Concise and Enantioselective Total Synthesis of (-)-Mehranine, (-)-Methylenebismehranine, and Related Aspidosperma Alkaloids

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Movassaghi, M. *et al.*
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Movassaghi, M
From MIT

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- **Double-Cyclization Strategy in 2012**
- **Transannular-Cyclization Strategy in 2014**
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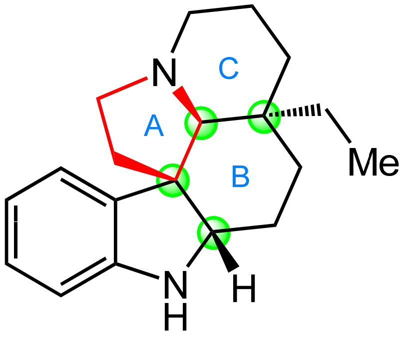
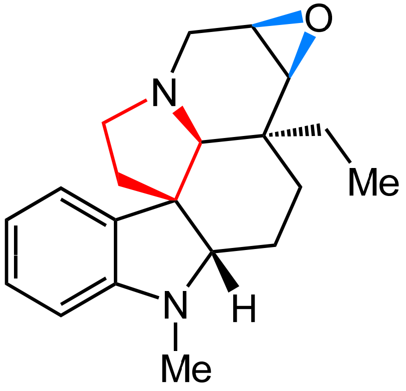
Introduction



(-)-**1**

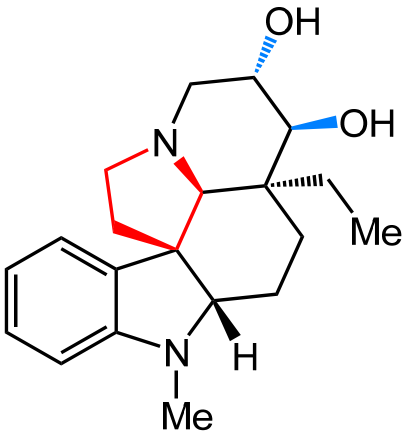
白坚木



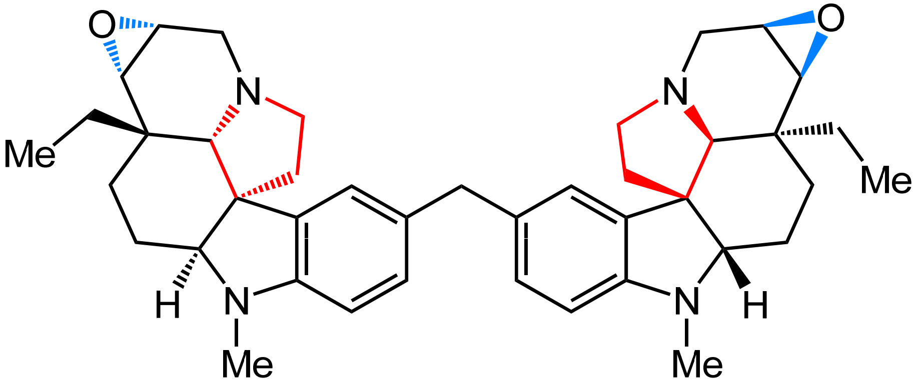
(-)-**2**

马蹄花

Introduction



(+)-**3**

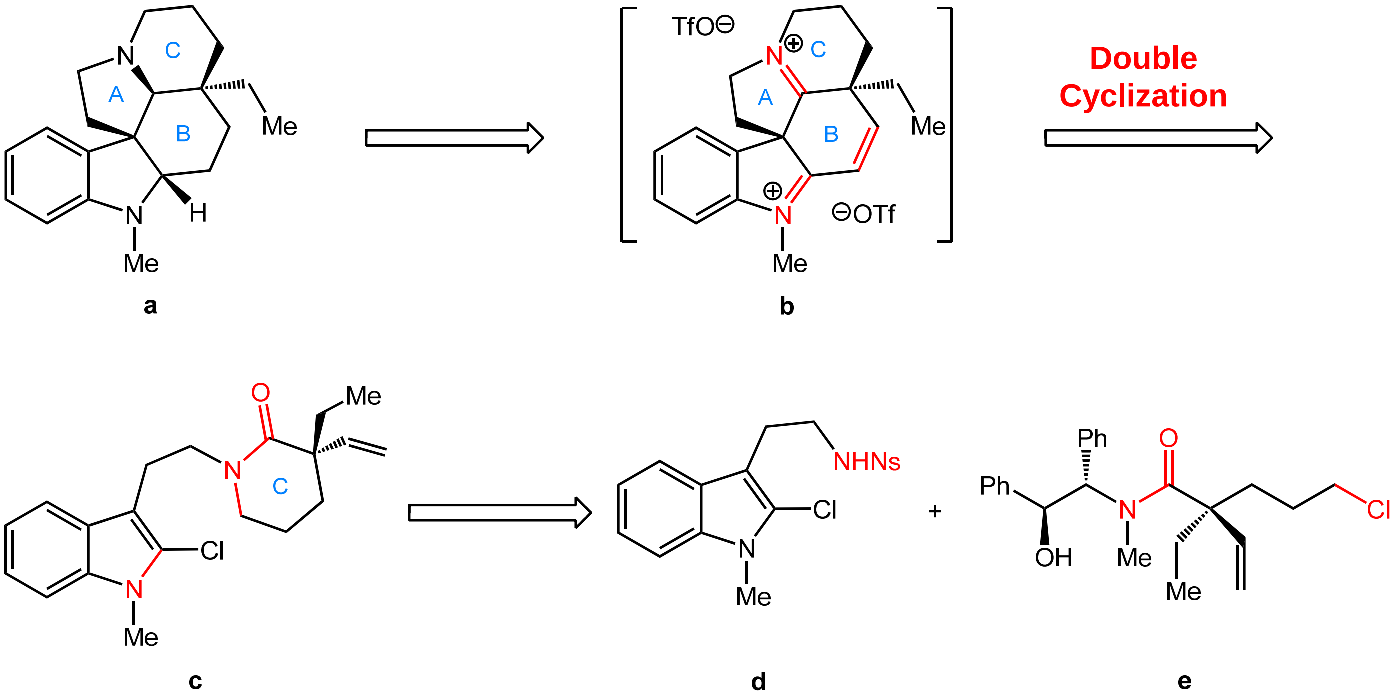


(-)-**4**

狗牙花

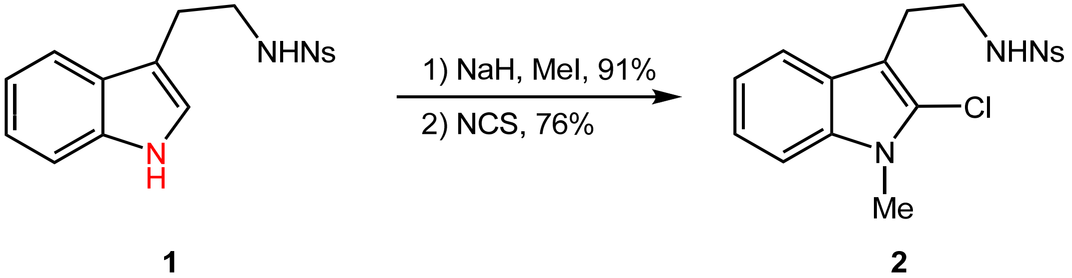
Double-Cyclization Strategy in 2012

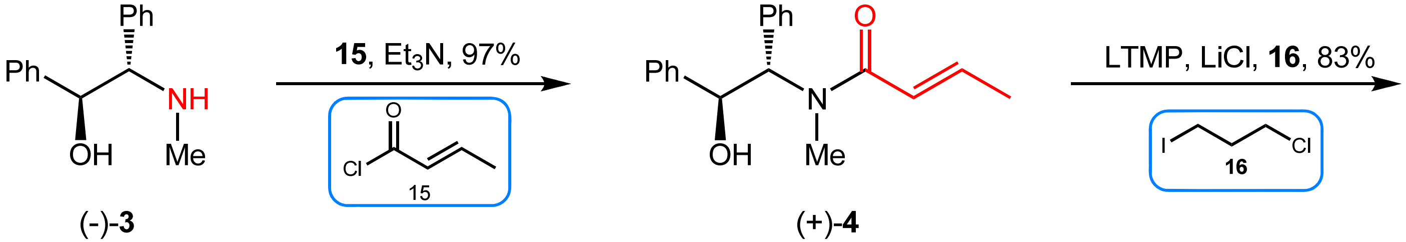
Retrosynthetic Analysis:

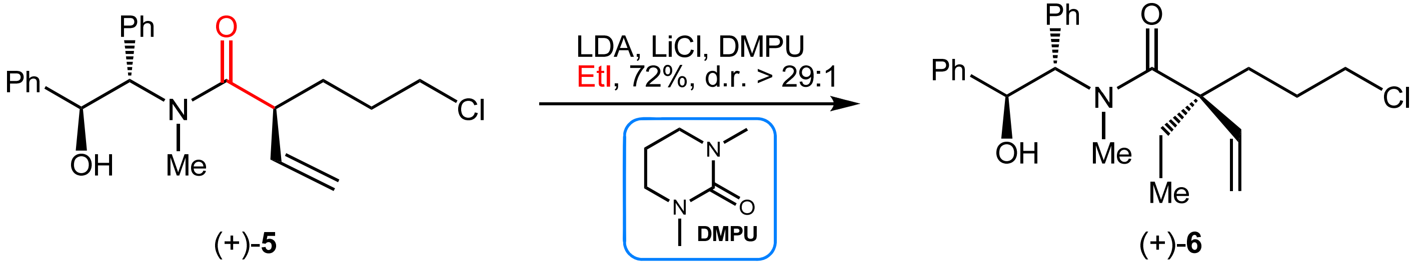


Movassaghi, M. *et al*. *Angew. Chem. Int. Ed.* **2012**, *51*, 4572.

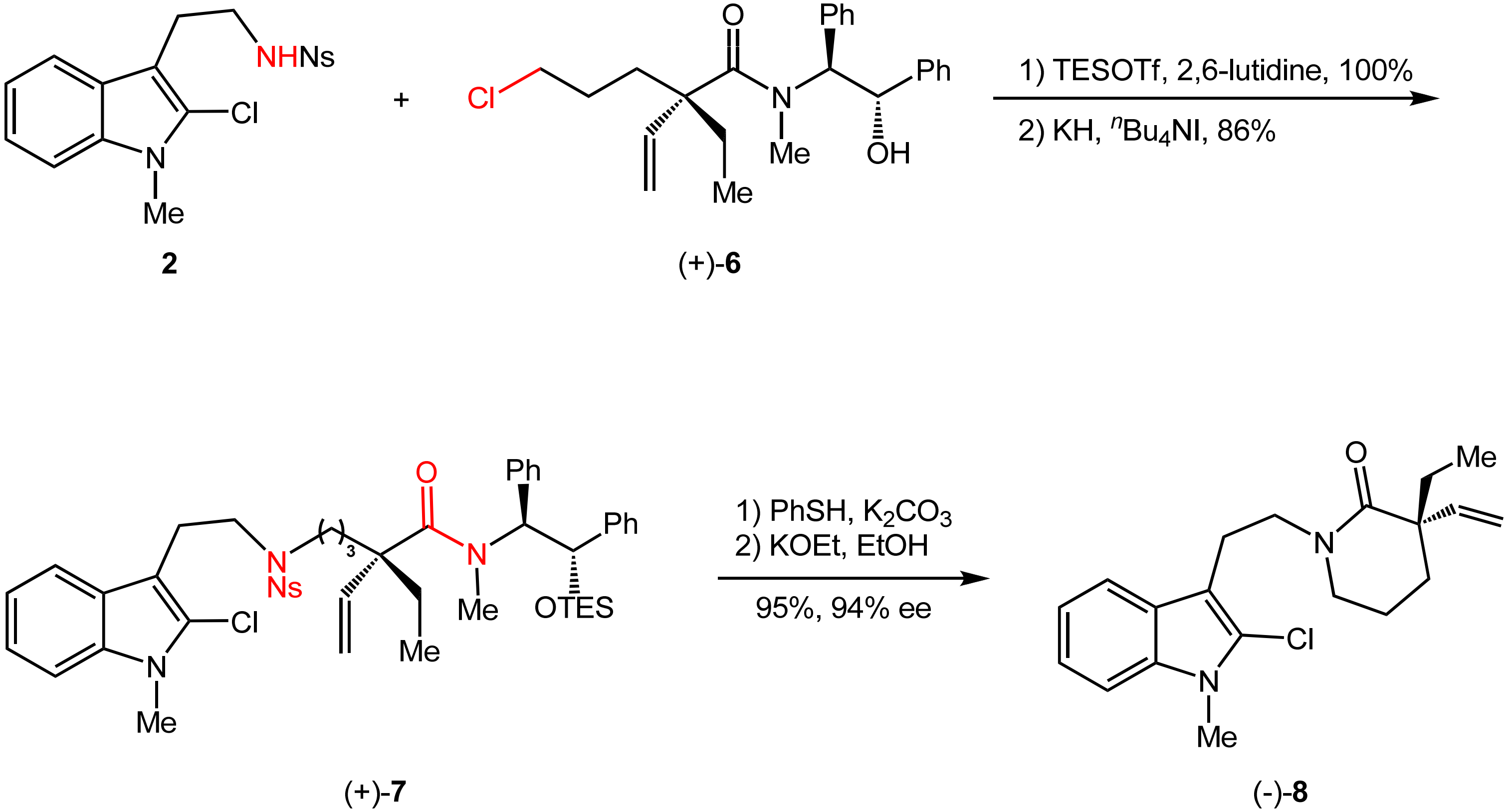
Synthesis of Tryptamine Lactam







Synthesis of Tryptamine Lactam



1) TESOTf, 2,6-lutidine, 100%

2) KH, $^{n}Bu_4NI$, 86%

2 + (+)-**6**

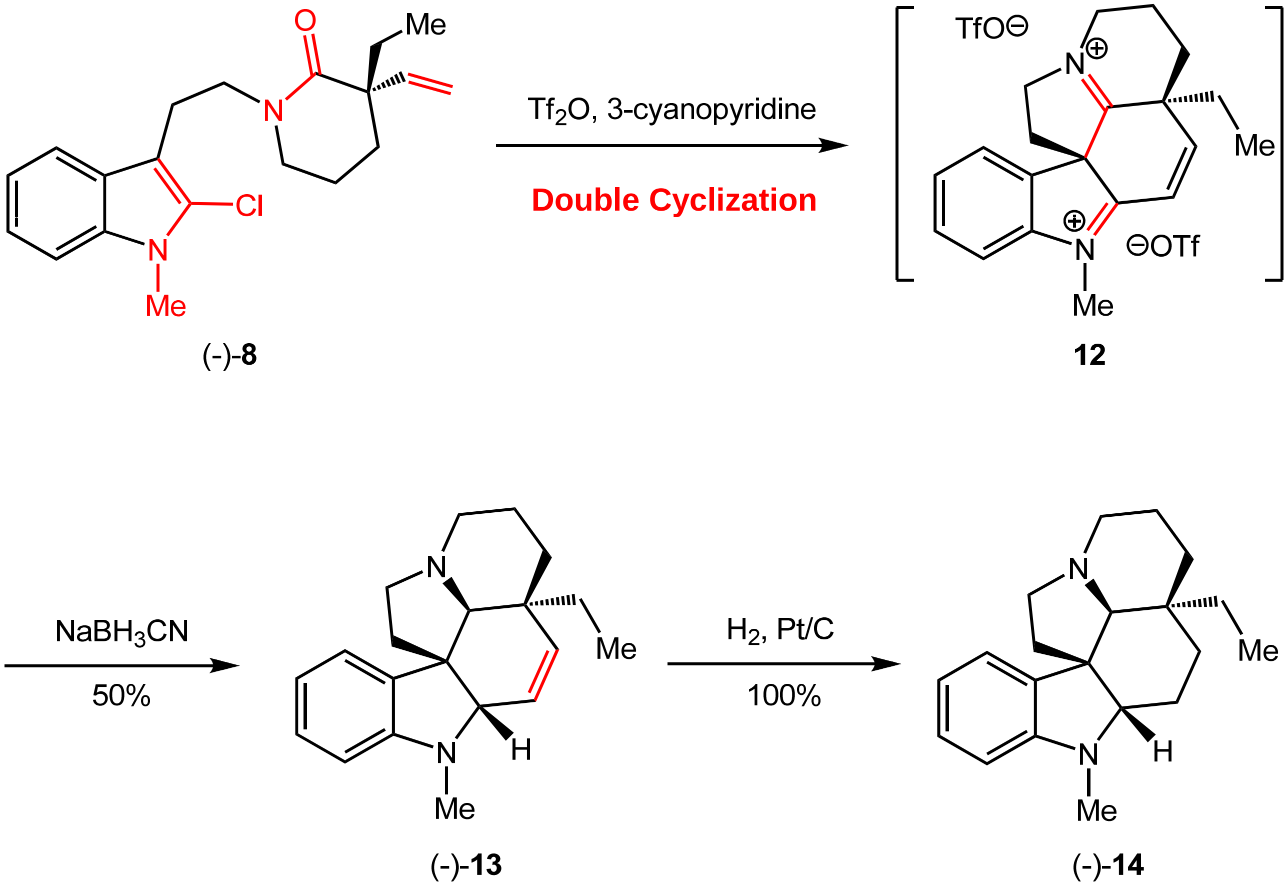
1) PhSH, K_2CO_3

2) KOEt, EtOH

95%, 94% ee

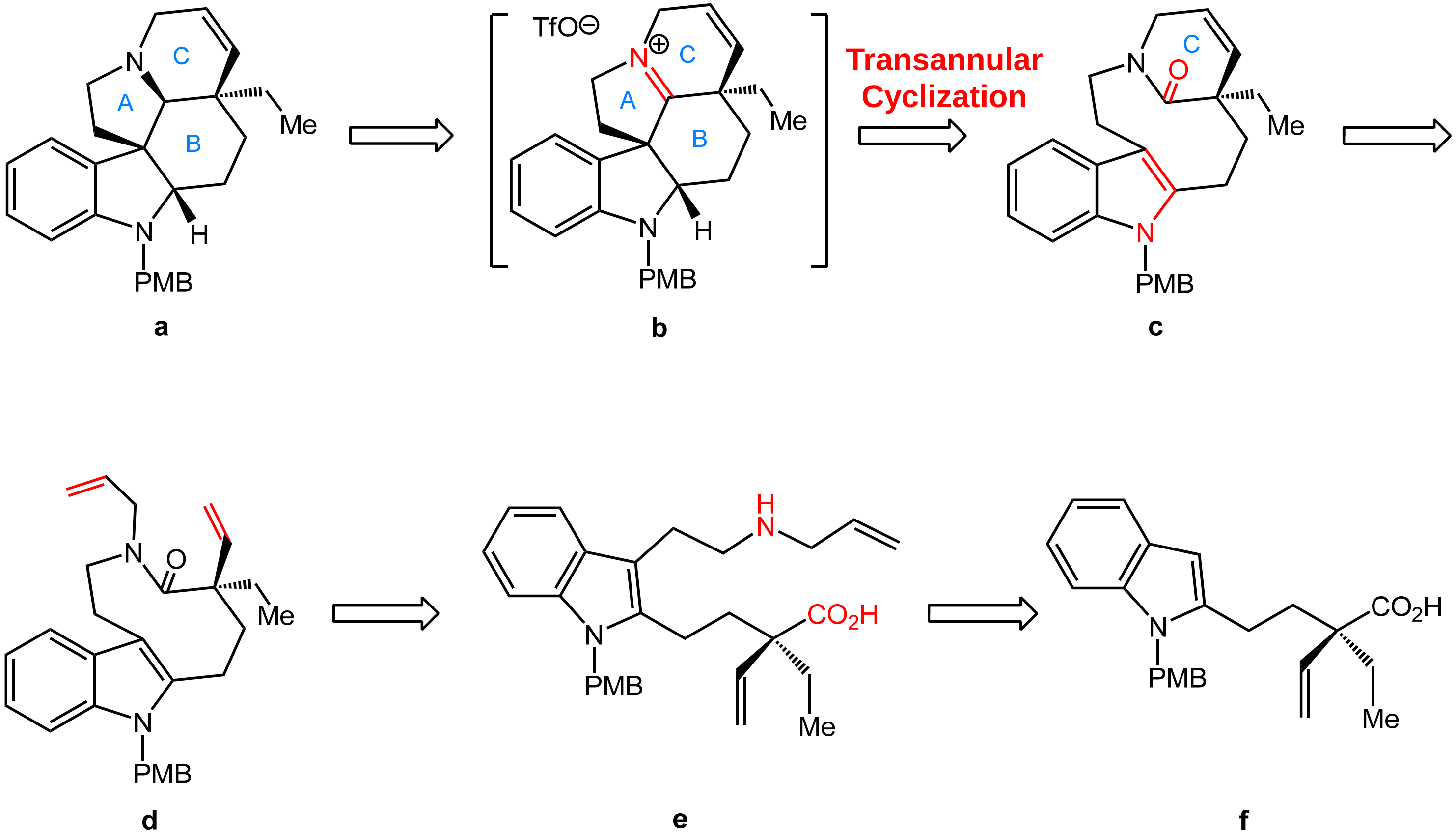
(+)-**7** → (-)-**8**

Synthesis of Aspidosperma Alkaloid



Transannular-Cyclization Strategy In 2014

Retrosynthetic Analysis:



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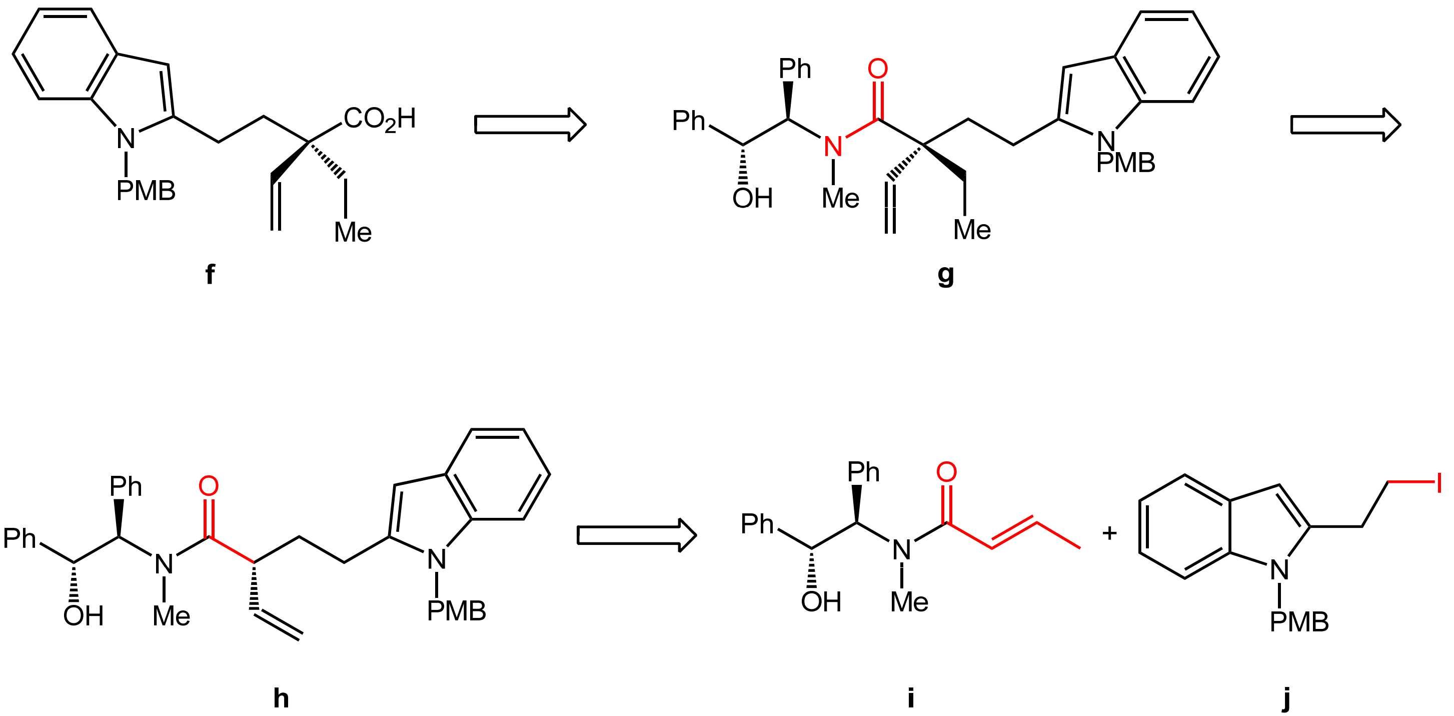
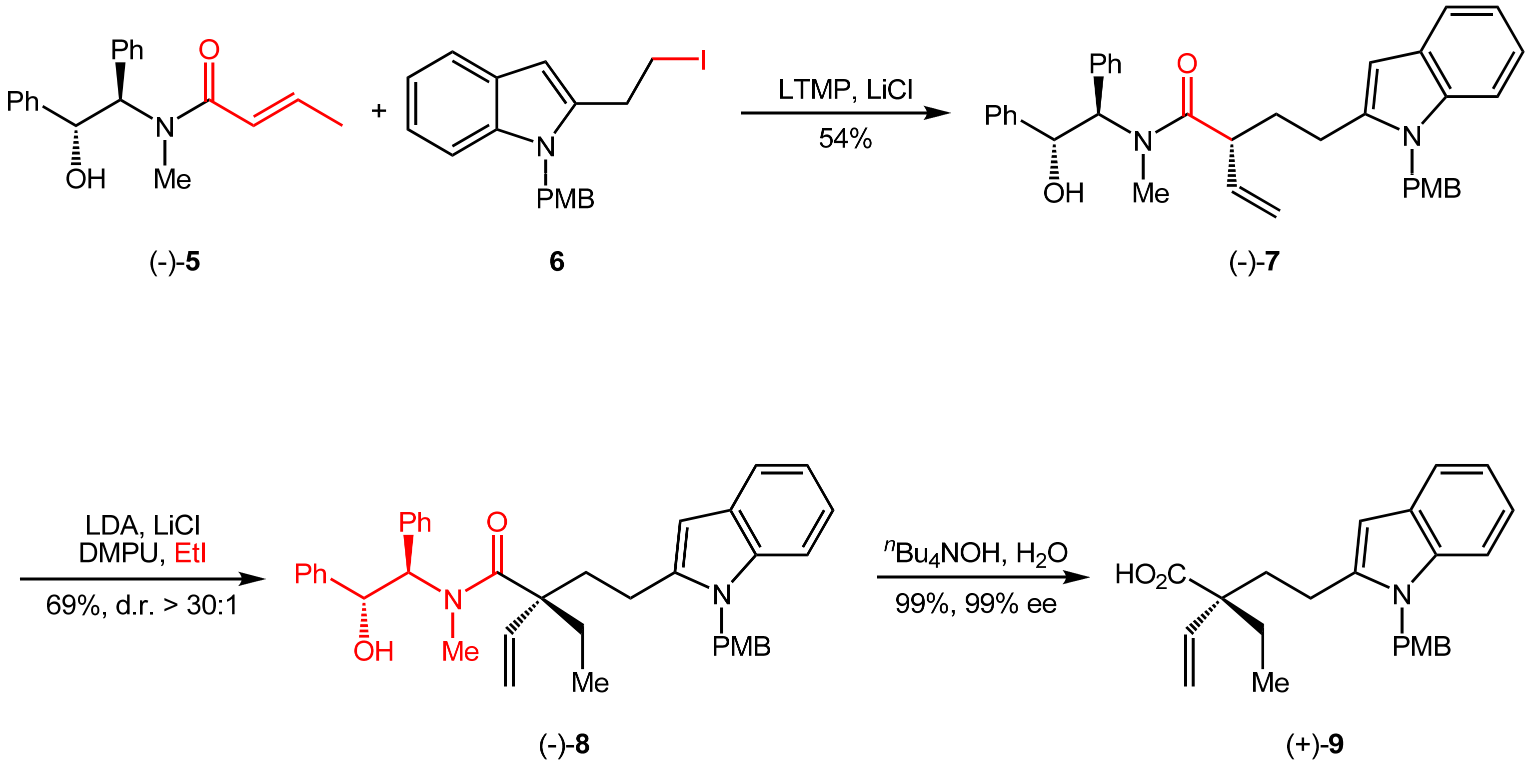
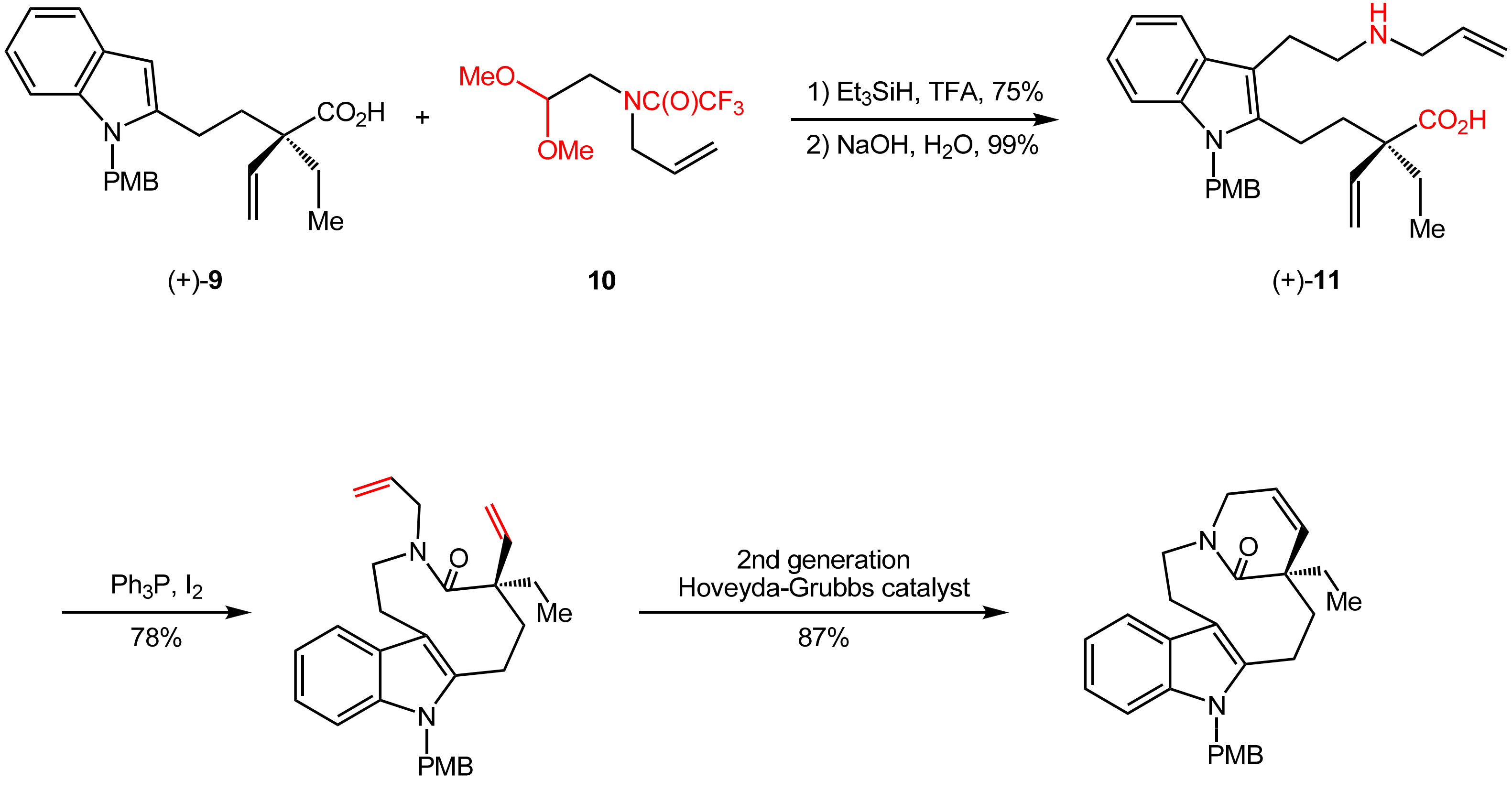
Transannular-Cyclization Strategy In 2014



Synthesis of Cyclization Precursor



Synthesis of Cyclization Precursor



(+)-**9**

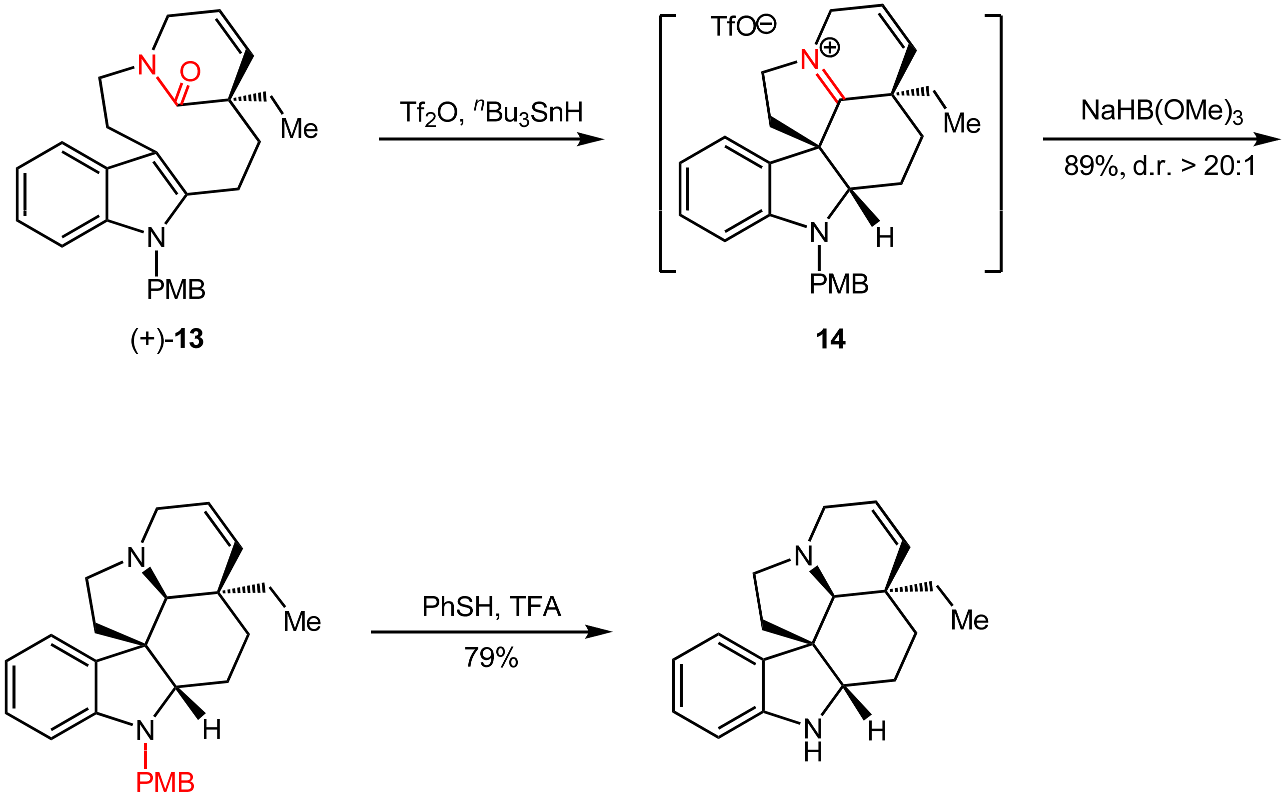
10

(+)-**11**

(+)-**12**

(+)-**13**

Synthesis of Aspidosperma Alkaloid



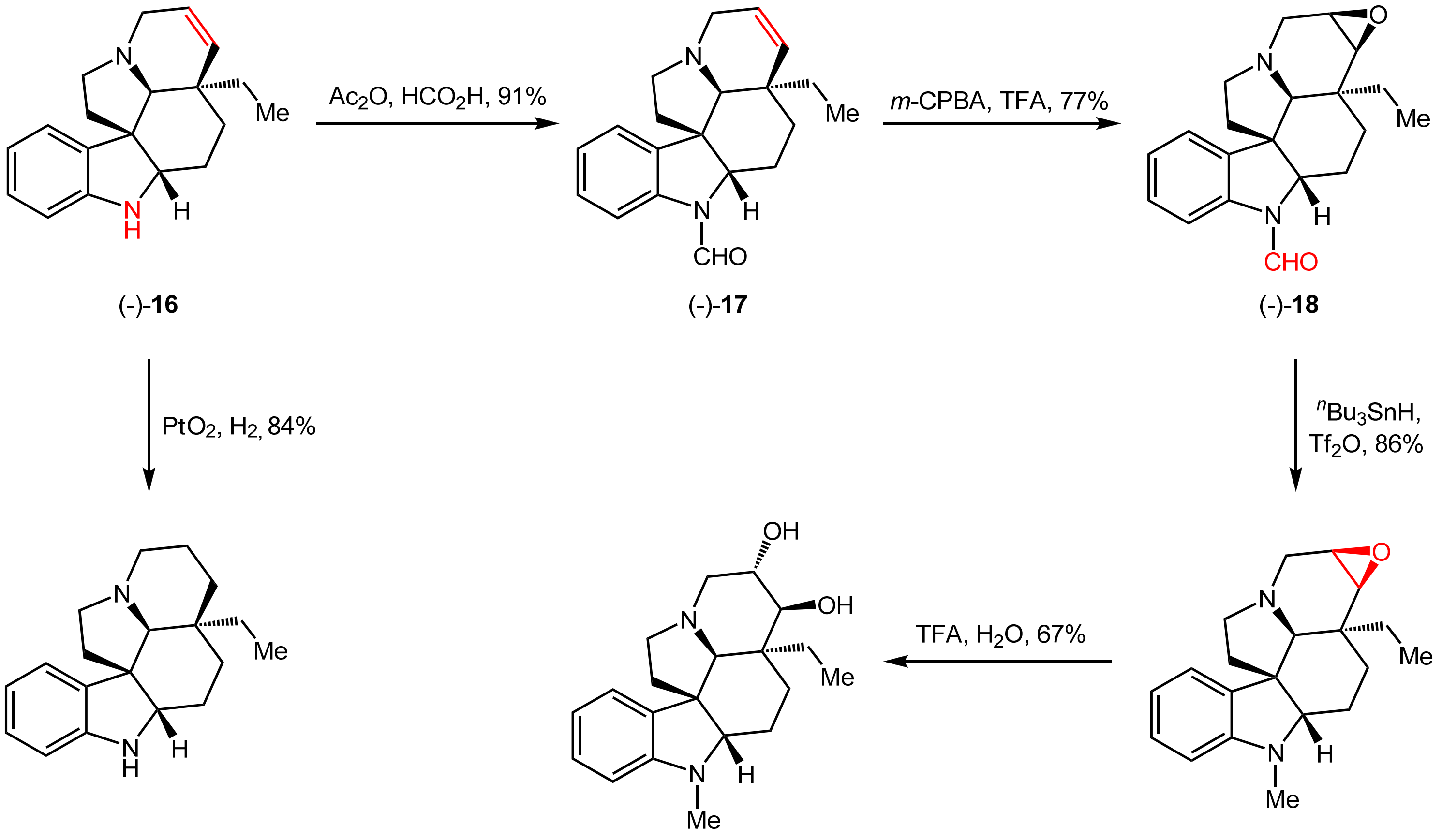
(+)-**13**

14

(+)-**15**

(-)-**16**

Synthesis of Aspidosperma Alkaloid



(-)-**16**

(-)-**17**

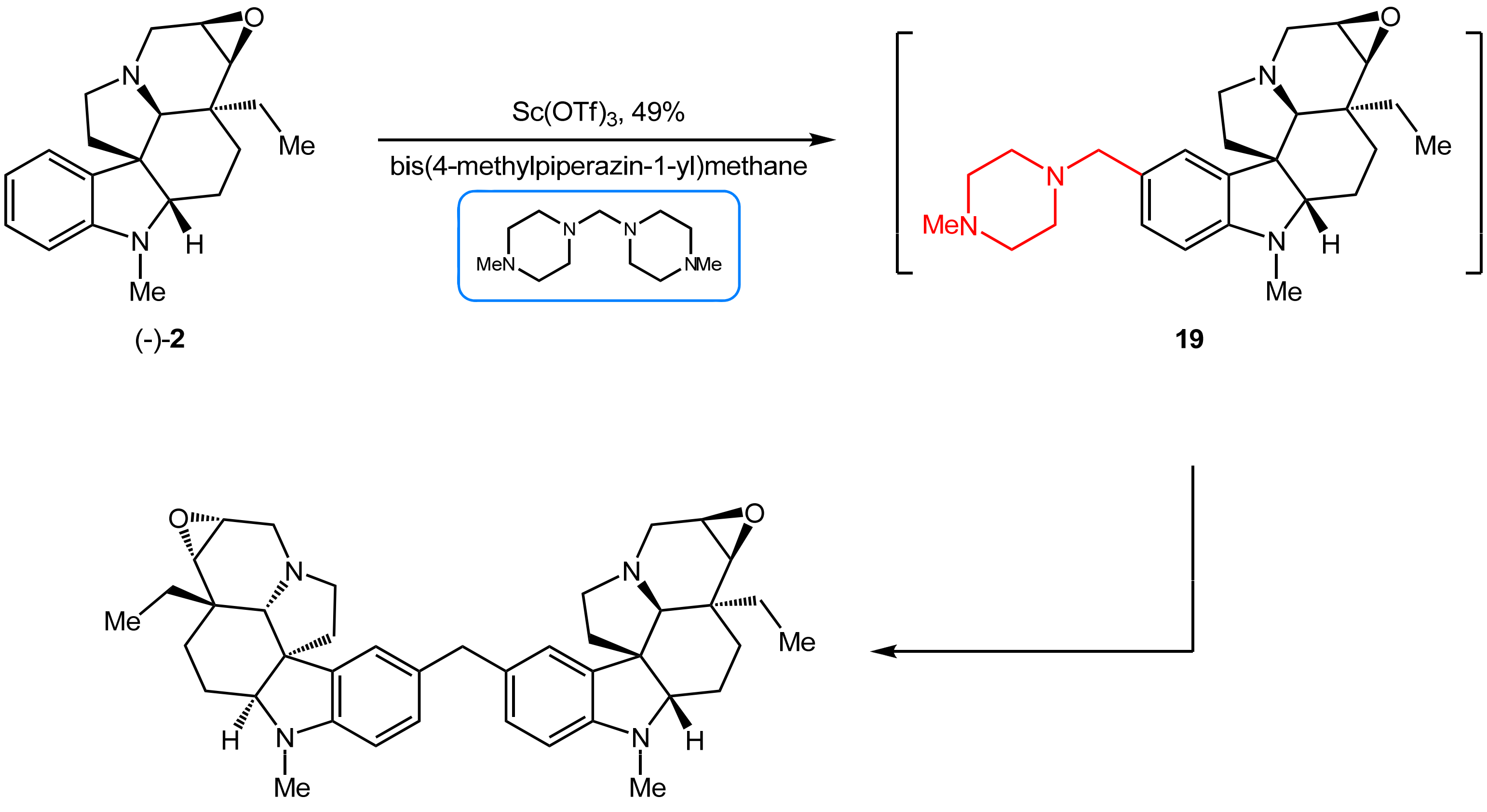
(-)-**18**

(-)-**1**

(+)-**3**

(-)-**2**

Synthesis of Aspidosperma Alkaloid



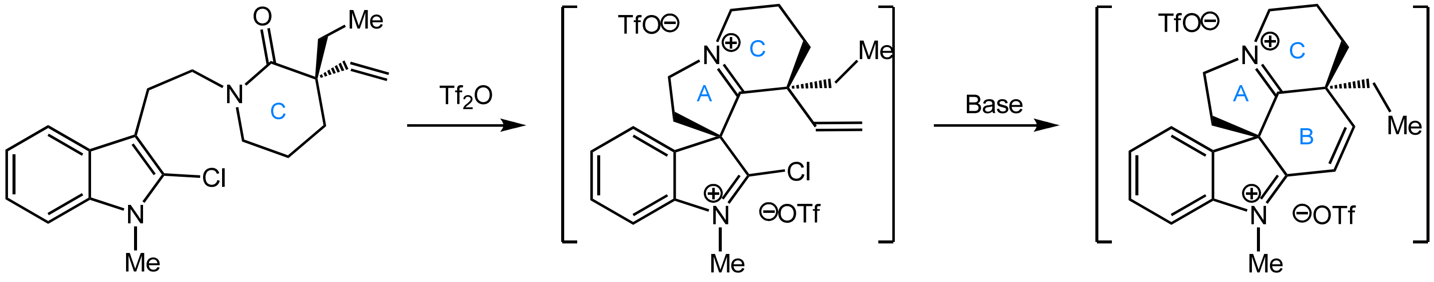
(-)-**2**

19

(-)-**4**

Summary

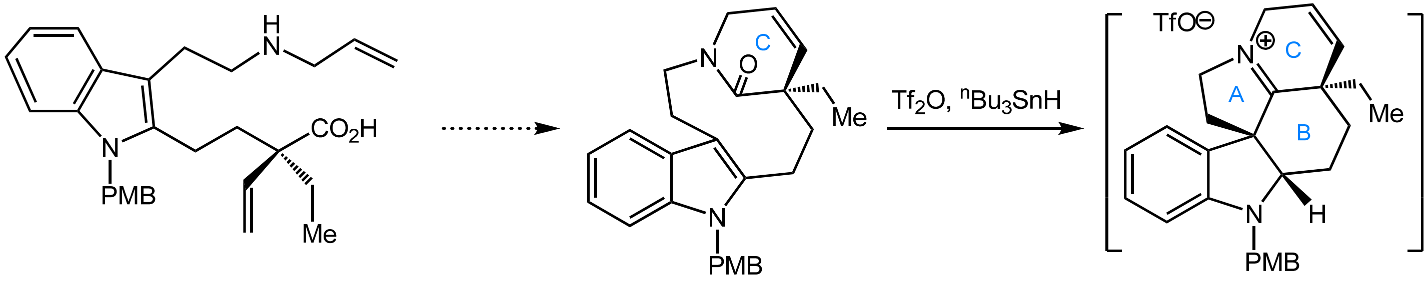
Double-Cyclization Strategy



(-)-**8** **11** **12**

9 steps linear sequence, 24% yield

Transannular-Cyclization Strategy



(+)-**11** (+)-**13** **14**

11 steps linear sequence, 11% yield

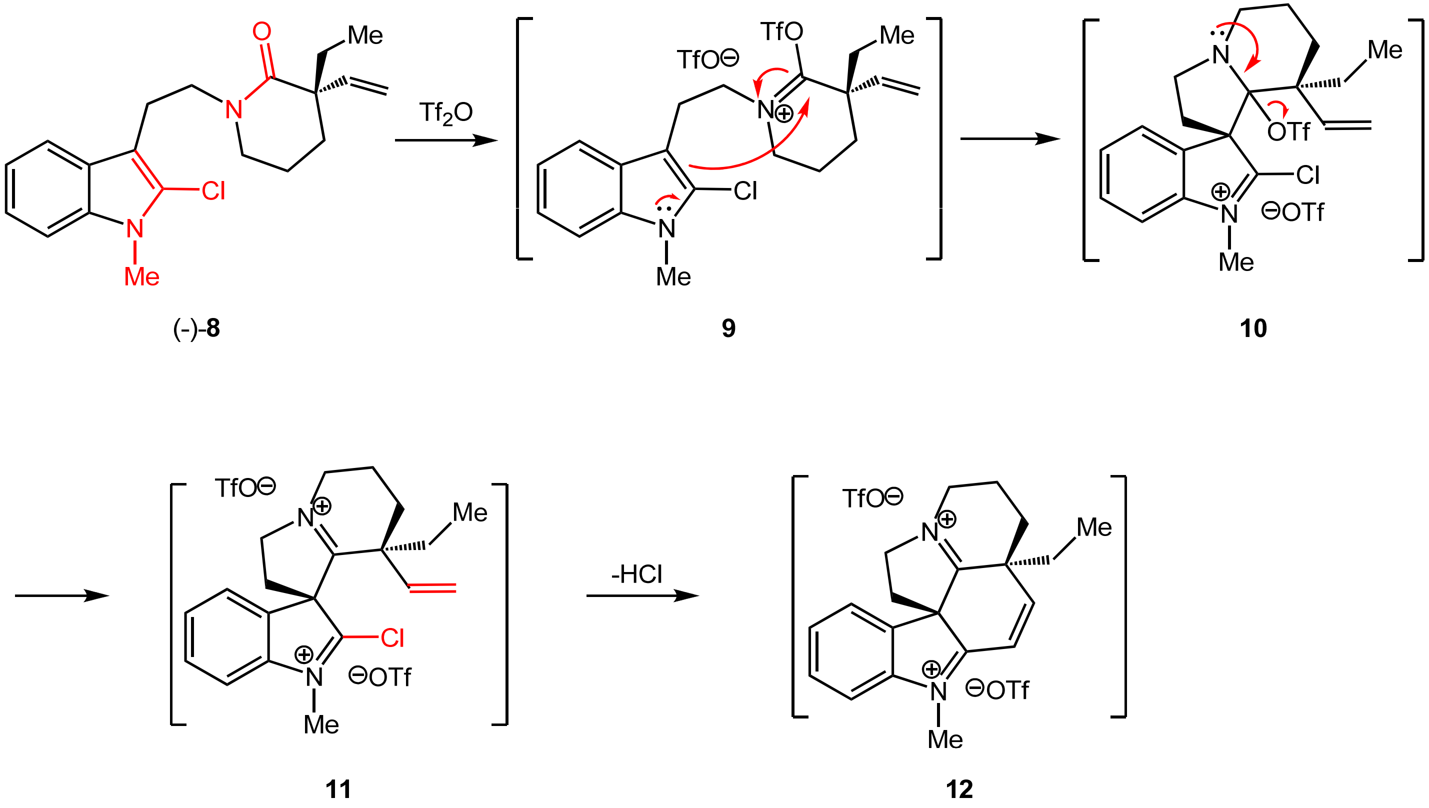
The Aspidosperma alkaloids are a subset of the monoterpene indole alkaloids with great structural diversity in their characteristic pentacyclic skeleton which contains at least four consecutive stereogenic centers. In addition to (-)-aspidospermidine (**1**), the archetype of this family of natural products with only the unfunctionalized pentacyclic core structure, several members with oxidation at C6 and C7 positions are known. (-)-Mehranine (**2**) was first isolated from Tabernaemontana divaricata in 1995, but it was also found in Tabernaemontana bovina together with its hydrated congener (+)-(6*S*,7*S*)-dihydroxy-*N*-methylaspidospermidine (**3**) in 1998. Moreover, the intriguing (-)-mehranine-derived dimers (-)-methylenebismehranine (**4**) and (+)-tabernaebovine (**5**) were also isolated from Tabernaemontana bovina; they possess connectivities through a methylene bridge at both C15 atoms and a direct C2–C15’ bond between two (-)-mehranine monomers, respectively.

While aspidospermidine (**1**) has served as a classic target for the application of new synthetic methodologies, no total syntheses of the oxidized monomers (-)-**2** and (+)-**3** or the dimers (-)-**4** and (+)-**5** have been reported to date. Herein, we present the first total synthesis of (-)-mehranine (**2**) and (-)-methylenebismehranine (**4**) as well as access to (+)-(6*S*,7*S*)-dihydroxy-*N*-methylaspidospermidine (**3**) and (-)-aspidospermidine (**1**) based on a highly diastereoselective transannular cyclization.

In summary, we have developed a highly enantio- and diastereoselective route to monomeric and dimeric Aspidosperma alkaloids with oxidation at the C6 and C7 positions, which allowed for the synthesis of four natural products. The key step is a transannular spirocyclization induced by the electrophilic activation of a nine-membered lactam, which afforded a 6,7-unsaturated pentacycle in high yield and with excellent level of diastereoselection. The resulting versatile intermediate (-)-6,7-didehydroaspidospermidine allowed for the synthesis of (-)-aspidospermidine (**1**) by simple hydrogenation and for the first total synthesis of (-)-mehranine (**2**) through the stereoselective epoxidation of the C6–C7 double bond.

Hydrolysis of the epoxide afforded (+)-(6*S*,7*S*)-dihydroxy-*N*-methyl-aspidospermidine (**3**) and a scandium trifluoromethane-sulfonate-mediated dimerization of (-)-mehranine (**2**) resulted in the first total synthesis of (-)-methylenebismehranine (**4**). While further development of the required new synthetic methodologies described here, including the mild reduction of formamide and advanced-stage dimerization of (-)-mehranine (**2**), forbroader application is ongoing, our highly efficient new synthetic strategy outlined above forms the basis of our approach to other members of this family of complex alkaloids.

Mechanism



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