Total Synthesis of (−)-Lepenine

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Fukuyama, T. *et al.*
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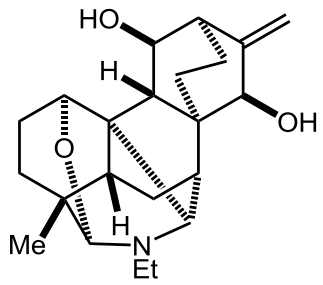
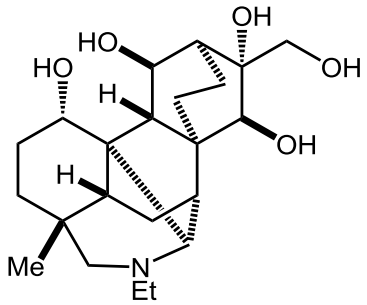
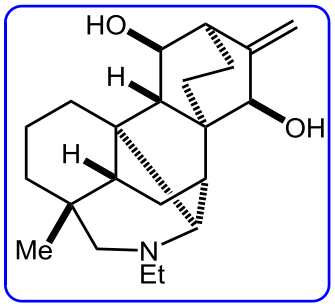
Introduction



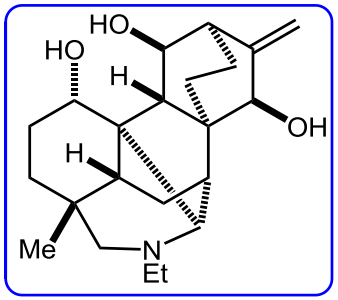
Kirinine (吉乌碱)



Aconicarmine
(光翠雀碱)



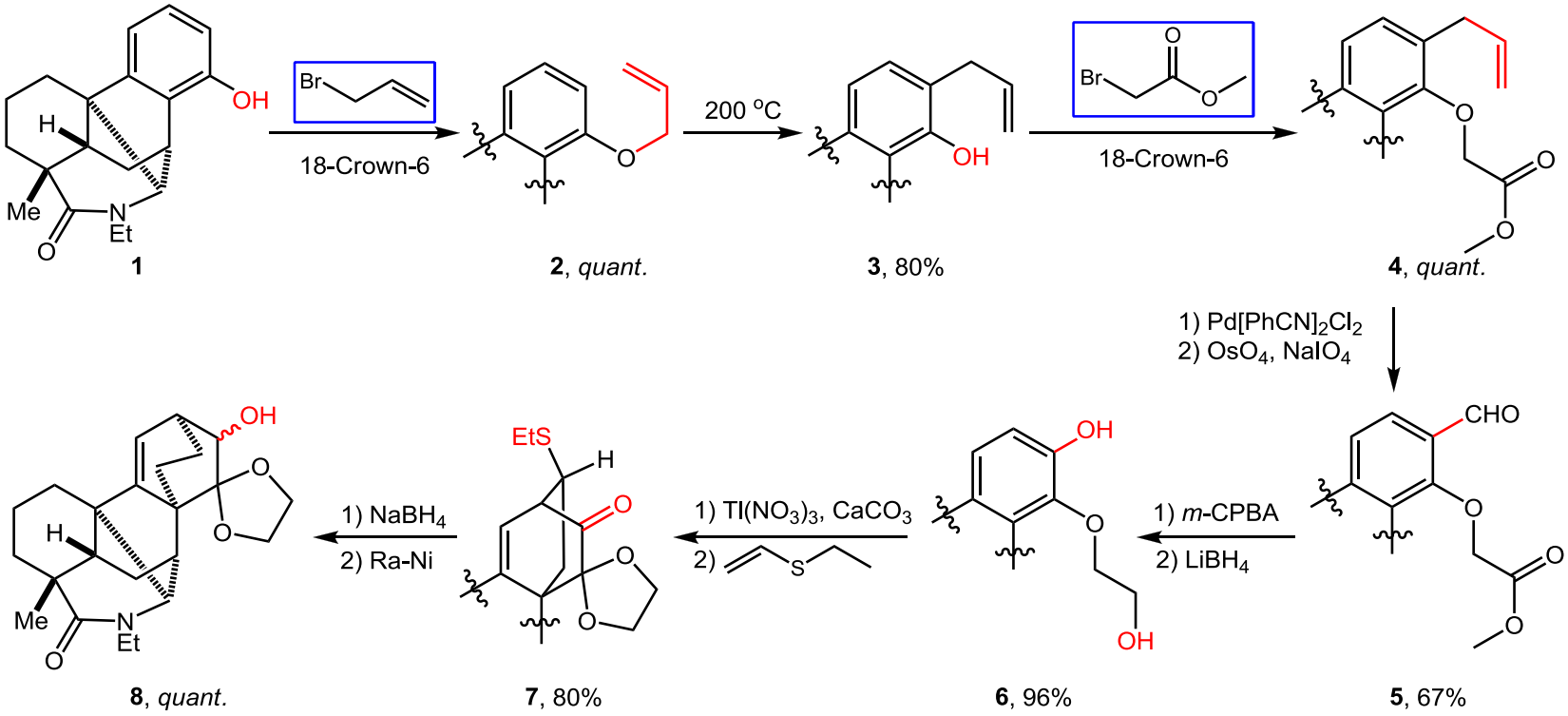
Denudatine
(无毛翠雀亭)



Lepenine
(雷波乌碱)

- an attractive and challenging hexacyclic system
- a polycyclic system containing a nitrogen atom
- tetradecahydrophenanthrene and bicyclo [2.2.2] skeleton

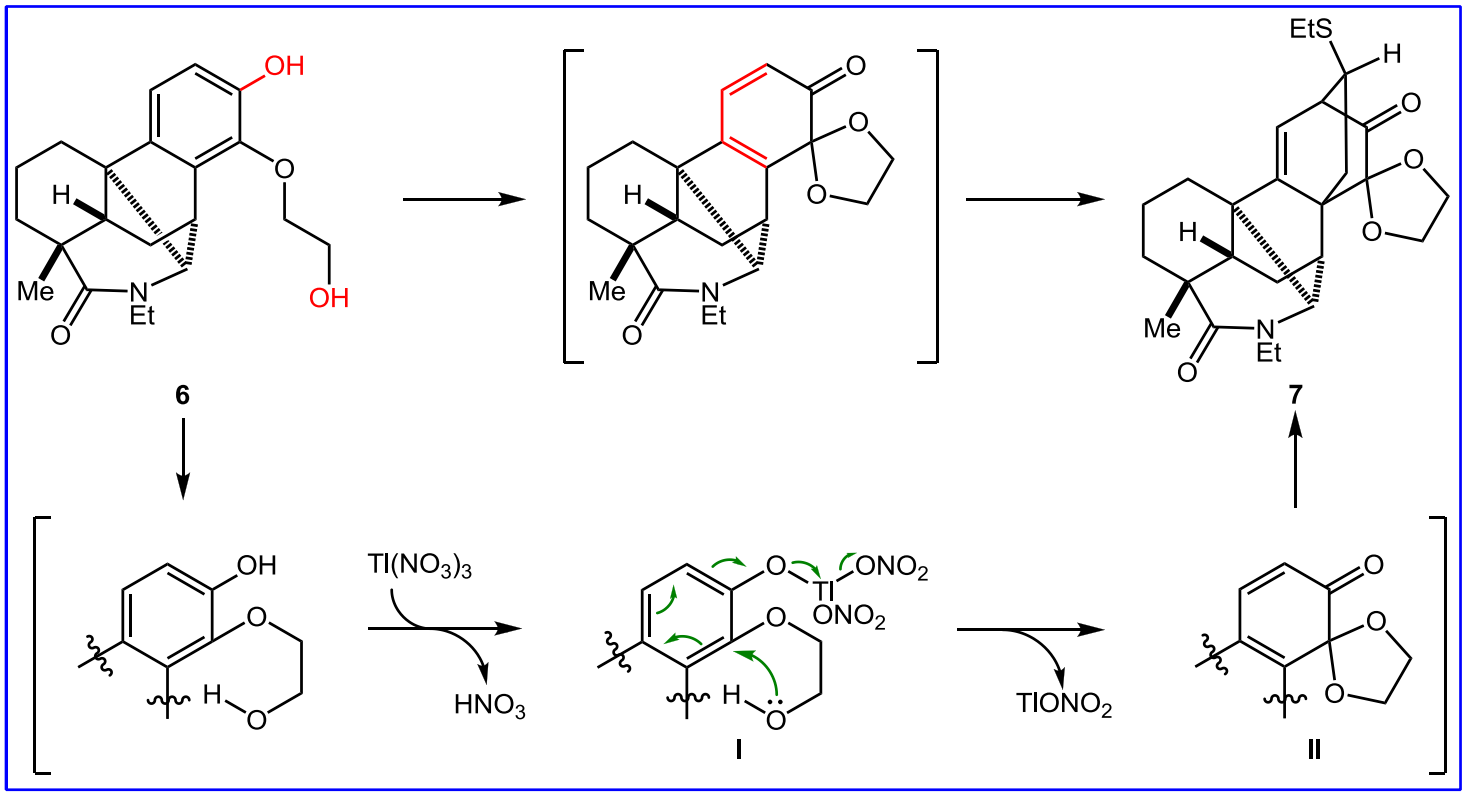
Synthesis of Racemic Diacetyloxodenudatine



Wiesner, K. *Heterocycles* **1980**, *14*, 23.

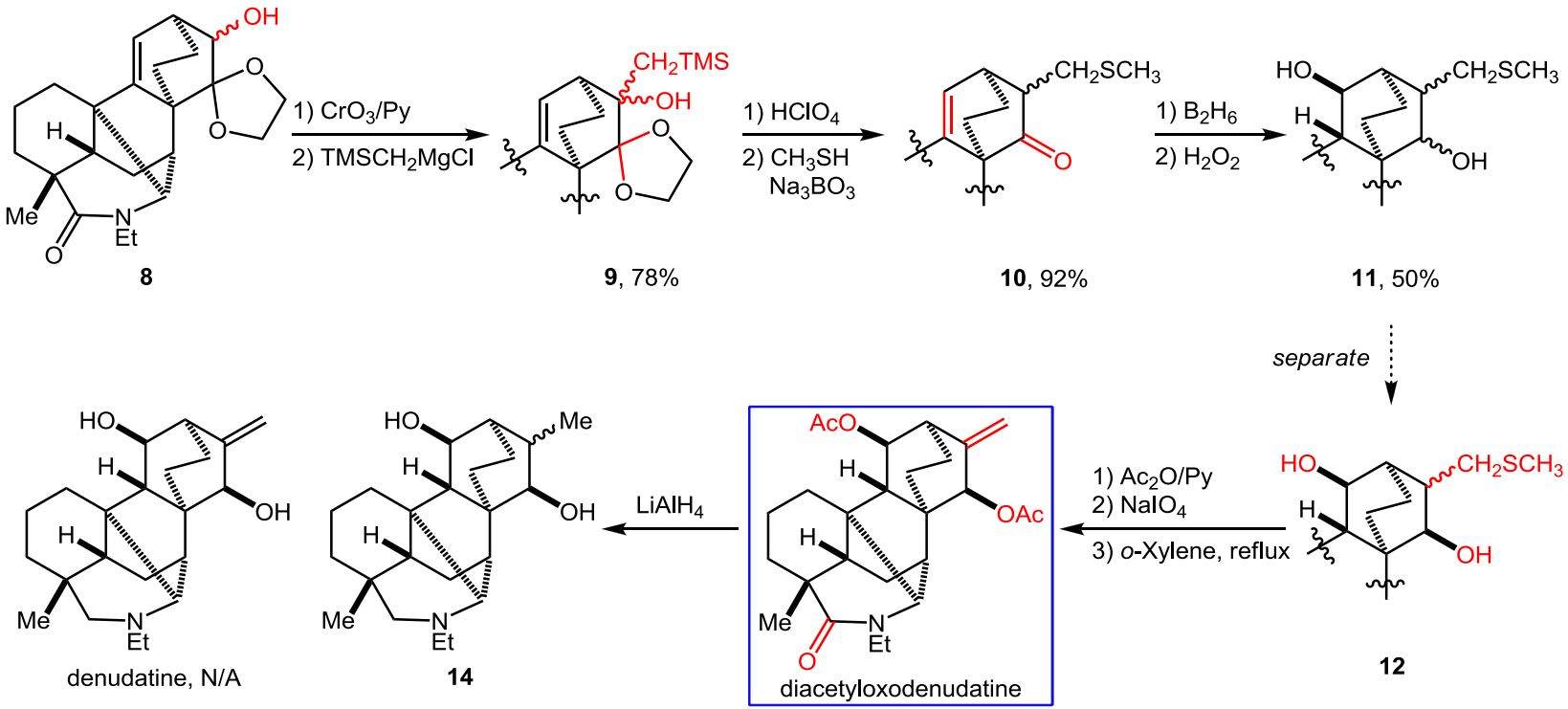
Synthesis of Racemic Diacetyloxodenudatine

Oxidation of Phenols to Quinone Using Thallium(III) Nitrate



McKillop, A. *J. Org. Chem.* **1976**, *41*, 282.

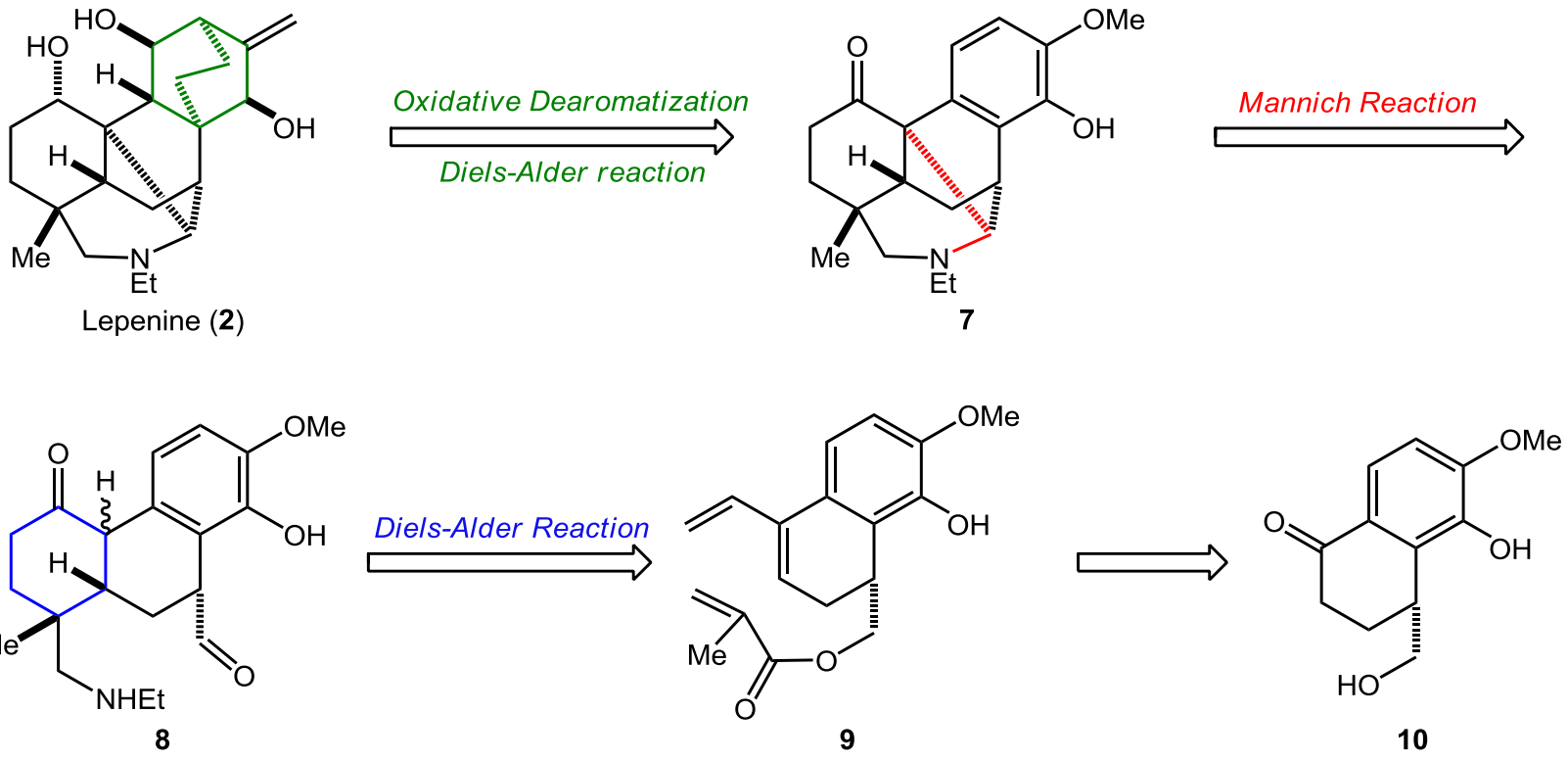
Synthesis of Racemic Diacetyloxodenudatine



Wiesner, K. *Heterocycles* **1980**, *14*, 23.

Total Synthesis of (−)-Lepenine

Retrosynthetic Analysis



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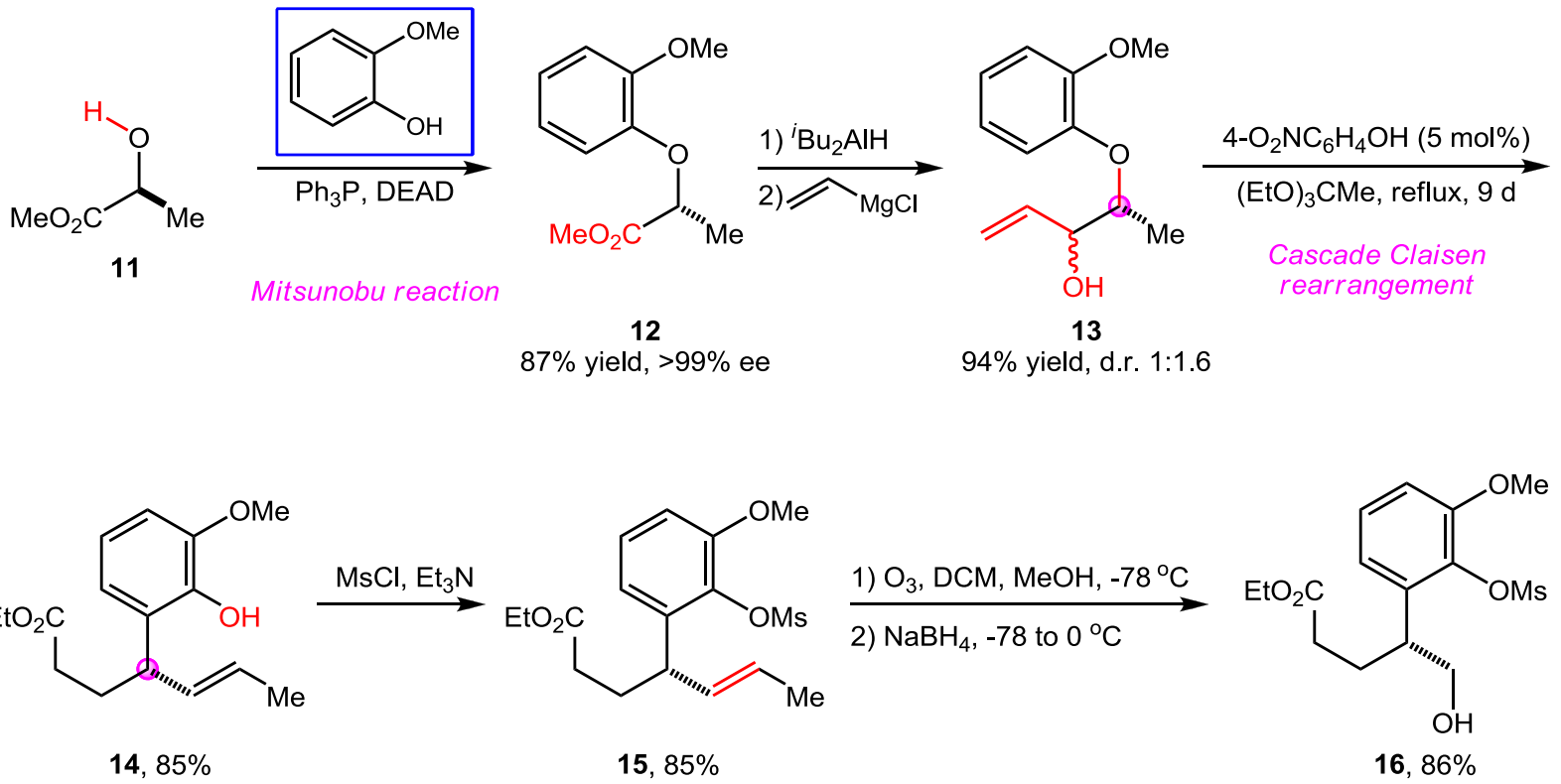
Construction of the Phenanthrene Skeleton



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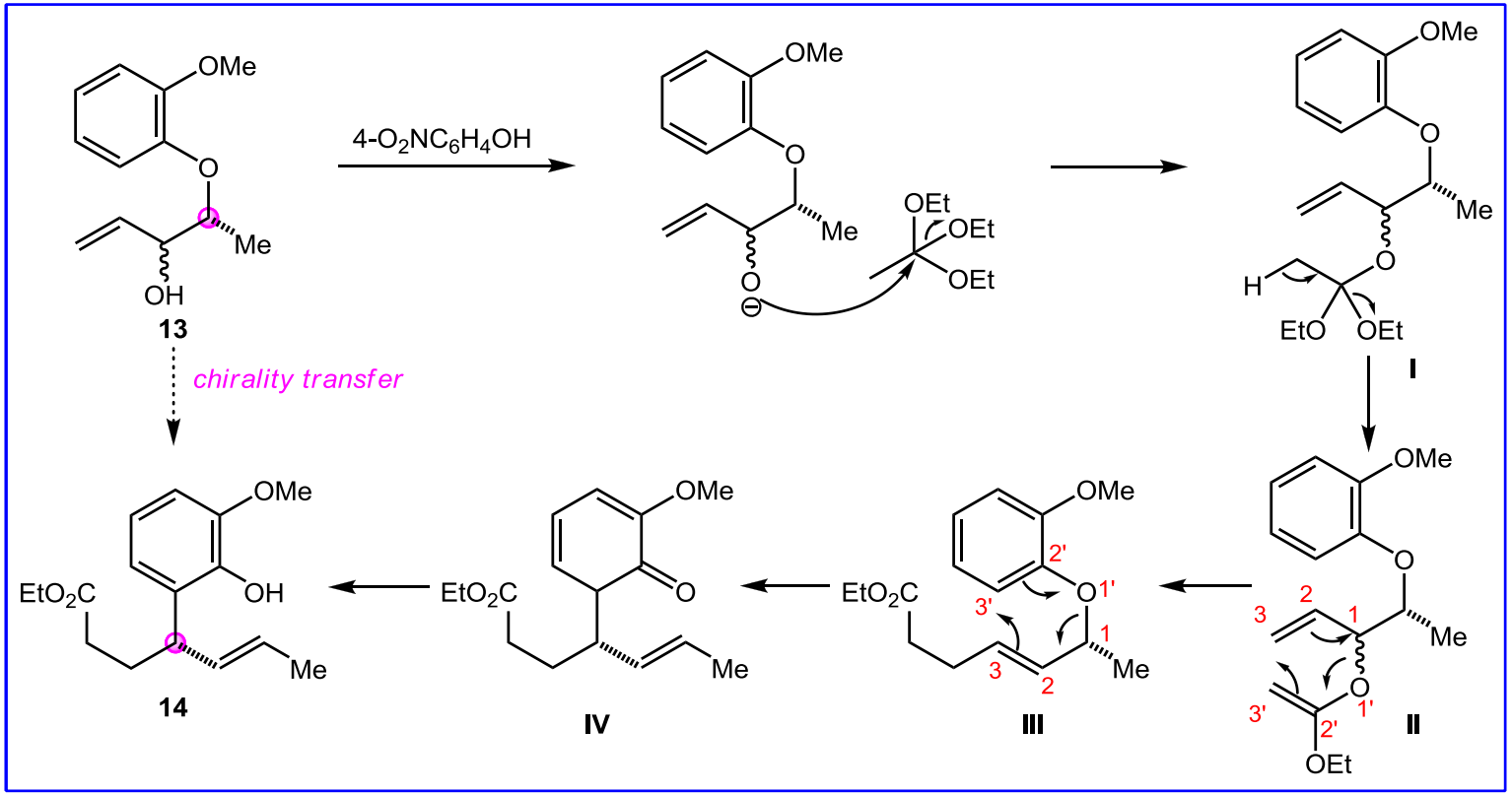
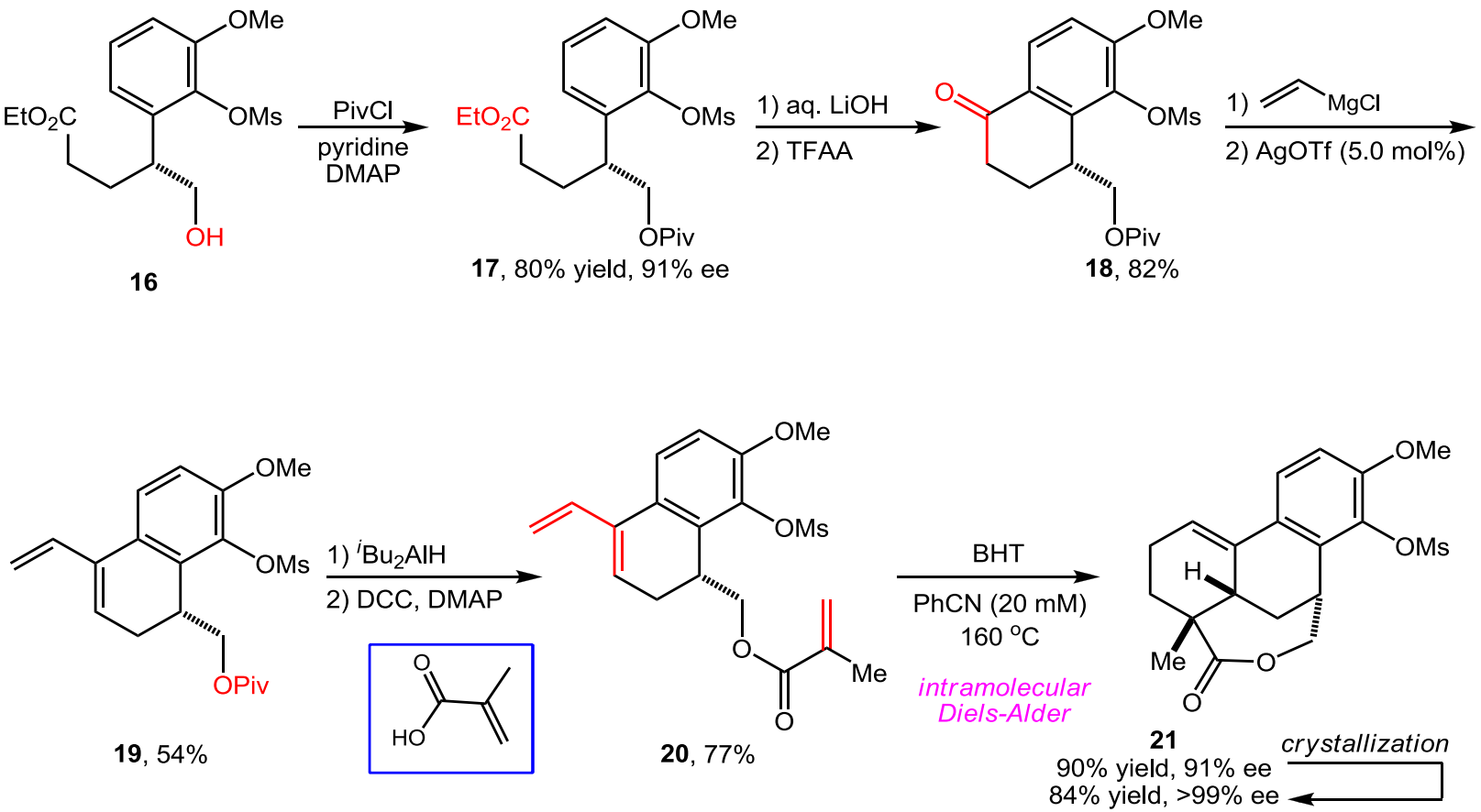
Construction of the Phenanthrene Skeleton

Cascade Claisen Rearrangement Reaction



Chida, N. *Tetrahedron Lett*. **2008**, *49*, 358.

Construction of the Phenanthrene Skeleton



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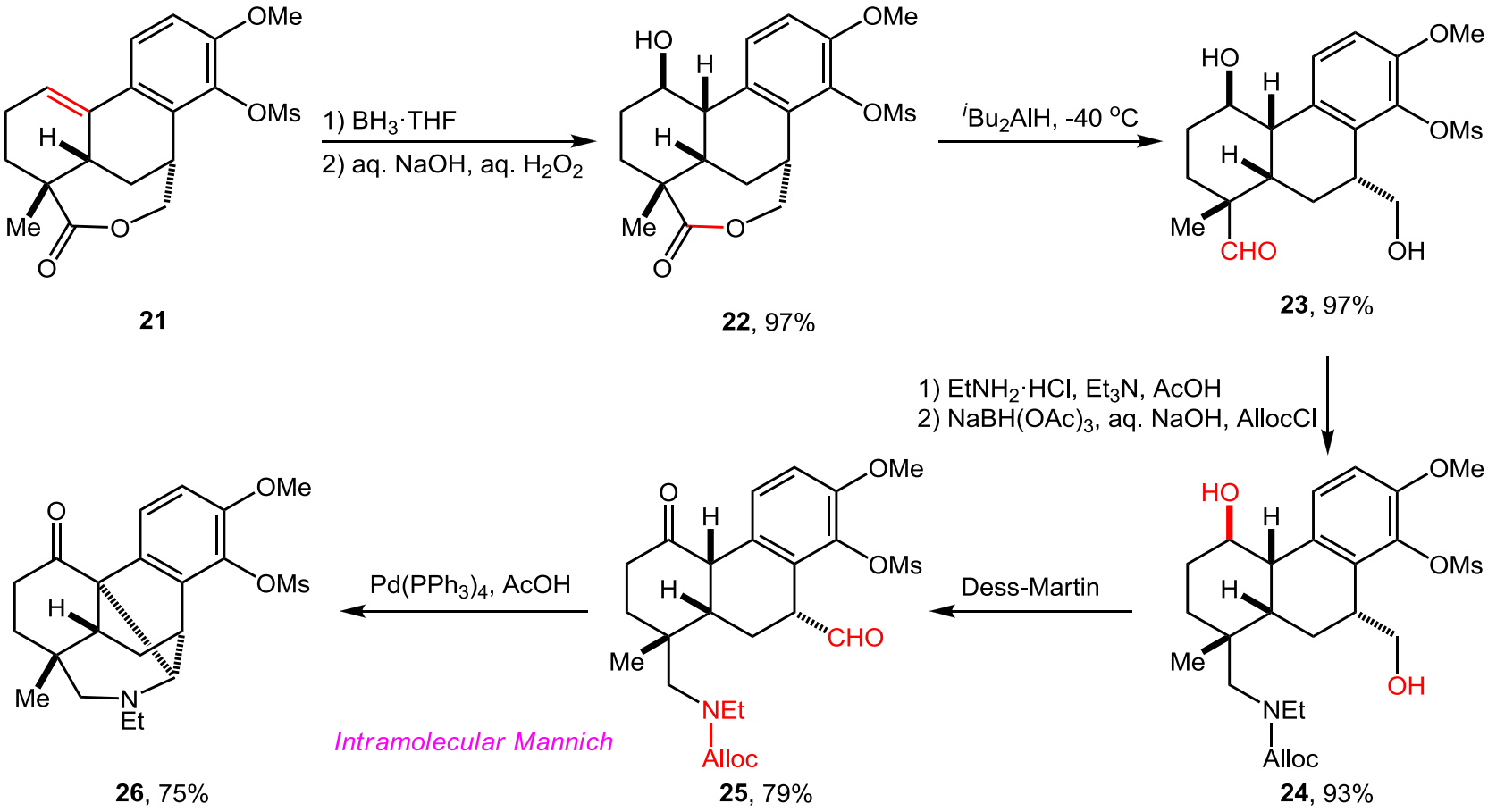
Intramolecular Mannich Reaction



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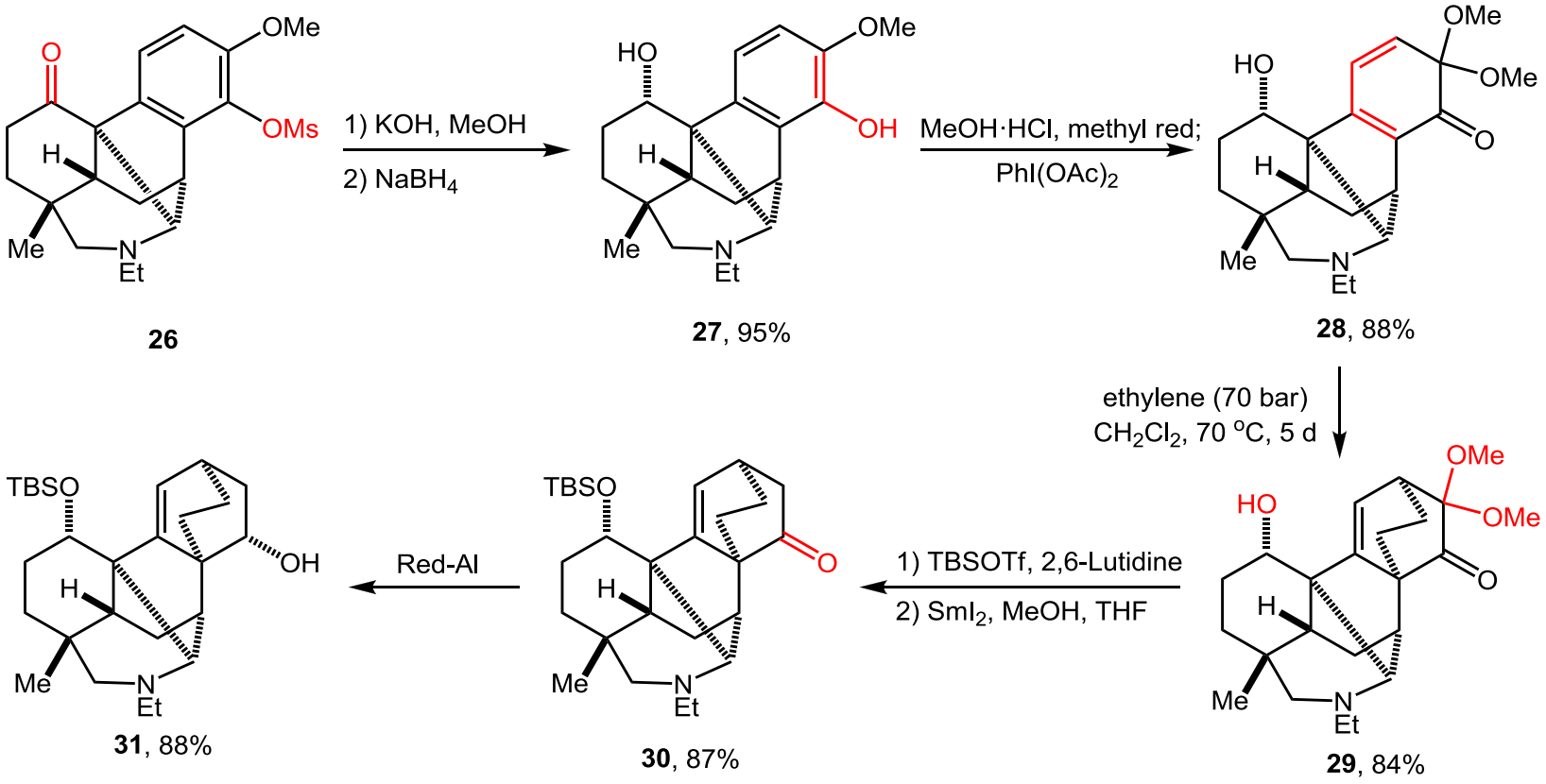
Construction of the Bicyclo [2.2.2] Skeleton



26

27, 95%

28, 88%

29, 84%

30, 87%

31, 88%

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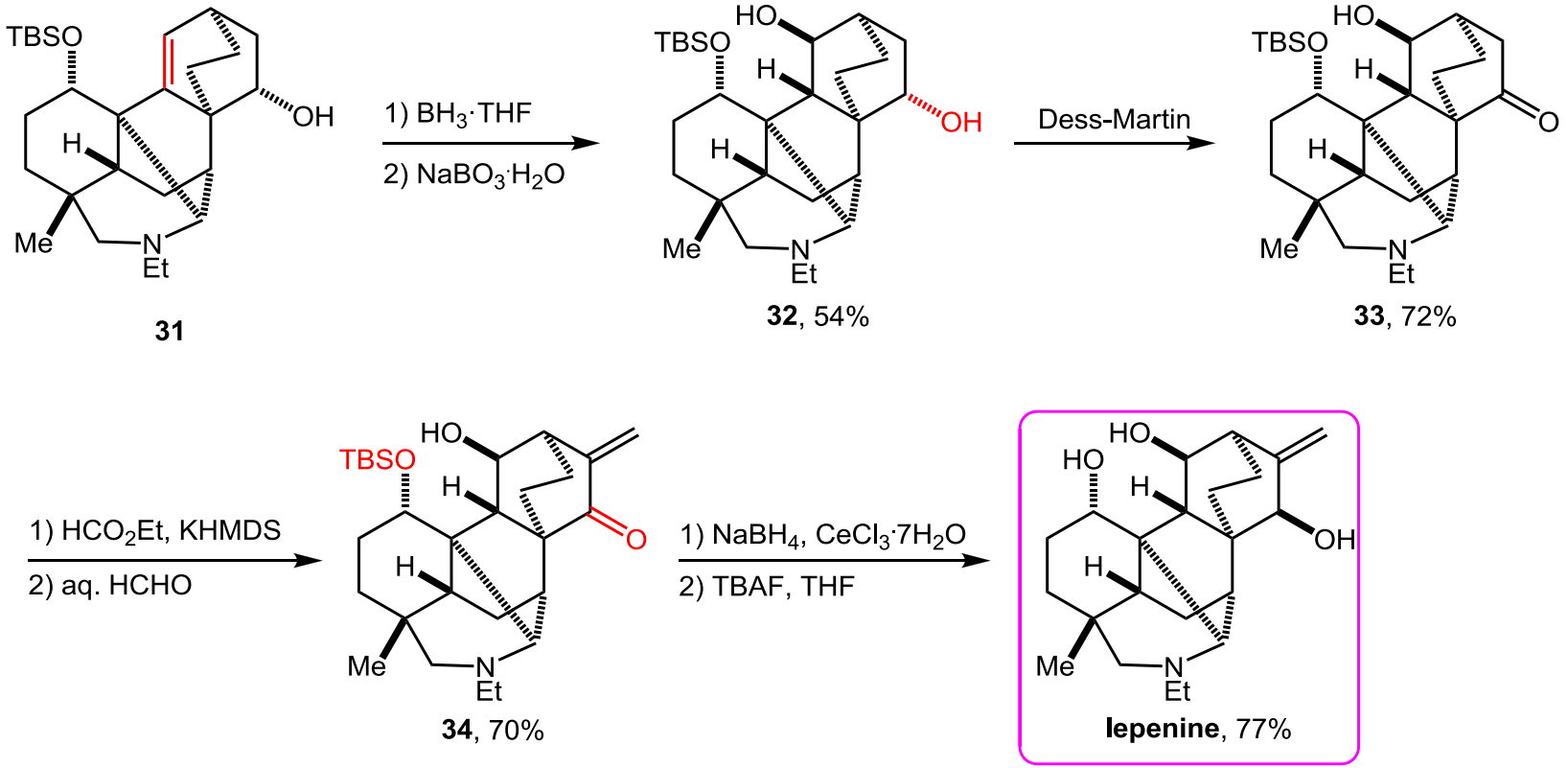
Total Synthesis of Lepenine



31

32, 54%

33, 72%

34, 70%

lepenine, 77%

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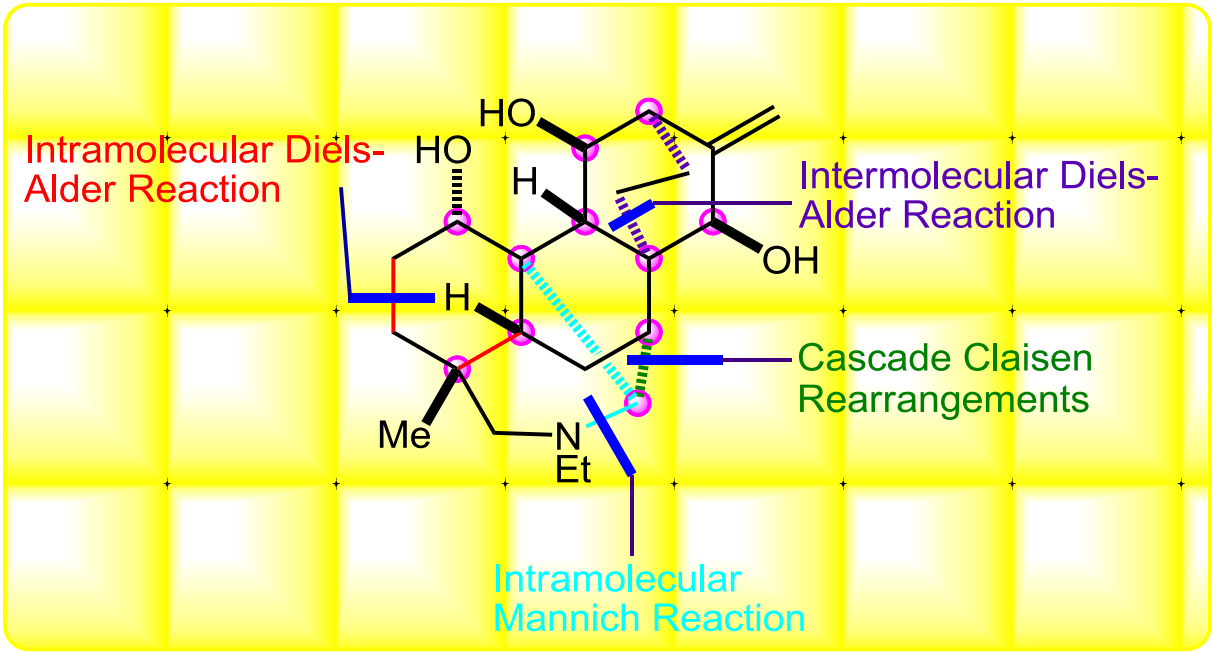
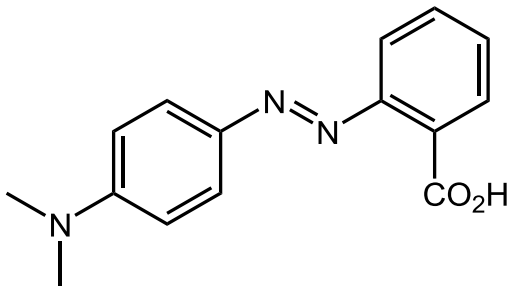
Summary


Intramolecular Diels-Alder Reaction
HO
HO
H
H
OH
Me
N
Et
Intermolecular Diels-Alder Reaction
Cascade Claisen Rearrangements
Intramolecular Mannich Reaction

Diterpenoid alkaloids feature a range of complex chemical structures that possess many functional groups on a rigid polycyclic system. These compounds have attracted the attention of organic chemists for the past several decades. To date, extensive synthetic efforts have resulted in the successful total syntheses of atisine, veatchine, garryine, delphinine, talatisamine, napelline, chasmanine, nominine, and neofinaconitine. As shown in Figure 1, the denudatine family is a group of diterpenoid alkaloids containing more than 30 compounds, such as denudatine (**1**), lepenine (**2**), stenocarpine (**3**), dictysine (**4**), aconicarmine (**5**) and kirinine B (**6**). These compounds are especially interesting because they are chemical and biosynthetic precursors of aconitine-type alkaloids, which are well-known for their potent bioactivity such as inhibition of the voltage-dependent sodium ion channel.

Moreover, the denudatine framework includes an attractive and challenging hexacyclic system that comprises tetradecahydrophenanthrene, a polycyclic system containing a nitrogen atom, and a bicyclo [2.2.2] skeleton. While a synthetic study of denudatine (**1**) was reported by Wiesner and coworkers, no total synthesis of denudatine-type alkaloids has been accomplished to date. Herein we wish to disclose the first total synthesis of a denudatine-type alkaloid, lepenine.

In summary, we have achieved the straightforward asymmetric synthesis of lepenine, the first member of the denudatine-type alkaloids that succumbed to total synthesis. Our synthesis features an effective construction of the complex hexacyclic system via a tethered intramolecular Diels−Alder reaction, an intramolecular Mannich reaction, and a Diels−Alder reaction between an *ortho*-quinone monoketal and ethylene. Another key feature of the synthesis is a chirality transfer from L-lactic acid methyl ester *via* a Claisen rearrangement.



甲基红
(methyl red)

酸碱直指示剂

1. 甲基红本身为酸性，变色范围pH值4.4~6.2，颜色转变点的pH=5.0
2. 在酸性环境中呈红色，在碱性环境中呈黄色。
3. 每10 L试液用1滴甲基红即可。