ORGANIC LETTERS

2006
Vol. 8, No. 1
115−118

Facile Construction of the Pentacyclic Framework of Subincanadine B. Synthesis of 20-Deethylenylated Subincanadine B and 19,20-Dihydrosubincanadine B

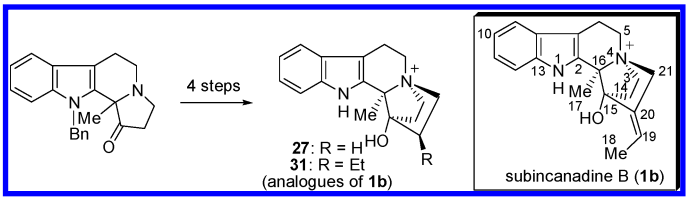
Yanqin Liu,[†] Shengjun Luo,[†] Xingnian Fu,[†] Fang Fang,[†] Zeyang Zhuang,[†,‡] Wanting Xiong,[†] Xueshun Jia,[‡] and Hongbin Zhai*[,†]

Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai, China 200032, and Department of Chemistry, Shanghai University, Shanghai, China 200436

zhaih@mail.sioc.ac.cn

Received October 31, 2005

ABSTRACT



We describe a facile approach for effectively constructing the pentacyclic framework of subincanadine B. The seven-step assembly of tetracyclic ketone 14 featured Michael addition, Pictet–Spengler cyclization, and Dieckmann condensation. From this key ketone intermediate, two analogues of subincanadine B, i.e., 20-deethylenylated subincanadine B (27) and 19,20-dihydrosubincanadine B (31), were synthesized in four steps, respectively.

Indole alkaloids are an important class of biologically active natural products that have tremendous potential for new drug development.[1] Kobayashi and co-workers described in 2002 the isolation of subincanadines A−F (**1a**−**1c**, **2a**, **2b**, and **3**) from the bark of the Brazilian medicinal plant *Aspidosperma subincanum* Mart (Figure 1).[2] Subincanadines A−C (**1a**−**1c**), three novel quaternary alkaloids, possess an unprecedented 1-azoniatricyclo[4.3.3.0^{1,5}]undecane framework. The remaining three subincanadines feature either a 1-azabicyclo[5.2.2]undecane [for subincanadines D−E (**2a**, **2b**)] or a 1-azabicyclo[4.3.1]decane skeleton [for subincanadine F (**3**)]. Preliminary biological experiments were conducted on these compounds. For instance, it was found that subincanadines E (**2b**) and F (**3**) were cytotoxic against murine lymphoma L1210 cells (IC$_{50}$: **2b**, 0.3 μg/mL; **3**, 2.4 μg/mL) and human epidermoid carcinoma KB cells (IC$_{50}$: **2b**, 4.4 μg/mL; **3**, 4.8 μg/mL) in vitro.[2] Surprisingly, no reports have appeared so far addressing the synthesis of subincanadines. Fascinated by their unique structural characteristics and impressive pharmacological activity, we took the initiative to tackle on assembling the subincanadine family alkaloids.

Herein we wish to report our investigations centered at the synthesis of the pentacyclic framework of subincanadine B. The overall synthetic strategy is outlined in Figure 2. Commercially available tryptamine (**4**) was chosen as the starting material, from which tetrahydrocarboline **5** might be obtained via Michael addition and Pictet−Spengler

[†] Shanaghai Institute of Organic Chemistry.
[‡] Shanaghai University.

(1) Wright, C. W.; Phillipson, J. D. *Phytother. Res.* **1990**, *4*, 127.
(2) Kobayashi, J.; Sekiguchi, M.; Shimamoto, S.; Shigemori, H.; Ishiyama, H.; Ohsaki, A. *J. Org. Chem.* **2002**, *67*, 6449.

10.1021/ol0526367 CCC: $33.50
Published on Web 12/10/2005

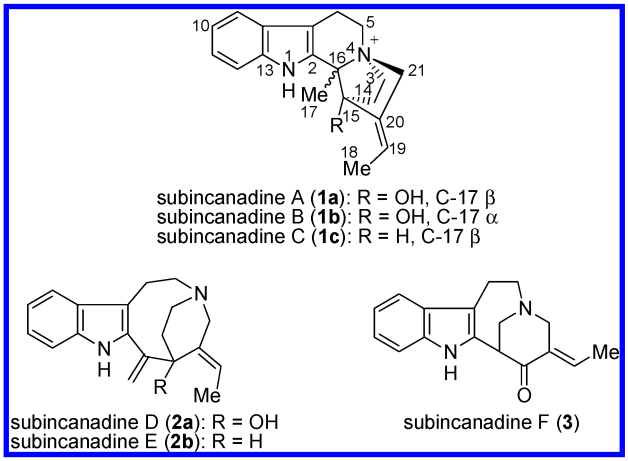


Figure 1.

cyclization.[3] Dieckmann condensation and decarboxylation would transform **5** to tetracyclic ketone **6**. Introducing a side chain onto C-15 would allow the formation of the azoniacycle (i.e., ring E, see **7**).

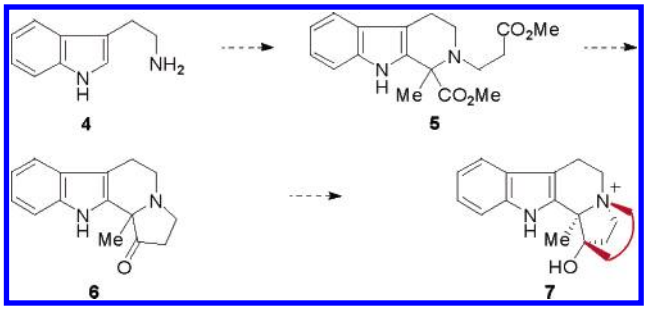
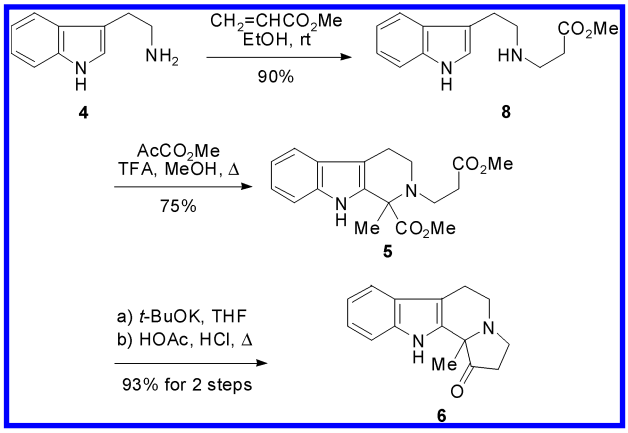


Figure 2.

As described in Scheme 1, treatment of tryptamine (**4**) with methyl acrylate (1 equiv) in EtOH at room temperature

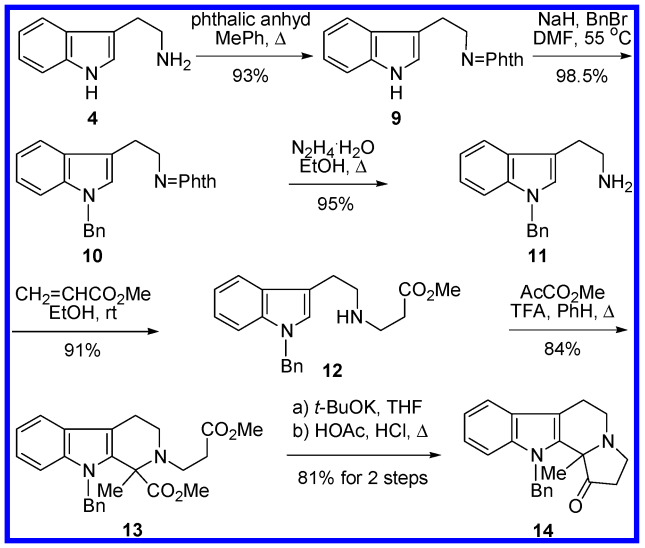
Scheme 1



afforded in high yield (90%) the Michael adduct **8**,[4] which was converted to diester **5** in 75% via Pictet−Spengler reaction by reacting with methyl pyruvate in the presence of trifluoroacetic acid in refluxing methanol for 4 days. Dieckmann condensation of **5** (effected with *t*-BuOK) followed by decarboxylative hydrolysis with HOAc and HCl at reflux led to the formation of tetracyclic ketone **6** as a white solid in 93% yield for the two steps.

To install ring E of subincanadine B, nucleophilic addition to the carbonyl of ketone **6** was vigorously attempted. Direct reaction of **6** with excess nucleophiles such as vinylmagnesium bromide and the lithium enolate of EtOAc (used for model reactions), without prior nitrogen protection, could not be accomplished. Moreover, protecting **6** as an *N*-Boc, TBS, EE, or Ac derivative by standard protocols[5] proved to be unfruitful. It seemed that the nitrogen protection might have to be performed at an earlier stage. Thus, **4** was converted to *N*-benzyltryptamine[6] (**11**) in high overall yield by a three-step reaction sequence consisting of (i) phthalamide formation of the primary amine moiety by refluxing **4** with phthalic anhydride in toluene in a Dean−Stark apparatus,[7] (ii) indole nitrogen benzylation by treating **9** with NaH and benzyl bromide in DMF at 55 °C, and (iii) transamidation to release the primary amino group by heating **10** with excess hydrazine in refluxing ethanol (Scheme 2).[8]

Scheme 2



Michael addition of **11** with methyl acrylate (1 equiv) in ethanol at room temperature provided **12** in 91% yield.

(3) For a review on the Pictet−Spengler reaction, see: (a) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797. For its recent, elegant applications, see: (b) Yu, J.; Wang, T.; Liu, X.; Deschamps, J.; Flippen-Anderson, J.; Liao, X.; Cook, J. M. *J. Org. Chem.* **2003**, *68*, 7565. (c) Yu, J.; Wearing, X.; Cook, J. M. *J. Org. Chem.* **2005**, *70*, 3963.

(4) Huizenga, R. H.; Pandit, U. K. *Tetrahedron* **1991**, *47*, 4155.

(5) *Protective Groups in Organic Synthesis*, 3rd ed.; Greene, T. W., Wuts, P. G. M., Eds.; John Wiley: New York, 1999; Chapter 7; p 494 and references therein.

(6) For preparation of 1-benzyltryptamine, see: Benson, S. C.; Lee, L.; Yang, L.; Snyder, J. K. *Tetrahedron* **2000**, *56*, 1165.

(7) Luo, S. J.; Zificsak, C. A.; Hsung, R. P. *Org. Lett.* **2003**, *5*, 4709.

Whereas refluxing **12** and methyl pyruvate with TFA in methanol or with acetic acid in acetonitrile[9] failed to generate **13**, refluxing them with *p*-toluenesulfonic acid (TSA) in benzene[4] did furnish the product but only in very low yield. Finally, tricycle **13** could be obtained via Pictet−Spengler reaction in 84% yield by exposing **12** and methyl pyruvate to TFA in benzene[10] at reflux for 2 days. Diester **13** was converted into N-protected tetracyclic ketone **14** in a similar manner in 81% yield as described in Scheme 1.

With the N-protected tetracyclic ketone **14** in hand, considerable efforts were devoted to attaching a side chain onto ring D in order to generate the azoniacycle (i.e., ring E) of subincanadine B. A variety of anionic nucleophiles of different complexity (such as **15b**−**23b**,[11] generated from **15a**−**23a**,[12] respectively, Figure 3) were employed to react

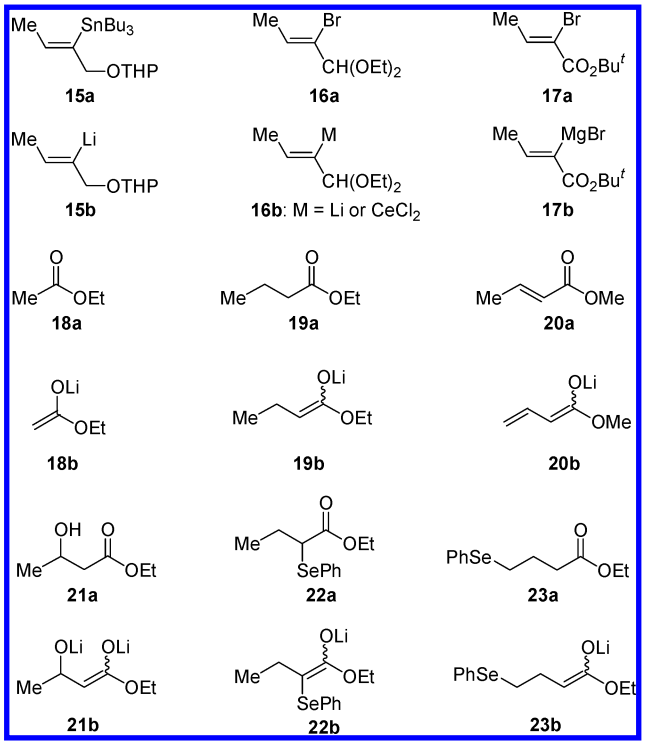
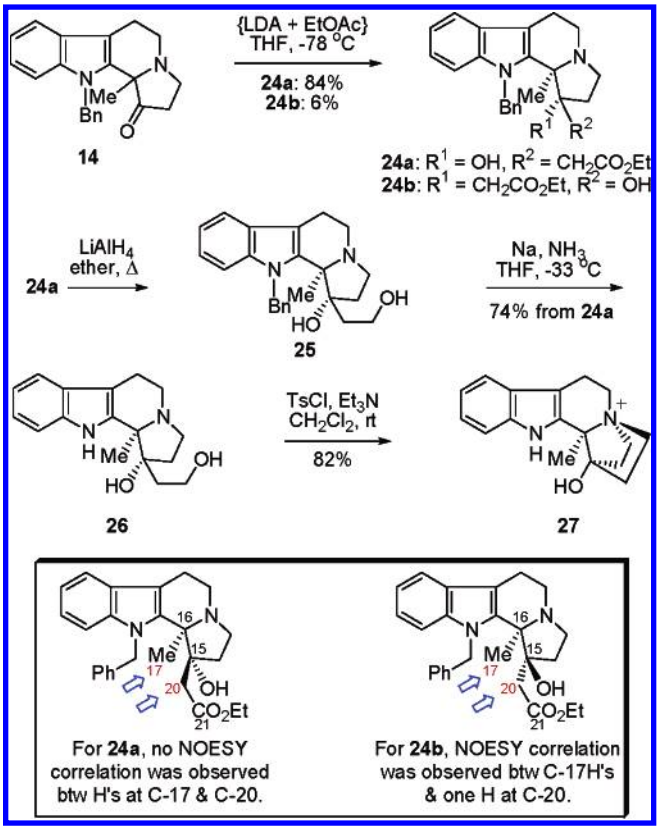


Figure 3. Anionic nucleophiles.

with the carbonyl of **14** in the hope of fulfilling the goal. If the side chains could be put in place, the CH_2OTHP (as in **15a**), $CH(OEt)_2$ (as in **16a**), and CO_2R (R = Me, Et, and Bu^t, as in **17a**−**23a**) moieties would be converted to methylenes with a leaving group for intramolecular ammonium formation at a later stage. The hydroxyl (as in **21a**) and phenylselenyl (as in **22a** and **23a**) would be utilized to form the carbon−carbon double bonds. As a matter of fact, among the reagents listed in Figure 3, only the enolates **18b** and **19b** could form adducts with **14** in good yields. Ketone **14** featured a rather rigid skeleton, and the limited steric accessibility around the carbonyl has to be taken into consideration. Thus, the fate of the nucleophilic addition to **14** might be dependent upon the overall reactivity and steric hindrance of the attacking nucleophiles. Hence, we next pursued the synthesis of the analogues of subincanadine B as our immediate objective, by taking advantage of the successful adduct formation of **14** with the lithium enolates of ethyl acetate and ethyl butyrate.

As outlined in Scheme 3, aldol condensation of **14** with the lithium enolate of ethyl acetate proceeded smoothly at

Scheme 3



−78 °C and produced the pair of isomers **24a** (84%) and **24b** (6%). The configuration of C-15 relative to that of C-16 for the two diastereomers was elucidated with the aid of NOESY analysis, as shown in the box in Scheme 3.[13] NOESY correlation can be observed between the C-17 protons and one of the C-20 protons for aldol **24b**, indicating that the C-16-methyl and the C-15-(ethoxycarbonyl)methyl

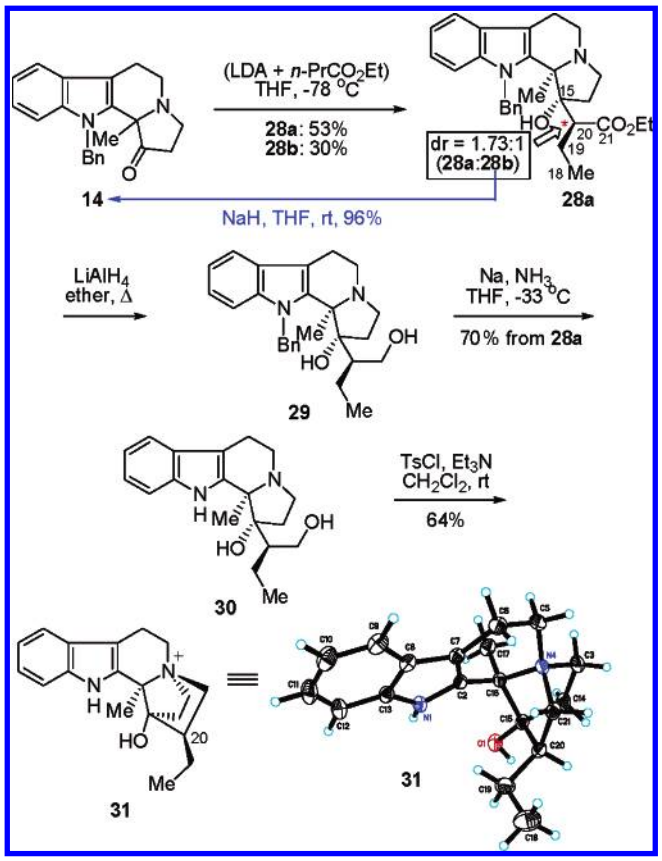
(8) Sheehan, J. C.; Bolhofer, W. A. *J. Am. Chem. Soc.* **1950**, *72*, 2786.
(9) Lu, Y.; Just, G. *Tetrahedron* **2000**, *56*, 4355.
(10) Kawate, T.; Yamanaka, M.; Nakagawa, M. *Heterocycles* **1999**, *50*, 1033.
(11) Generation of anion **16b**: (a) Smith, A. B., III; Levenberg, P. A.; Jerris, P. J.; Scarborough, R. M., Jr.; Wovkulich, P. M. *J. Am. Chem. Soc.* **1981**, *103*, 1501. (b) Anion **17b**: Thibonnet, J.; Vu, V. A.; Berillon, L.; Knochel, P. *Tetrahedron* **2002**, 4787. (c) Anion **20b**: Johnson, P. R.; White, J. D. *J. Org.* Chem. **1984**, *49*, 4424. (d) Anion **21b**: Swaren, P.; Massova, I.; Bellettini, J. R.; Bulycher, A.; Maveyraud, L.; Kotra, L. P.; Miller, M. J.; Mobashery, S.; Samama, J.-P. *J. Am. Chem. Soc.* **1999**, *121*, 5353.
(12) Preparation of compound **15a**: (a) Ensley, H. E.; Buescher, R. R.; Lee, K. *J. Org. Chem.* **1982**, *47*, 404. (b) Compound **22a**: Guindon, Y.; Faucher, A.-M.; Bourque, E.; Caron, V.; Jung, G.; Landry, S. R. *J. Org. Chem.* **1997**, *62*, 9276. (c) Compound **23a**: Dowd, P.; Kennedy, P. *Synth. Commun.* **1981**, *11*, 935.

(13) The numbering system adopted here is that for subincanadines A−C.

groups are in a *cis* relation. Meanwhile, no NOESY correlation is present between the C-17 and C-20 protons for aldol **24a**, which reveals that the methyl (C-17) is located on the same side of the pyrrolidine ring as the hydroxyl at C-15. The stereoselectivity of the nucleophilic addition could be explained as the enolate approached the carbonyl from the less hindered face, avoiding steric interaction with the methyl residing at C-16. Complete reduction of ester **24a** with $LiAlH_4$ in hot ether furnished 1,3-diol **25**, which was debenzylated with excess sodium in liquid ammonia at −33 °C to afford N-deprotected diol **26** in good overall yield (74% yield over the two steps). Tosylation of the primary hydroxyl of **26** with TsCl (120 mol %) in the presence of triethylamine in CH_2Cl_2 at room temperature, followed by spontaneous intramolecular ammonium formation, resulted in the generation of 20-deethylenylated subincanadine B (**27**) as colorless crystals in 82% yield.

In a similar manner, two major stereoisomers, tentatively assigned[14] as **28a** and **28b**, were produced in 51% and 30% yields, respectively, as a result of the aldol condensation of ketone **14** and the lithium enolate of ethyl butyrate (Scheme 4). The diastereomeric ratio was found to be approximately 1.7:1 in terms of C-20. Following the same protocol developed for **24a**, N-debenzylated 1,3-diol **30** was obtained from the major aldol **28a** in 70% yield. By treating diol **30** with TsCl (120 mol %) and excess triethylamine in dichloromethane at room temperature, the sequential sulfonation/cyclization (i.e., intramolecular ammonium formation) successfully took place to afford in 64% overall yield 19,20-dihydrosubincanadine B (**31**) as colorless crystals. The exact three-dimensional structure was determined for **31** by X-ray crystallographic analysis, which also confirmed the relative configuration of aldol **28a** proposed earlier. Subjecting the minor isomeric aldol, **28b**, to the same sequence of the manipulations applied to **28a** (consisting of ester reduction, N-debenzylation, and primary hydroxyl tosylation), no desirable cyclized ammonium was isolable. This is presumably because the final cyclization step of the monotosylate produced from **28b** might require a too high activation energy as a result of the disfavored transition state for the intramolecular S_N2 reaction. Nevertheless, **28b** could be converted back via a clean retro-aldol reaction to afford ketone **14** in 96% yield by the treatment with NaH (200 mol %) in THF (16 mL for 0.79 mmol of **28b**) at room temperature for 5 h. Thus, the recycle of the seemingly less useful diastereomer **28b** could be accomplished with ease.

Scheme 4



In conclusion, we have described a facile approach for effectively constructing the pentacyclic framework of subincanadine B. The seven-step assembly of tetracyclic ketone **14** featured Michael addition, Pictet−Spengler cyclization, and Dieckmann condensation. From this key ketone intermediate, two analogues of subincanadine B, i.e., 20-deethylenylated subincanadine B (**27**) and 19,20-dihydrosubincanadine B (**31**), were synthesized in four steps, respectively. The total synthesis of subincanadines is ongoing in our laboratory.

Acknowledgment. We thank NSFC (no. 20372073), STCSM ("Post-Venus" Program, no. 05QMH1416), GCCP of ECNU, and Ministry of Human Resources of PRC for financial support.

Supporting Information Available: Experimental procedures and analytical data (including CIF file). This material is available free of charge via the Internet at http://pubs.acs.org.

OL0526367

(14) The relative configuration of **28a** was subsequently confirmed by the correlation to the X-ray crystallographic structure of **31** (see the main text).