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Total Synthesis of Indole Alkaloid (±)-Subincanadine E

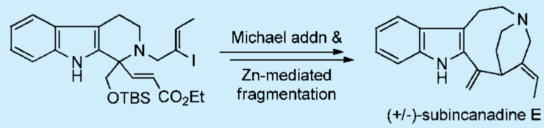
Jingjing Tian,[†] Qiuchen Du,[†] Rui Guo,[†] Yun Li,[†] Bin Cheng,[†] and Hongbin Zhai*,[†,‡]

[†]State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China

[‡]Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin 300071, China

Ⓢ *Supporting Information*

ABSTRACT: The first total synthesis of indole alkaloid (±)-subincanadine E has been accomplished. Ni(COD)$_2$-mediated intramolecular Michael addition and zinc-mediated fragmentation reaction served as two key transformations.



Subincanadines A–G (**1a–g**, Figure 1) were isolated from the bark of the Brazilian medicinal plant *Aspidosperma subincanum* Mart by Kobayashi and co-workers.[1] Among these natural products, subincanadine E (**1e**), also named pericine, was first isolated from *Picralima nitida* cell suspension cultures by Joachim Stockigt in 1982.[2] Subincanadine E is a tetracyclic indole alkaloid that consists of an unusual 1-azabicyclo[5.2.2]-undecane moiety containing two aza-heterocycles and two exocyclic double bonds. It was considered as a possible precursor of apparicine[2b] and was found to have cytotoxicity against murine lymphoma L1210 cells (IC$_{50}$, 0.3 μg/mL) and human epidermoid carcinoma KB cells (IC$_{50}$, 4.4 μg/mL) based on in vitro preliminary biological experiments.[1a] Although there have appeared a series of reports on the total synthesis or synthetic studies of subincanadines A,[3] B,[3,4] C,[5] and F[6] due to their unique chemical structures and significant biological activities, the synthesis of the rest of the subincanadine alkaloids has not been reported so far.

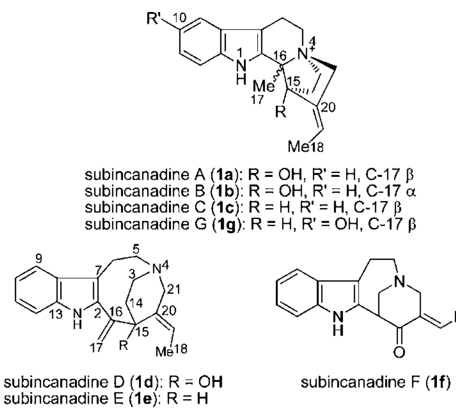
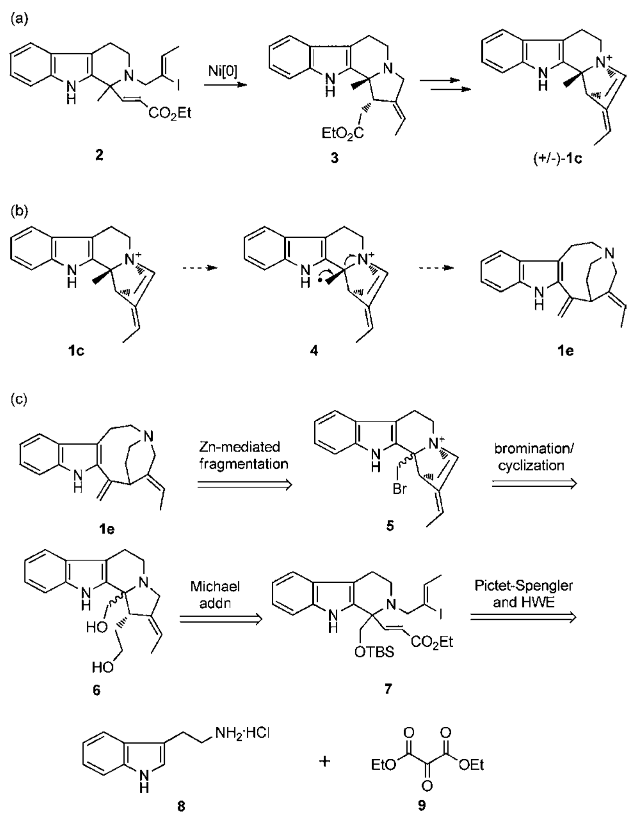


Figure 1. Structures of subincanadines A–G.

We reported the first total synthesis of (±)-subincanadine C (**1c**) through Ni(COD)$_2$-mediated intramolecular Michael addition (**2** → **3**) as a key step in 2011 (Scheme 1a).[5] Kobayashi suggested that **1c** could be biosynthetically derived from **1e**, which itself could be generated from stemmadenine;[1a] however, no reports have addressed whether **1c** could be the biosynthetic precursor of **1e**. We envisioned that **1c** could be potentially transformed into **1e** through the fragmentation of radical intermediate **4** (Scheme 1b). Based upon this hypothesis, we designed a concise synthetic strategy for **1e**

Scheme 1. (a) Overview of the Completed Synthesis of (±)-Subincanadin C (1c). (b) Proposal Regarding Biosynthetic Conversion of Subincanadine C (1c) to Subincanadine E (1e). (c) Retrosynthetic Analysis of (±)-Subincanadine E (1e)



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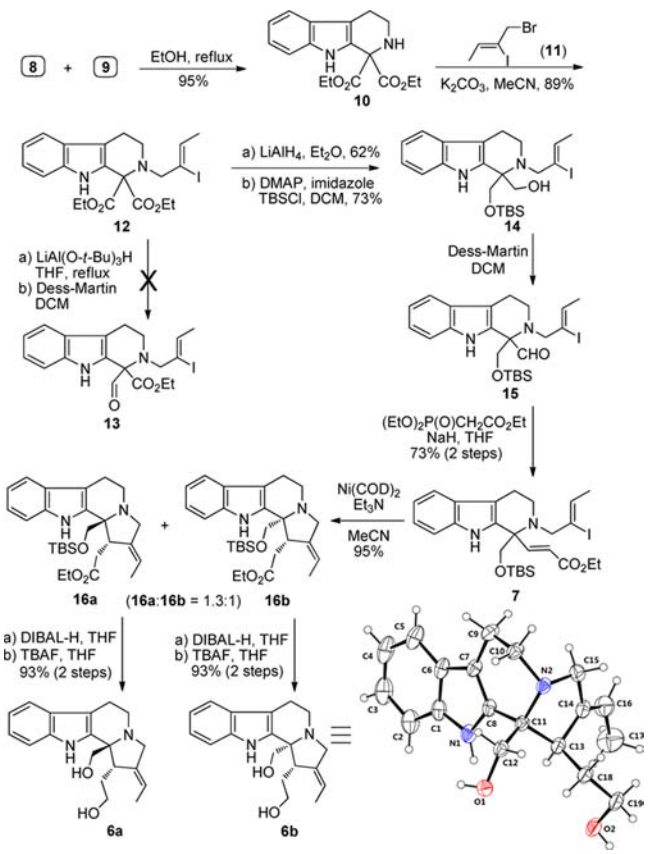
(Scheme 1c), in which a zinc-mediated fragmentation reaction (5 → 1e) mimicking the one outlined in Scheme 1b was adopted for the cleavage of C16–N4 bond (see the numbering code for subincanadines A–C and G in Figure 1) and completing the installment of the 1-azabicyclo[5.2.2]undecane ring system with an exocyclic double bond. Pentacycle **5** may be generated from sequential double bromination and intramolecular ammonium formation of diol **6**. The tetracyclic framework within **6** may be constructed by $Ni(COD)_2$-mediated intramolecular Michael addition[5,7] from ester **7**, which could be obtained through a series of transformations including Pictet–Spengler condensation of tryptamine hydrochloride (**8**) with tricarbonyl **9**, allylation of the secondary amine, and manipulation of the two ester groups.

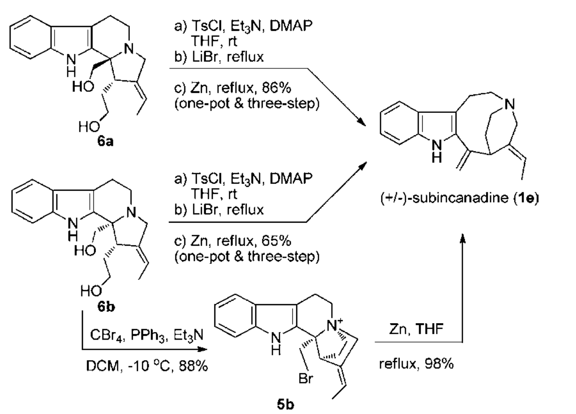
As shown in Scheme 2, our synthesis commenced from the Pictet–Spengler condensation of commercially available tryptamine hydrochloride salt (**8**) with tricarbonyl **9** and the subsequent N-alkylation with bromide **11**,[8] affording tertiary amine **12** in good yield. Attempted conversion of diester **12** into ester–aldehyde **13** proved to be unsuccessful, through either (i) partial reduction of one of the ester groups with DIBAL-H[9] or (ii) full reduction of one of the ester groups with $LiAl(O\text{-}t\text{-}Bu)_3H$[10] followed by oxidation with Dess–Martin periodinane; instead, decarbonylation took place in both cases.[11] Subsequently, we focused on the synthesis of aldehyde **15**, which was achieved via a three-step operation including (i) full reduction of diester **3** to form a diol, (ii) protection of one of the hydroxyls to furnish TBS ether **14**, and (iii) oxidation of the remaining hydroxyl to generate a formyl group. Because of its stability problem, aldehyde **15** was used directly in the next step without further purifications. HWE olefination of **15** with triethyl phosphonoacetate and NaH led smoothly to unsaturated ester **7**. At this stage, all the carbon and nitrogen atoms required in the target molecule have been successfully installed. $Ni(COD)_2$-mediated intramolecular Michael addition[5,7] of **7** was realized in the presence of triethylamine at ambient temperature, and tetracycles **16a** and **16b** (dr =1.3:1) were produced in 54% and 41% yields, respectively. Both of the diastereomers are useful for the synthesis of the target molecule **1e**. Reduction of **16a** and **16b** with DIBAL-H followed by silyl ether deprotection with TBAF delivered diols **6a** and **6b**, respectively. The structure of **6b** was unambiguously confirmed by X-ray diffraction analysis.

Scheme 2. Synthesis of 6a and 6b



The remaining major tasks for the total synthesis of **1e** would include intramolecular ammonium formation and C16–N4 bond fragmentation. Metal-mediated fragmentation has been elegantly applied to constructing carbon–carbon double bonds[12] and has culminated in the total synthesis of several natural products.[13] However, to the best of our knowledge, zinc-mediated fragmentation involving quaternary ammonium salt has never been utilized in the total synthesis of alkaloids. With diols **6a** and **6b** in hand, the sequential bromination and cyclization was carefully investigated under various conditions. Treatment of diol **6a** sequentially with TsCl/Et_3N/DMAP and LiBr effected the anticipated bromination/cyclization to give a pentacyclic quaternary ammonium salt, which was then subjected to zinc-mediated fragmentation to form (±)-subincanadine E (**1e**) in 86% yield over a one-pot, three-step process starting from **6a** (Scheme 3). The target molecule (±)-**1e** was also obtained from diol **6b** in a one-pot fashion. Furthermore, subjecting **6b** with CBr_4/PPh_3/Et_3N[14] afforded pentacyclic ammonium **5b** (88%), which was reacted with Zn in THF at reflux to furnish (±)-**1e** in almost quantitative yield. In contrast, reaction of **6a** with CBr_4/PPh_3/Et_3N under exactly the same conditions applied to **6b** could not deliver any pentacyclic ammonium (i.e., a stereoisomer of **5b**) at all.

Scheme 3. Completion of the Total Synthesis of (±)-1e



In summary, the first total synthesis of (±)-subincanadine E has been realized in 10 operations (for the shortest synthetic routes) from tryptamine hydrochloride salt. The synthesis features (i) $Ni(COD)_2$-mediated intramolecular Michael addition to rapidly access the tetracyclic skeleton of **16a**/**16b**, (ii) sequential double bromination/cyclization to form 1-azoniatricyclo[4.3.3.0]undecane backbone of **5** (e.g., **5b**), and (iii) zinc-mediated fragmentation to construct the unique 1-azabicyclo[5.2.2]undecane ring system with an exocyclic double

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bond. Asymmetric total synthesis of (+)-subincanadine E is currently underway in our laboratory.[15]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: zhaih@lzu.edu.cn.

Notes

The authors declare no competing financial interest.

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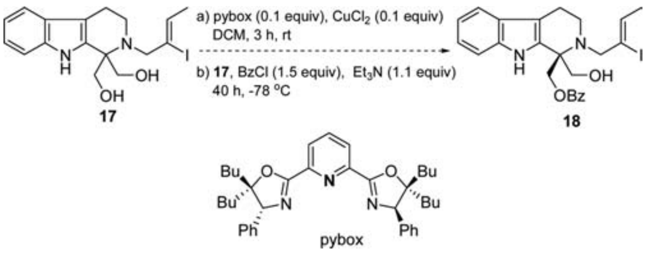
(15) An asymmetric synthesis of subincanadine E could be potentially achieved by desymmetrization[16] of diol **17** (obtained in one step from diester **12** via reduction) to give mono benzoate **18** (an analogue of **14**) in an enantiopure form.



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