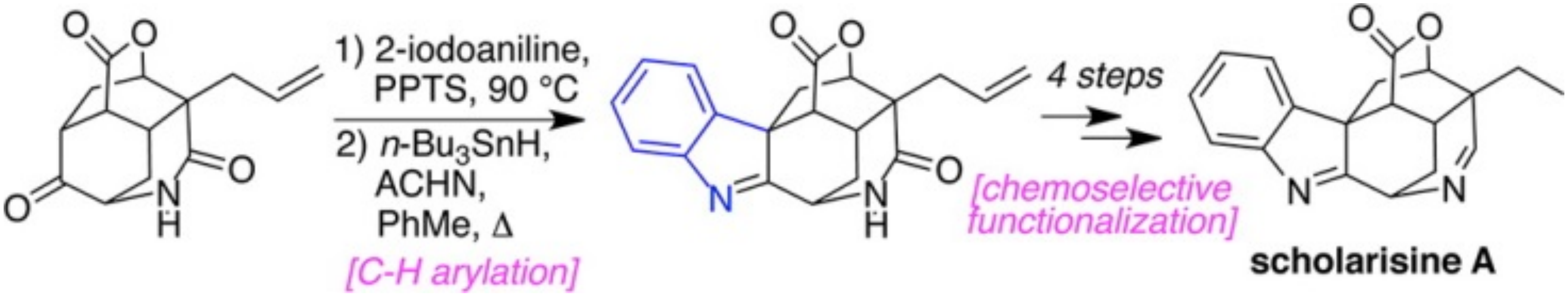
A Concise Total Synthesis of (+)-Scholarisine A Empowered by a Unique C–H Arylation

Myles W. Smith and Scott A. Snyder. *J. Am. Chem. Soc.*, **2013**, *135*, 12964–12967



Liming Cao
Wipf Group Current Literature
9/21/2013

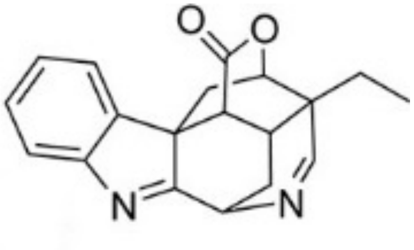
Alstonia scholaris (L.) R. Br.

- Scholarisine A is an akuammiline alkaloid first isolated by Luo in 2007 from *Alstonia scholaris* (L.) R. Br. in the Yunnan province in China.
- The bark has been traditionally used to treat gastrointestinal conditions, malaria, cutaneous diseases, tumors, ulcers, chronic respiratory conditions (such as asthma and bronchitis), helminthiasis, and agalactia in India, China, Australia and Africa.
- The leaves have been historically used in “dai” ethnopharmacy to treat chronic respiratory diseases in Yunnan.
- The leaf extract, developed as a commercially available traditional Chinese medicine, has also been prescribed in hospitals and sold over the counter in drug stores.

Org. Lett. **2008**, *10*, 577
Integr. Cancer Ther. **200**9, *8*, 273
J. Ethnopharmacol. **2010,** *129*, 293
J. Ethnopharmacol. **2010**,129, 174
Integr. Cancer Ther. **2010**, *9*, 261
A Modern Herbal (Vol. 1). New York, Dover Publications, *1971*, 29
Chin. J. Integr. Med. 2012 Mar 28
http://www.kwps.kh.edu.tw/plant/k3c39.htm

Scholarisine A

- The structure was elucidated by 1D and 2D NMR, FTIR, UV, and HRMS:
  - An indolenine fused to a strained carbocylic cage, adorned with tertiary and quaternary stereocenters
  - Potentially labile imine and bridging lactone functional groups.

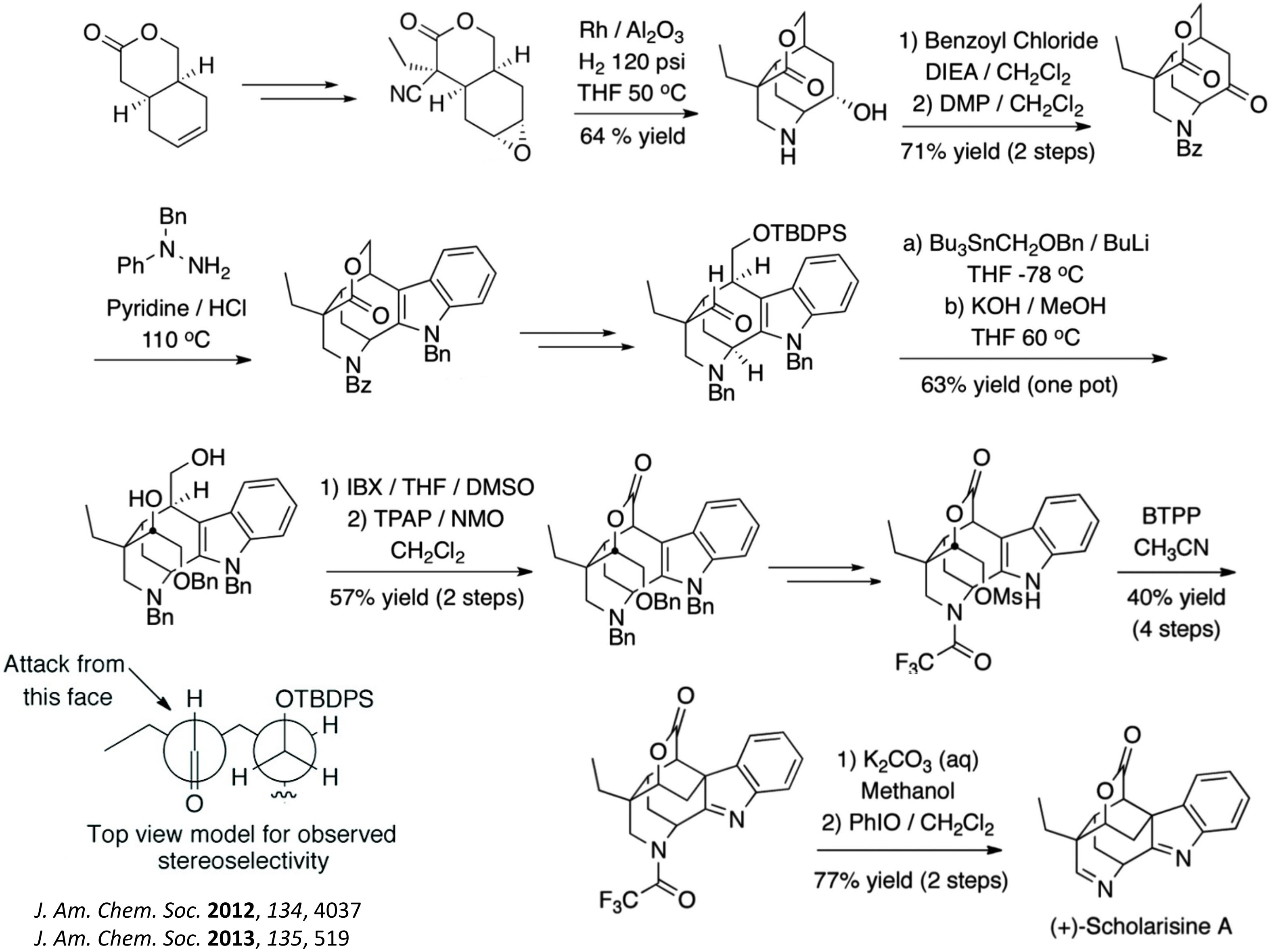


scholarisine A

- Its biological properties remain unexplored.

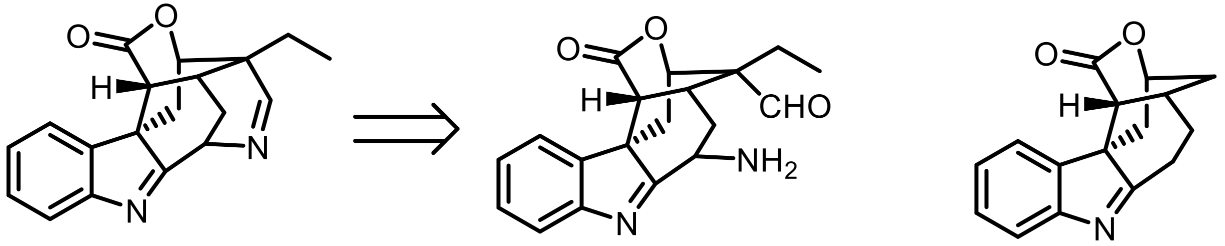
Org. Lett. **2008**, *10*, 577
J. Am. Chem. Soc., **2013**, *135*, 12964

Smith's total synthesis of (+)-Scholarisine A



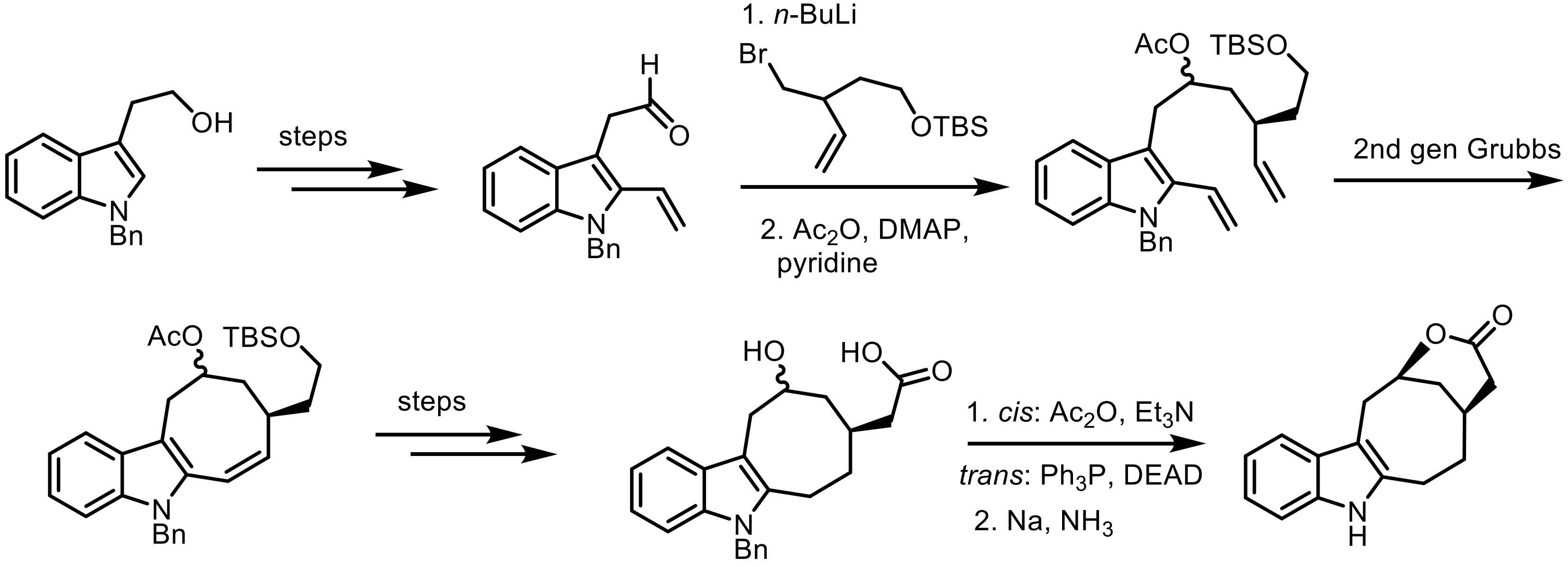
J. Am. Chem. Soc. **2012**, *134*, 4037
J. Am. Chem. Soc. **2013**, *135*, 519

Higuchi’s model study



scholarisine A

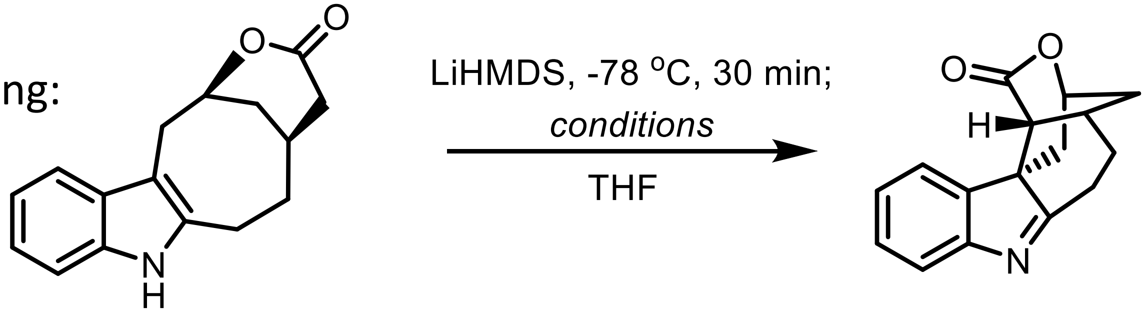
model system



Chem.—Eur. J. **2013**, *19*, 4255

Higuchi's model study

Intramolecular oxidative coupling:



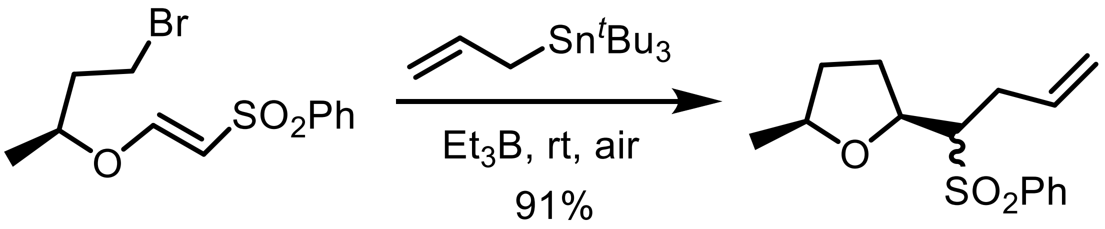
:

Entry	Oxidant	T[^{o}C]	T	Yield [%]
1	Fe(acac)$_3$	RT[a]	1 h	0
2	Cu(2-ethylhexanoate)$_2$	RT[a]	2 h	7
3	I$_2$	-78	40 min	59
4	ICl	-78	2 h	28
5	NIS	-78	2 h	63
6	PhI(OAc)$_2$	-78	2 h	32

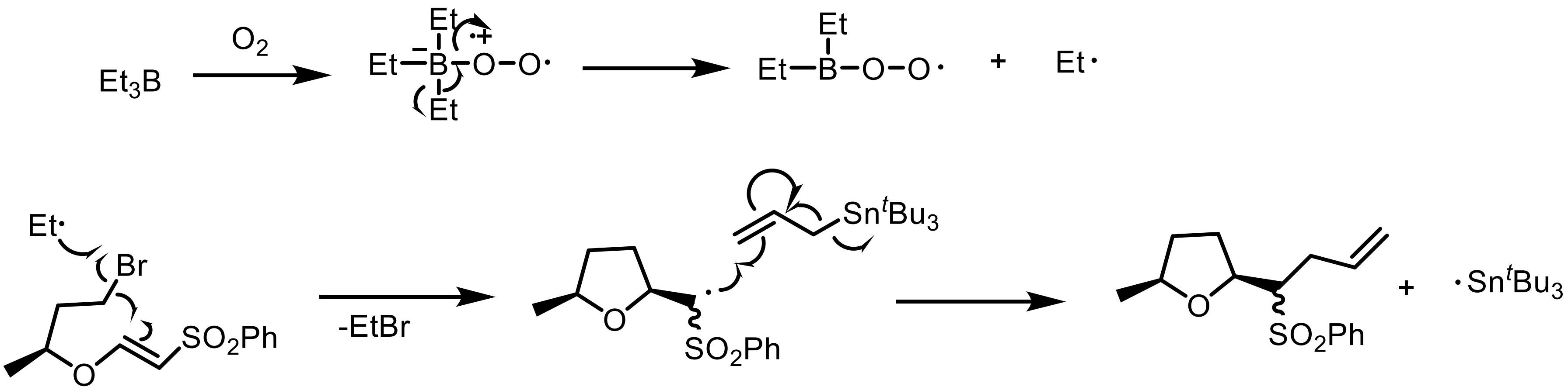
[a] Addition of oxidant at -78 ^{o}C.

Chem.—Eur. J. **2013**, *19*, 4255

An example of a tandem radical cyclization/Keck allylation

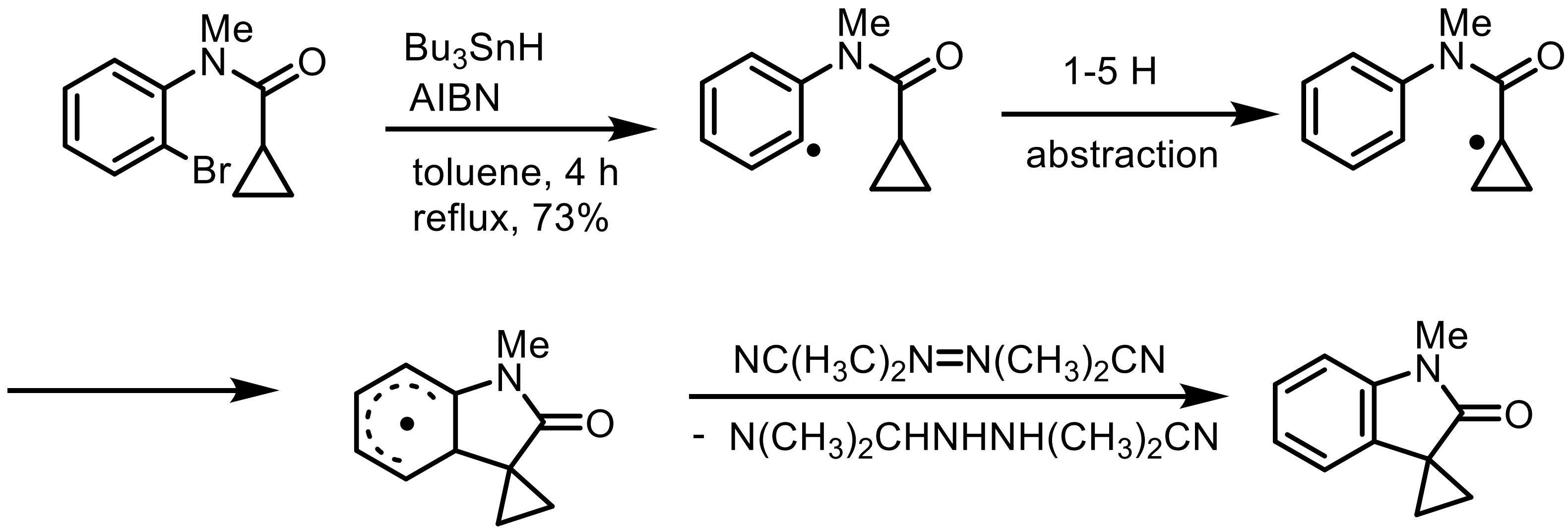


Mechanism:



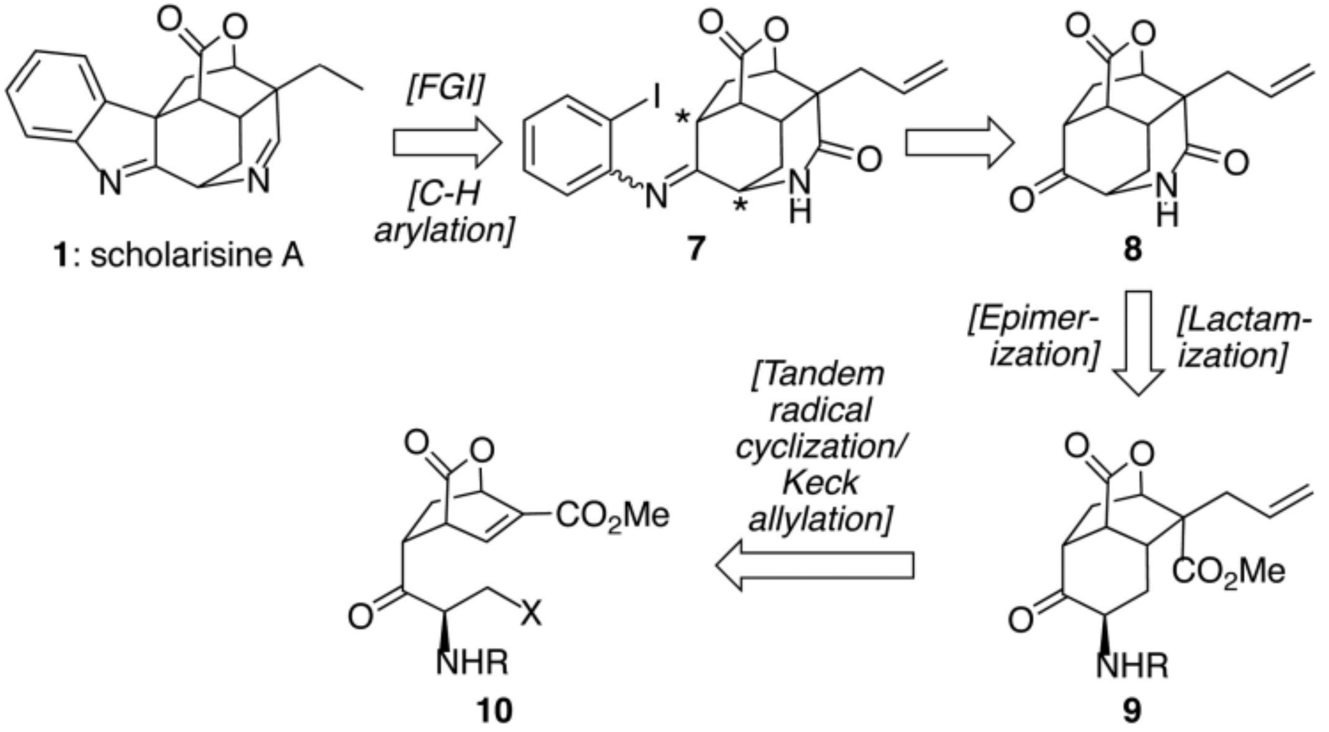
Tetrahedron Lett. **1997**, *38*, 8165
Pure Appl. Chem. **2007**, *79*, 223

Radical-based H-atom transfer/cyclization approaches towards oxindoles



J. Chem. Soc., Chem. Commun. **1995**, 977
Angew. Chem., Int. Ed. **2004,** *43,* 95

Title paper: retrosynthetic analysis



Challenges for C-H arylation:

1. Nonenolizable and potentially labile imine substrate
2. Positional selectivity between two different tertiary centers required if imine stereochemistry is not product-determinining

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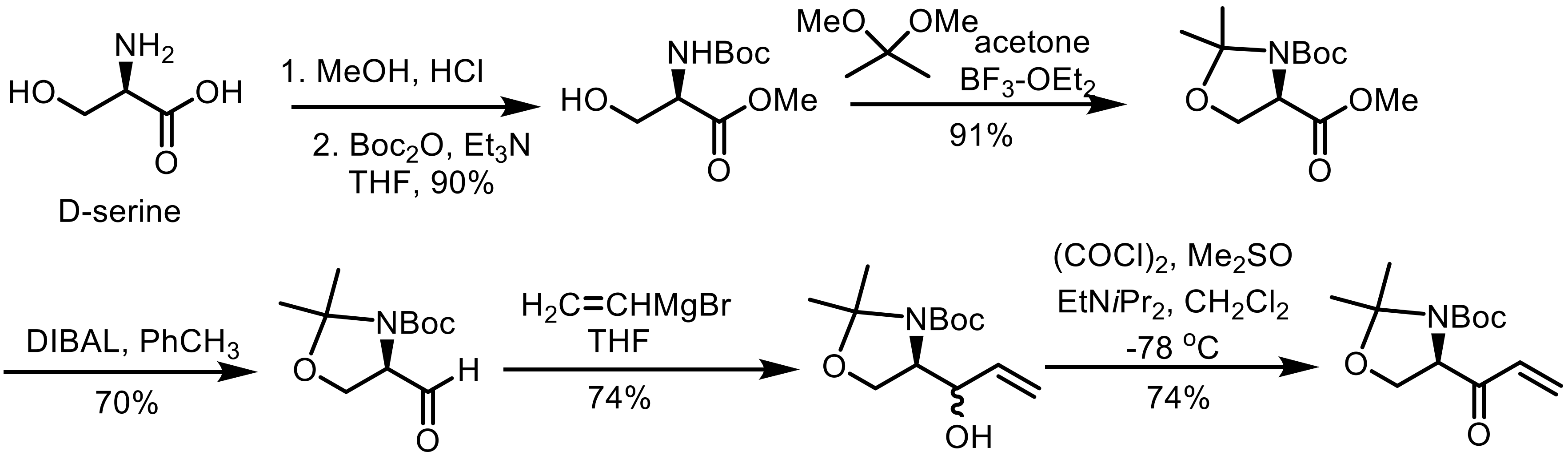
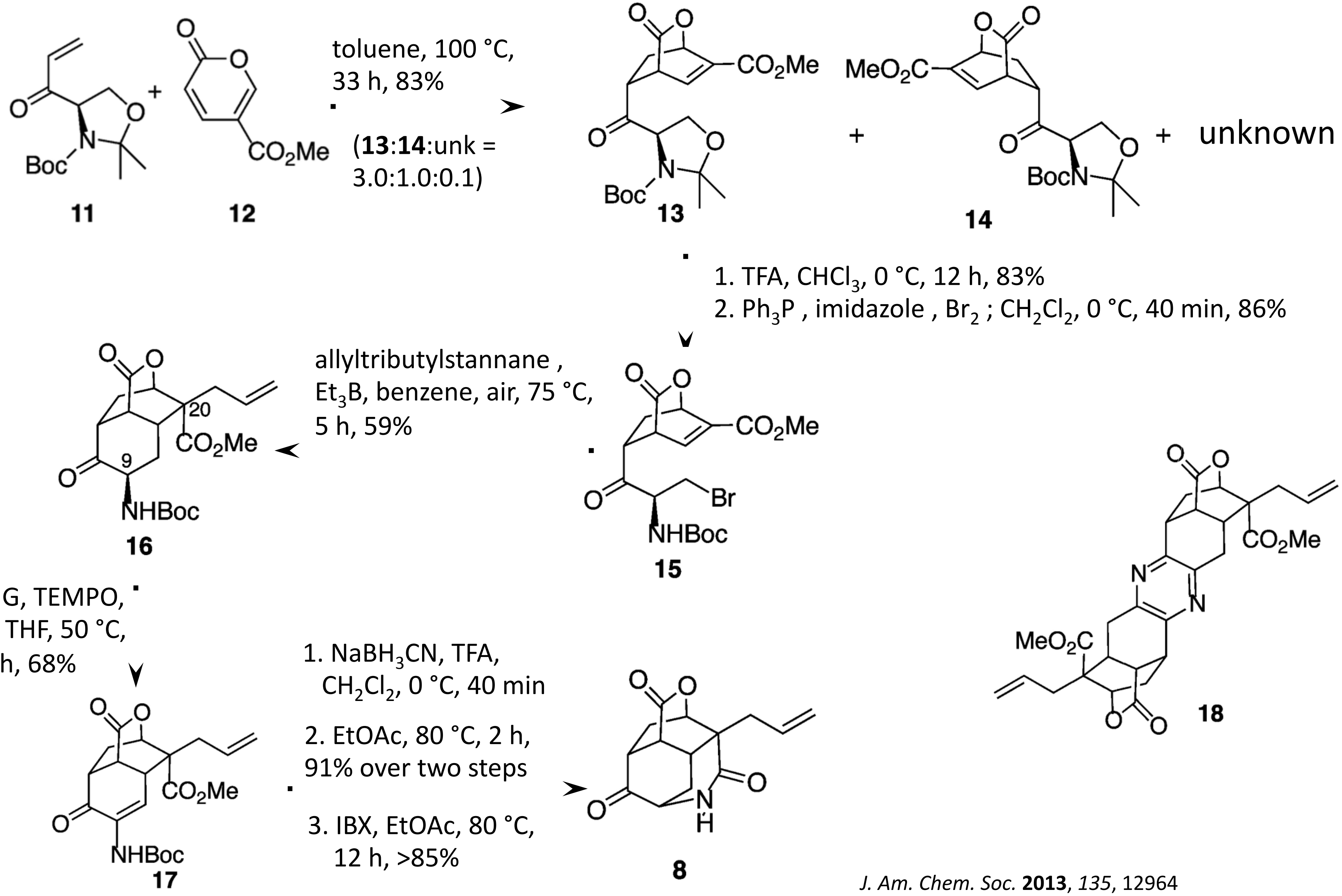
Starting material



Tetrahedron **1995**, *51*, 8121
Synthesis **1994**, 31

Preparation of the core of scholarisine A



11 + **12**

toluene, 100 °C, 33 h, 83%

(**13**:**14**:unk = 3.0:1.0:0.1)

13 + **14** + unknown

1. TFA, $CHCl_3$, 0 °C, 12 h, 83%
2. Ph_3P , imidazole , Br_2 ; CH_2Cl_2, 0 °C, 40 min, 86%

15

allyltributylstannane , Et_3B, benzene, air, 75 °C, 5 h, 59%

16

TMG, TEMPO, air, THF, 50 °C, 12 h, 68%

17

1. $NaBH_3CN$, TFA, CH_2Cl_2, 0 °C, 40 min
2. EtOAc, 80 °C, 2 h, 91% over two steps
3. IBX, EtOAc, 80 °C, 12 h, >85%

8

18

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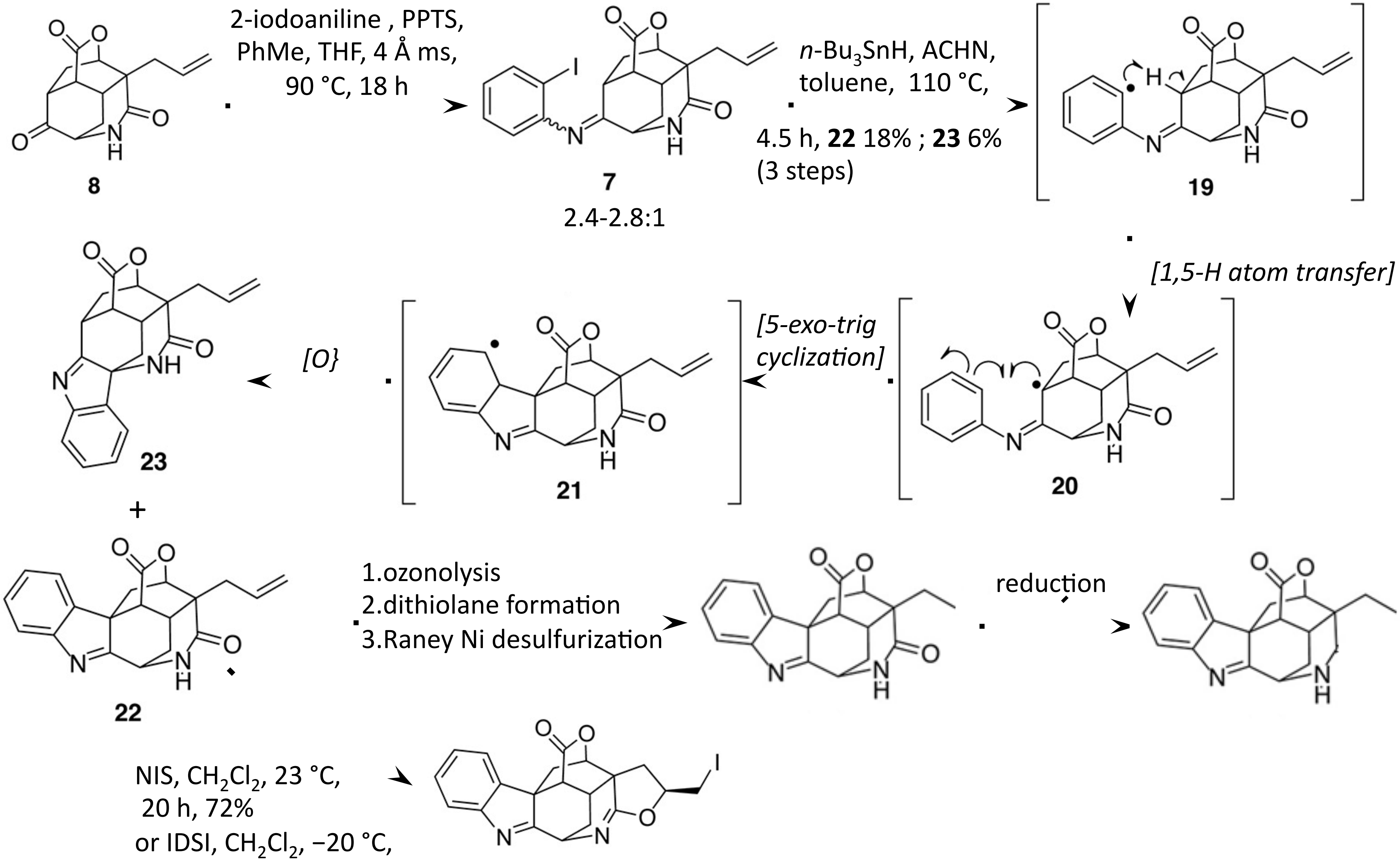
Completion of the total synthesis of (+)-scholarisine A



8

2-iodoaniline , PPTS, PhMe, THF, 4 Å ms, 90 °C, 18 h

7

2.4-2.8:1

n-Bu$_3$SnH, ACHN, toluene, 110 °C, 4.5 h, **22** 18% ; **23** 6% (3 steps)

19

[1,5-H atom transfer]

20

[5-exo-trig cyclization]

21

[O}

23

+

22

1.ozonolysis
2.dithiolane formation
3.Raney Ni desulfurization

reduction

NIS, CH_2Cl_2, 23 °C, 20 h, 72%
or IDSI, CH_2Cl_2, −20 °C, 45 min, 27%

24

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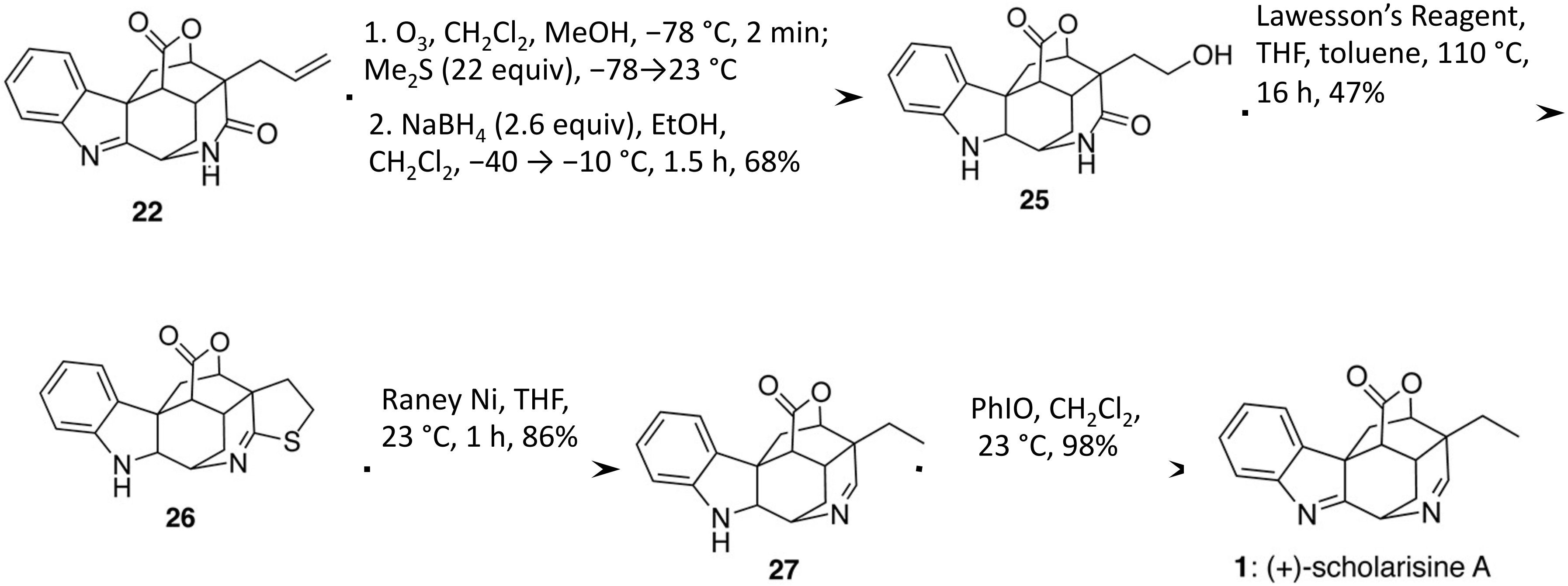
Completion of the total synthesis of (+)-scholarisine A



22

1. O_3, CH_2Cl_2, MeOH, −78 °C, 2 min; Me_2S (22 equiv), −78→23 °C

2. $NaBH_4$ (2.6 equiv), EtOH, CH_2Cl_2, −40 → −10 °C, 1.5 h, 68%

25

Lawesson's Reagent, THF, toluene, 110 °C, 16 h, 47%

26

Raney Ni, THF, 23 °C, 1 h, 86%

27

PhIO, CH_2Cl_2, 23 °C, 98%

1: (+)-scholarisine A

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Conclusion

- An enantioselective synthesis of (+)-scholarisine A was completed in 14 steps from known compound (15 steps from commercial materials).
- Key steps include:
  - an efficient and diastereoselective pyrone Diels–Alder reaction to rapidly form the appropriately functionalized [2.2.2]-bicycle
  - a radical cyclization/Keck allylation to concurrently forge the [3.3.1]-bicycle and C-20 quaternary center
  - an indolenine annulation at a nonenolizable tertiary center via a novel late-stage radical C–H arylation
  - the use of a pendant hydroxyl group to facilitate the chemoselective reduction of an extremely unreactive lactam
- Future work:
  - applying the developed strategy to related targets
  - exploring the scope of the C–H arylation step
  - probing the biochemical potential of scholarisine A itself

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