Few Selected Total Synthesis in 2007

Group Meeting
June 1, 2007

Anil Kumar Gupta

Total Synthesis without Protecting Groups

- Chemoselectivity !!

Solution: Protecting group

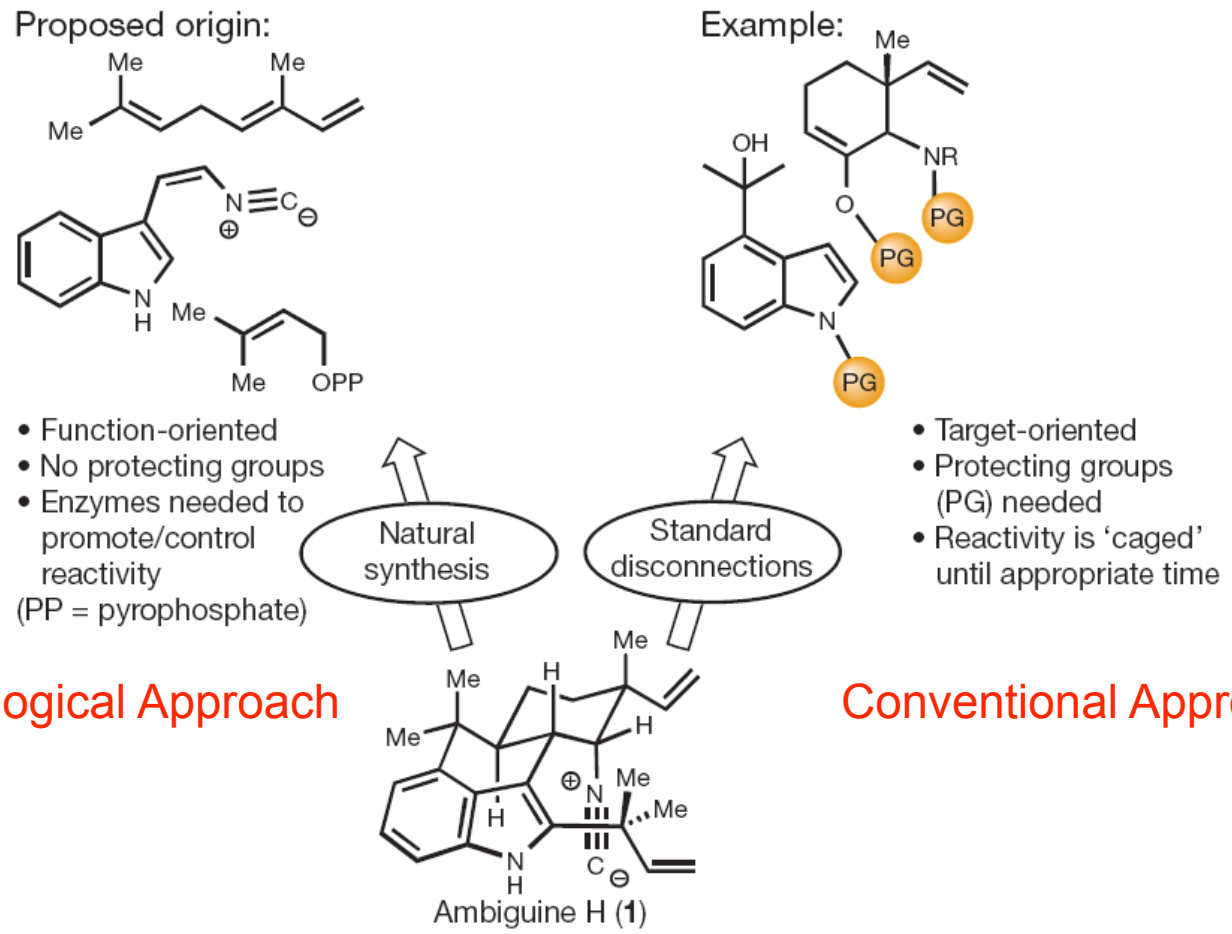
BUT……..It adds….

- Cost
- Complexity of synthesis
- At least 2 steps each to a synthetic sequence
- Also, sometimes lowers efficiency and yield
- Difficulty in their removal
- Unintented Side reactions(sometimes)

Sierra, M. A. & de la Torre, M. C. Dead Ends and Detours, Direct Ways to Successful Total Synthesis (Wiley-VCH, Weinheim, 2004)

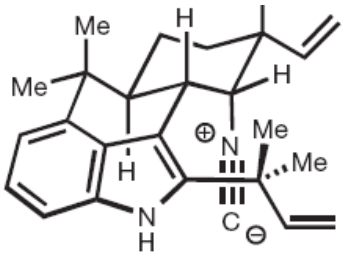
Hapalindole, Fischerindole, Welwitindolinone, and Ambiguine alkaloids

cation-olefin cyclization

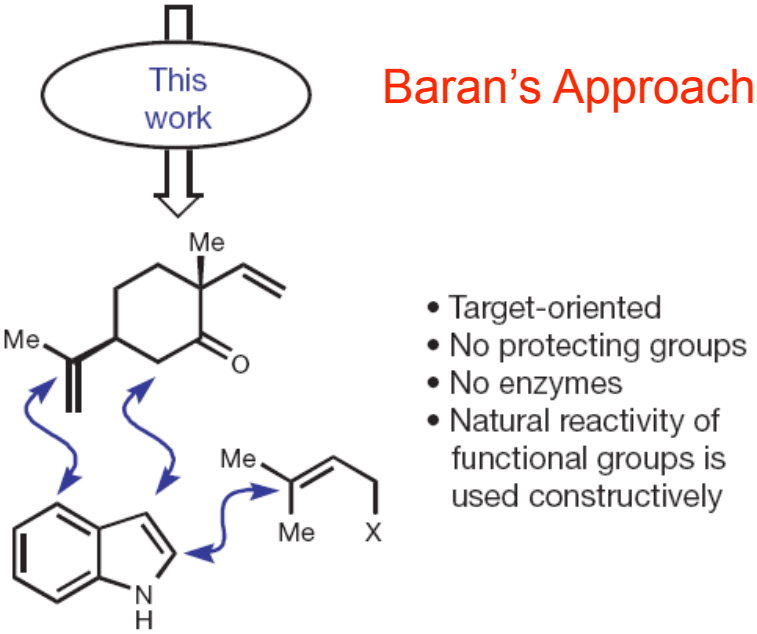


Baran, P. S. & Richter, J. M. *Nature,* **2007**,446, 404

Hapalindole, Fischerindole, Welwitindolinone, and Ambiguine alkaloids



Ambiguine H (**1**)



Baran's Approach

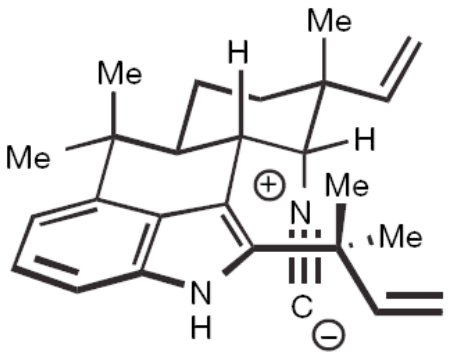
- Target-oriented
- No protecting groups
- No enzymes
- Natural reactivity of functional groups is used constructively

Biological Activity:

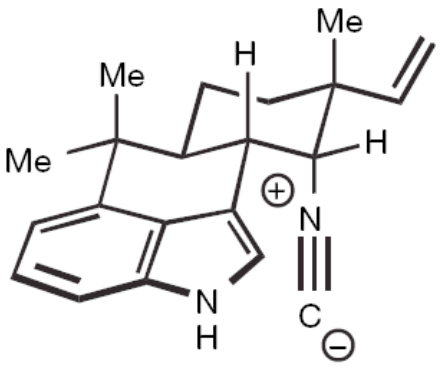
- Antifungal, Antibacterial,
- Antimycotic and Anticancer
- Further testing prevented by the paucity of this material (~5 mg).

Baran, P. S. & Richter, J. M. *Nature,* **2007**,446, 404

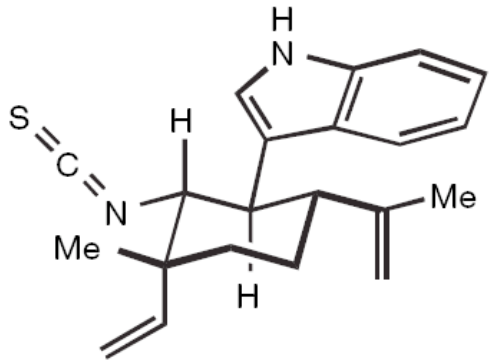
Hapalindole, Fischerindole, Welwitindolinone, and Ambiguine alkaloids



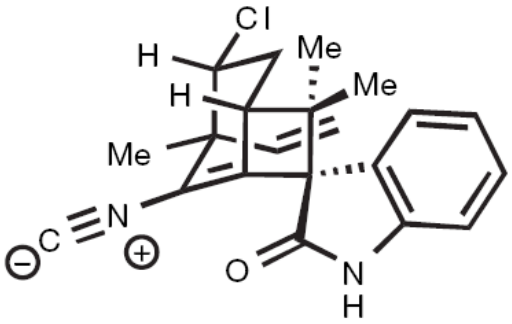
Ambiguine H (**1**)



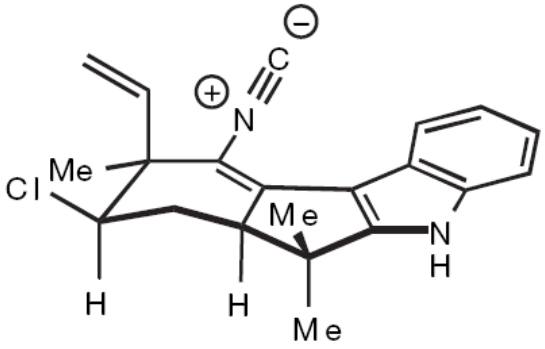
Hapalindole U (**2**)



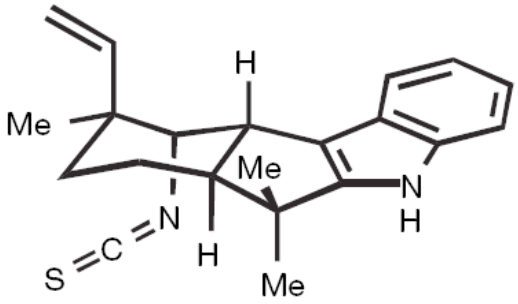
Hapalindole Q (**3**)



Welwitindolinone A (**4**)



Fischerindole I (**5**)



Fischerindole U (**6**)

Baran, P. S. & Richter, J. M. *Nature,* **2007**,446, 404

Hapalindole U and Ambiguine H

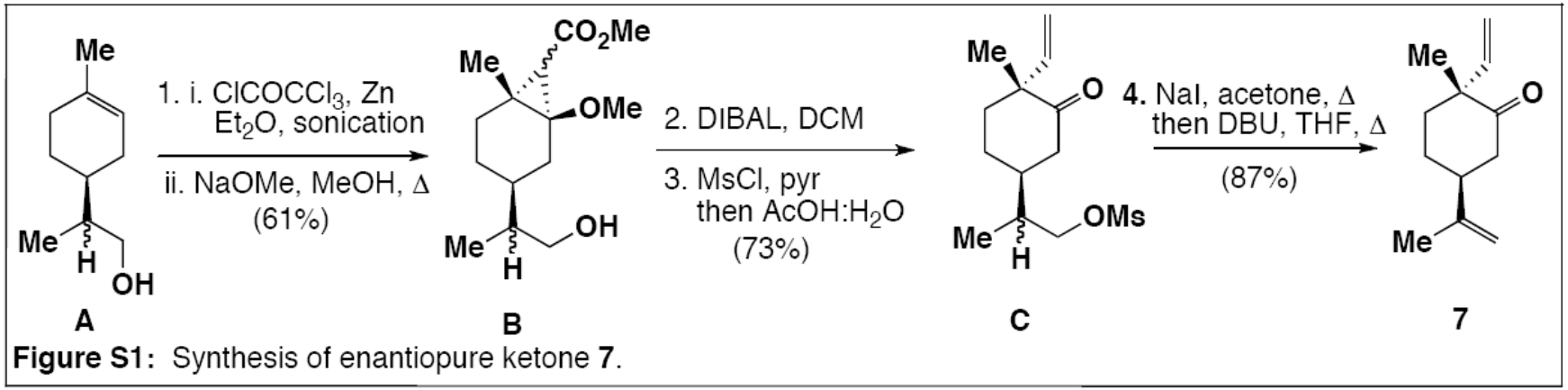
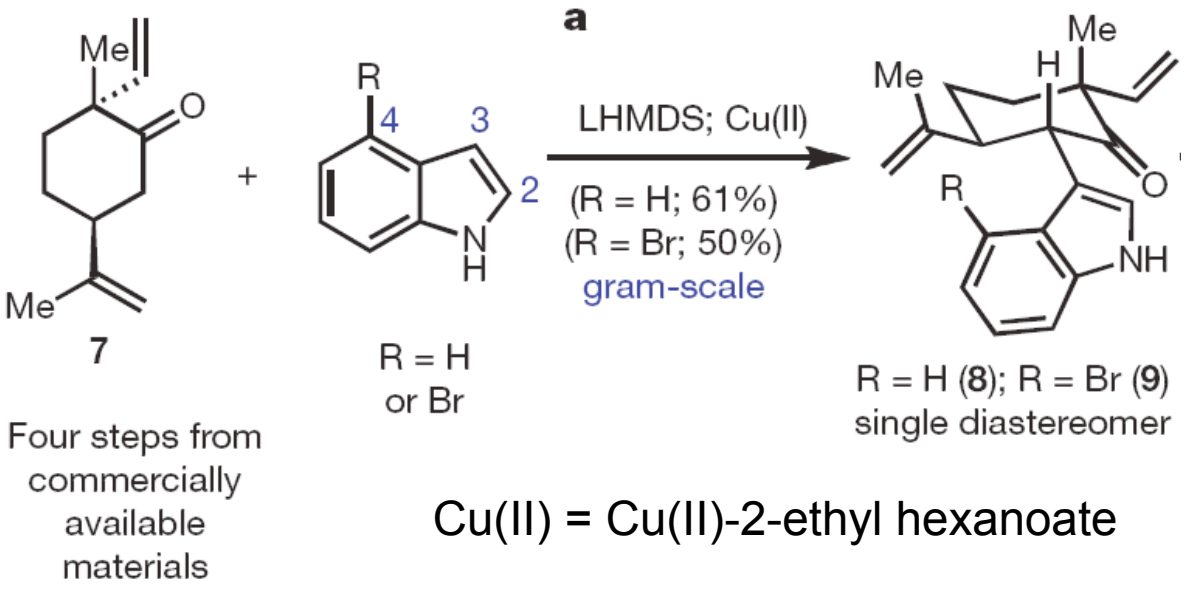
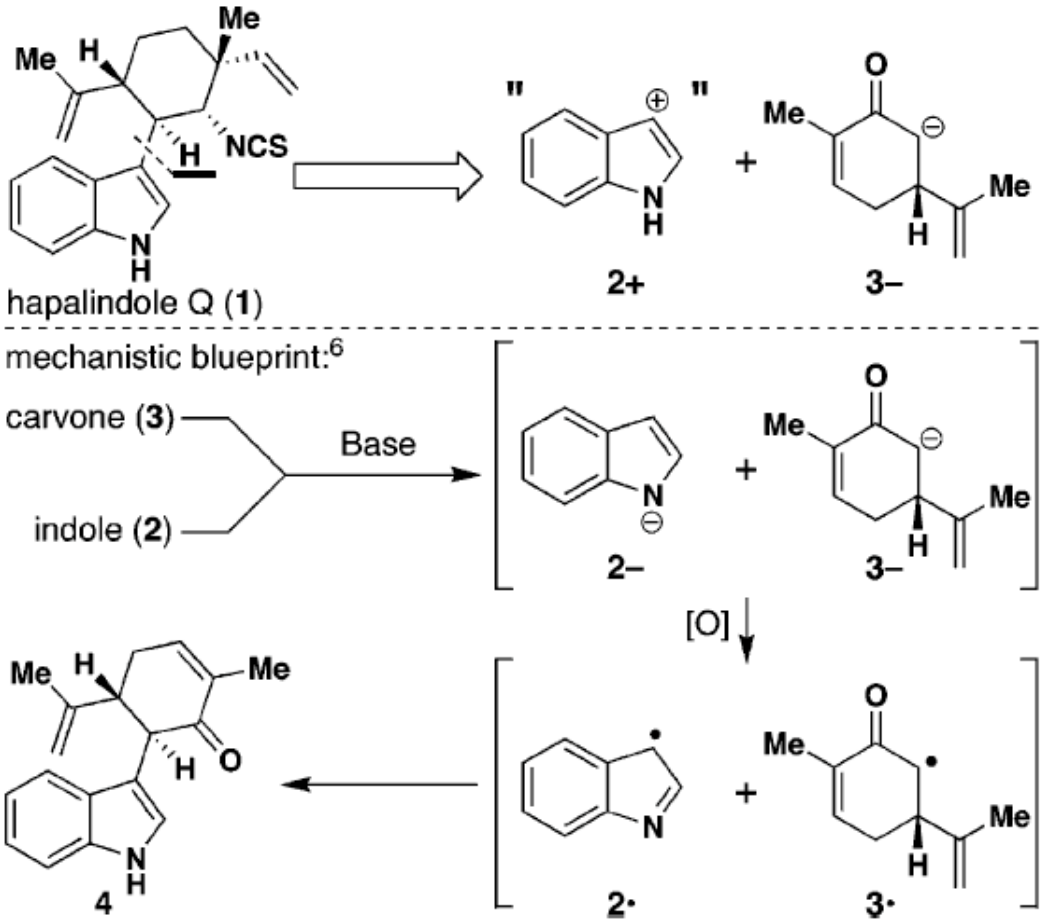


Figure S1: Synthesis of enantiopure ketone **7**.



Cu(II) = Cu(II)-2-ethyl hexanoate

Direct Coupling of Indoles with Carbonyls Compounds

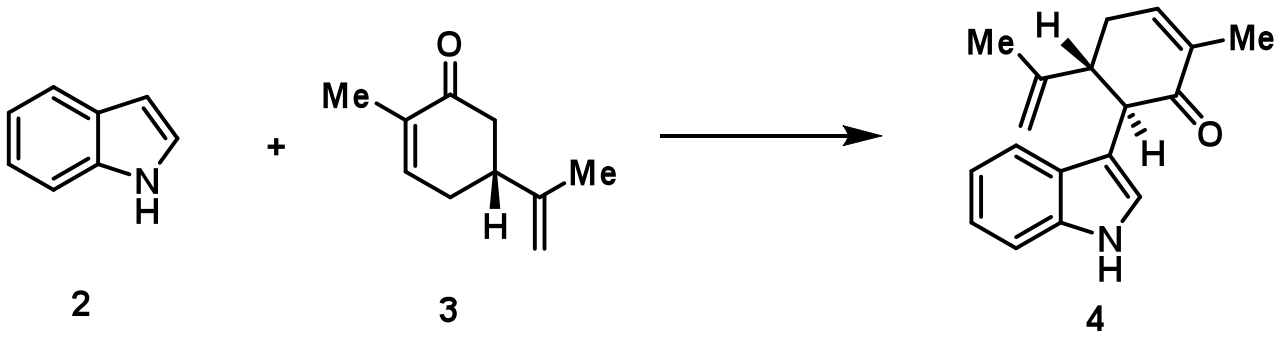


Oxidative dimerization of enolates???

Large excess of one of the partners avoids homocoupling

Baran, P. S. & Richter, J. M. *J. Am. Chem. Soc.* **2004**,*126*, 7450–7451

Optimization



2 3 4

Table 1. Selected Optimization Results of **2** + **3** → **4**

indole (**2**) + carvone (**3**) —THF, Base, then [O]; [O] = $FeCl_3$/DMF (Fe) or Copper(II)2-ethylhexanoate (Cu)→ **4**

Entry	Conditions	Yield (%)[a]
1	**2** (1.0 eq), **3** (3.0 eq), LDA (4.0 eq), Fe (4.0 eq), –78 to 23 °C	*ca* 15
2	**2** (1.0 eq), **3** (3.0 eq), LDA (4.0 eq), Cu (4.0 eq), –78 to 23 °C	24
3	**2** (1.0 eq), **3** (1.0 eq), LDA (2.0 eq), Cu (2.0 eq), –78 to 0 °C	24
4	**2** (3.0 eq), **3** (1.0 eq), LDA (4.0 eq), Cu (4.0 eq), –78 to 0 °C	32
5	**2** (2.0 eq), **3** (1.0 eq), LHMDS (3.0 eq), Cu (1.5 eq), –78 °C	53 (70)[b]

[a] Isolated yield after chromatography. [b] Yield based on recovered sm.

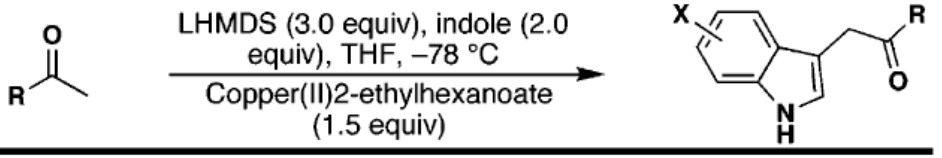
Optimum Protocol

Baran, P. S. & Richter, J. M. *J. Am. Chem. Soc.* **2004**,*126*, 7450–7451

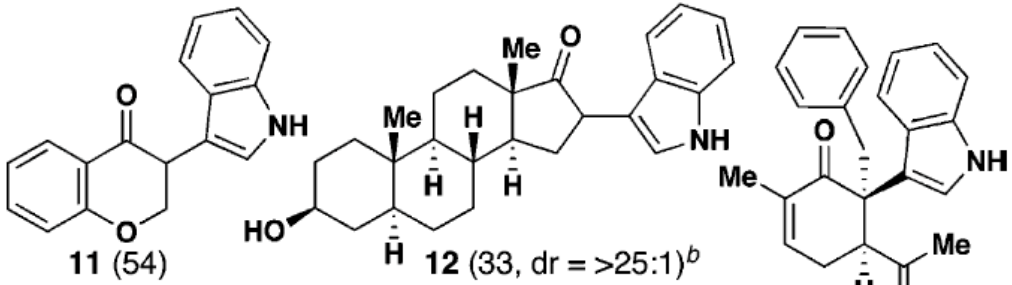
Scope

- Free Alcohols
- Hindered Indoles
- Amides
- Functionalized Indoles

Table 2. Preparation of α-Indole Carbonyl Compounds



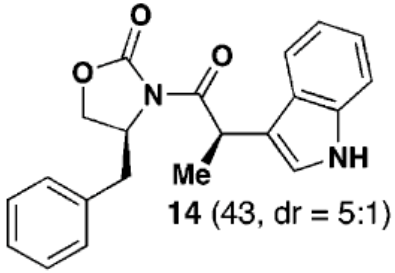
Product (Yield %)[a]



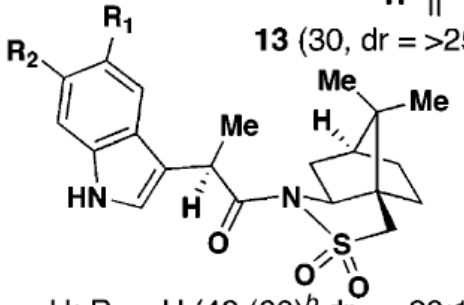
11 (54)

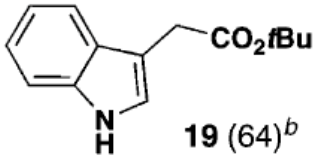
12 (33, dr = >25:1)[b]

13 (30, dr = >25:1)[b]



14 (43, dr = 5:1)



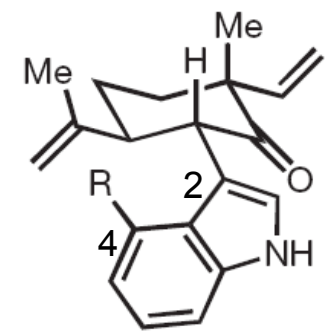


19 (64)[b]

15: R_1 = H; R_2 = H (48 (60)[b] dr = >20:1)[c]
16: R_1 = F; R_2 = H (30 (90)[b] dr = 10:1)
17: R_1 = H; R_2 = Me (36 (96)[b] dr = 10:1)
18: R_1 = H; R_2 = OMe (37 (49)[b], dr = 17:1)[c]

Baran, P. S. & Richter, J. M. *J. Am. Chem. Soc.* **2004**,*126*, 7450–7451

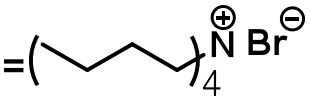
Hapalindole U and Ambiguine H *contd….*

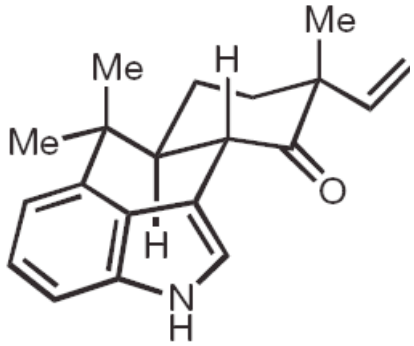


R = H (**8**); R = Br (**9**)
single diastereomer

Friedal-Crafts annulation failed!!!
Cyclization at C-2

6-exo-trig
$[Pd(P(o\text{-}tol)_3OAc]_2$ (5mol%)
$NaOCHO, TBAB, Et_3N$
65%

TBAB = 



10

reductive Heck-type annulation

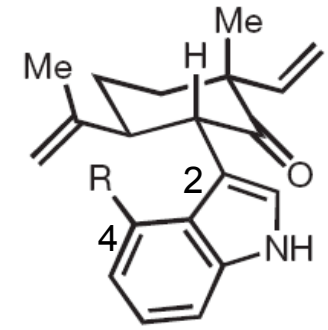
9 → **10**

10 mol. % Pd, Et_3N (2.2 equiv), HCO_2Na (1.25 equiv), DMF, 80 °C

Entry	Pd-source, additives, time	Yield (%)[a]
1	$Pd(OAc)_2$, TBAC (1.0 equiv), Et_3N (2.5 equiv), 15 h	18[b]
2	$Pd(OAc)_2$, Ph_3P (0.2 equiv), 15 h	39[c]
3	$Pd_2(dba)_3$, TBAB (2.0 equiv), Et_3N (2.2 equiv), 15 h	22
4	$Pd(PPh_3)_4$, TBAB (2.0 equiv), Et_3N (2.2 equiv), 15 h	42
5	Herrmann's catalyst, TBAB (2.0 equiv), 15 h	50
6	$Pd(OAc)_2$, TBAB (2.0 equiv), Et_3N (2.2 equiv), *added over 5 h*	<10[d]
7	Herrmann's catalyst, TBAB (2.0 equiv), Et_3N (2.2 equiv), *added over 5 h*	65[d]

[a] isolated yield after chromatography; [b] conditions from ref. 26; [c] conditions from ref. 25; [d] isolated yield after 5 h (syringe pump) addition complete

Hapalindole U and Ambiguine H *contd….*



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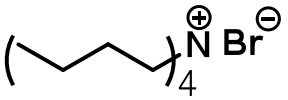
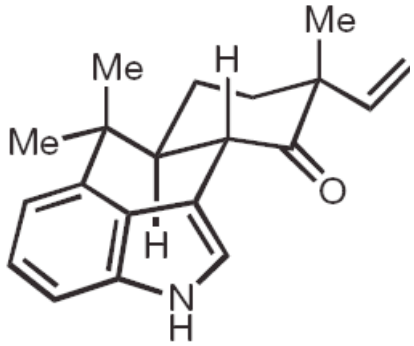
65%

TBAB = 



10

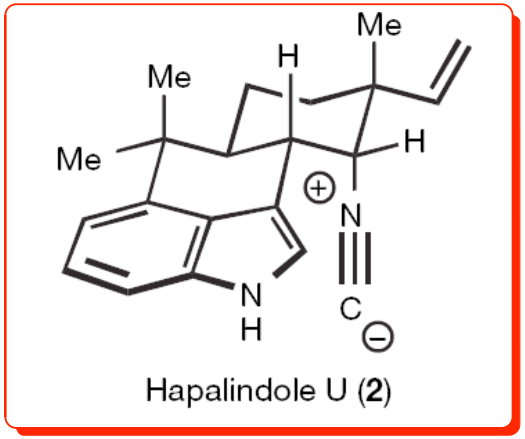
1

NH_4OAc, $NaBH_3CN$
MeOH/THF,
MW(150°C),2.5 min
then
HCOOH,CDMT
DMAP,NMM,DCM
2h,25°C

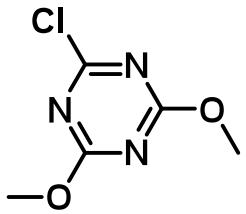
2

$COCl_2$, ET_3N
DCM 0°C

60% (2 steps)

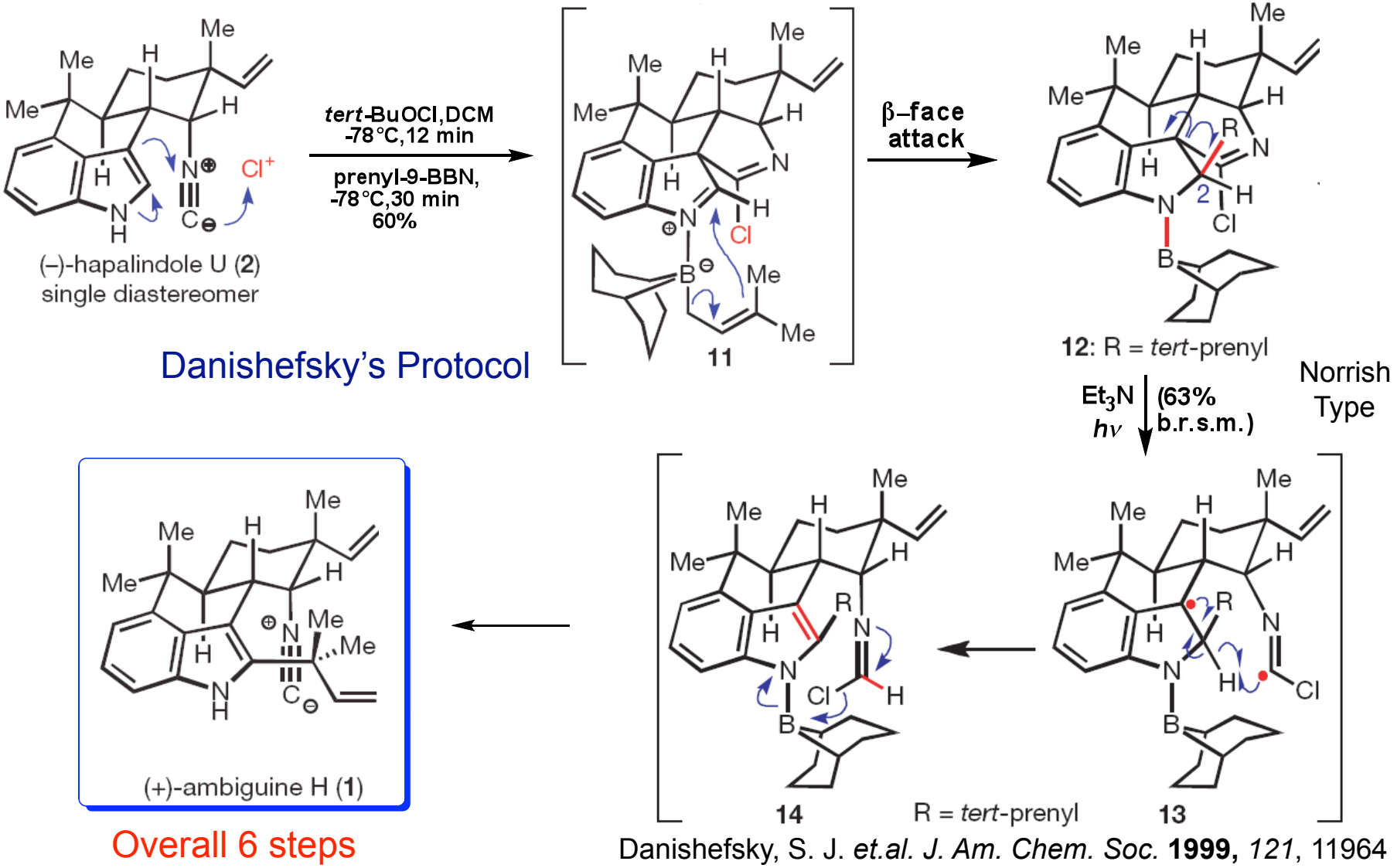


Hapalindole U (**2**)

CDMT = 

Previous synthesis: racemic,multiple PGs,20 steps

Hapalindole U and Ambiguine H *contd….*

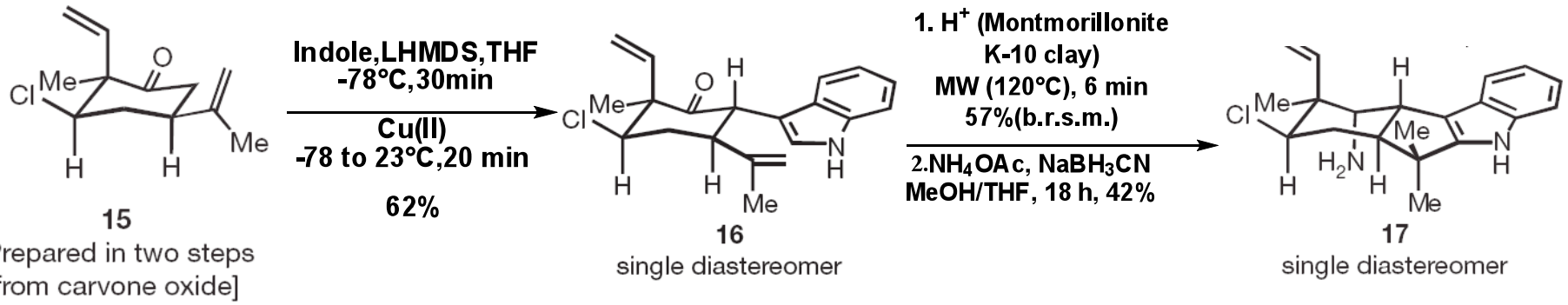


Danishefsky's Protocol

Overall 6 steps

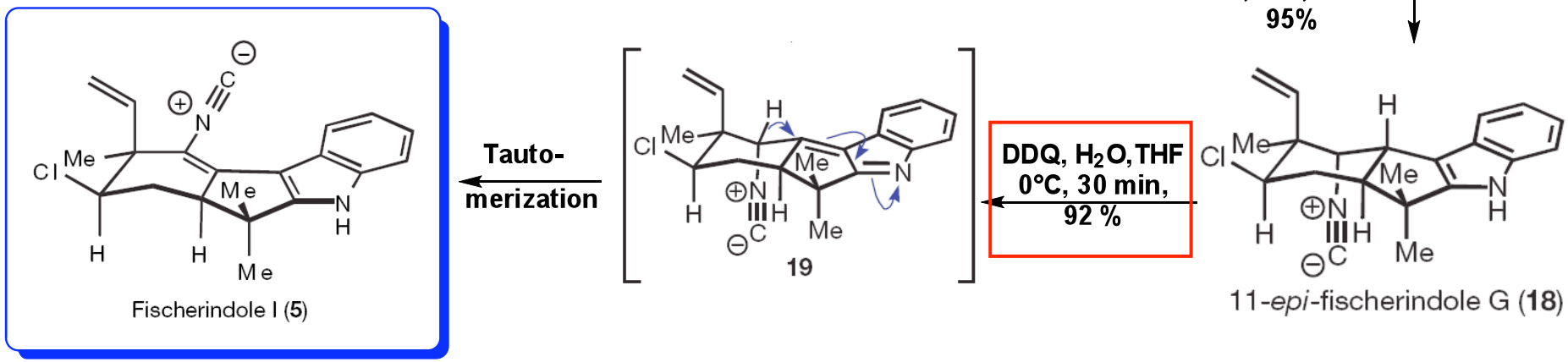
Danishefsky, S. J. *et.al. J. Am. Chem. Soc.* **1999,** *121*, 11964

Fischerindole I and Welwitindolinone A (Revised)



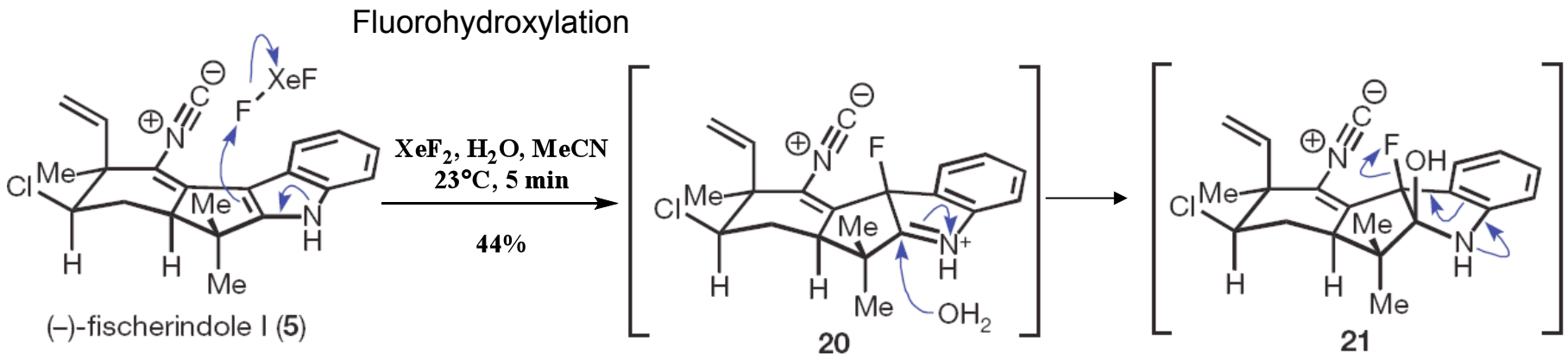
*Previous Synthesis : 6.9 % and 1.7% (from **15**)

This Time: 13.0 % and 5.7%(from **15**)

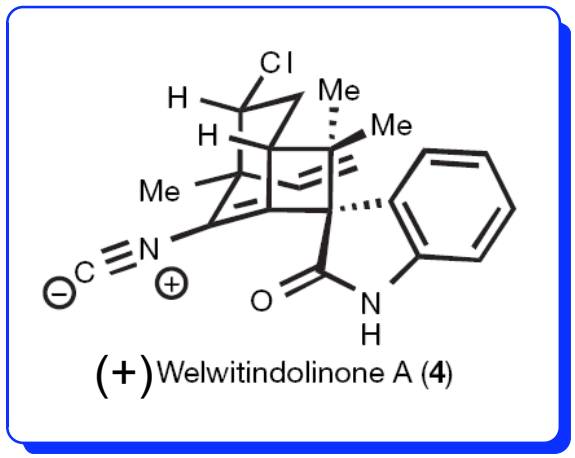


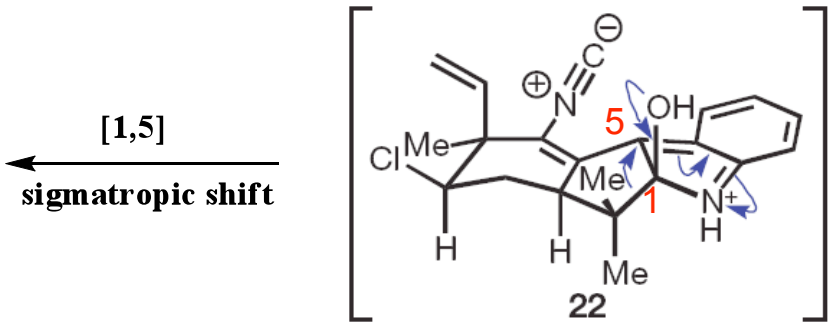
*Baran, P. S. *et.al. J. Am. Chem. Soc.* **2005,** *127*, 15394

Fischerindole I and Welwitindolinone A



Other reported synthesis: 25 steps
6 PGs, racemic product





Shellhamer, D. F. *et al. J. Chem. Soc. Perkin Trans. II*, **1991,** 401

Guidelines followed……

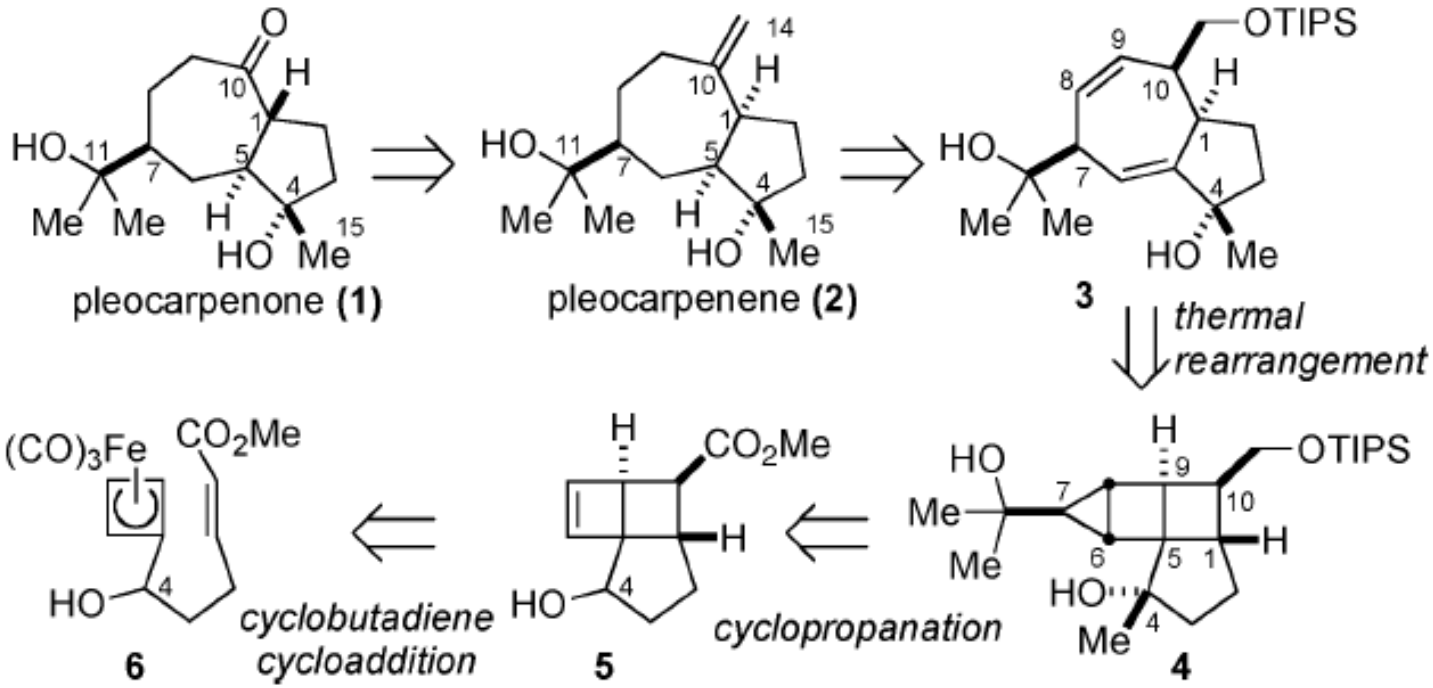
- Redox reactions that do not form C–C bonds should be minimized
- The percentage of C–C bond-forming events within the total number of steps in a synthesis should be maximized
- Disconnections should be made to maximize convergency
- The overall oxidation level of intermediates should linearly escalate during assembly of the molecular framework (except in cases where there is strategic benefit such as an asymmetric reduction)

Guidelines followed……

- Where possible, cascade (tandem) reactions should be designed and incorporated to elicit maximum structural change per step
- The innate reactivity of functional groups should be exploited so as to reduce the number of (or perhaps even eliminate) protecting groups
- Effort should be spent on the invention of new methodology to facilitate the aforementioned criteria and to uncover new aspects of chemical reactivity
- If the target molecule is of natural origin, biomimetic pathways (either known or proposed) should be incorporated to the extent that they aid the above considerations

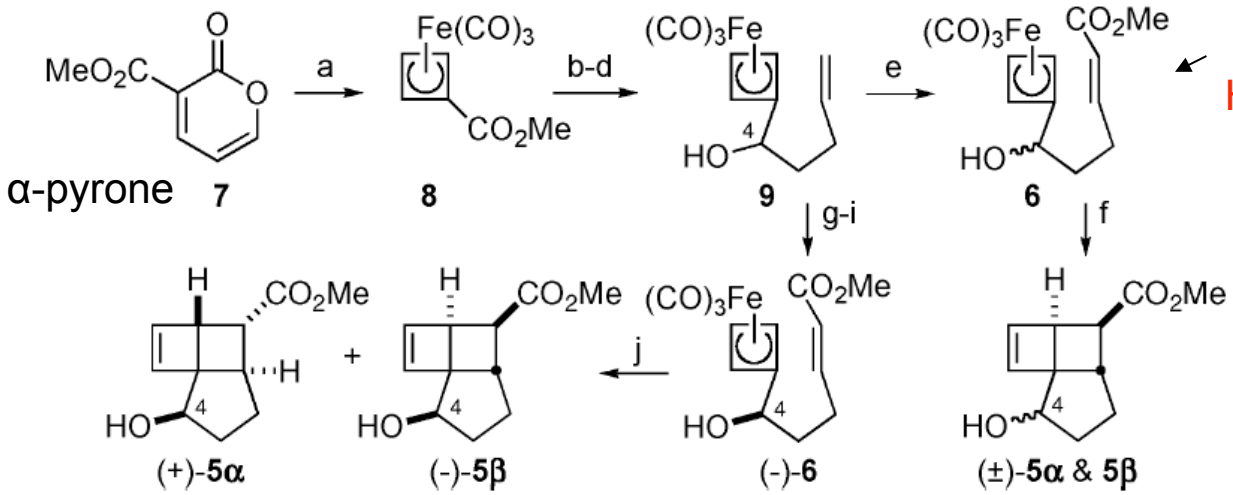
Pleocarpene and Pleocarpenone

Scheme 1. Retrosynthesis of Pleocarpenone and Pleocarpenene



Pleocarpene and Pleocarpenone

Scheme 2. Preparation of the Cyclobutene **5**[a]



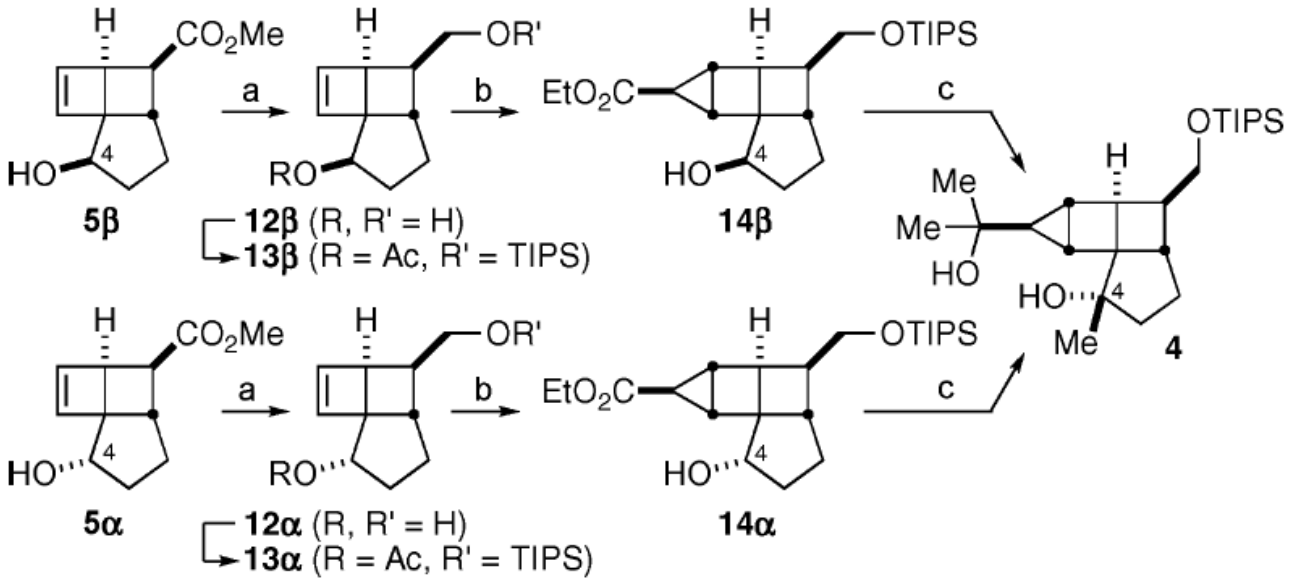
RCM using Hoyeda-Grubbs 2nd generation catalyst

[a] Reaction conditions: (a) *hν*, PhH; $Fe_2(CO)_9$, 64%; (b) DIBAL, Et_2O, 0 °C to rt, 95%; (c) MnO_2, CH_2Cl_2, 4 Å MS, 83%; (d) $CH_2{=}CHCH_2CH_2MgBr$, Et_2O, −78 °C, 96%; (e) $CH_2{=}CHCO_2Me$ (10 equiv), Grubbs' second cat. (**10**) (2.5 mol %), 60 °C, (94%, 13:1 *E*:*Z*); (f) CAN, acetone, (91%, 3.3:1 *β*:α); (g) MnO_2, CH_2Cl_2, 4 Å MS (90%); (h) catechol borane, (3a*S*)-tetrahydro-1-methyl-3,3,-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole (**11**) (15 mol %), toluene, −78 °C (96%, 92% ee); (i) $CH_2{=}CHCO_2Me$ (10 equiv), **10** (2.5 mol %), 60 °C, (94%, 13:1 *E*:*Z*); (j) CAN, acetone; separation on 10 wt % $AgNO_3$ on silica gel (80%, 2.7:1 *β*:α).

Snapper et.al. JACS,**2007,** *129*, 486

Pleocarpene and Pleocarpenone

Scheme 3. Cyclopropanation of Cyclobutene **5**[a]

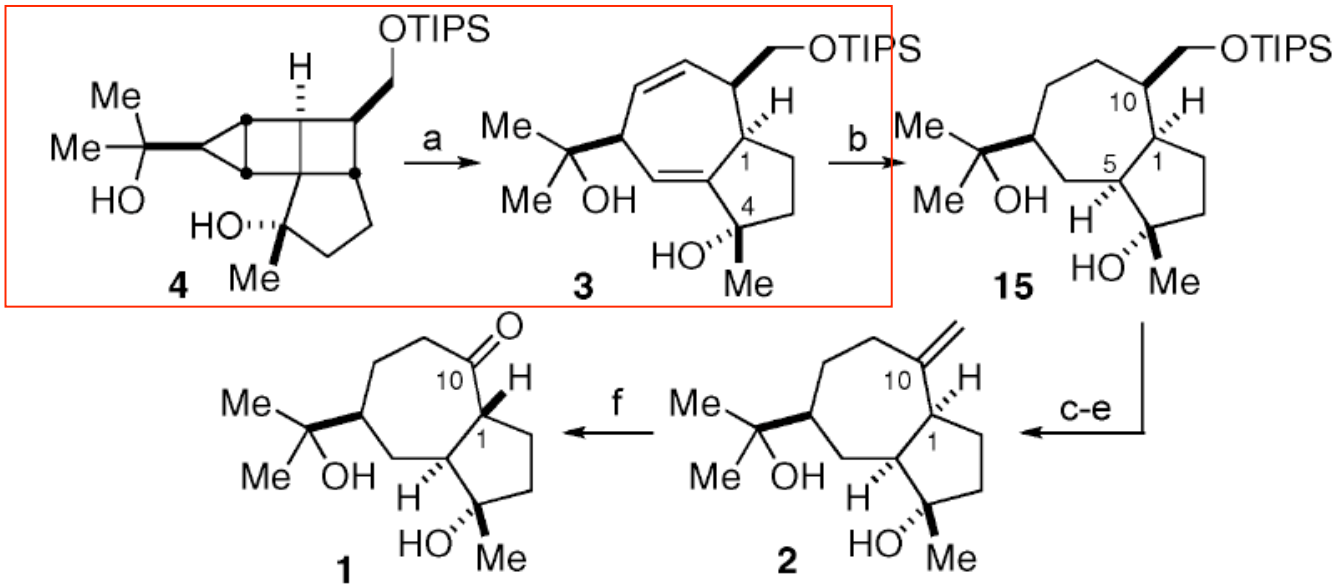


[a] Data shown for one enantiomeric series. Reaction conditions: (a) (i) LAH, THF, 0 °C to rt; (ii) TIPSCl, DMAP, Et_3N, THF, 4 Å MS; Ac_2O (87−89%); (b) EDA, $Cu(acac)_2$ (5 mol %), CH_2Cl_2, reflux; EtOH, rt; then $NaOEt_{(s)}$ (93−95%); (c) $(COCl)_2$, DMSO, THF, −62 °C; Et_3N, rt; MeMgCl, −78 °C (79−82%).

Snapper et.al. JACS,**2007,** *129*, 486

Pleocarpene and Pleocarpenone

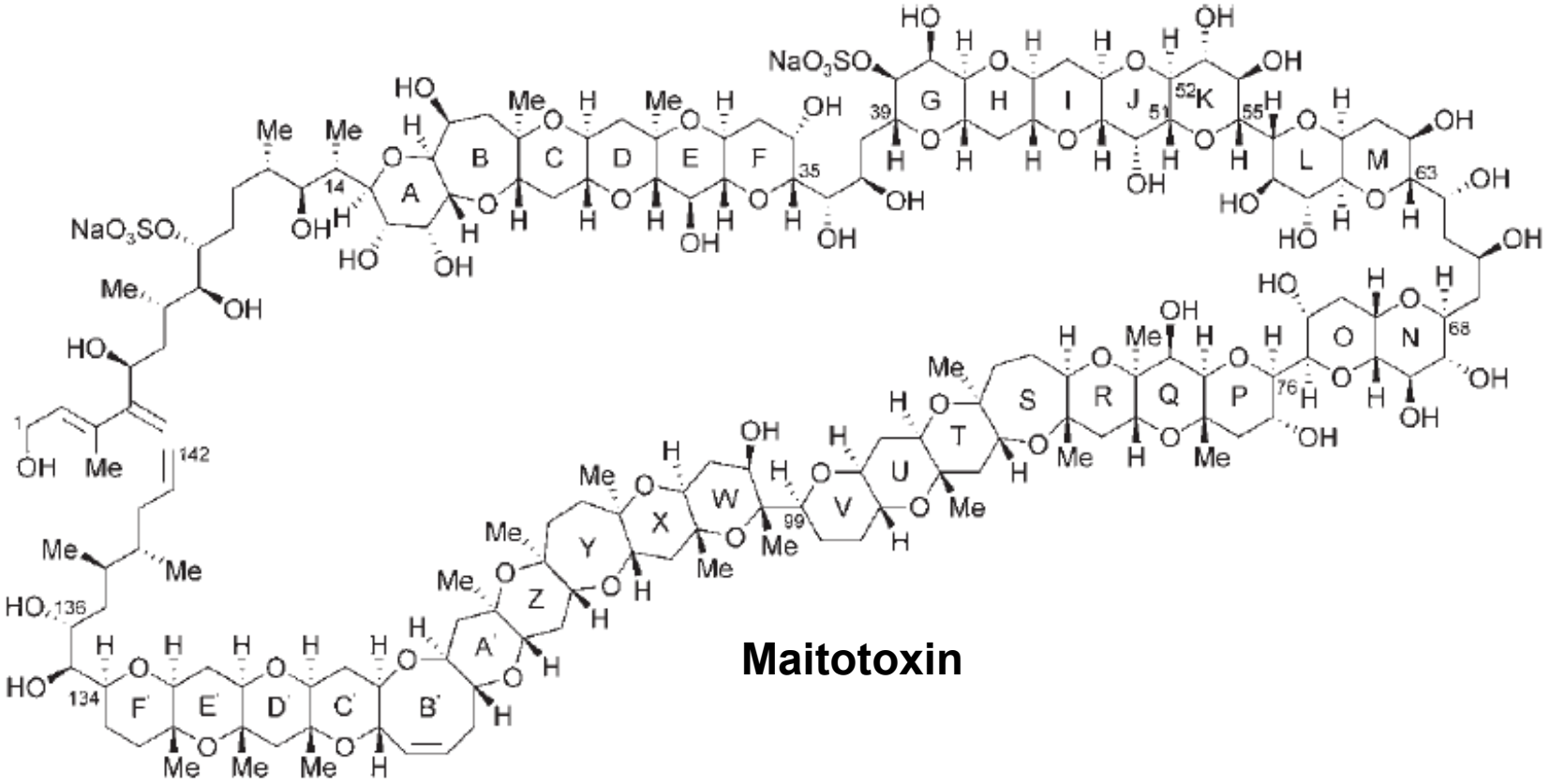
Scheme 4. Completion of the Total Synthesis[a]



[a] Reaction conditions: (a) benzene, 200 °C, DBU (15 mol %) (76%); (b) W.R. Grace 2800 RaNi, H_2 (100 atm), acetone, 63%; (c) TBAF, THF, 99%; (d) TsCl, Et_3N, DMAP, THF, CH_2Cl_2, 99%; (e) NaI, DBU, DMF, 80 °C, 83%; (f) O_3, MeOH, −78 °C; DMS, rt; NaOMe (85%).

Snapper et.al. JACS,**2007,** *129*, 486

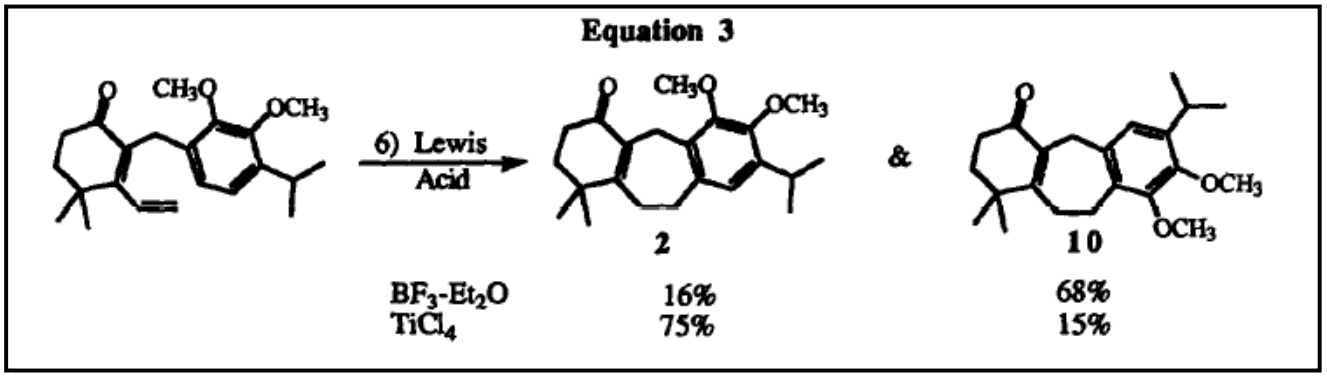
Mother Nature still provides significant synthetic challenges

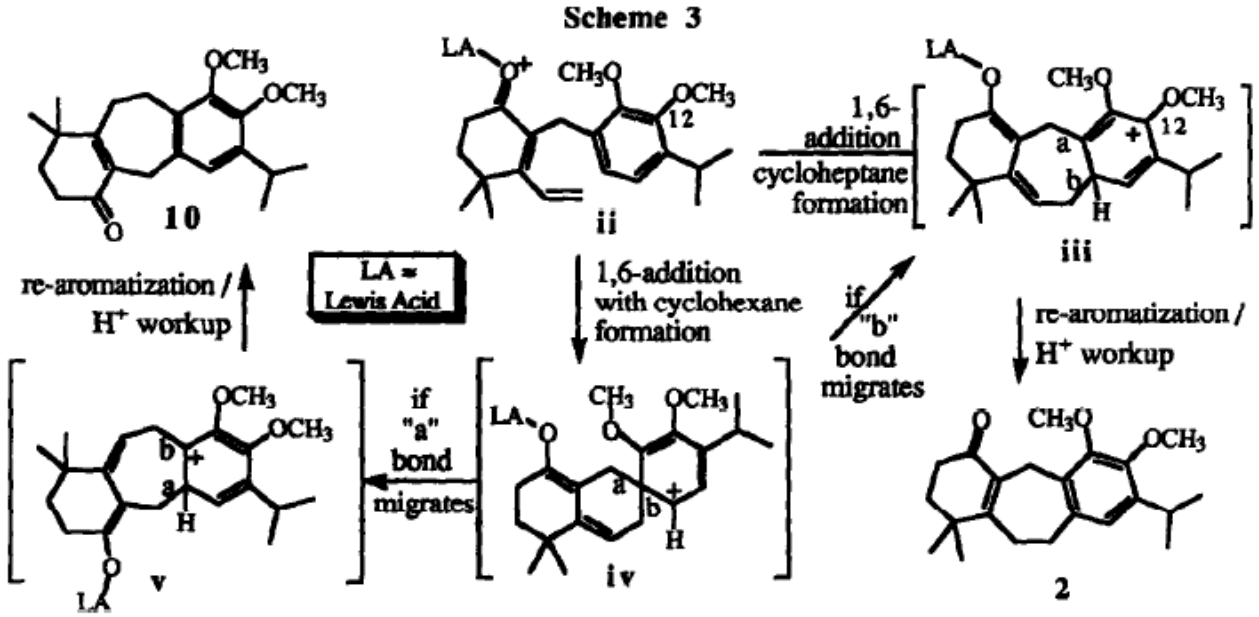


Maitotoxin

Thanks

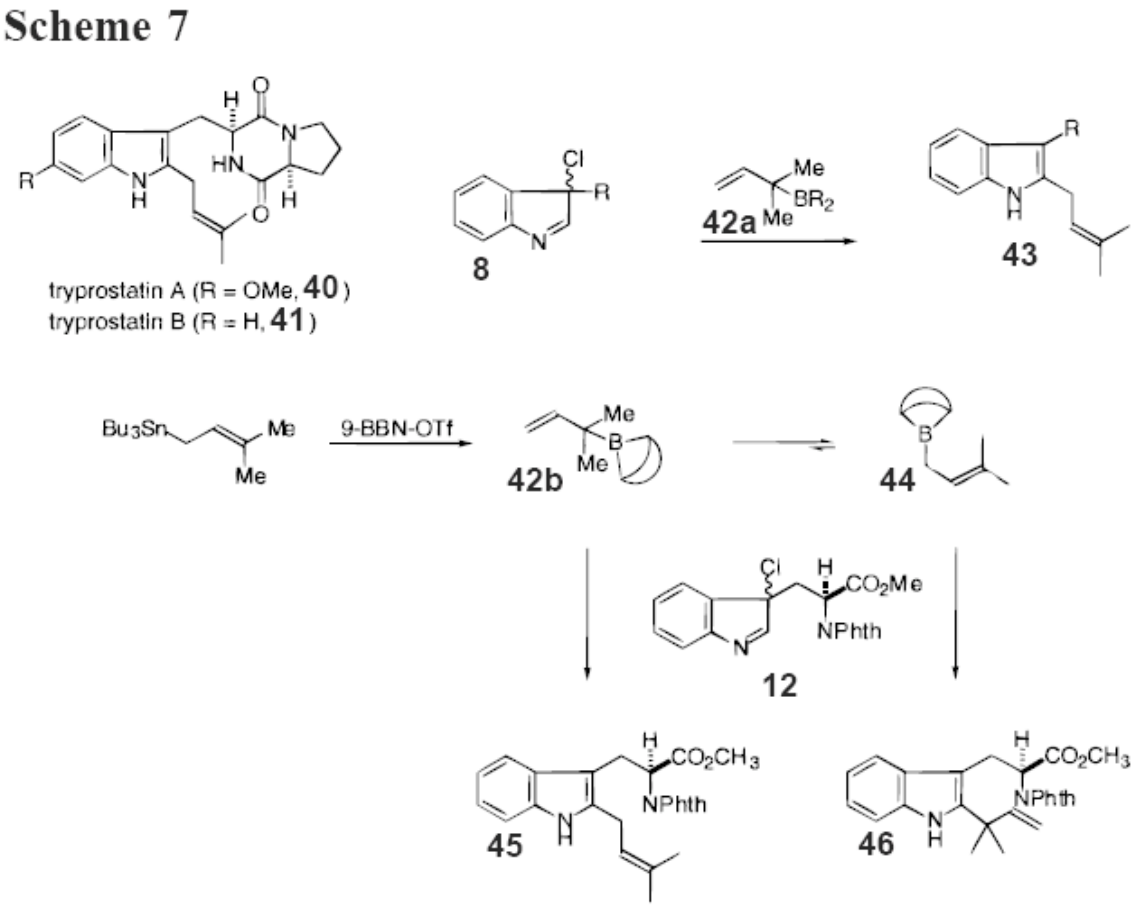
The Total Synthesis of (±)Barbatusol





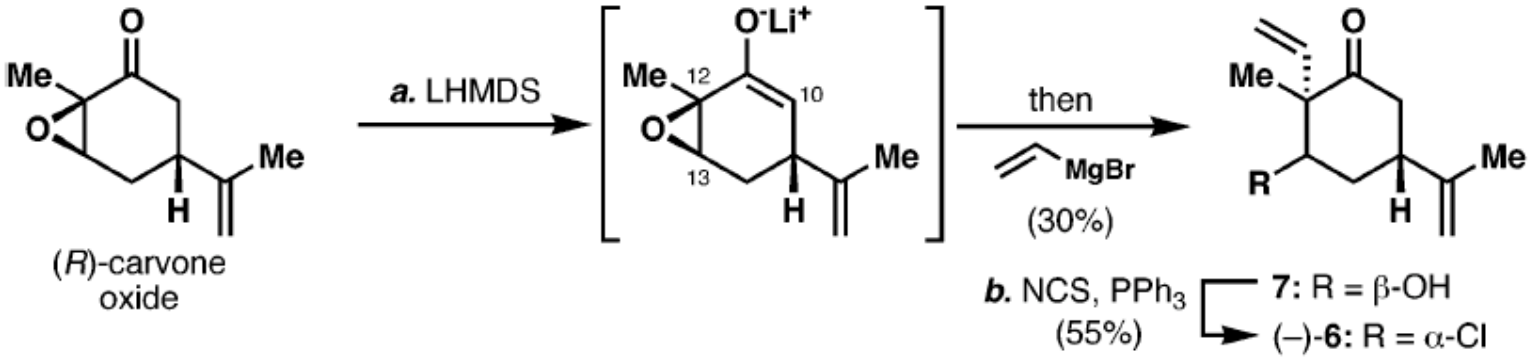
Tetrahedron Letters **1993**, *34*,445

Danishefsky's protocol of prenylation



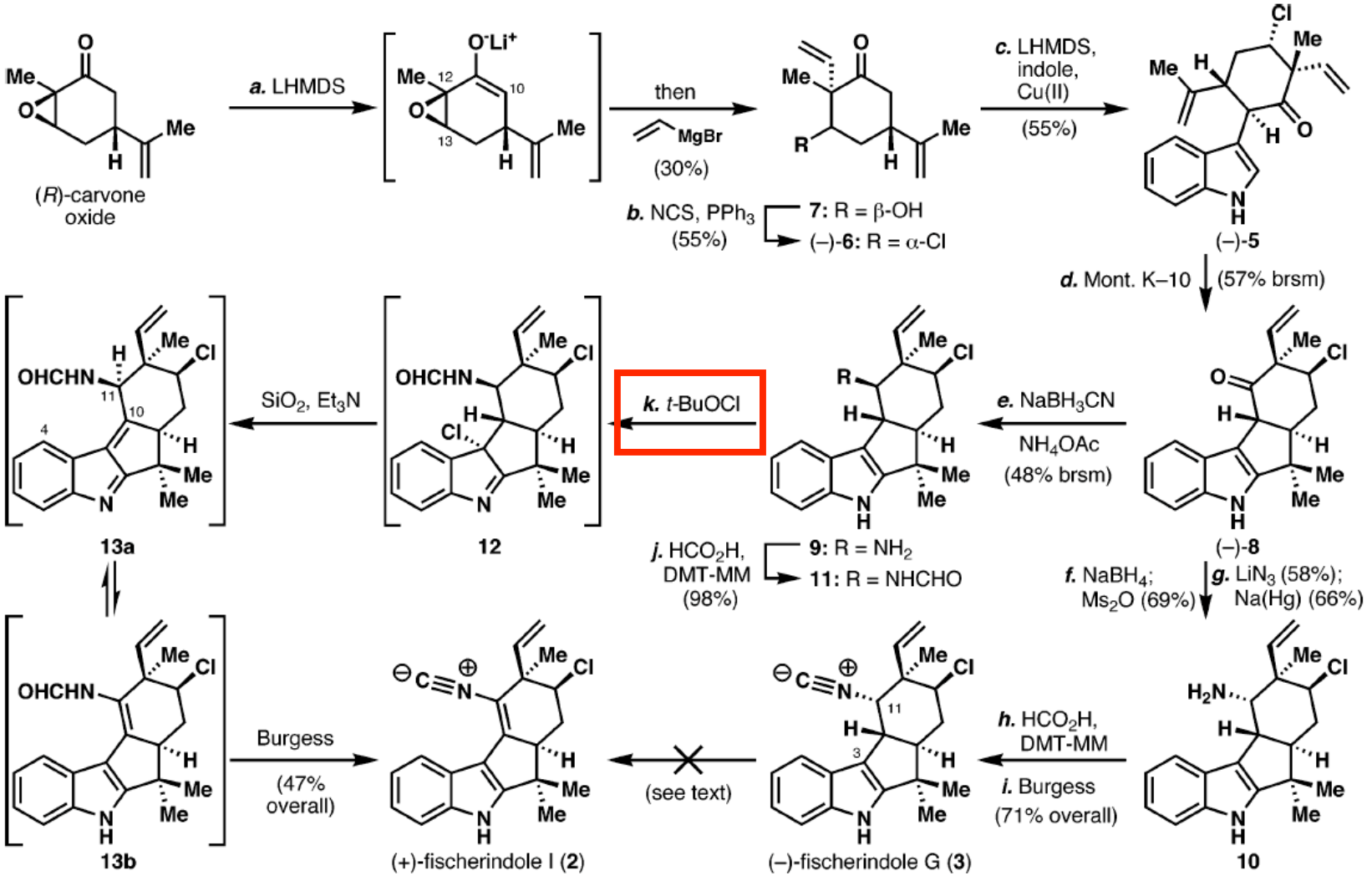
Danishefsky, S. J. *et.al. J. Am. Chem. Soc.* **1999,** *121*, 11964

Preparation of **15**



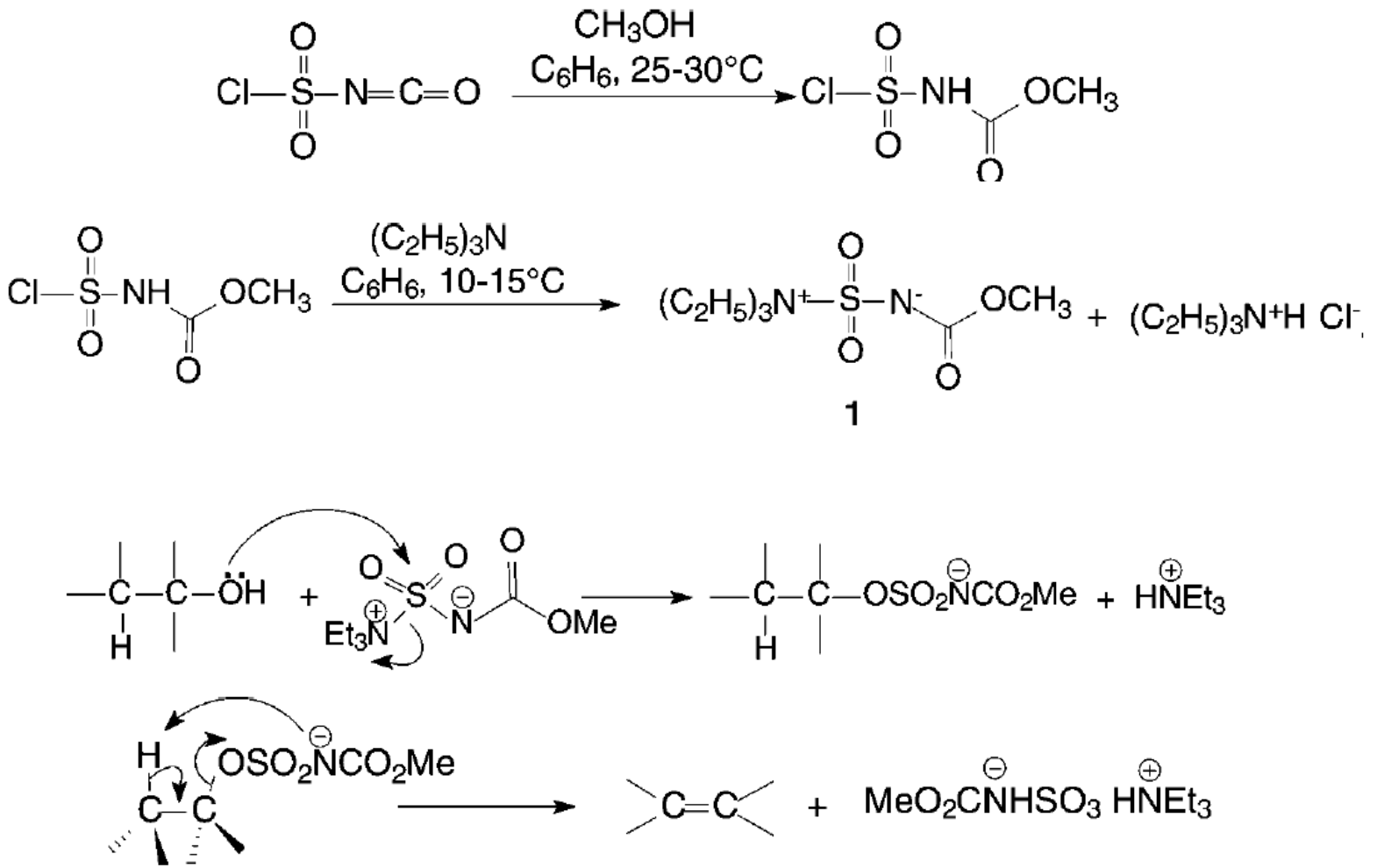
Baran, P. S. *et.al. J. Am. Chem. Soc.* **2005,** *127*, 15394

Fischerindole I and Welwitindolinone A (Previous)



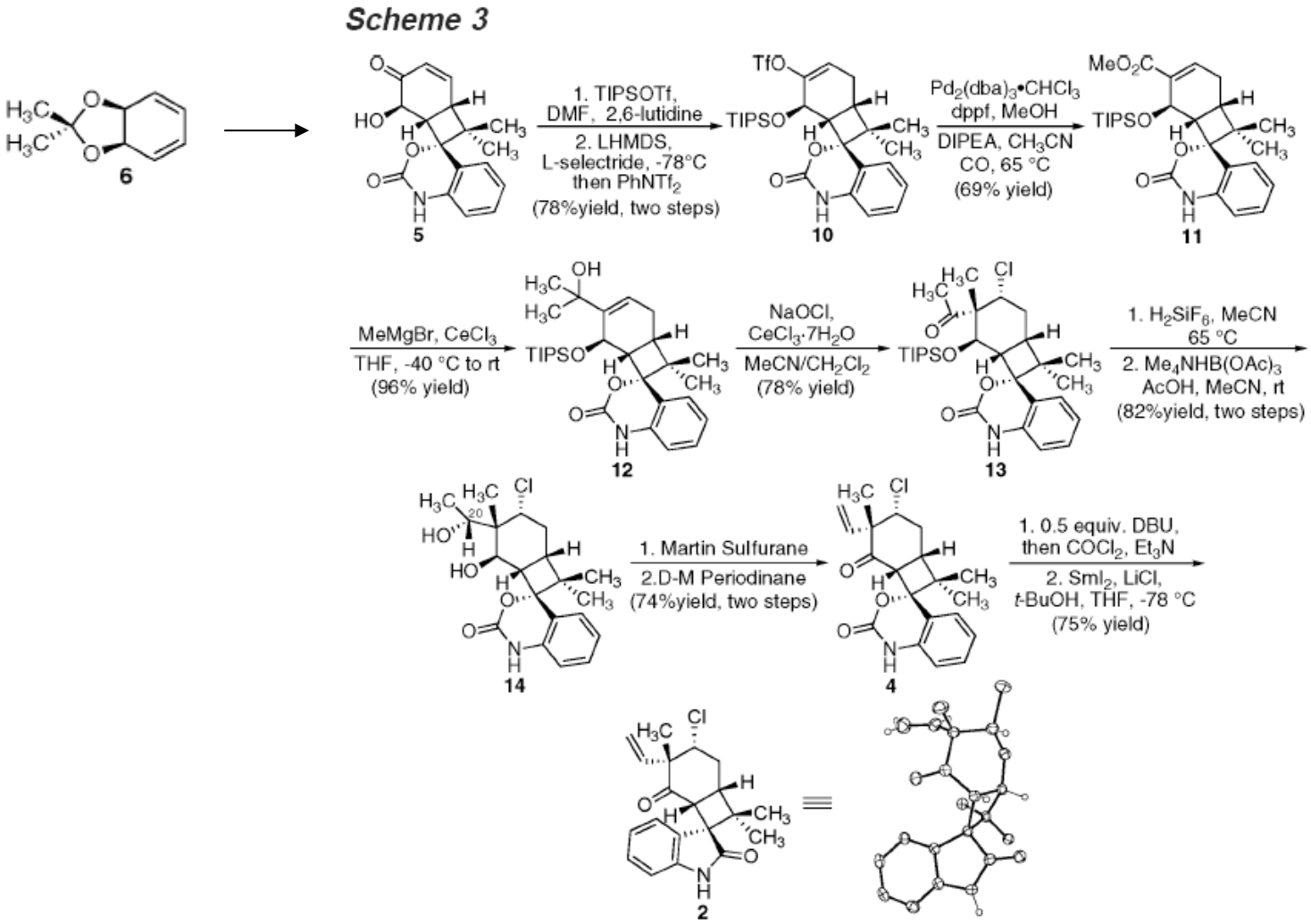
Baran, P. S. *et.al. J. Am. Chem. Soc.* **2005,** *127*, 15394

Burgess Reagent



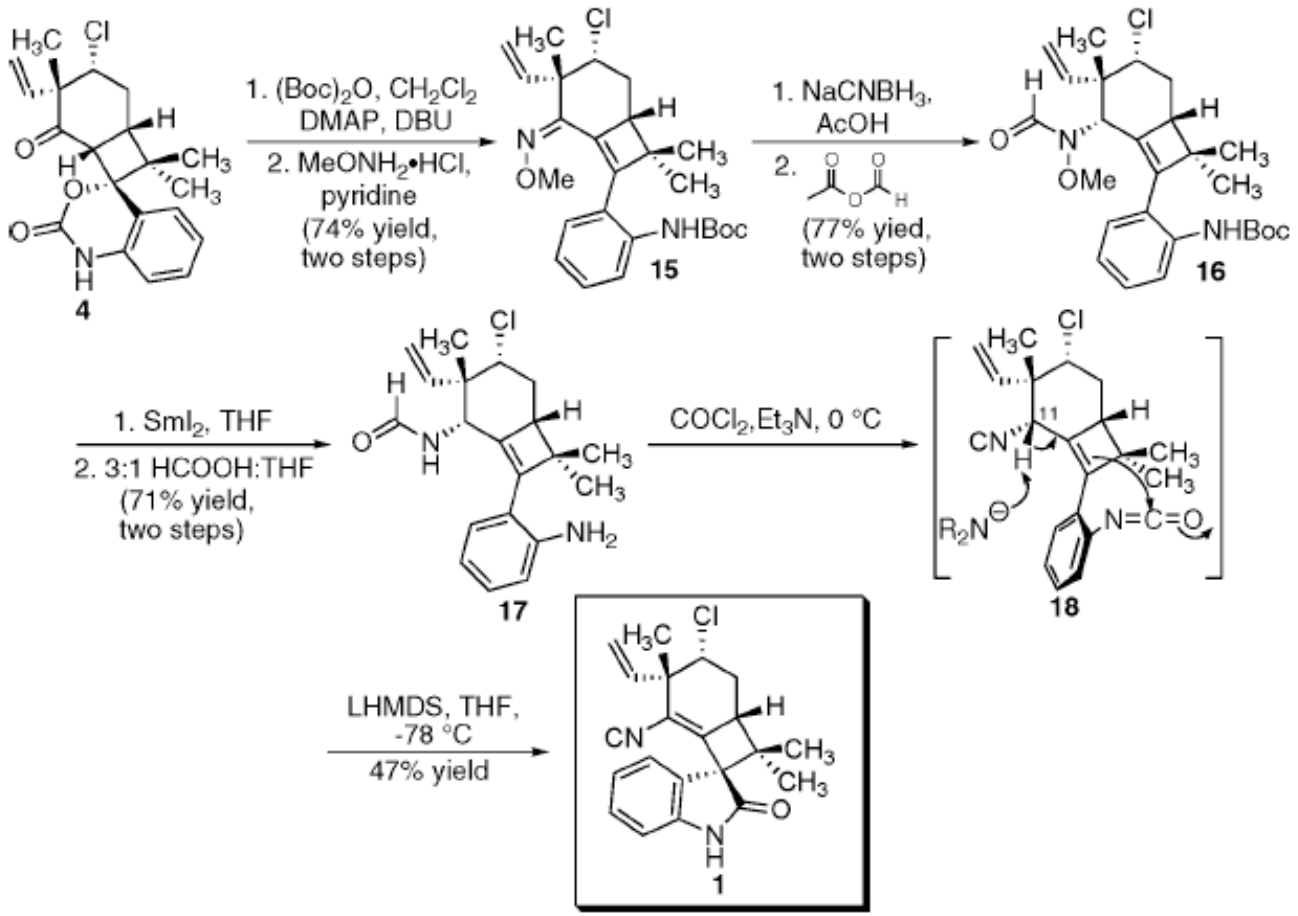
Baran, P. S. *et.al. J. Am. Chem. Soc.* **2005,** *127*, 15394

Total Synthesis of (±) Welwitindolinone A



Reisman, S. E. *et.al. J. Am. Chem. Soc.* **2006,** *128*, 1448

Total Synthesis of (±) Welwitindolinone A



Reisman, S. E. *et.al. J. Am. Chem. Soc.* **2006,** *128*, 1448