Total Synthesis of (–)-Lepenine

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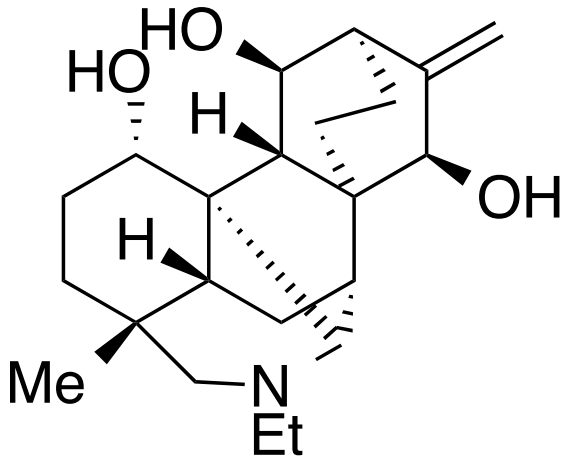
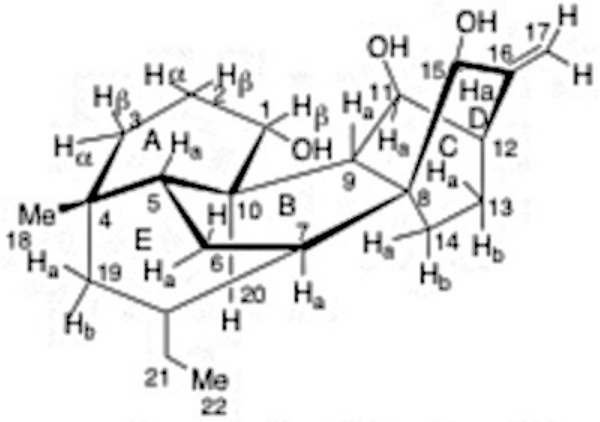


Ruiting Liu
Wipf Group Current Literature
06/06/2014

(-)-Lepenine

- First isolated from aconitum kusnezoffii
- Belongs to the denudatine family of diterpenoid alkaloids
- Chemical and biosynthetic precursors of aconitine-type alkaloids, which has potential bioactivity such as inhibition of the voltage-dependent sodium ion channel.

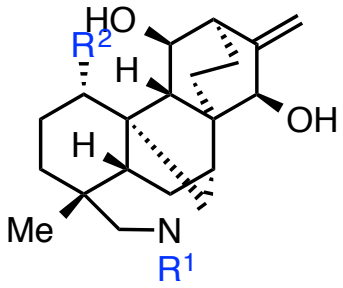


stereostructure of lepenine (**5**)

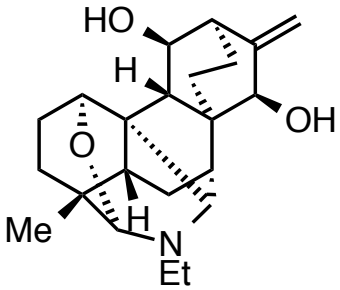
Nat. Prod. Rep. **2010**, 27, 529
Heterocycles, Vol 49, No. 1, **1998**, 327-341

Denudatine type alkaloids

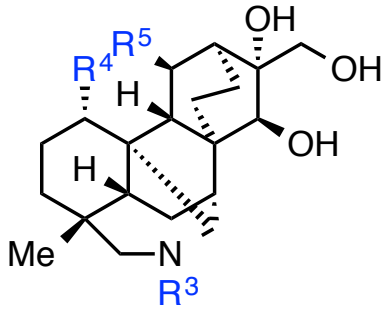
- Framework of denudatine type alkaloids contains an hexacyclic system that comprises tetradecahydrophenanthrene, a polycyclic system containing a nitrogen atom, a bicyclo [2.2.2] skeleton.
- No formal total synthesis of denudatine-type alkaloids has been accomplished



R^1=Et, **R^2=H: denudatine**
R^1=Et, **R^2=OH: lepenine**
R^1=Me, R^2=OH :stenocarpine

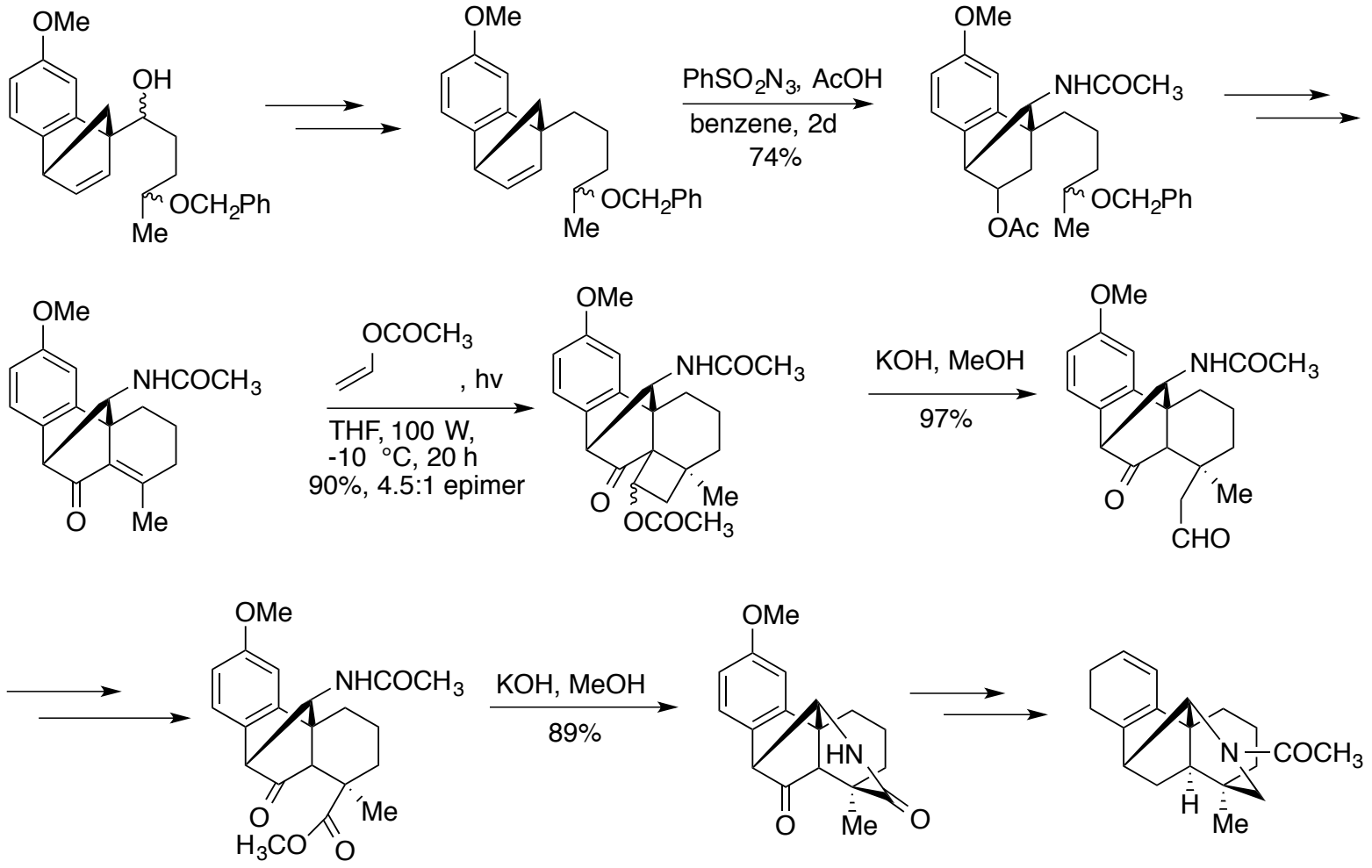


Kirinine B



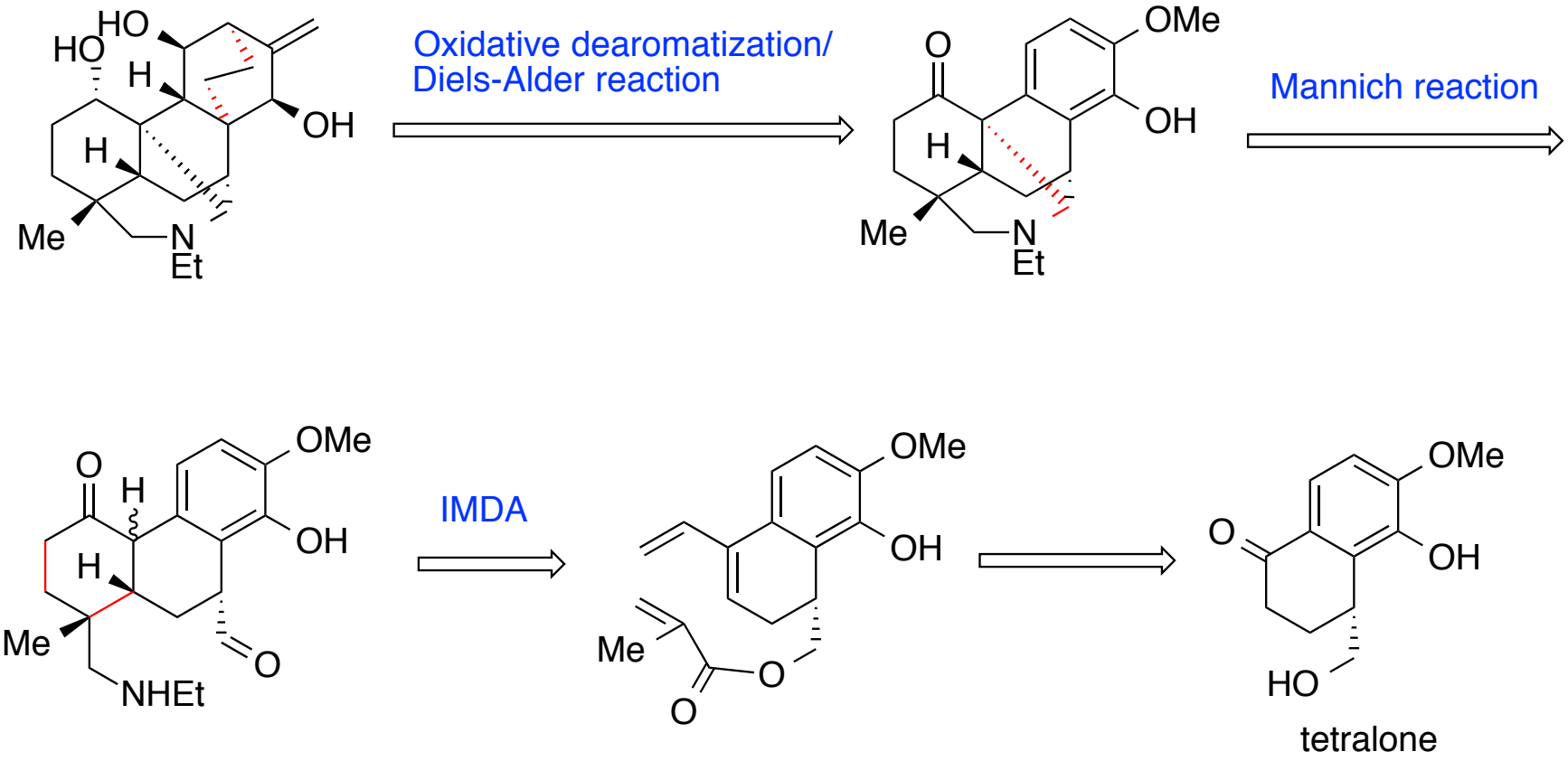
R^3=Me, R^4=H, R^5=H: dictysine
R^3=Et, R^4=OH, R^5=OH: dictysine

Wiesner's synthesis of denudatine skeleton

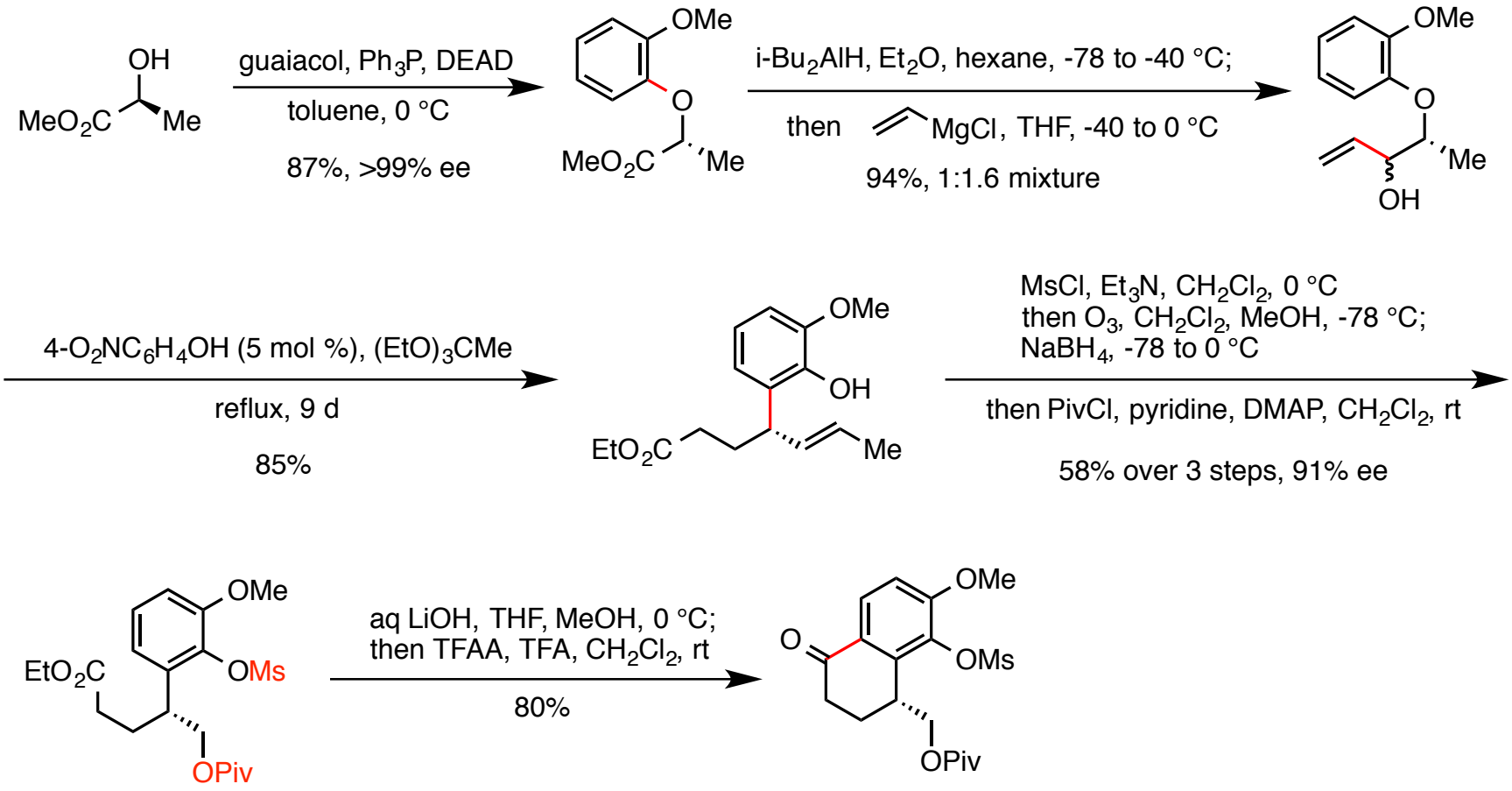


Can. J. Chem. Vol. 52, **1974**, 1042-1049

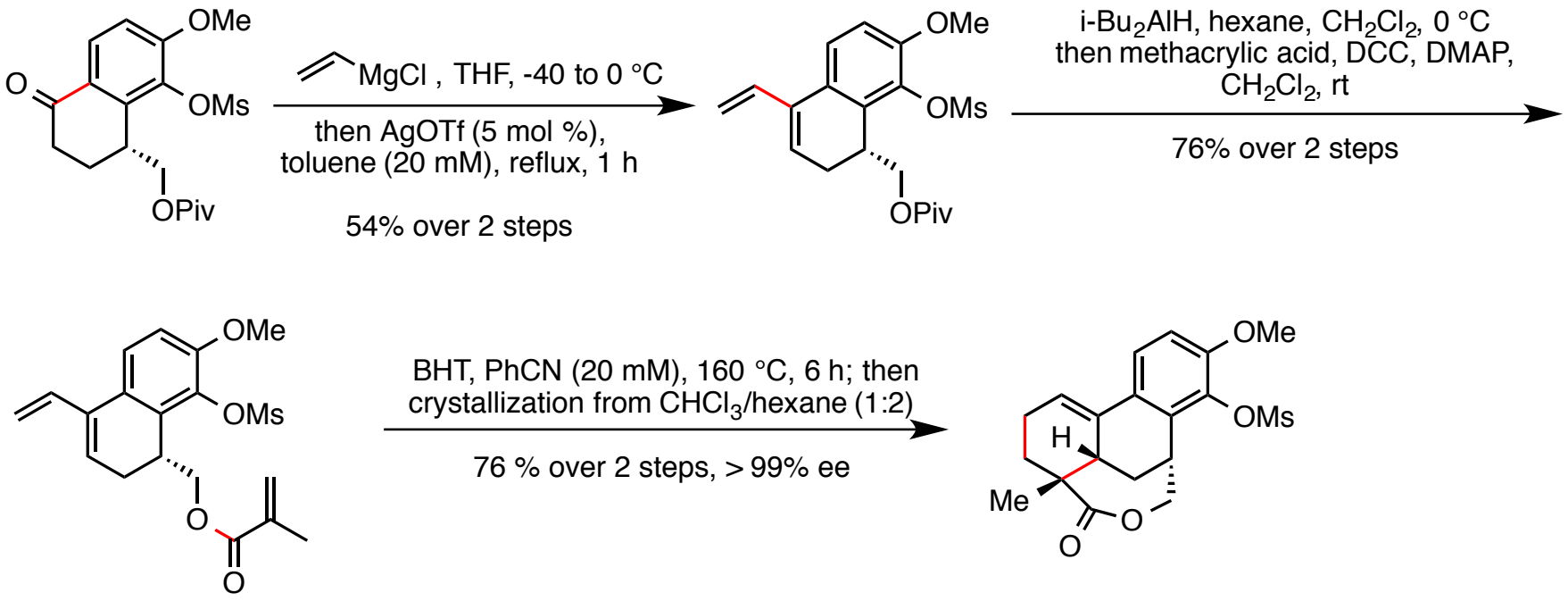
This work


HO
HO
H
OH
H
Me
N
Et
Oxidative dearomatization/
Diels-Alder reaction
O
OMe
OH
H
Me
N
Et
Mannich reaction
O
H
OMe
OH
H
Me
NHEt
O
IMDA
OMe
OH
Me
O
O
OMe
O
OH
HO
tetralone

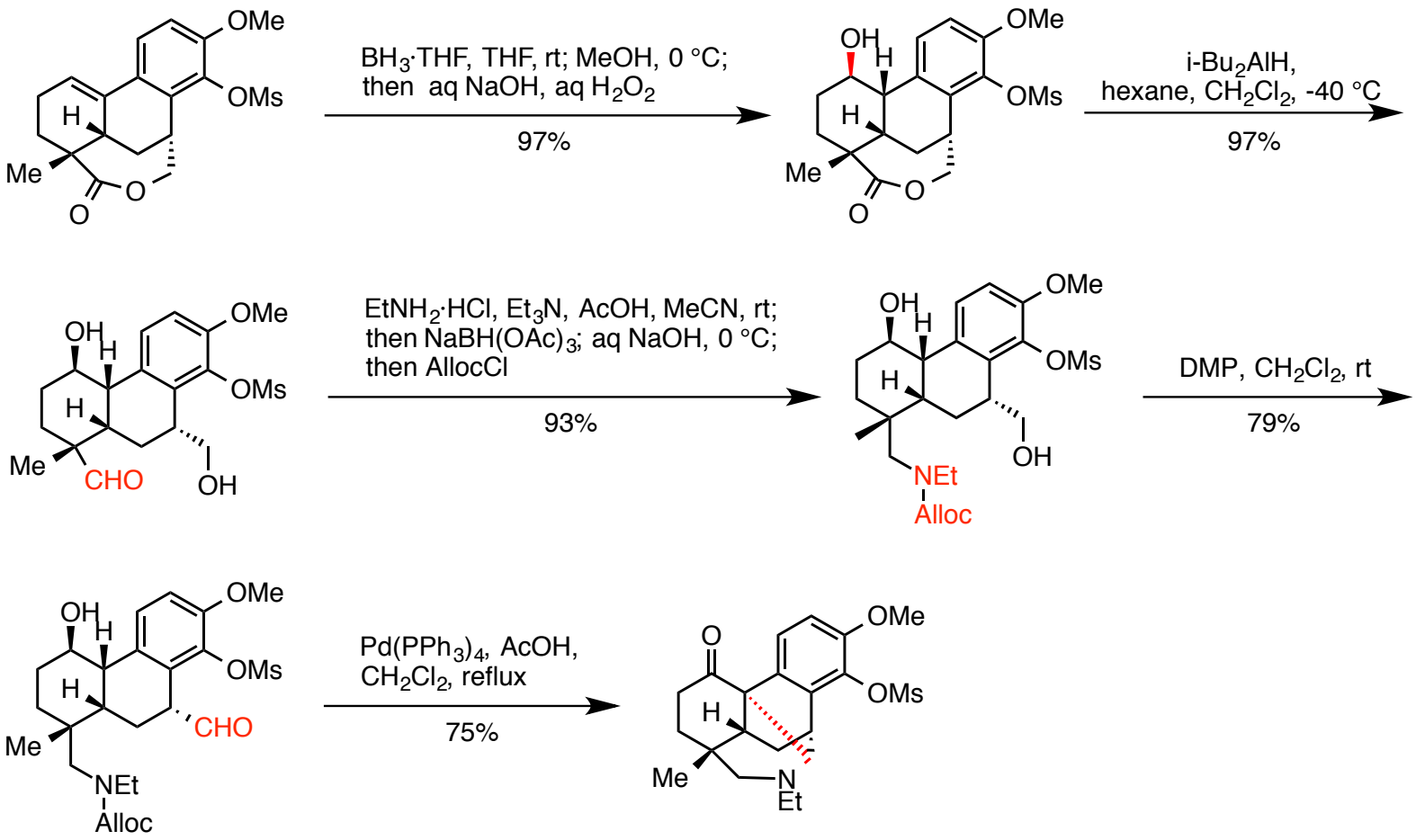
Phenanthrene Skeleton



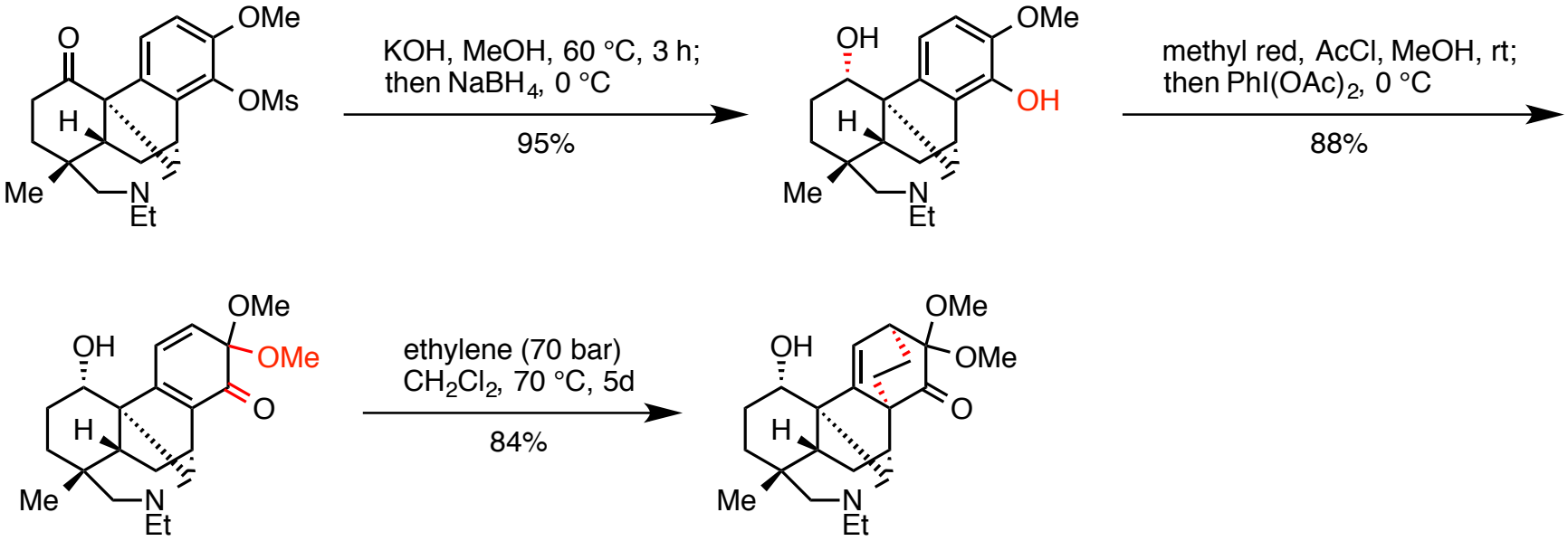
Phenanthrene Skeleton



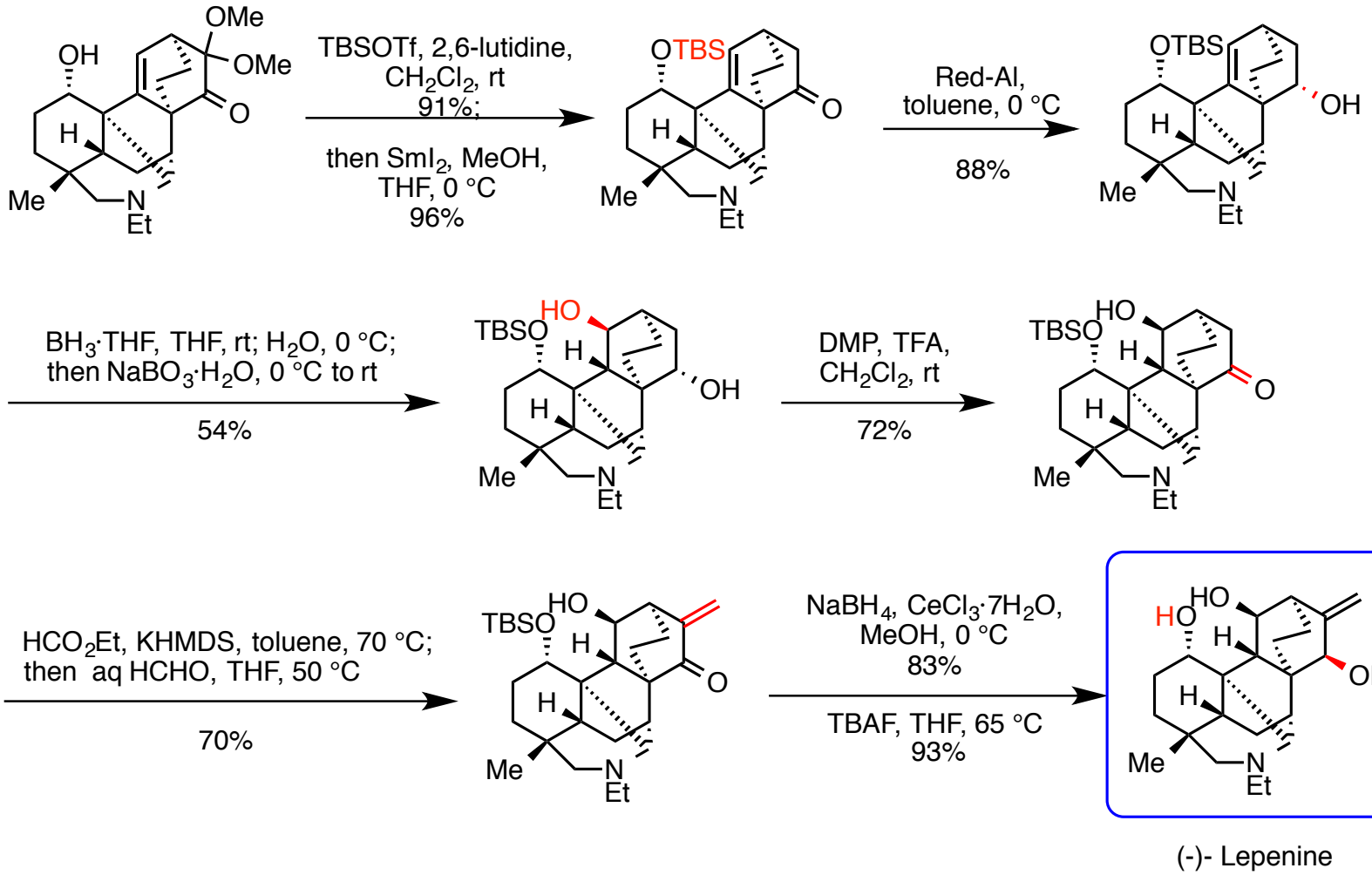
Intramolecular Mannich Reaction



Construction of the Bicyclo [2.2.2] skeleton



Final steps



(-)- Lepenine

Conclusion

- First total synthesis of (-)-lepenine
- Effective synthesis with feature reactions such as claisen rearrangement, IMDA, intramolecular Mannich reaction, DA reaction between ortho-quinone monoketal and ethylene