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Total Synthesis of (−)-Conolutinine

Xiangyang Feng,[†,‡,∥] Guangde Jiang,[‡,∥] Zilei Xia,[‡,∥] Jiadong Hu,[†,‡] Xiaolong Wan,[§] Jin-Ming Gao,[†] Yisheng Lai,[*,‡] and Weiqing Xie[*,†,§]

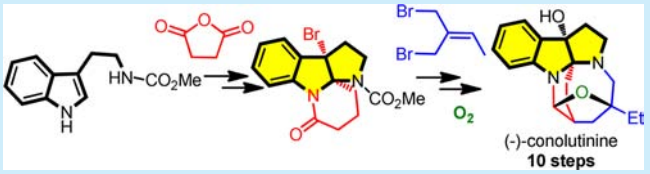
[†]Shaanxi Key Laboratory of Natural Products & Chemical Biology, College of Science, Northwest A&F University, 22 Xinong Road, Yangling 712100, Shaanxi, China

[‡]State Key Laboratory of Natural Medicines, Jiangsu Key Laboratory of Drug Discovery for Metabolic Diseases, Center of Drug Discovery, China Pharmaceutical University, 24 Tongjiaxiang, Nanjing 210009, China

[§]State Key Laboratory of Bioorganic & Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Lingling Lu, Shanghai 200032, China

Supporting Information

ABSTRACT: The first enantioselective synthesis of (−)-conolutinine was achieved in 10 steps. The synthesis featured a catalytic asymmetric bromocyclization of tryptamine to forge the tricycle intermediate. Hydration of an alkene catalyzed by $Co(acac)_2$ was also employed as a key step to diastereoselectively introduce the tertiary alcohol moiety. The absolute configuration of (−)-conolutinine was established to be (2*S*,5a*S*,8a*S*,13a*R*) based on this asymmetric total synthesis.



Cyclotryptamine alkaloids constitute a family of indole alkaloids incorporated with hexahydropyrrolo[2,3,-*b*]-indole (HPI) fragment with broadly biological activities.[1] Among these indole alkaloids, terpenoid indole alkaloids (Figure 1; e.g., minfiensine (**1**),[2] vincorine (**2**),[3] and conolutinine (**3**) was established by extensive 2D NMR analysis, and its absolute configuration was empirically assigned by its hypothetic biosynthetic pathway from velbanamine. Structurally, conolutinine contains three quaternary carbon centers, two of which are vicinal including a diazospiro one. Additionally, an HPI moiety coupled with fused oxadiazepine-tetrahydrofuran rings renders conolutinine to adopt a rigid cage-like conformation. In our continuous efforts to synthesize cyclotryptamine alkaloids,[5] herein we would like to report the first total asymmetric synthesis of (−)-conolutinine relying on our recently reported asymmetric bromocyclization of tryptamine.[5b]

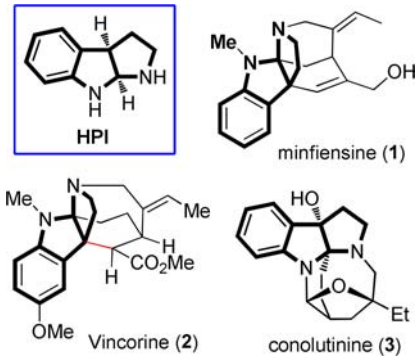


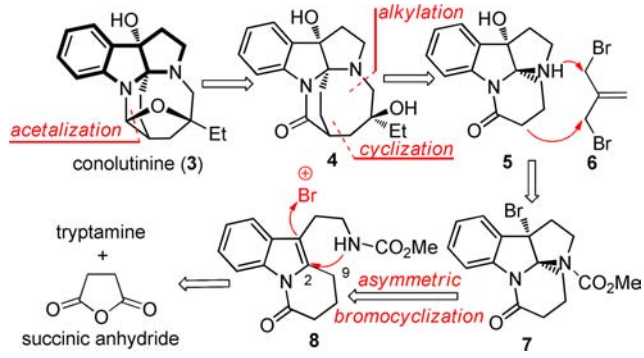
Figure 1. Representative terpenoid indole alkaloids incorporated with hexahydropyrrolo [2,3-*b*]indole (HPI) framework.

conolutinine (**3**)[4]) are structurally impressive, as those alkaloids usually possess a complex ring system and continuous quaternary carbon centers, which posed a formidable synthetic challenge for chemists. To date, numerous synthesis and synthetic studies of terpenoid indole alkaloids have been reported with an innovative methodology or strategy being applied for a concise and enantioselective synthesis.[2,3]

Conolutinine (**3**), a new member of terpenoid indole alkaloid with interesting activity to reverse multidrug resistance in vincristine-resistant KB cells, was isolated by Kam in 2009 from Malaysian *Tabernaemontana*.[4] The gross structure of

As depicted in Scheme 1, we envisioned that (−)-conolutinine could be obtained by partial reduction of amide of

Scheme 1. Retrosynthetic Analysis of Conolutinine (3)



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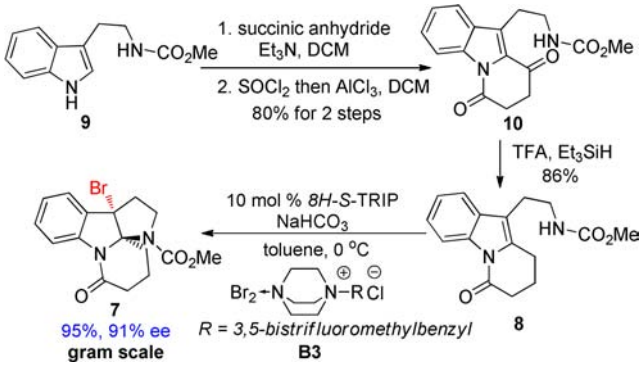
hydroxyl-pyrroloindoline **4** followed by acetalization to construct a bridged tetrahydrofuran ring. For the synthesis of **4**, the formation of a tertiary alcohol from a terminal olefin via an oxidation/diastereoselective ethylation sequence would lead to a pentacyclic intermediate, which could be accessible from pyrroloindoline **5** through *N*-alkylation and sequential cyclization with allyl dibromide **6**. To this end, amine **5** could be generated by hydrolysis and deprotection of bromo-pyrroloindoline **7**. *S*-8*H*-TRIP catalyzed asymmetric bromocyclization of tryptamine derivative **8** would enable the construction of bromo-pyrroloindoline **7** with desired stereochemistry.[5b] Finally, disconnection of indole **8** from amide and C2−C9 bonds afforded tryptamine and succinic anhydride.

As shown in Scheme 2, the synthesis commenced with condensation of tryptamine **9** with succinic anhydride, which

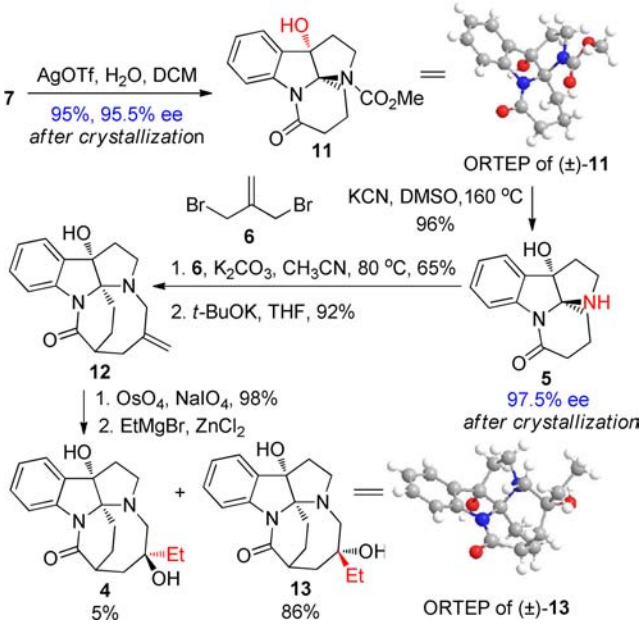
Scheme 2. Synthesis of Bromo-pyrroloindoline 7



was further advanced to ketone **10** via an intramolecular Friedel−Craft reaction promoted by $AlCl_3$ in 80% yield over two steps.[6] To remove the ketone moiety of **10**, Pd/C[7a] catalyzed hydrogenation was attempted while irreproducible yields (0−100%) resulted, which depended on the reaction scale and quality of Pd/C. Switching to other reduction conditions provided low yields (Raney/Ni/H_2, $NaBH_4$[7b]) or decomposition of ketone **10** (Wolff−Kishner reduction[7c]). Eventually, reduction was successively achieved by using TFA/Et_3SiH,[7d] affording indole **8** in 86% yield. To our delight, enantioselective bromocyclization of indole **8** could be efficiently realized even on gram scale by employing our developed protocol,[5b] providing bromo-pyrroloindoline **7** in 95% yield and 91% ee.

With a reliable supply of bromo-pyrroloindoline **7** being secured, formation of an azocane ring was executed. Hydrolysis of the bromide of **7** with the assistance of AgOTf[8] gave hydroxyl-pyrroloindoline **11** in 95% yield, whose relative structure was substantiated by X-ray crystallography[10] (Scheme 3). However, removal of the methoxycarbamate of **11** met with much difficulty than was expected, owing to the lability of hydroxyl-pyrroloindoline **11**. Commonly employed reagent TMSI[9a] only resulted in decomposition of hydroxyl-pyrroloindoline **11**. Basic conditions for hydrolysis of methoxycarbamate (40% aq KOH,[9b] KOTMS[9c]) were also ineffective with only unchanged starting material recovered. Fortunately, nucleophilic deprotection by heating **11** with KCN[9d] in DMSO to 160 °C provided pyrroloindoline **5** in 96% yield. Other nucleophilic reagents such as NaI[9e] and *n*-PrSLi[9f] were not viable for the deprotection. At this stage, enantiopurity of **5** could be improved to 97.5% ee after crystallization. *N*-Allylation of amine **5** with allylic dibromide **6** in dilute MeCN and

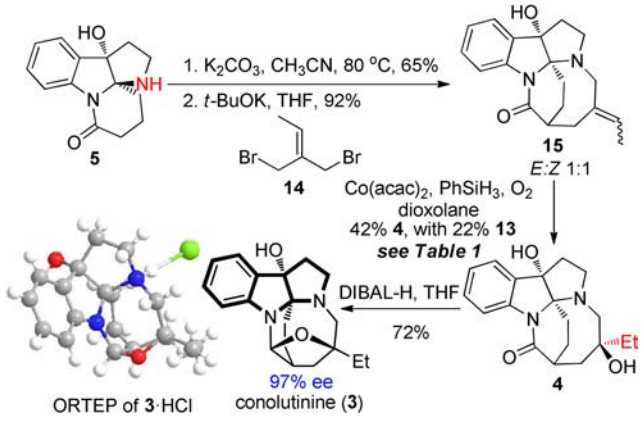
Scheme 3. Synthesis of Diol 4



consecutive cyclization mediated by *t*-BuOK smoothly effected pentacycle **12**. It is critical to use *t*-BuOK as a base as other bases (e.g., LiHMDS, NaHMDS; see Supporting Information) were deleterious for the reaction, leading to much lower yields. Disappointingly, oxidation of the terminal olefin by OsO_4/$NaIO_4$, followed by introduction of tertiary alcohol by an ethylation reaction ($EtMgBr/ZnCl_2$[6]), gave good diastereoselectivity (dr 1:15) in favor of undesired isomer **13**[10,11] (86% yield), indicating that the *β*-face of the pentacycle intermediate was sterically less crowded.

To set up the desired stereoconfiguration of the hydroxyl, direct hydration of the trisubstituted olefin of pentacycle **15** was thus formulated by taking advantage of the inherent spatial bias of the pentacycle framework (Scheme 4). For this purpose, bis-

Scheme 4. Completion of Synthesis of (−)-Conolutinine



alkylation of pyrroloindoline **5** using dibromide **14**[12] and subsequent ring closure successfully led to pentacycle **15** in 50% yield over two steps. Considering the instability of **15** toward strong acids used for hydration reactions, a metal mediated radical oxidation condition was judiciously selected for its mild reaction conditions and functionalities compatibility. Different reaction conditions[13] were surveyed, and

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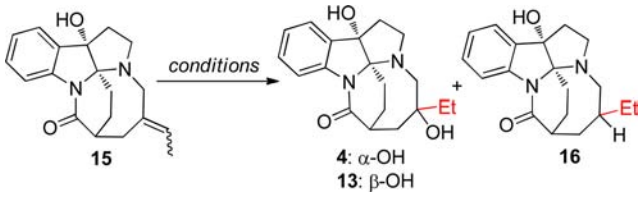
Table 1. Reaction Condition Survey for Hydration of 15



entry	catalyst	solvent	reductant	4 (%)[d]	13 (%)[d]	16 (%)[d]
1[a]	$Fe_2(ox)_3$	H_2O	$NaBH_4$	28	5	25
2[a]	$Fe_2(SO_4)_3$	H_2O	$NaBH_4$	13	<5	26
3[a]	$Fe(NO)_3$	H_2O	$NaBH_4$	5	<5	29
4[b]	$Co(acac)_2$	dioxane	$PhSiH_3$	33	17	N.D.
5[c]	$Co(acac)_2$	dioxane	$PhSiH_3$	42	22	N.D.
6[c]	$Co(acac)_2$	dioxane	$PhSiMeH_2$	21	21	N.D.
7[c]	$Co(acac)_2$	THF	$PhSiH_3$	40	22	N.D.

[a]Fe salt (3.18 mmol) in H_2O (180 mL) saturated air was cooled to 0 °C, and a mixture of **15** (0.53 mmol), $NaBH_4$ (2.12 mmol) in 0.1 M HCl (1.0 mL), CF_3CH_2OH (0.2 mL), and H_2O (2 mL) was added dropwise. [b]A solution of **15** (0.32 mmol) in 1,4-dioxane (3 mL) was bubbled with O_2 for 15 min, and then $Co(acac)_2$ (0.064 mmol) was added. Silane (2.25 mmol) in 1,4-dioxane (3 mL) was added over 60 min via syringe pump. [c]Using hydrochloride salt of **15** as substrate. [d]Isolated yields.

selected results are displayed in Table 1 (*vide infra*). As anticipated, desired isomer **4** was predominantly produced by following Boger' recipe using excessive $Fe_2(ox)_3$[13b−d] and $NaBH_4$ (dr 6:1, Table 1, entry 1). However, low isolated yields (28%) resulted, as substantial reduction product **16** was also formed. Screening of different catalysts and other variations gave no improvement (entries 1−3, Supporting Information). Subsequently, Mukaiyama's procedure[13e−h] was evaluated and led to a comparable isolated yield with decreased diastereoselectivity (dr 2:1, Table 1, entry 4). However, this procedure was more appealing to us for a cleaner reaction mixture (no reduction product **16**) and operational convenience (no need for an excess of metal complex and very dilute conditions). To our delight, a slightly higher yield (42%, Table 1, entry 5) was obtained when a hydrochloride salt of **15** was used, presumably due to its improved stability toward the reaction conditions. Any change to the reaction conditions was detrimental to the reaction (Table 1, entries 6−7, and Supporting Information).

To complete the synthesis, semireduction of amide with DIBAL-H followed by spontaneous acetalization smoothly produced conolutinine (**3**) in 72% yield (Scheme 4). The physical data (NMR and optical rotation) of synthetic conolutinine were in agreement with the reported data. Furthermore, X-ray crystallography of the hydrochloride salt of synthetic conolutinine (**3**) confirmed the absolute configuration of (−)-conolutinine (**3**).[10]

In summary, a 10-step asymmetric synthesis of (−)-conolutinine was achieved by employing enantioselective bromocyclization of tryptamine. The synthesis also featured a late-stage Co-catalyzed radical oxidation of alkene to diastereoselectively construct a tertiary alcohol with the desired stereoconfiguration. Based on this total synthesis, the absolute configuration of (−)-conolutinine was determined to be (2*S*,5a*S*,8a*S*,13a*R*).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02046.

Experimental procedures, spectral data and copies of all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: yslai@cpu.edu.cn.
*E-mail: xiewq@nwafu.edu.cn.

Author Contributions

‖X.F., G.J., and Z.X. contributed equally.

Notes

The authors declare no competing financial interest.

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