Review of “Natural Product Synthesis” on Nature Chemistry (2011~2013)

Speaker: Dr. Tao Xu

Dong group seminar

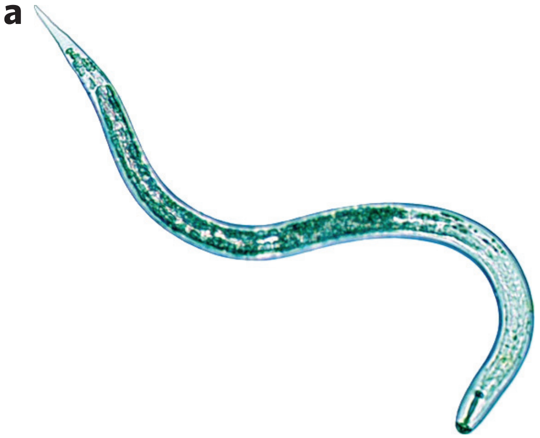
January 29th, 2014

Contents

- 5 publications in 2011
- 4 publications in 2012
- 5 publications in 2013

  Selective in-depth discussion
- Conclusion and summary

Solanoeclepin A-combating hunger



Potato cyst nematodes

Cyst nematodes
on potato’s root

Potatoes affected by
Cyst nematodes

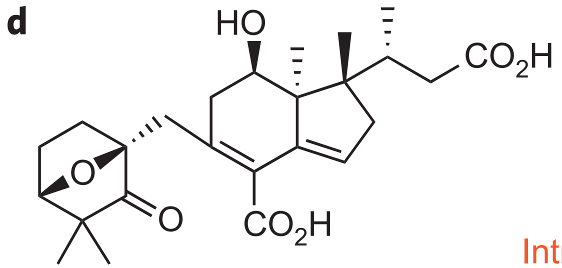
* Cyst nematodes are parasites that live on and destroy plants such as soybeans, potatoes

* Damage caused by cyst nematodes are worldwide. (> 50 countries reported)

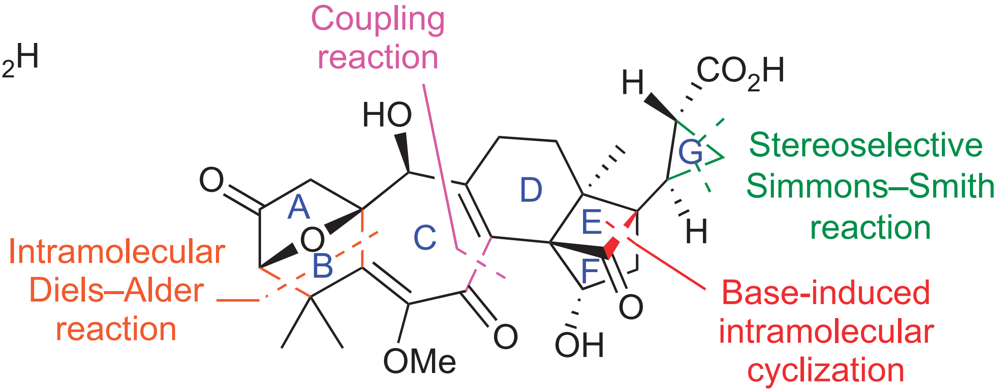
* Mechanisms have been figured out and Chemists were needed.

Tanino K, Miyashita M etc. *Nat. Chem*. 3:484

Total Synthesis of Solanoeclepin A



Glycinoeclepin A (**1**)



Solanoeclepin A (**2**)

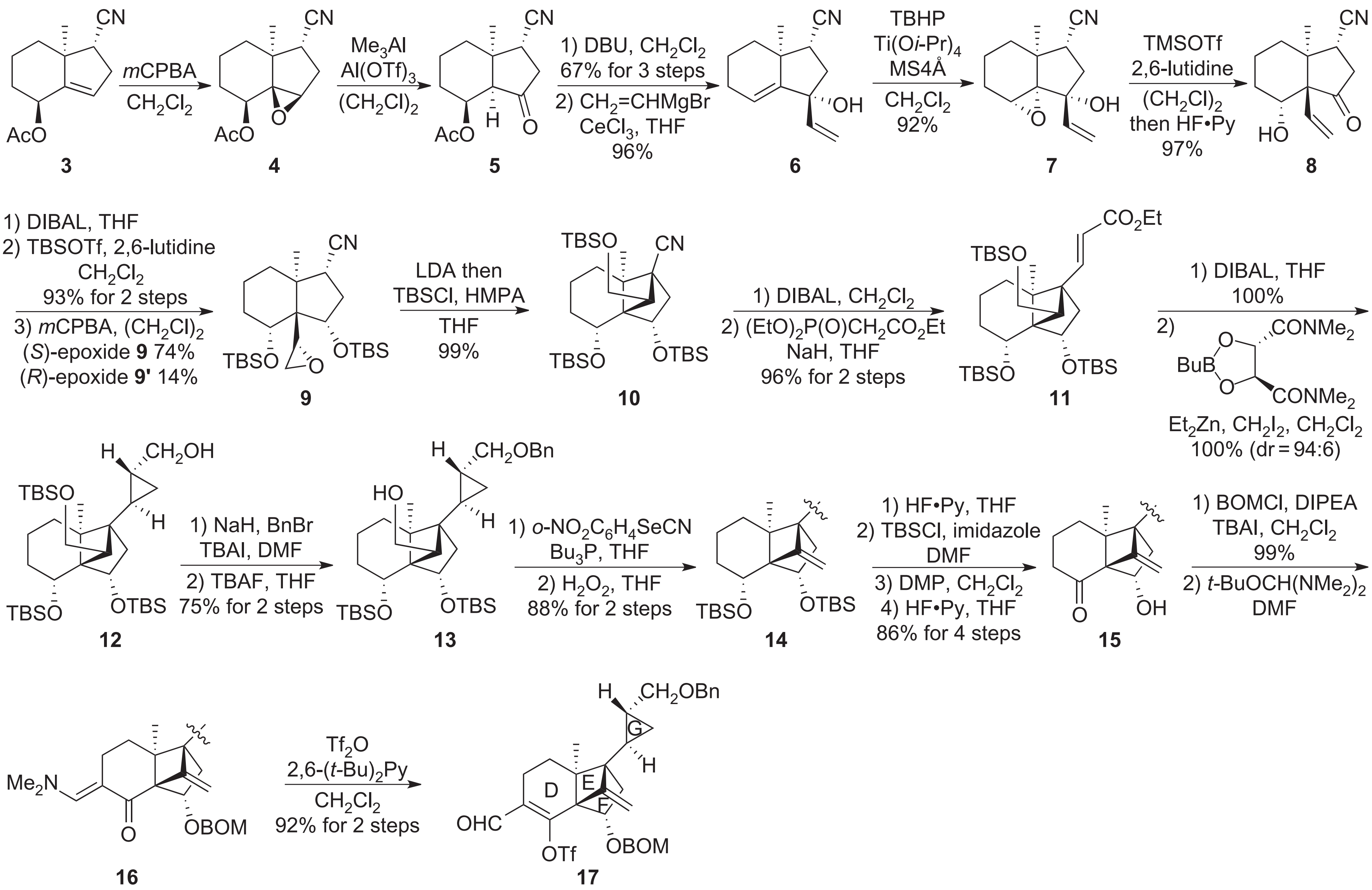
Isolation: 1) Masamune, T. *Nature* **1982**, *297*, 495.
2) Masamune, T. *J. Chem. Soc. Chem. Commun*. **1985**, 222.

50 ug out of 113 kg
dry roots of kidney bean

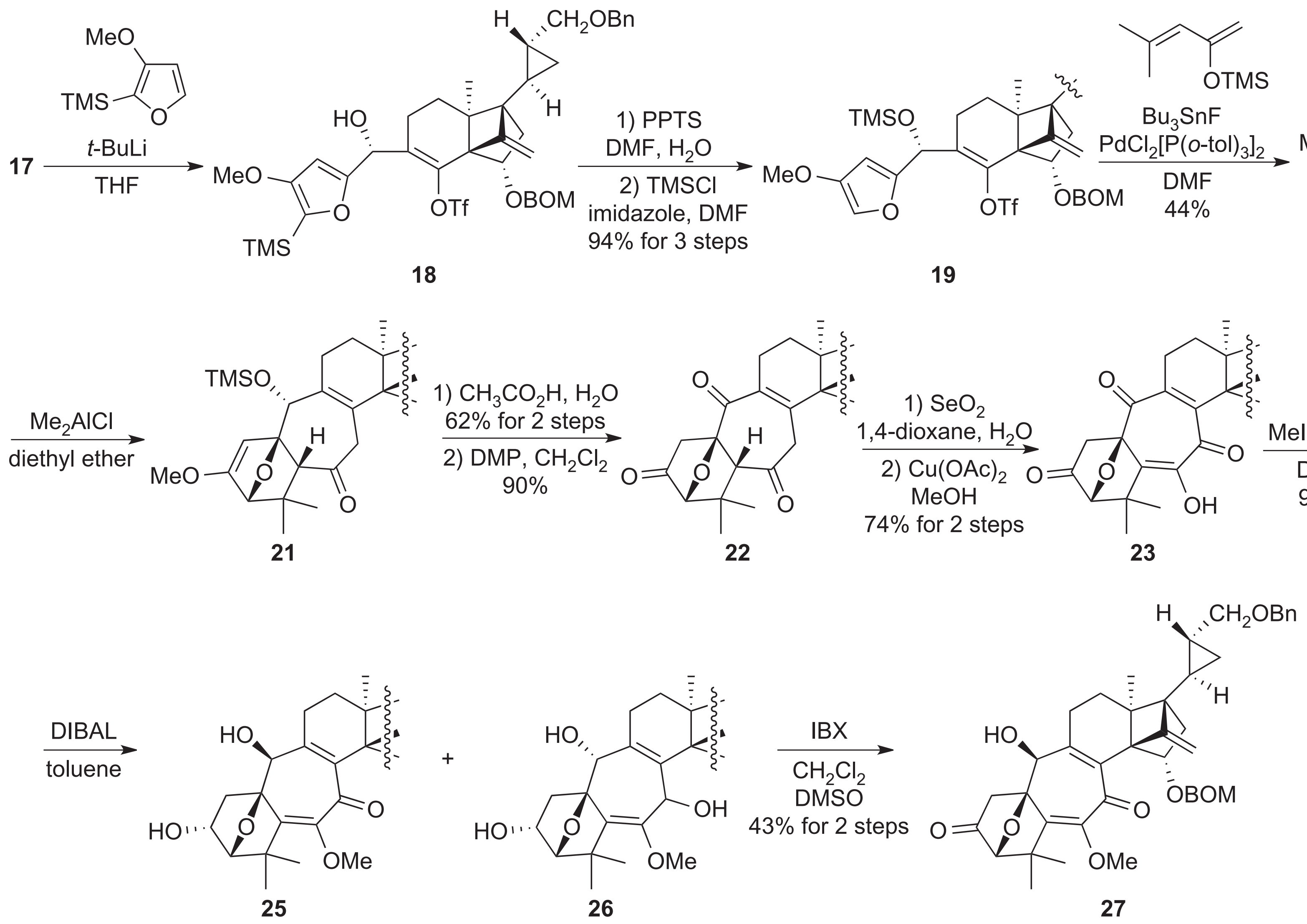
Isolation: 1) Mulder, J. G., CT Int. Appl. WO 93 02 083 (**1992**) (Chem. Abstr. 118, 185844z).
2) Schenk, H. et al. Croat. Chem. Acta 72, 593–606 (**1999**).

- Agricultural chemicals and nematicides kill plants as well.
- Hatching stimulation could be an alternative.
- Four hatching stages, stage II are root infectious and detrimental.
- Spreading stimulus over potato files after harvest.

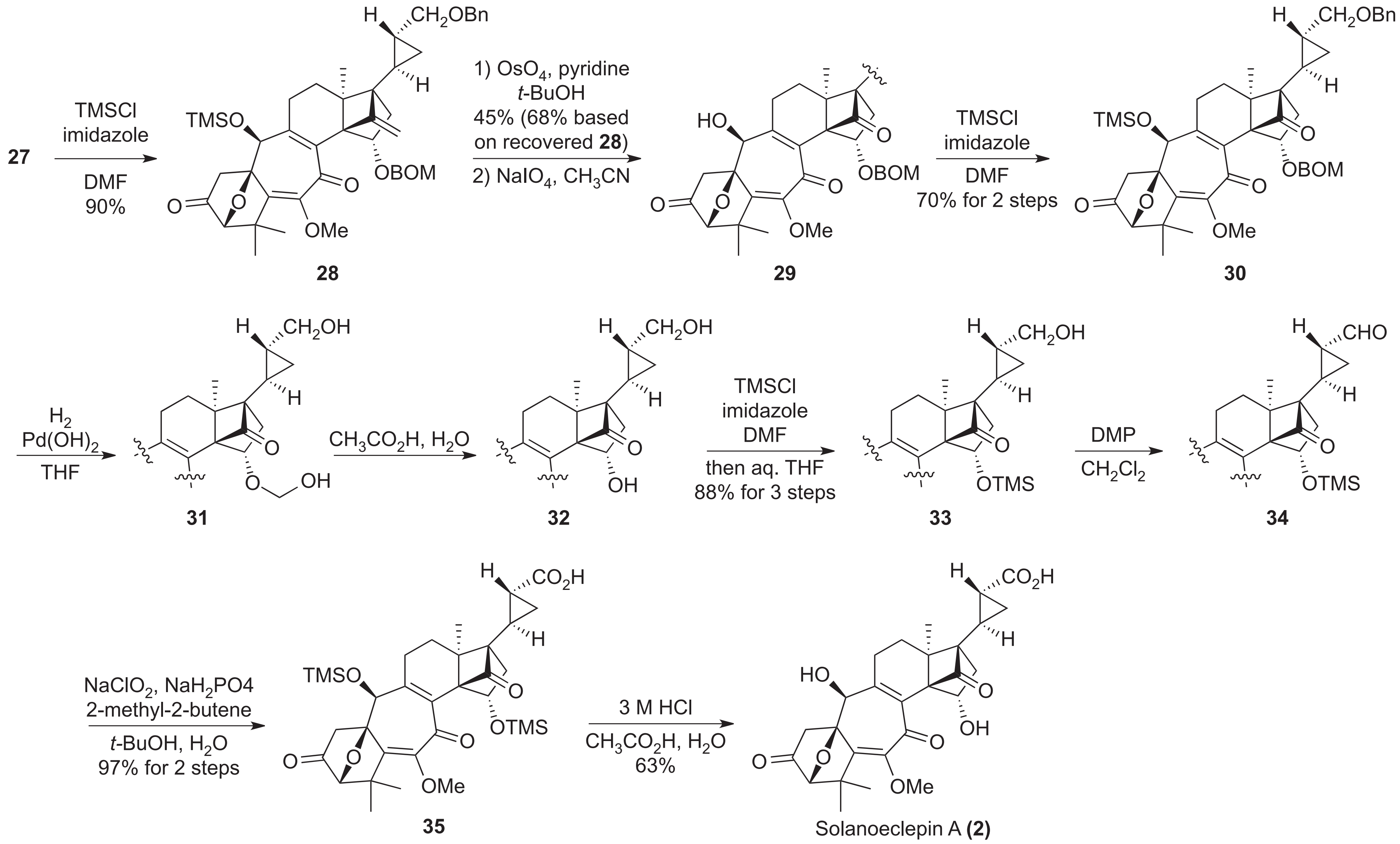
Total Synthesis of Solanoeclepin A



Total Synthesis of Solanoeclepin A



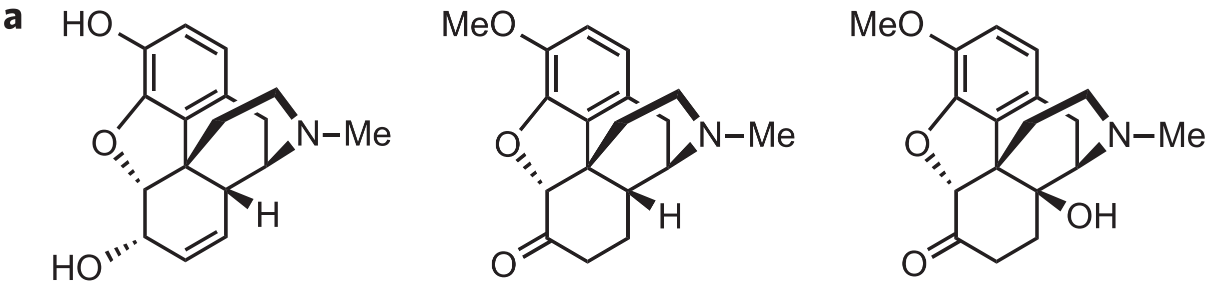
Total Synthesis of Solanoeclepin A



Total synthesis of solanoeclepin A

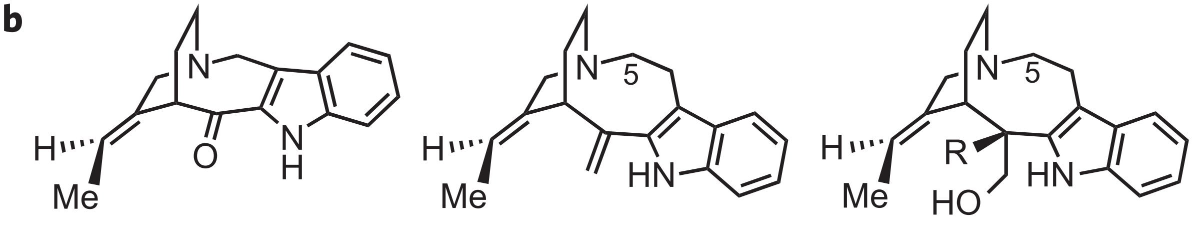
- First total synthesis of solanoeclepin A achieved in 0.18% yield and 52 steps from 3-Me cyclohexenone. (average yield 88.6%)
- The synthetic sample is only 65% as effective indicate a cofactor maybe responsible for hatching stimulation.

Conolidine-fighting chronic pain



Morphine Hydrocodone Oxycodone

Common opioid analgesics morphine, hydrocodone and oxycodone. Although extremely effective, well-known side effects are obvious such as addiction, depression, nausea and constipation



1
Conolidine

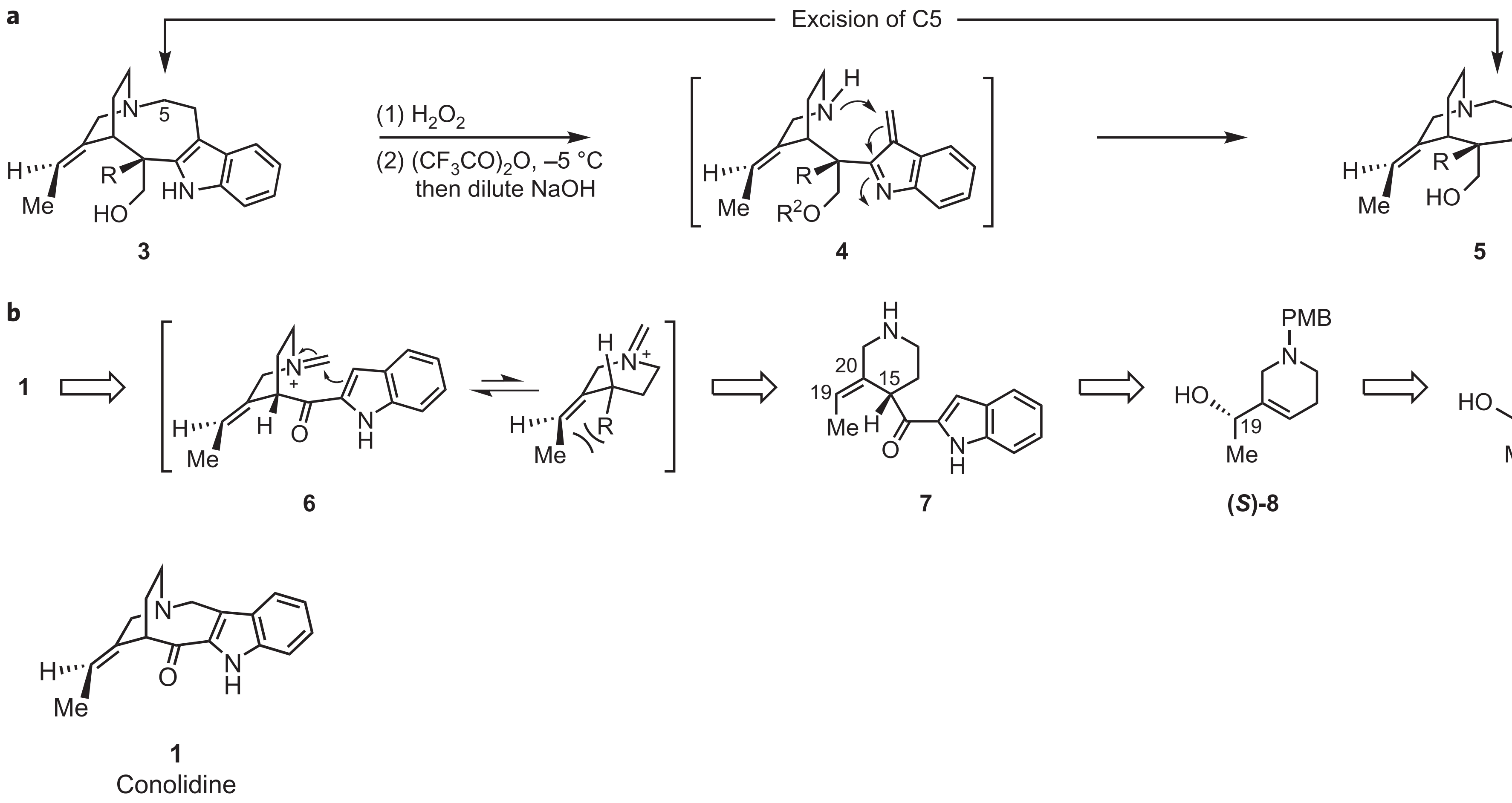
2
Pericine

3
Stemmadenine
(R = CO_2Me)

Conolidine, are rare alkaloids derived from plants used in traditional Chinese medicine. Conolidine itself can be isolated in just 0.00014% yield from the stem bark of T. divaricata.

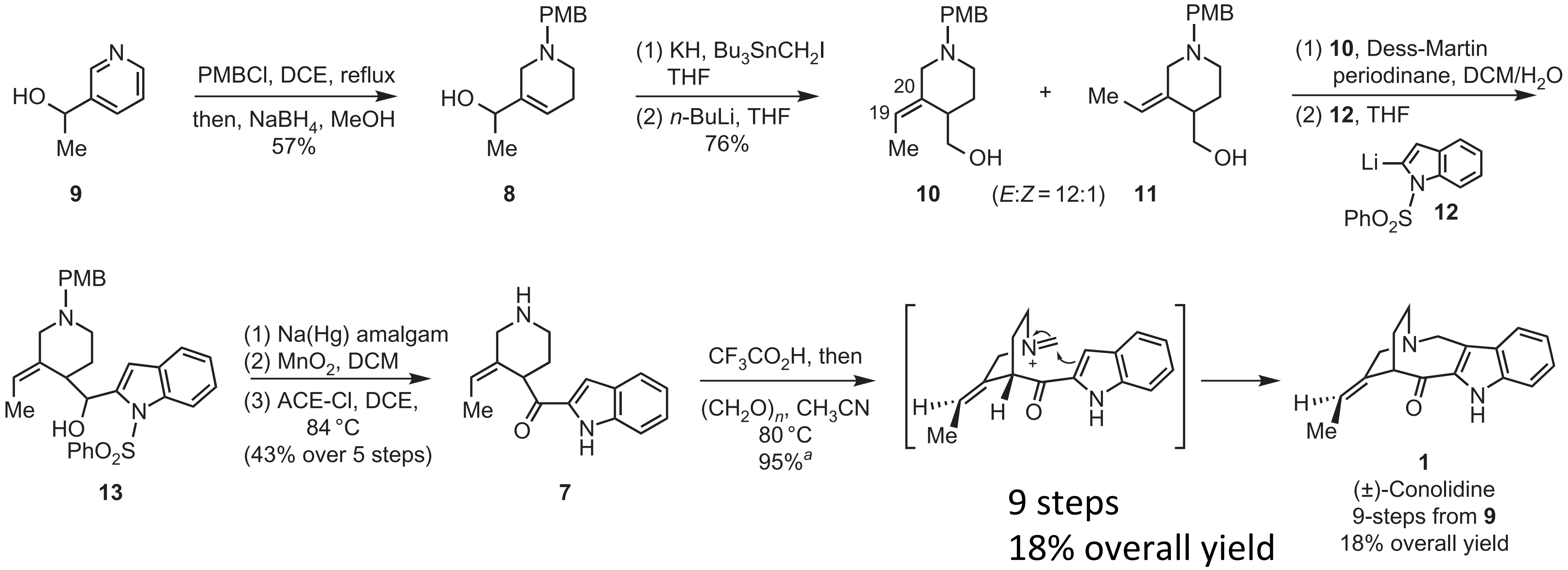
1) Kam, T.-S., Pand, H.-S., Choo, Y.-M. & Komiyama, K *Chem. Biodivers.* 1, 646 (2004).

Synthetic design and total synthesis

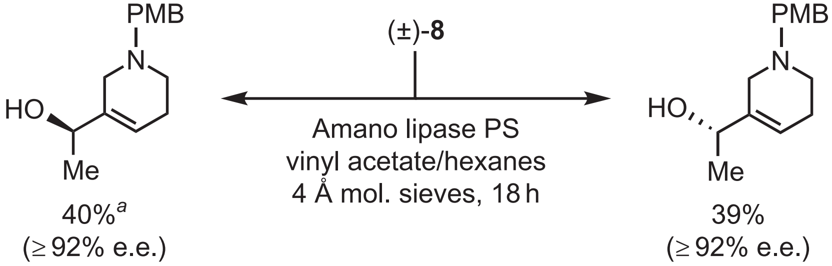


Bohn L. M.; Micalizio G. C. etc. *Nature Chemistry*, **2011,** 3, 449.

Total synthesis of conolidine

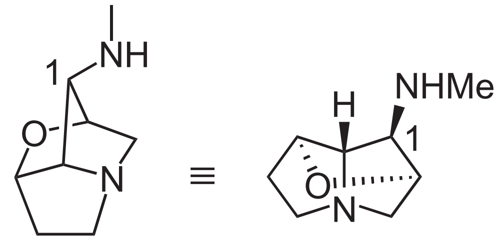


9 steps
18% overall yield

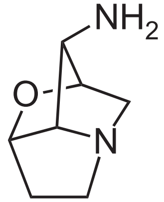


	Relative potencies (ED$_{50}$, mg kg^{-1})	
Drug	**Phase 1**	**Phase 2**
(−)-Conolidine sulfate	5.6 (4.0–7.8)	6.0 (3.7–9.7)
Morphine sulfate	4.6 (3.3–6.4)	2.4 (1.7–3.2)

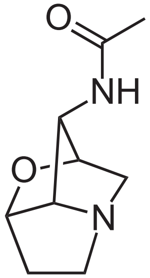
Loline alkoilds-new bottle with old wine



Loline (**1**)

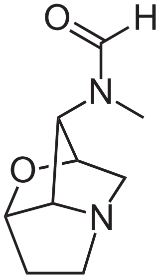


Temuline (**2**)
(norloline)

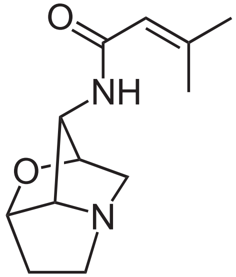


N-acetyl
norloline (**3**)

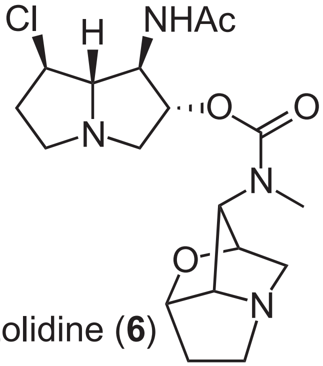
- Loline has been known over 100 years
- Heterocyclic structure
- No specific bioactivity reported
- Two total synthesis reported



N-formyl
loline (**4**)



N-senecioyl
norloline (**5**)



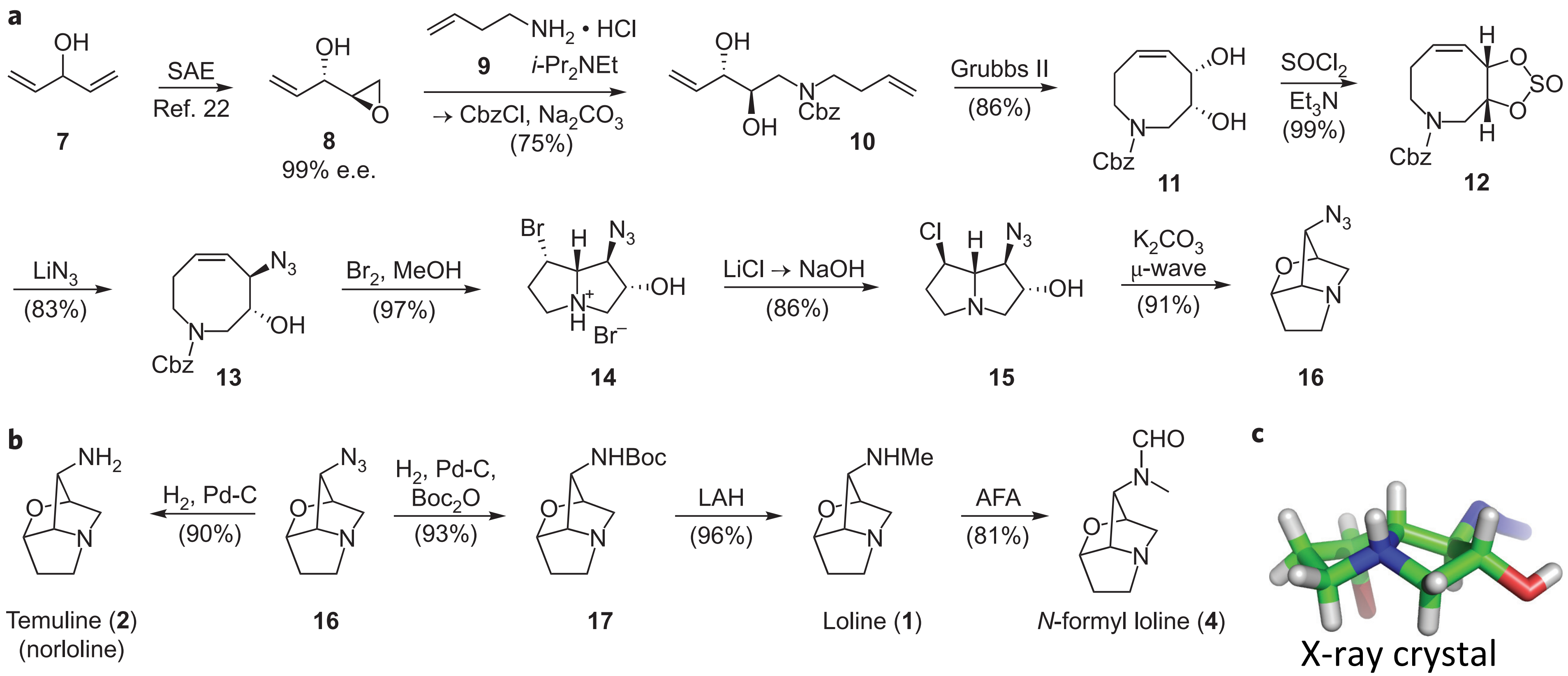
Lolidine (**6**)

Introduction: Ideal synthesis (Baran)

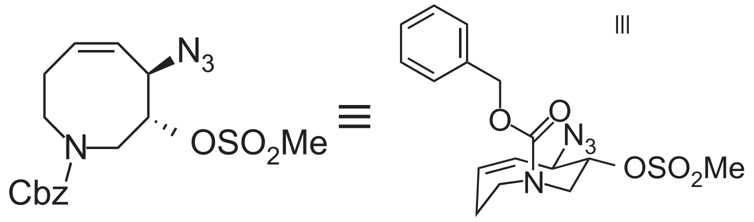
- ➢ Atom-economic (Trost, 1991)
- ➢ Step-economic (Wender, 2009)
- ➢ Protecting group free (Baran, 2007)
- ➢ Redox-economic (Baran, 2009)

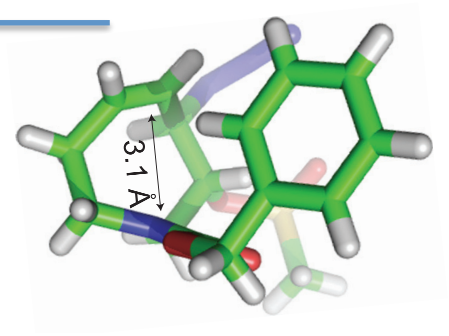
Cakmak, M.; Mayer, P.; Trauner, D. *Nat. Chem*. **2011**, *3*, 543.

An efficient synthesis of loline alkloid



X-ray crystal structure of 14

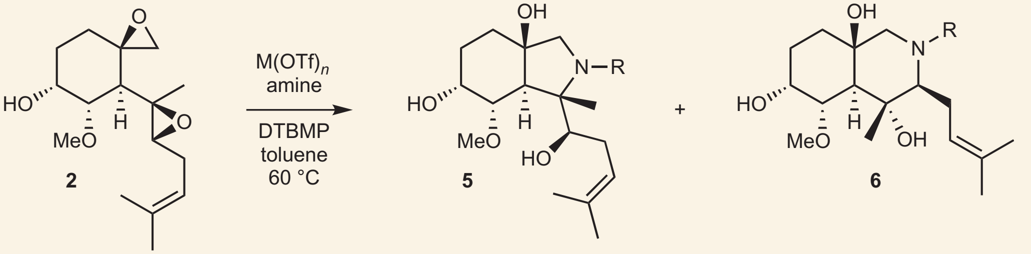


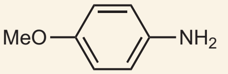
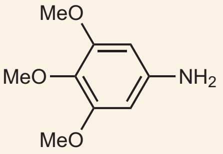
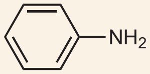
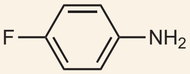
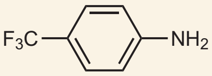
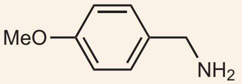
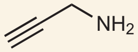
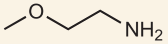
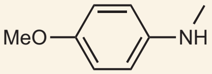
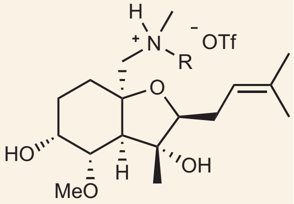
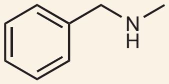


10 steps

One protecting group

DOS as a reaction discovery approach



Entry	Amine	M(OTf)$_n$ (reaction conditions)	Reaction time	% yield 5:6
1	 (**a**)	La(OTf)$_3^{*}$ Zn(OTf)$_2^{\dagger}$	7 h 29 h	**91**:3 9:**76**
2	 (**b**)	La(OTf)$_3^{*}$ Zn(OTf)$_2^{\dagger}$	3 h 24 h	**84**:0 6:**80**
3	 (**c**)	La(OTf)$_3^{*}$ Zn(OTf)$_2^{\dagger}$	29 h 29 h	**89**:2 8:**65**
4	 (**d**)	La(OTf)$_3^{*}$ Zn(OTf)$_2^{\dagger}$	36 h 29 h	**87**:0 10:**88**
5	 (**e**)	La(OTf)$_3^{*}$ Zn(OTf)$_2^{\dagger}$	4 d 48 h	**40**:0 10:**61**
6	 (**f**)	La(OTf)$_3^{\ddagger}$ Zn(OTf)$_2^{\dagger}$ Mg(OTf)$_2^{\S}$	20 h 60 h 16 h	**62**:25 0:57 13:**82**
7	 (**g**)	La(OTf)$_3^{\ddagger}$ Zn(OTf)$_2^{\dagger}$ Mg(OTf)$_2^{\S}$	24 h 60 h 36 h	**66**:32 0:2 18:**74**
8	 (**h**)	La(OTf)$_3^{\ddagger}$ Zn(OTf)$_2^{\dagger}$ Mg(OTf)$_2^{\S}$	20 h 60 h 20 h	**49**:20 0:11 12:**37**
9	 (**i**)	La(OTf)$_3^{\ddagger}$ R = PMP **7** (74%)		
10	 (**j**)	La(OTf)$_3^{\ddagger}$ R = Bn **8** (75%)		

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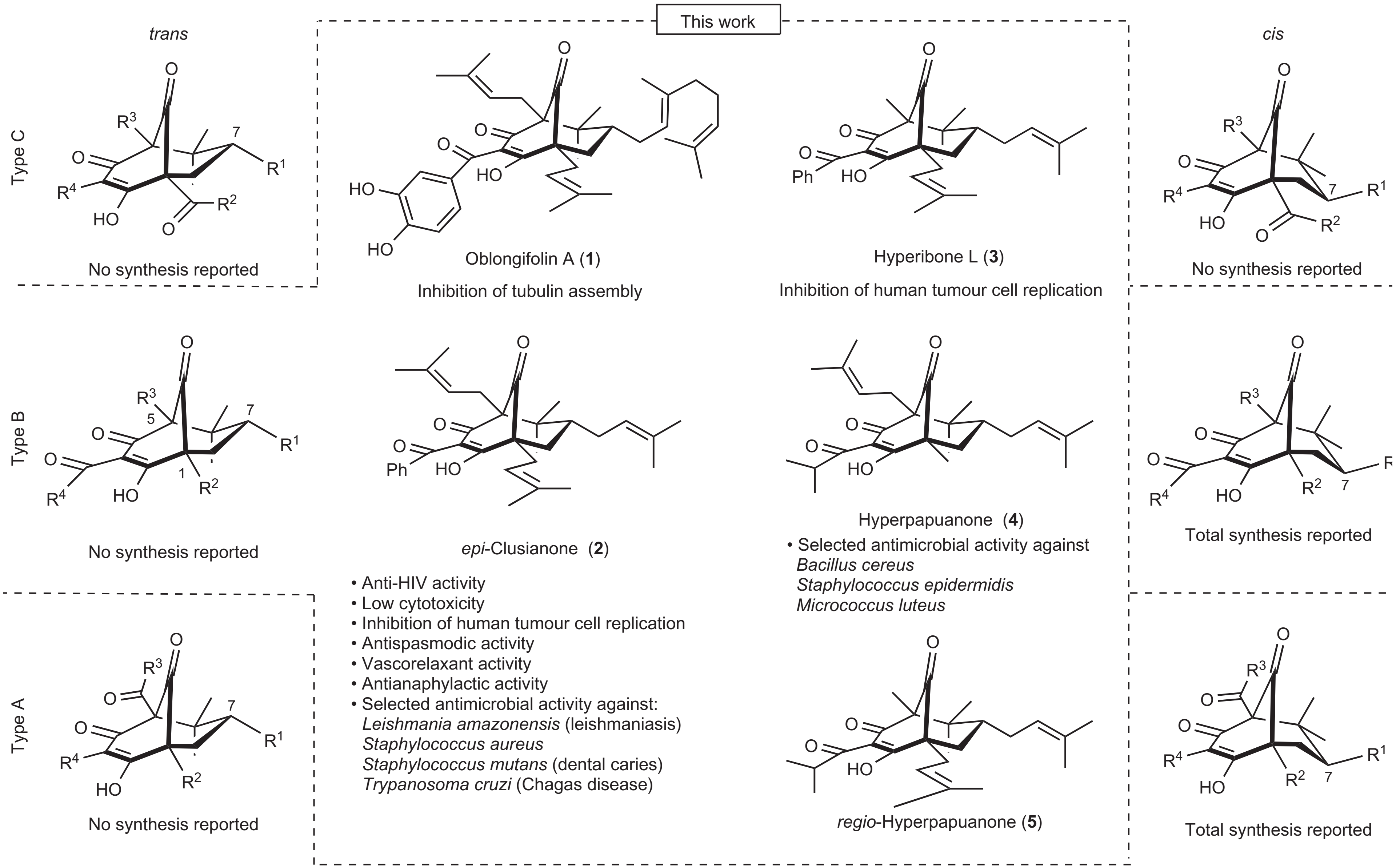
*La(OTf)$_3$ (10 mol%), DTBMP (60 mol%), amine (1.1 equiv.). †Zn(OTf)$_2$ (10 mol%), DTBMP (60 mol%), amine (1.1 equiv.). ‡La(OTf)$_3$ (50 mol%), DTBMP (1.5 equiv.), amine (2.0 equiv.). §Mg(OTf)$_2$ (50 mol%), DTBMP (1.5 equiv.), amine (2.0 equiv.). DTBMP, 2,6-di-*tert*-butyl-4-methylpyridine; PMP, *p*-methoxyaniline.

Porco, J. A.; Snyder, J. K. etc. *Nat. Chem*. **2011**, *3*, 969.

[3,3,1]nonane-triones-classical chemistry rules



No synthesis reported

Oblongifolin A (**1**)

Inhibition of tubulin assembly

Hyperibone L (**3**)

Inhibition of human tumour cell replication

No synthesis reported

No synthesis reported

epi-Clusianone (**2**)

- Anti-HIV activity
- Low cytotoxicity
- Inhibition of human tumour cell replication
- Antispasmodic activity
- Vascorelaxant activity
- Antianaphylactic activity
- Selected antimicrobial activity against:
  Leishmania amazonensis (leishmaniasis)
  Staphylococcus aureus
  Staphylococcus mutans (dental caries)
  Trypanosoma cruzi (Chagas disease)

Hyperpapuanone (**4**)

- Selected antimicrobial activity against
  Bacillus cereus
  Staphylococcus epidermidis
  Micrococcus luteus

regio-Hyperpapuanone (**5**)

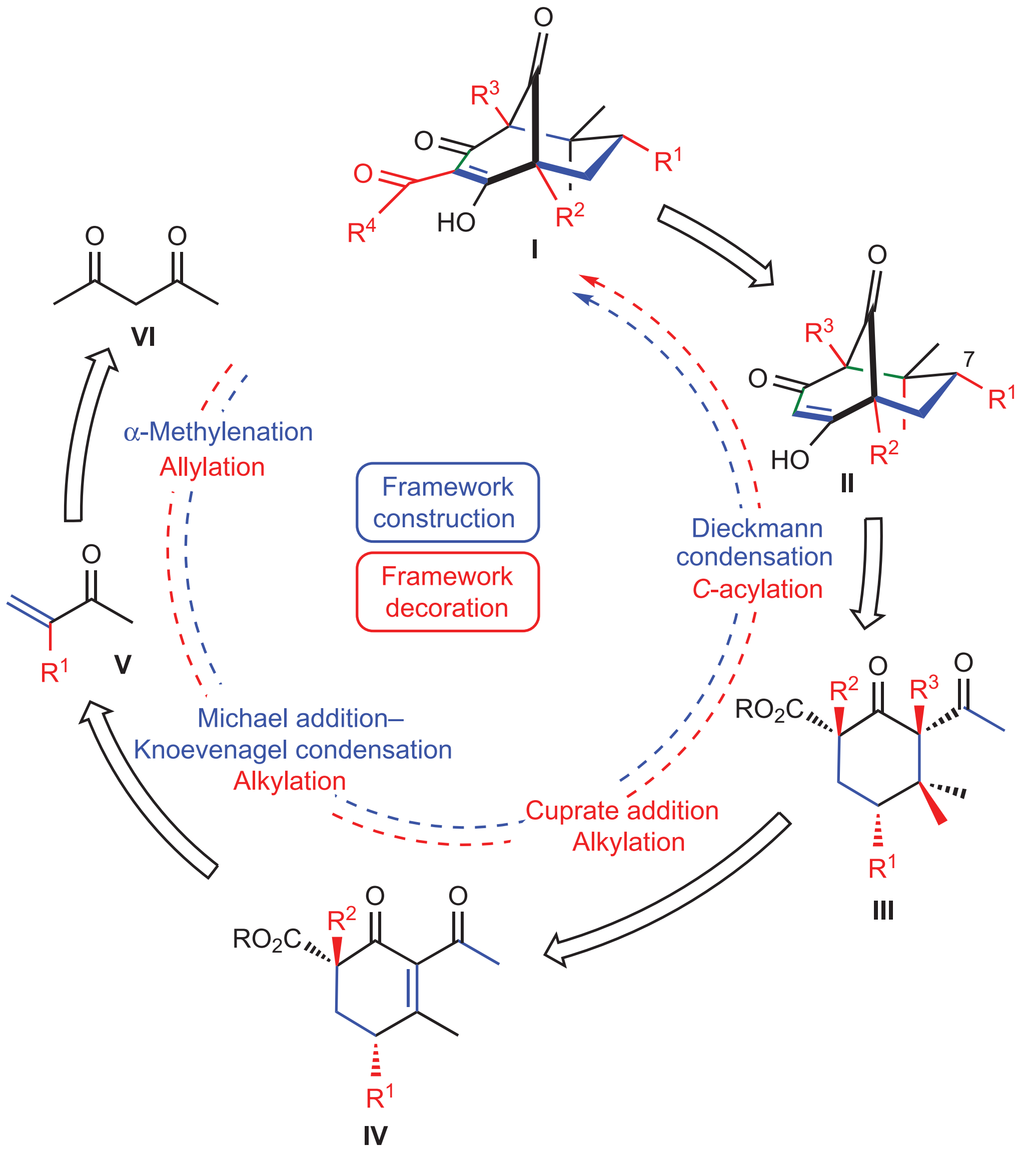
Total synthesis reported

No synthesis reported

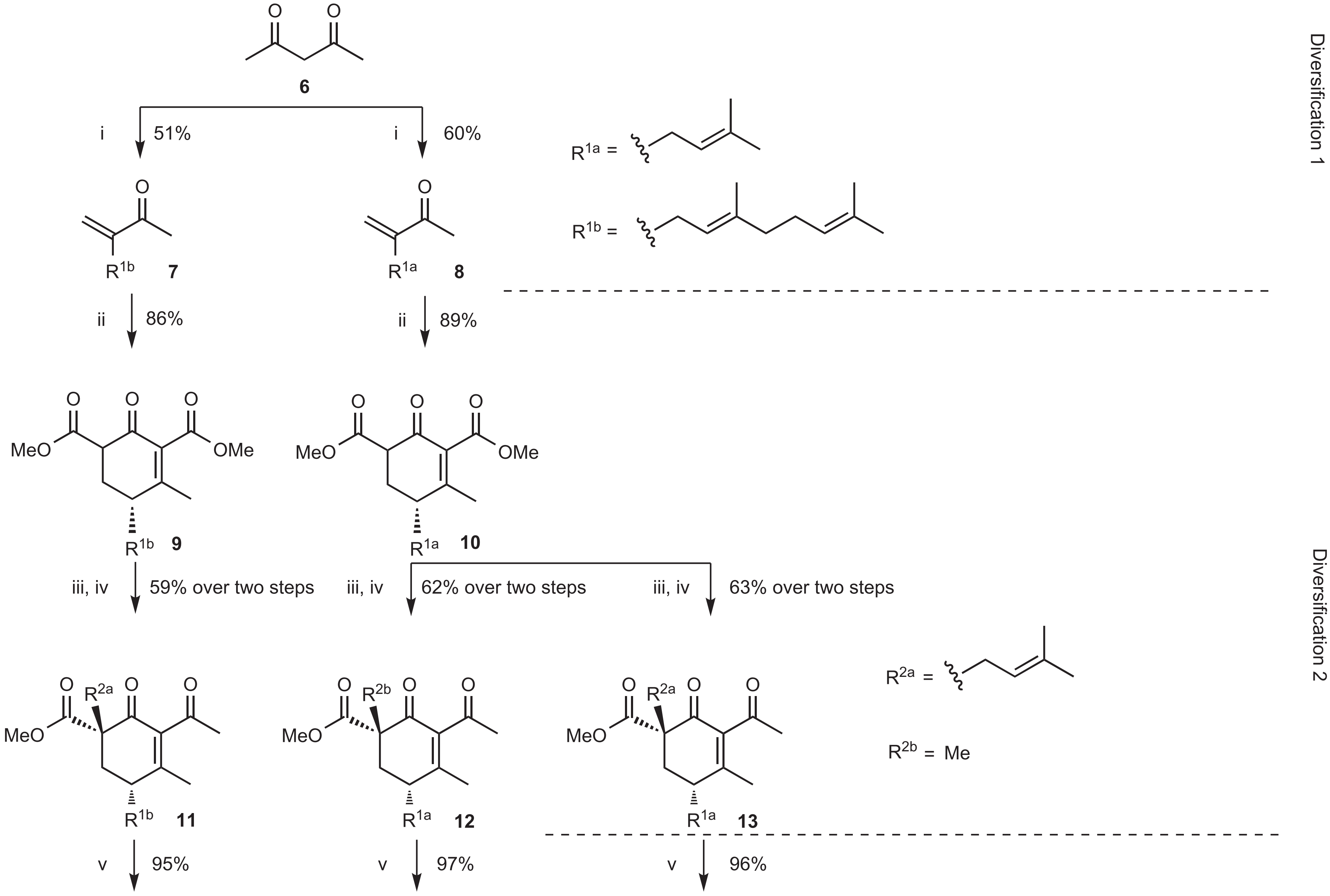
Total synthesis reported

Nicole Biber, Katrin Möws, Bernd Plietker *Nature Chemistry* **2011**, *3*, 938.

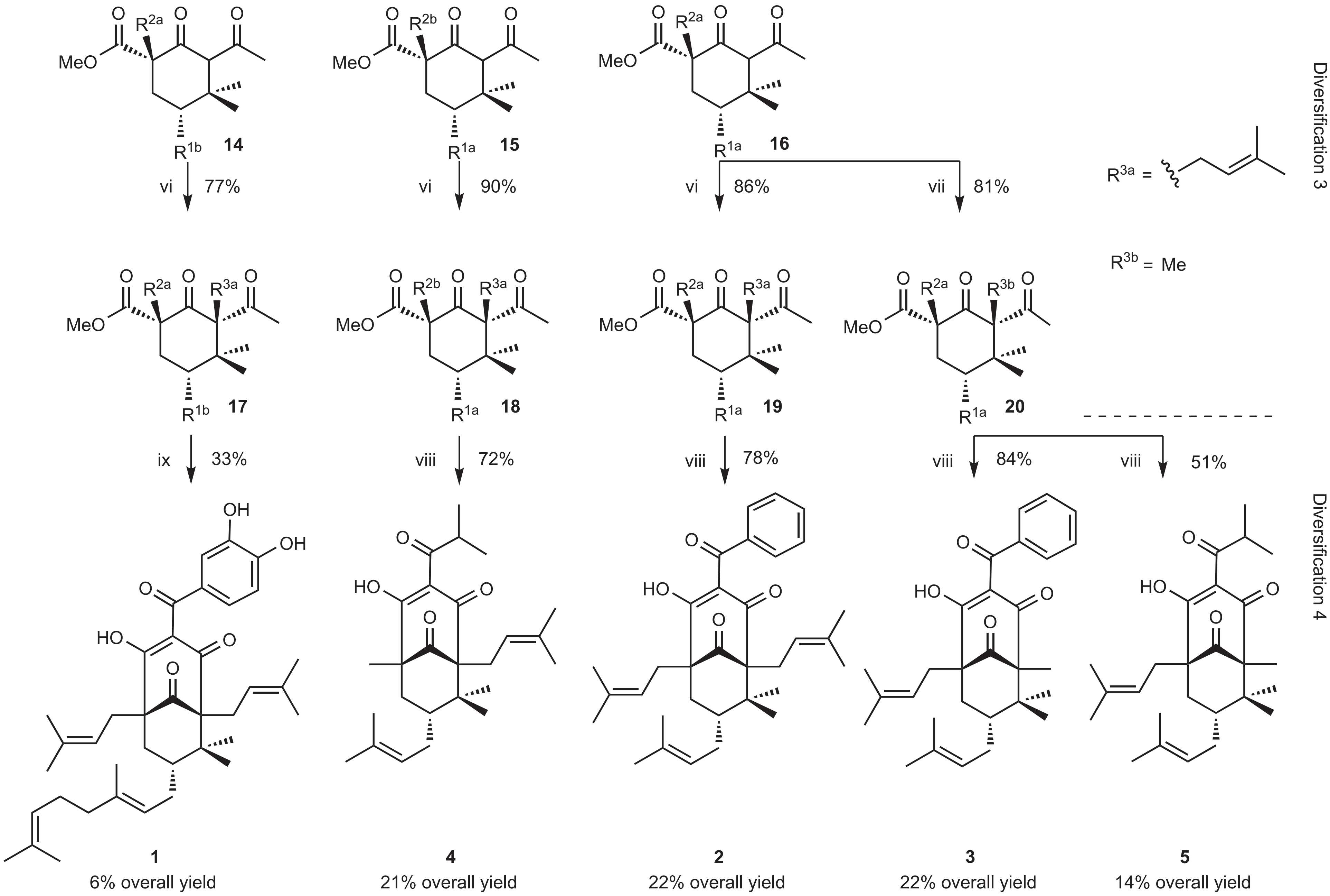
Retrosynthetic analysis-classical chemistry rules



Rodeschini, V., Ahmad, N. M. & Simpkins, N. S. Org. Lett. **2006** *8*, 5283.



6
i
51%
i
60%
7
8
R1b
R1a
R1a =
R1b =
ii
86%
ii
89%
MeO
OMe
9
10
iii, iv
59% over two steps
iii, iv
62% over two steps
iii, iv
63% over two steps
R2a
R2b
11
12
13
R2a =
R2b = Me
v
95%
v
97%
v
96%
Diversification 1
Diversification 2

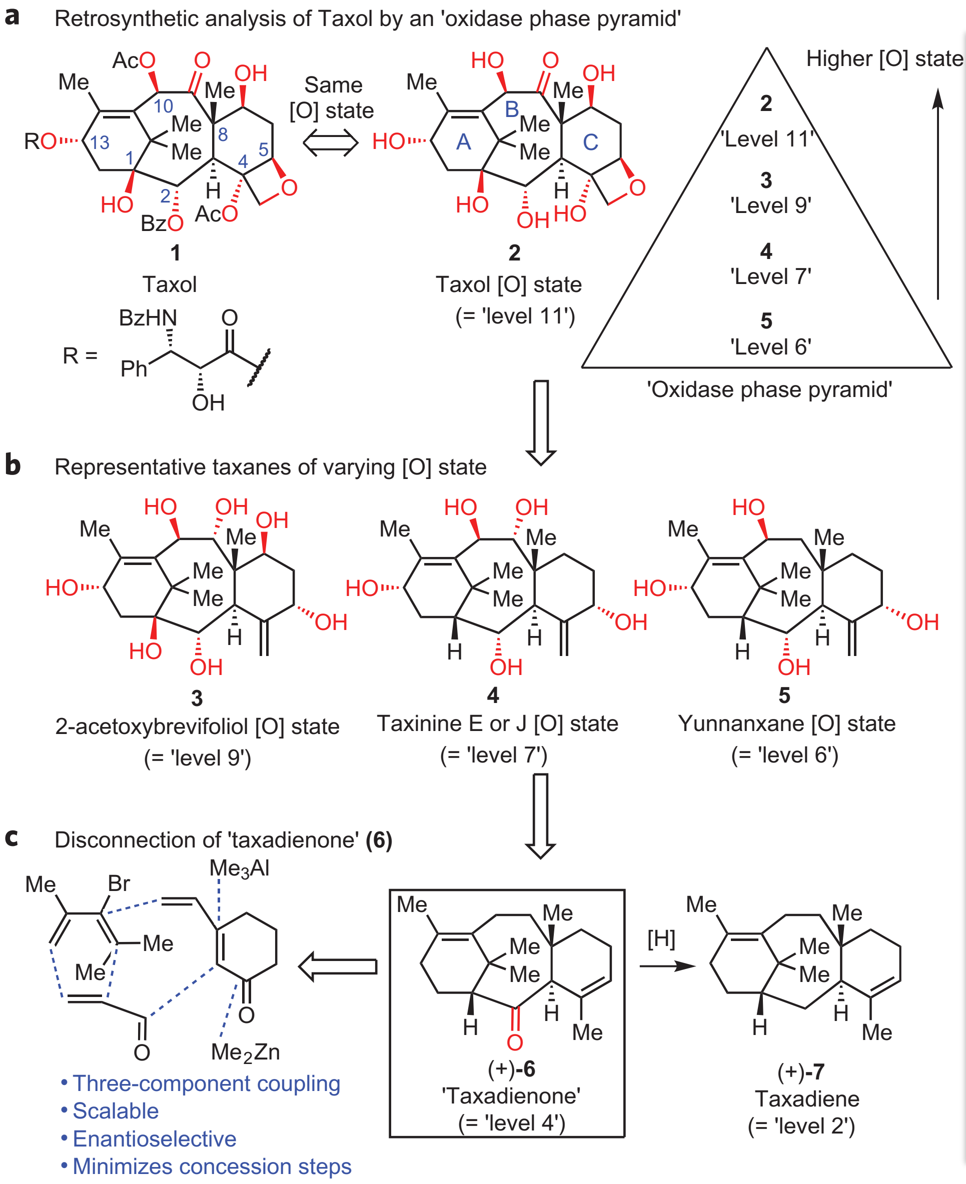

MeO
R2a
R2b
R1a
R1b
R3a
R3b
14
15
16
17
18
19
20
vi 77%
vi 90%
vi 86%
vii 81%
ix 33%
viii 72%
viii 78%
viii 84%
viii 51%
R3a =
R3b = Me
Diversification 3
Diversification 4
HO
OH
1
6% overall yield
4
21% overall yield
2
22% overall yield
3
22% overall yield
5
14% overall yield

Summary

- 5 publications in 2011 (multi-targets wl <10 steps, single target shd biological test)
- 4 publications in 2012
- 5 publications in 2013

  Selective in-depth discussion
- Conclusion and summary

Enantioselective synthesis of taxanes-scale it up



a Retrosynthetic analysis of Taxol by an 'oxidase phase pyramid'

b Representative taxanes of varying [O] state

c Disconnection of 'taxadienone' **(6)**

- Three-component coupling
- Scalable
- Enantioselective
- Minimizes concession steps

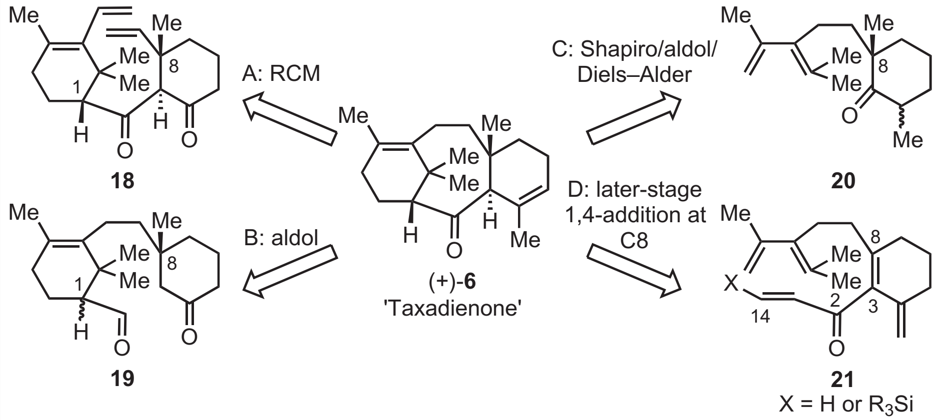
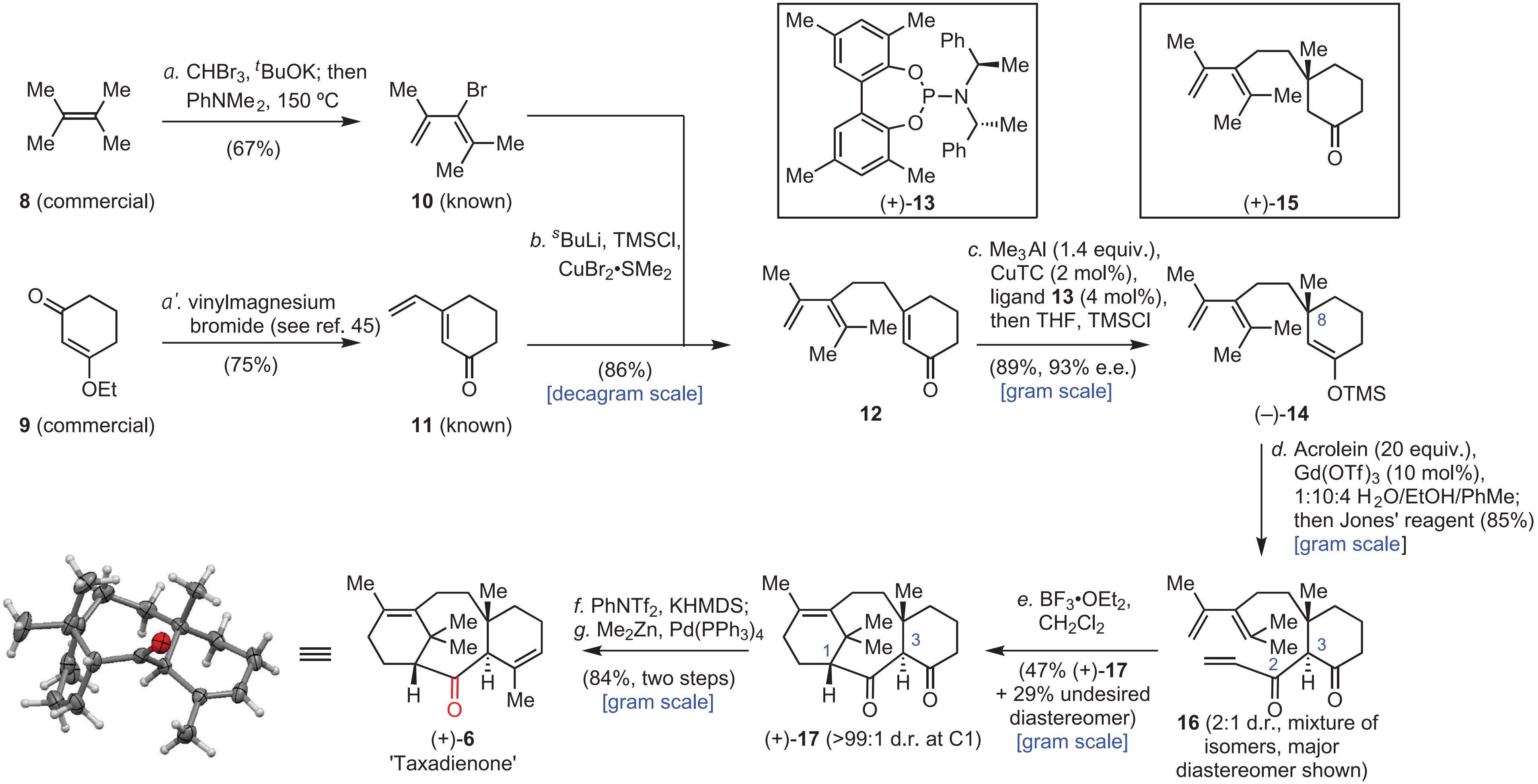
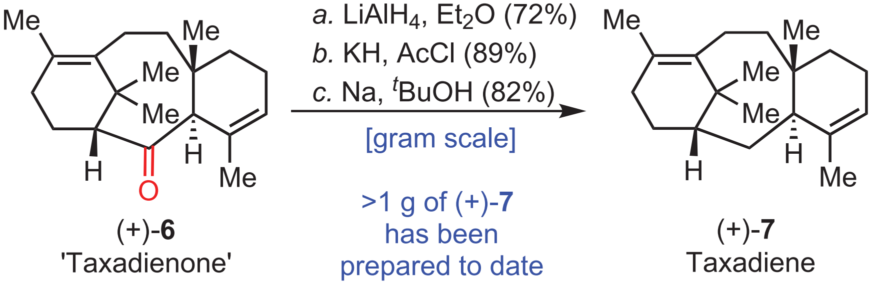


Figure 4 | Initial synthetic investigations towards the synthesis of taxadienone (6). Disconnection A: an RCM approach would require many more steps in building the taxane framework. Disconnection B: the required aldol closure simply did not proceed. Disconnection C: a Shapiro reaction, followed by aldol and Diels–Alder reactions, is strategically similar to the successful synthetic route, but the stereochemistry at C8 could not be set stereoselectively. Disconnection D: conjugate addition at C8 to install the methyl unit did not proceed, because only the undesired conjugate addition onto C14 occurred.

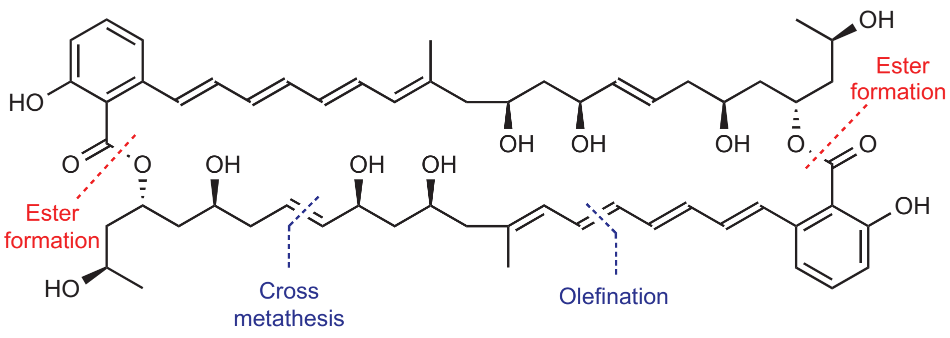
Mendoza, A.; Ishihara, Y.; Baran, P. S. *Nat. Chem*. **2012**, *4*, 21



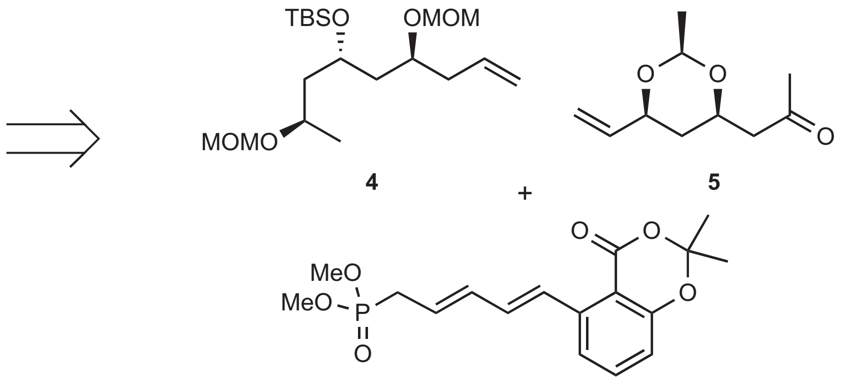


First lab-prepared **7** (>1g)
7 steps for **6** in 18% yield
10 steps for **7**

Marinomycin A-macrolide not my favorite



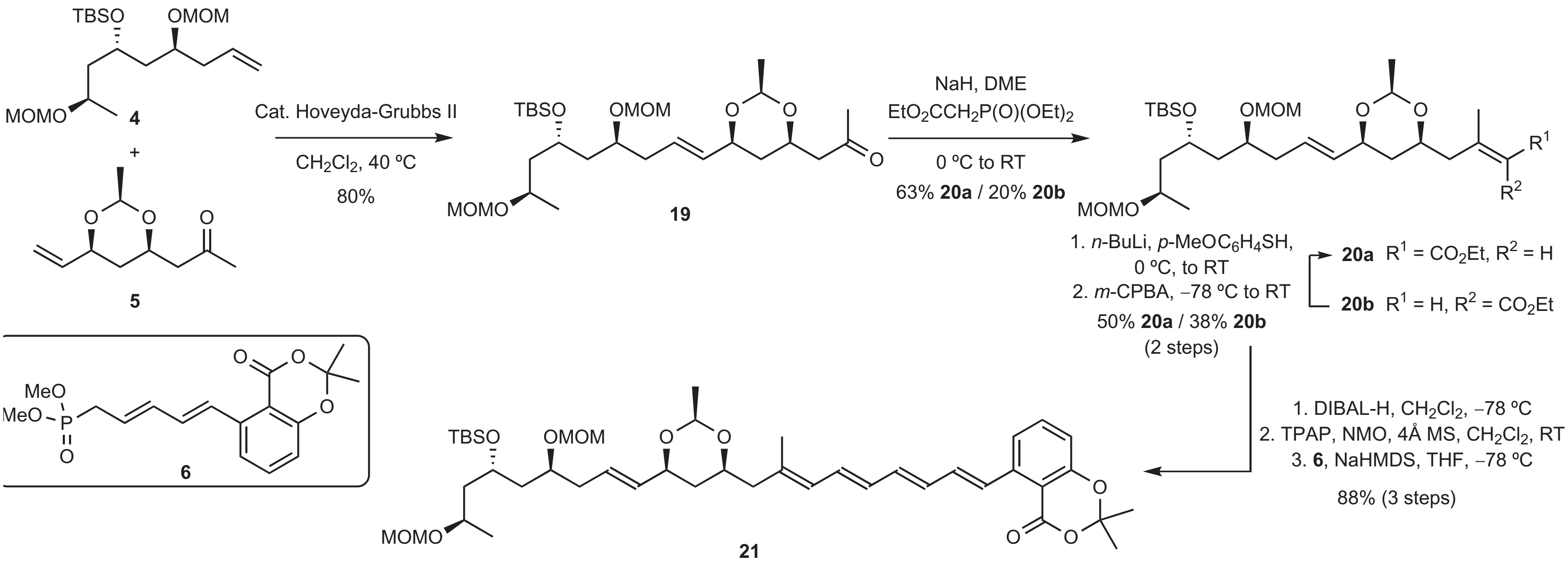
Marinomycin A **(1)**

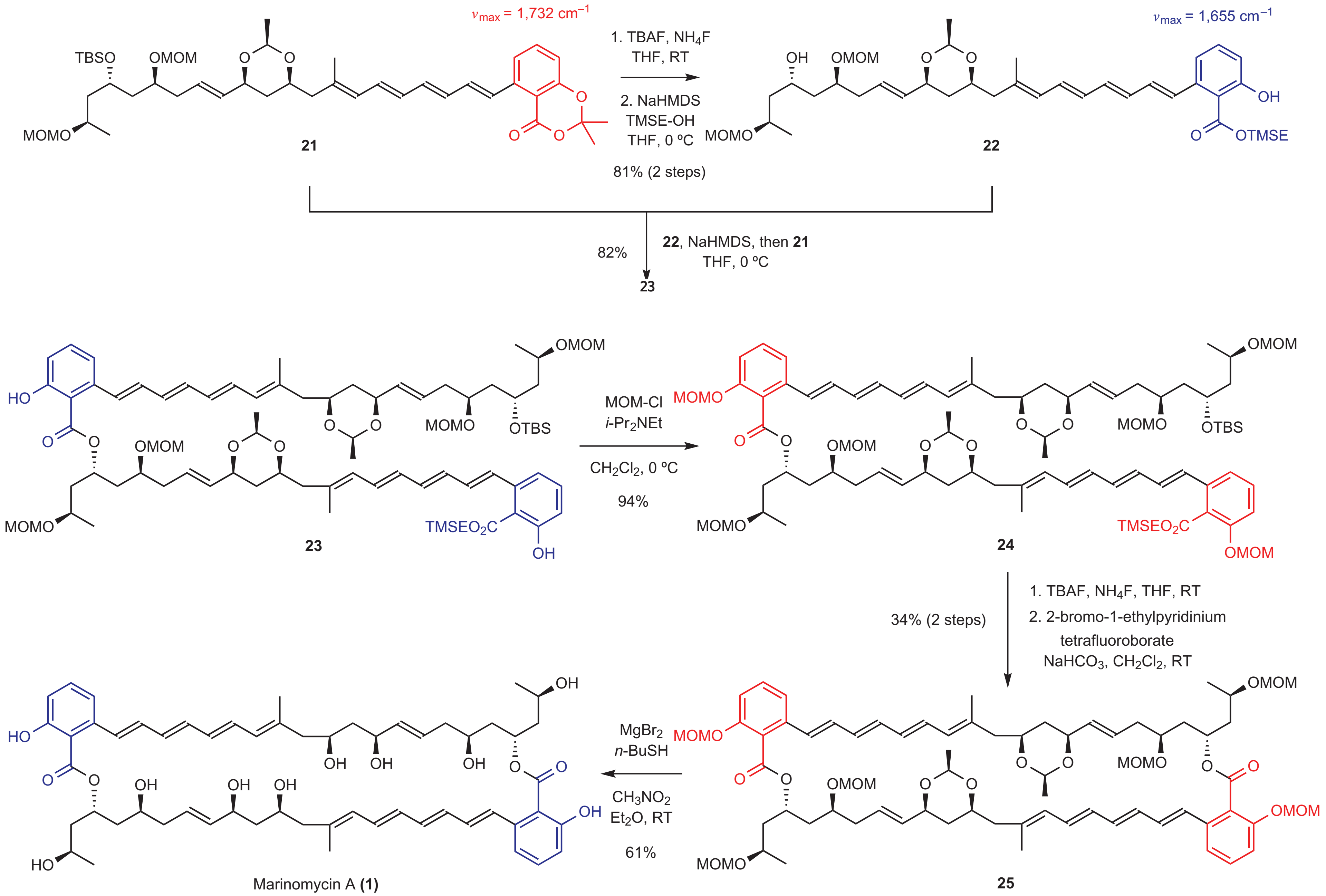


Potent MRSA and VREF antibiotic (0.13 uM)

Isolate from marine actinomycete near La Jolla

Nicolaou, K. C. et al. *J. Am. Chem. Soc.* **2007** *129*, 1760.

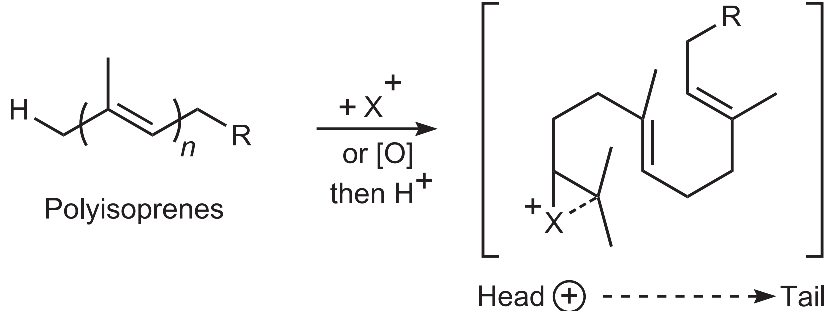




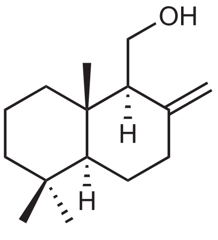
P. A. Evans et al. *Nat. Chem.* **2007** *129*, 1760.

Strained terpene synthesis-Tail-to-Head cyclization

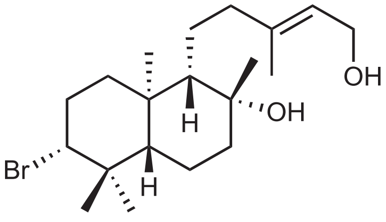
a Head-to-tail polycyclization



- Non-stop: complete charge propagation
- Reproducible in bulk solvent
- Extensively studied and used in synthesis

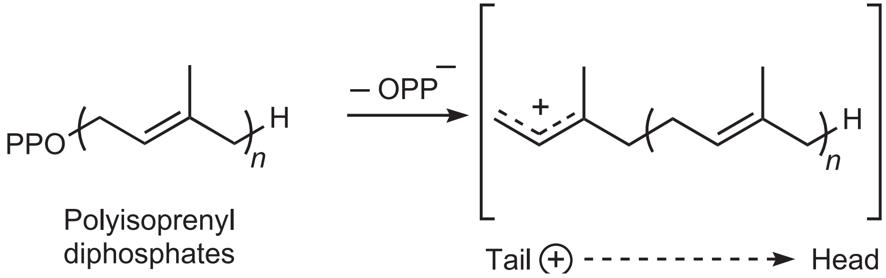


Albicanol

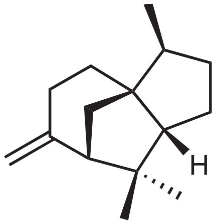


Aplysin-20

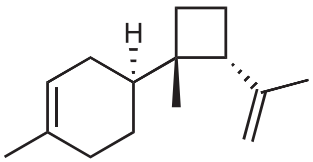
b Tail-to-head polycyclization



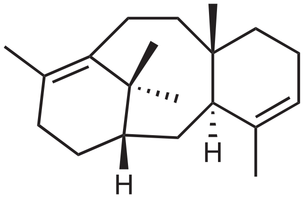
- Non-stop: complete charge propagation
- Never reproduced in bulk solvent
- Under-explored



β-Funebrene (**1a**)



Cumacrene (**2**)



Taxa-4,11-diene

S. V. Pronin, R. A. Shenvi *Nat. Chem*. **2012** *4*, 915.

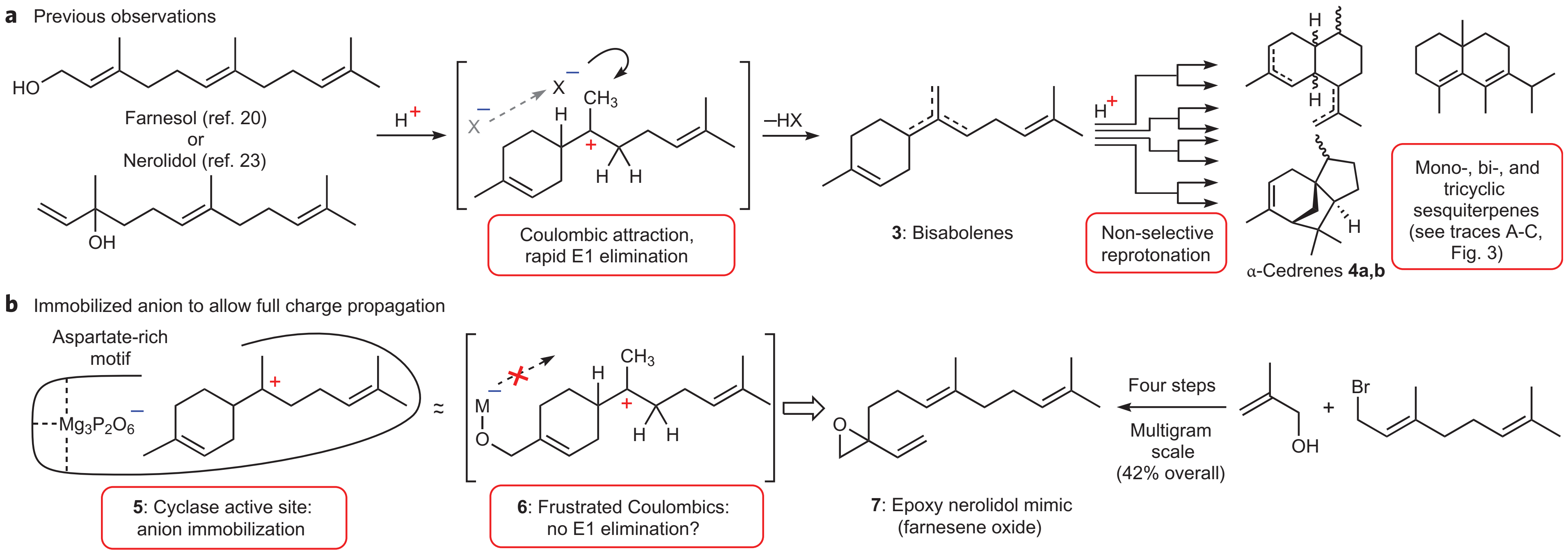
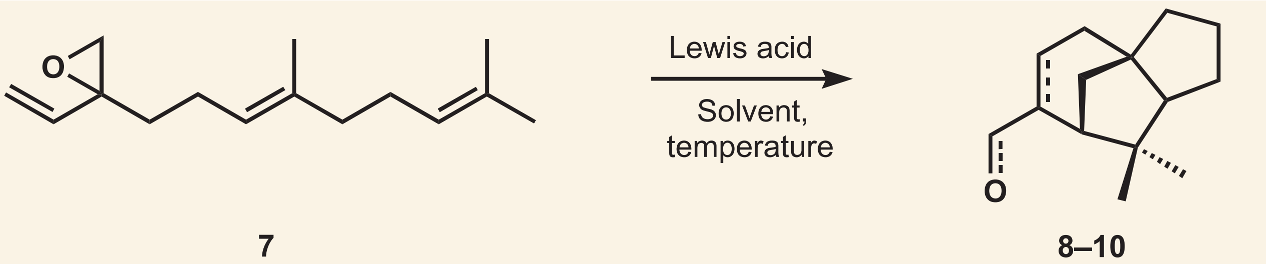
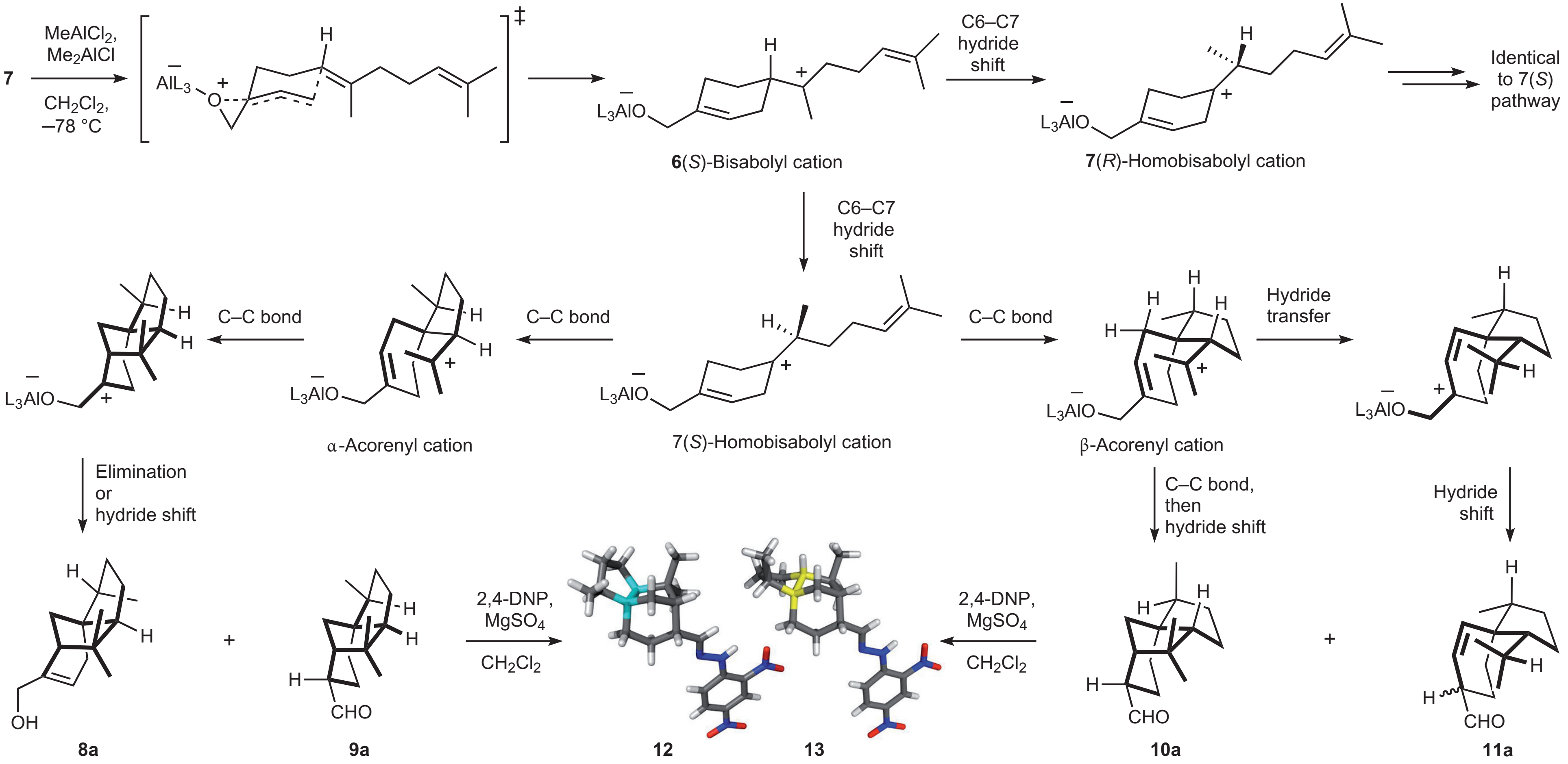


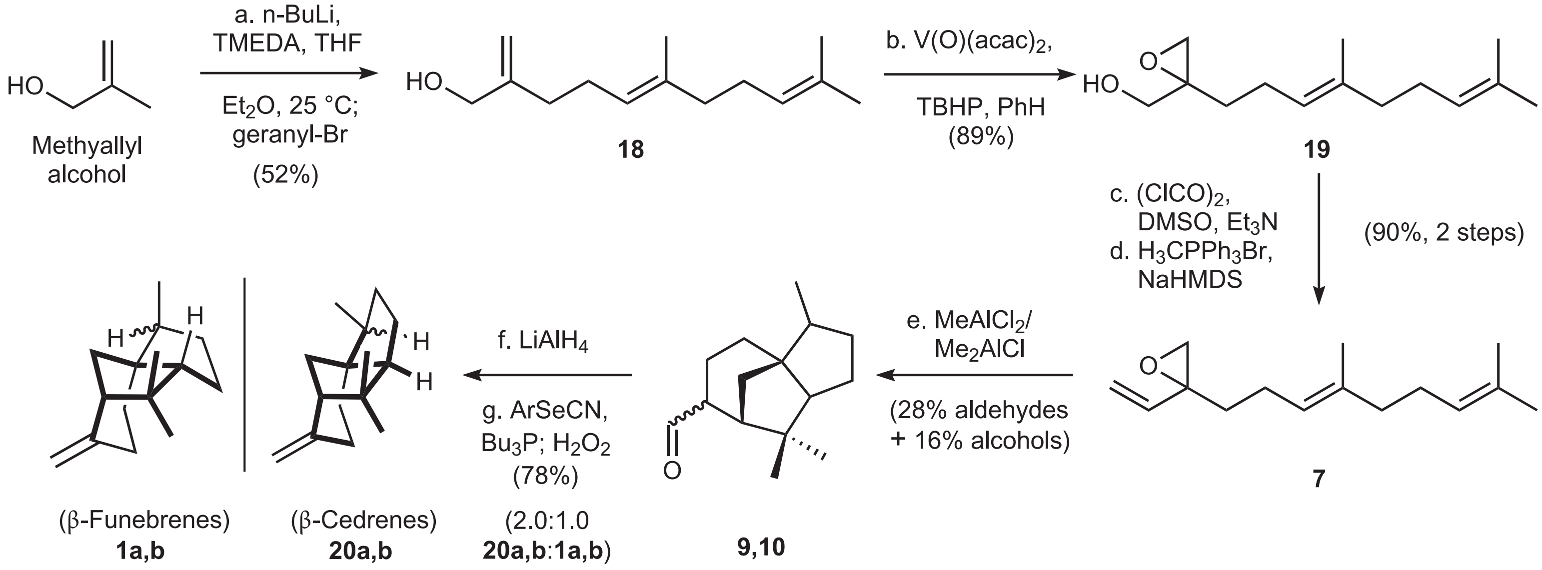
Figure 2 | Mechanistic comparisons of bulk solvent and cyclase active sites. a, Brønsted acid cyclization leads to an ion pair that rapidly undergoes S_N1 elimination if cyclization is disfavoured. **b**, Cyclase active sites sequester the pyrophosphate anion, a strategy that could be mimicked in bulk solvent by non-dissociating ligands on a Lewis acid.

S. V. Pronin, R. A. Shenvi *Nat. Chem*. **2012** *4*, 915.

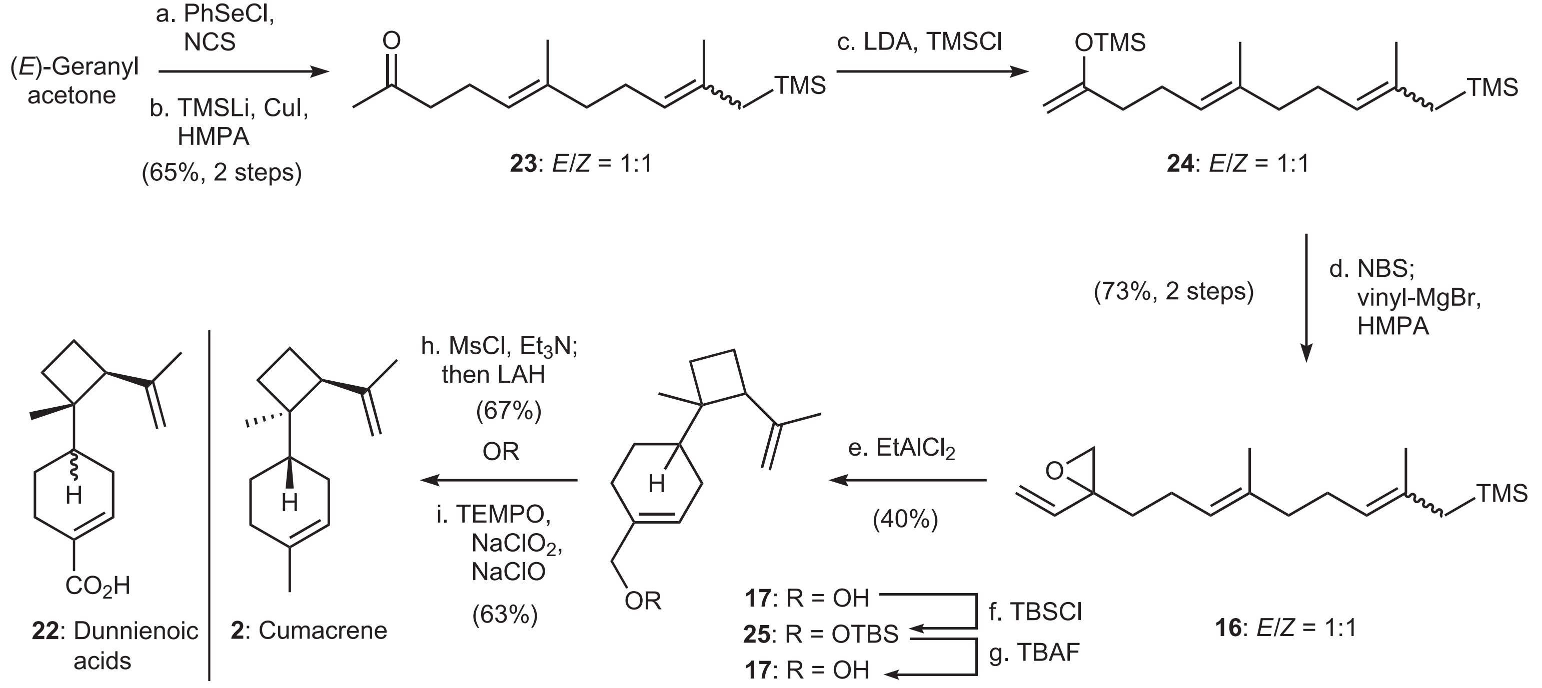

Lewis acid
Solvent,
temperature
7
8–10


7
MeAlCl$_2$,
Me$_2$AlCl
CH$_2$Cl$_2$,
–78 °C
‡
6(S)-Bisabolyl cation
C6–C7
hydride
shift
7(R)-Homobisabolyl cation
Identical
to 7(S)
pathway
C6–C7
hydride
shift
C–C bond
C–C bond
α-Acorenyl cation
7(S)-Homobisabolyl cation
C–C bond
β-Acorenyl cation
Hydride
transfer
Elimination
or
hydride shift
C–C bond,
then
hydride shift
Hydride
shift
8a
9a
2,4-DNP,
MgSO$_4$
CH$_2$Cl$_2$
12
13
2,4-DNP,
MgSO$_4$
CH$_2$Cl$_2$
10a
11a

a Total syntheses of β-funebrenes and β-cedrenes



b Total syntheses of cumacrene and dunnienoic acids

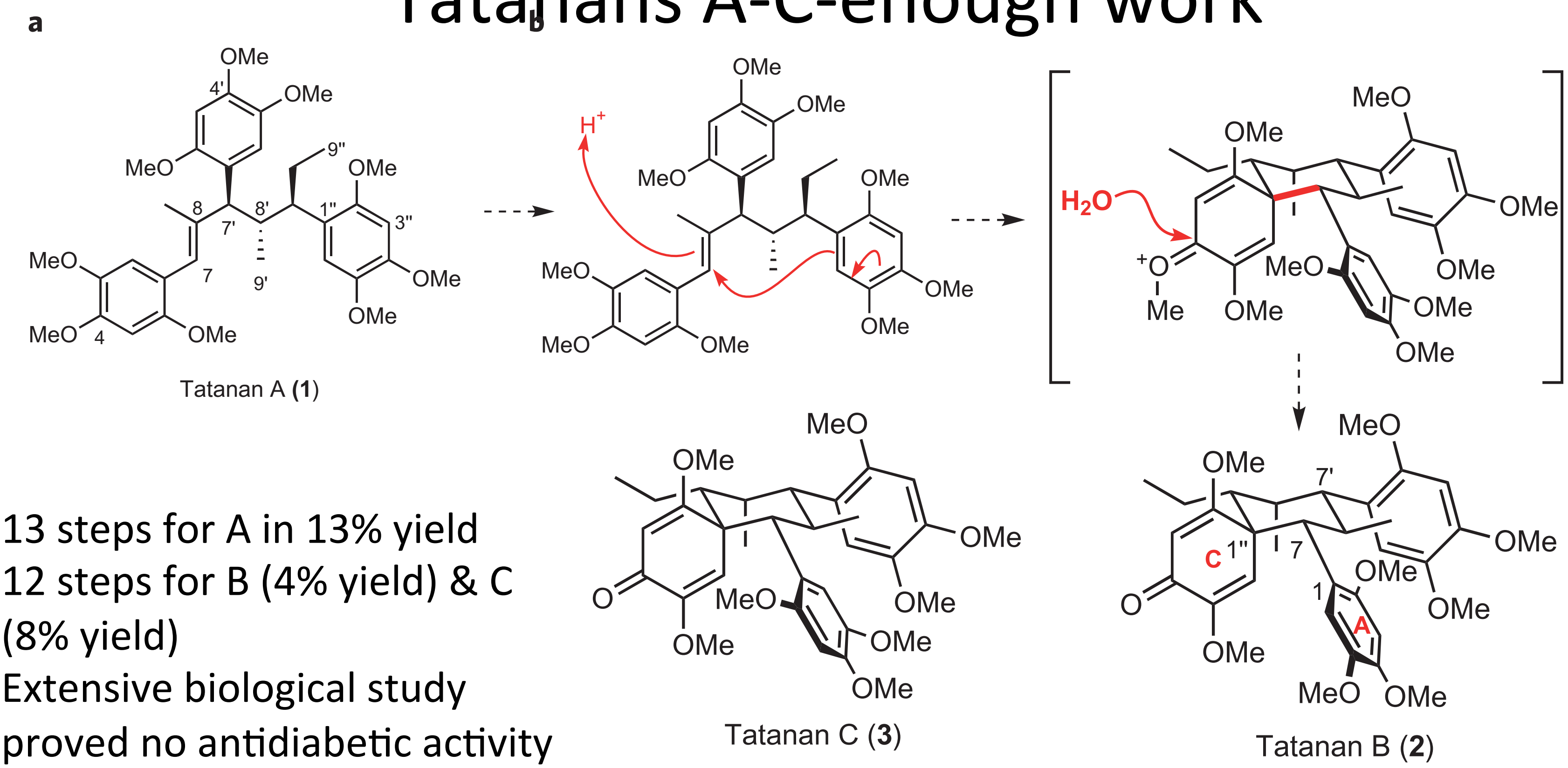


Summary

- 5 publications in 2011 (multi-targets wl <10 steps, single target shd biological test)
- 4 publications in 2012 (old TMs play efficiency; simple TMs play concept; bioactivity unness.)
- 5 publications in 2013

  Selective in-depth discussion
- Conclusion and summary

Tatanans A-C-enough work



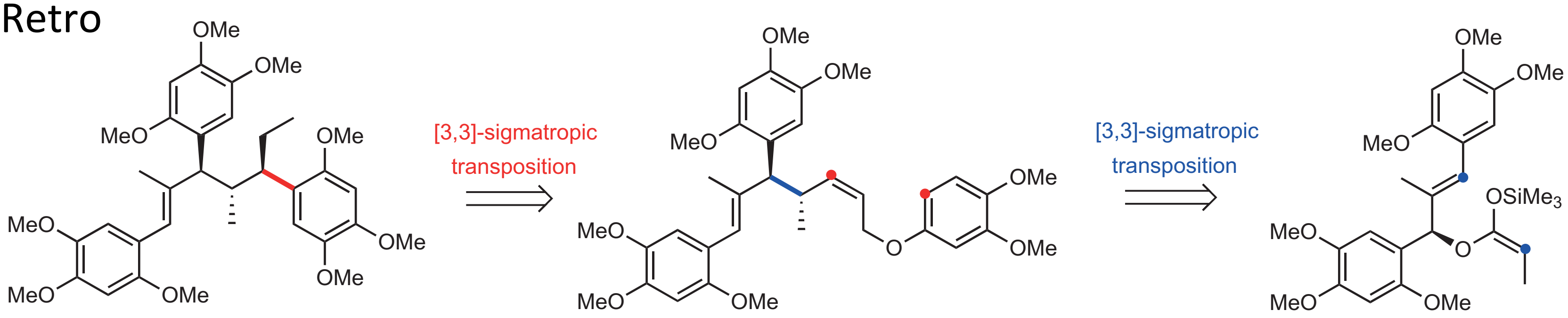
Tatanan A (**1**)

Tatanan C (**3**)

Tatanan B (**2**)

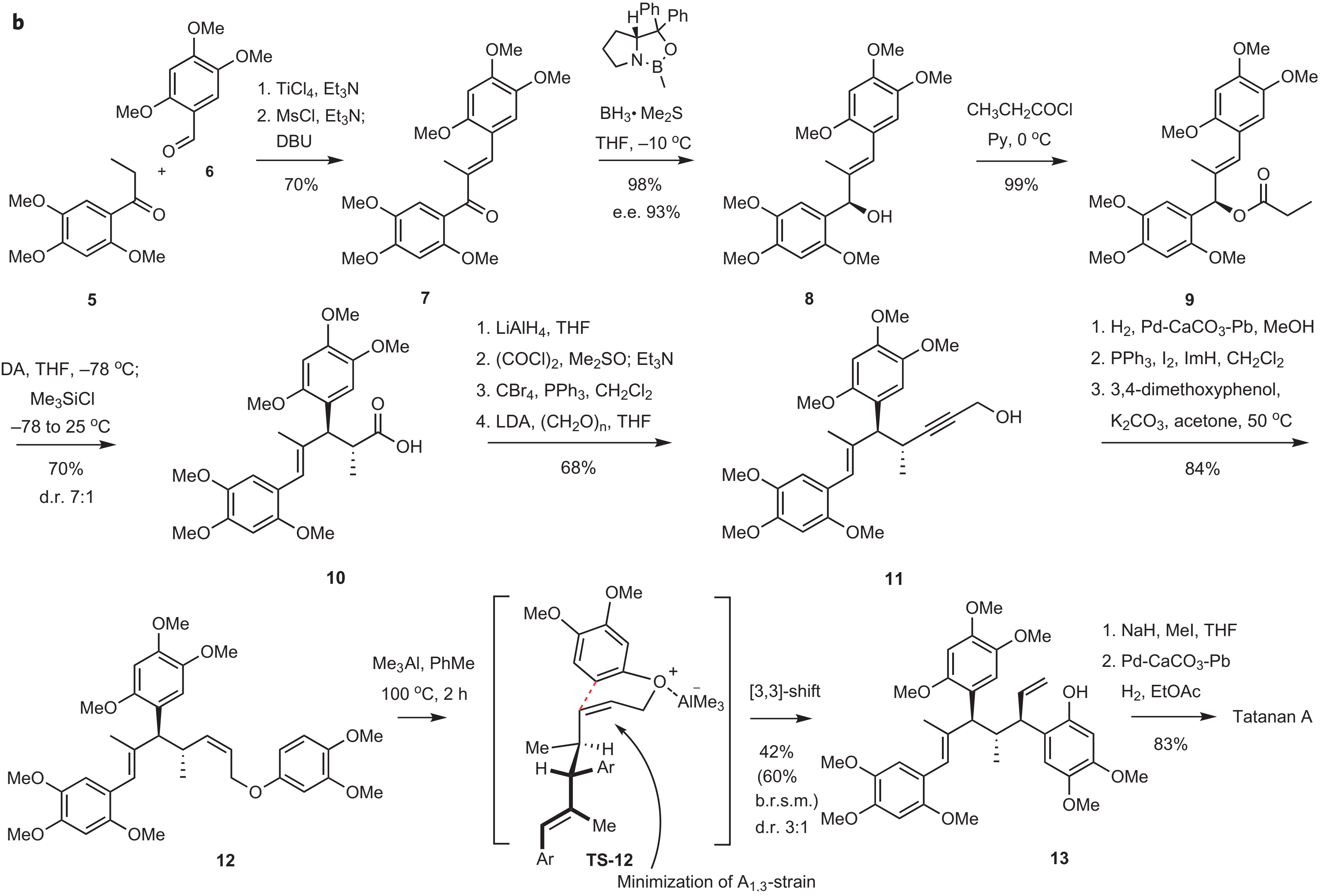
13 steps for A in 13% yield
12 steps for B (4% yield) & C (8% yield)
Extensive biological study proved no antidiabetic activity

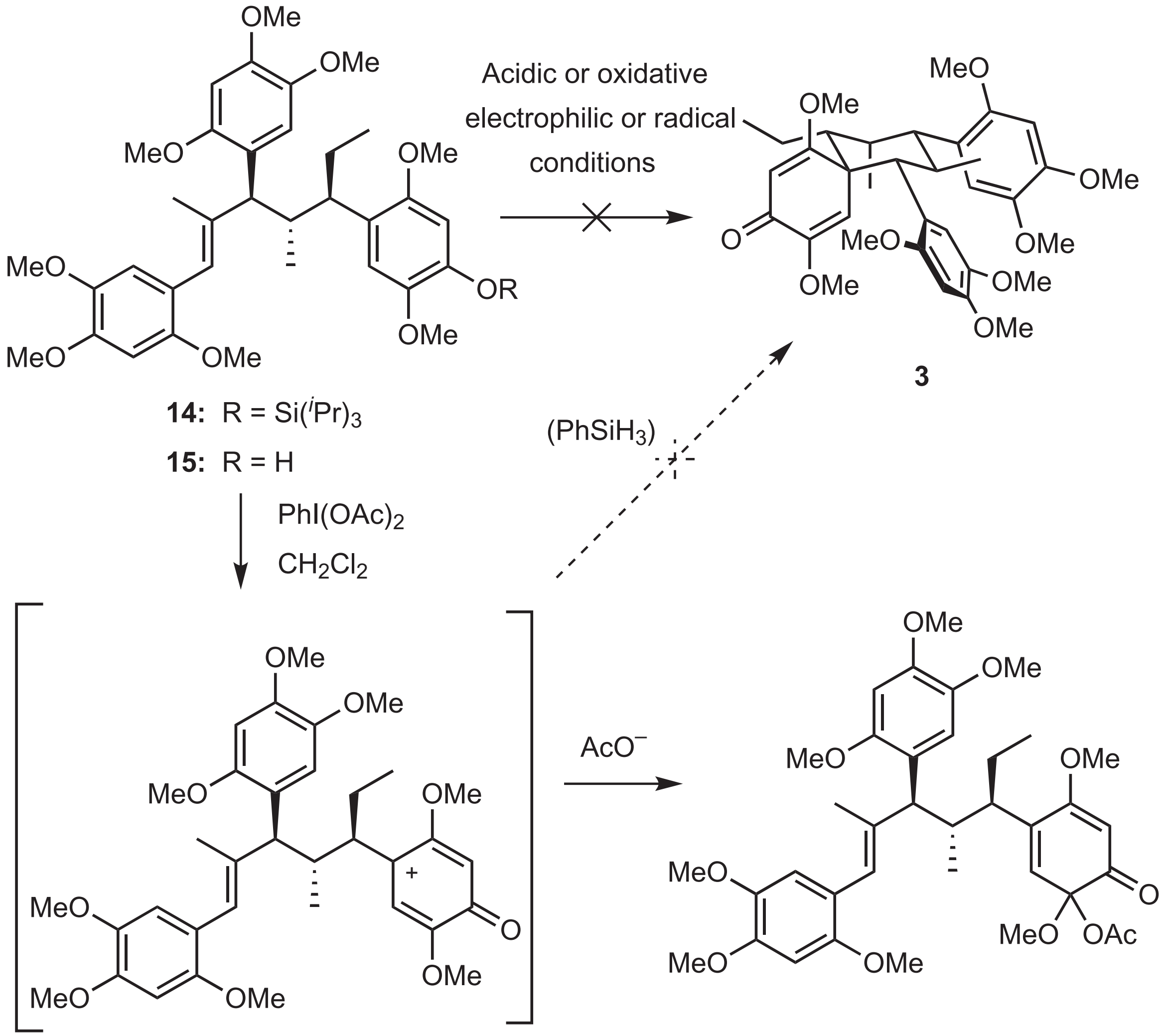
Retro



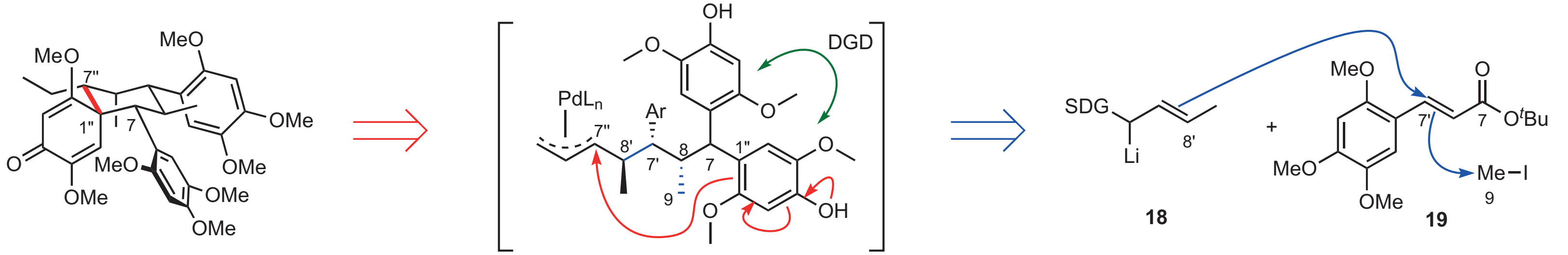
Xiao, Q. Zakarian, A. et. al. *Nat. Chem.* **2013**, *5*, 410.

Synthesis of tantanans A




Acidic or oxidative
electrophilic or radical
conditions
14: R = Si(^{i}Pr)$_3$
15: R = H
PhI(OAc)$_2$
CH$_2$Cl$_2$
(PhSiH$_3$)
AcO$^-$
3
OMe
MeO
OR
OAc
O
+

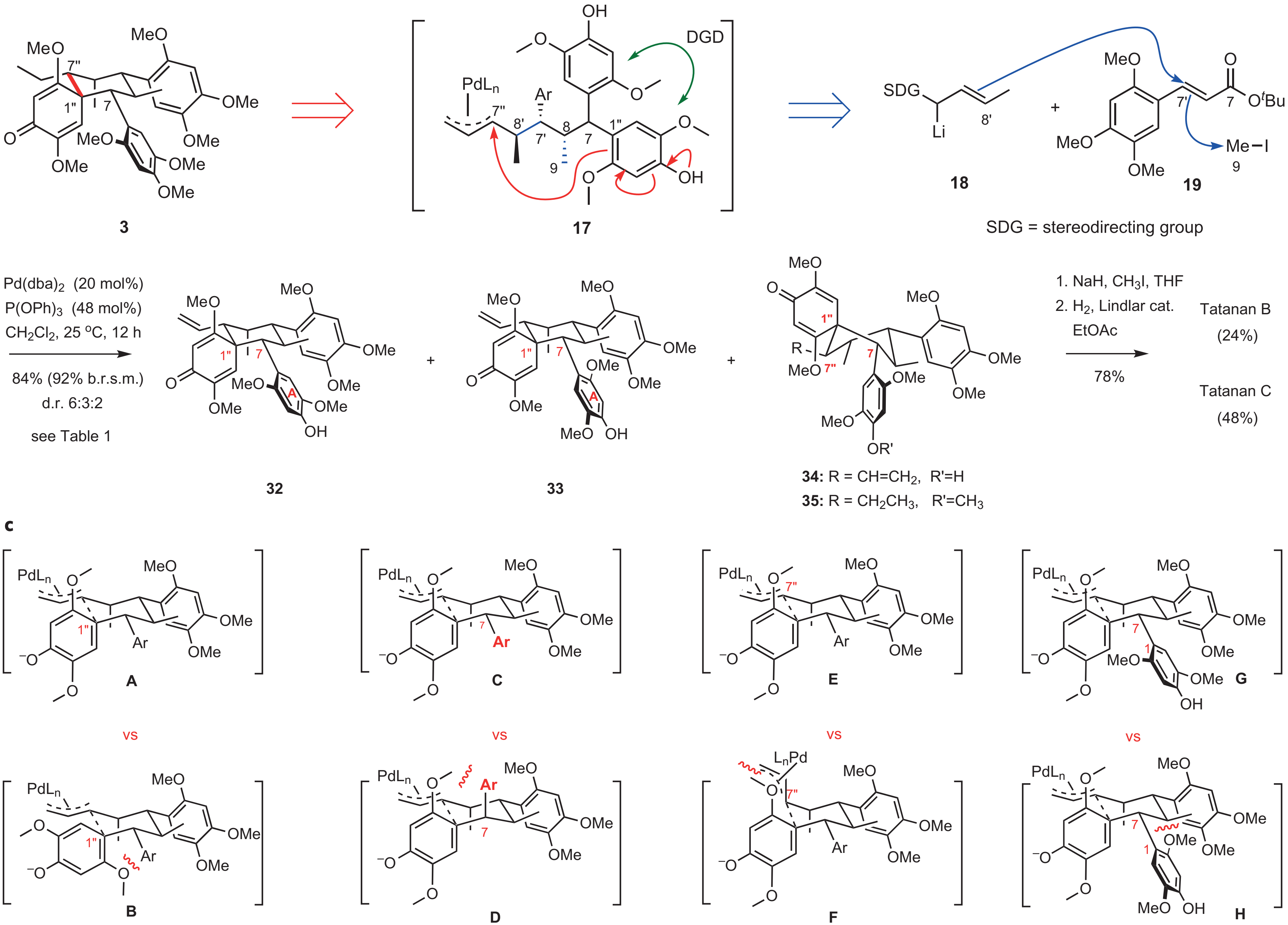
Redesign of synthesis



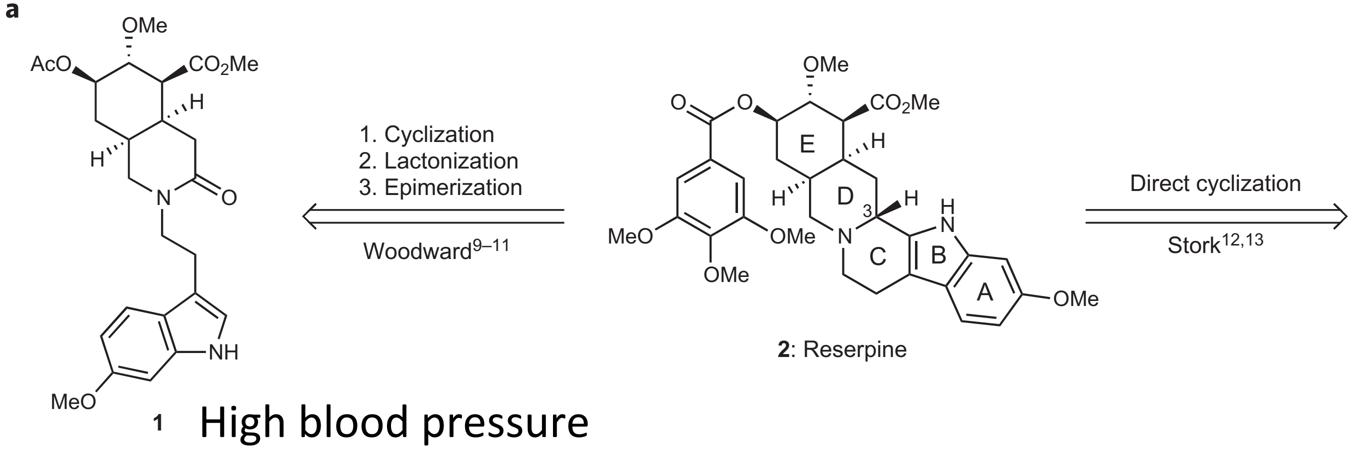
3 **17** **18** **19**

SDG = stereodirecting group

features of design: ● Dearomatization with π-allyl palladium complex ● Diastereotopic group differentiation (DGD) ● Conjugate addition to set the acyclic stereotriad

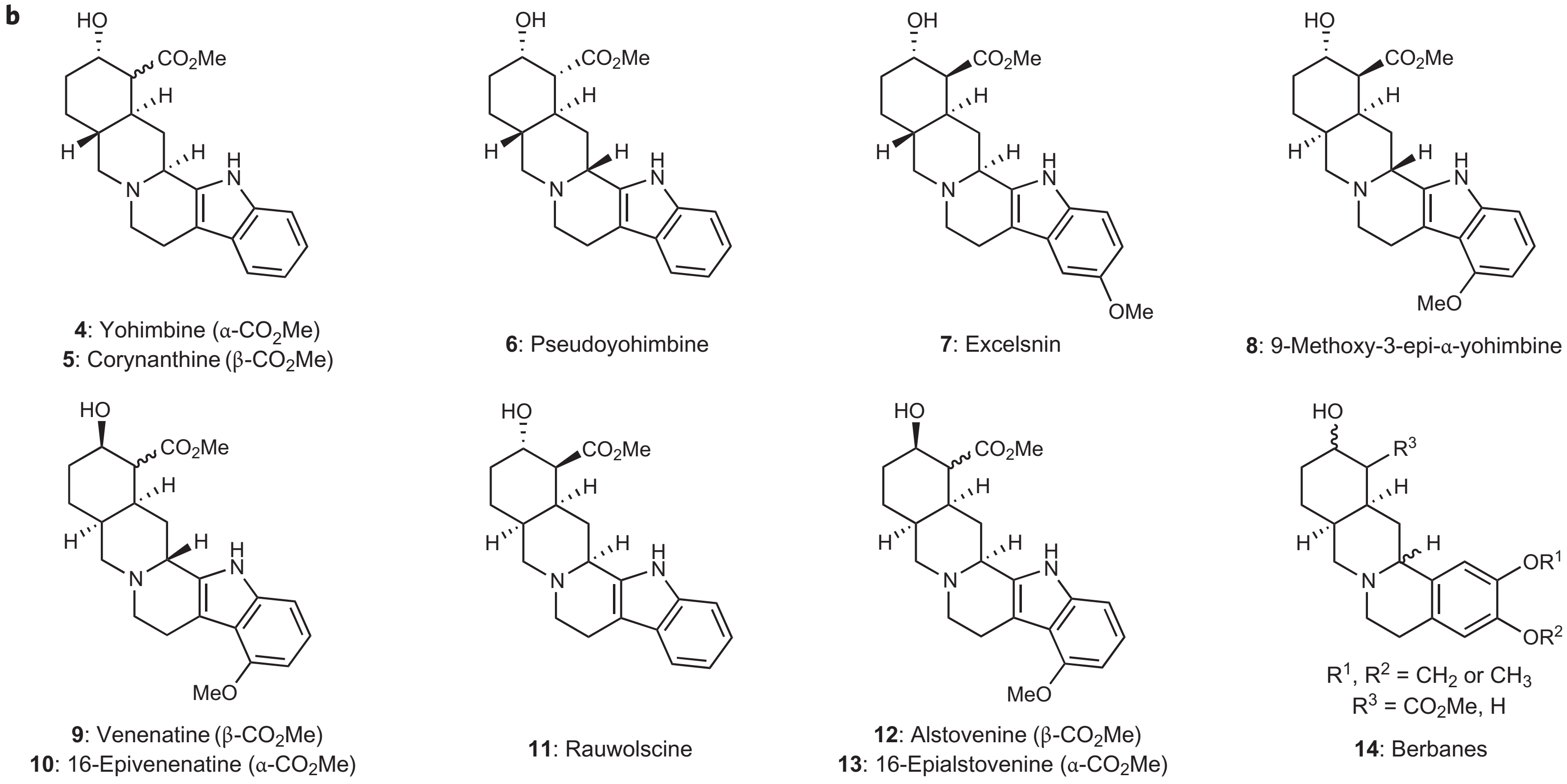

3
17
DGD
PdL$_n$
18
19
SDG = stereodirecting group
Me−I
9
Pd(dba)$_2$ (20 mol%)
P(OPh)$_3$ (48 mol%)
CH$_2$Cl$_2$, 25 °C, 12 h
84% (92% b.r.s.m.)
d.r. 6:3:2
see Table 1
32
33
34: R = CH=CH$_2$, R'=H
35: R = CH$_2$CH$_3$, R'=CH$_3$
1. NaH, CH$_3$I, THF
2. H$_2$, Lindlar cat. EtOAc
78%
Tatanan B (24%)
Tatanan C (48%)
c
A
vs
B
C
vs
D
E
vs
F
G
vs
H

Yohimbinoid-on the shoulder of giants



2: Reserpine

High blood pressure



4: Yohimbine (α-CO_2Me)
5: Corynanthine (β-CO_2Me)

6: Pseudoyohimbine

7: Excelsnin

8: 9-Methoxy-3-epi-α-yohimbine

9: Venenatine (β-CO_2Me)
10: 16-Epivenenatine (α-CO_2Me)

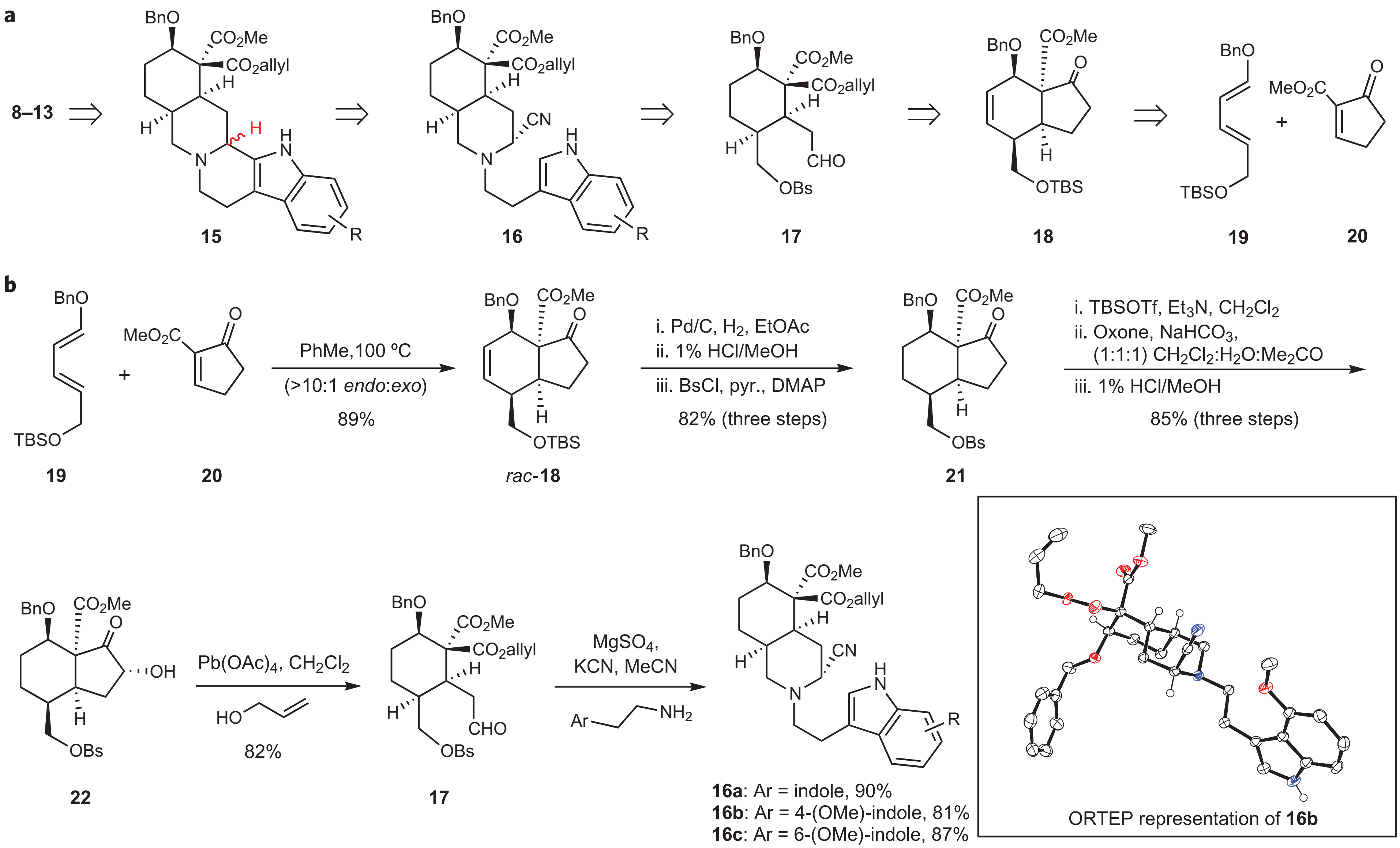
11: Rauwolscine

12: Alstovenine (β-CO_2Me)
13: 16-Epialstovenine (α-CO_2Me)

R^1, R^2 = CH_2 or CH_3
R^3 = CO_2Me, H

14: Berbanes

Retrosynthesis and precursor assembly



16a: Ar = indole, 90%
16b: Ar = 4-(OMe)-indole, 81%
16c: Ar = 6-(OMe)-indole, 87%

ORTEP representation of **16b**

Tantillo, D. J.; Sarpong, R. et. al. *Nat. Chem*. **2013**, *5*, 126.

Indole effect in stereoselectivity

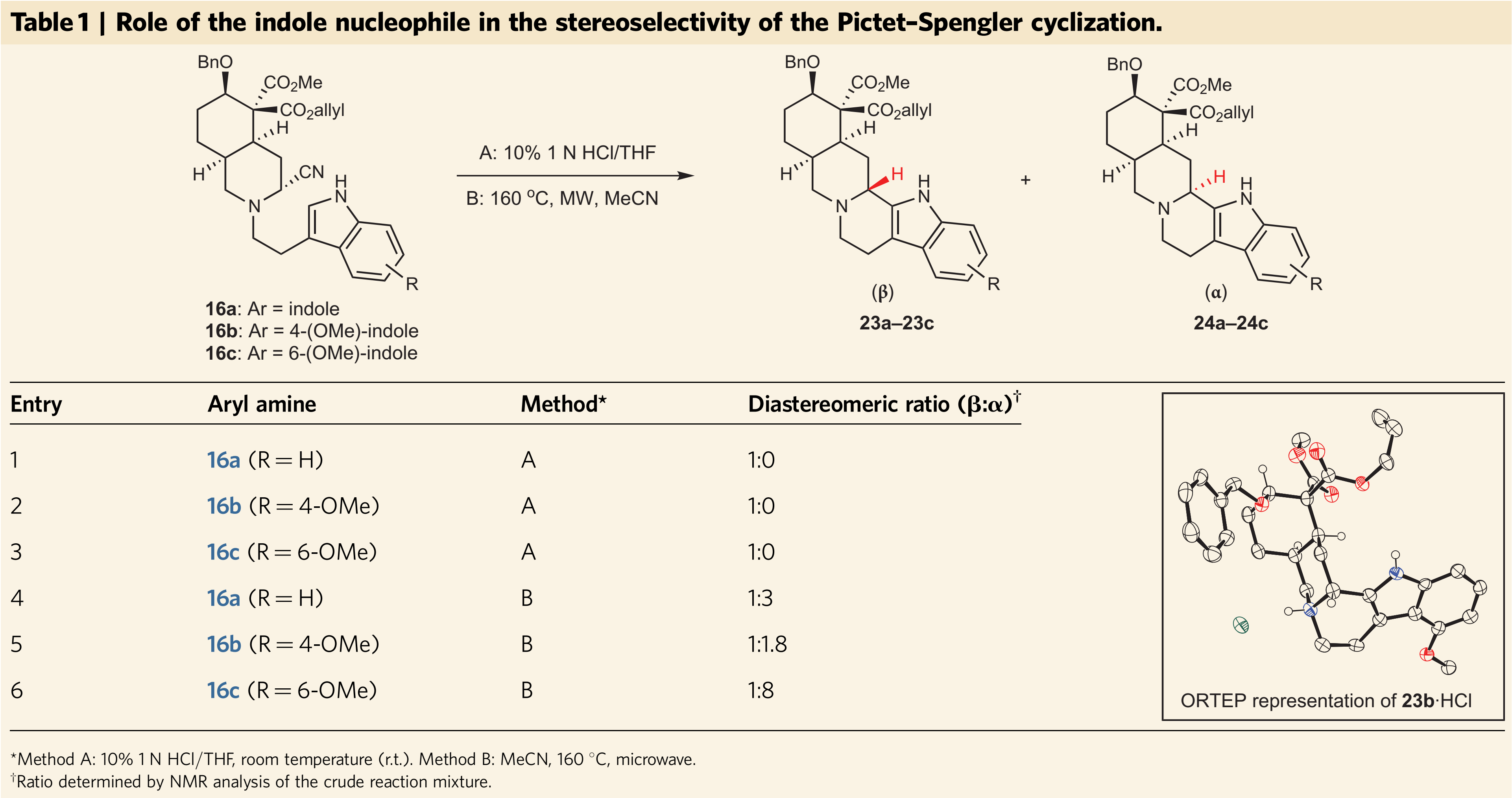


Table 1 | Role of the indole nucleophile in the stereoselectivity of the Pictet–Spengler cyclization.

A: 10% 1 N HCl/THF

B: 160 °C, MW, MeCN

16a: Ar = indole
16b: Ar = 4-(OMe)-indole
16c: Ar = 6-(OMe)-indole

(β)
23a–23c

(α)
24a–24c

Entry	Aryl amine	Method*	Diastereomeric ratio (β:α)†
1	**16a** (R = H)	A	1:0
2	**16b** (R = 4-OMe)	A	1:0
3	**16c** (R = 6-OMe)	A	1:0
4	**16a** (R = H)	B	1:3
5	**16b** (R = 4-OMe)	B	1:1.8
6	**16c** (R = 6-OMe)	B	1:8

ORTEP representation of **23b**·HCl

*Method A: 10% 1 N HCl/THF, room temperature (r.t.). Method B: MeCN, 160 °C, microwave.
†Ratio determined by NMR analysis of the crude reaction mixture.

Solvents effect in cyclization

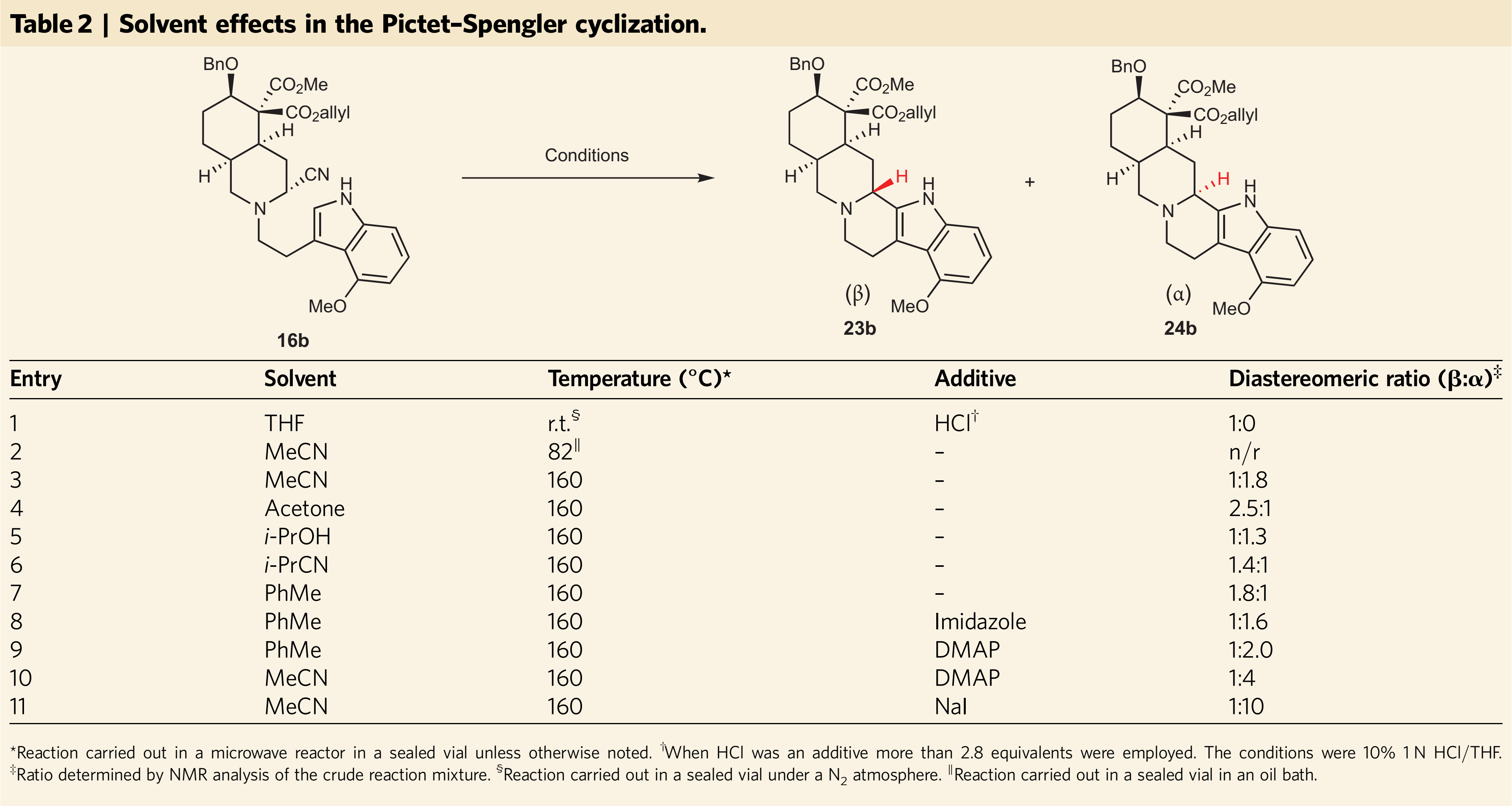


Table 2 | Solvent effects in the Pictet–Spengler cyclization.

16b → **23b** + **24b**

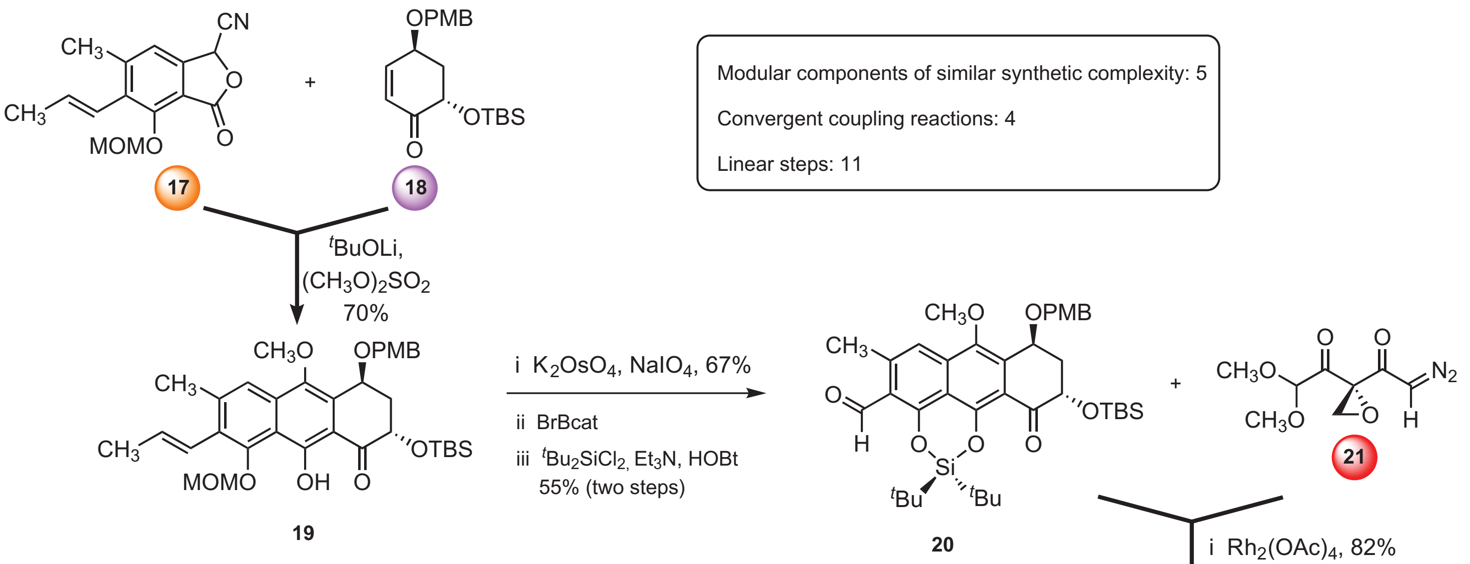
Entry	Solvent	Temperature (°C)*	Additive	Diastereomeric ratio (β:α)[‡]
1	THF	r.t.[§]	HCl[†]	1:0
2	MeCN	82[‖]	–	n/r
3	MeCN	160	–	1:1.8
4	Acetone	160	–	2.5:1
5	*i*-PrOH	160	–	1:1.3
6	*i*-PrCN	160	–	1.4:1
7	PhMe	160	–	1.8:1
8	PhMe	160	Imidazole	1:1.6
9	PhMe	160	DMAP	1:2.0
10	MeCN	160	DMAP	1:4
11	MeCN	160	NaI	1:10

*Reaction carried out in a microwave reactor in a sealed vial unless otherwise noted. [†]When HCl was an additive more than 2.8 equivalents were employed. The conditions were 10% 1 N HCl/THF. [‡]Ratio determined by NMR analysis of the crude reaction mixture. [§]Reaction carried out in a sealed vial under a N_2 atmosphere. [‖]Reaction carried out in a sealed vial in an oil bath.

Same key reactions
Same solvent system
very similar substrate

surely produced similar yield! (65% vs 72%)

Trioxacarcin A-Myers is Myers

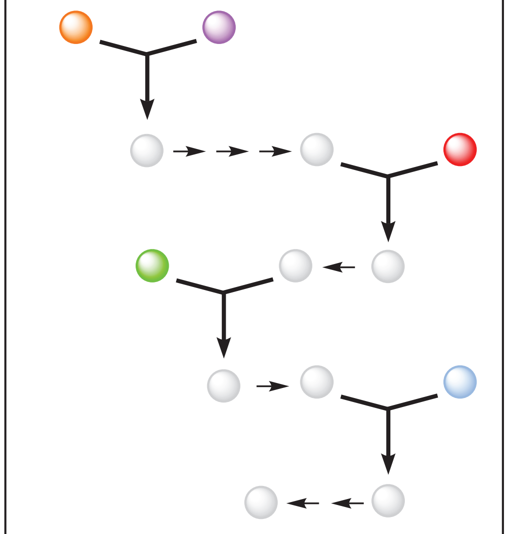


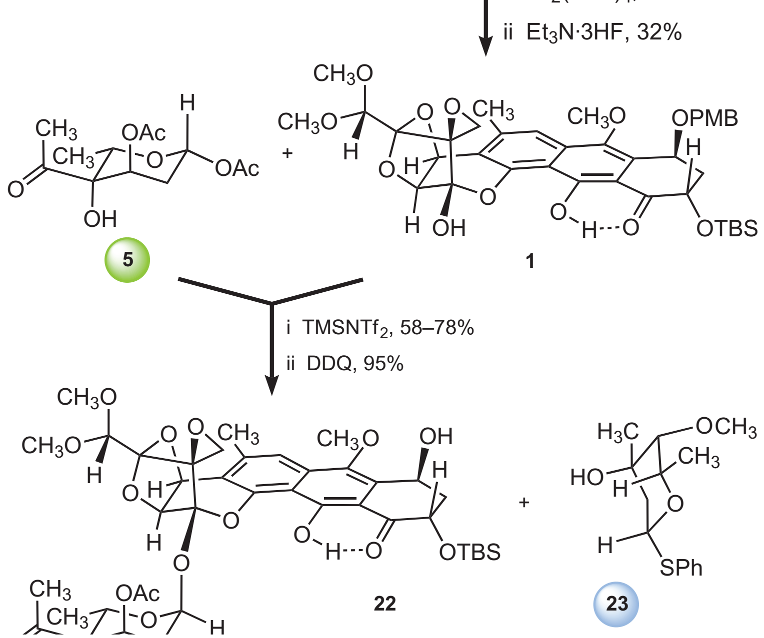
Modular components of similar synthetic complexity: 5

Convergent coupling reactions: 4

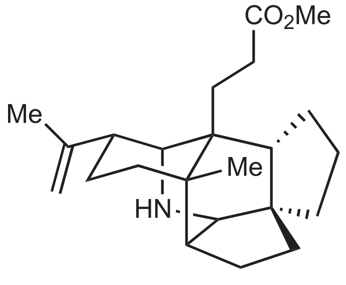
Linear steps: 11

Graphical schematic

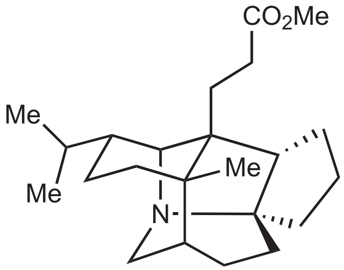




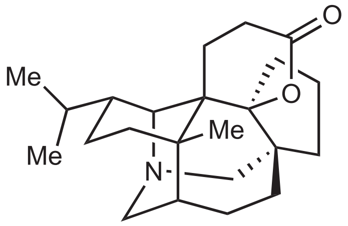
Daphenylline-classic total synthesis



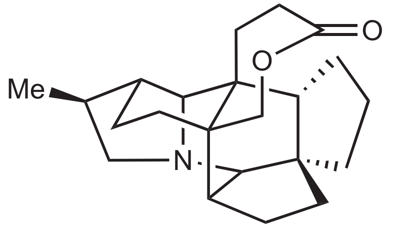
1 Methyl homoseco-daphniphyllate



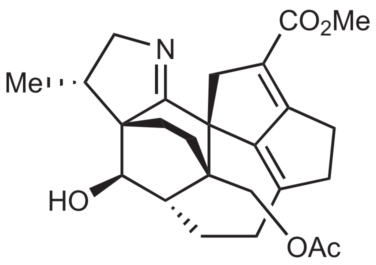
2 Methyl homo-daphniphyllate



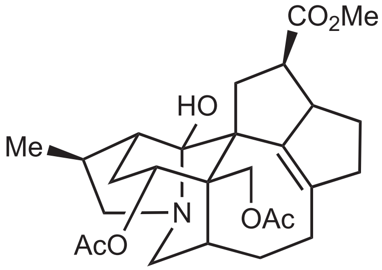
3 Daphnilactone A



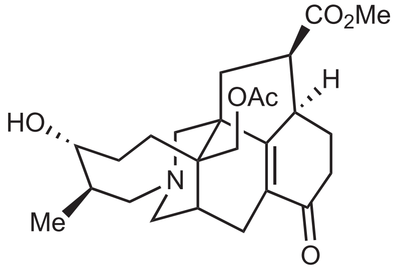
4 Bukittinggine



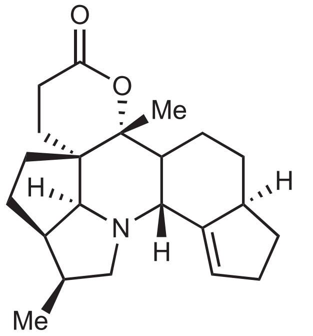
5 Daphmanidin E



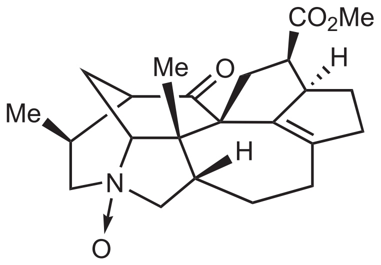
Yuzurimine



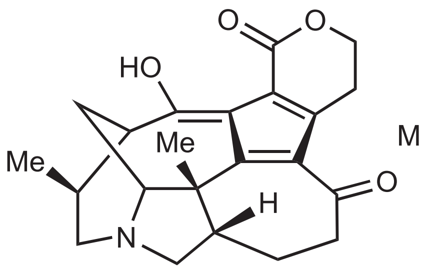
Daphmanidin C



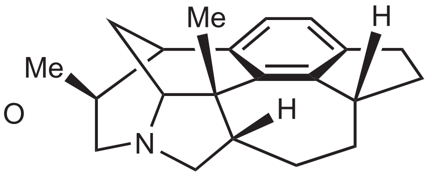
Calyciphylline B



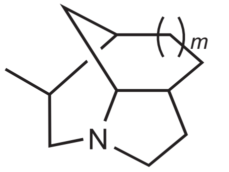
6 Calyciphylline A



7 Daphnicyclidin A



8 Daphenylline

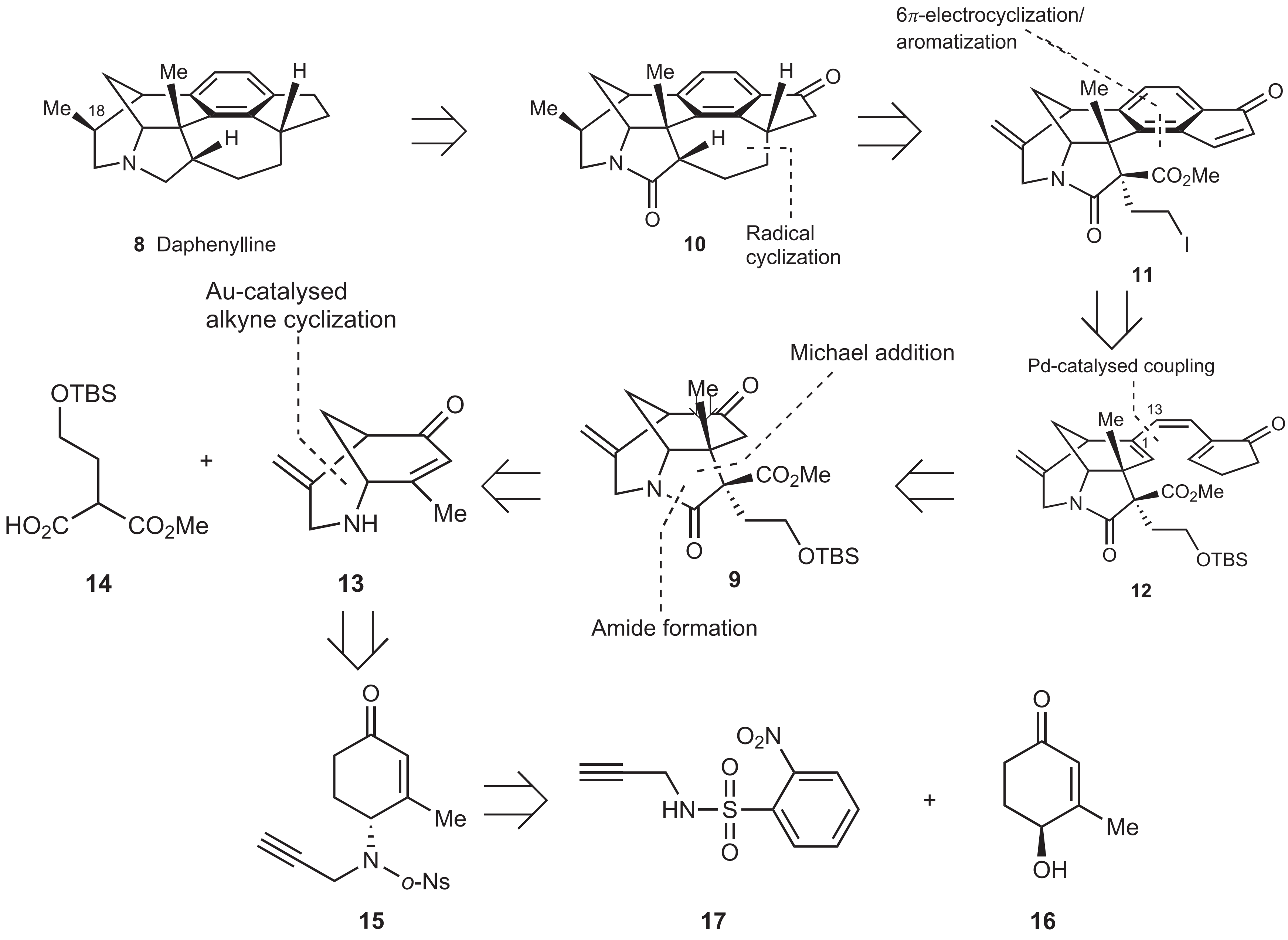


m = 1 or 2

6,*n*,5-bridged tricycle

Zhang, Q. et al. *Org. Lett*. **2009**, *11*, 2357.

Retrosynthesis


8 Daphenylline

10

Radical cyclization

6π-electrocyclization/ aromatization

11

Pd-catalysed coupling

12

Michael addition

Amide formation

9

Au-catalysed alkyne cyclization

14

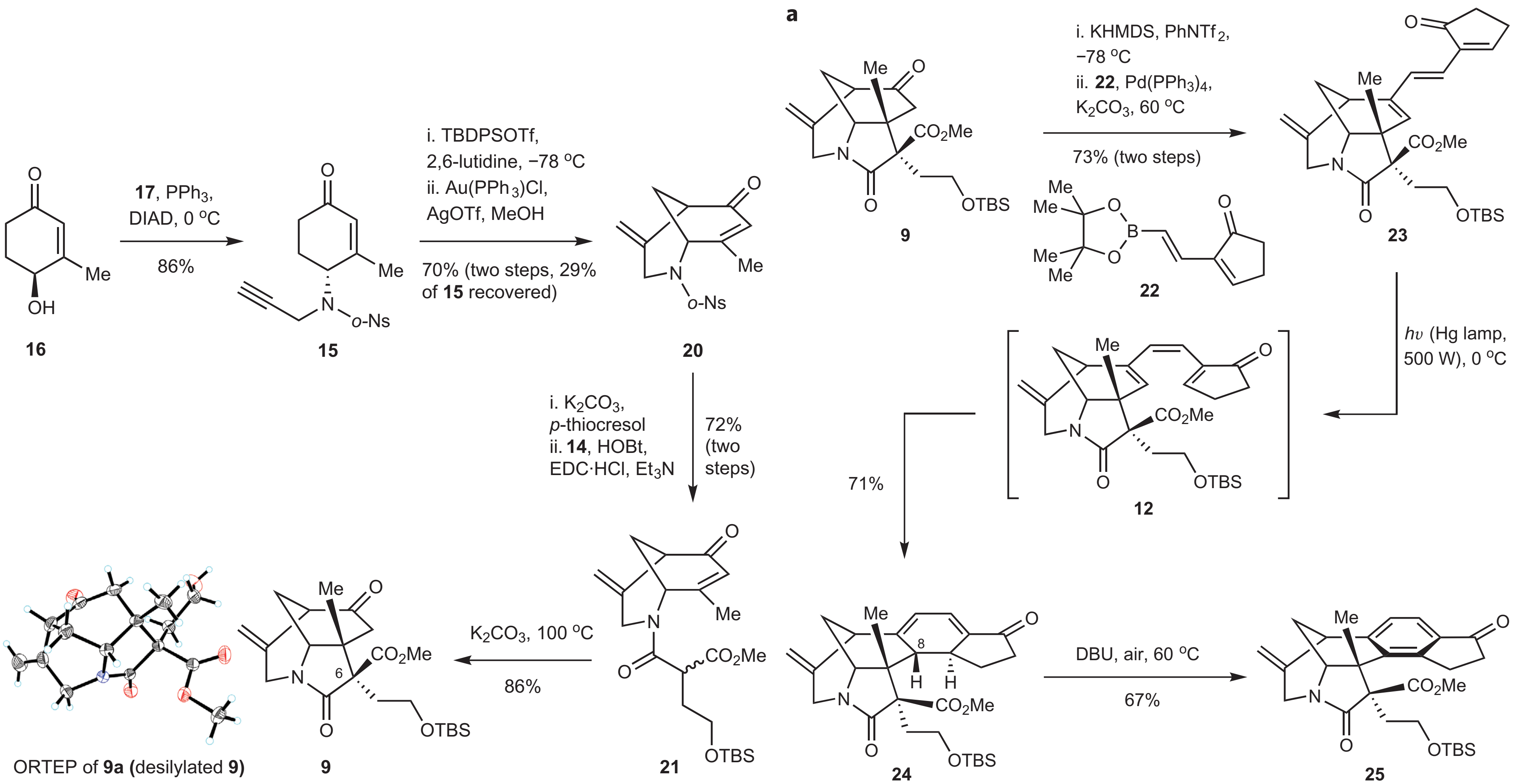
13

15

17

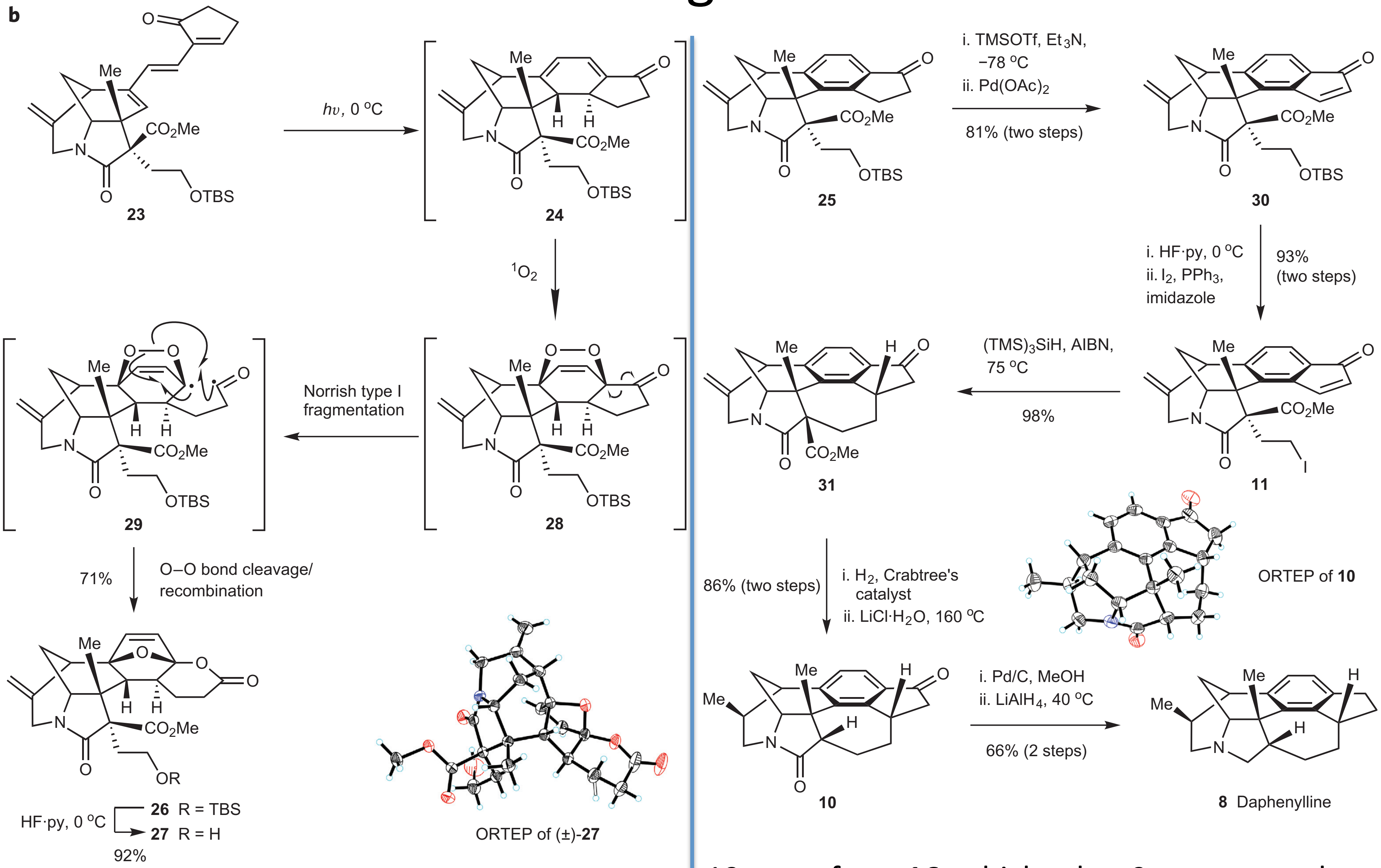
16

Forward synthesis



Lu, Z.; Li ,Y.; Deng, J.; Li, A. *Nat. Chem*. **2013**, *5*, 679.

Final game



19 steps from **16,** which takes 9 steps to make.

Summary

- 5 publications in 2011 (multi-targets wl <10 steps, single target shd biological test)
- 4 publications in 2012 (old TMs play efficiency; simple TMs play concept; bioactivity unness.)
- 5 publications in 2013 (classic total synthesis, efficiency could be low if TMs are complex)
- Conclusion and summary

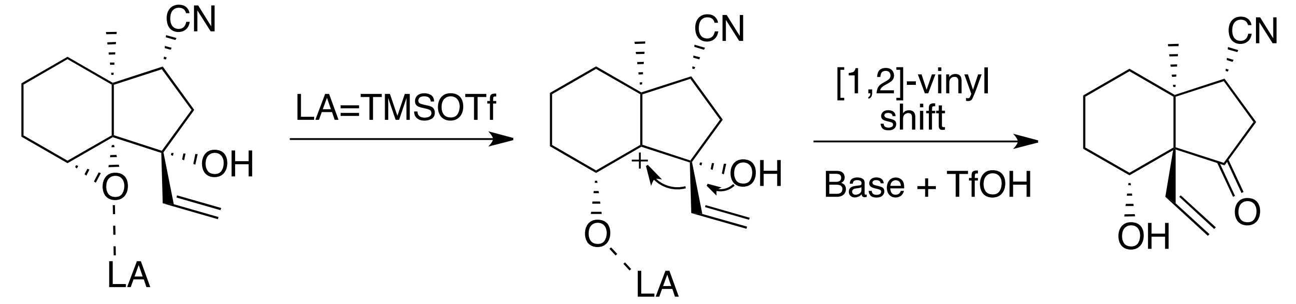
Conclusion

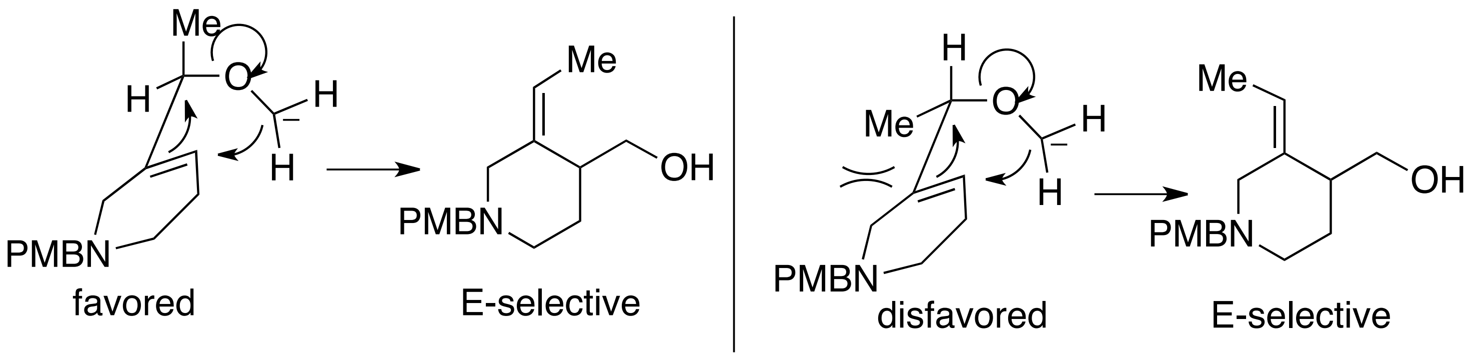
- How to sell your chemistry
- Sell it big and sell the concept
- Efficiency - the most eye-catching feature
- Are you sleepy?


2014 HAPPY NEW YEAR
中国年

Answers to questions

Semi pinacol rearragement





favored

E-selective

disfavored

E-selective