ORGANIC LETTERS

2011
Vol. 13, No. 21
5782–5783

Fast and Protecting-Group-Free Synthesis of (±)-Subincanadine C

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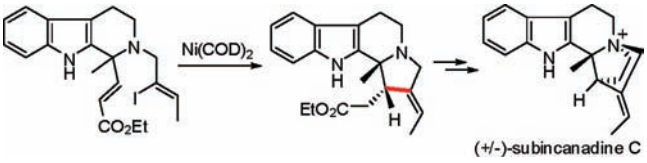
Received August 30, 2011

ABSTRACT



The first total synthesis of (±)-subincanadine C has been accomplished in a protecting-group-free fashion. This pentacyclic indole alkaloid was synthesized in six steps from the known intermediate 4, featuring Ni(COD)$_2$-mediated intramolecular Michael addition as a key transformation.

Kobayashi and co-workers reported the isolation of a series of structurally intriguing indole alkaloids, subincanadines A–G (**1a**–**1g**, Figure 1), from the barks of the Brazilian medicinal plant *Aspidosperma subincanum* Mart.[1] Because of their unique structural characteristics and impressive pharmacological activities, several laboratories have been actively engaged in the synthesis of subincanadines A,[2] B,[2] and F.[3] Herein we wish to report the first total synthesis of (±)-subincanadine C (**1c**), a novel quaternary indole alkaloid, featuring an unprecedented 1-azoniatricyclo[4.3.3.0^{1,5}]undecane backbone.

The retrosynthetic analysis for (±)-subincanadine C (**1c**) is outlined in Scheme 1. We envisioned that the pentacyclic target molecule could be accessed from tetracycle **2** via reduction of the ester group followed by halogenation and intramolecular nucleophilic substitution. Compound **2** itself could be constructed by Ni(COD)$_2$-mediated intramolecular Michael addition[4] of unsaturated ester **3**, which in turn could be generated from the known intermediate **4** through simple transformations.

Our synthesis commenced from the known intermediate **4**,[5] prepared via a Pictet–Spengler reaction of tryptamine hydrochloride with ethyl pyruvate (Scheme 2). Compound

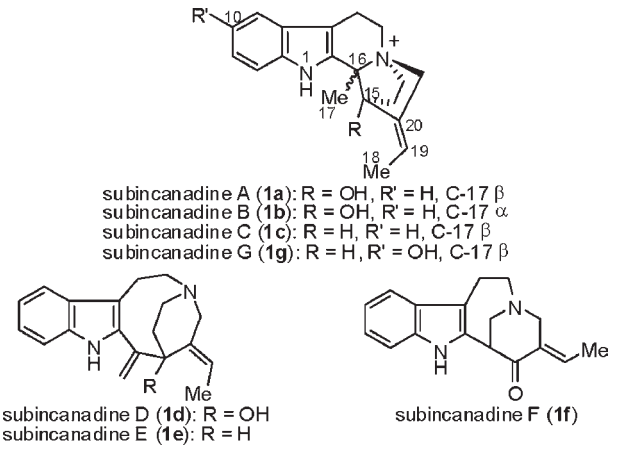


Figure 1. Structures of subincanadines A–G.

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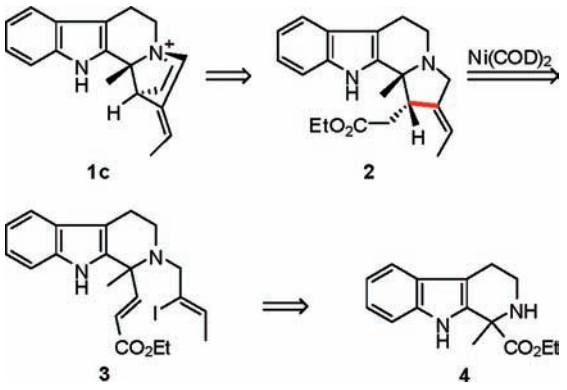
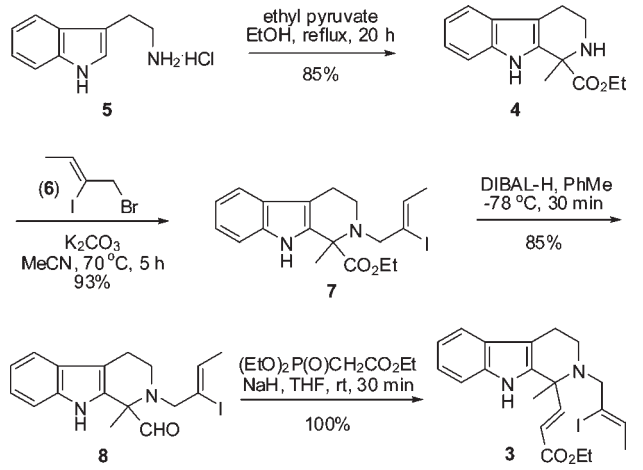
10.1021/ol202349g
Published on Web 10/04/2011

Scheme 1. Retrosynthetic Analysis of **1c**



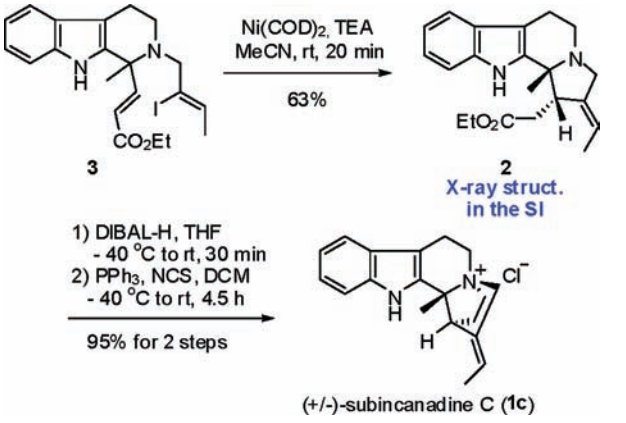
Scheme 2. Synthesis of Unsaturated Ester **3**



4 was alkylated with bromide **6**[6] in MeCN in the presence of K_2CO_3 to give vinyl iodide **7** in 93% yield. Upon partial reduction of the ester group and subsequent Horner–Wadsworth–Emmons (HWE) olefination, unsaturated ester **3** was produced from **7** in an 85% overall yield.

With compound **3** in hand, the key intramolecular Michael addition was carefully investigated under various conditions (e.g., SmI_2, Bu_3SnH/AIBN, $Pd(OAc)_2$, or $Ni(COD)_2$,[4] etc.). Although unsatisfactory results were obtained with most of the above reagent systems, treatment of vinyl iodide **3** with 1.5 equiv of $Ni(COD)_2$ and 3 equiv of triethylamine in MeCN at room temperature did afford the desired cyclization[4] product **2** (in 23% yield). Delightfully, a much better yield (63%) was achieved for **2** when 5 equiv of $Ni(COD)_2$ and 10 equiv of triethylamine were used (Scheme 3). The *cis*-relationship between the hydrogen atom at C-15 and the methyl (C-17) as well as the (*E*)-configuration of the double bond in **2** was unambiguously confirmed by X-ray crystallographic analysis (see the Supporting Information). The reduction of **2** with DIBAL-H in THF afforded a primary alcohol, which was treated with PPh_3 and NCS[7] to lead to a 93% overall yield of (±)-subincanadine C (**1c**) via sequential chlorination and intramolecular nucleophilic substitution. The ^1H and ^{13}C NMR spectroscopic data of this alkaloid were in agreement with those disclosed in the literature.[1a]

Scheme 3. Completion of the Total Synthesis of **1c**



In summary, (±)-subincanadine C (**1c**) has been synthesized in a protecting-group-free fashion from the known compound **4** in only six steps and with an overall yield of 46%, which represents the first total synthesis of this indole alkaloid. The $Ni(COD)_2$-mediated intramolecular Michael addition is worth noting for the current synthesis.

Acknowledgment. We are grateful to the generous financial support from the National Basic Research Program of China (973 Program: 2010CB833200), NSFC (21172100; 20625204), "111" Program of MOE, and Ministry of Science and Technology (2009ZX09501-018).

Supporting Information Available. Experimental procedures and analytical data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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