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Total Synthesis of (−)-Goniomitine

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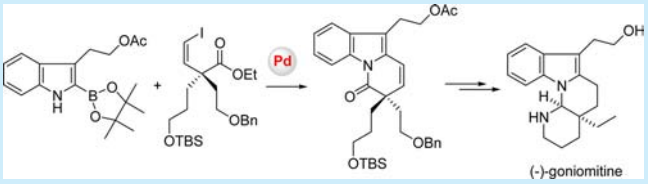
Supporting Information

ABSTRACT: The total synthesis of (−)-goniomitine has been accomplished in 11 steps starting from commercially available diethyl L-malate. The synthesis features a chiral pool approach to prepare the chiral C-9 unit containing a quaternary carbon center, an Ir-catalyzed C−H borylation to synthesize the 2-indoleboronic acid pinacol ester, and a Suzuki reaction to couple together the two key intermediates. Notably, the high degree of convergence of this strategy makes it particularly amenable to the total synthesis of other aspidosperma family natural products.



(−)-Goniomitine is a new type of the well-known aspidosperma family of indole natural products (Figure 1). It was isolated from the root bark of *Gonioma malagasy* by Husson and co-workers in 1987.[1] Its unique structure as well as its potential biological activities has inspired chemists to develop a number of synthetic approaches.[2−8] So far, seven syntheses have been reported including three asymmetric syntheses. In 1991, Takano's group reported the first enantio-controlled total synthesis of (−)-goniomitine from the chiral cyclopentadienone synthon in 28 steps.[2] In 2008, Pagenkopf's group achieved the total synthesis of (±)-goniomitine by utilizing a formal [3 + 2] cycloaddition between the nitrile and cyclopropane derivatives as the key transformation step.[3] In addition, the group of Waser reported the total syntheses of (±)-goniomitine based on an intramolecular cyclization of aminocyclopropane in 2010,[4] and Mukai's group accomplished the total syntheses of (−)- and (+)-goniomitine via the cross-metathesis strategy between the 2-vinylindole derivative and the chiral oxazolopiperidone lactams in 2011.[5] Recently, Bach's group reported an elegant and efficient strategy to synthesize (±)-goniomitine by employing the Pd(II)-catalyzed regioselective 2-alkylation of indoles as the key step,[6] Zhu's group reported the total synthesis of (±)-goniomitine by using a one-pot oxidation/reduction/cyclization sequence,[7] and Lewin and co-workers reported a biomimetic semisynthesis of (−)- and (+)-goniomitine starting from vincadifformine.[8]

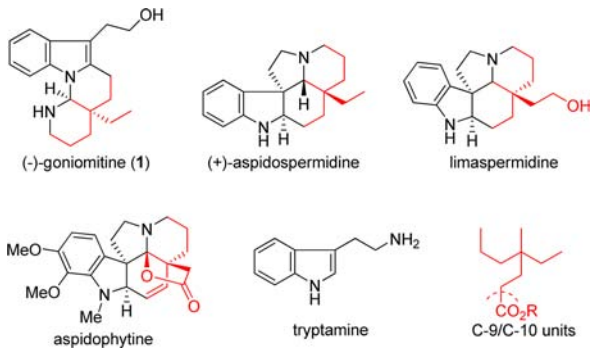


Figure 1. Structures of (−)-goniomitine and representative aspidosperma family of monoterpenoid indole alkaloids.

The aspidosperma family of monoterpenoid indole alkaloids is generated biosynthetically by a combination of tryptamine with the nontryptophan C-9/C-10 units containing a quaternary carbon center (Figure 1).[9] The C-9/C-10 units in different natural products contain ethyl, 2-hydroxyethyl, or acetate groups (marked in red). Inspired by the aspidosperma biosynthesis pathway, we envisioned that coupling a tryptamine (indole) with the C-9/C-10 units might be one of the best methods of choice for the synthesis of these types of indole alkaloids because of the general applicability. However, the synthesis of the quaternary carbon center is one of the main challenges.[10] Accordingly, an efficient method for the synthesis of the chiral C-9/C-10 units needs to be developed. Herein, we report a general strategy for the total synthesis of the aspidosperma family of monoterpenoid indole alkaloids, which led to the novel and efficient total synthesis of (−)-goniomitine.

Our retrosynthetic analysis of **1** is outlined in Scheme 1. We envisioned that the D ring of goniomitine could be formed through an intramolecular cyclization of compound **2** in the last step. Compound **2** could be easily synthesized from the key intermediate **3** via functional group transformations. The key intermediate **3** could be prepared from 2-indoleboronic acid pinacol ester **4** and the chiral vinyl iodide **5** through the Suzuki cross-coupling reaction. The 2-indoleboronic acid pinacol ester **4** could be easily prepared via the Ir-catalyzed C−H borylation reaction.[11] In addition, the key chiral moiety **5** containing the

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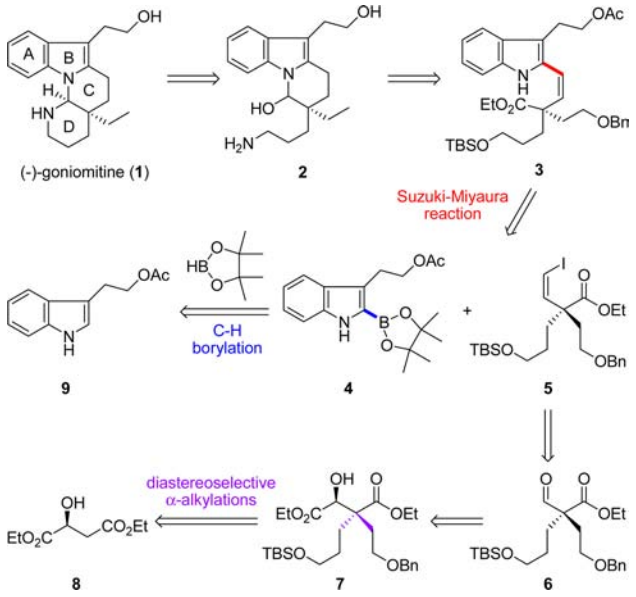
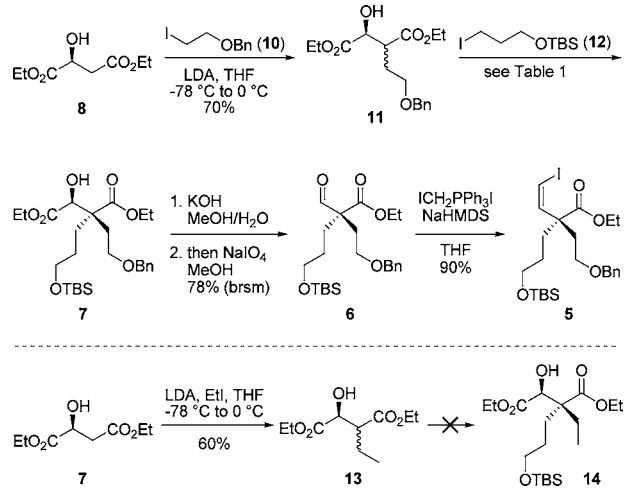
Scheme 1. Retrosynthesis of (−)-Goniomitine



all-carbon quaternary center could be prepared in enantiomeric form via a successive diastereoselective α-alkylations of the diethyl L-malate **8** by following a literature procedure.[12] The key chiral moiety **5** could also be applied to the total synthesis of another aspidosperma family of monoterpenoid indole alkaloids, such as limaspermidine and aspidophytine.

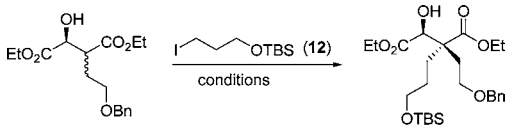
Our synthesis commenced with the preparation of the key intermediate **5** as illustrated in Scheme 2. The first α-alkylation

Scheme 2. Synthesis of the Chiral Vinyl Iodide 5



of diethyl L-malate with iodide **10** gave the product **11** in 70% yield. Unexpectedly, the second α-alkylation of **11** with iodide **12** using previously reported conditions (LDA) did not produce the desired product and the starting material was recovered (Table 1, entry 1).[13] Subsequently, a variety of conditions (base, equiv of base) were examined. When LiHMDS was used as the base in the presence of HMPA, **7** was obtained in 11% yield, albeit with low de (Table 1, entry 2). When HMPA was removed, the yield and de value of **7** were improved (entry 3). When toluene and Et_3N were used as the solvent, although the de value of **7** was improved, the yield was dramatically decreased (entry 4).[14] As suggested by Collum and

Table 1. Optimization of the Reaction Conditions[a]



entry	base	equiv	solvent	yield	de
1	LDA	2.2	THF	0%	–
2[b]	LHMDS	2.2	THF	11%	30%
3	LHMDS	2.2	THF	20%	70%
4	LHMDS	2.2	Et_3N + toluene	7%	>90%
5[c]	**LHMDS**	**4**	**THF**	**40%(53%)**	**>95%**
6	LHMDS	6	THF	21%	>95%

[a]Reaction conditions: **11** (0.1 mmol), **12** (0.3 mmol), in solvent (4.0 mL), isolated yields. [b]HMPA was added. [c]Yield based on recovered starting material in parentheses.

Kim's work,[15] the amount of LiHMDS was increased. We found that when 4 equiv of LiHMDS were used, the desired product **7** was obtained as a single detectable diastereomer in 40% yield along with recovery of 25% starting material (entry 5). However, further increasing LiHMDS to 6 equiv resulted in a decreased yield (entry 6). It is worth mentioning that the starting material was not consumed completely in all the tested reactions and a prolonged reaction time led to a decreased yield.

Selective saponification of diester **7** furnished α-hydroxy acid,[16] which was oxidized with $NaIO_4$ to provide the desired aldehyde **6** in 60% yield with recovery of 23% starting material α-hydroxy acid.[17] Finally, the Stork−Wittig reaction of aldehyde **6** afforded the targeted *Z* vinyl iodide **5** in 90% yield.[18] We observed that the ratio of the *Z*/*E*-isomer increased when HMPA was present in the Stork−Wittig reaction. Moreover, this short sequence proved robust and allowed the ready access to the multigram scale of this pivotal building block.

Attempts to prepare compound **14** using EtI instead of iodide **10** were also made (Scheme 2). Surprisingly, although the first α-alkylation of diethyl L-malate **7** provided the desired product **13** in 60% yield, the second step α-alkylation of the monoalkylation product **13** with iodide **12** failed to give the desired **14** even after screening a variety of reaction conditions.[19]

The total synthesis of goniomitine is shown in Scheme 3. Treatment of indole **9** with pinBH, $[Ir(OMe)(COD)]_2$, and 4,4′-di-*tert*-butyl-2,2′-bipyridine (dtbpy) afforded the corresponding 2-indoleboronate **4** in 80% yield.[11] Unexpectedly, Suzuki coupling of boronate **4** and vinyl iodide **5** furnished tricyclic compound **15** directly in 86% yield instead of the desired bicyclic product **3**.[20] This result indicated that a cascade of the Suzuki coupling/C-ring cyclization sequence occurred, thus streamlining the synthesis. Simultaneous reduction of the double bond and deprotection of the benzyl ether of **15** with Pd/C and H_2 produced compound **16** in 90% yield.[21] Transformation of the hydroxyl group of compound **16** to the iodide group with PPh_3, I_2, and imidazole gave **17** in 81% yield. Reductive removal of iodide with Raney-Nickel followed by deprotection of TBS with TBAF provided alcohol **18** in 71% yield over two steps.[22] Mitsunobu reaction of alcohol **18** with diphenylphosphoryl azide (DPPA) afforded azide **19** in 81% yield. Finally, reduction of the acetyl group, the lactam, and azide group in **19** with $LiAlH_4$ followed by treatment of the

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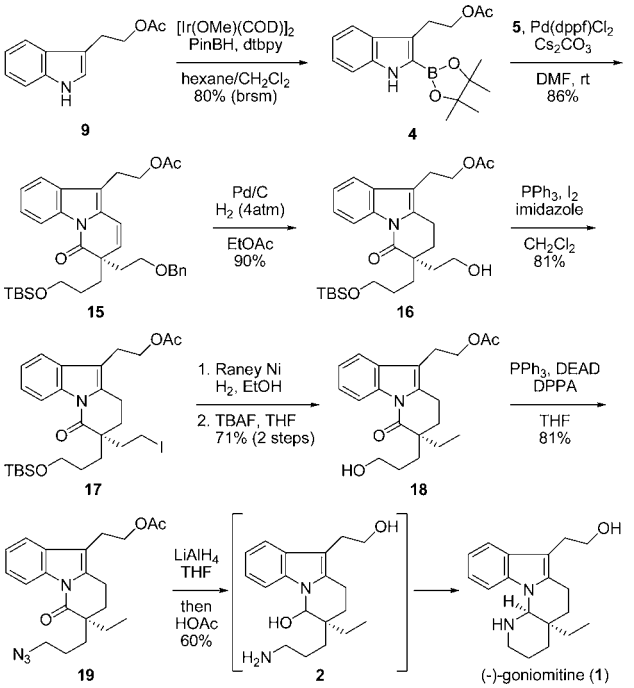
Scheme 3. Synthesis of (−)-Goniomitine



corresponding reaction mixture with HOAc/THF/H_2O furnished the natural product (−)-goniomitine in one step in 60% yield. All the spectroscopic data of **1** were in agreement with those of natural and synthetic goniomitine reported in the literatue.[2−8]

In summary, we have accomplished the total synthesis of natural product (−)-goniomitine in 11 linear steps starting from commercially available diethyl L-malate. The synthesis features a straightforward chiral pool approach to prepare the chiral moiety, a highly efficient Ir-catalyzed C−H borylation to synthesize the 2-indoleboronic acid pinacol ester, and a Suzuki reaction to couple the two key intermediates. Notably, the high degree of convergence of this strategy makes it particularly amenable to the total synthesis of other members of the aspidosperma family of natural products.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental procedures, and ^1H and ^{13}C NMR spectra of compounds **1**, **4**−**7**, **10**, **12**, **15**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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