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First Asymmetric Total Syntheses of (−)-Subincanadines A and B, Skeletally Rearranged Pentacyclic Monoterpenoid Indole Alkaloids in *Aspidosperma subincanum*

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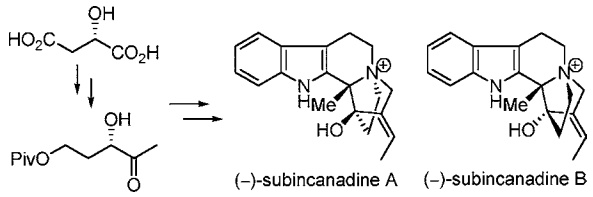
ABSTRACT



We achieved the first asymmetric total syntheses of novel *Aspidosperma* indole alkaloids, (−)-subincanadines A and B, which involve an intramolecular diastereoselective Pictet–Spengler cyclization and an intramolecular Nozaki–Hiyama–Kishi reaction as key steps in the total syntheses.

Several structurally unique indole alkaloids, named subincanadines A−G (**1**−**7**) (Figure 1), have been isolated from a Brazilian medicinal plant, *Aspidosperma subincanum*, by Kobayashi et al.[1] Among them, subincanadines A−C and G (**1**−**4**) have a novel pentacyclic skeleton with a 1-azoniatricyclo[5.2.2.0^{1,6}]undecane moiety. Further, the presence of a chiral quaternary carbon at the C-16 position is a characteristic that distinguishes these alkaloids from hitherto known monoterpenoid indole alkaloids having a β-carboline skeleton.[2] Quite recently, an approach for the construction of the framework of subincanadine B in the racemic form was reported in this journal.[3] Herein, we disclose the first asymmetric total syntheses of (−)-subincanadine A (**1**) and (−)-subincanadine B (*ent*-**2**), which involve an intramolecular diastereoselective Pictet−Spengler cyclization and an intramolecular Nozaki−Hiyama−Kishi reaction[4] as key steps in the concise total syntheses.

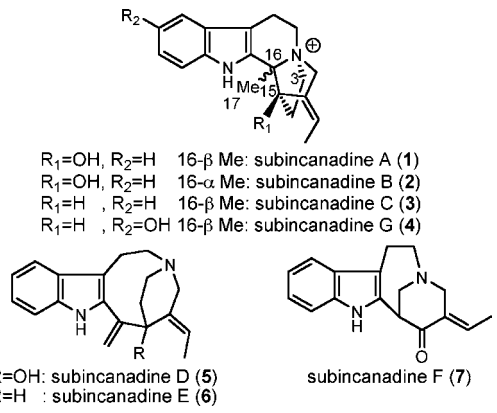


Figure 1. Structures of subincanadines.

(1) (a) Kobayashi, J.; Sekiguchi, M.; Shimamoto, S.; Shigemori, H.; Ishiyama, H.; Ohsaki, A. *J. Org. Chem.* **2002**, *67*, 6449. (b) Ishiyama, H.; Matsumoto, M.; Sekiguchi, M.; Shigemori, H.; Ohsaki, A.; Kobayashi, J. *Heterocycles* **2005**, *66*, 651.

(2) (a) *The Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; Supplement to Vol. 25, Part 4 of The Chemistry of Heterocyclic Compounds; Wiley: Chichester, 1994. (b) Takayama, H.; Kitajima, M.; Kogure, N. *Curr. Org. Chem.* **2005**, *9*, 1445.

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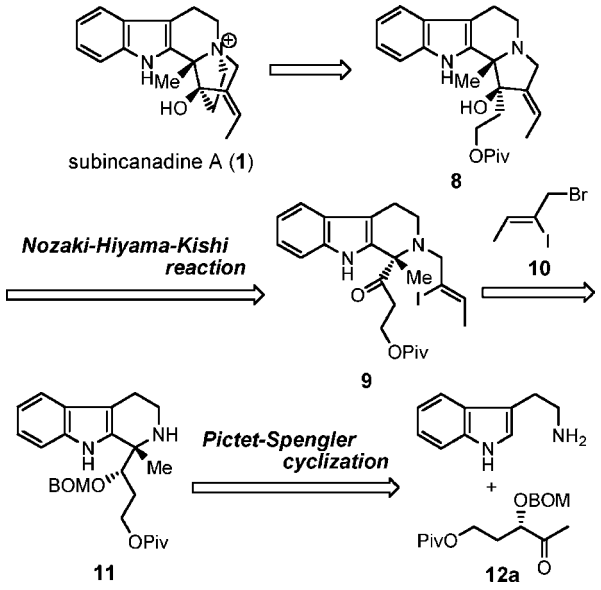
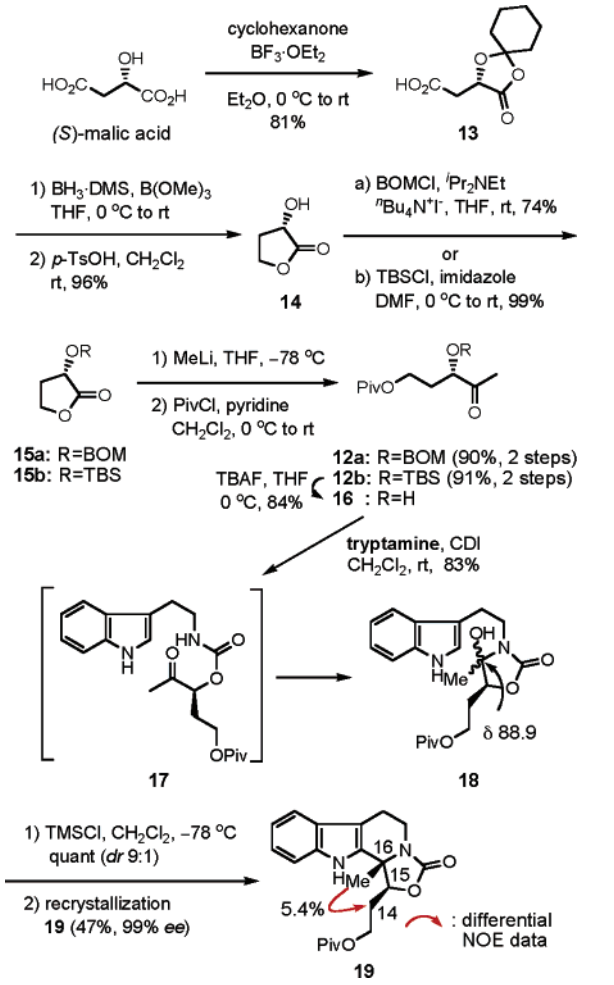
Scheme 1. Retrosynthetic Analysis



Our initial synthetic plan is shown in Scheme 1. The Pictet−Spengler reaction using ketone derivatives has not been studied much[5] compared with that using aldehyde derivatives; however, we anticipated that the Pictet−Spengler cyclization of tryptamine with ketone **12a** bearing an optically active secondary alcohol at the α position should provide 1,1-disubstituted tetrahydro-β-carboline derivative **11** in a diastereoselective and enantioselective manner. The Nozaki−Hiyama−Kishi reaction of ketone derivative **9**, which can be obtained by alkylation of the secondary amine with allyl bromide **10** and transformation of the secondary hydroxyl group, should provide tetracyclic intermediate **8**. Subsequent ring closure between the amine and the primary alcohol was expected to complete the total synthesis.

We initially attempted the conventional Pictet−Spengler reaction of tryptamine with optically active ketone **12a**, which was prepared from (*S*)-malic acid via a six-step operation (Scheme 2) including protection of the 1,2-carboxylic acid−alcohol residue,[6] reduction of the remaining carboxylic acid, formation of a γ-lactone,[7] BOM ether protection of the secondary hydroxyl group, preparation of methyl ketone by treatment with methyllithium, and finally

Scheme 2



protection of the resultant primary alcohol. The reaction conducted in DCM in the presence of TFA under reflux conditions provided two 1,1-disubstituted tetrahydro-β-carboline compounds such as **11** in a nondiastereoselective manner, and both products showed low optical activity, probably owing to the racemization of the chiral center in **12a** during the reaction under acidic conditions.

Then, we devised the intramolecular Pictet−Spengler reaction using carbamate **17** that tethered tryptamine and optically active ketone **16**. Hydroxy ketone **16** was prepared from γ-lactone **14** via a four-step operation (Scheme 2): TBS protection of the secondary hydroxyl group,[7] preparation of methyl ketone **12b** by treatment with methyllithium, protection of the resultant primary alcohol, and finally removal of the protecting group from the secondary alcohol. Carbamate **17**, obtained in 83% yield by the condensation of tryptamine and **16** with 1,1′-carbonyldiimidazole (CDI),[8] was found to exist in the hemi-aminoacetal form **18** in solution as demonstrated by the chemical shift appearing at δ 88.9 (C-16) in the ^{13}C NMR spectrum (Scheme 2).

Several acids and solvents were examined in our attempt to obtain high diastereoselectivity in the Pictet−Spengler

(3) Liu, Y.; Luo, S.; Fu, X.; Fang, F.; Zhuang, Z.; Xiong, W.; Jia, X.; Zhai, H. *Org. Lett.* **2006**, *8*, 115.

(4) (a) For a review, see: Fürstner, A. *Chem. Rev.* **1999**, *99*, 991. (b) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281. (c) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048. (d) For an example of intramolecular reaction between ketone and vinylbromide, see: Trost, B. M.; Pinkerton, A. B. *Org. Lett.* **2000**, *2*, 1601.

(5) For examples of Pictet−Spengler cyclization using ketone derivatives, see: (a) Rodríguez, J. G.; Gil-Lopetegui, P. *J. Heterocycl. Chem.* **1993**, *30*, 373. (b) Horiguchi, Y.; Nakamura, M.; Kida, A.; Komada, H.; Saitoh, T.; Sano, T. *Heterocycles* **2003**, *59*, 691. (c) Kuo, F.-M.; Tseng, M.-C.; Yen, Y.-H.; Chu, Y.-H. *Tetrahedron* **2004**, *60*, 12075.

(6) Hanessian, S.; Tehim, A.; Chen, P. *J. Org. Chem.* **1993**, *58*, 7768.

(7) Schinzer, D.; Bauer, A.; Schieber, J. *Chem.−Eur. J.* **1999**, *5*, 2492.

(8) D'Addona, D.; Bochet, C. G. *Tetrahedron Lett.* **2001**, *42*, 5227.

cyclization of compound **18**. The best result was obtained when TMSCl was used as the Lewis acid in DCM at −78 °C, affording **19** in quantitative yield as a 9:1 mixture of diastereomers.[9] This mixture was separated by recrystallization to give single diastereomer **19**, the enantiomeric excess of which was determined to be 99% by chiral HPLC analysis.[10] The stereochemistry of the major product was determined by NOE experiments: irradiation of the protons on the methyl group at C16 caused a significant enhancement of the protons on the methylene group (C14) of the side chain, demonstrating the cis relationship of those groups as well as the *S* configuration at the C-16 position. The high diastereoselectivity of the cyclization could be interpreted by the plausible acyliminium intermediate,[11] in which the indole nucleus would attack from the less-hindered side (anti from the side chain), as depicted in Figure 2.

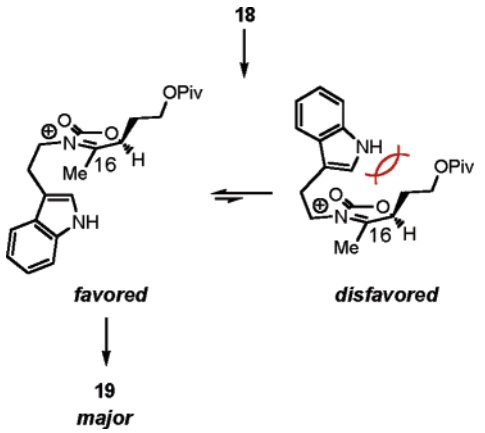
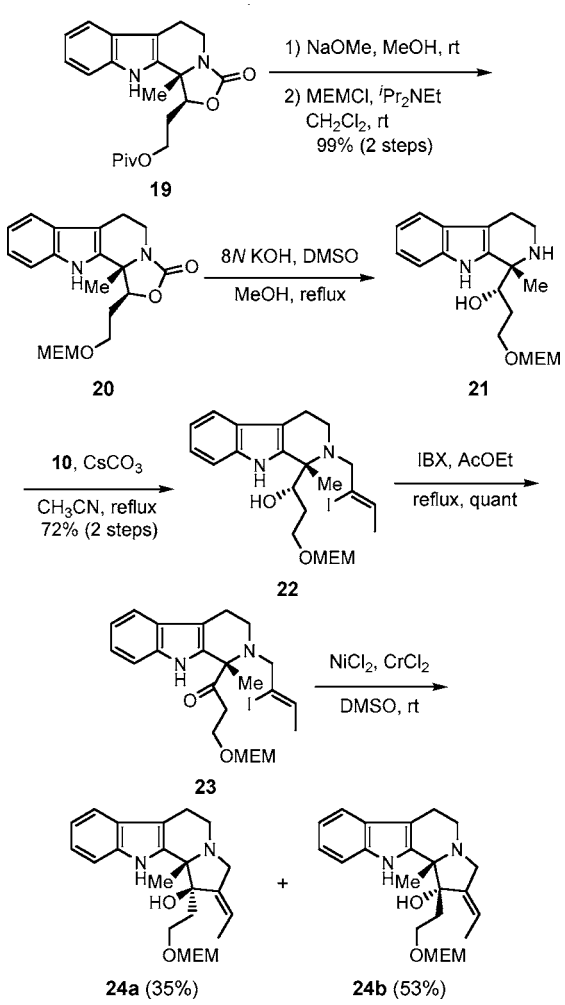


Figure 2. Possible mechanism in intramolecular Pictet−Spengler cyclization.

Next, the protecting group on the primary alcohol was switched to an MEM ether by a conventional procedure to afford compound **20** (Scheme 3). The carbonyl group in **20** was removed by alkaline hydrolysis, and the resulting secondary amine was alkylated with allylic bromide **10**[12] to give iodide **22** in 72% overall yield from **20**. The secondary alcohol in **22** was then oxidized with IBX[13] to afford ketone **23**, which was a key substrate for the construction of the D ring in the Nozaki−Hiyama−Kishi reaction. Treatment of **23** with $NiCl_2$ and $CrCl_2$ in DMSO at room temperature gave two tetracyclic compounds **24a** and **24b** in 35% and 53% yield, respectively. The stereochemistry of the newly formed stereogenic center in **24a** and **24b** was elucidated by NOE experiments (Scheme 4). Irradiation of the protons on the methyl group at C16 in **24b** caused a significant enhancement of the protons on the methylene group (C14) of the side chain, demonstrating the cis relationship of these groups. On the other hand, no NOE was observed between the protons on the methyl group at C16 and the protons on the methylene group (C14) of the side chain in **24a**, implying the anti relationship of these groups. Moreover, by irradiating H-19 in both tetracyclic compounds, a significant enhancement of H-21 was observed, respectively, revealing the retention of the geometry of the double bond.[14]

Scheme 3



In the final stage, the protecting group of the primary alcohol in **24a** was removed in 82% yield by treating with TMSCl/NaI in MeCN[15] and the resulting free alcohol was

(9) Diastereomeric ratio was determined by ^{1}H NMR spectroscopy.

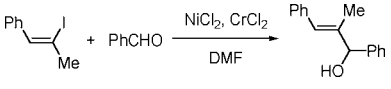
(10) Starting from achiral hydroxy ketone **16**, we synthesized racemic **19** that was used for the control experiments on chiral HPLC analysis.

(11) For reviews of the chemistry of *N*-acyliminium ions, see: (a) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367. (b) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817. (c) For an example of intramolecular cyclization through an acyliminium ion, see: Henegouwen, W. G. B.; Fieseler, R. M.; Rutjes, F. P. J. T.; Hiemstra, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2214. (d) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2005**, *127*, 1473. (e) Nielsen, T. E.; Meldal, M. *Org. Lett.* **2005**, *7*, 2695.

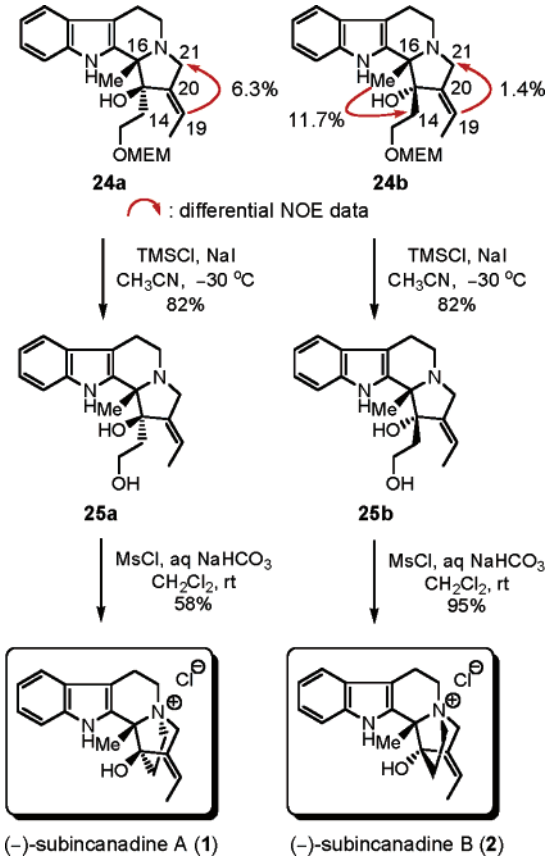
(12) Takayama, H.; Watanabe, F.; Kitajima, M.; Aimi, N. *Tetrahedron Lett.* **1997**, *38*, 5307.

(13) More, J. D.; Finney, N. S. *Org. Lett.* **2002**, *4*, 3001.

(14) Isomerization of the geometry in trisubstituted alkenyl halide in an intermolecular Nozaki−Hiyama−Kishi reaction was reported. See ref 4b.



Scheme 4



mesylated under conventional conditions to furnish spontaneously a pentacyclic quaternary ammonium compound. The product was completely identical to natural **1** in all respects including the optical property: synthetic, $[\alpha]^{25}_{D}$ −10° (*c* 0.34, MeOH); natural, $[\alpha]^{23}_{D}$ −11° (*c* 1.0, MeOH).[1a] The spectroscopic data of the pentacyclic compound prepared from **25b** were also identical to those of subincanadine B (**2**) except for the optical rotation: synthetic, $[\alpha]^{25}_{D}$ −43° (*c* 0.35, MeOH); natural, $[\alpha]^{23}_{D}$ +41° (*c* 1.0, MeOH).[1a] Therefore, the synthetic compound corresponds to the enantiomer of natural subincanadine B (**2**).

In conclusion, we achieved the first concise asymmetric total syntheses of (−)-subincanadine A (16 steps, 2.7% overall yield) and the *ent* form of natural subincanadine B (16 steps, 6.8% overall yield), using (*S*)-malic acid as the starting material. The syntheses involve an intramolecular diastereoselective Pictet−Spengler cyclization and an intramolecular Nozaki−Hiyama−Kishi reaction as key steps, and the absolute configuration of the natural products was demonstrated.

Acknowledgment. This work was partly supported by Uehara Memorial Foundation.

Supporting Information Available: Experimental procedures and copies of ^{1}H and ^{13}C NMR spectral data for compounds **12b**, **16**, **18**−**25**, and synthetic (−)-subincanadines A and B (**1** and *ent*-**2**). This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) Nicolaou, K. C.; Yue, E. W.; LaGreca, S.; Nadin, A.; Yang, Z.; Leresche, J. E.; Tsuri, T.; Naniwa, Y.; DeRiccardis, F. *Chem.−Eur. J.* **1995**, *1*, 467.