any member of Class III. The approach was strategically different from all subsequent routes to members of this class, and it began with the very early construction of the D ring. This was achieved by generating the benzo-fused [3.3.1] bicyclononane **4.2** from the Birch alkylation product[30] **4.1**. In compound **4.2** the fused benzenoid moiety was to serve as a precursor to ring E. In order to prepare for the Diels–Alder step that would generate the ABC subunit, compound **4.2** was converted into the diazoketone **4.3** by a short sequence of reactions: acid-induced decarboxylation of the β-ketoacid subunit, hydroxyl protection, and diazo transfer[31] by the Regitz protocol. At that point, photochemical Wolff ring contraction of **4.3** afforded, after a further two steps (amide **4.4**→nitrile), the required system **4.5**, with the C ring in a form suitable for participation in Diels–Alder cycloaddition. When **4.5** (containing the CD ring system) and **4.6** (containing the A ring) were heated in the presence of a catalytic lanthanide complex, an excellent yield of adduct **4.7** was obtained via a Diels–Alder *endo* transition state. This short and effective construction of the tetracyclic ABCD core with a fused benzenoid unit also set in place the proper relative stereochemistry along the perimeter of the skeleton. Desilylation of the silyl enol ether in **4.7** resulted in a *trans*-decalone, and reduction of the carbonyl, as well as MOM protection of the resulting alcohol, then gave the advanced intermediate **4.8**, representing the ABCD system. The main task left at this stage was conversion of the benzenoid unit into the required ring E piperidine, as shown later (Scheme 11).

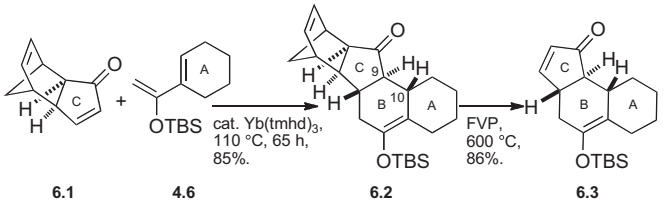
3.1.2. Construction of the ABC system—(−)-GB 13 and (−)-himgaline (Chackalamannil). Chackalamannil's group reported[19a] the first total synthesis of the Class III alkaloid (−)-himgaline; this was achieved by way of (−)-GB 13, and the approach (Scheme 5) was related to the Class I alkaloid himbacine synthesis achieved in the same laboratory.[13] The intermediate **5.7** (a single enantiomer) is enantiomeric to the tricyclic core of (+)-himbacine and this relationship illustrates a potential synthetic connection between the Class I and Class III alkaloids. The single enantiomer of the starting propargylic alcohol derivative **5.1**[19b] was converted into the benzyl ester **5.2** by standard



Scheme 5. Chackalamannil's approach to the ABC core of (−)-GB 13 and (−)-himgaline. *Single enantiomer. Bn=benzyl, DCC=*N*,*N*′-dicyclohexylcarbodiimide, TIPSOTf=triisopropylsilyl trifluoromethanesulfonate, DMP=Dess–Martin periodinane, NaHMDS=sodium hexamethyldisilazide, TMSOTf=trimethylsilyl trifluoromethanesulfonate, NBS=*N*-bromosuccinimide, AIBN=azobisisobutyronitrile.

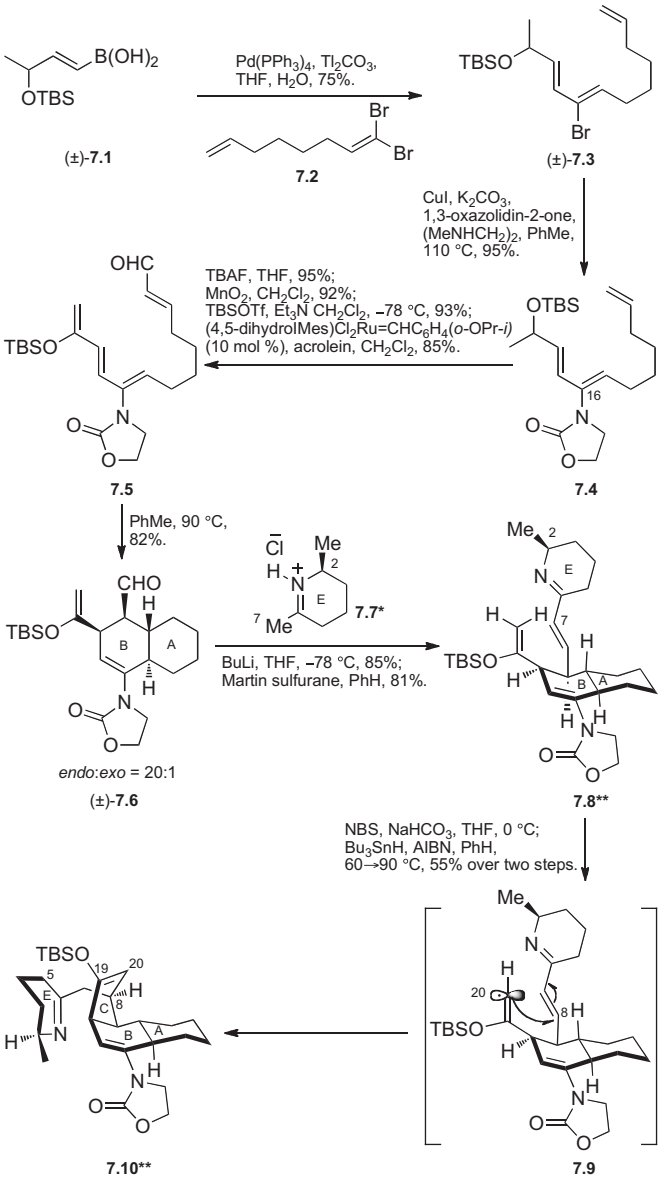
methods, and DCC-mediated coupling with **5.3**, followed by semi-hydrogenation of the triple bond, resulted in the triene **5.4**. On being heated to a high temperature, this compound underwent intramolecular cycloaddition. Base-induced epimerization α to the lactone carbonyl in the *exo*-adduct **5.5** gave the required cis 5/6 system **5.6**. This compound was converted into **5.7** by a short sequence, which involved hydrogenation of the endocyclic double bond and hydrogenolysis (removal of the benzyl group), acid chloride formation, reduction of the acid chloride to an aldehyde and then Wittig methylenation. Reduction of the lactone unit in **5.7**, silylation of the resulting primary hydroxyl, and oxidation of the remaining secondary alcohol then gave the bicyclic ketone **5.8** with the required absolute stereochemistry at each stereogenic center. Compound **5.8** was converted into **5.9** by ozonolysis, HWE olefination, and α-halogenation of the methyl ketone moiety. These steps set the stage for the key 5-*exo-trig* radical cyclization which, in the event, worked well under standard conditions and resulted in the stereocontrolled formation of the C(20)–C(8) bond, generating the BC ring system with the desired cis ring fusion. The stereochemical outcome at C(8) is the consequence of a chair-like transition state in the radical closure.[32] The further elaboration of **5.11** is dealt with in Scheme 12.

3.1.3. Construction of the ABC system—(±)-GB 13 (Sarpong). The Sarpong strategy[18] for making the ABC system of racemic GB 13 is similar to that used by Mander in the sense that the same diene (**4.6**) was used for Diels–Alder cycloaddition and under similar conditions. In Sarpong's case (Scheme 6), the dienophile carried a norbornene masking unit instead of the D and E ring precursors of the Mander route. The stereochemistry of the product **6.2** appears to be the result of in situ epimerization at C(9) of an initial Diels-Alder *endo* adduct. This result correctly set the natural *anti* stereochemistry of the C(9) and C(10) hydrogens. Flash vacuum pyrolysis at 600 °C, served to dismantle the [2.2.1] bicyclic moiety and release the tricyclic ABC system **6.3**. Although this route is the shortest to the ABC core, the trans stereochemistry of the decalin has still to be set and the BC ring fusion stereochemistry requires adjustment from trans to cis, as described later (Scheme 13).



Scheme 6. Sarpong's approach to the ABC core of (±)-GB 13. FVP=flash vacuum pyrolysis.

3.1.4. Construction of the ABCE system—both enantiomers of GB 13 (Movassaghi). A very elegant approach to Class III alkaloids was developed by Movassaghi's[17] group, who reported the first total synthesis of both enantiomers of GB 13, thus establishing the absolute stereochemistry of the natural material, which had previously[2e,25] been misassigned. Independently of this synthetic result, the absolute configuration was also established by crystallographic means.[33] Suzuki coupling between the racemic boronic acid **7.1** (see Scheme 7) and the geminal dibromide **7.2** gave (±)-**7.3**. Copper-catalyzed coupling with 1,3-oxazolidin-2-one (**7.3**→**7.4**) introduced a masking group for a ketone carbonyl (see **14.2**→**2**, Scheme 14). The silyl ether segment of **7.4** was converted into a silyl enol ether by standard procedures, and cross metathesis between the terminal double bond of **7.4** and acrolein was then used to introduce the α,β-unsaturated aldehyde moiety of **7.5**. IMDA reaction of **7.5** proceeded with the required



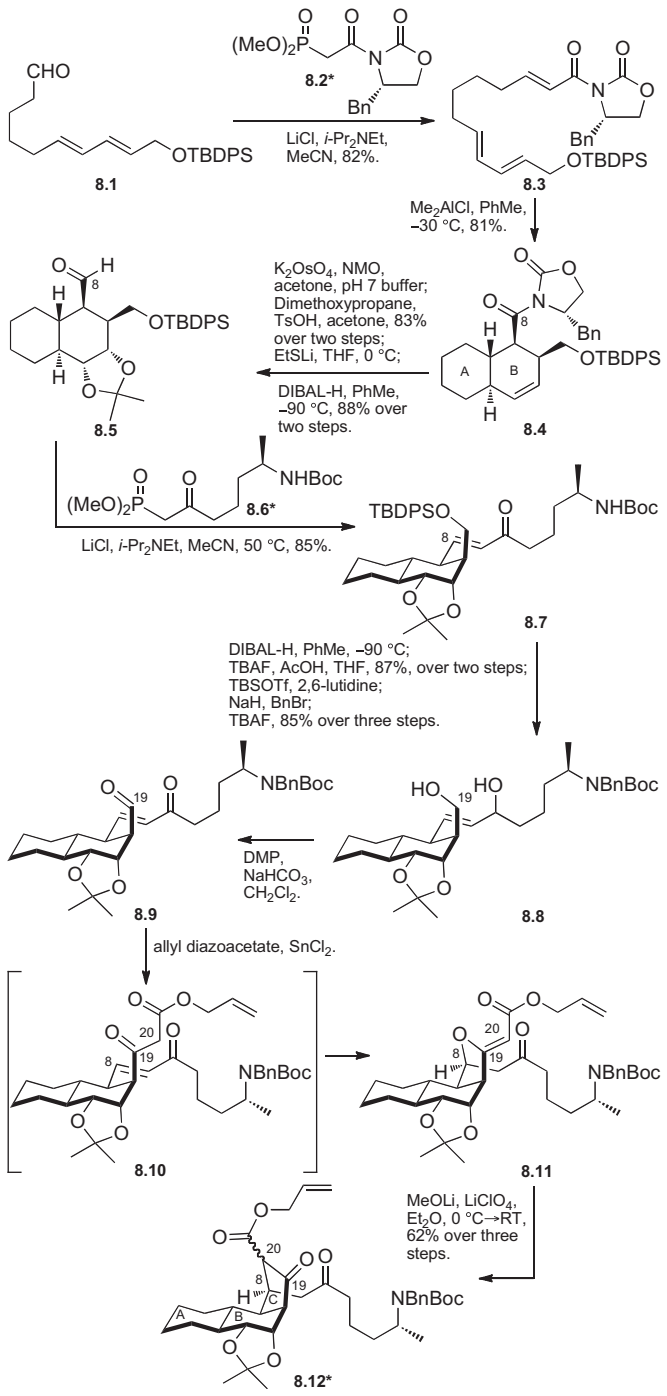
Scheme 7. Movassaghi's approach to the ABCE core of GB 13. *Single enantiomer. **Two diastereomers, only the desired one is shown. TBSOTf=*tert*-butyldimethylsilyl trifluoromethanesulfonate, IMes=1,3-dimesitylimidazol-2-ylidene.

diastereocontrol, giving rise to the cis stereochemistry of the substituents on ring B. The oxazolidinone group served not only as a masking group for a ketone but its presence also specifically favored the s-*cis* conformation of the diene unit in **7.4**; this conformation is essential for the Diels–Alder reaction that converted the next intermediate (**7.5**) into (±)-**7.6**. At this point, ring E was attached by reacting the lithiated enamine derived from the optically pure imine **7.7** with the racemic aldehyde **7.6** and dehydrating the resulting alcohols. The next step was a diastereocontrolled 5-*exo-trig* radical cyclization (related to that used in the route followed by Chackalamannil's group) to convert the ABE system **7.8** into the very advanced ABCE intermediate **7.10**. This crucial step occurred smoothly, giving the product as a mixture of two diastereoisomers. The observed stereochemical outcome at C(8) is the result of the same factors—involvement of a chair-like transition state—that applied to the radical cyclization step in the Chackalamannil synthesis (see **5.9**→**5.11**). Examination of the tetracyclic intermediate **7.10** reveals that, structurally, it is essentially one crucial step—formation of the C(5)–C(19) bond—away from the complicated structure of GB 13. The introduction of ring E

at an early stage, using the optically pure iminium salt **7.7**, makes this route very concise, and the approach illustrates the helpful influence on the synthetic planning exerted by Movassaghi's biosynthetic proposal for Class II and III alkaloids. The further elaboration of **7.10** is dealt with in Scheme 14.

3.1.5. Construction of the ABC system—(+)-GB 13 and (+)-himgaline (Evans). Another approach, this time to (+)-GB 13 (*ent*-**2**) and (+)-himgaline (*ent*-**3**), was reported by Evans and Adams (Scheme 8).[20] Their strategy was somewhat related to Movassaghi's except for the route to the C and E rings. The former ring was assembled by a Michael reaction instead of a radical cyclization as used in the Movassaghi and Chackalamannil syntheses, and the E ring came from an acyclic chain (as described later in Scheme 15).

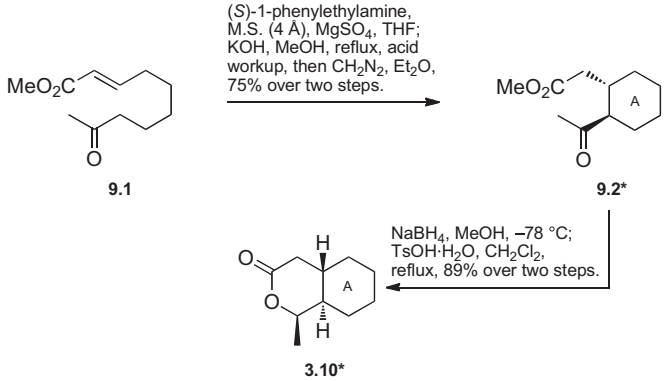
The starting aldehyde **8.1** in the Evans approach was converted into **8.3** by Horner–Emmons–Wadsworth olefination, using the optically pure phosphonate **8.2**. A diastereocontrolled intramolecular Diels–Alder reaction then furnished the substituted *trans*-decalin **8.4**. This intermediate was elaborated further to **8.5** by a four-step sequence, which included diastereoselective vicinal dihydroxylation in the B ring, protection of the resulting diol, conversion of the C(8) carbonyl into a thioester, and finally, DIBAL reduction to release the C(8) carbonyl as an aldehyde. This aldehyde was homologated by another HWE olefination with the known enantiomerically pure phosphonate **8.6**[11b] so as to obtain the α,β-unsaturated ketone **8.7**. The carbonyl group was then reduced to temporarily prevent the possibility of a conjugate addition process when the silicon protecting group was removed in the next step. The nitrogen was then benzylated by a three-step procedure that involved silylation of both hydroxyls, *N*-alkylation, and finally removal of the silicon protecting groups to give **8.8**. Dess–Martin oxidation of both hydroxyls then set the stage for installation of a β-ketoester unit selectively at the C(19) aldehyde. This was achieved by the Roskamp protocol,[34] the aldehyde **8.9** being treated with allyl diazoacetate in the presence of a Lewis acid to produce **8.10**. The enolate from this β-ketoester underwent an intramolecular Michael reaction via the C(19) oxygen to furnish the vinyl ether **8.11**. This step is reversible under basic conditions and, on treatment with LiOMe, the vinyl ether was converted into the product of Michael reaction via the C(20) carbon to form the desired C(8)–C(20) bond with total stereocontrol at C(8) in **8.12**, thus completing the construction of ring C. The relative stereochemical outcome at C(8) is the same as that observed by the groups of Chackalamannil and Movassaghi during their 5-*exo*-*trig* radical cyclizations and, presumably, represents the thermodynamically favored configuration. The remainder of Evans's synthesis is discussed later (in Scheme 15).



Scheme 8. Evans's approach to the ABC core of (+)-GB 13 and (+)-himgaline. *Single enantiomer. NMO=*N*-methylmorpholine-*N*-oxide, Ts=*p*-toluenesulfonyl, DIBAL=diisobutylaluminum hydride.

The starting aldehyde **8.1** in the Evans approach was converted into **8.3** by Horner–Emmons–Wadsworth olefination, using the optically pure phosphonate **8.2**. A diastereocontrolled intramolecular Diels–Alder reaction then furnished the substituted *trans*-decalin **8.4**. This intermediate was elaborated further to **8.5** by a four-step sequence, which included diastereoselective vicinal dihydroxylation in the B ring, protection of the resulting diol, conversion of the C(8) carbonyl into a thioester, and finally, DIBAL reduction to release the C(8) carbonyl as an aldehyde. This aldehyde was homologated by another HWE olefination with the known enantiomerically pure phosphonate **8.6**[11b] so as to obtain the α,β-unsaturated ketone **8.7**. The carbonyl group was then reduced to temporarily prevent the possibility of a conjugate addition process when the silicon protecting group was removed in the next step. The nitrogen was then benzylated by a three-step procedure that involved silylation of both hydroxyls, *N*-alkylation, and finally removal of the silicon protecting groups to give **8.8**. Dess–Martin oxidation of both hydroxyls then set the stage for installation of a β-ketoester unit selectively at the C(19) aldehyde. This was achieved by the Roskamp protocol,[34] the aldehyde **8.9** being treated with allyl diazoacetate in the presence of a Lewis acid to produce **8.10**. The enolate from this β-ketoester underwent an intramolecular Michael reaction via the C(19) oxygen to furnish the vinyl ether **8.11**. This step is reversible under basic conditions and, on treatment with LiOMe, the vinyl ether was converted into the product of Michael reaction via the C(20) carbon to form the desired C(8)–C(20) bond with total stereocontrol at C(8) in **8.12**, thus completing the construction of ring C. The relative stereochemical outcome at C(8) is the same as that observed by the groups of Chackalamannil and Movassaghi during their 5-*exo*-*trig* radical cyclizations and, presumably, represents the thermodynamically favored configuration. The remainder of Evans's synthesis is discussed later (in Scheme 15).

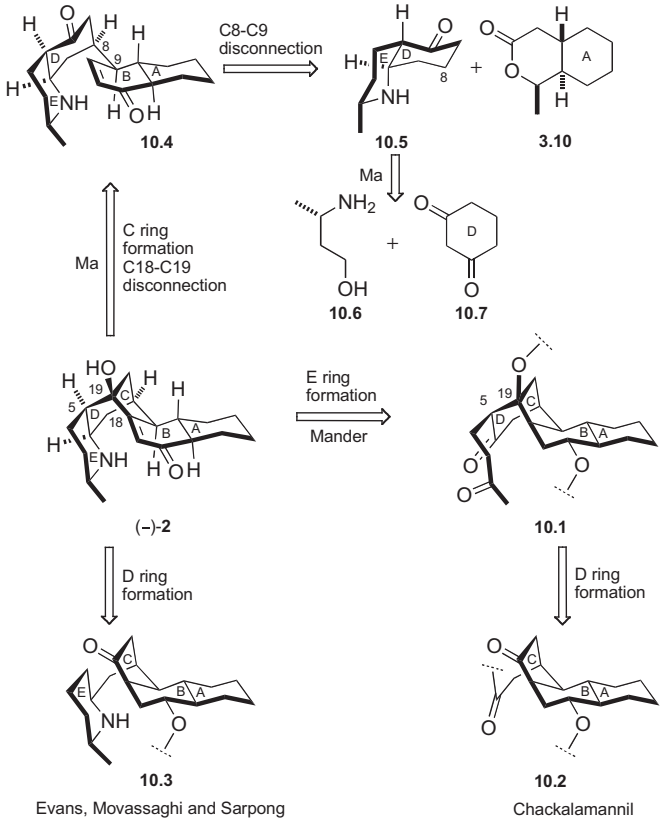
3.1.6. Construction of a bicyclic lactone incorporating ring A—(−)-GB 13, (−)-himgaline, and (+)-GB 16 (Ma). As mentioned earlier the approach used by Ma[21] in his synthesis of (−)-GB 13, (−)-himgaline, and (+)-GB 16 is conceptually different from all other routes: an asymmetric Michael reaction[35] involving ketoester **9.1** and (*S*)-1-phenylethylamine was used to obtain the A ring (**9.2**, see Scheme 9) instead of the Diels–Alder approach adopted by other groups discussed so far. Diastereoselective reduction of the ketone carbonyl in **9.2**, followed by exposure to acidic conditions, gave lactone **3.10**. This lactone served as the precursor to ring B but, as stated earlier, both the B and C rings were built much later onto the ADE system and hence will be discussed in due course (in Scheme 17).



Scheme 9. Ma's approach to the bicyclic lactone incorporating ring A. *Single enantiomer. M.S.=molecular sieves.

3.2. Completion of the Class III pentacyclic ABCDE system of GB 13 and the hexacyclic ABCDEF system of himgaline

Building the D and E rings onto the tricyclic ABC system (Chackalamannil, Evans, and Sarpong) or completing whichever of the rings D or E was not already present in the more advanced polycyclic structures **4.8** (Mander) and **7.10** (Movassaghi) proved to be the most complex part of the synthesis of Class III alkaloids. The retrosynthetic disconnections for these tasks are summarized in Scheme 10. One of the promising disconnections of the E ring of GB 13 simplifies the structure to the 1,5-dicarbonyl system **10.1**. Both Mander and Chackalamannil followed this strategy. Structure **10.1** closely resembles Mander's intermediate **11.4** (see Scheme 11). From **10.1**, disconnection of the C(5)–C(19) bond gives the tricyclic ABC system **10.2**. Structure **10.2** resembles Chackalamannil's intermediate **12.1** (see Scheme 12). In the synthetic direction, the C(5)–C(19) bond was formed in the Chackalamannil approach by a Lewis acid catalyzed cyclization so as to make the D ring, but in Mander's route, this ring was already in place.

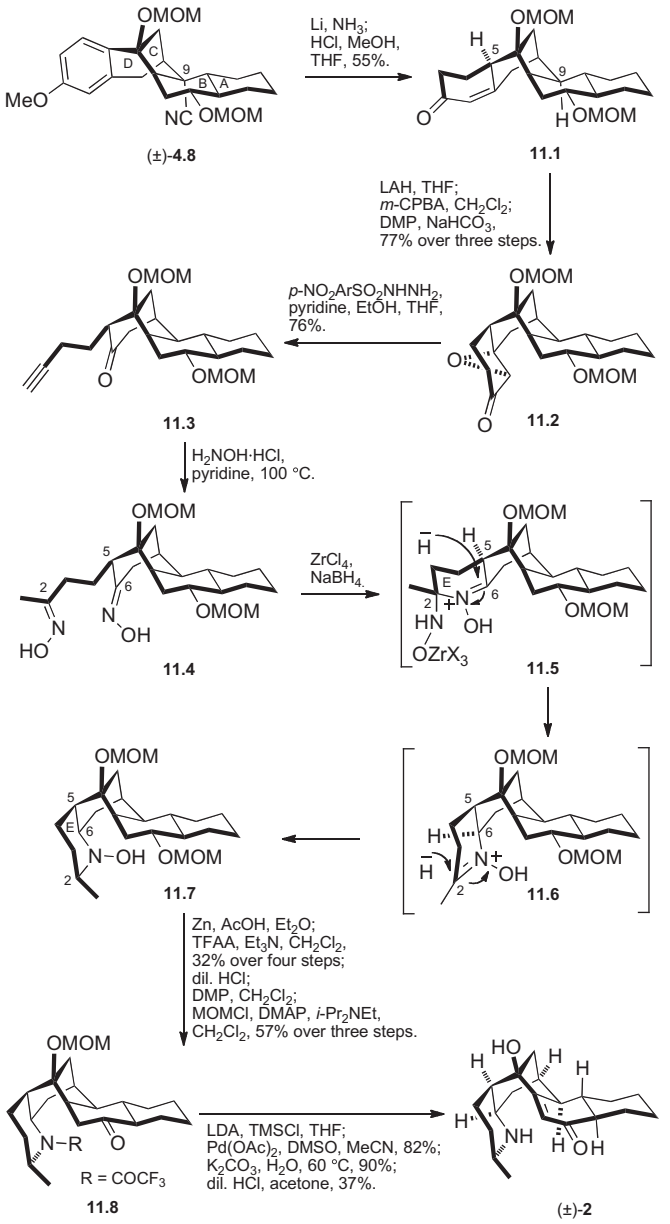


Scheme 10. Retrosynthetic analysis for the D and E rings of Class III alkaloids.

An alternative method for dealing with the problems posed by rings D and E starts by disconnection of the C(5)–C(19) bond of the D ring and leads to the tetracyclic ABCE system **10.3**, which, in turn, can be synthesized from the tricyclic ABC system of type **3.1** (see Scheme 3). The intermediate of type **10.3** was shown above in the Movassaghi route to (−)-GB 13 (Scheme 7, see **7.10**). The same type of disconnection was also used by the groups of Evans (see the Evans intermediate **15.3** in Scheme 15) and Sarpong (see Sarpong's intermediate **13.4** in Scheme 13). In the case of the Sarpong approach, the C(5)–C(19) bond was formed by a metal catalyzed reaction, as described later (Scheme 13), while Evans and Movassaghi used enamine-based processes, both of which are also described later (Schemes 14 and 15). A notable feature of Sarpong's procedure is that a readily available substituted pyridine serves as the precursor to the piperidine E ring.

Finally, Ma's very efficient convergent strategy offered a distinctive way of overcoming the synthetic challenges present in these pentacyclic and hexacyclic alkaloids. His plan was to bisect the pentacyclic core of (−)-GB 13 into two equally complex substructures. Hence, the first key disconnection was C(18)–C(19) (mentioned earlier in Scheme 3) to give the ABDE tetracycle **10.4**, which resembles **3.8** (Scheme 3) as well as Ma's actual intermediate (**17.7**, Scheme 17). The further disconnection C(8)–C(9) then splits the molecule into two bicyclic units, the lactone **3.10** (see **3.8**→**3.9**→**3.10** in Scheme 3), and the bicyclic piperidine **10.5**. The DE unit was made separately from a single enantiomer of the amino alcohol **10.6** and the simple diketone **10.7**.

3.2.1. Completion of the pentacyclic ABCDE system of (±)-GB 13: ABCD→ABCDE (Mander). As stated during the discussion of the synthesis of the ABCD subunit (see Scheme 4), the aim of the Mander group[15,16] was to synthesize an all-*cis* piperidine moiety from a benzene ring. Mander's intermediate **4.8** was converted into **11.1** (Scheme 11) by Birch reduction and acid hydrolysis.

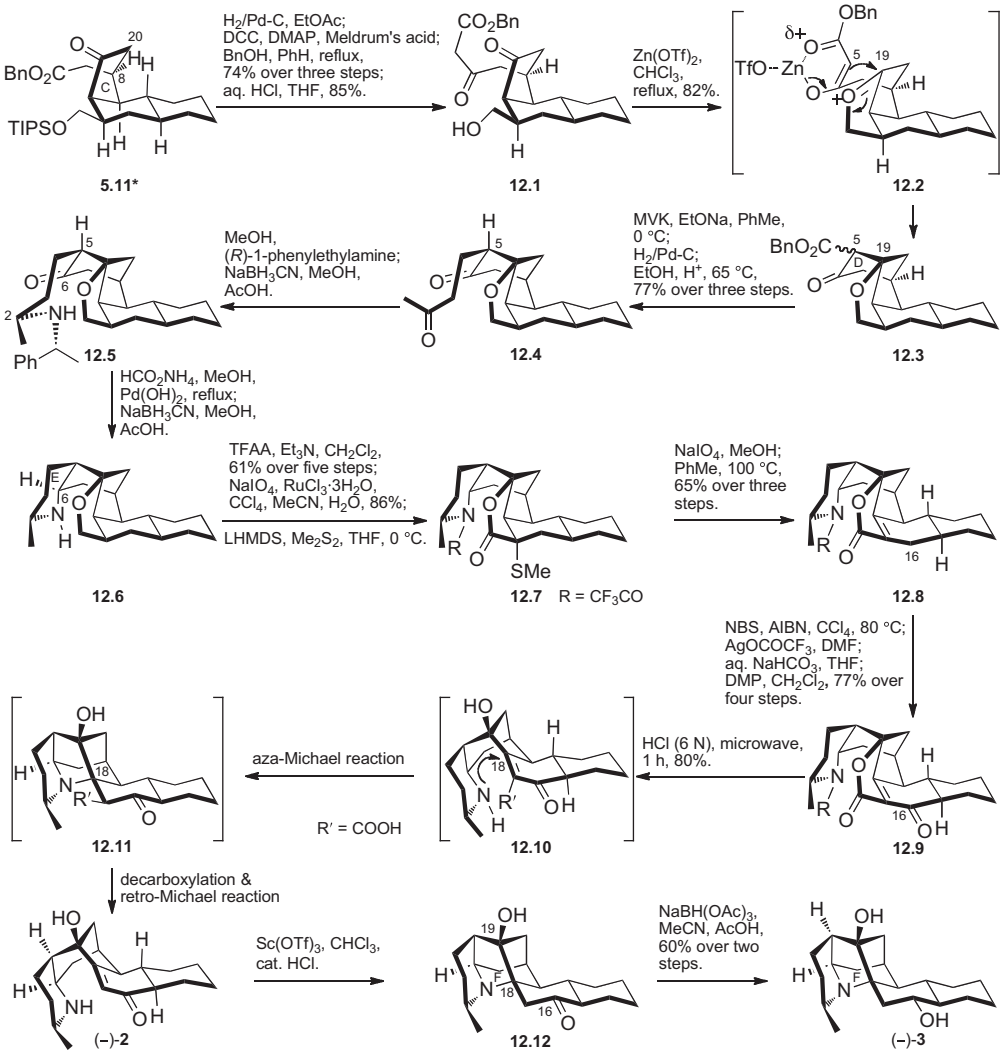


Scheme 11. The ABCD→ABCDE conversion—(±)-GB 13 (Mander). *m*-CPBA=*meta*-chloroperoxybenzoic acid, TFAA=trifluoroacetic anhydride, DMSO=dimethyl sulfoxide.

During the reduction, decyanation occurred with retention of stereochemistry [protonation of the intermediate anion at C(9) occurs from the *exo* face of the molecule] and during acid hydrolysis the usual isomerization of the double bond into conjugation with the ketone carbonyl took place. The protonation at C(5) during the hydrolysis/double bond isomerization stage was stereoselective, leading to the equatorial disposition of the carbon chain at C(5).

The next step in Mander's plan called for epoxidation of the double bond of the cyclohexenone unit of **11.1**, but this could not be achieved directly and so a three step sequence of carbonyl reduction, epoxidation, and alcohol oxidation was used to make **11.2**, which was then subjected to Eschenmoser fragmentation to the desired product **11.3**. This was then converted[36] into the bis-oxime **11.4** by treatment with hydroxylamine hydrochloride. Reductive cyclization of **11.4** to **11.7**, using a reagent made from $ZrCl_4$ and $NaBH_4$, served to create the all-*cis* piperidine unit with the proper stereochemistry at C(2).[37] The adduct of the reagent with the oxime oxygen is arbitrarily represented in Scheme 11 as $-OZrX_3$, but the composition of the reagent is unknown. Presumably, during the reductive cyclization of **11.4** to **11.7**, a hydride approaches the first intermediate iminium ion (**11.5**) axially to the newly formed E ring; this trajectory, which also corresponds to approach from the less hindered *exo* face, sets the eventual C(6) stereochemistry. The second iminium reduction (see **11.6**) also involves axial approach to ring E from the less hindered *exo* face, giving rise to the desired C(2) stereochemistry. The same steric and stereoelectronic factors were also invoked by Mander in the synthesis of the skeleton of the Class II alkaloid himandrine (see later, Scheme 20). With the formation of **11.7**, the pentacyclic core of GB 13 was complete, but a number of functional group manipulations were still required to reach the natural product. Cleavage of the N–OH bond released a free amino group, which was protected as a trifluoroacetate, and then the MOM groups were removed. The secondary hydroxyl was oxidized and the remaining tertiary alcohol was reprotected as a MOM ether (**11.7**→**11.8**). Introduction of the double bond in ring B by the Saegusa protocol, followed by removal of the two remaining protecting groups, afforded racemic GB 13.

3.2.2. Completion of the hexacyclic ABCDEF system of (−)-himgaline: ABC→ABCDEF (Chackalamannil). The Chackalamannil group adopted[19a] a linear approach to convert their intermediate **5.11** (Scheme 5) into **12.1** (Scheme 12). Hydrogenolysis of the benzylic group in **5.11** and DCC-mediated coupling of the resulting acid with Meldrum's acid, followed by heating with benzyl alcohol,



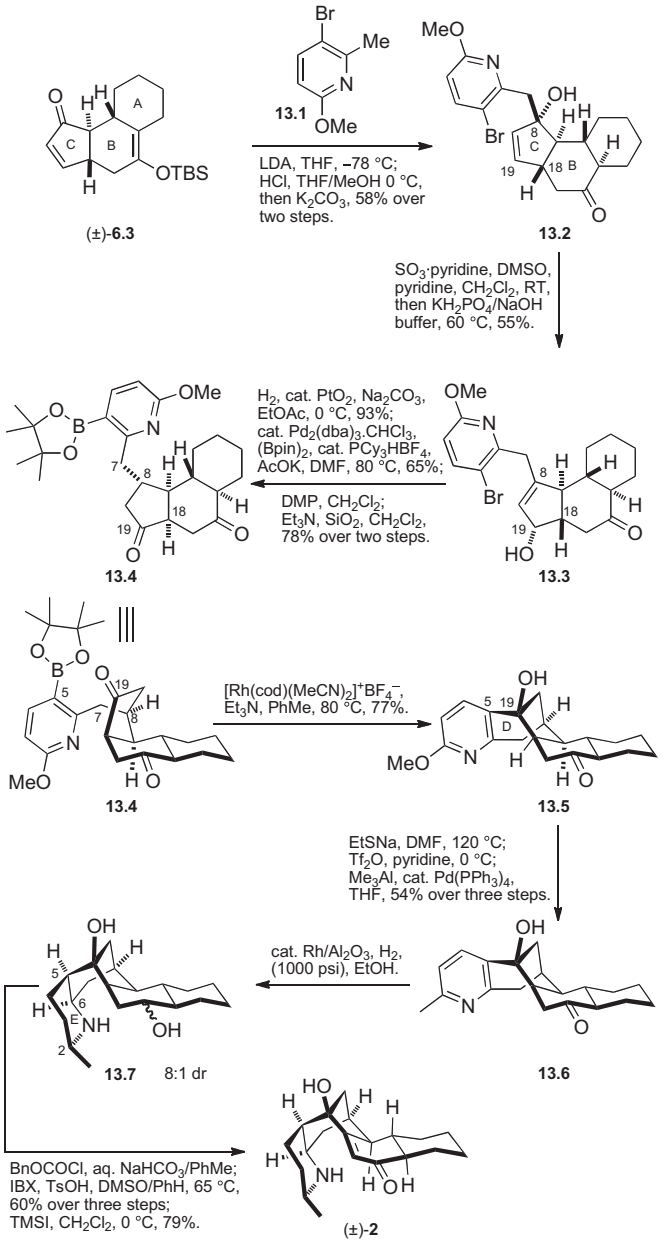
Scheme 12. The ABC→ABCDEF conversion—(−)-himgaline (Chackalamannil). *Single enantiomer. MVK=methyl vinyl ketone, DMF=*N*,*N*-dimethylformamide.

gave a β-ketoester, which was converted into **12.1** by removal of the triisopropylsilyl group under acidic conditions. At that stage, ring D was formed (as in **12.3**) by the action of the Lewis acid $Zn(OTf)_3$, presumably through formation of the oxonium intermediate **12.2**, which was captured intramolecularly so as to produce the required stereochemistry at C(19). Condensation of **12.3** with methyl vinyl ketone, followed by hydrogenolysis of the benzyl ester, and decarboxylation, resulted in the 1,5-diketone **12.4** with the indicated stereochemistry at C(5). This compound is clearly related to Mander's intermediate **11.4**. Reductive amination with the chiral amine (*R*)-1-phenylethylamine produced **12.5**, very largely with the indicated stereochemistry at C(2). Hydrogenolysis of the nitrogen protecting group resulted in formation of an imine with the C(6) carbonyl; this imine was reduced with sodium cyanoborohydride, the stereochemical outcome being attributed to the same factors that operated in the corresponding step of the Mander synthesis (see **11.4**→**11.5**→**11.6**→**11.7** in Scheme 11). This reduction gave an all-*cis* piperidine unit (**12.6**) as the major diastereoisomer. The remaining tasks were to dismantle the cyclic ether and to generate the α,β-unsaturated carbonyl unit in the B ring of GB 13. Protection of the amine nitrogen in **12.6** as a trifluoroacetate and oxidation of the cyclic ether subunit to a lactone under standard conditions ($RuCl_3 \cdot 3H_2O$, $NaIO_4$) was followed by thiomethylation α to the lactone carbonyl to yield mainly **12.7**. The stereochemistry of the SMe group was appropriate for the intended *syn* elimination which provided **12.8**. At this point, the required carbonyl group in ring B was introduced by four standard operations (**12.8**→**12.9**): allylic bromination at C(16), treatment with silver trifluoroacetate to replace the bromine, hydrolysis of the resulting ester to a C(16) alcohol, and oxidation to a carbonyl group.

The amino group of **12.9** was deprotected under acidic conditions, and it then underwent an intramolecular aza-Michael reaction (see **12.10**) to yield the β-ketoacid **12.11**. This compound looses carbon dioxide via the classical six-membered transition state, and the resulting enolate undergoes a retro-Michael reaction to afford (−)-GB 13. The conversion of (−)-GB 13 to (−)-himgaline (**3**) was straightforward. Lewis acid catalyzed intramolecular Michael reaction, followed by stereoselective reduction of the carbonyl group, using a hydride source internally coordinated to the C(19) tertiary hydroxyl, finished the first total synthesis of (−)-himgaline.

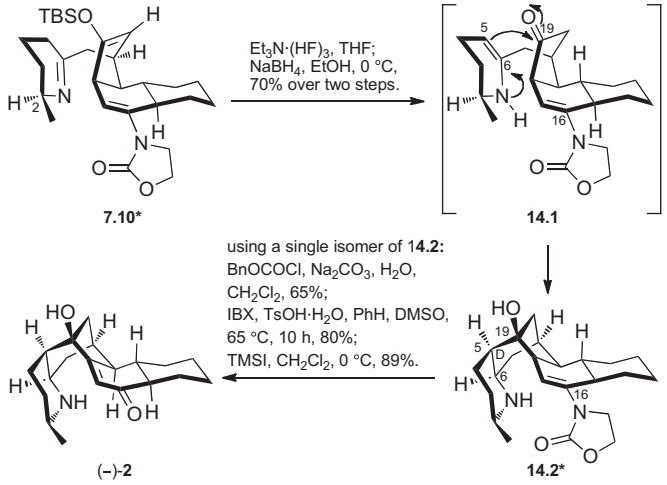
3.2.3. Completion of the pentacyclic ABCDE system of (±)-GB 13: ABC→ABCDE (Sarpong). Diastereocontrolled attachment of the substituted pyridine ring **13.1** (the E ring precursor) to the tricyclic intermediate **6.3** is a key step in Sarpong's synthesis[18] of (±)-GB 13 (Scheme 13). The stereochemistry of the angular hydrogen next to the enone carbonyl group of **6.3** appears to direct the 1,2-addition, and then hydrolysis of the silyl enol ether unit gave **13.2** (the *trans*-decalin).

As mentioned earlier with respect to Sarpong's approach, it was necessary to epimerize C(18) in order to get the required cis BC ring fusion, and to accomplish this step an allylic hydroxyl transposition from C(8) to C(19) was required, so as to convert **13.2** into **13.3**. After extensive screening of different conditions, the use of the Parikh–Doering reagent was identified as the most effective method for this interconversion. With **13.3** in hand, diastereocontrolled hydrogenation (which occurred from the desired face) set the C(8) stereochemistry. The aryl bromide unit was then converted into a boronate and the C(19) hydroxyl was oxidized. With the ketone carbonyl present, the required epimerization at C(18) to afford **13.4** was easily achieved. At this stage, the next step was construction of the C(5)–C(19) bond. The initial approach was via halogen–metal exchange on the bromo analog of **13.4** (Br instead of B) in the expectation that 1,2-addition to the carbonyl would occur, but this approach failed. A reported procedure[38] for the addition of arylboronic acids to ketones, using a palladium catalyst, was also unsuccessful. These difficulties led the Sarpong group to invent a new reaction—rhodium(I)-catalyzed aryl boron addition to an unactivated carbonyl (**13.4**→**13.5**). The shape of **13.4** ensures that attack of the aryl boron species occurs from the *exo* face, as shown. The MeO group was then replaced by a methyl group in three steps (**13.5**→**13.6**). Hydrogenation then afforded the piperidine ring with all substituents cis, hydrogenation having occurred very largely (ca. 8:1) from the *exo* face. This step not only sets the cis fusion between rings D and E but also the stereochemistry of the methyl group at C(2). The keto group on ring B was also reduced during the hydrogenation. From **13.7**, Cbz protection of the amino group, oxidation of the ring B hydroxyl with IBX, and deprotection of the nitrogen completed the synthesis of (±)-GB 13.

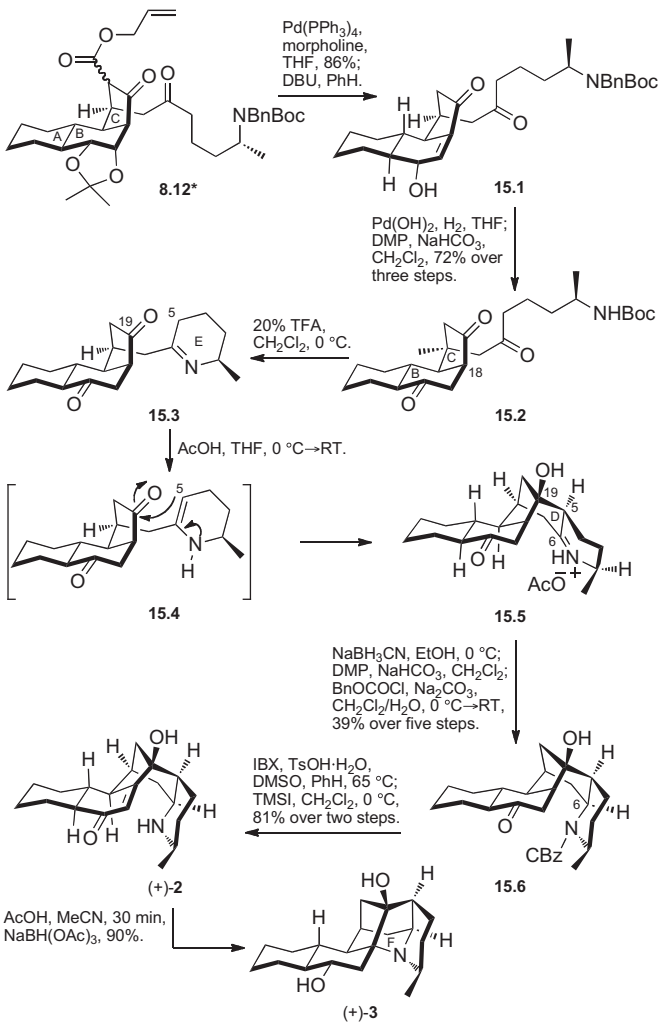


Scheme 13. The ABC→ABCDE conversion—(±)-GB 13 (Sarpong). $(Bpin)_2$=bis(pinacolato) diboron, dba=dibenzylideneacetone, cod=1,5-cyclooctadiene, Tf=trifluoromethanesulfonic, IBX=*o*-iodoxybenzoic acid.

3.2.4. Completion of the pentacyclic ABCDE system of both enantiomers of GB 13: ABCE→ABCDE (Movassaghi). The very advanced stage ABCE intermediate **7.10**, as a mixture of diastereoisomers, made by Movassaghi[17] (see Scheme 7) was converted into the pentacyclic GB 13 core by a very short sequence, and then into GB 13 itself (Scheme 14). Hydrolysis of the silyl enol ether triggers an enamine condensation with the C(19) ketone that is generated. Reduction of the resulting imine gave **14.2** and, at this stage, it was possible to separate the diastereomers; the desired one was converted into (−)-GB 13 in three simple steps: protection of the nitrogen with a Cbz group, generation of an enone by the action of IBX on the C (16) enamine unit, and deprotection of the ring E nitrogen. The whole sequence was repeated with the other enantiomer of the ring E segment (**7.7**) to produce the unnatural (+)-GB 13. With both enantiomers of GB 13 available the absolute configuration of the natural material was easily assigned, as indicated earlier.



Scheme 14. The ABCE→ABCDE conversion—both enantiomers of GB 13 (Movassaghi). *Two diastereomers.

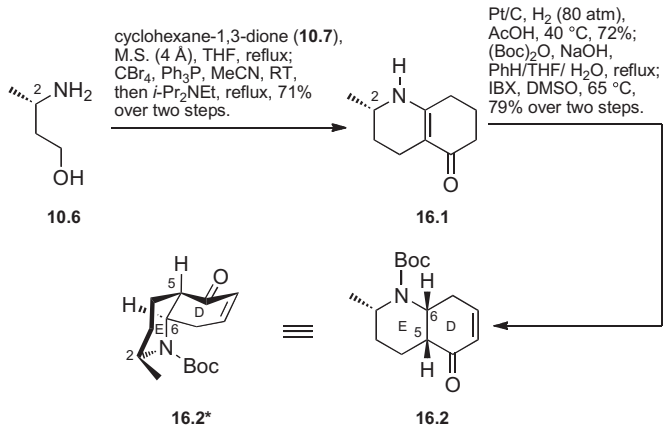


Scheme 15. The ABC→ABCDE conversion—(+)-himgaline (Evans). *Single enantiomer.

3.2.5. Completion of the hexacyclic ABCDEF system of (+)-himgaline: ABC→ABCDEF (Evans). The D ring synthesis developed by Evans and Adams[20] is very similar to Movassaghi's approach. First, ring E was formed from a linear chain attached to the ABC unit to obtain an ABCE tetracyclic precursor, as shown in Scheme 15. Compound **8.12** was first treated with a palladium catalyst to effect removal of the allyl group and allow spontaneous decarboxylation. Then DBU-mediated acetonide elimination produced the allylic alcohol **15.1**. Hydrogenation of the double bond in **15.1** from the more accessible under face, and simultaneous removal of the *N*-benzyl group, followed by Dess–Martin oxidation of the secondary hydroxyl, then produced the ABC system **15.2** with the desired cis BC ring fusion.

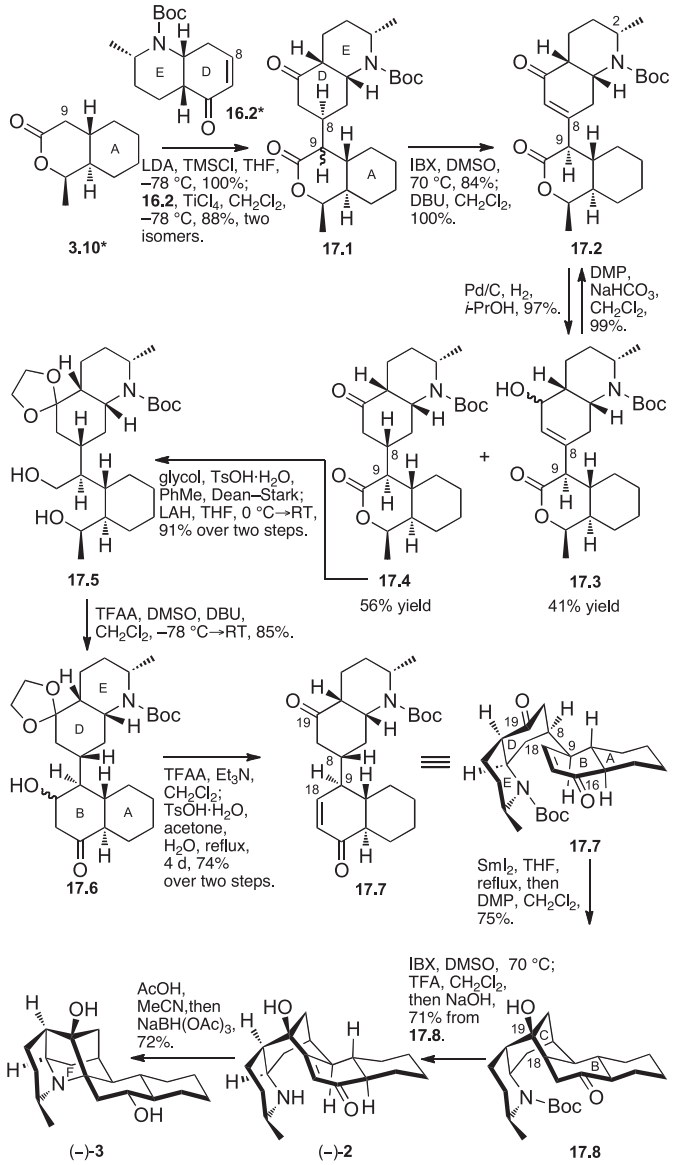
From **15.2**, an acid-mediated cyclization (CF_3CO_2H), similar to that used by Baldwin[11] during his biomimetic synthesis of (+)-himbacine (see Scheme 2), generated ring E in the form of the cyclic imine **15.3**. In the next step, an enamine cyclization in the presence of acetic acid was used for generating ring D (**15.3**→**15.4**→**15.5**). The stereochemical outcome at C(5) and C(19) was the required natural stereochemistry, as observed in Movassaghi's (−)-GB 13 synthesis (see Scheme 14, **7.10**→**14.1**→**14.2**). Hydride reduction of the iminium ion **15.5** in an axial direction with respect to the piperidine ring produced the required C(6) stereochemistry, but the simultaneous unwanted reduction of the ketone carbonyl in ring B could not be avoided. Oxidation (Dess–Martin periodinane) and N-protection (CbzCl) resulted in compound **15.6**, which has the required pentacyclic structure of *ent*-**2**. The double bond in the B ring was introduced by using IBX, and then removal of the CBz group gave (+)-GB 13. Conversion of *ent*-**2** to *ent*-**3** was achieved via an intramolecular aza-Michael reaction (in the presence of acetic acid), followed by diastereocontrolled reduction of the ketone carbonyl, as reported by Chackalamannil (see Scheme 12).

3.2.6. Completion of the hexacyclic ABCDEF system of (−)-himgaline: DE→ABDE→ABCDEF (Ma). Ma's strategy[21] was to make the DE system, which was later combined with the intermediate **3.10** containing the A ring, and this step was followed by construction of the B and C rings. From the above discussion of all the other routes it is evident that Ma's route bears no relationship to any of them. His construction of the DE system was straightforward, as shown in Scheme 16. Like Mander, he also started with the D ring, but used cyclohexane-1,3-dione (**10.7**). Condensation of **10.7** with the optically pure amino alcohol **10.6** having the proper C(2) stereochemistry, followed by conversion of the primary hydroxyl to a leaving group (bromide) and S_N2 displacement, afforded **16.1**. Diastereocontrolled hydrogenation gave rise to the desired cis ring fusion, the stereochemical outcome being controlled by the C(2) methyl group. The ketone was also reduced under the hydrogenation conditions. Protection of the nitrogen (Boc) and IBX-mediated oxidation generated enone **16.2**. With this all-*cis*



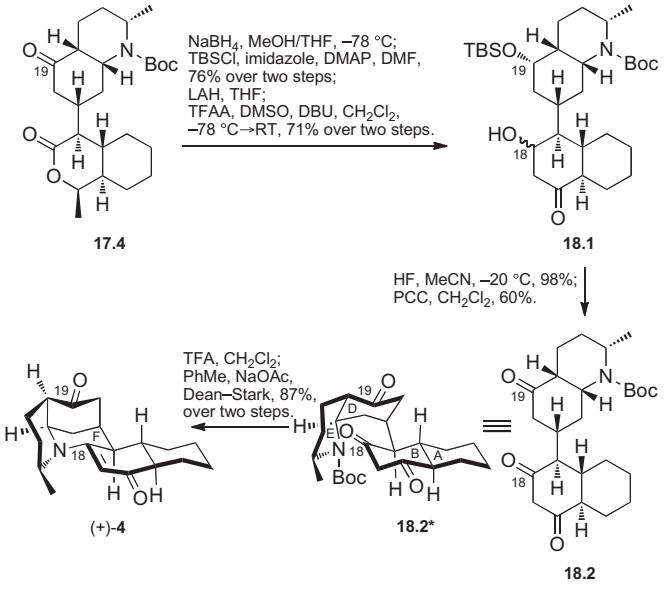
Scheme 16. Approach to the DE ring system of (−)-GB 13 and (−)-himgaline (Ma). *Single enantiomer.

piperidine DE unit in hand, Ma coupled it with **3.10**—a key step where he implemented his convergent strategy, making the approach very efficient (Scheme 17). The silyl enol ether derived from **3.10** underwent a Mukaiyama–Michael addition onto **16.2** from the *exo* face, thus generating the unwanted C(8) stereochemistry as in **17.1**. This was a mixture of C(9) epimers (3.5:1) with the major product having the wrong C(9) stereochemistry. Hence, at this stage, adjustment of both the C(8) and C(9) stereocenters was necessary. IBX-mediated oxidation formed an enone and DBU-induced epimerization fixed the C(9) stereochemistry (see **17.2**) as present in the target. Hydrogenation [presumably from the *exo* face directed away from the C(2) methyl group] gave a mixture of **17.3** and **17.4**, the latter having the desired C(8) stereochemistry. Compound **17.3** was oxidized back to **17.2** by DMP. With the proper C(8)–C(9) stereochemistry in the ADE system **17.4**, the next task was to convert the lactone to the B ring. Ketal formation and reduction using LAH furnished the diol **17.5**. After screening a number of conditions, it was found that Swern oxidation in the presence of DBU instead of triethylamine[39] was effective in producing the desired keto aldehyde, which then



Scheme 17. The DE→ABDE→ABCDE Conversion—(−)-himgaline (Ma). *Single enantiomer.

underwent intramolecular aldol condensation in situ to generate the *trans*-decalins **17.6**. This very advanced tetracyclic ABDE intermediate was converted into enone **17.7** by two simple operations—dehydration and acid hydrolysis. The final part of the synthesis was to construct the C(18)–C(19) bond to form the five-membered C ring, a step, which also produces the [3.2.1] bicyclic moiety. This very late-stage C ring formation was achieved by a novel method—samarium iodide mediated carbonyl–alkene reductive coupling; this step is another strategic difference between Ma's route and the other five syntheses of Class III alkaloids. The reductive coupling went smoothly in refluxing THF, and DMP oxidation of the mixture of products [**17.8** with some over-reduced C(16) alcohol] gave **17.8**. Two more simple steps, dehydrogenation with IBX to generate the enone in the B ring and removal of the nitrogen protecting group gave (−)-GB 13. Conversion of this product to (−)-himgaline was done by essentially the same method as used by both Evans and Chackalamannil. Before the reductive coupling step **17.7**→**17.8**, the existing C(8)–C(9) bond can be axial or equatorial with respect to ring D, but only when it is axial is cyclization geometrically possible, and the newly formed C(18)–C(19) bond then has to be axial to ring D.



Scheme 18. Completion of the synthesis of (+)-GB 16 (Ma). *Single enantiomer. PCC=pyridinium chlorochromate.

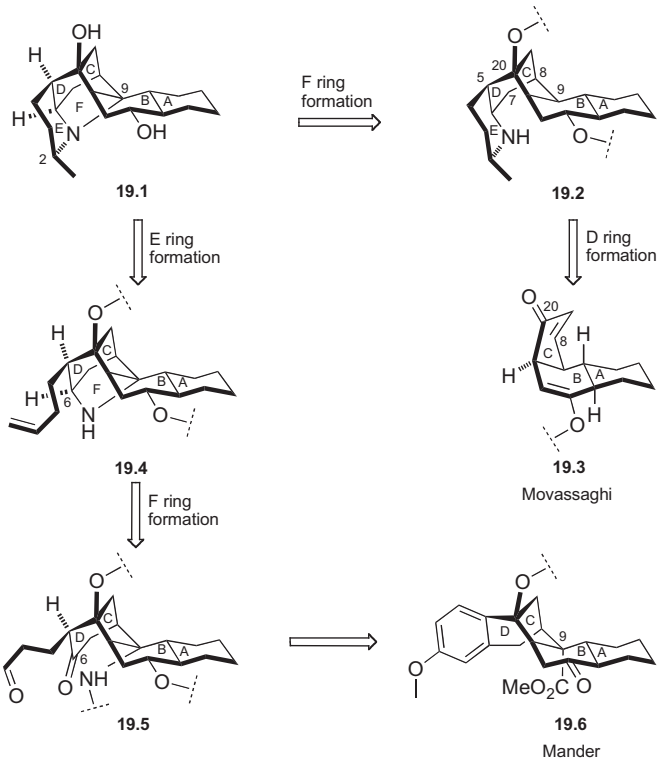
3.2.7. Total synthesis of (+)-GB 16 (Ma). Along with the synthesis of (−)-GB 13 and (−)-himgaline, Ma's group also reported[21] the first total synthesis of the pentacyclic alkaloid (+)-GB 16, using an intermediate (**17.4**), which was prepared during the course of their (−)-GB 13 work. The challenge involved in the synthesis of the pentacyclic GB 16 would appear to be much less than for other Class III alkaloids because of the absence of the strained C ring, and hence of the strained [3.2.1] bicyclic unit. Instead, the six-membered F ring [N–C(18) bond] is present, but methods for its formation had already been established in the GB 13→himgaline conversion [(−)-**2**→(−)-**3**]. Compound **17.4** was advanced into the tetracyclic GB 16 ABDE core (**18.1**) in a four step sequence (Scheme 18): reduction of the C(19) carbonyl, O-silylation, LAH reduction, and DBU-mediated Swern oxidation, which was followed by in situ intramolecular aldol condensation, this sequence being similar to that used to convert **17.4** into **17.6** (see Scheme 17). Desilylation of the TBS ether and oxidation yielded trione **18.2**. Removal of the *N*-protecting group, followed by intramolecular condensation with the C(18) carbonyl finished the total synthesis. An attempt to reach GB 16 from the even more advanced stage intermediate **17.6** from their (−)-GB 13 work failed because the ketal protecting group at C(19) could not be removed.

4. Analysis of routes to the Class II alkaloids

In the above sections, the six approaches to the penta- and hexacyclic Class III galbulimima alkaloids have been analyzed; the next section covers the two approaches for the Class II alkaloid himandrine, structurally one of the most complex of the galbulimima family. The synthesis of the racemic hexacyclic core of himandrine by Mander will be analyzed first, followed by a discussion of the first total synthesis of (−)-himandrine, an achievement that was accomplished by Movassaghi.

4.1. Retrosynthetic analysis of the himandrine system

The hexacyclic core of himandrine (Class II) with its *trans*-decalin, all-*cis* piperidine, and fused CDE systems is similar to the core of the Class III alkaloids, but the five-membered F ring of himandrine with its C(9) spiro center presents an additional complication. In the case of the Class III alkaloid himgaline, it had been known that the F ring could be generated from GB 13, as indicated earlier, but for the F ring of himandrine such experimental precedent was not available. The challenge of the F ring synthesis was overcome by two completely different approaches, and the retrosynthesis is shown in Scheme 19. From the analyses described so far, one obvious disconnection of the hexacyclic core **19.1** is the N–C(9) bond, which simplifies the structure to the pentacyclic GB 13 core **19.2**. A novel formal [3+3] annulation [see C(5)–C(20) and C(7)–C(8) disconnections], which was very different from his route to (−)-GB 13 (Scheme 14), and also more efficient, was employed by Movassaghi[22] for building the D and E rings of **19.2** onto the tricyclic ABC unit **19.3**. The ABC system **19.3** resembles substructures already discussed (see Scheme 3, **3.1**).

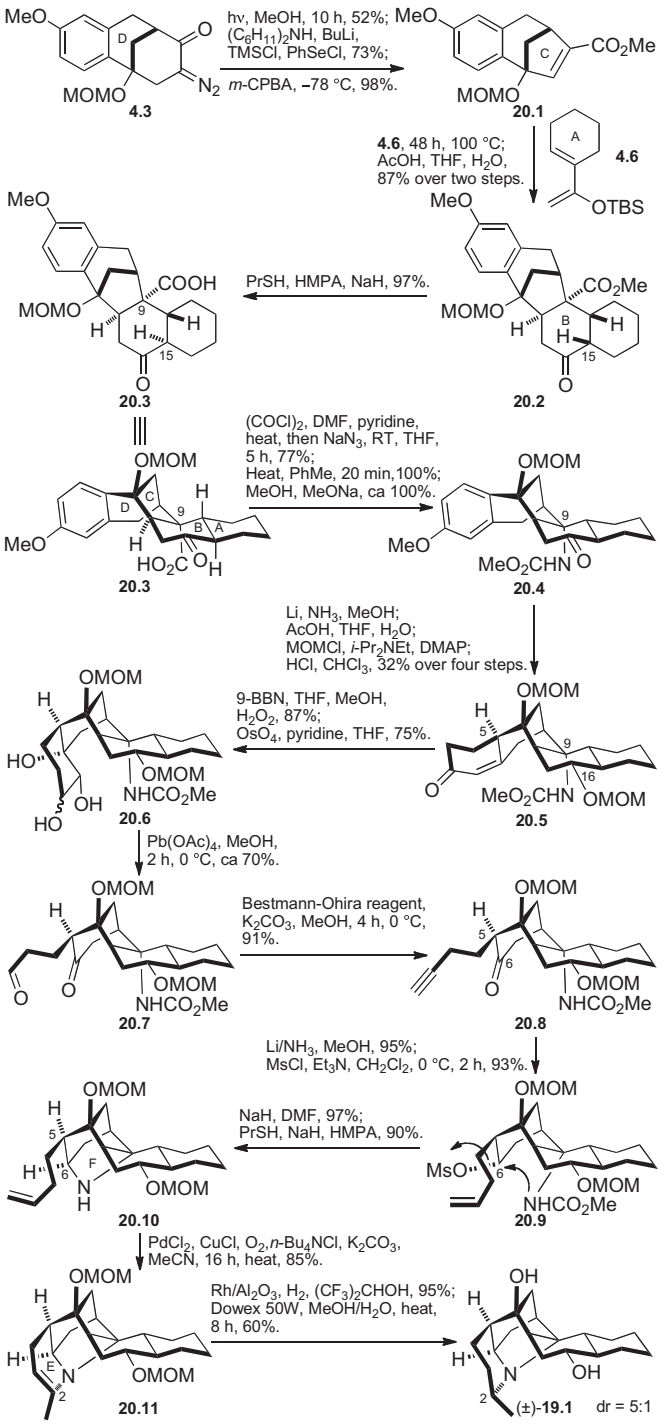


Scheme 19. Retrosynthetic analysis of Class II alkaloids.

A different approach was chosen by Mander[23] which involved synthesis of ring E at a very late stage from an intermediate of type **19.4** [see N–C(2) disconnection of **19.1**]. Disconnection of the N–C(6) bond in the pentacyclic system **19.4** gives an ABCD tetracycle with a 1,5-dicarbonyl functionality (see **19.5**). This type of system can be obtained from a tetralin in which the benzene ring is fused onto the D ring, as in **19.6**—an approach similar to the Mander route to racemic GB 13 (see Schemes 4 and 11).

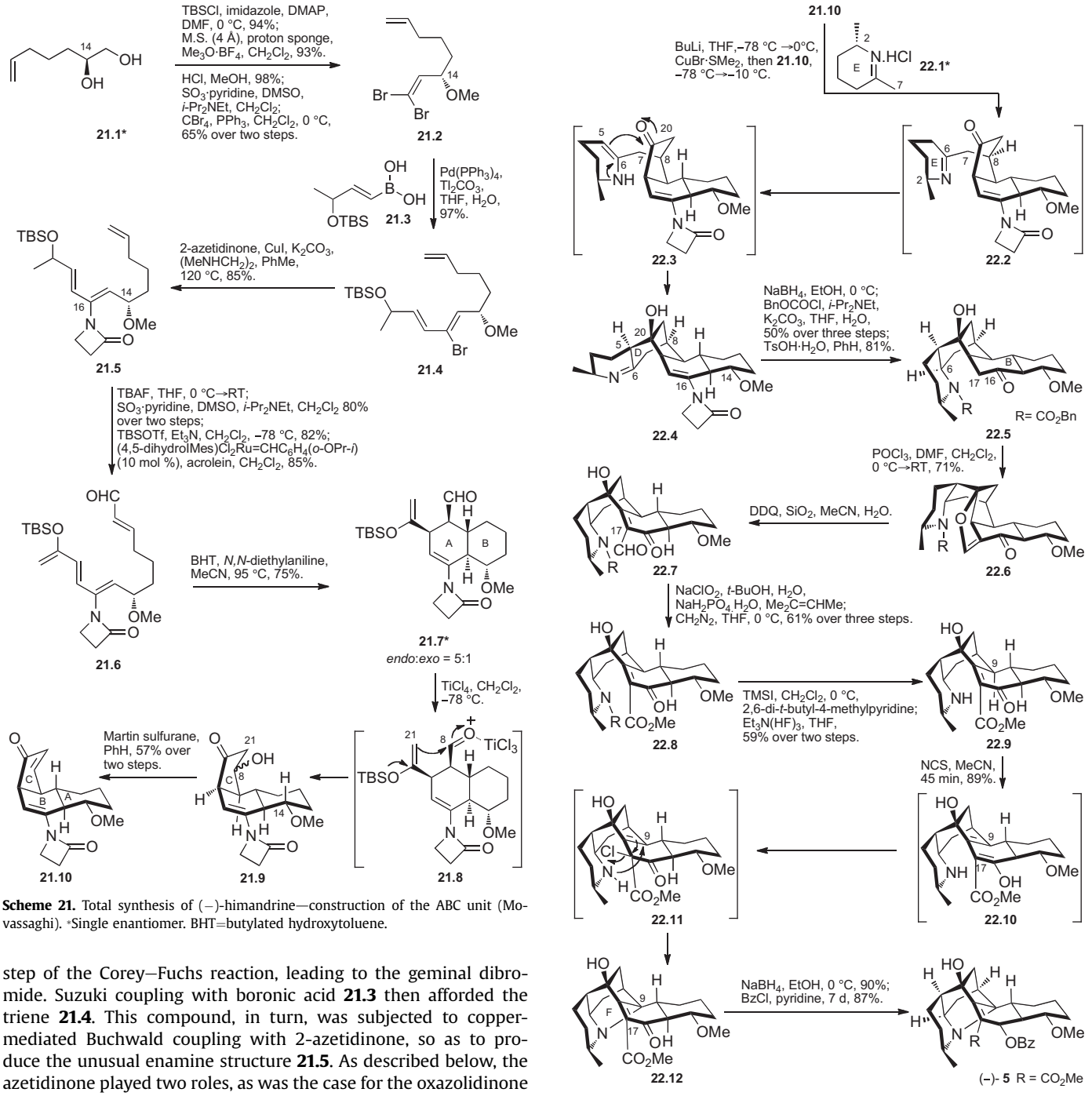
4.1.1. Synthesis of the hexacyclic core of himandrine (Mander). The same diazoketone[15,16] that Mander used for his synthesis of (±)-GB 13 (compound **4.3**, Scheme 4) was also used[23] for the synthesis of the himandrine skeleton. Wolff ring contraction of **4.3** (Scheme 20) in the presence of methanol afforded the required methyl ester, and the double bond in the eventual C ring was then introduced by standard selenium chemistry (**4.3**→**20.1**). An *endo*-selective Diels–Alder reaction with **4.6**, followed by hydrolysis of the resulting enol ether, gave the *cis*-decalone **20.2**. Hydrolysis of the hindered methyl ester by the thiolate method was accompanied by epimerization at C(15) to generate the required *trans*-decalone **20.3**, and the stage was now set for introducing the nitrogen at C(9). This was achieved by converting the acid to its acyl azide via the acid chloride, followed by Curtius rearrangement and reaction of the resulting isocyanate with methoxide (**20.3**→**20.4**). The success of this Curtius rearrangement was a critical step as it generated the proper N–C(9) stereochemistry at an early stage, thus simplifying the subsequent construction of the spirocyclic F ring. With C(9)—the eventual spiro center—correctly set, the next task was construction of ring E. Birch reduction, similar to that shown in Scheme 11 for the synthesis of **11.1**, served to reduce both the benzene ring and the decalone carbonyl [C(16)]. Hydrolysis of the enol ether resulting from the Birch reduction, and MOM protection of the C(16) hydroxyl, followed by acid-mediated double bond isomerization to form a conjugated cyclohexenone subunit, yielded **20.5**. Attempted Eschenmoser fragmentation along the lines used in the synthesis of **11.3** (see Scheme 11) with intermediate **20.5** failed, and so an alternative approach was adopted. This involved reduction of the ketone, dihydroxylation of the double bond to generate **20.6**, and then triol cleavage with lead tetraacetate to afford the 1,5-dicarbonyl compound **20.7**. Finally, the desired acetylene **20.8** was obtained in high yield using the Bestmann–Ohira reagent. Another lithium/ammonia reduction then converted the alkyne to an alkene and also gave a C(6) equatorial alcohol, which was converted to its mesylate **20.9**. The strained F ring was then generated by a high-yielding intramolecular S_N2 displacement initiated by deprotonation of the nitrogen with sodium hydride. This reaction set the desired C(6) stereochemistry. Thiolate-mediated hydrolysis of the resulting carbamate then gave **20.10**, at which point closure of the E ring was performed by using an oxidative Wacker-like procedure (**20.10**→**20.11**). Extensive screening was then required in order to establish the proper conditions for reduction of the enamine **20.11**, but eventually an unusual catalyst-solvent combination—Rh/Al_2O_3 in hexafluoroisopropanol—was found to effect the desired reduction. This hydrogenation from the axial (with respect to the E ring) *exo* face controls the C(2) stereochemistry, and hydrolysis of the MOM ether then released the hexacyclic core (**19.1**) of himandrine. A notable difference between this route by Mander and that used in his synthesis of GB 13 lies in the approach to the E ring. Instead of a reductive cyclization (see **11.4**→**11.7**) used for GB 13 (Scheme 11), construction of the himandrine skeleton relied on an oxidative Wacker-like process.

4.1.2. First total synthesis of a Class II alkaloid: (−)-himandrine (Movassaghi). Movassaghi has also reported extensive work on himandrine and has achieved an impressive total synthesis of the



Scheme 20. Synthesis of (±)-hexacyclic core of himandrine (Mander). HMPA=hexamethylphosphoric triamide, 9-BBN=9-borabicyclo[3.3.1]nonane, Ms=methanesulfonyl.

natural alkaloid.[22,24] The route was strongly influenced by his biosynthetic hypothesis[26] as well as his experience in synthesizing (−)-GB 13, and is very different from Mander's approach, especially as the N–C(9) bond was formed at a very late stage—just a couple of steps away from the final target. The enantiopure diol **21.1**, having the desired C(14) stereochemistry, was converted (Scheme 21) into **21.2** by a straightforward sequence of five steps: protection of the primary hydroxyl by silylation, protection of the remaining secondary hydroxyl as a methyl ether, removal of the silyl group, Parikh–Doering oxidation to an aldehyde, and the first



Scheme 21. Total synthesis of (−)-himandrine—construction of the ABC unit (Movassaghi). *Single enantiomer. BHT=butylated hydroxytoluene.

Scheme 22. Completion of the total synthesis of (−)-himandrine (Movassaghi). *Single enantiomer. DDQ=2,3-dichloro-5,6-dicyanobenzoquinone, NCS=*N*-chlorosuccinimide, Bz=benzoyl.

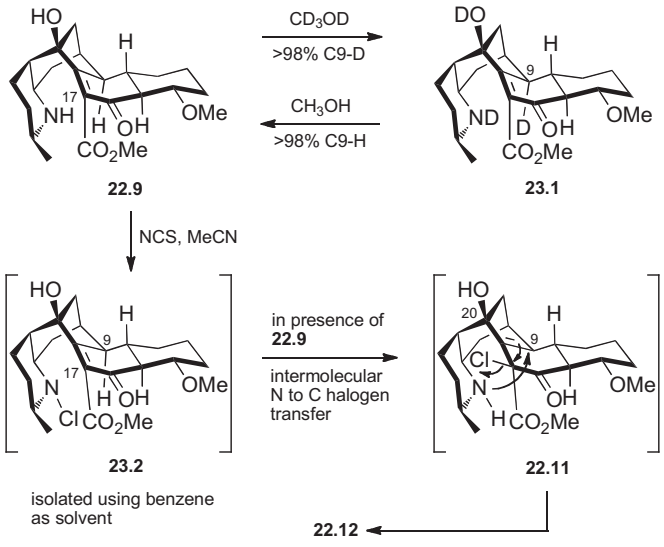
step of the Corey–Fuchs reaction, leading to the geminal dibromide. Suzuki coupling with boronic acid **21.3** then afforded the triene **21.4**. This compound, in turn, was subjected to copper-mediated Buchwald coupling with 2-azetidinone, so as to produce the unusual enamine structure **21.5**. As described below, the azetidinone played two roles, as was the case for the oxazolidinone unit in Movassaghi's synthesis of GB 13 (see Scheme 7). The advantage of using an azetidinone over an oxazolidinone was that the former—but not the latter—required such mild conditions for hydrolysis (see **22.4**→**22.5**, Scheme 22) that no elimination of the C(14) methoxy group occurred. Desilylation of **21.5**, Parikh–Doering oxidation, silyl enol ether formation, and finally, cross metathesis was used to convert **21.5** into the α,β-unsaturated aldehyde **21.6**, and the stage was now set for an intramolecular Diels–Alder reaction. This was brought about by mild heating, and the process followed the expected *endo* pathway to give, as the major product, the *trans*-decalin **21.7** as a single isomer. Next, an intramolecular Mukaiyama aldol reaction (**21.7**→**21.8**→**21.9**), followed by dehydration, generated the *cis*-fused ring C (**21.9**→**21.10**). This ionic process for making ring C of (−)-himandrine stands in contrast to the method that Chackalamannil and Movassaghi used in their work on (−)-GB 13, as they both employed a radical cyclization to generate the C ring (see Scheme 5, **5.9**→**5.11** and Scheme 7, **7.8**→**7.10**).

With **21.10** in hand, Movassaghi attached the D and E rings by using a formal [3+3] annulation, which was a method his group had developed previously.[40] Application of this new procedure was more effective for the D and E ring synthesis in (−)-himandrine than the strategy used for the corresponding rings in the (−)-GB 13 synthesis (see **7.6**→**7.8** in Scheme 7 and **7.10**→**14.2** in Scheme 14). The conversion of **21.10** into **22.4** was done without isolation of intermediates (Scheme 22), and the sequence of reactions that was used served to establish the correct stereochemistry at C(5), C(8),

and C(20). During this sequence a single enantiomer of **22.1** underwent 1,4-addition to the enone **21.10** from the less hindered *exo* face. The resulting imine **22.2** tautomerized to an enamine (**22.3**), which cyclized onto the C(20) carbonyl. Reduction of the resultant imine **22.4** gave the required C(6) stereochemistry, and Cbz protection of the amine that was formed in the reduction, followed by removal of the azetidinone unit, resulted in **22.5**.

The next task was to introduce an ester functionality at C(17) on ring B. Treatment of **22.5** with Vilsmeier's reagent yielded the cyclic vinyl ether **22.6**, and oxidation with DDQ gave the unsaturated β-keto aldehyde **22.7**. The aldehyde group was converted to an ester (**22.8**), using standard chemistry, and Cbz removal then afforded the pentacyclic compound **22.9**. Now the stage had been reached for constructing ring F. An oxidative spirocyclization was effected with *N*-chlorosuccinimide to give **22.12** via the intermediate **22.11**. Two further simple steps—reduction with sodium borohydride and benzoylation then completed the first total synthesis of (−)-himandrine.

Formation of the C(9) spiro center (**22.9**→**22.12**) is an intricate sequence and its mechanism was investigated by Movassaghi. Exposure of **22.9** to deuterated methanol (Scheme 23) showed that the C(9) hydrogen was exchanged with deuterium with retention of configuration. This observation also proved that the piperidine nitrogen is basic enough to cause deprotonation at C(9), and the retention of the C(9) stereochemistry on exchange is consistent with an intramolecular mechanism. Under the conditions of the oxidative spirocyclization, the formation of *N*-chloro compound **23.2** (Scheme 23) was proved, as it was actually isolated from the reaction mixture when the reaction was performed in benzene instead of acetonitrile. However, isolated **23.2** failed to undergo the required spirocyclization, presumably because the nitrogen was not basic enough to cause deprotonation at C(9) (no deuterium exchange was observed when **23.2** was dissolved in deuterated methanol). However, **23.2** was converted to the spirocycle **22.12** in the presence of the unchlorinated **22.9**. This observation suggests that an intermolecular N→C(17) chlorine transfer occurs from **23.2** to **22.9** to generate **22.11** via dienol **22.10**, and **22.11** then undergoes an intramolecular S_N2' displacement, giving the observed **22.12**. An alternative pathway involving C(9) halogenation was regarded as unlikely since placing a bulky protecting group on the C(20) alcohol in order to shield C(17), prevented halogenation at C(17), and no spirocyclization was then observed. The former mechanism is related to Movassaghi's view of the biosynthetic route to Class II alkaloids.[26]



Scheme 23. Mechanistic study during the synthesis of (−)-himandrine (Movassaghi).

5. Conclusions

The total synthesis of himandrine represents the most advanced work in this area and is also a highlight of organic synthesis. Much of the progress on the synthesis of these structurally intricate alkaloids was achieved by a graceful application of simple and well-known reactions, especially the asymmetric Michael reaction for ring A; aldol condensation for ring B; Diels–Alder cycloaddition for the AB rings; samarium iodide mediated carbonyl–enone reductive coupling, radical cyclization and Mukaiyama aldol condensation for ring C; enamine cyclization for ring D; Birch reduction and Eschenmoser fragmentation for ring E; and the aza-Michael reaction and S_N2' displacement for ring F. In a few situations, these classical processes were supplemented by new methods, in particular Sarpong's D ring assembly for GB 13 introduced a rhodium-catalyzed addition of an arylborane to an unactivated ketone, and Movassaghi developed a formal [3+3] annulation in the construction of ring D of himandrine. The syntheses show the power of the classical methods and illustrate how attempts to make structurally complex natural products provide opportunities for development of new reactions.[41]

Acknowledgements

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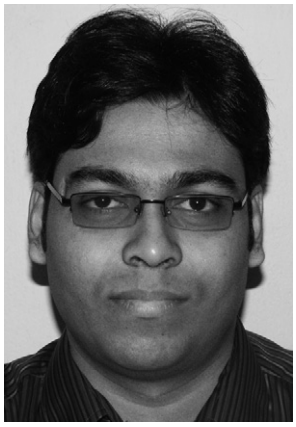
References and notes

1. A selected list of alkaloid syntheses published in 2010 is: (a) Seiple, I. B.; Su, S.; Young, I. S.; Lewis, C. A.; Yamaguchi, J.; Baran, P. S. *Angew. Chem., Int. Ed.* **2010**, *49*, 1095–1098; (b) Smith, B. J.; Sulikowski, G. A. *Angew. Chem., Int. Ed.* **2010**, *49*, 1599–1602; (c) Liu, P.; Seo, J. H.; Weinreb, S. M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2000–2003; (d) Laemmerhold, K. M.; Breit, B. *Angew. Chem., Int. Ed.* **2010**, *49*, 2367–2370; (e) De Simone, F.; Gertsch, J.; Waser, J. *Angew. Chem. , Int. Ed.* **2010**, *49*, 5767–5770; (f) Okano, K.; Fujiwara, H.; Noji, T.; Fukuyama, T.; Tokuyama, H. *Angew. Chem., Int. Ed.* **2010**, *49*, 5925–5929; (g) Uraguchi, D.; Nakamura, S.; Ooi, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 7562–7565; (h) Beemelmanns, C.; Reissig, H.-U. *Angew. Chem., Int. Ed.* **2010**, *49*, 8021–8025; (i) Martin, C. L.; Overman, L. E.; Rohde, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 4894–4906; (j) Iwasa, E.; Hamashima, Y.; Fujishiro, S.; Higuchi, E.; Ito, A.; Yoshida, M.; Sodeoka, M. *J. Am. Chem. Soc.* **2010**, *132*, 4078–4079; (k) Fischer, D. F.; Sarpong, R. *J. Am. Chem. Soc.* **2010**, *132*, 5926–5927; (l) Yuan, C.; Chang, C.-T.; Axelrod, A.; Siegel, D. *J. Am. Chem. Soc.* **2010**, *132*, 5924–5925; (m) Perry, M. A.; Morin, M. D.; Slafer, B. W.; Wolckenhauer, S. A.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2010**, *132*, 9591–9593; (n) Liau, B. B.; Shair, M. D. *J. Am. Chem. Soc.* **2010**, *132*, 9594–9595; (o) Zuo, Z.; Xie, W.; Ma, D. *J. Am. Chem. Soc.* **2010**, *132*, 13226–13228; (p) Kim, J.; Movassaghi, M. *J. Am. Chem. Soc.* **2010**, *132*, 14376–14378; (q) Ramharter, J.; Weinstabl, H.; Mulzer, J. *J. Am. Chem. Soc.* **2010**, *132*, 14338–14339; (r) Campbell, E. L.; Zuhl, A. M.; Liu, C. M.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 3009–3012; (s) Mañas, C. G.; Paddock, V. L.; Bochet, C. G.; Spivey, A. C.; White, A. J. P.; Mann, I.; Oppolzer, W. *J. Am. Chem. Soc.* **2010**, *132*, 5176–5178; (t) Kato, D.; Sasaki, Y.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 3685–3687; (u) Trzupek, J. D.; Lee, D.; Crowley, B. M.; Marathias, V. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2010**, *132*, 8506–8512; (v) Wu, H.; Xue, F.; Xiao, X.; Qin, Y. *J. Am. Chem. Soc.* **2010**, *132*, 14052–14054.
2. (a) Binns, S. V.; Dunstan, P. J.; Guise, G. B.; Holder, G. M.; Hollis, A. F.; McCredie, R. S.; Pinhey, J. T.; Prager, R. H.; Rasmussen, M.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1965**, *18*, 569–573; (b) Mander, L. N.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1967**, *20*, 981–1019; (c) Mander, L. N.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1967**, *20*, 1021–1027; (d) Guise, G. B.; Mander, L. N.; Prager, R. H.; Rasmussen, M.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1967**, *20*, 1029–1035; (e) Mander, L. N.; Prager, R. H.; Rasmussen, M.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1967**, *20*, 1473–1491.
3. (a) Ritchie, E.; Taylor, W. C. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic: New York, NY, 1967; Vol. 9, pp 529–543; (b) Ritchie, E.; Taylor, W. C. In *The Alkaloids*; Manske, R. H. F., Ed.; Academic: New York, NY, 1971; Vol. 13, pp 227–271; (c) Brown, R. F. C.; Drummond, R.; Fogerty, S. E.; Hughes, G. K.; Pinhey, J. T.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1956**, *9*, 283–287.
4. (a) Mander, L. N.; Willis, A. C.; Herlt, A. J.; Taylor, W. C. *Tetrahedron Lett.* **2009**, *50*, 7089–7092; (b) Bradford, T. A.; Willis, A. C.; White, J. M.; Herlt, A. J.; Taylor, W. C.; Mander, L. N. *Tetrahedron Lett.* **2011**, *52*, 188–191.
5. Himgrine (see Ref. 3a) was previously considered to be in Class IV, but now that its structure has been established (see Ref. 4), it is seen to be a member of Class I.
6. (+)-GB 16 (see Ref. 3a) was previously considered to be in Class IV, but now that its structure has been established (see Ref. 4), it is seen to be a member of Class III.

7. This number results from the reclassification described in Refs. 5 and 6.
8. (a) Malaska, M. J.; Fauq, A. H.; Kozikowski, A. P.; Aagaard, P. J.; McKinney, M. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 61–66; (b) Kozikowski, A. P.; Fauq, A. H.; Miller, J. H.; McKinney, M. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 797–802; (c) Darroch, S. A.; Taylor, W. C.; Choo, L. K.; Mitchelson, F. *Eur. J. Pharmacol.* **1990**, *182*, 131–136; (d) Anwar-ul, S.; Gilani, H.; Cobbin, L. B. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1986**, *332*, 16–20.
9. (a) Malaska, M. J.; Fauq, A. H.; Kozikowski, A. P.; Aagaard, P. J.; McKinney, M. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 1247–1252; (b) Miller, J. H.; Aagaard, P. J.; Gibson, V. A.; McKinney, M. *J. Pharmacol. Exp. Ther.* **1992**, *263*, 663–667; (c) Doods, H. N. *Drugs Future* **1995**, *20*, 157–164.
10. The following syntheses (not all of which involve IMDA reactions) or synthetic approaches are not included in the present review: (a) Wong, L. S.-M.; Sherburn, M. S. *Org. Lett.* **2003**, *5*, 3603–3606; (b) Takadoi, M.; Katoh, T.; Ishiwata, A.; Terashima, S. *Tetrahedron* **2002**, *58*, 9903–9923; (c) Takadoi, M.; Terashima, S. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2871–2873; (d) Hofman, S.; Gao, L.-J.; Van Dingenen, H.; Hosten, N. G. C.; Van Haver, D.; De Clercq, P. J.; Milanesio, M.; Viterbo, D. *Eur. J. Org. Chem.* **2001**, 2851–2860; (e) Chackalamannil, S.; Davies, R. J.; Wang, Y.; Asberom, T.; Doller, D.; Wong, J.; Leone, D.; McPhail, A. T. *J. Org. Chem.* **1999**, *64*, 1932–1940; (f) Takadoi, M.; Katoh, T.; Ishiwata, A.; Terashima, S. *Tetrahedron Lett.* **1999**, *40*, 3399–3402; (g) Doller, D.; Chackalamannil, S.; Czarniecki, M.; McQuade, R.; Ruperto, V. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 901–906; (h) Hofman, S.; De Baecke, G.; Kenda, B.; De Clercq, P. J. *Synthesis* **1998**, 479–489; (i) De Baecke, G.; De Clercq, P. J. *Tetrahedron Lett.* **1995**, *36*, 7515–7518; (j) For the synthesis of the Class I alkaloid himandravine, see: Chackalamannil, S.; Davies, R.; McPhail, A. T. *Org. Lett.* **2001**, *3*, 1427–1429; (k) For synthetic studies towards the Class I alkaloid himgravine, see: Baldwin, J. E.; Chesworth, R.; Parker, J. S.; Russell, A. T. *Tetrahedron Lett.* **1995**, *36*, 9551–9554.
11. (a) Tchabanenko, K.; Adlington, R. M.; Cowley, A. R.; Baldwin, J. E. *Org. Lett.* **2005**, *7*, 585–588; (b) Tchabanenko, K.; Chesworth, R.; Parker, J. S.; Anand, N. K.; Russell, A. T.; Adlington, R. M.; Baldwin, J. E. *Tetrahedron* **2005**, *61*, 11649–11656.
12. (a) Hart, D. J.; Wu, W.-L. *J. Am. Chem. Soc.* **1995**, *117*, 9369–9370; (b) Hart, D. J.; Li, J.; Wu, W.-L.; Kozikowski, A. P. *J. Org. Chem.* **1997**, *62*, 5023–5033.
13. Chackalamannil, S.; Davies, R. J.; Asberom, T.; Doller, D.; Leone, D. *J. Am. Chem. Soc.* **1996**, *118*, 9812–9813.
14. Collins, D. J.; Culvenor, C. C. J.; Lamberton, J. A.; Loder, J. W.; Price, J. R. *Plants for Medicines*; CSIRO Publishing: Melbourne, 1990, pp 101–106.
15. Mander, L. N.; McLachlan, M. M. *J. Am. Chem. Soc.* **2003**, *125*, 2400–2401.
16. McLachlan, M. M. W.; O'Connor, P. D.; Fairweather, K. A.; Willis, A. C.; Mander, L. N. *Aust. J. Chem.* **2010**, *63*, 742–760.
17. Movassaghi, M.; Hunt, D. K.; Tjandra, M. *J. Am. Chem. Soc.* **2006**, *128*, 8126–8127.
18. Larson, K. K.; Sarpong, R. *J. Am. Chem. Soc.* **2009**, *131*, 13244–13245.
19. (a) Shah, U.; Chackalamannil, S.; Ganguly, A. K.; Chelliah, M.; Kolotuchin, S.; Buevich, A.; McPhail, A. *J. Am. Chem. Soc.* **2006**, *128*, 12654–12655; (b) Chackalamannil, S.; Xia, Y.; Greenlee, W. J.; Clasby, M.; Doller, D.; Tsai, H.; Asberom, T.; Czarniecki, M.; Ahn, H.-S.; Boykow, G.; Foster, C.; Agans-Fantuzzi, J.; Bryant, M.; Lau, J.; Chintala, M. *J. Med. Chem.* **2005**, *48*, 5884–5887.
20. Evans, D. A.; Adams, D. J. *J. Am. Chem. Soc.* **2007**, *129*, 1048–1049.
21. Zi, W.; Yu, S.; Ma, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 5887–5890.
22. Movassaghi, M.; Tjandra, M.; Qi, J. *J. Am. Chem. Soc.* **2009**, *131*, 9648–9650.
23. (a) O'Connor, P. D.; Mander, L. N.; McLachlan, M. M. W. *Org. Lett.* **2004**, *6*, 703–706; (b) O'Connor, P. D.; Signore, G. D.; McLachlan, M. M. W.; Willis, A. C.; Mander, L. N. *Aust. J. Chem.* **2010**, *63*, 1477–1491.
24. A relatively simple model representing the ABF ring subunit has been described recently: Liang, H.; Ciufolini, M. A. *Org. Lett.* **2010**, *12*, 1760–1763.
25. Mander, L. N.; Prager, R. H.; Rasmussen, M.; Ritchie, E.; Taylor, W. C. *Aust. J. Chem.* **1967**, *20*, 1705–1718.
26. See Supporting information of Ref. 17.
27. Kelly, W. L. *Org. Biomol. Chem.* **2008**, *6*, 4483–4493.
28. Cativiela, C.; Fraile, J. M.; García, J. I.; Mayoral, J. A.; Pires, E.; Royo, A. J. *Tetrahedron* **1993**, *49*, 4073–4084.
29. Byeon, C.-H.; Chen, C.-Y.; Ellis, D. A.; Hart, D. J.; Li, J. *Synlett* **1998**, 596–598.
30. Hook, J. M.; Mander, L. N. *J. Org. Chem.* **1980**, *45*, 1722–1725.
31. Regitz, M.; Rüter, J. *Chem. Ber.* **1968**, *101*, 1263–1270.
32. (a) Beckwith, A. L. J.; Lawrence, T.; Serelis, A. K. *J. Chem. Soc., Chem. Commun.* **1985**, 484–485; (b) Beckwith, A. L. J.; Easton, C. J.; Lawrence, T.; Serelis, A. K. *Aust. J. Chem.* **1985**, 545–556; (c) Beckwith, A. L. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925–3941.
33. Willis, A. C.; O'Connor, P. D.; Taylor, W. C.; Mander, L. N. *Aust. J. Chem.* **2006**, *59*, 629–632.
34. Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258–3260.
35. (a) Dumas, F.; d'Angelo, J. *Tetrahedron: Asymmetry* **1990**, *1*, 167–170; (b) Hirai, Y.; Terada, T.; Momose, T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 509–516; (c) Fujiwara, Y.; Okamoto, M. *Chem. Pharm. Bull.* **1989**, *37*, 1458–1464.
36. Pradhan, S. K.; Akamanchi, K. G.; Divakaran, P. P.; Pradhan, P. M. *Heterocycles* **1989**, *28*, 813–839.
37. Itsuno, S.; Sakurai, Y.; Ito, K. *Synthesis* **1988**, 995–996.
38. (a) Liu, G.; Lu, X. *J. Am. Chem. Soc.* **2006**, *128*, 16504–16505; (b) Liu, G.; Lu, X. *Tetrahedron* **2008**, *64*, 7324–7330.
39. Boger, D. L.; Hüter, O.; Mbiya, K.; Zhang, M. *J. Am. Chem. Soc.* **1995**, *117*, 11839–11849.
40. Movassaghi, M.; Chen, B. *Angew. Chem., Int. Ed.* **2007**, *46*, 565–568.
41. During the final checking of this manuscript, a review on the synthesis of the galbulimima alkaloids appeared: Rinner, U.; Lentsch, C.; Aichinger, C. *Synthesis* **2010**, 3763–3784.

Biographical sketch



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