
Galbulimima alkaloids
Dan Jansen
Shenvi Lab Group Meeting
August 8, 2011

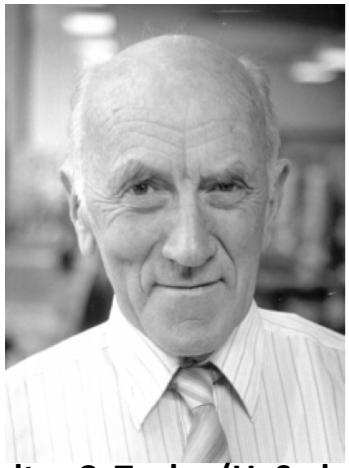
Outline

- Figures in Galbulimima alkaloid chemistry
- Isolation
- Biological activity
- Basic Structure
- Biosynthesis
- Chemistry

Important figures in Galbulimima alkaloid chemistry

Ernest Ritchie (U. Sydney)

Lewis N. Mander (ANU)



Walter C. Taylor (U. Sydney)

Samuel Chackalamannil (Schering)

Jack Baldwin (Oxford)

Mohammad Movassaghi (MIT)

Dawei Ma (Shanghai IOC)

Galbulimima

http://www.mobot.org/mobot/research/apweb/orders/magnolialesweb.htm

http://www.fossilflowers.org/imgs/ws1/na/Himantandraceae_Galbulimima_baccata_18730.html

8. GALBULIMIMA BACCATA, *Bail.*

(a) Port. under surface of a leaf, (b) fl. bud, (c) the outer sepal, (d) port. surface of a sep., (e) fl. bud, sepals removed, (f) one of the outer staminodia ? petals, (g) a scale, (h) a fruit, (i) sect. fruit containing no perfect seeds, (k) sect. fruit containing four perfect seeds, (l) seeds, (m) seed enclosed in its loose rugged coat, (n) long. sect. seed, (o) trans. sect seed. (a), (d), (f), and (g) enl.; (b), (c), (e), (h), and (o) nat. size.

http://www.mobot.org/mobot/research/apweb/images/galbulimimahabit.html

https://www.thieme-connect.com/media/synthesis/201022/e274_f1.jpg

Botanical: Galbulimima baccata

Common: Magnolia, Northern Pigeonberry Ash

Family: Himantandraceae

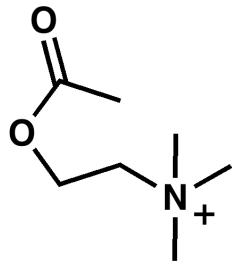
Traditional uses

- “In Papua New Guinea, a decoction of bark of *Galbulimima belgraveana* is drunk to invigorate health before war, and to give hallucination and premonition.”
- “The chewing of Galbulimima bark is reported to produce a destructive frenzy often accompanied by violence. Physical restraint is sometimes required.”
- Large doses may account for hallucinogenic effect (atropine overdose) or an alkaloid with novel psychoactive activity (possibly G.B. 18) may be responsible

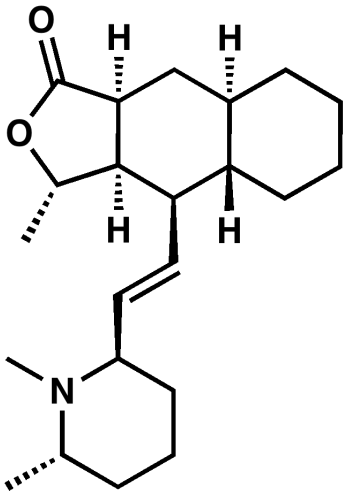
Source: Psychoactive properties of Galbulimima bark. J Psychoactive Drugs. 2005 Mar;37(1):109-11.

Modern medicine

- The medicinal properties of *Galbulimima belgraveana* are attributed to piperidine alkaloids, such as (+)-himbacine, which are structurally similar to acetylcholine and are therefore muscarinic receptor antagonist/ agonist (Zholos AV *et al.*, 1997).
- Anticholinergic activity has prompted their study as potential source of drugs for the treatment of Alzheimer's diseases, cardiac bradycardia and glaucoma.



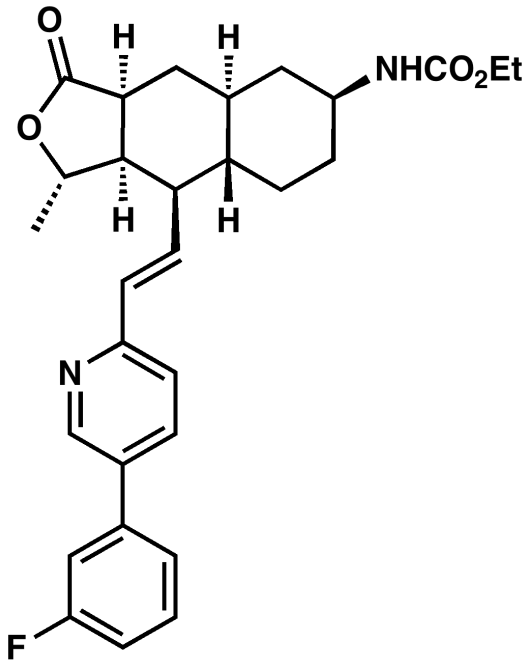
acetylcholine



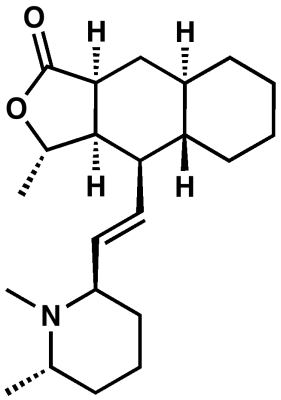
(+)-himbacine

Modern medicine (cont.)

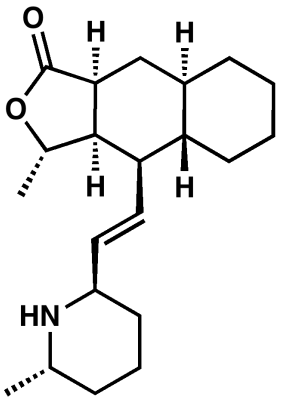
- SCH 530348
  - Thrombin receptor (PAR-1) inhibitor in Phase-III clinical trials for acute coronary syndrome and secondary prevention of CV events in high-risk patients
  - Synthesized as an analog as a result of total synthesis of himbacine by Chackalamannil
  - Was originally synthesized as an analog as a result of total synthesis for antimuscarinic drug program
  - Anti-PAR-1 activity found by HTS



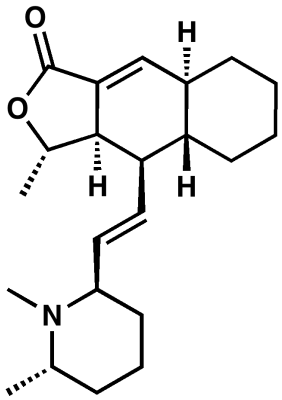
The Galbulimima alkaloids – Class I



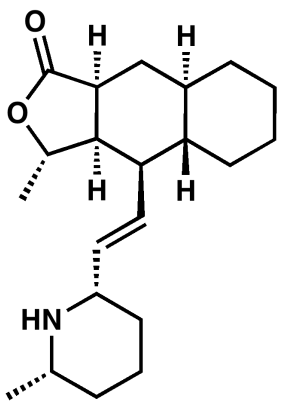
(+)-himbacine



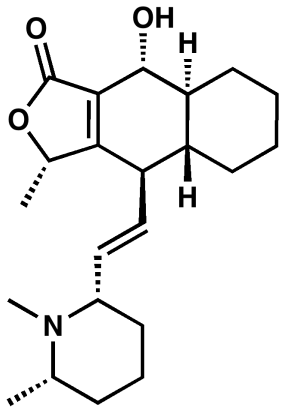
(+)-himbeline



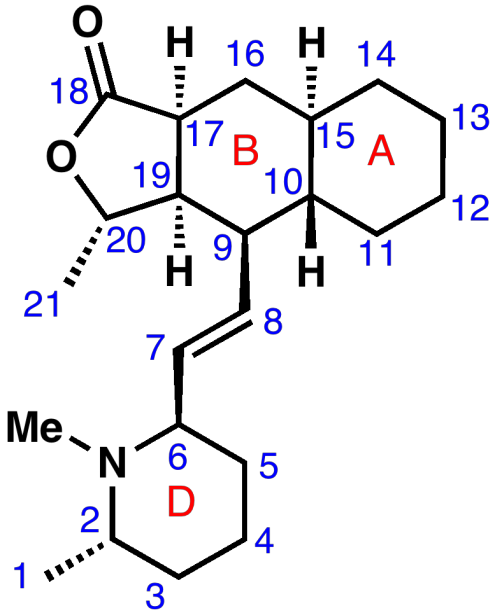
himgravine



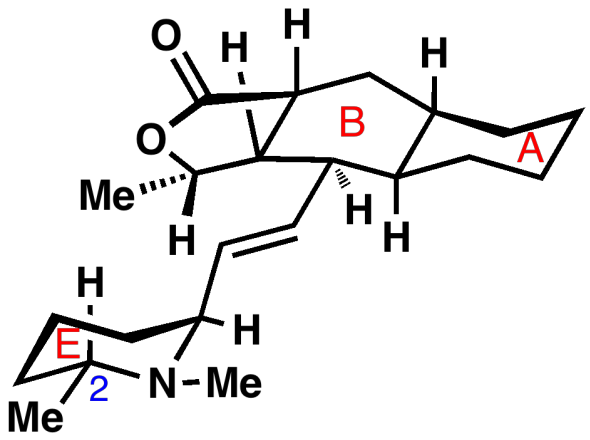
himandravine



himgrine

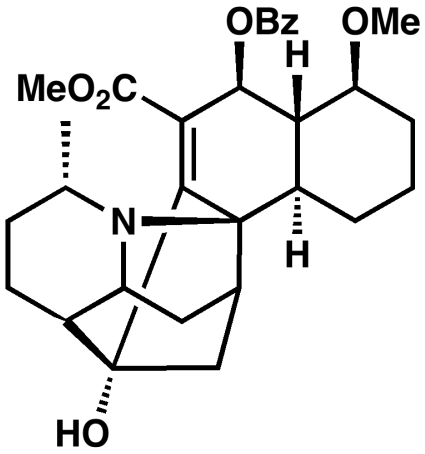


(+)-himbacine

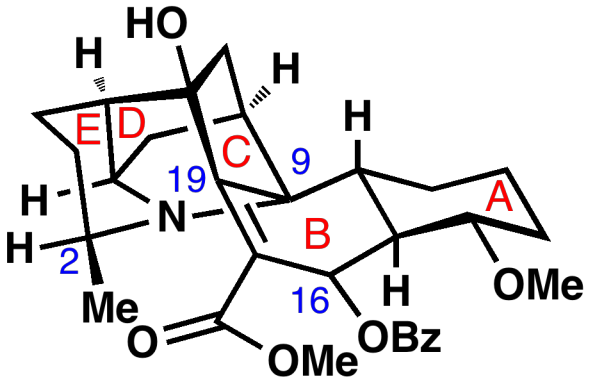


himbacine

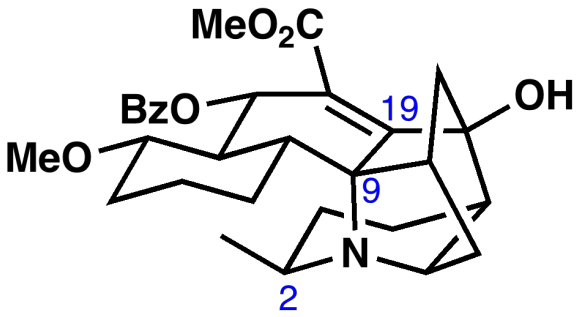
The Galbulimima alkaloids – Class II



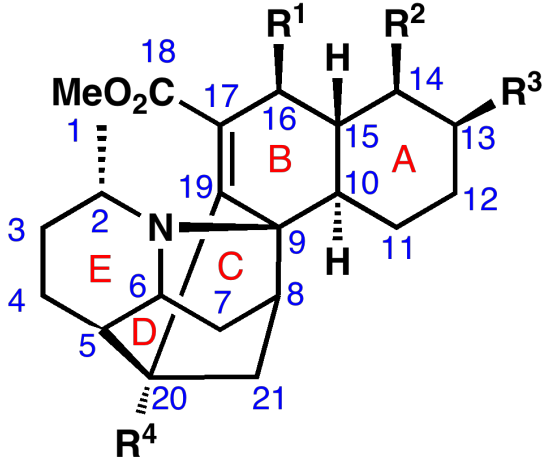
himandrine



himandrine



himandrine

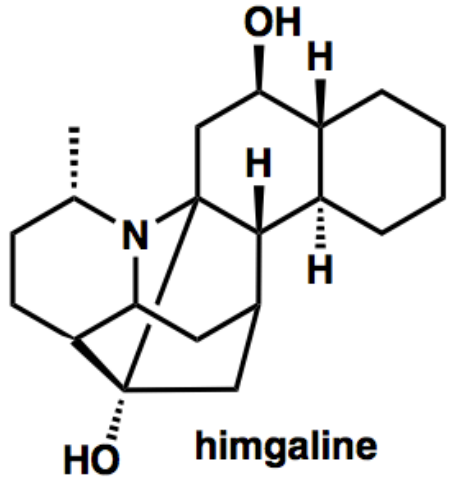


Class II Scaffold

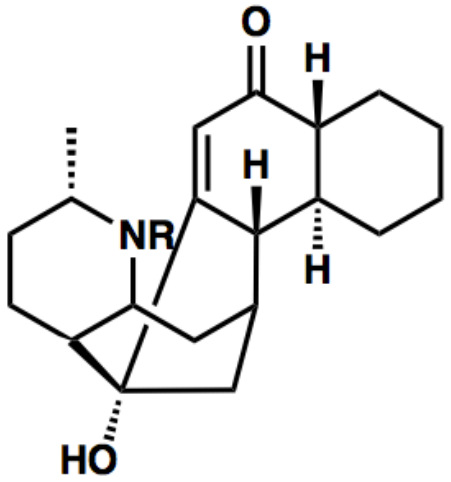
Alkaloid	R^1	R^2	R^3	R^4
7 himbosine	OAc	OCOPh	OAc	OAc
8 himandridine	OCOPh	OMe	OH	OH
9 G.B. 1	OAc	OCOPh	OAc	OH
10 G.B. 2	OAc	OAc	OAc	OAc
11 G.B. 3	OH	OH	OAc	OAc
12 G.B. 4	OH	OH	OCOPh	OAc
13 G.B. 5	OH	OH	OH	OAc
14 G.B. 6	OCOPh	OMe	OAc	OH
15 G.B. 7	OCOPh	OMe	OH	OAc
16 G.B. 8	OH	OMe	H	OH
17 G.B. 9	OAc	OMe	H	OH
18 G.B. 10	OAc	OMe	H	OAc
19 G.B. 11	OH	OH	H	OAc
20 G.B. 12	OAc	OAc	H	OAc

U. Rinner et al. *Synthesis* 2010, No. 22, pp 3763–3784

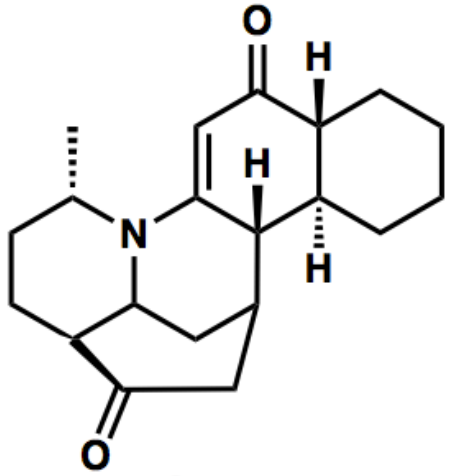
The Galbulimima alkaloids – Class III



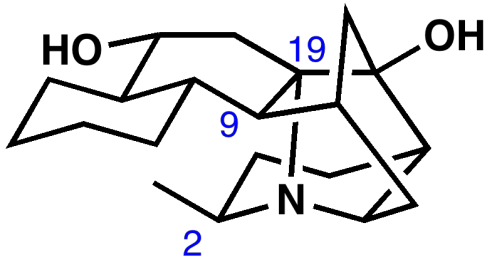
himgaline



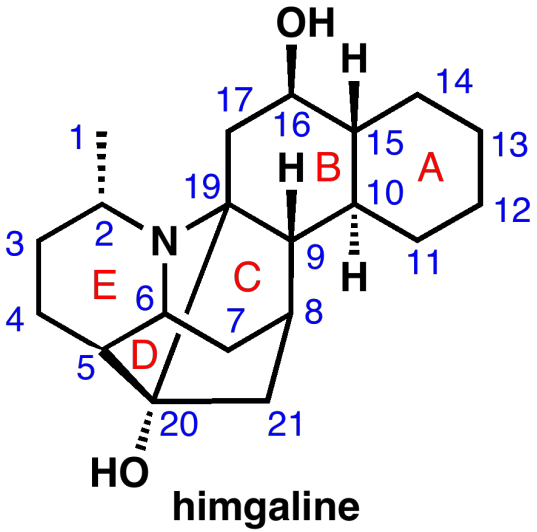
G.B. 13, R = H
himbadine, R = Me



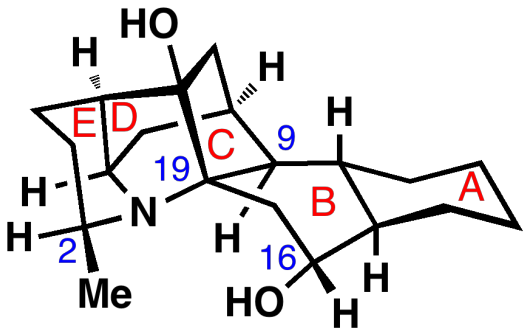
G.B. 16



himgaline



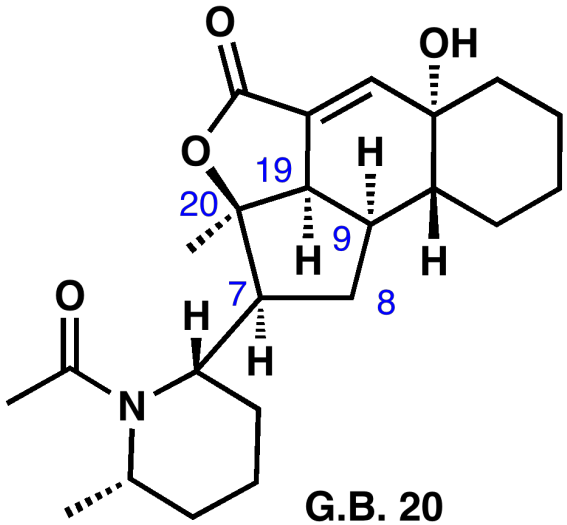
himgaline



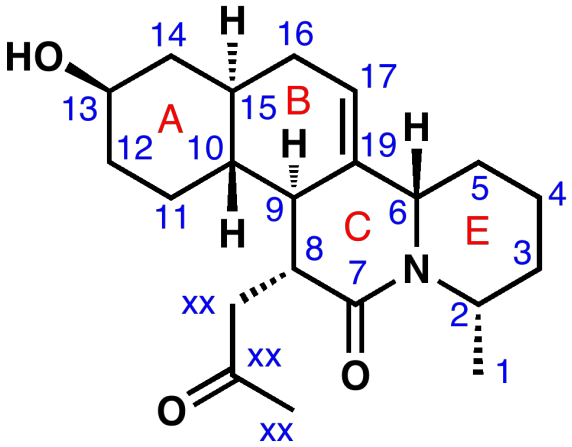
himgaline

U. Rinner et al. *Synthesis* 2010, No. 22, pp 3763–3784

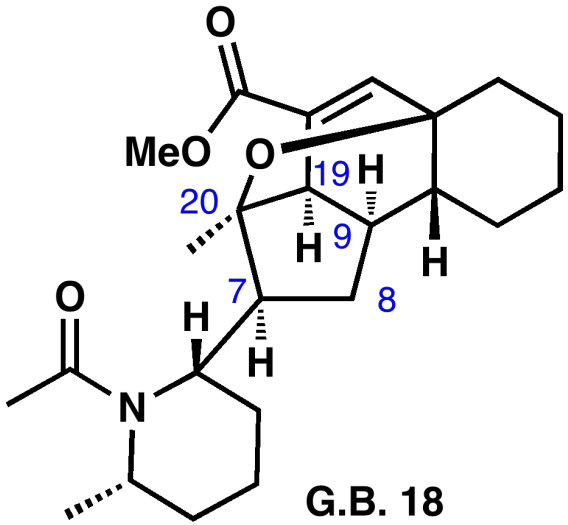
The Galbulimima alkaloids – Class IV



G.B. 20

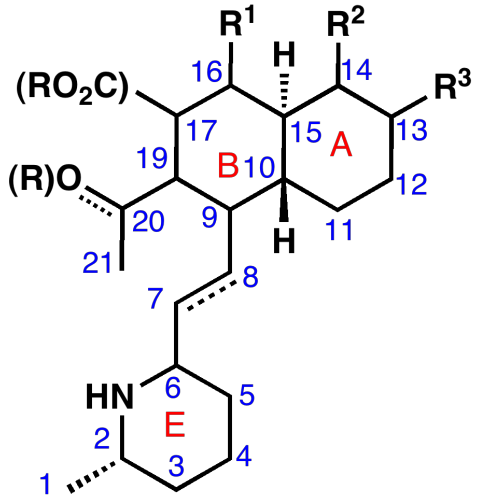


G.B. 17

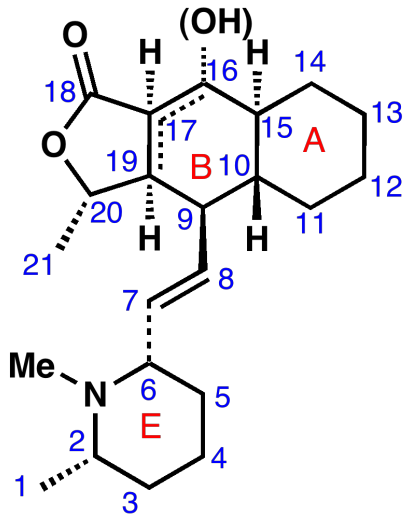


G.B. 18

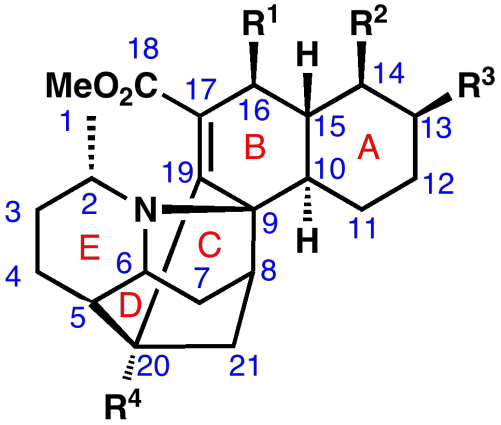
The Galbulimima alkaloids – summary



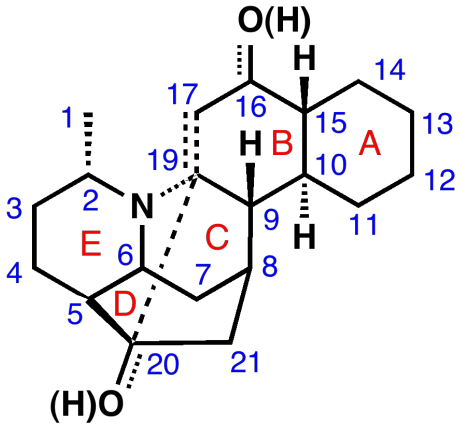
Galbulimima general scaffold



Class I Scaffold



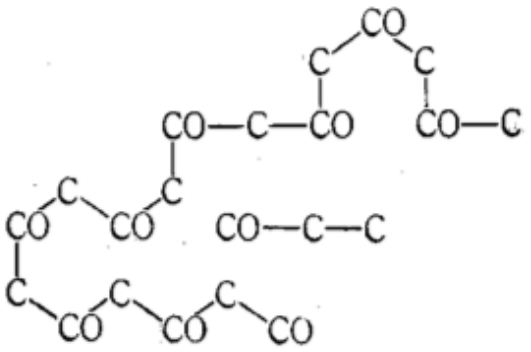
Class II Scaffold



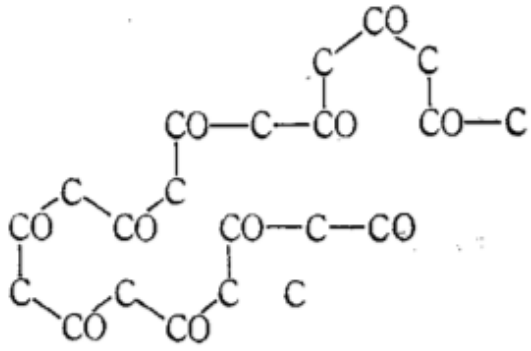
Class III scaffold

Early biosynthetic proposals

Taylor and Ritchie

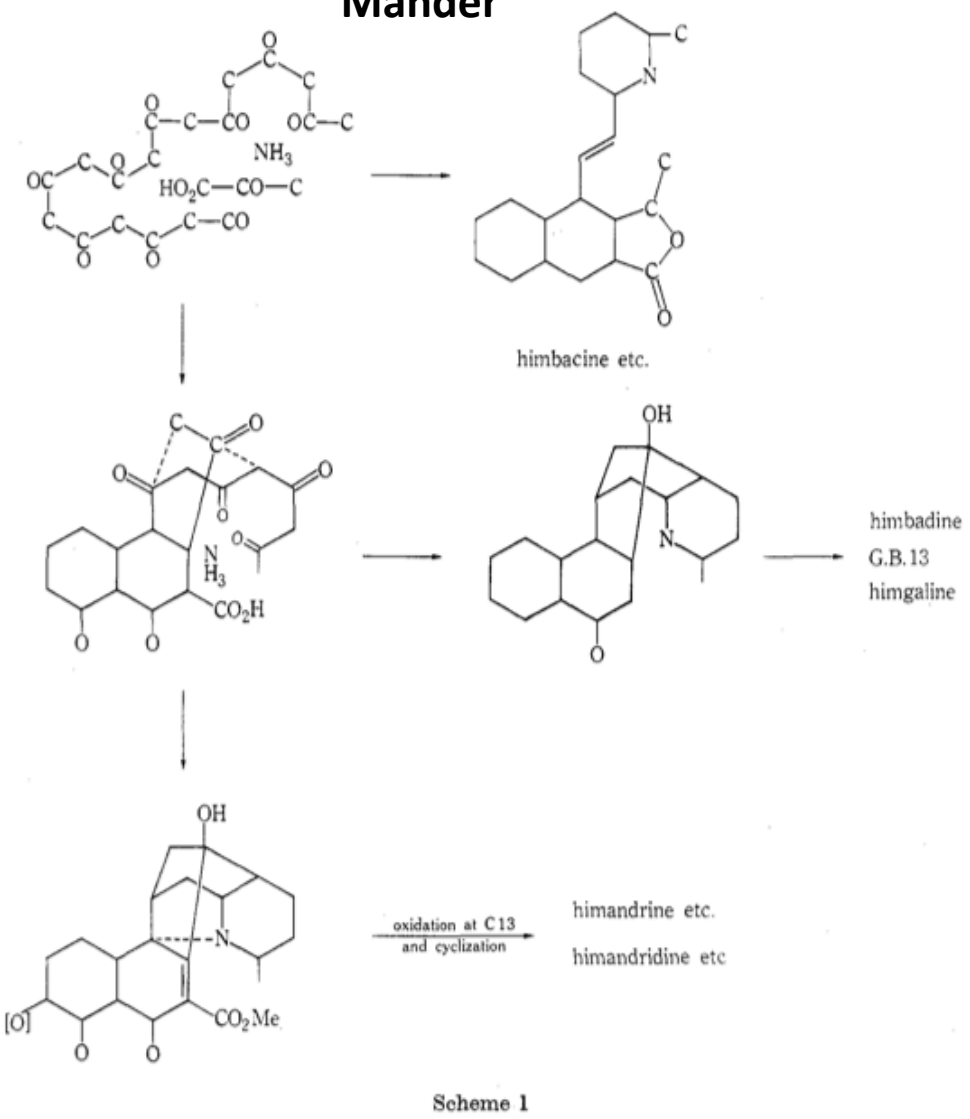


(XXVI)



(XXVII)

Mander

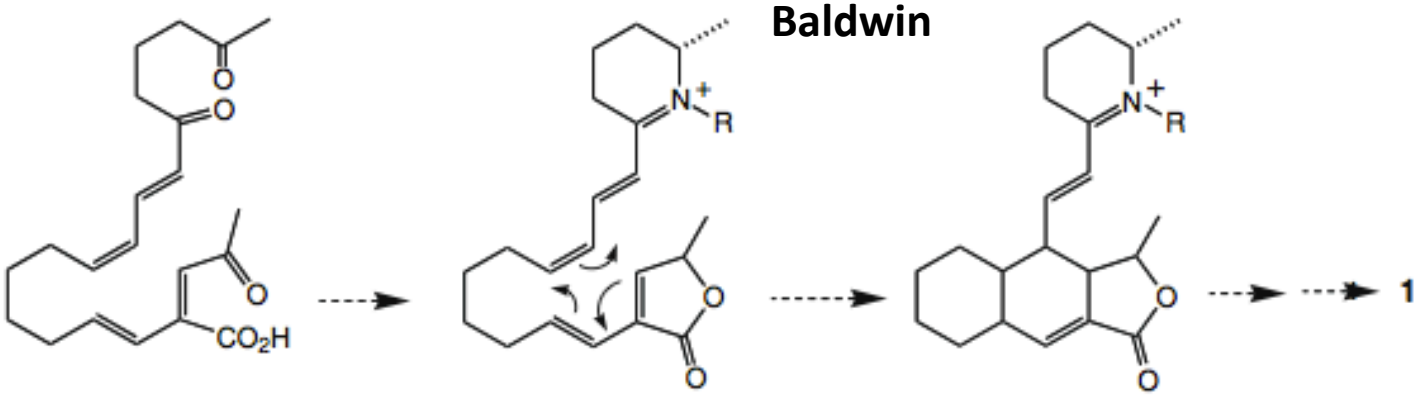


Scheme 1

Modern biosynthetic proposals

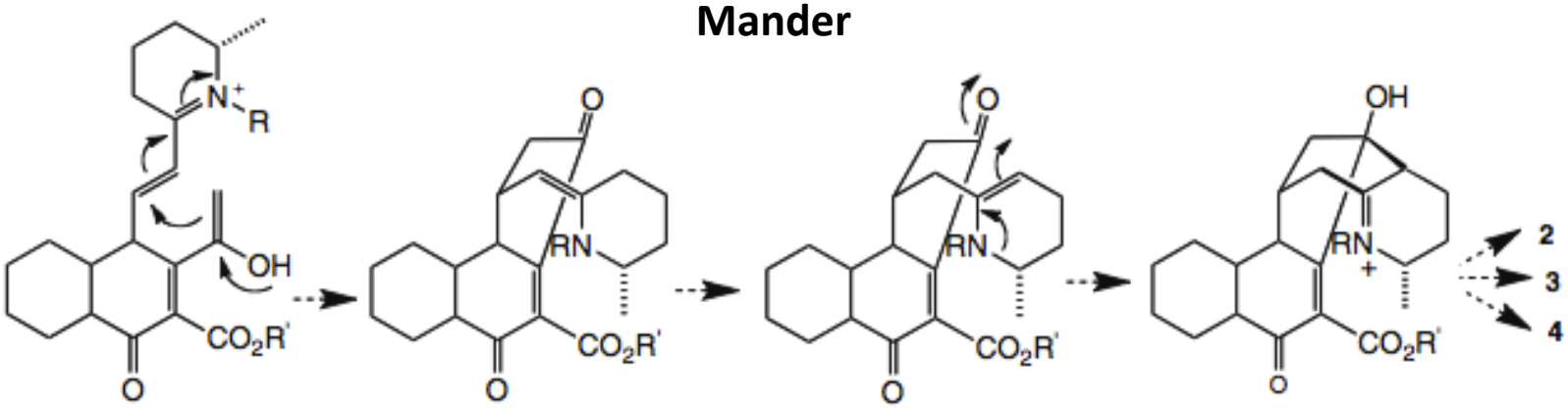
L. N. Mander et al./Tetrahedron Letters 50 (2009) 7089–7092

Baldwin



Scheme 1. Baldwin's hypothesis for the biosynthesis of Class 1 alkaloids.

Mander

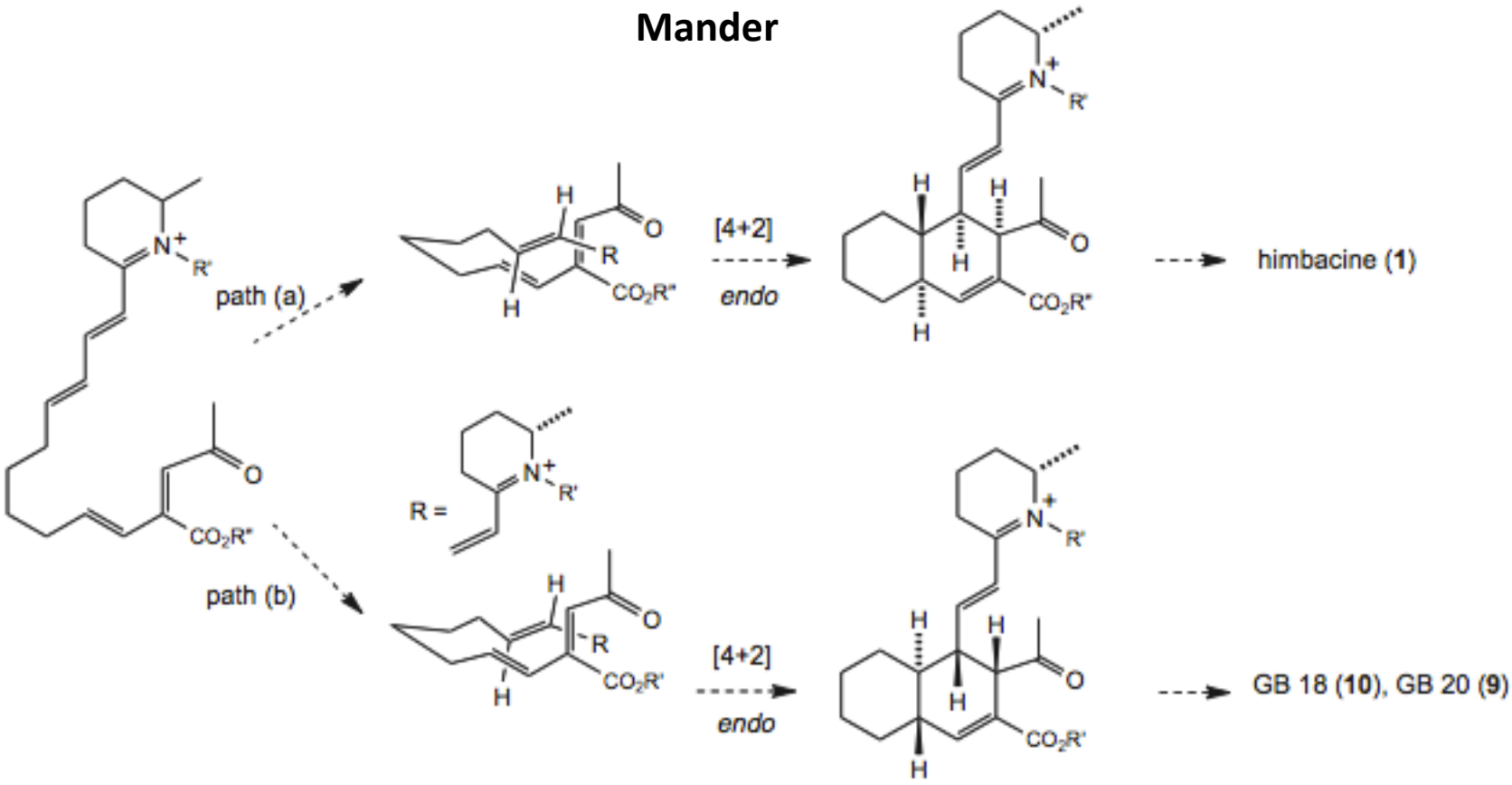


Scheme 2. Hypothesis for the biosynthesis of Class II and III alkaloids.

Modern biosynthetic proposals (cont.)

T. A. Bradford et al./Tetrahedron Letters 52 (2011) 188–191

Mander

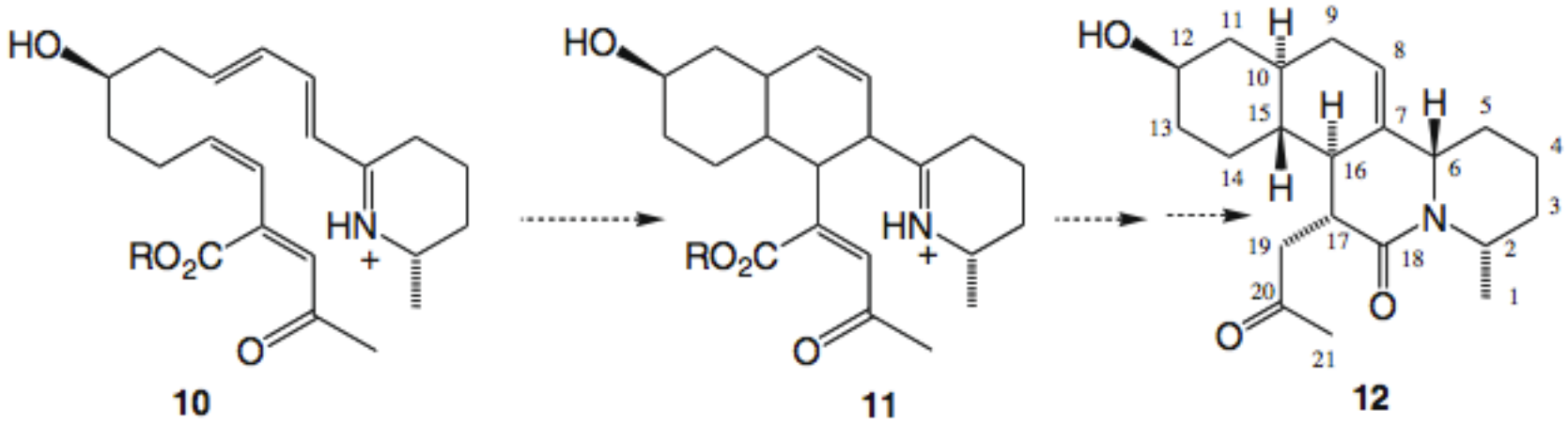


Scheme 1. Biosynthetic speculations.

Modern biosynthetic proposals (cont.)

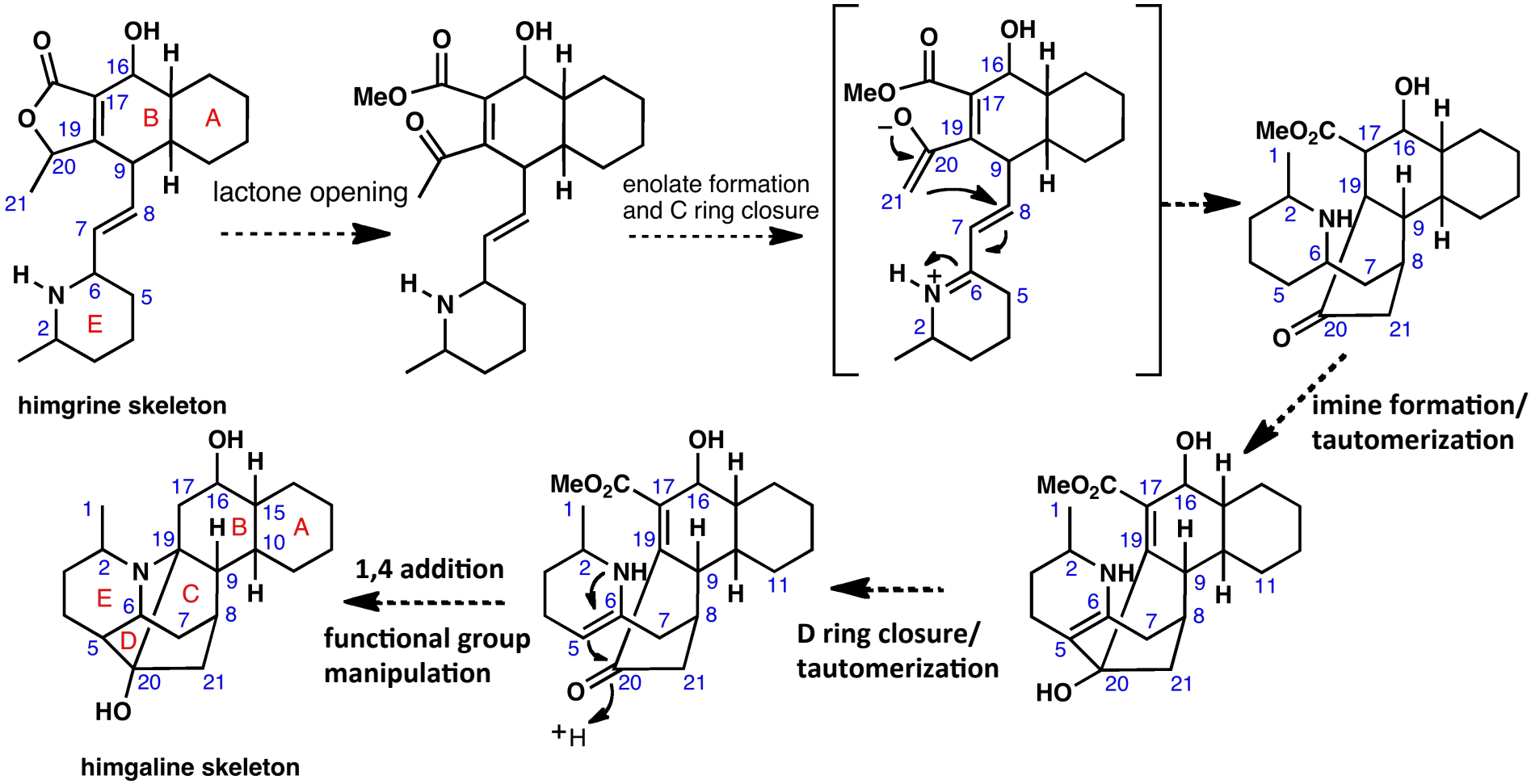
Mander

L. N. Mander et al. / Tetrahedron Letters 50 (2009) 7089–7092



Scheme 4. Structure of GB17 (**12**) and its speculative biosynthesis from **10**.

Biosynthesis – can the different classes of Galbulimima alkaloids be derived from each other?

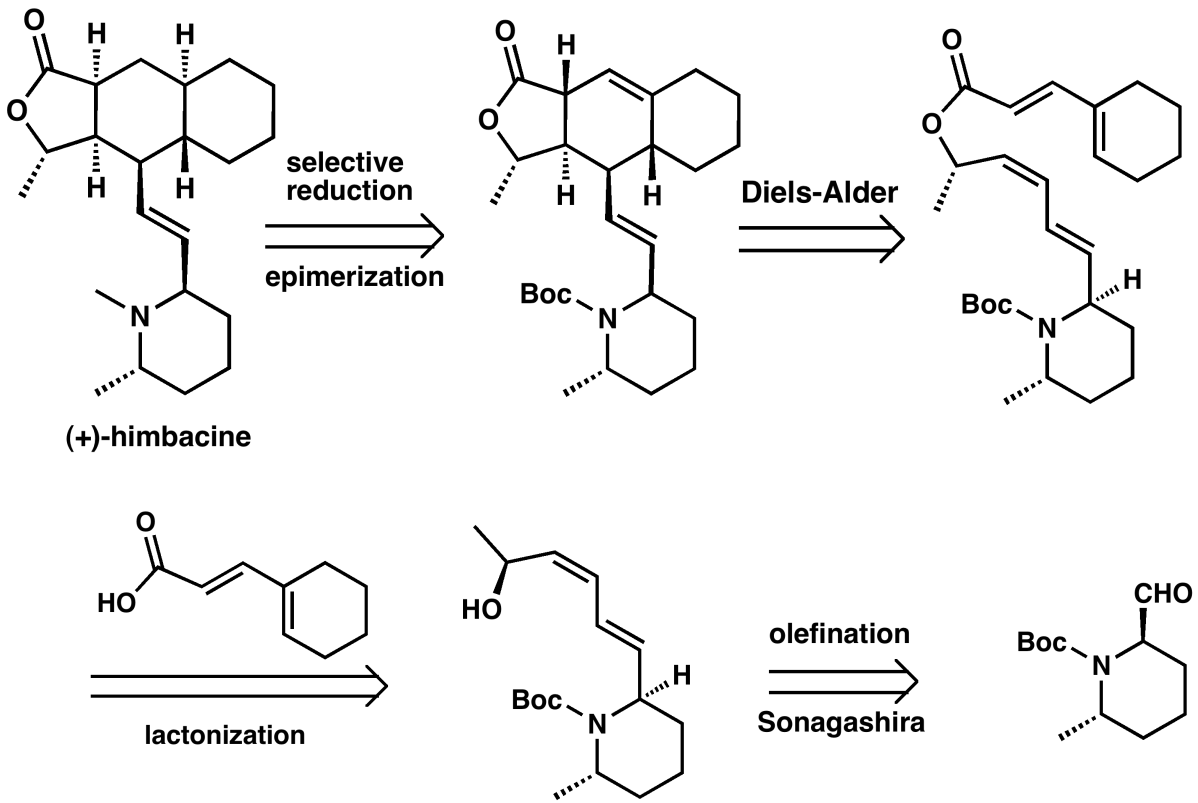


Total Synthesis of Galbulimima alkaloids

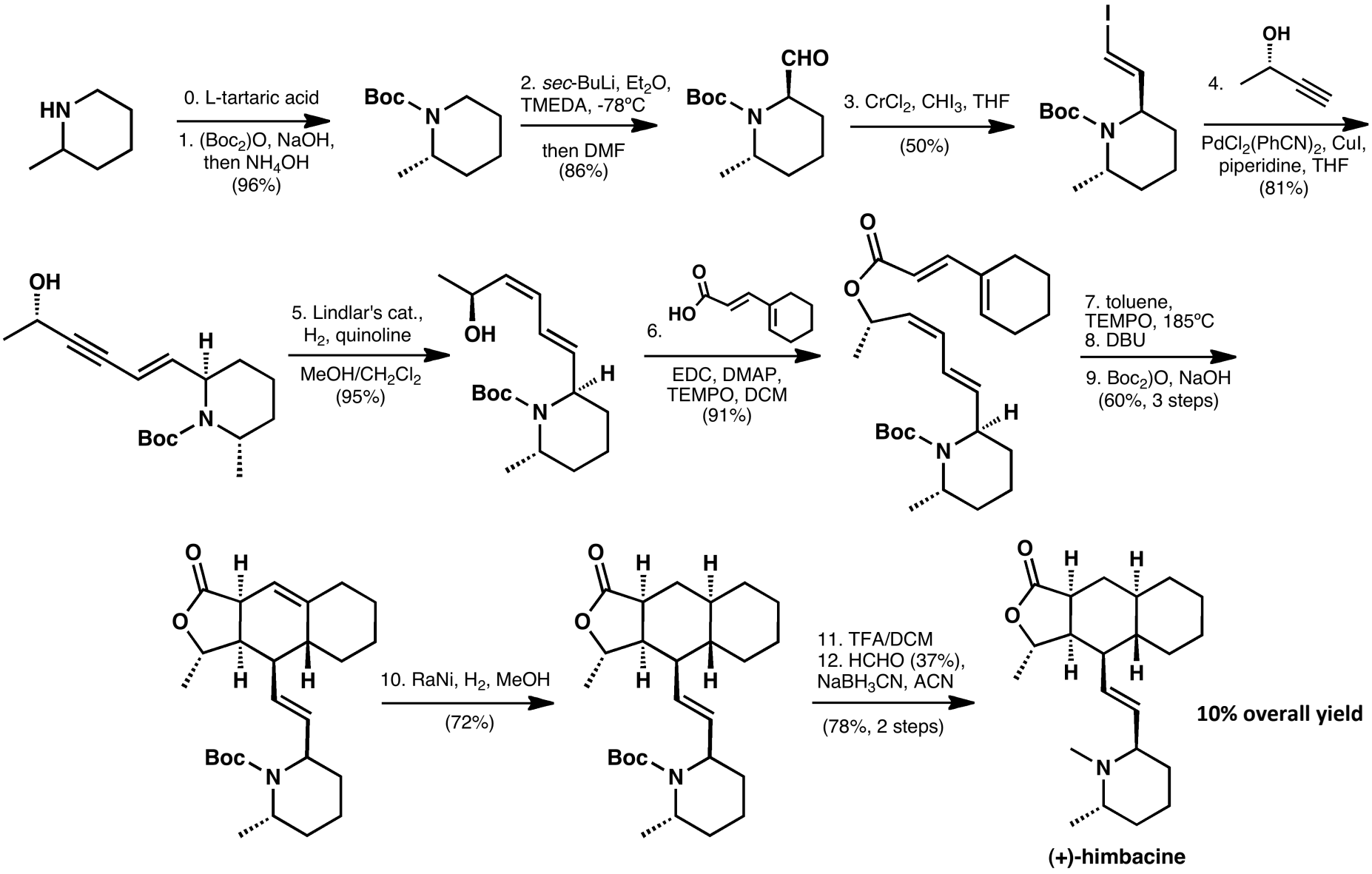
Table 1 Syntheses of Galbulimima Alkaloids

Alkaloid class	Compound	Author	Publication year	Number of steps	Overall yield
class I	himbacine/himbeline	Hart, Kozikowski[31]	1995	19 (himbeline) 20 (himbacine)	5.4% (himbeline) 3.8% (himbacine)
class I	himbacine/himbeline	Chackalamannil[32]	1996	11 (himbeline) 12 (himbacine)	12.4% (himbeline) 9.7% (himbacine)
class I	himbacine (formal synthesis)	Terashima[33]	1999	18	12.6%
class I	himandravine	Chackalamannil[34]	2001	12	17.0%
class I	himbacine (formal synthesis)	De Clercq[35]	2002	13	6.6%
class I	himbacine (formal synthesis)	Sherburn[36]	2003	26	2.4%
class I	himbacine/himbeline	Baldwin[37]	2005	12 (himbeline) 13 (himbacine)	3.1% (himbeline) 2.3% (himbacine)
class II	himandrine	Movassaghi[29]	2009	28	0.7%
class III	(±)-G.B. 13	Mander[38]	2003	30	0.2%
class III	G.B. 13/himgaline	Chackalamannil[39]	2006	31 (G.B. 13) 33 (himgaline)	0.5% 0.3%
class III	G.B. 13	Movassaghi[27]	2006	19	1.7%
class III	*ent*-G.B. 13/*ent*-himgaline	Evans[40]	2007	31 (*ent*-G.B. 13) 32 (*ent*-himgaline)	1.0% (*ent*-G.B. 13) 0.9% (*ent*-himgaline)
class III	(±)-G.B. 13	Sarpong[41]	2009	18	1.2%
class III	(–)G.B. 13/(+)-G.B. 16	Ma	2010	19/17	6.1%

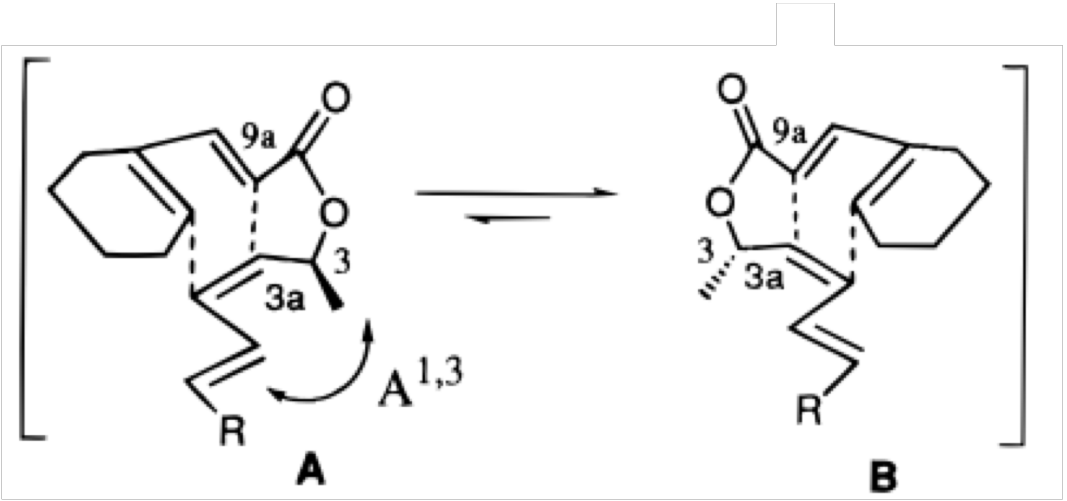
Retrosynthetic analysis – Himbacine - Chackalamannil



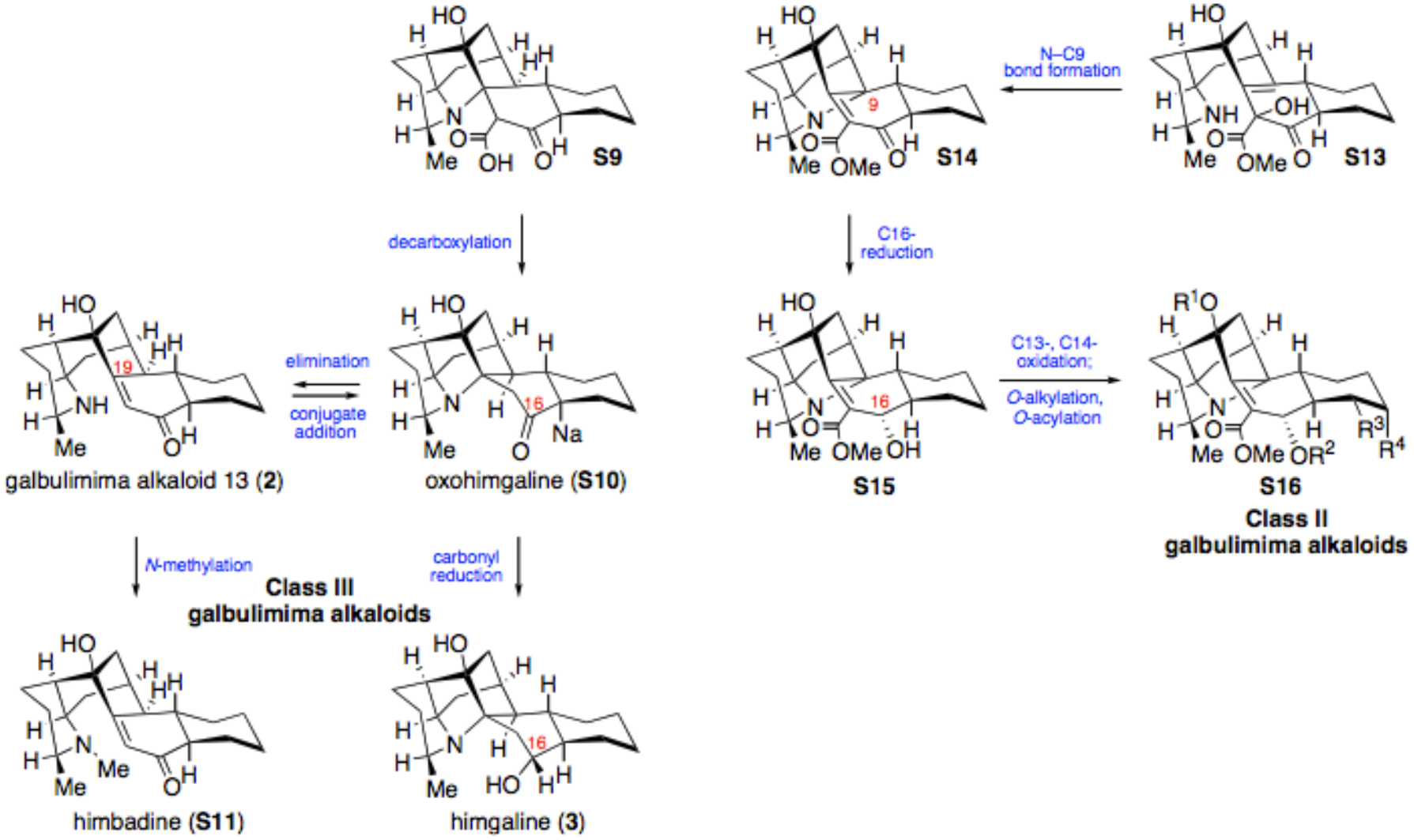
Total synthesis - Himbacine



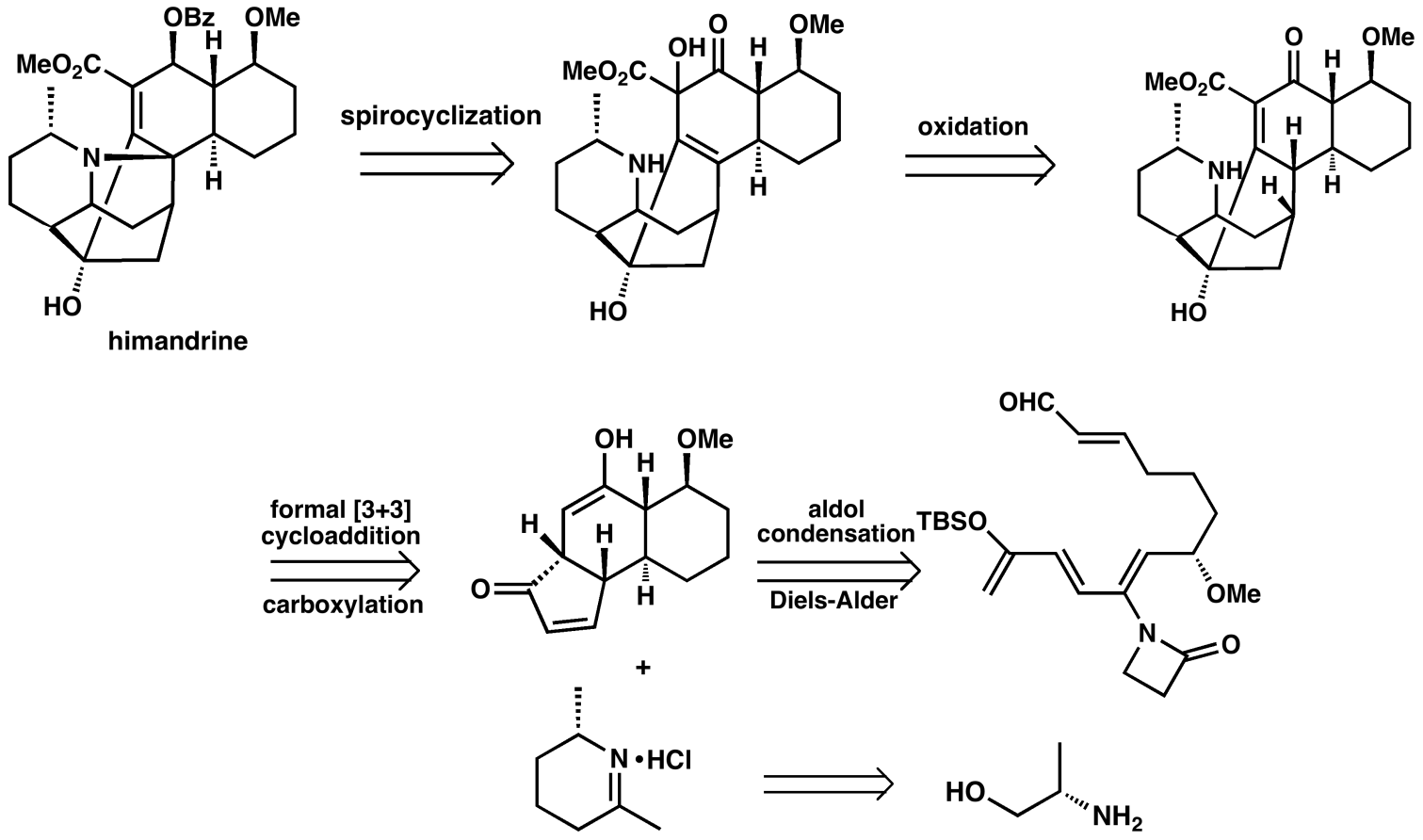
Total synthesis - Himbacine



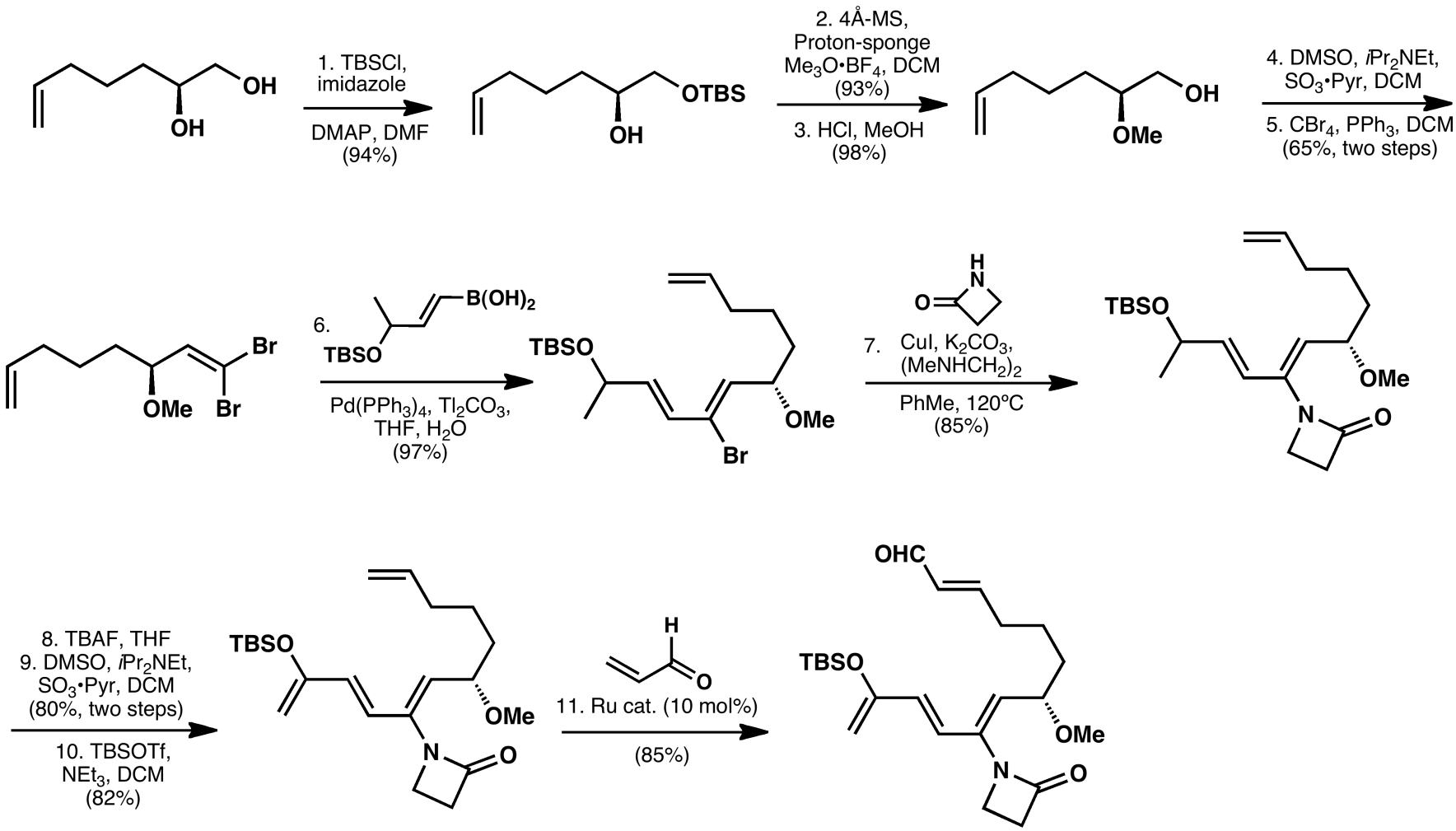
Biosynthesis – Movassaghi's proposal



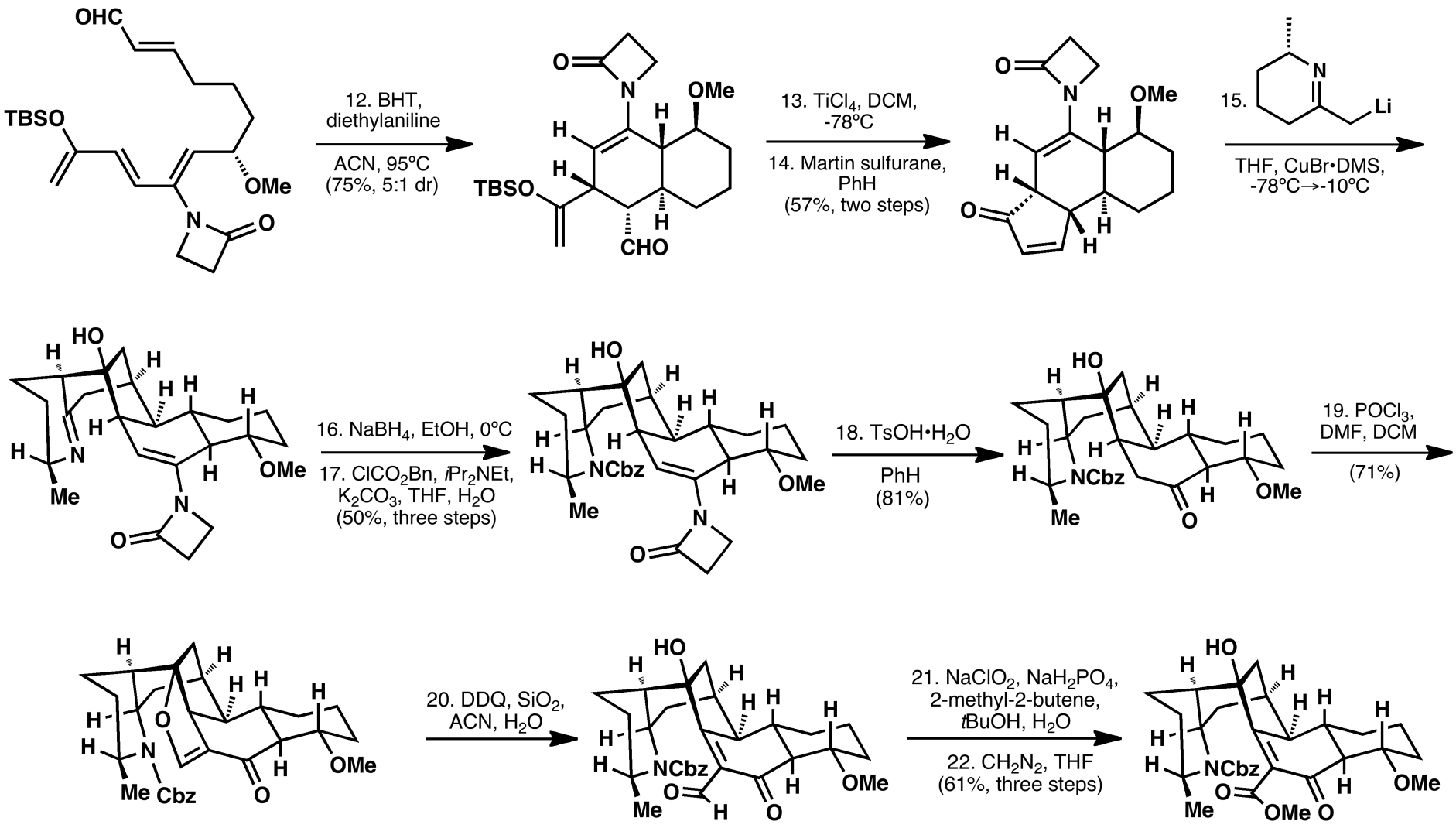
Retrosynthetic analysis – Himandrine - Movassaghi



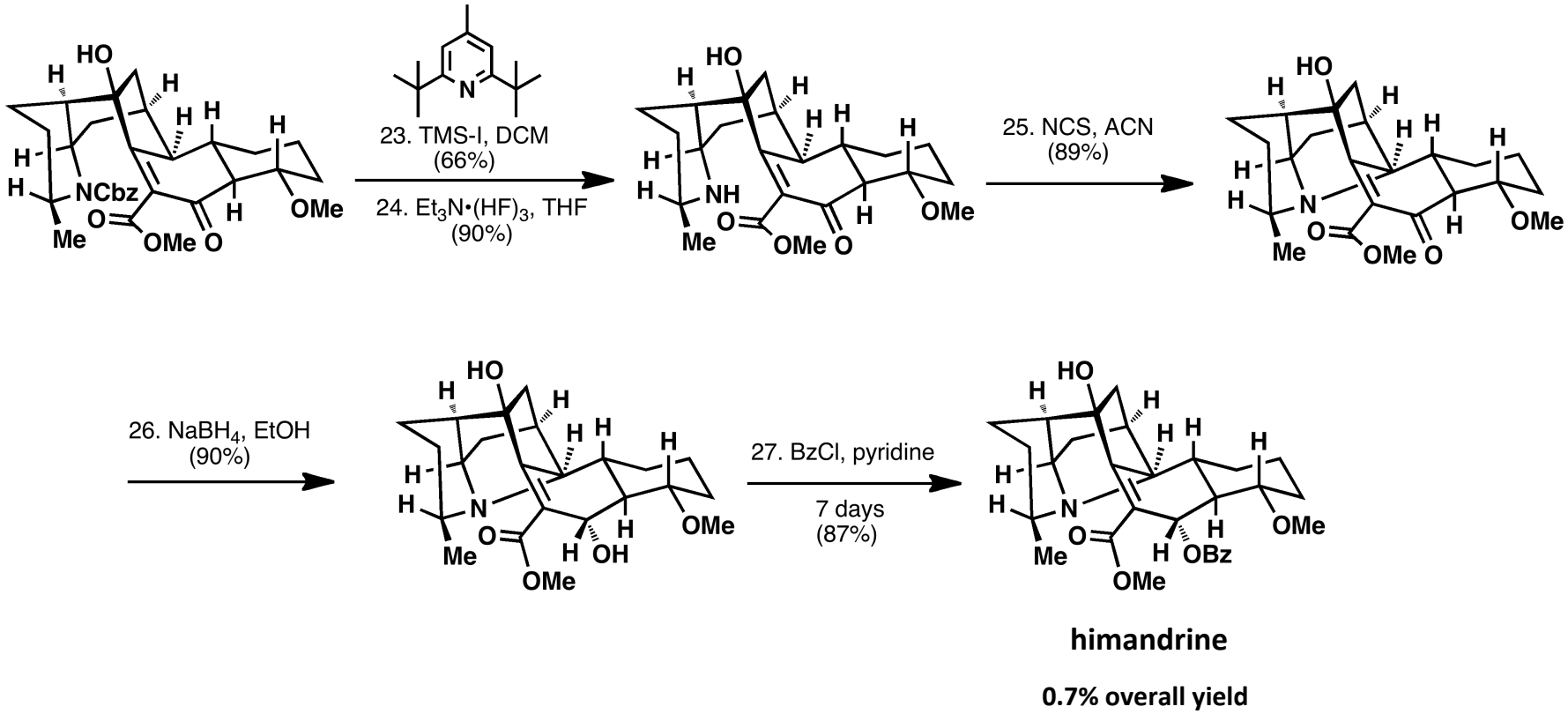
Total synthesis - Himandrine



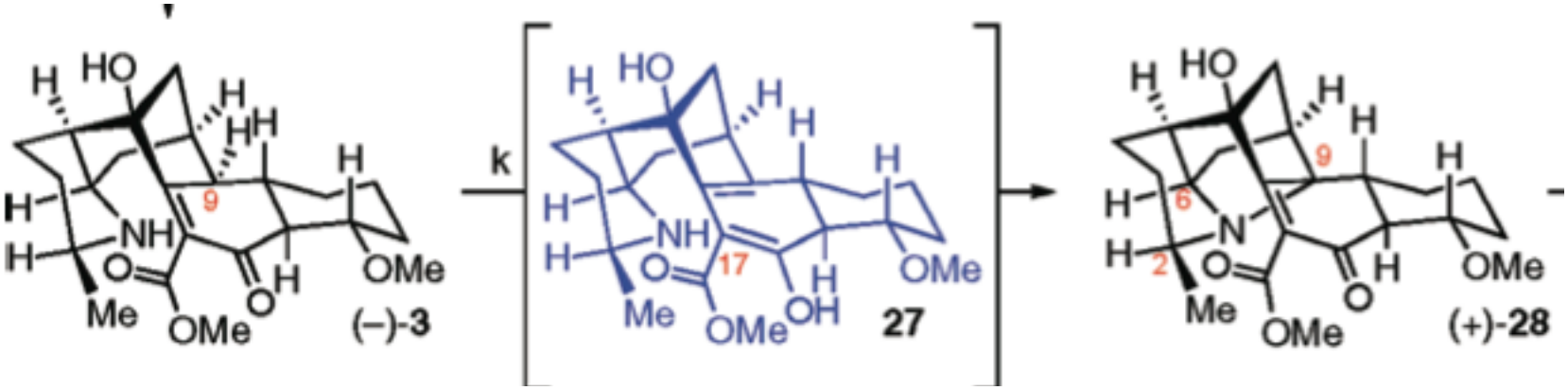
Total synthesis - Himandrine



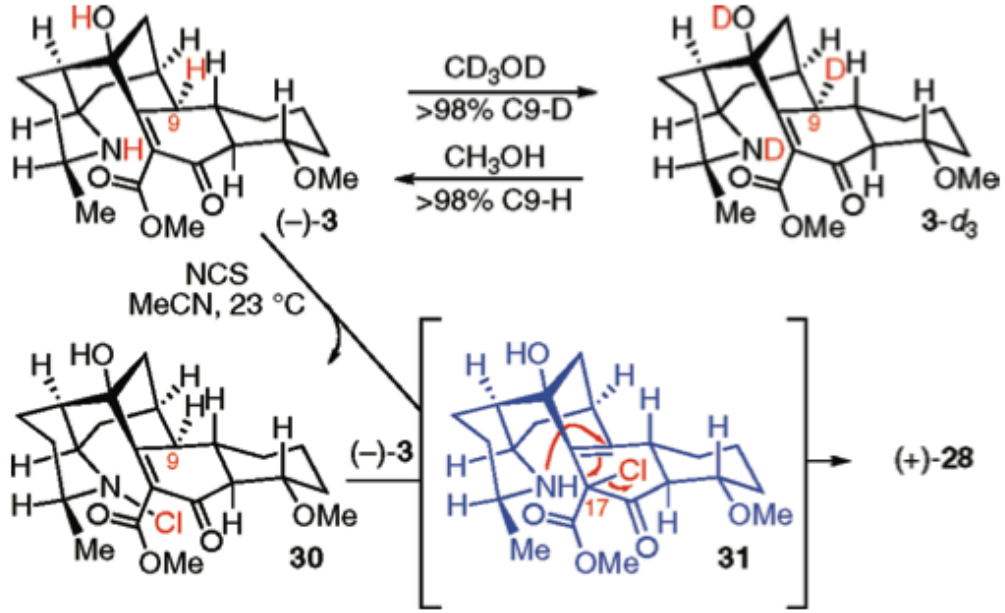
Total synthesis - Himandrine



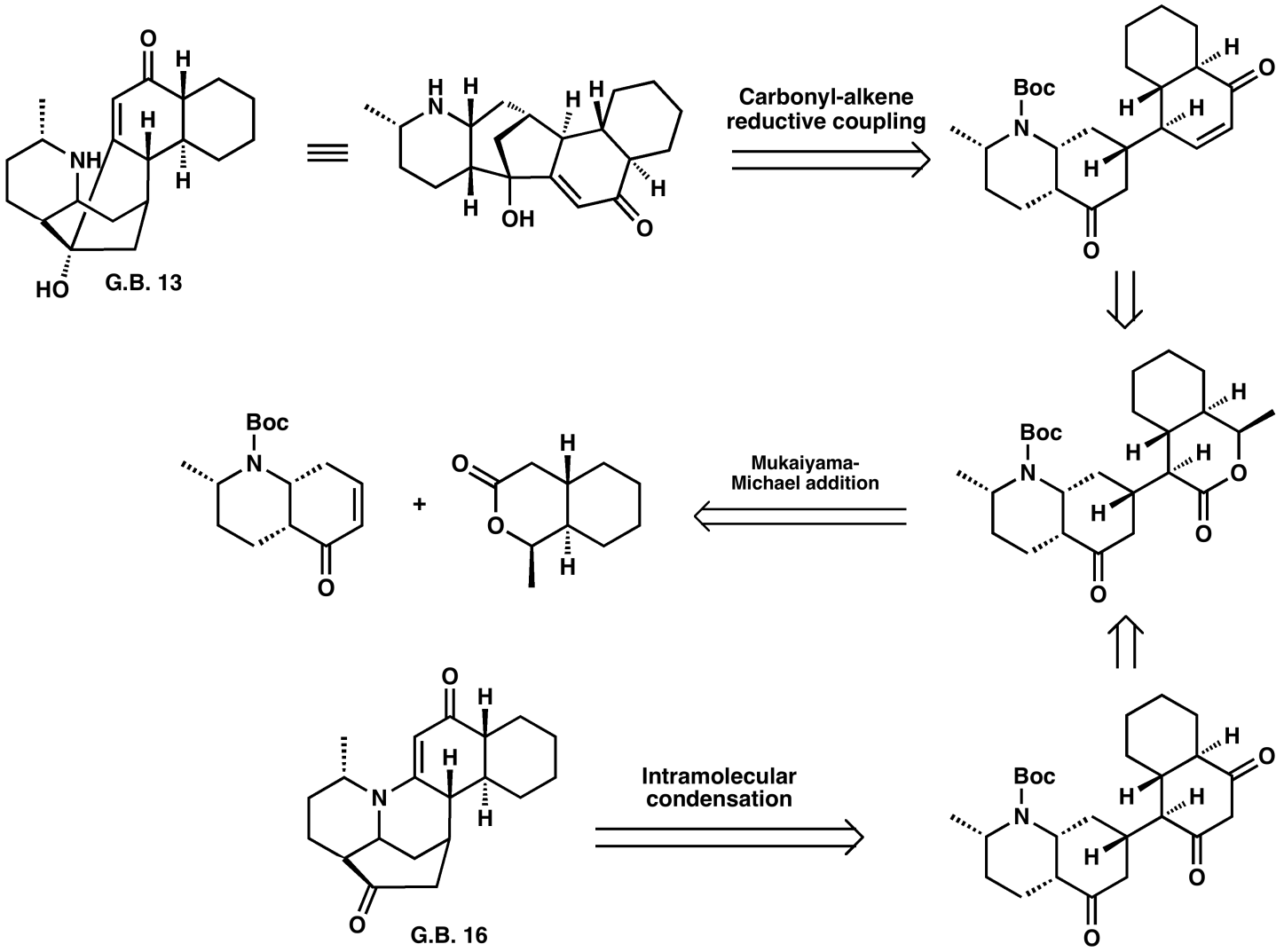
Spirocyclization



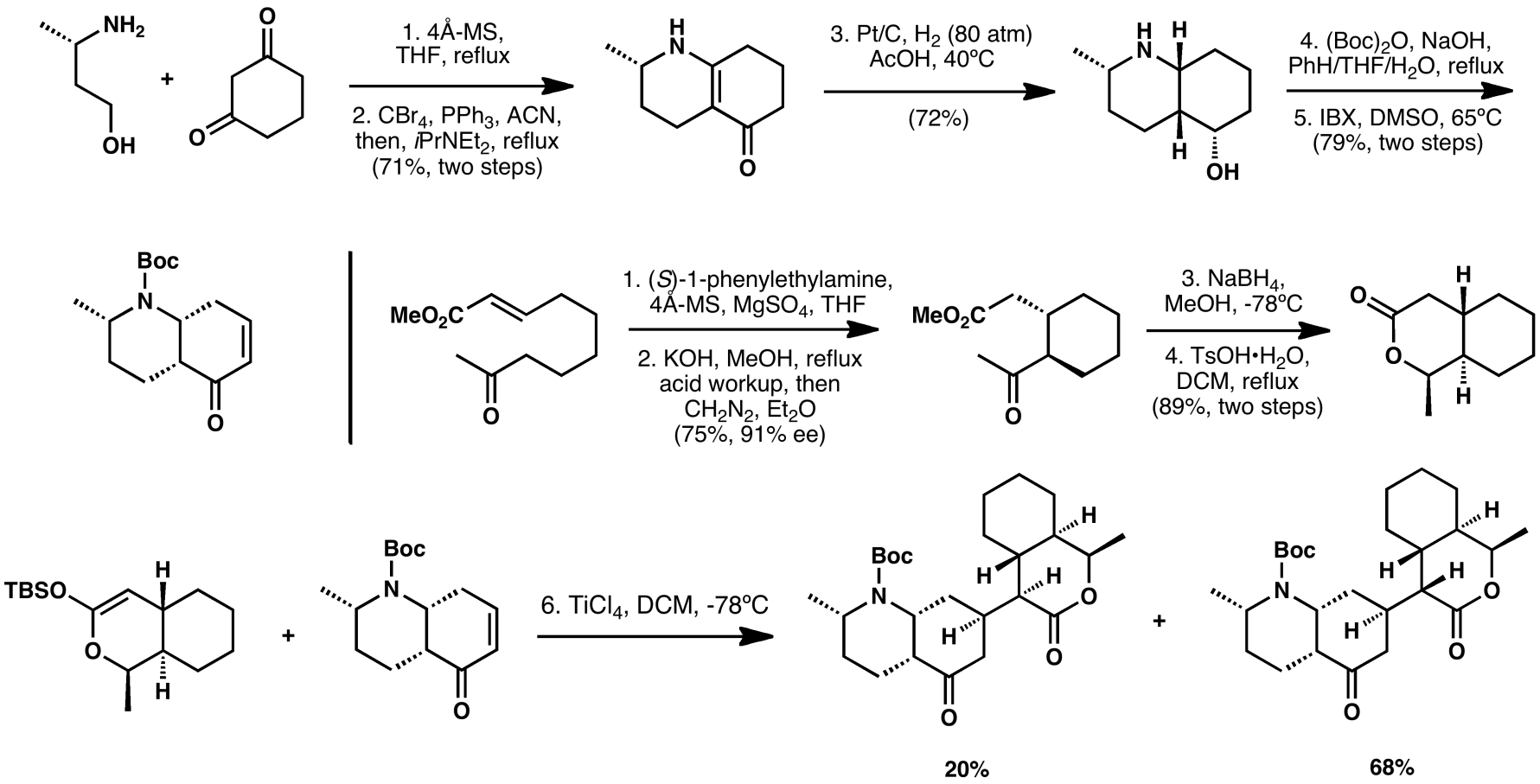
Scheme 4. Key Observations Relevant to N–C9 Bond Formation



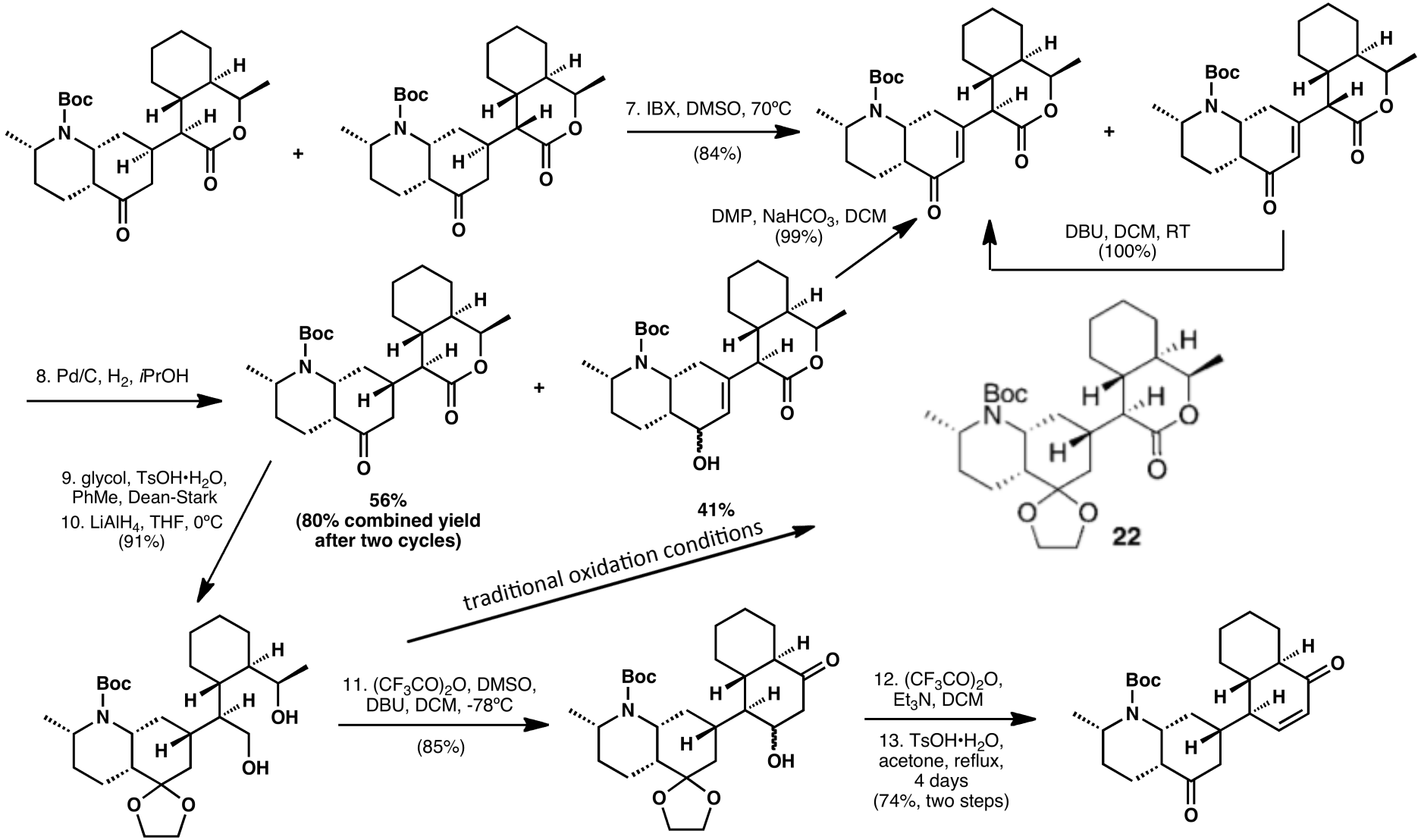
Retrosynthetic analysis – G.B. 13 and G.B. 16 - Ma



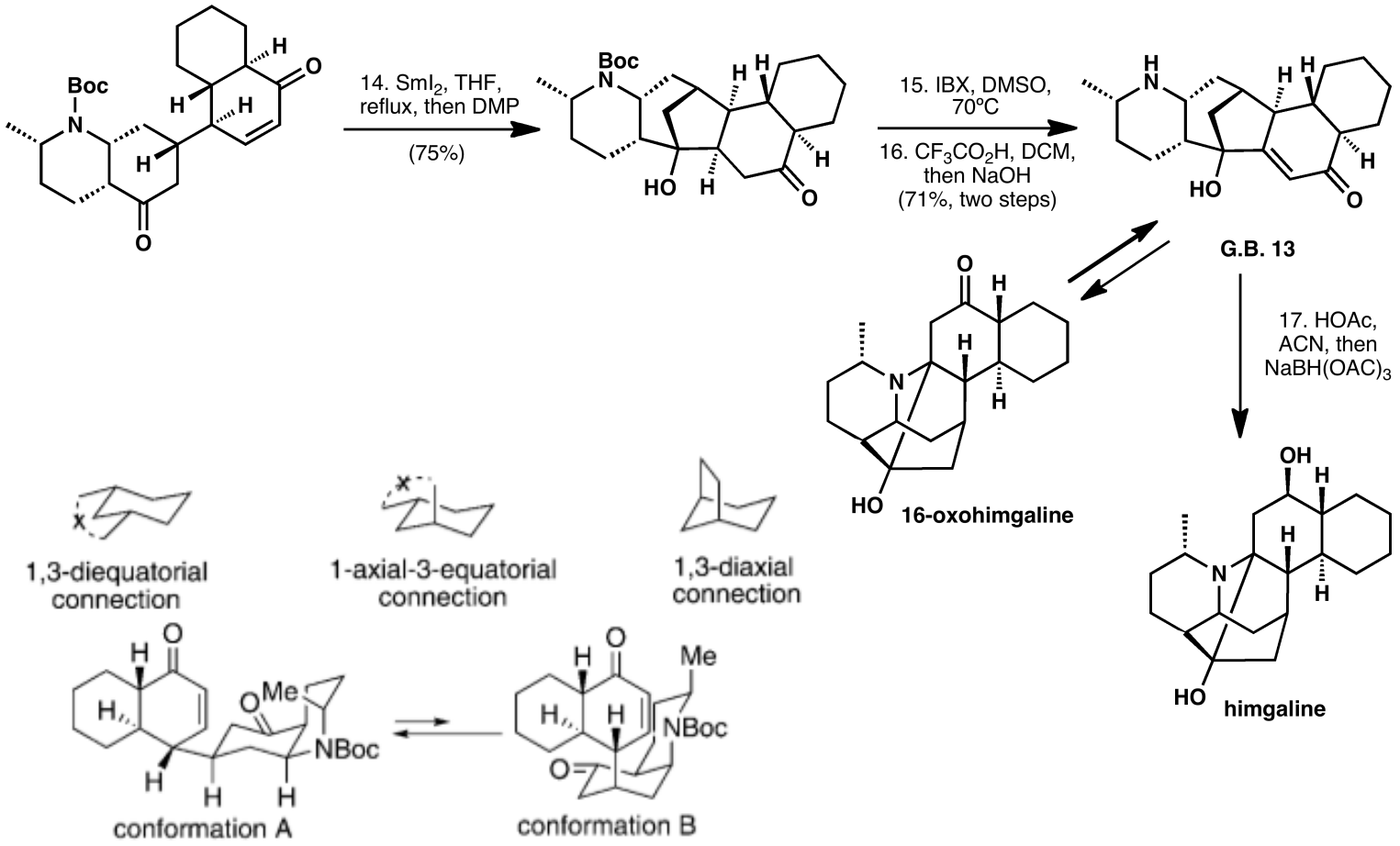
Total synthesis – G.B. 13



Total synthesis – G.B. 13

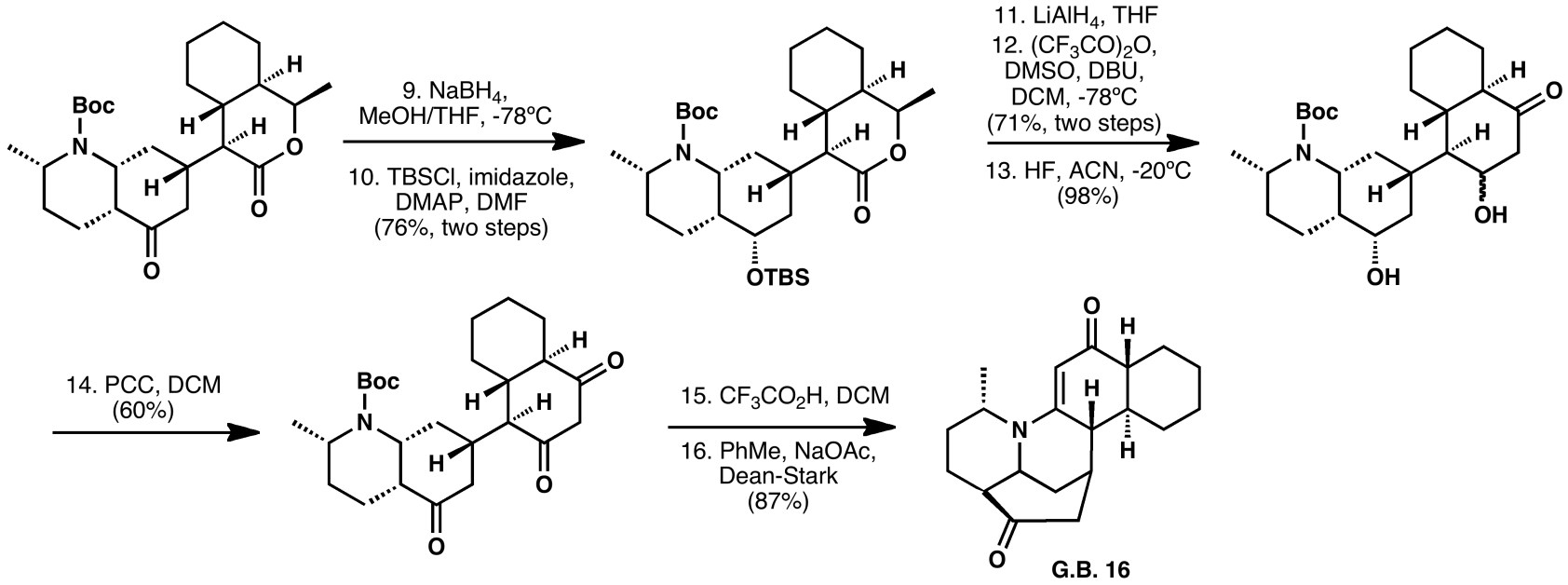


Total synthesis – G.B. 13

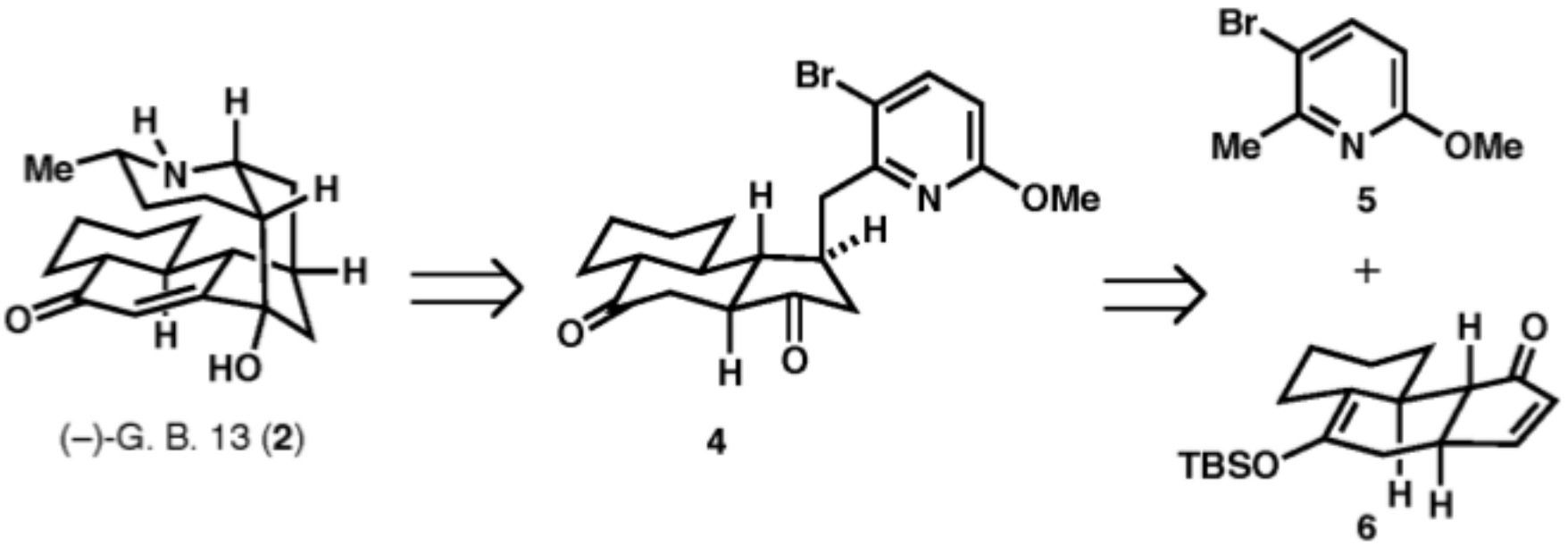


Scheme 6. The favored conformation for carbonyl–alkene reductive coupling of the enone **7**.

Total synthesis – G.B. 16



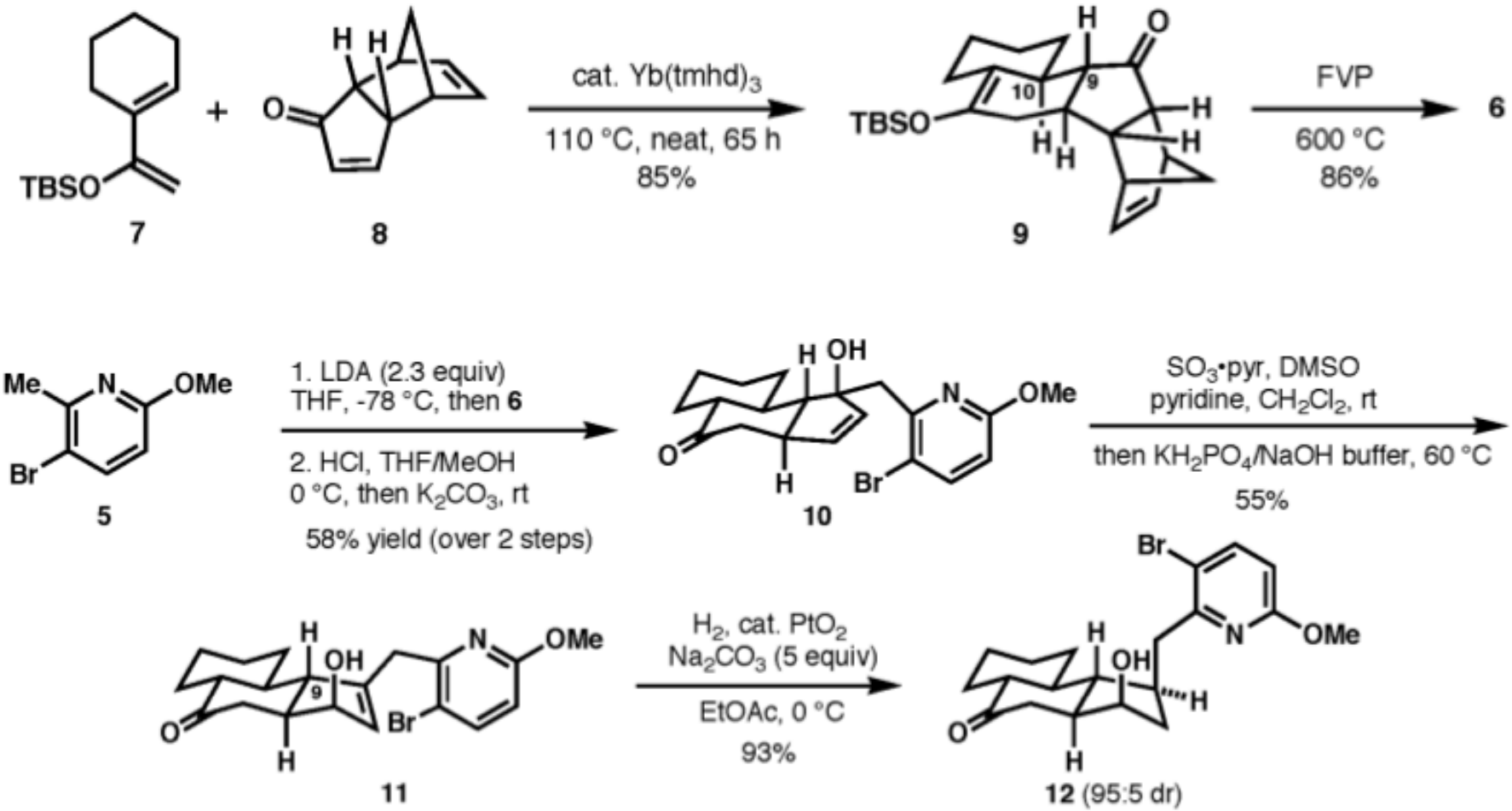
Sarpong's Retrosynthesis – G.B. 13



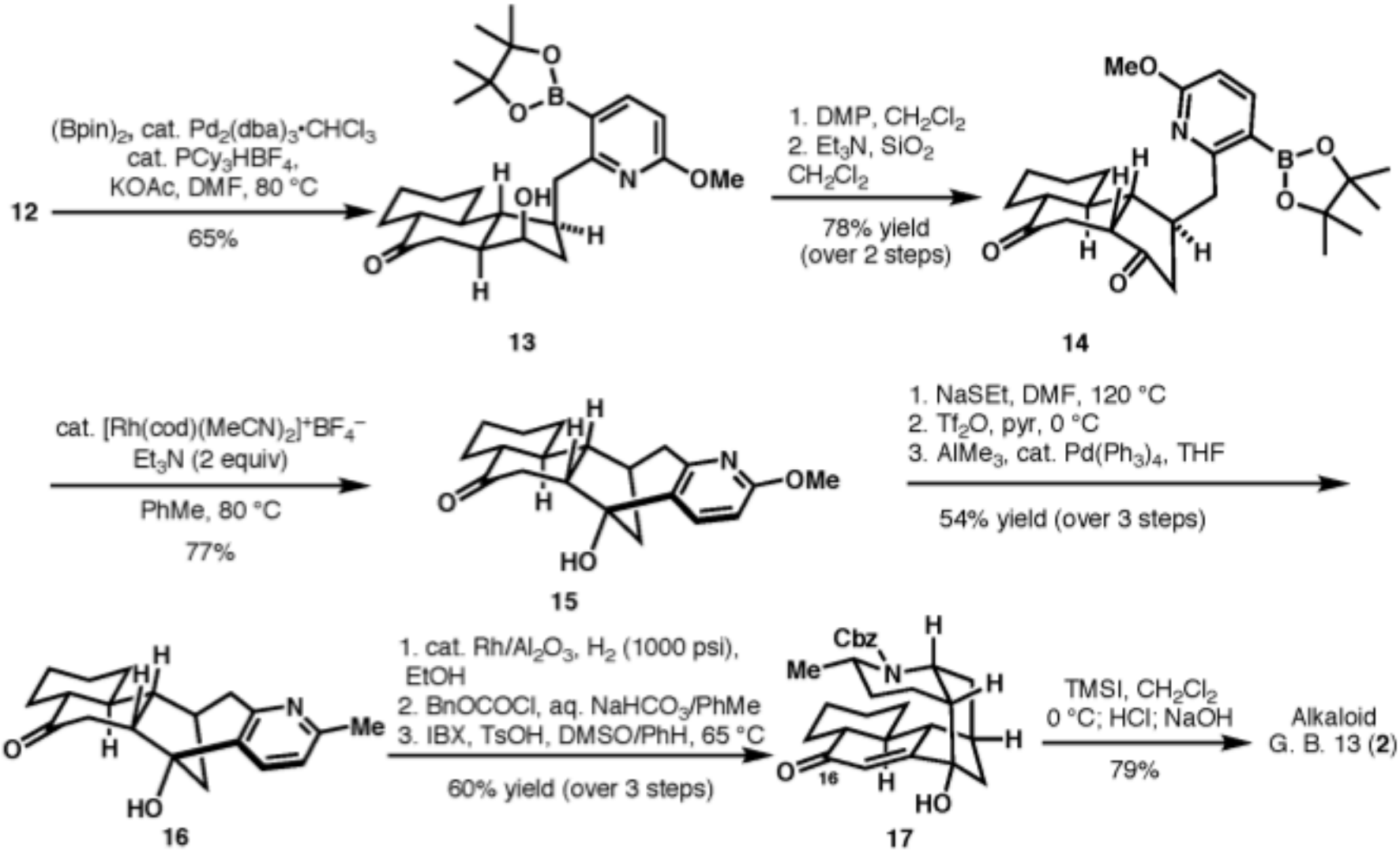
(–)-G. B. 13 (**2**)

4

Total Synthesis – G.B. 13 - Sarpong



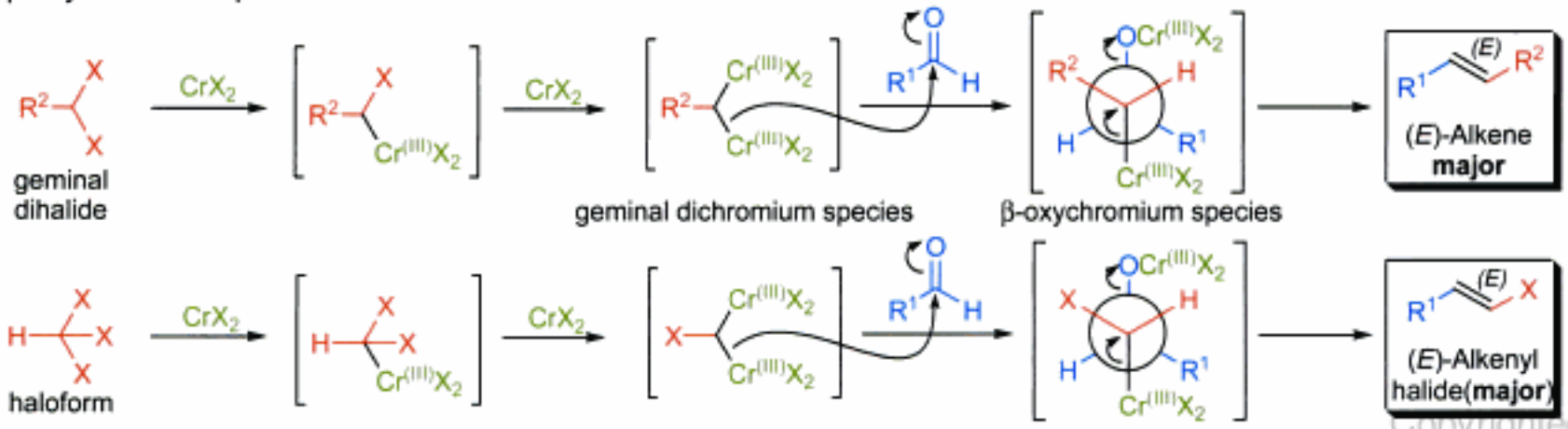
Total Synthesis – G.B. 13 - Sarpong



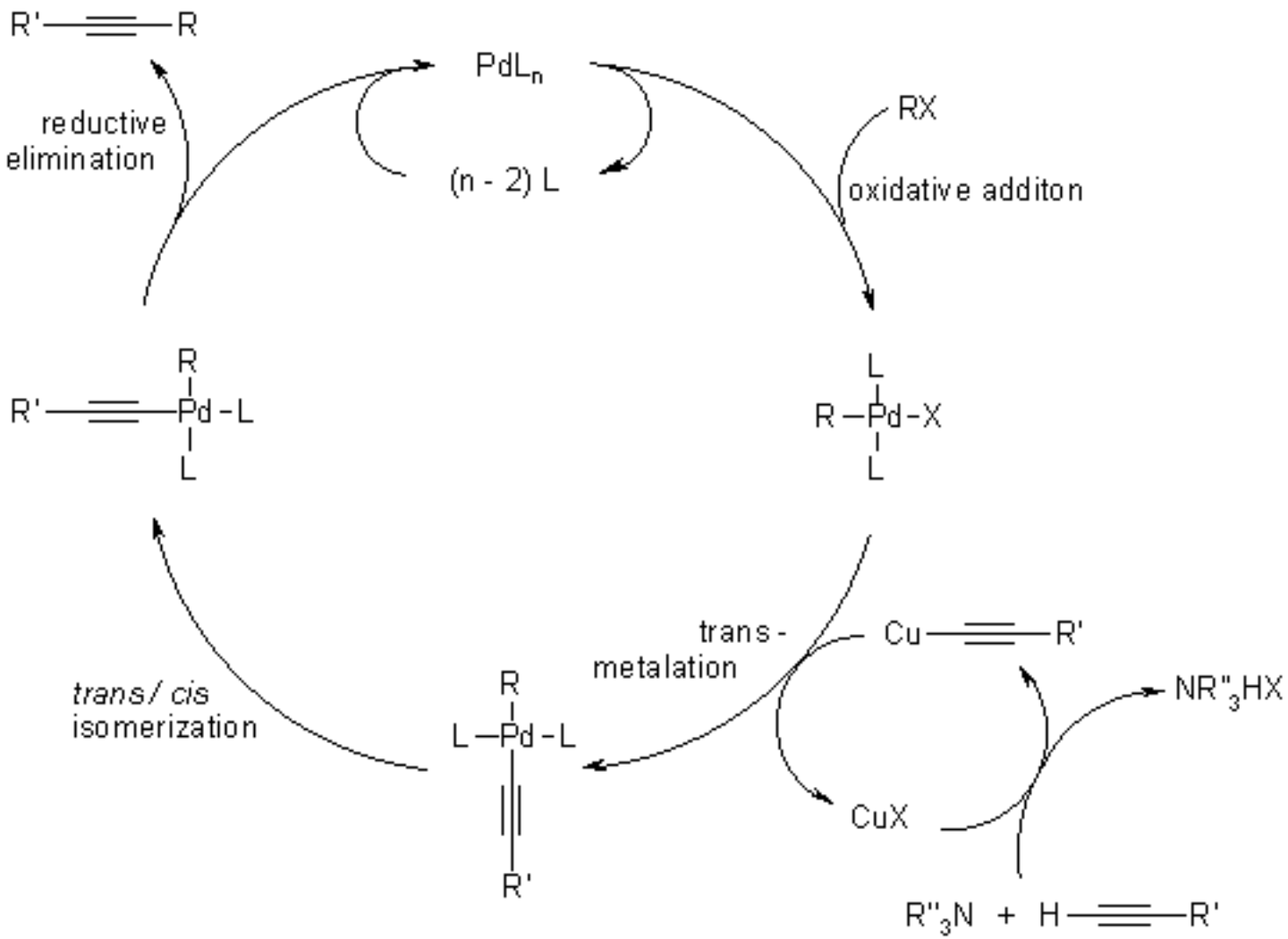
Takai olefination mechanism

Mechanism: [20,21,2,3,15,7]

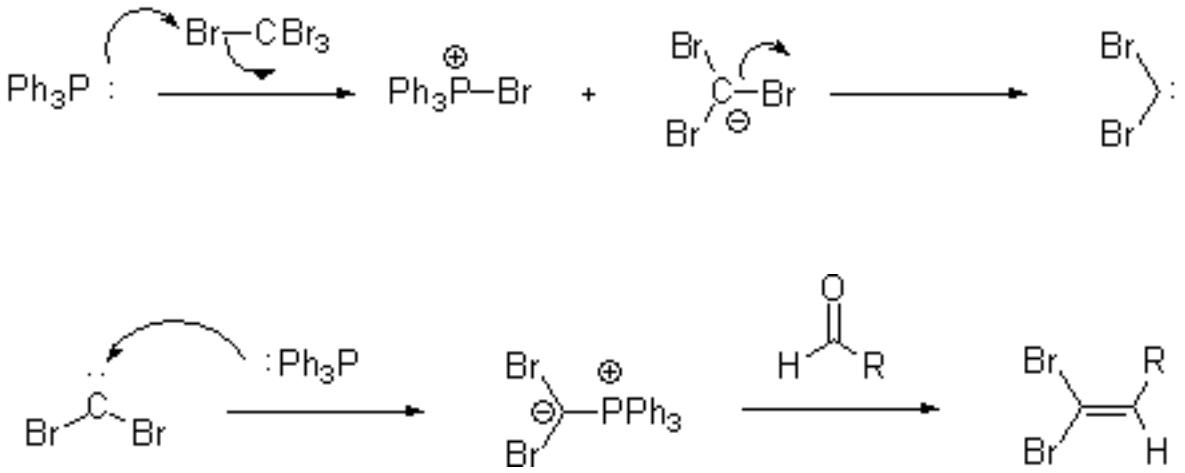
The exact mechanistic pathway is not known. However, it is believed that the *T-U olefination* proceeds *via* geminal-dichromium intermediates that are nucleophilic and attack the carbonyl compound. The (*E*)-alkene is formed from the β-oxychromium species.



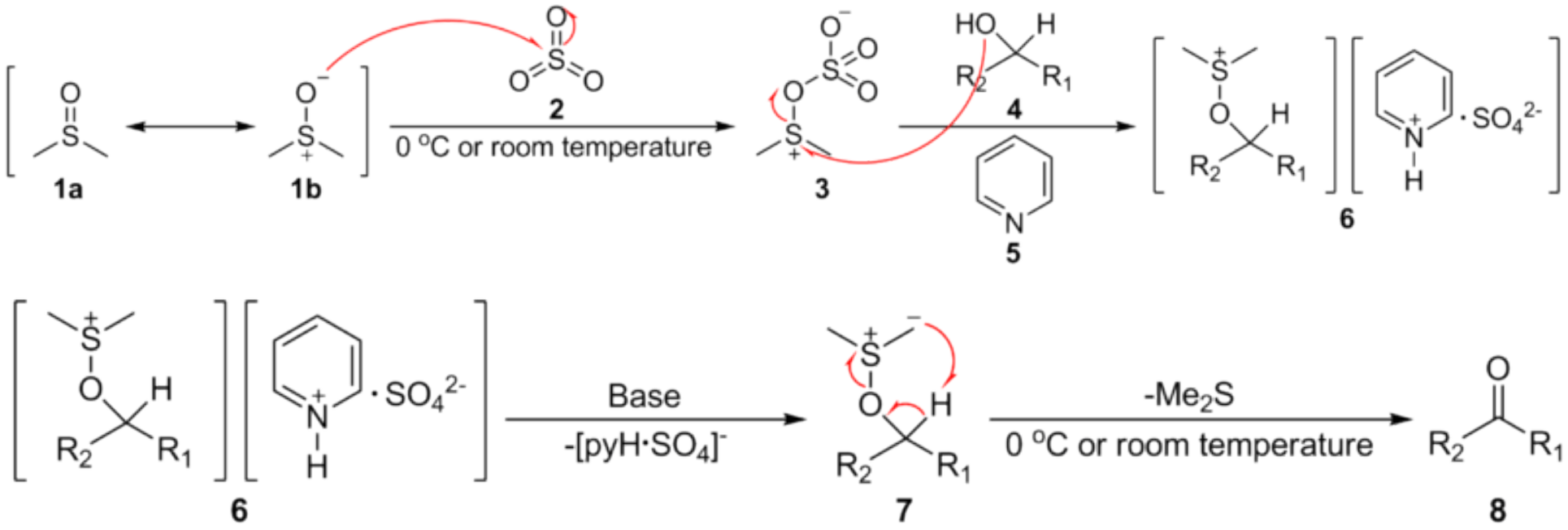
Sonogashira



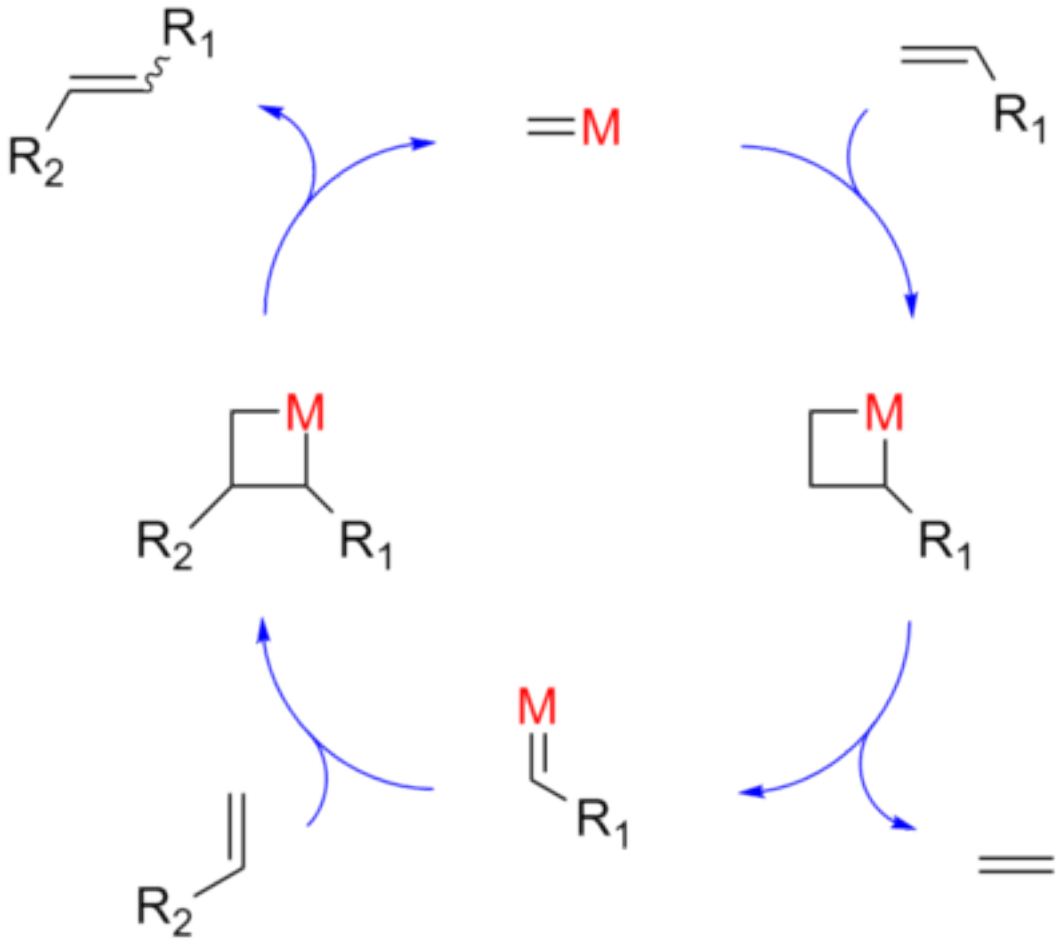
dibromoolefin



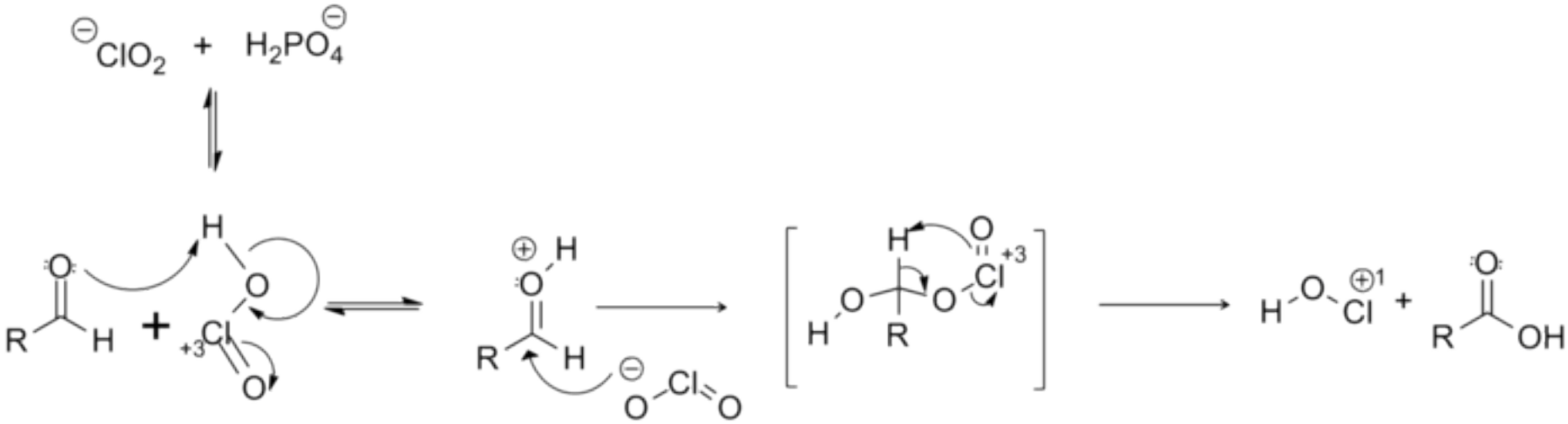
Parikh doering oxidation



Cross methathesis

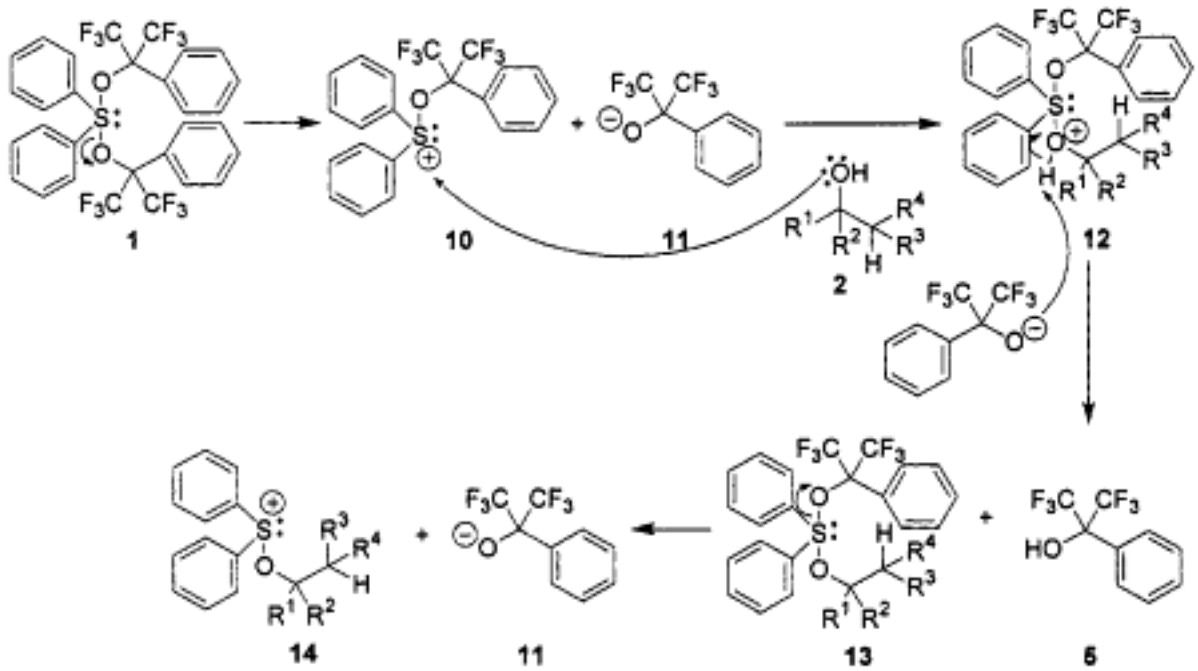


Pinnick oxidation mechanism



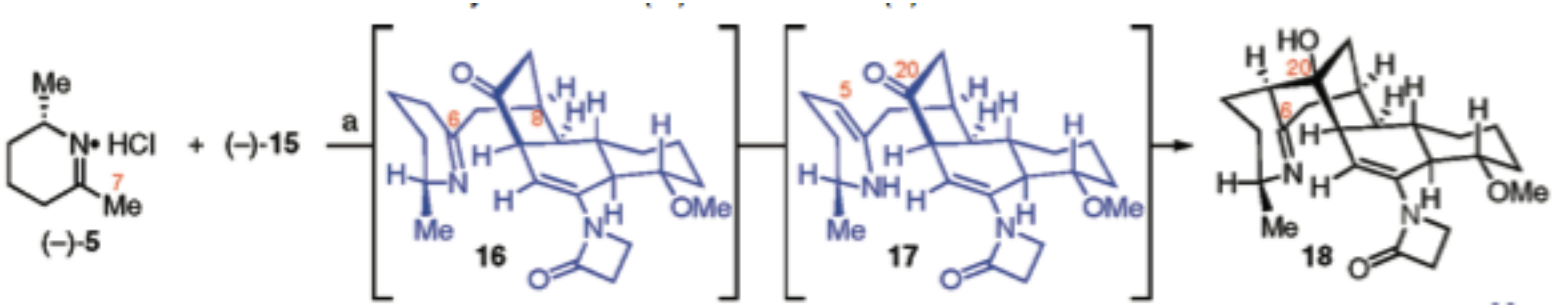
Martin sulfurane elimination

3.7.3 Mechanism[6]

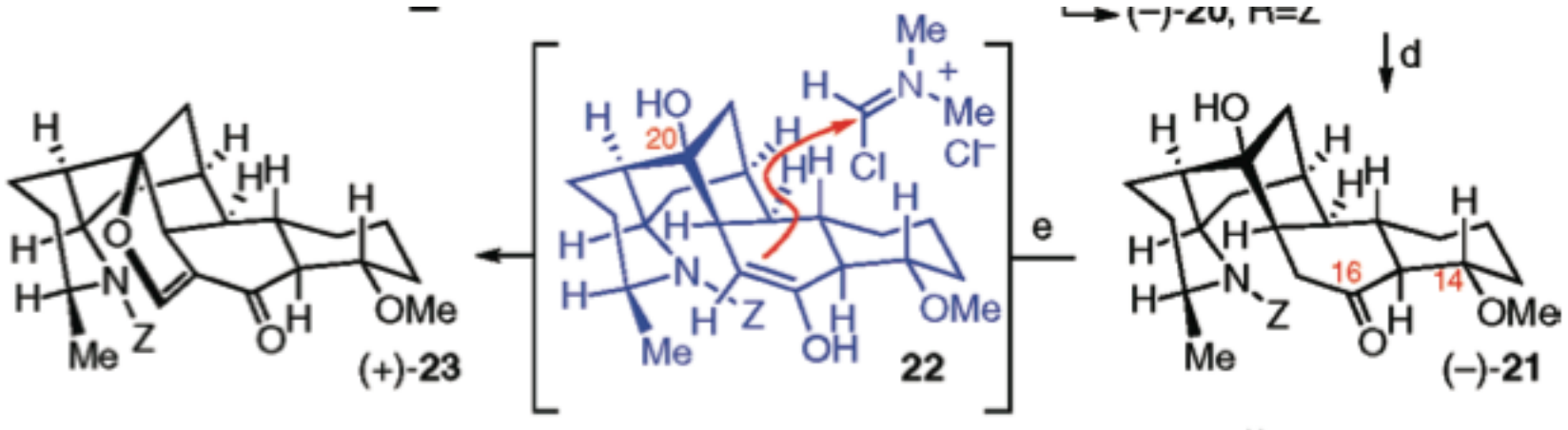


The mechanism commences with rapid exchange between the alkoxy ligands on sulfurane **1** and the reacting alcohol **2** to yield sulfurane **13** and alcohol **5**. Ionization of the other fluorinated alcohol yields alkoxide **11** and key alkoxysulfonium ion **14**. The structure of the alkoxy substituent in **14** (originally the starting alcohol) determines the ultimate course of the reaction. Reactions with tertiary alcohols follow option #1 below (R^1 and R^2 = C) and eliminate via an E1 pathway. Carbocation **15** is converted into alkene **3** upon reaction with alkoxide **11**. Secondary alcohol starting materials also yield the desired alkene products **3** but only after an E2 elimination (option #2). The requisite antiperiplanar geometry in this step enables stereospecific alkene generation from chiral secondary alcohols. Primary alcohols do not furnish alkenes and instead participate in S_N2 reactions that provide ethers like **16** (option #3).

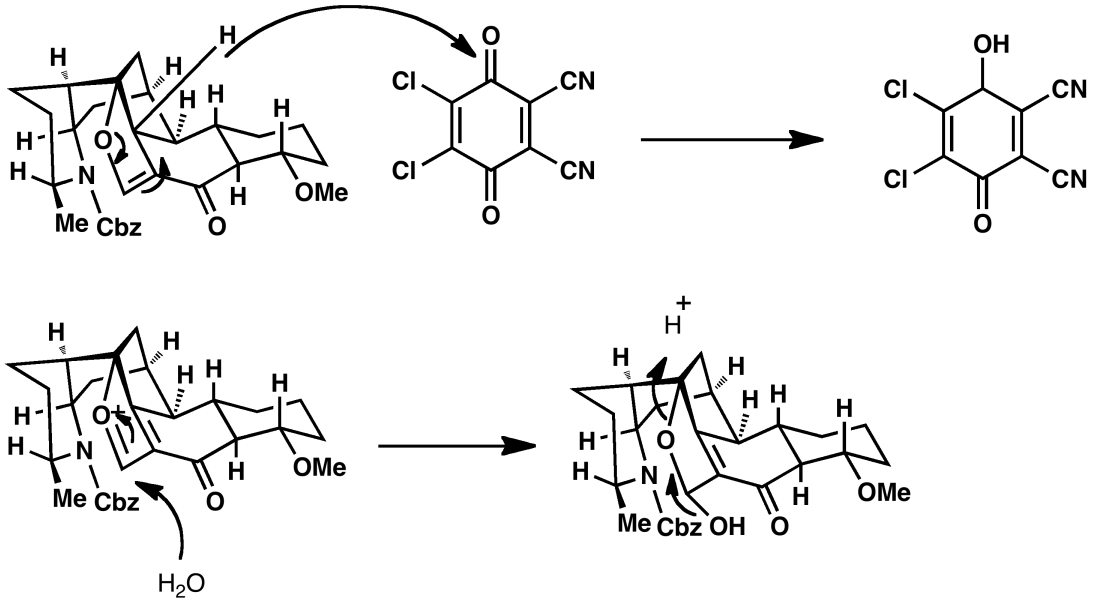
Formal 3+3 cycloaddition



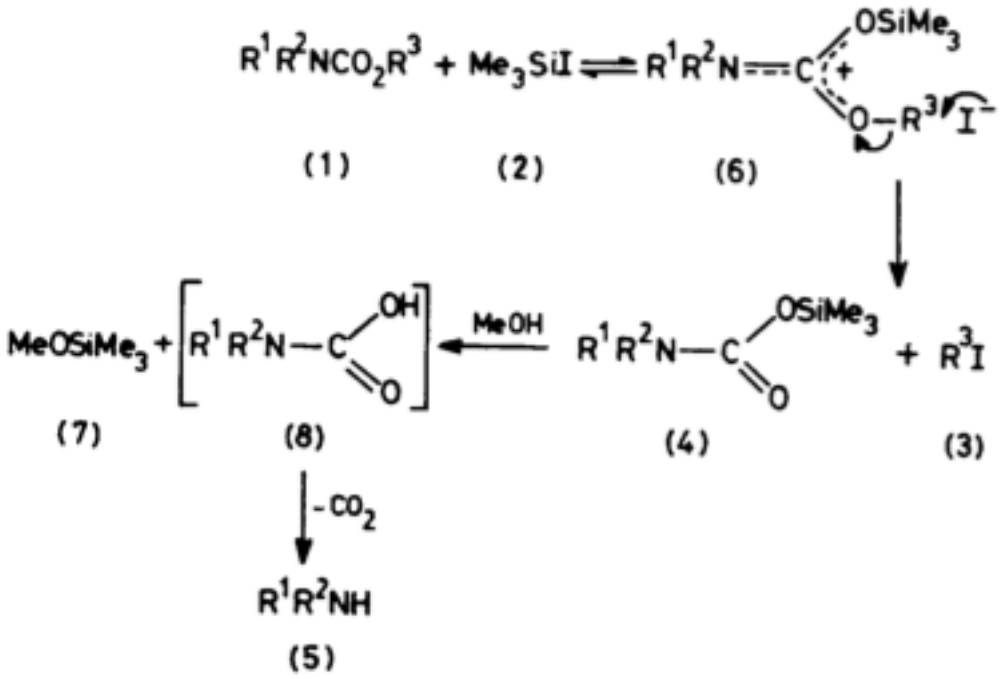
Vilsmeier reagent



DDQ dihydrofuran cleavage



TMS-I cleavage of carbamate



SCHEME

IBX enone oxidation

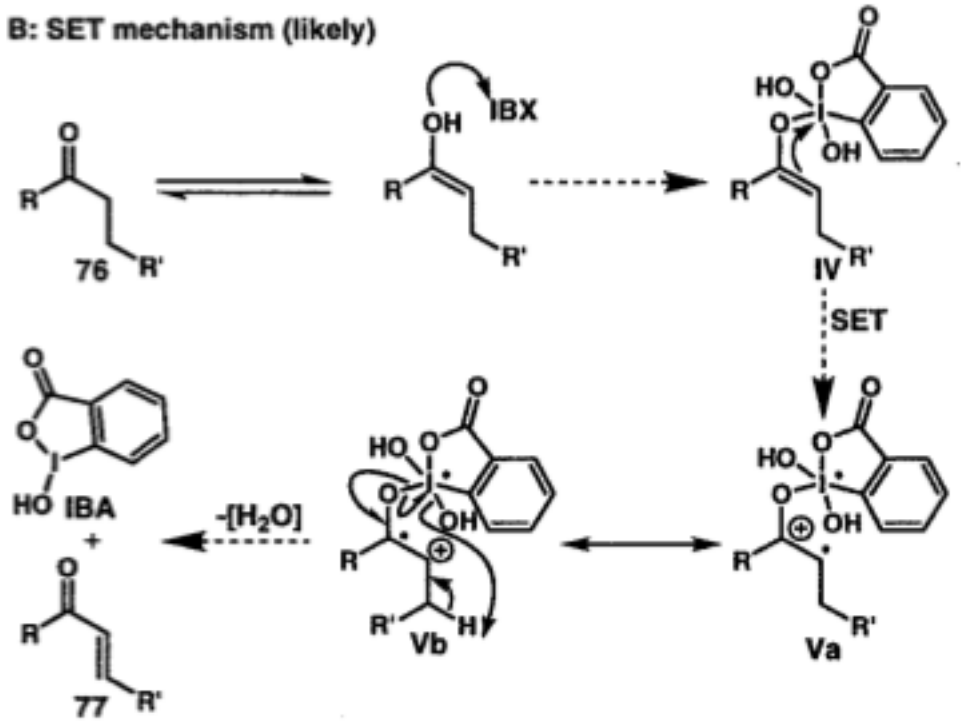


Figure 3. Possible ionic- (A) and SET-based (B) mechanisms for the dehydrogenation of carbonyl compounds by IBX. Alternatively IBX may also be considered to effect the initial enolization of the carbonyl compound to yield **IV** directly.

SmI2-DMP oxidation