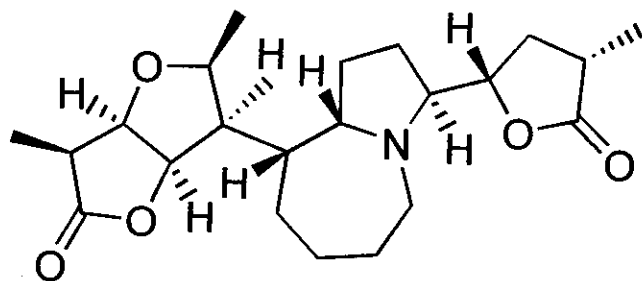


Parvistemonine and the *Stemona* Alkaloids



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October 2003

Outline:

- Stemona Plants
- Historical Use
- Biological Activity
- Structural Elucidation
- Classification
- Synthetic Approaches
- Wipf Group Research
- Current Approaches
- Conclusion

Stemona Plants:



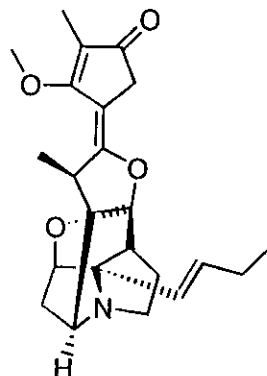
- All the known Stemona alkaloids are isolated from plants in the *Stemonaceae* family
- Stemona plants (also called *Roxburghia*) primarily grow in Southern Asia, Malaysia and Northern Australia in dry vegetation
- 3 genera of the family:
 - *Stemona* (largest genera with 25 species)
 - *Croomia*
 - *Stichoneuron*

Historical Use



- Stemona plants have tuberous roots. In traditional Japanese and Chinese folk medicine, the water extracts from these roots are used for both insecticidal and medicinal purposes
- Some of the medicinal uses are:
 - Treatment of respiratory diseases
 - Pulmonary tuberculosis
 - Bronchitis
 - Antihelmintics (anti-parasitic for both human and cattle use)

Biological Activity and Phytochemistry:



Aspargamine A

Perk. Trans 1,1995,391

- Research into the biological activity of roots and herbs used in folk medicine can be hindered due to difficulties in correctly identifying plant material
 - The same plant frequently has different names in different communities
 - When sold in the market, different families of plants may be classified together based on similarity in root appearance
 - Aspargamine A was attributed to the plant *Asparagus Racemosus* in 1995. Upon further investigation and plant comparison, it was concluded that this alkaloid must have been isolated from a *Stemona* plant instead

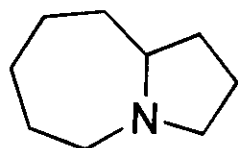
Biological Research and Phytochemistry (cont.)

- Biological studies have focused on the *Stemona* root extracts (although there have been some studies on leaf and rhizome extracts) and the activity of individual alkaloids
 - Tuberosstemonine acts as a glutamate inhibitor at the neuromuscular junction (*BrainRes.* **1985**, 334, 33)
 - Tuberosstemonine acts as an antihelmintic
 - Tuberosstemonine, Stemfoline and Didehydrostemfoline all showed insecticidal activity (*J.Agric.FoodChem.* **2002**, 50, 6383)

Extraction and Characterization

- The first isolation of a *Stemona* alkaloid was Tuberosemonine in 1934 by Suzuki
- With NMR, X-ray studies, degradative techniques, mass spec and synthetic manipulations, Tuberosemonine was the first *Stemona* alkaloid to have its structure elucidated in 1968 (*Tetrahedron*, 24,1968,2631)
- In the 1980's Ren-Sheng Xu did an extensive study of the *Stemona* species and reported the structure of many new alkaloids. There are now more than 42 known *Stemona* alkaloids (*Nat.Prod.Rep*,2000,17,117)
- In 1990, the structure of Parvistemonine was elucidated using X-ray studies, proton and carbon NMR, HMQC, COSY, NOESY, and MS (*ActaChim.Sinica*,1991,49,927)

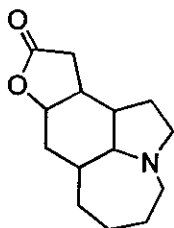
Classification of the Stemona Alkaloids



- One common feature among all the Stemona Alkaloids is the presence of the 1-azabicyclo[5.3.0]-decane ring system
- Within this group, there have been several methods proposed for classification. One approach divides the stemona alkaloids into 5 major groups
 - Stenine
 - Stemoamide
 - Tuberostemospirone
 - Stemonamine
 - Parvistemoline

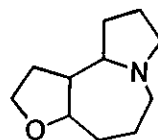
Core structure of Stemona Groups:

Stenine Core



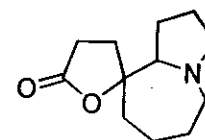
Stenine,
Tuberostemonine,
Tuberostemonine A,
Tuberostemoninol,
Didehydrotuberostemonine
Neotuberostemonine
Bisdehydroneotuberostemonine

Stemoamide Core



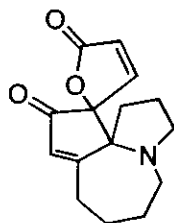
Stemoamide, Stemonine,
Neostemonine,
Bisdehydroneostemonine,
Protostemonine,
Didehydroprotostemonine,
Isoprotostemonine,
Tuberostemoamide,
Stemonine

Tuberostemospironine Core



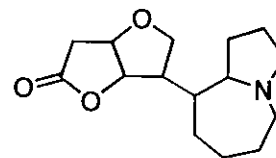
Tuberostemospironine,
Croomine,
Stemospironine,
Stemotinine,
Isostemotinine,
Stemonidine,
Didehydrocroomine

Stemonamine Core



Stemonamine
Isostemonamine,
Stemoamide,
Isostemonamide,
Maistemonine,
Oxysmaistemonine

Parvistemoline Core

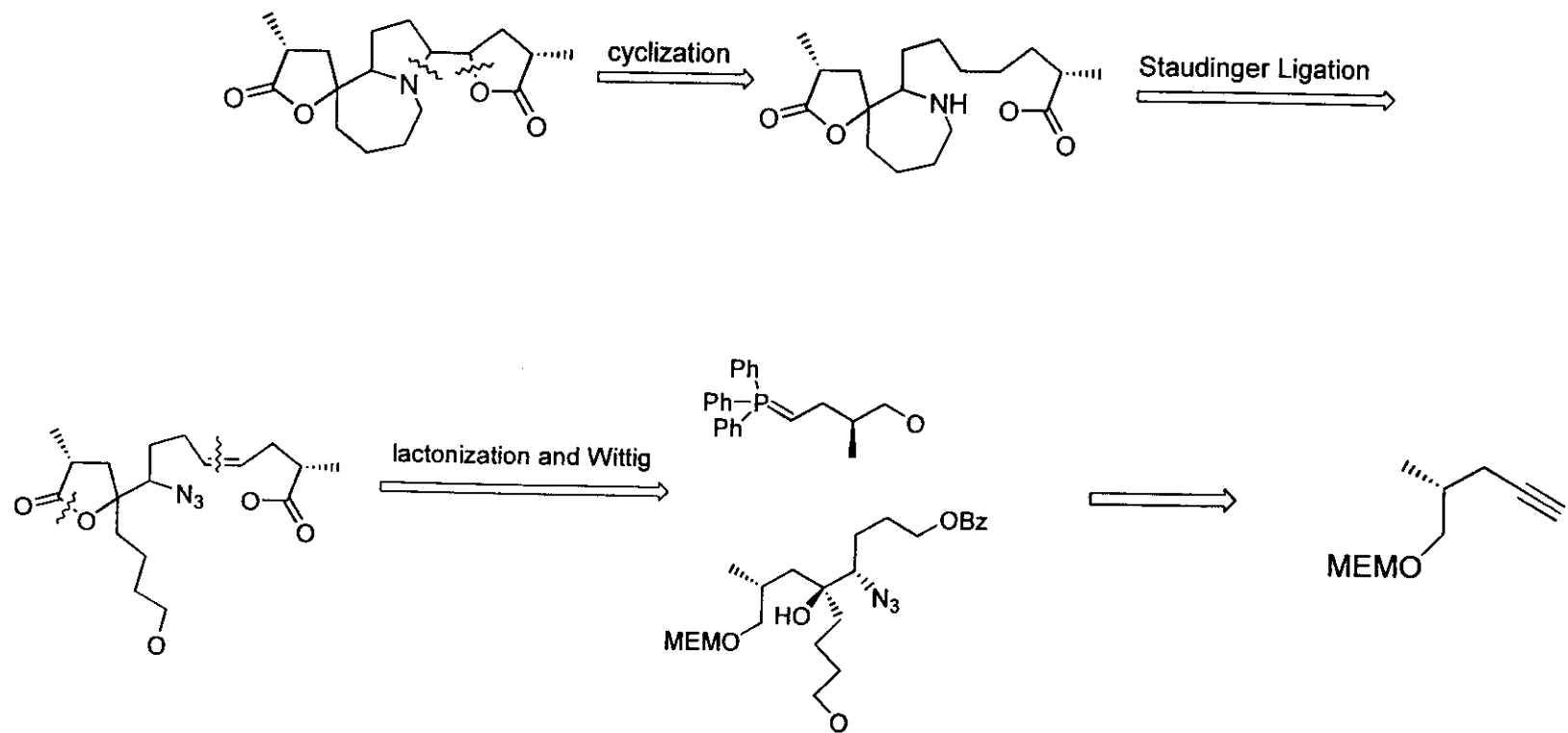


Parvistemoline
Parvistemoine
Didehydroparvistemoine

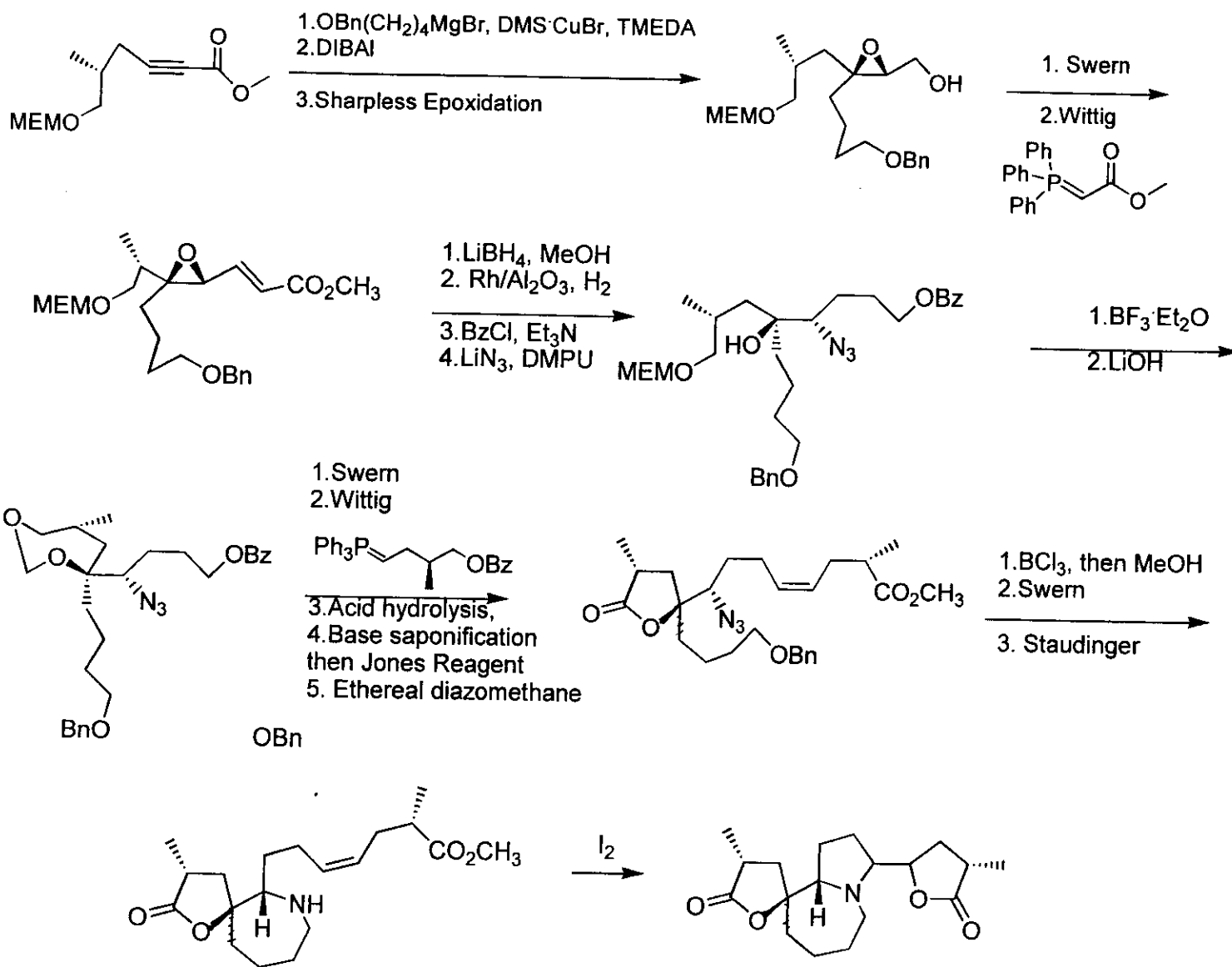
Synthesis

- (+)-Croomine was the first *Stemona* alkaloid to be synthesized by Williams (*J.A.C.S.*1989,111,1923)
- In 1993, Chen and Hart reported the first racemic synthesis of Stenine (*J.Org.Chem*,1993,58,384)
- In 1995, the Wipf group reported the first asymmetric synthesis of (-)-Stenine and the first synthesis of a *Stemona* alkaloid for the group (*J.A.C.S.*1995,117,11106)
- Synthetic approaches to the core structure have included Diels-Alder, [1+4]cycloadditions, oxidative cycloadditions, the Staudinger reaction and others

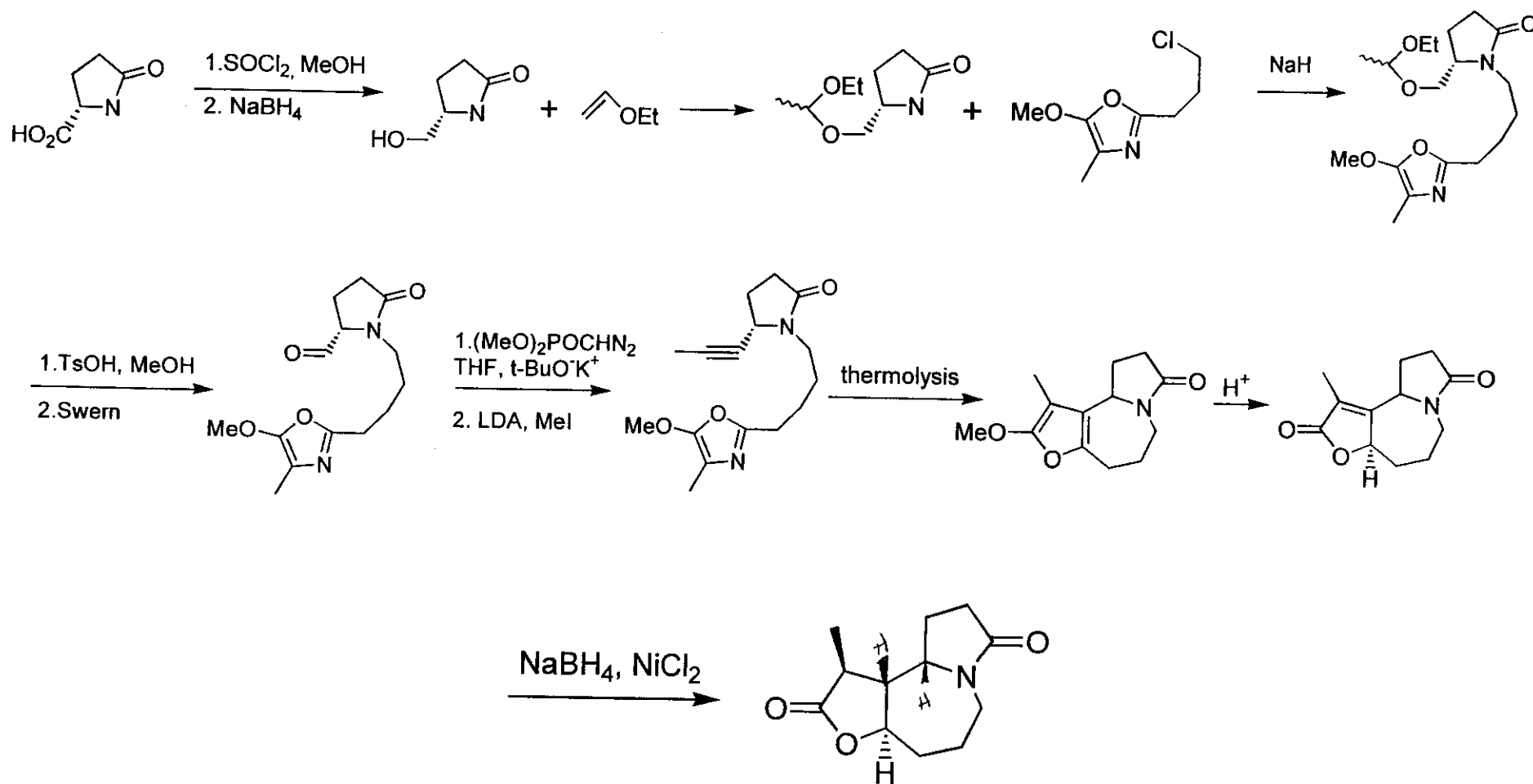
Retro synthesis of Williams approach to Croomine



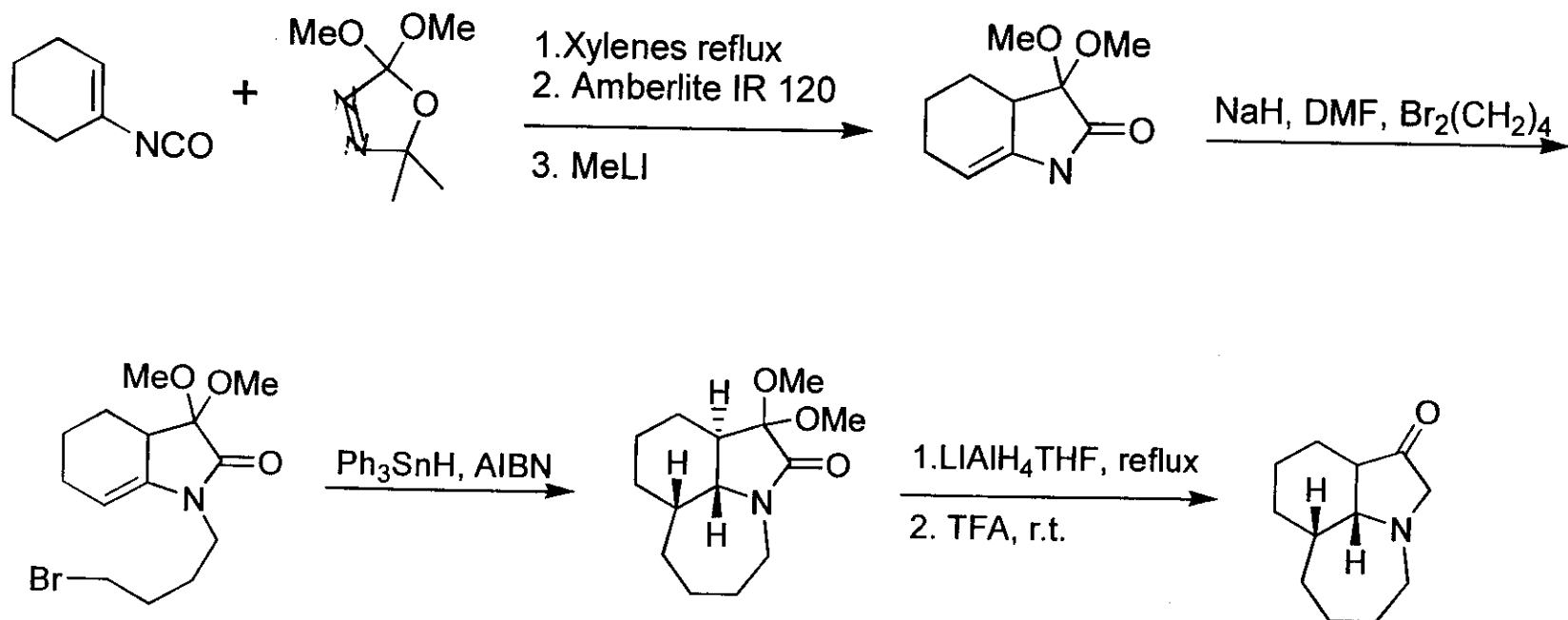
(+)-Croomine



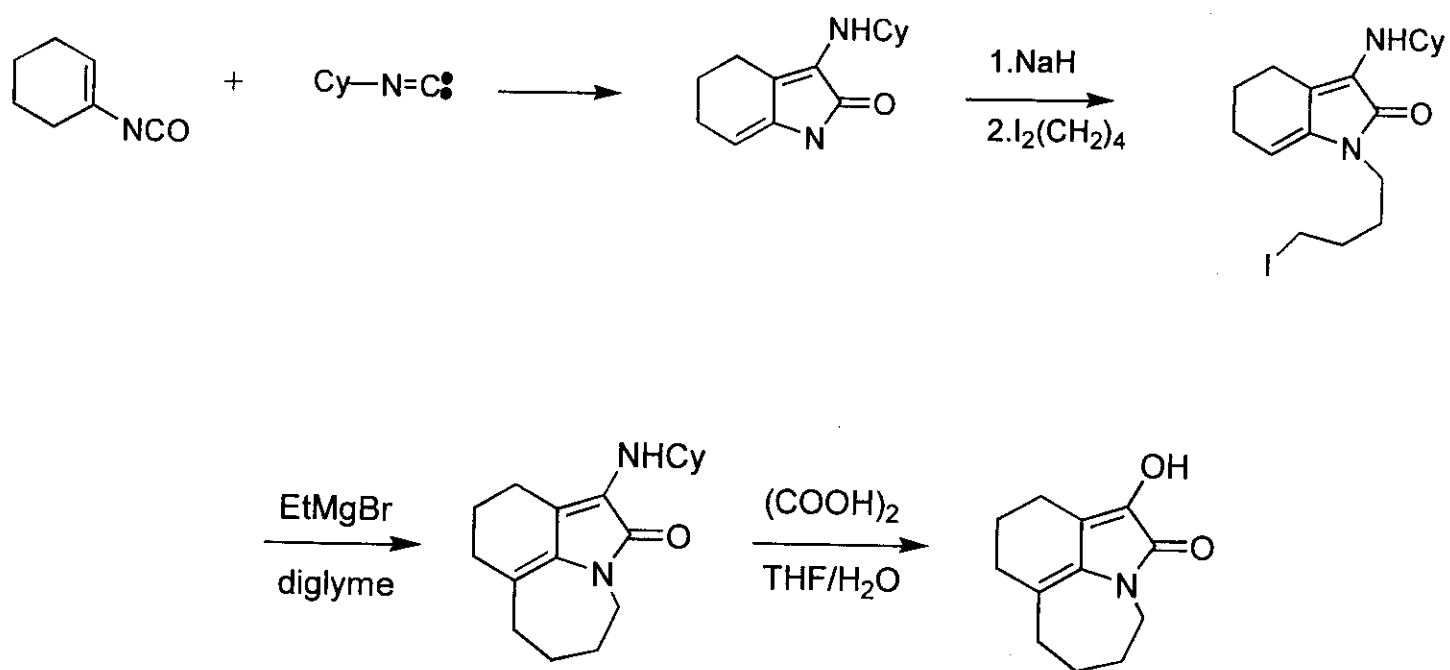
Jacobi (-)-Stemoamide Synthesis



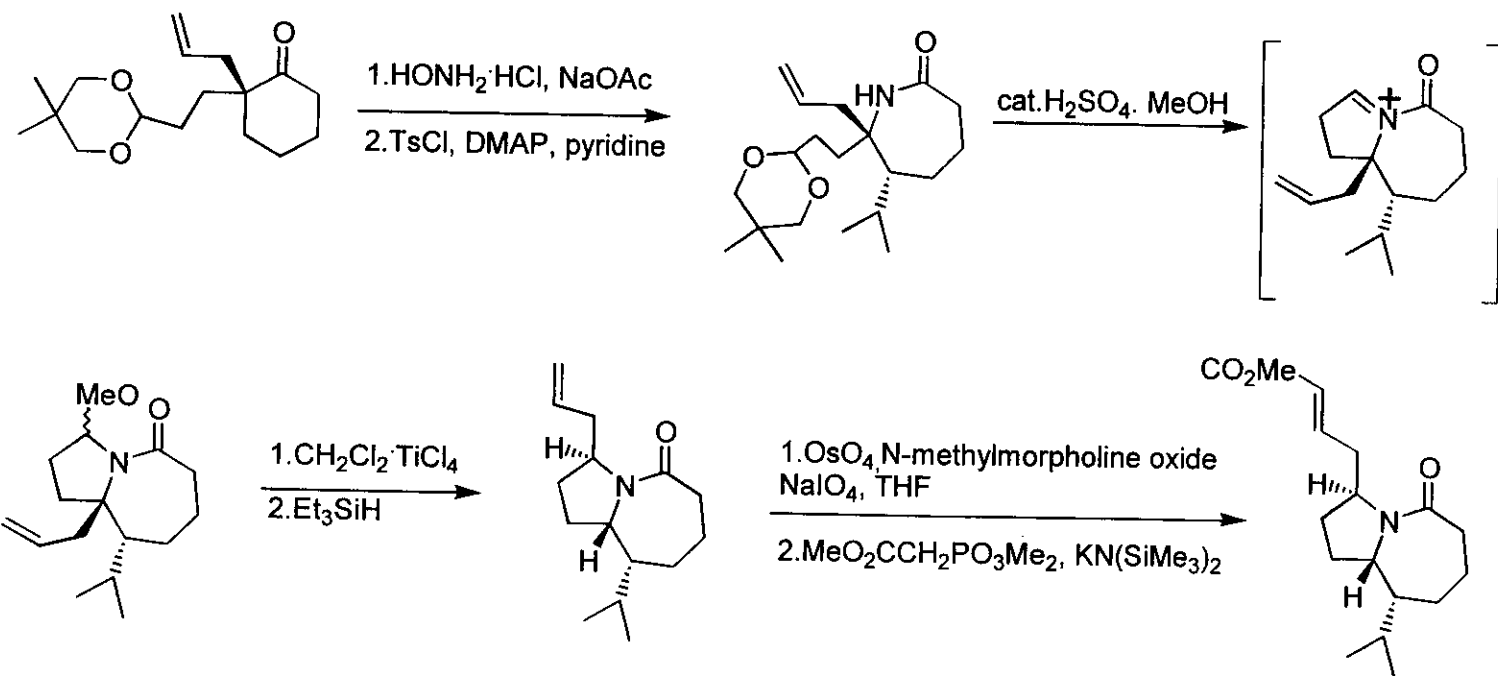
Rigby Synthesis of Azepinoindole Core



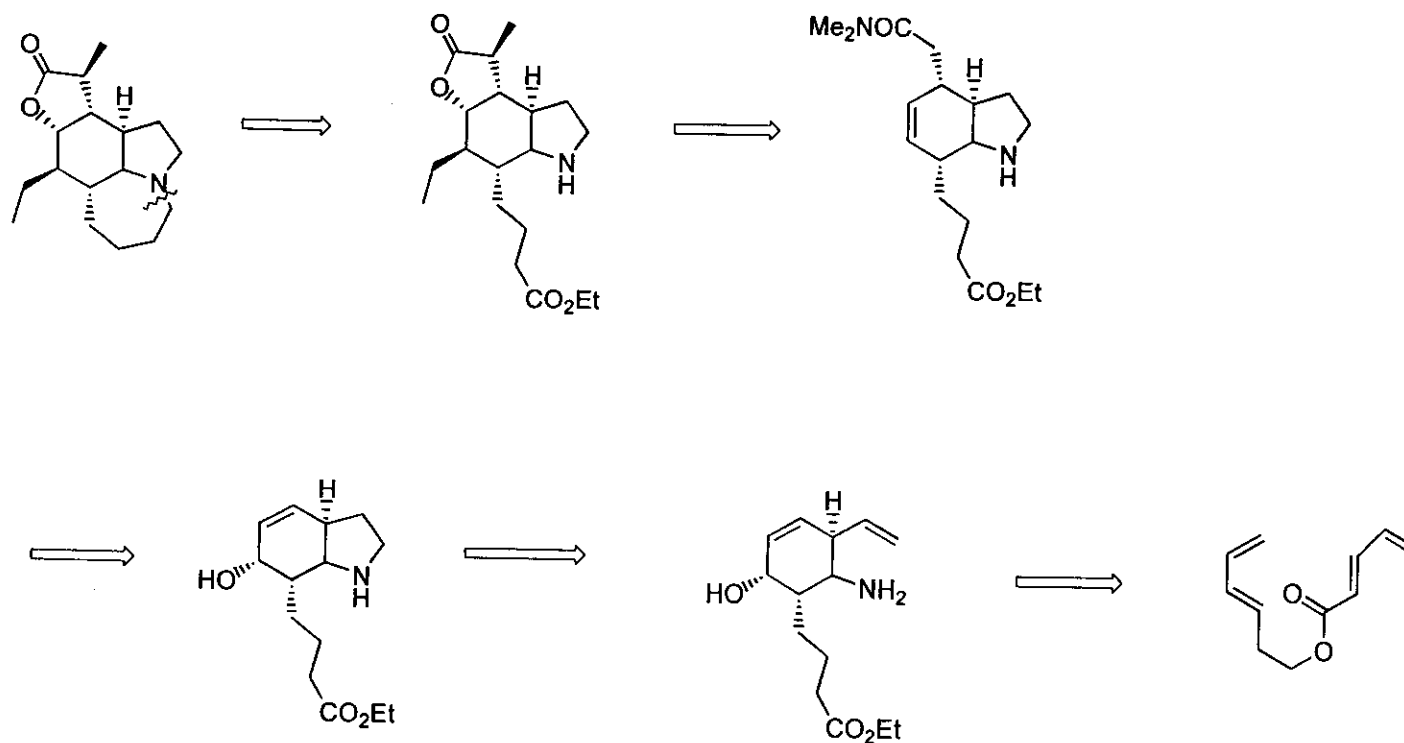
Rigby Approach to Azepinoindole Core



Other Approaches to Form the Azepine Core: Heathcock (2001)



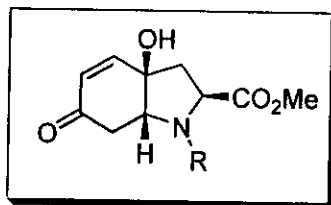
Hart and Chen Retrosynthesis for Stenine:



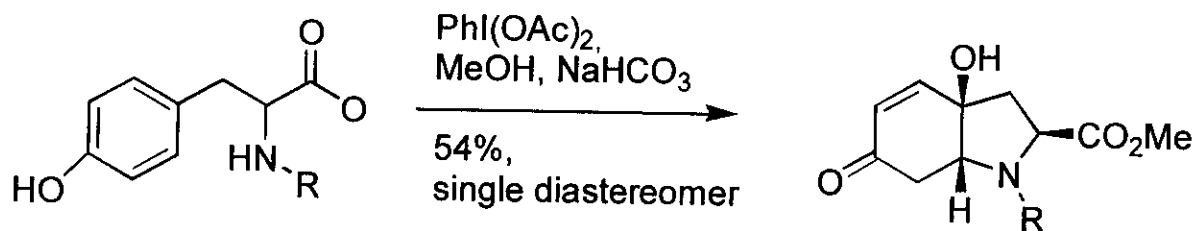
39 steps
9% yield

J. Org. Chem., 1993, 58, 384

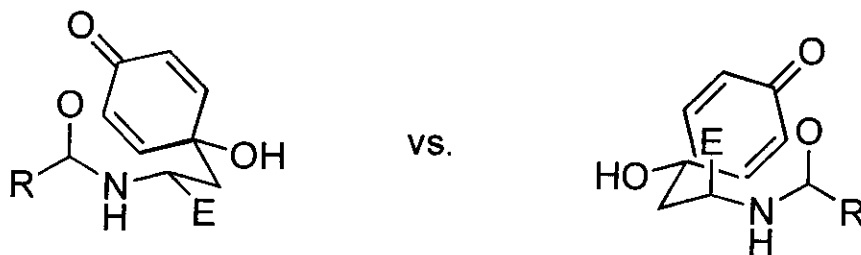
Wipf Group Research



Key Intermediate Target

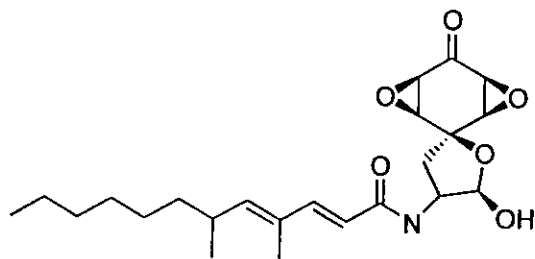


The excellent diastereoselectivity was later attributed to A 1-3 strain

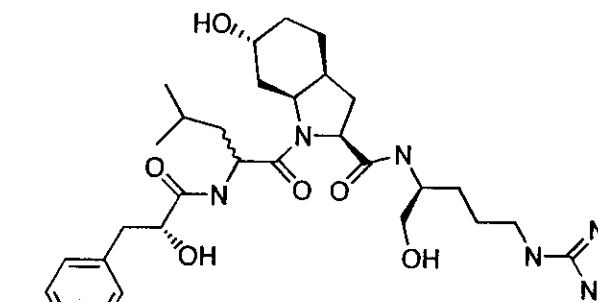


J.A.C.S. 1995, 117, 11106

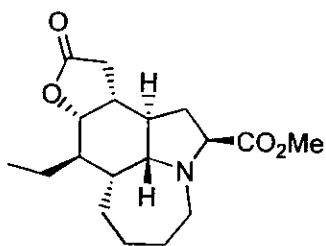
Synthetic targets that utilized the selective cyclization of tyrosine



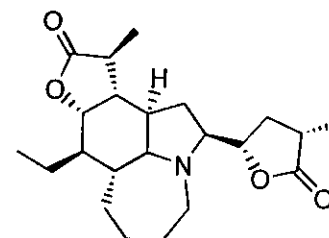
~~(+)-Aeuruginosin 298-A~~ Aranorosin
J. Org. Chem., **1993**, *58*, 1649



(+)-Aeuruginosin 298-A
Aranorosin
Org. Lett. **2000**, *2*, 4213

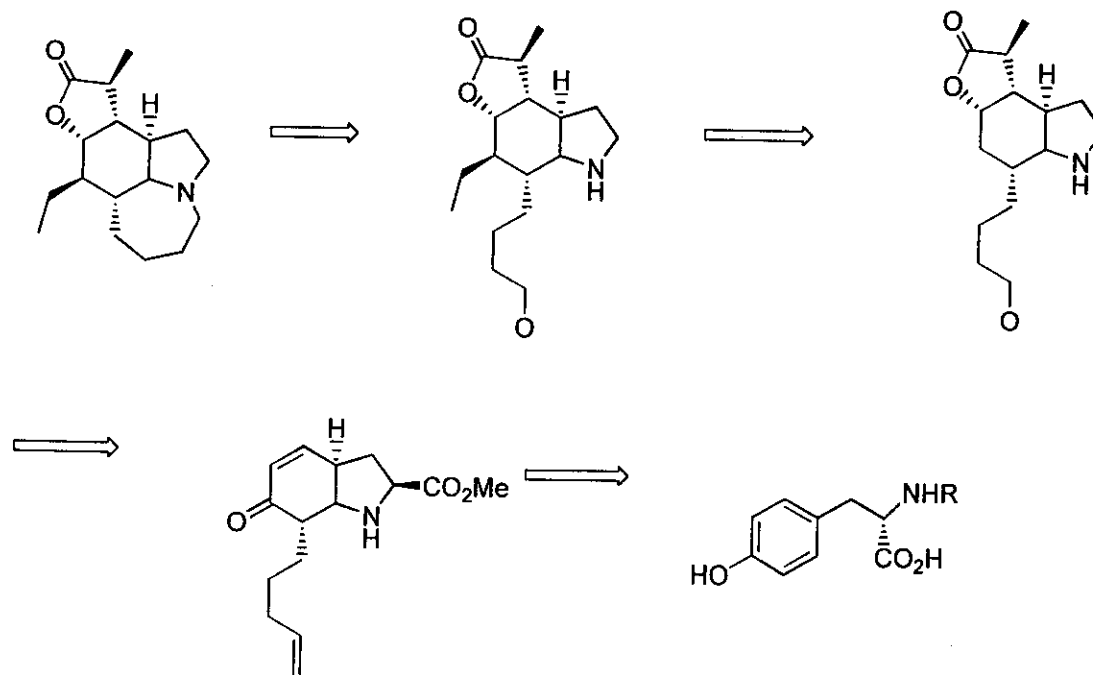


(-)-Stenine
J. A. C. S. **1995**, *117*, 11106



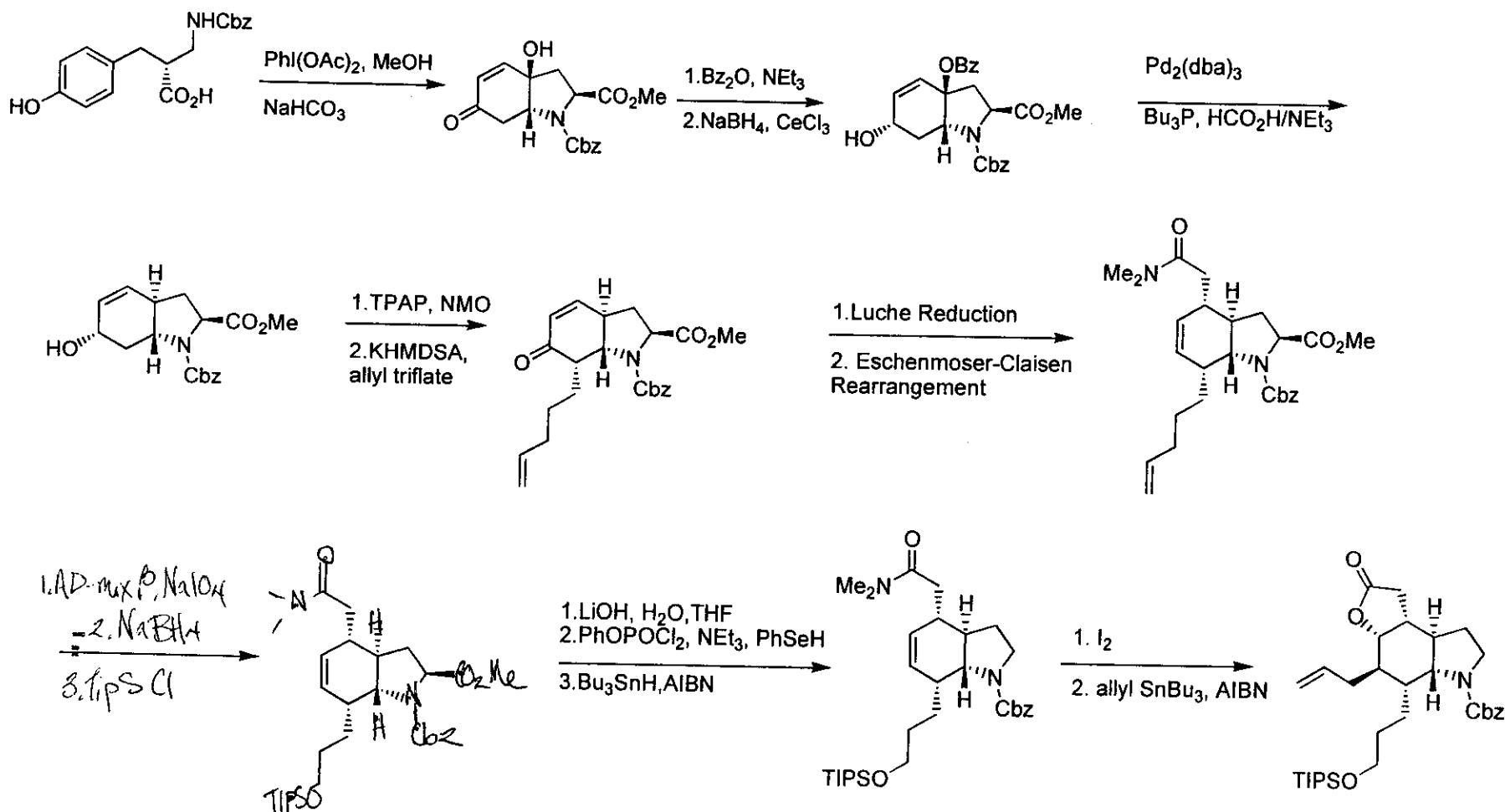
(-)-Tuberostemonine
J. A. C. S. **2002** *124*, 14848

Wipf Group Retrosynthesis of Asymmetric (-) Stenine

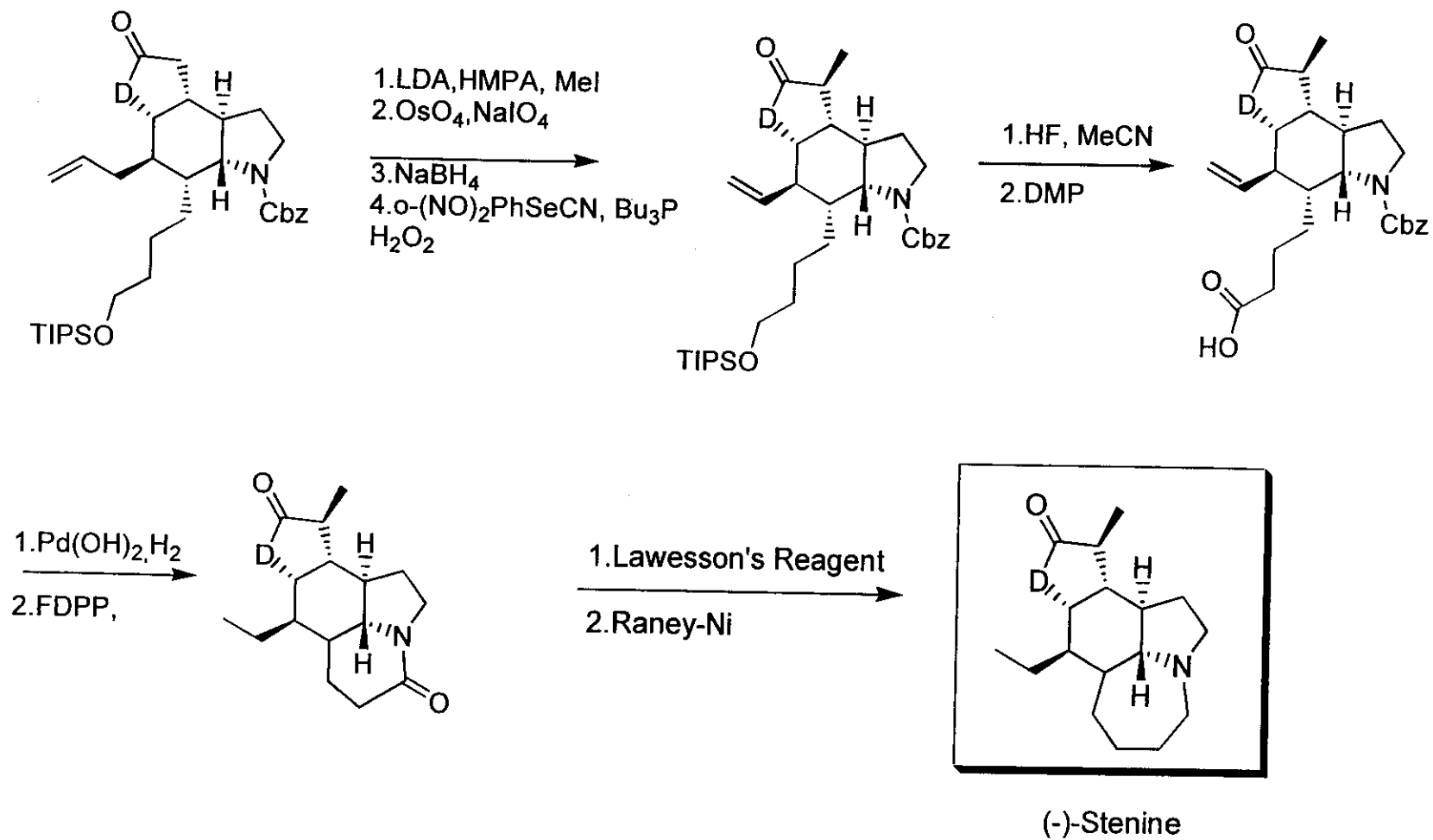


26 steps
1.2% yield

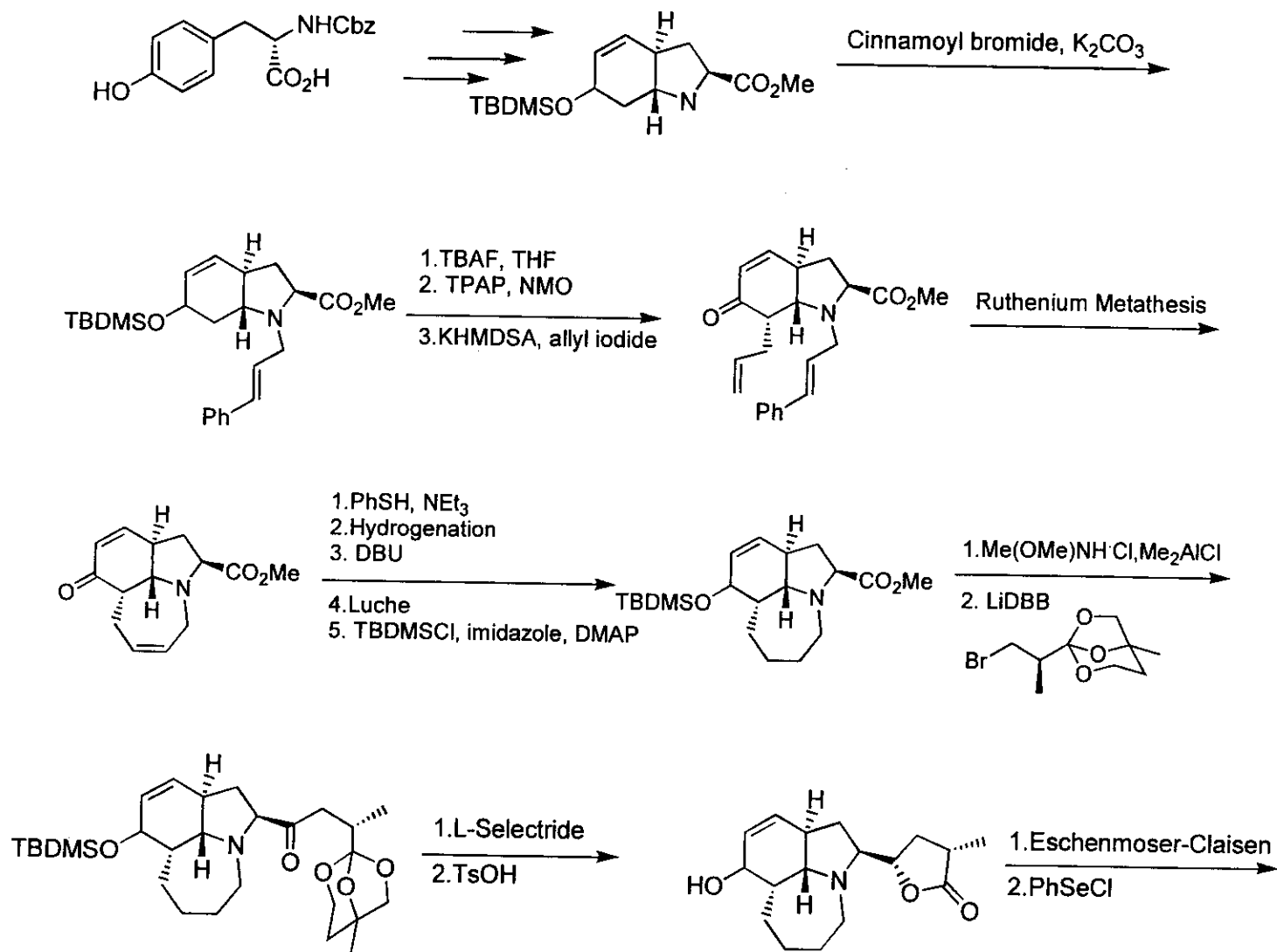
Total Synthesis of (-) Stenine



Total Synthesis of (-) Stenine (cont.)



Total Synthesis of Tuberostemonine



Synthesis of Tuberostemonine (cont.)

