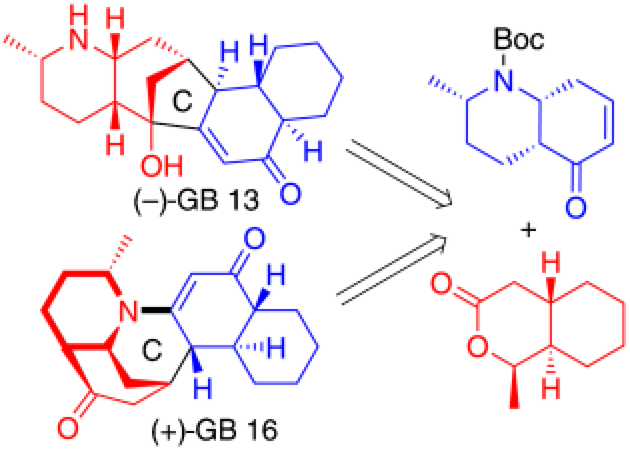
Galbulimima Alkaloids (-)-GB 13 and (+)-GB 16

Zi, W.; Yu, S.; Ma, D.

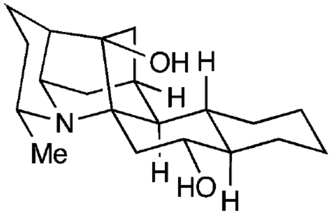
Angew. Chem. Int. Ed. **2010**, *49*, 5887–5890



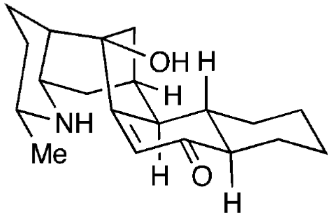
Current Literature
Jie Xu

08.28.10

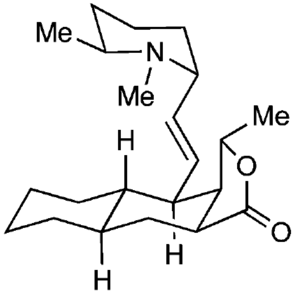
Isolation



(–)-Himgaline (**1**)



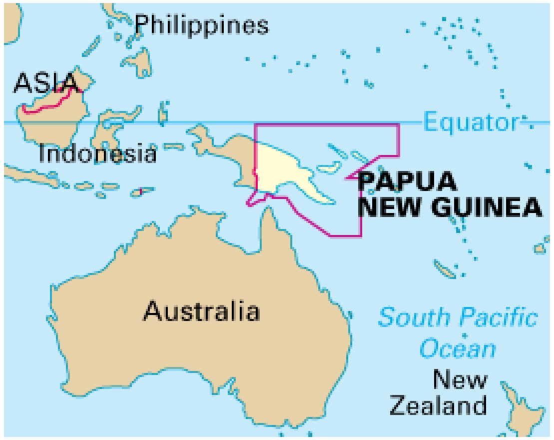
(–)-GB13 (**2**)



Himbacine (**3**)

Galbulimima belgraveana

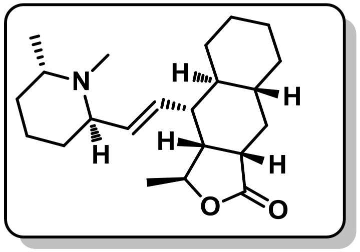
- ***Isolated from the bark of galbulimima belgraveana in northern Australia and Papua New Guinea***
- ***Structure confirmed by chemical degradation and spectroscopy (MS, IR, UV, NMR) analysis***



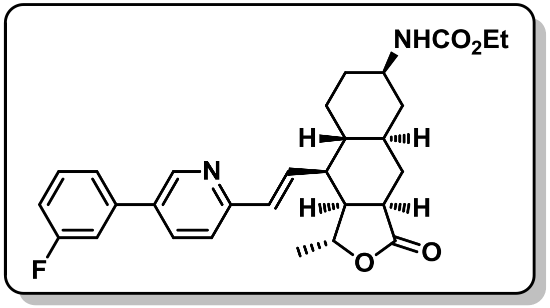
Taylor, W. C. *et al. Aust. J. Chem.* **1956**, *9*, 283.
Taylor, W. C. *et al. Aust. J. Chem.* **1965**, *18*, 569.
Taylor, W. C. *et al. Aust. J. Chem.* **1967**, *20*, 1473.
Taylor, W. C. *et al. Aust. J. Chem.* **1967**, *20*, 1705.
Mander, L. N. *et al. Tetrahedron Lett.* **2009**, *50*, 7089.

Biological Activity

- ***Galbulimima belgraveana bark has been used medicinally by Papua New Guinean tribes.***
- ***Himbacine displays potent muscarinic antagonist activity.***
- ***SCH 530348 is now in phase III clinical trials for treatment of acute coronary syndrome.***



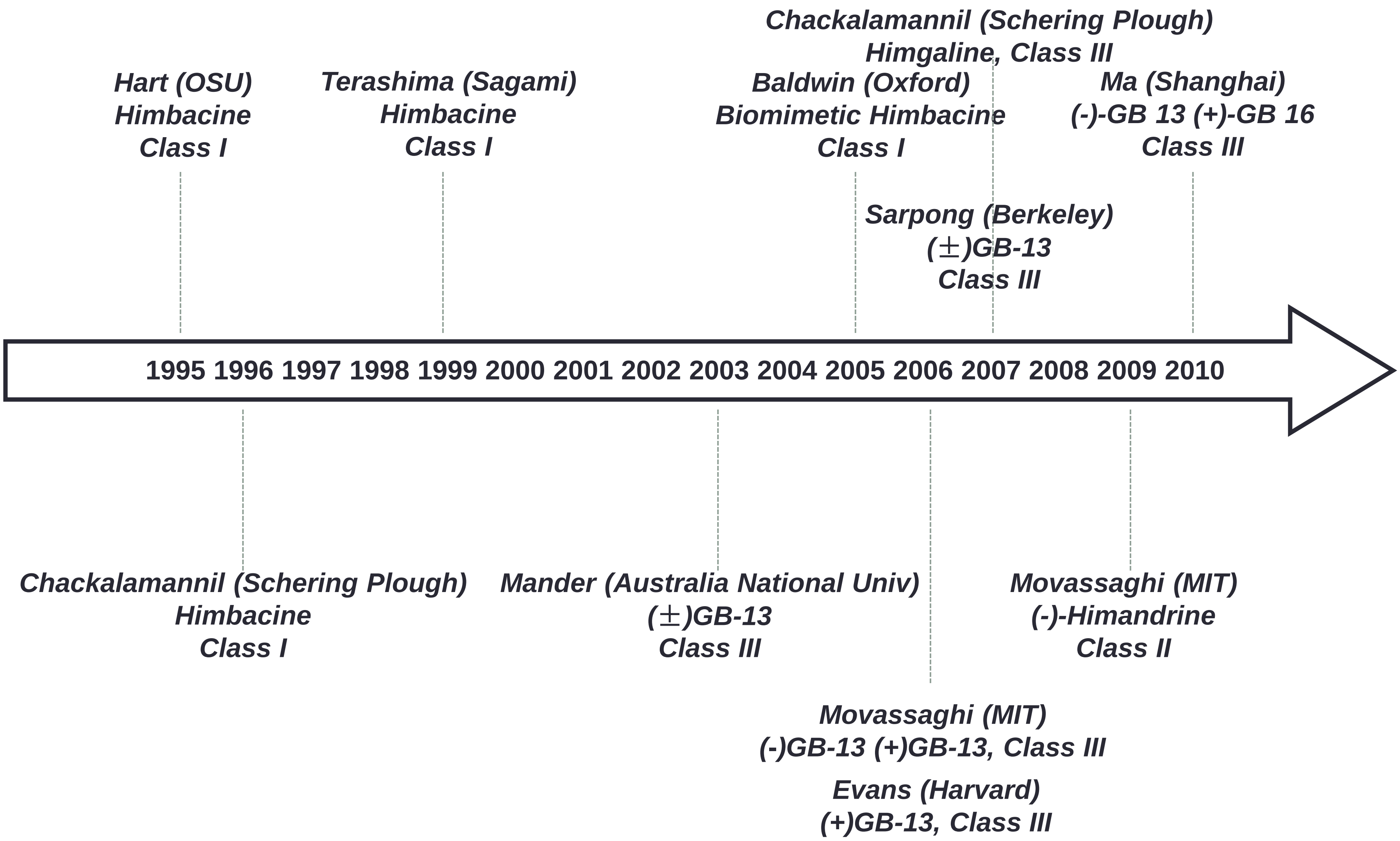
Himbacine



SCH 530348

Chackalamannil, S.; Wang, Y.; Greenlee, W. J.; Hu, Z.; Xia, Y.; Ahn, H.; Boykow, G.; Hsieh, Y.; Palamanda, J.; Agans-Fantuzzi, J.; Kurowski, S.; Graziano, M.; Chintala, M. *J. Med. Chem.* **2008**, *51*, 3061.
Malaska, M. J.; Fauq, A. H.; Kozikowski, A. P.; Aagaard, P. J.; McKinney, M. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 61.

Synthesis of Galbulimima Alkaloids



Hart (OSU)
Himbacine
Class I

Terashima (Sagami)
Himbacine
Class I

Baldwin (Oxford)
Biomimetic Himbacine
Class I

Chackalamannil (Schering Plough)
Himgaline, Class III

Sarpong (Berkeley)
(±)GB-13
Class III

Ma (Shanghai)
(-)-GB 13 (+)-GB 16
Class III

1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010

Chackalamannil (Schering Plough)
Himbacine
Class I

Mander (Australia National Univ)
(±)GB-13
Class III

Movassaghi (MIT)
(-)GB-13 (+)GB-13, Class III

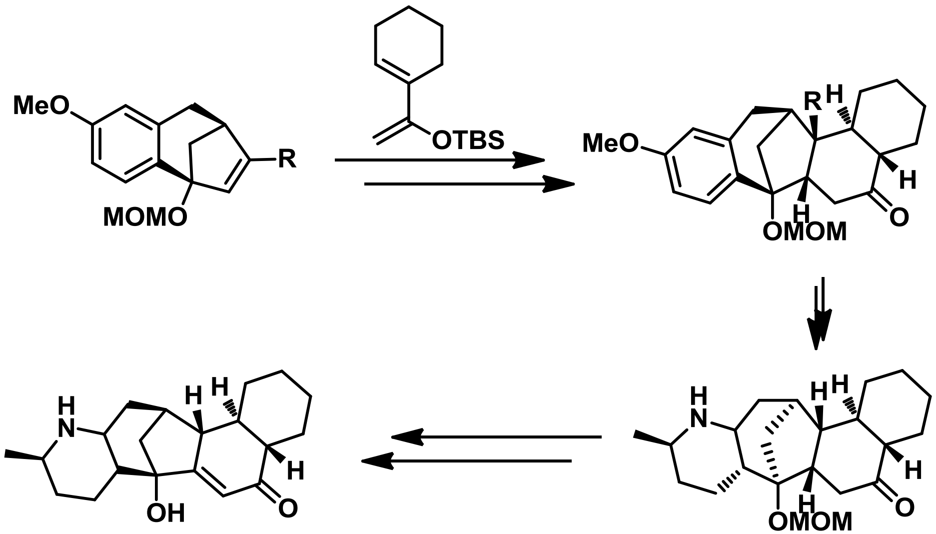
Evans (Harvard)
(+)GB-13, Class III

Movassaghi (MIT)
(-)-Himandrine
Class II

Synthesis of GB 13

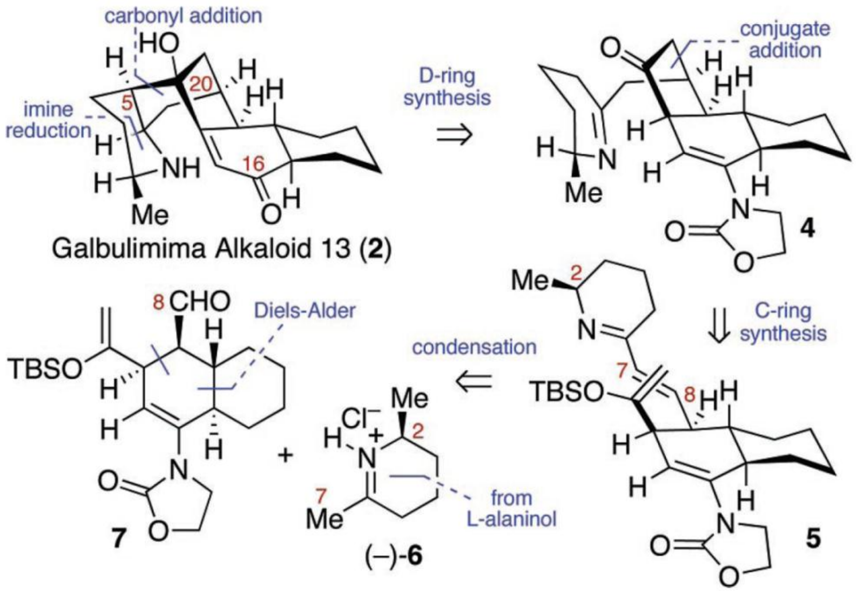
Mander Group(2003)

- ***First total synthesis of GB13***
- ***Yb(thd)$_3$ catalyzed DA reaction***
- ***30 steps 0.3% yield***



Movassaghi Group(2006)

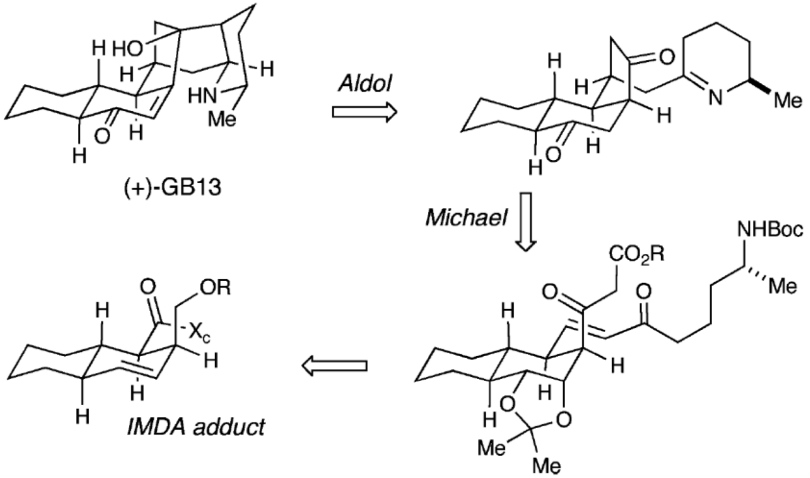
- ***First enatioselective synthesis of (-)-GB13 and (+)-GB 13***
- ***IMDA***
- ***Vinyl radical cyclization***
- ***Biomimetic enamine aldol addition***
- ***20 steps 1% yield***



Mander, L. N.; McLachlan, M. M. *J. Am. Chem. Soc.* **2003**, *125*, 2400

Movassaghi, M.; Hunt, D. K.; Tjandra, M. *J. Am. Chem. Soc.* **2006**, *128*, 8126.

Synthesis of GB 13

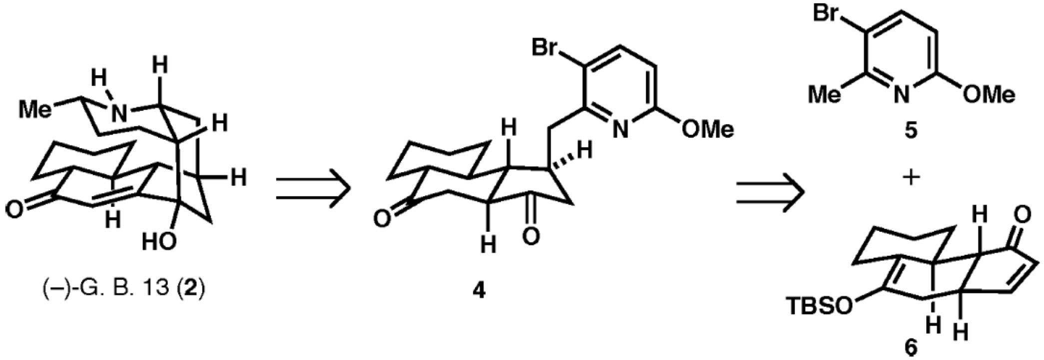


Evans Group(2006)

- ***HWE Olefination***
- ***IMDA***
- ***Michael Addition***
- ***Enamine aldol addition***
- ***28 steps 1% yield***

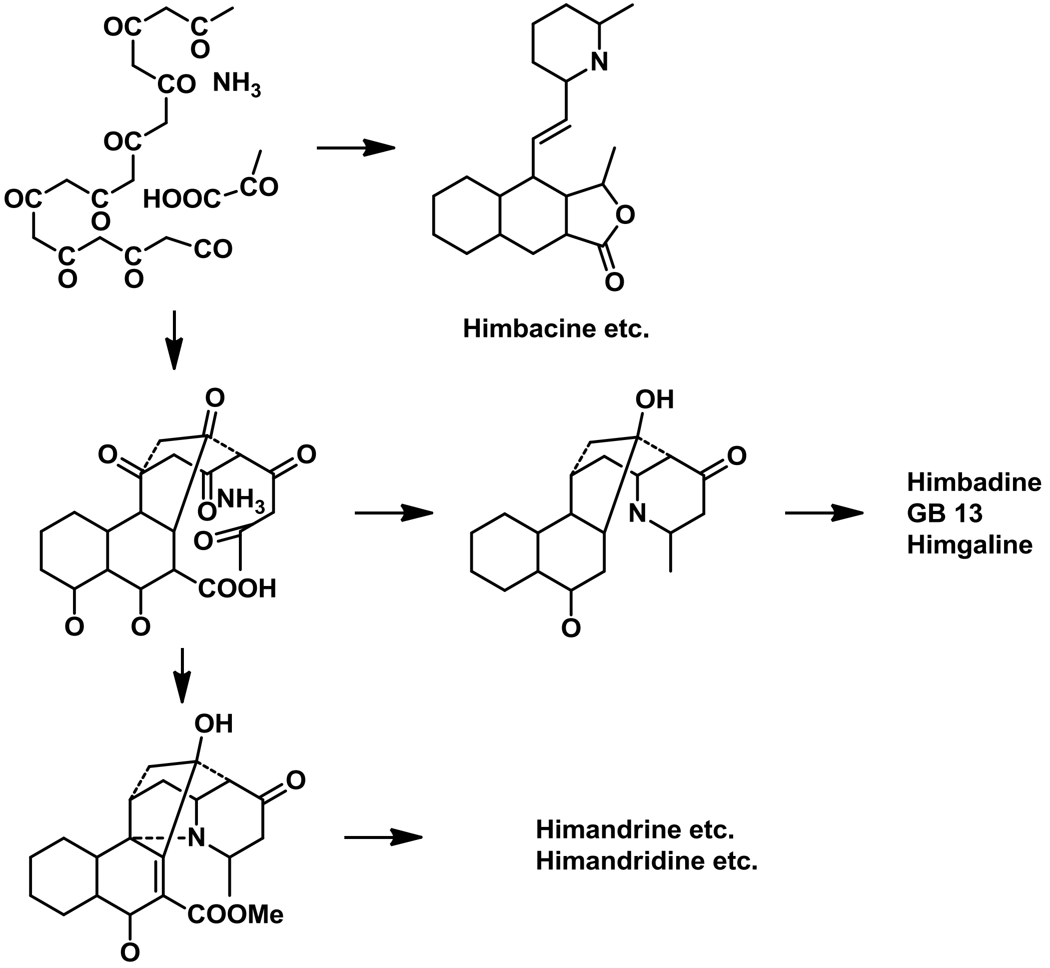
Sarpong Group(2009)

- ***Yb(tmhd)$_3$ catalyzed DA***
- ***1,3-allylic transportation***
- ***Rh(I)-cat ketone hydroarylation***
- ***18 steps 2% yield***



Evans, D.A.; Adams, D. J. *J. Am. Chem. Soc.* **2007**, *129*, 1048.
Larson, K. K.; Sarpong, R. *J. Am. Chem. Soc.* **2009**, *131*, 13244.

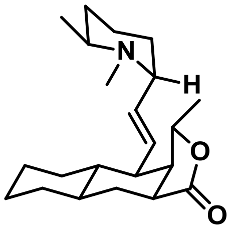
Biogenetic(Polyacetate Proposal)



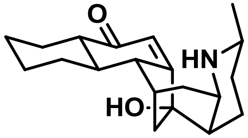
Himbacine etc.

Himbadine
GB 13
Himgaline

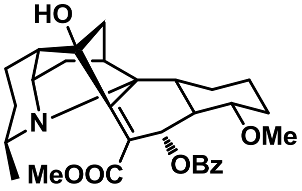
Himandrine etc.
Himandridine etc.



Himbacine



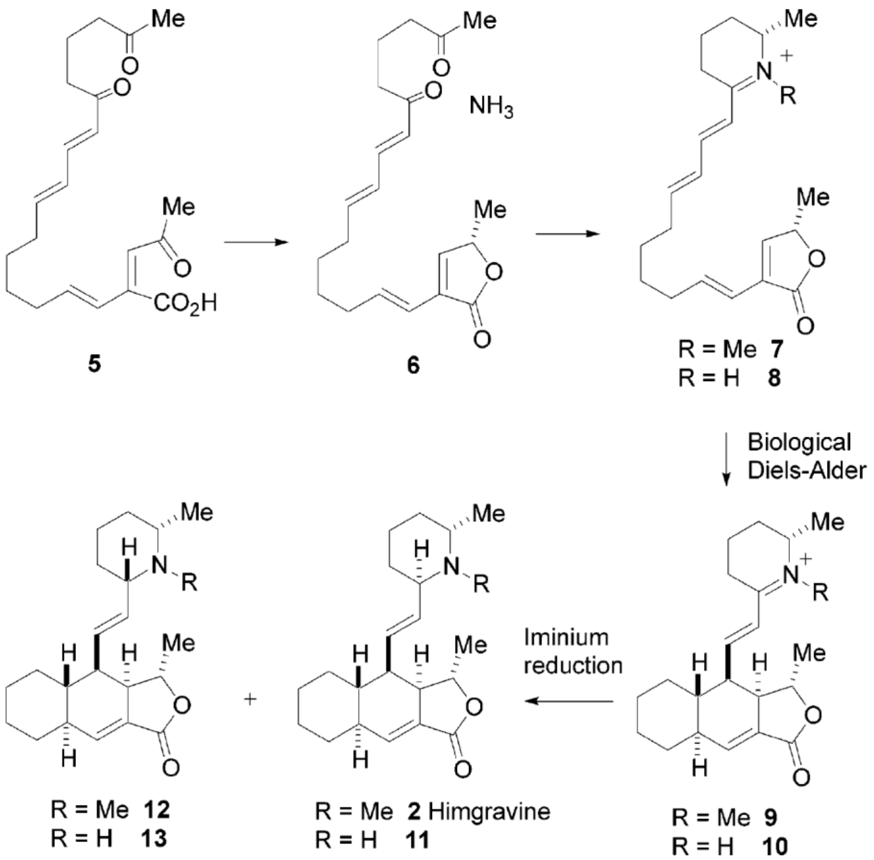
GB 13



Himandrine

Taylor, W. C. *et al. Aust. J. Chem.* **1967**, *20*, 1705.

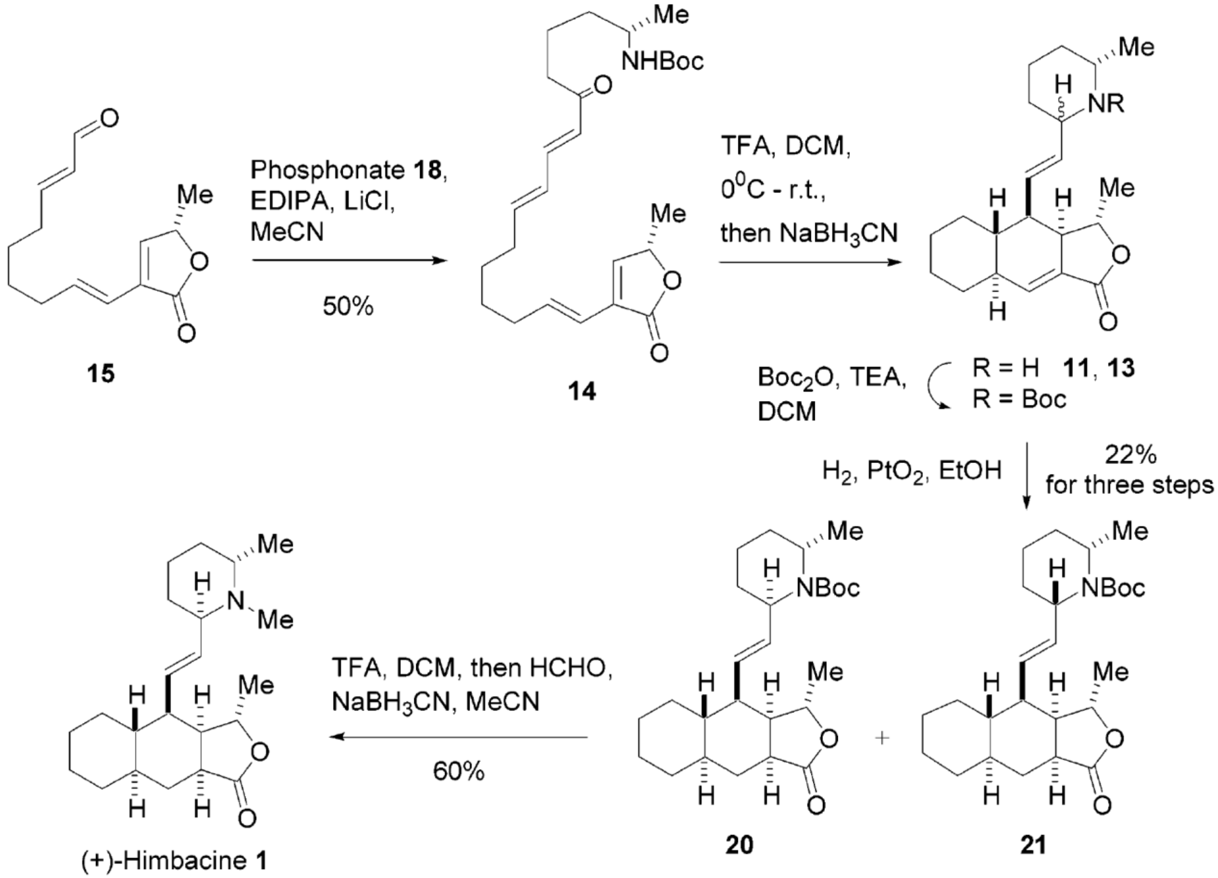
Biogenesis(Baldwin)



- ***Start from polyketide derivative***
- ***Reductive lactonisation to produce the butenolide***
- ***Reductive amination would give the iminium species***
- ***IMDA***
- ***Hydride reduction of the iminium ion would give the precursor of GB alkloids***

Tchabanenko, K.; Adlington, R. M.; Cowley, A. W.; Baldwin, J. E. *Org. Lett.* **2005**, *7*, 585.

Biomimetic Synthesis(Baldwin)

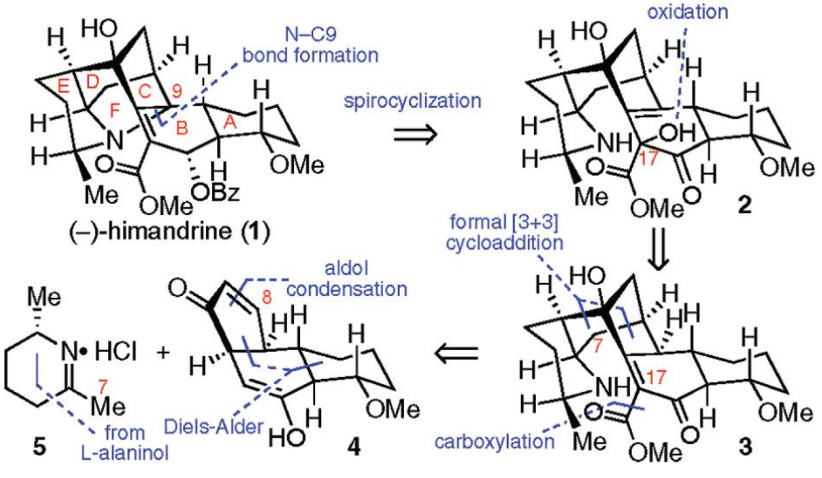


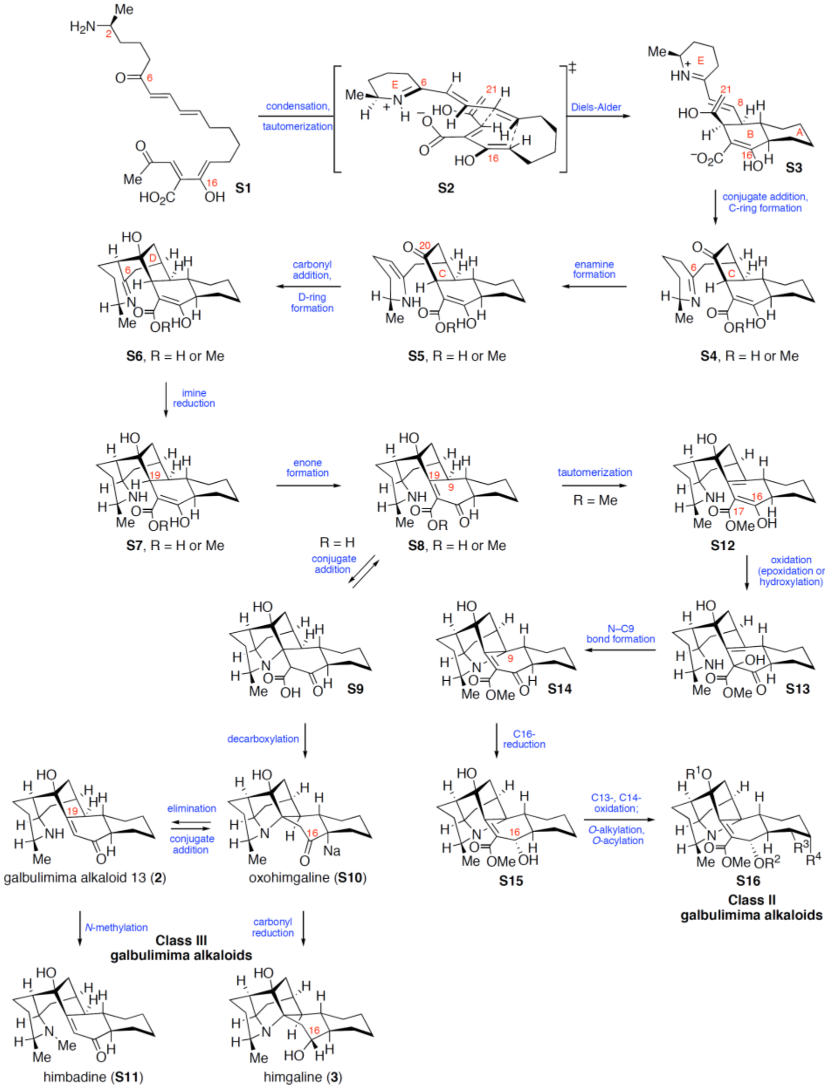
Tchabanenko, K.; Adlington, R. M.; Cowley, A. W.; Baldwin, J. E. *Org. Lett.* **2005**, *7*, 585.

Inspire from Biology

Movassaghi Group(2009)

- First total synthesis of Class II GB alkloids (-)-Himandrine
- 26 steps 0.6% yield

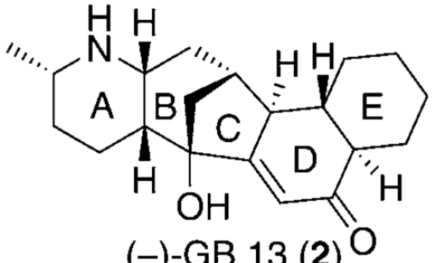




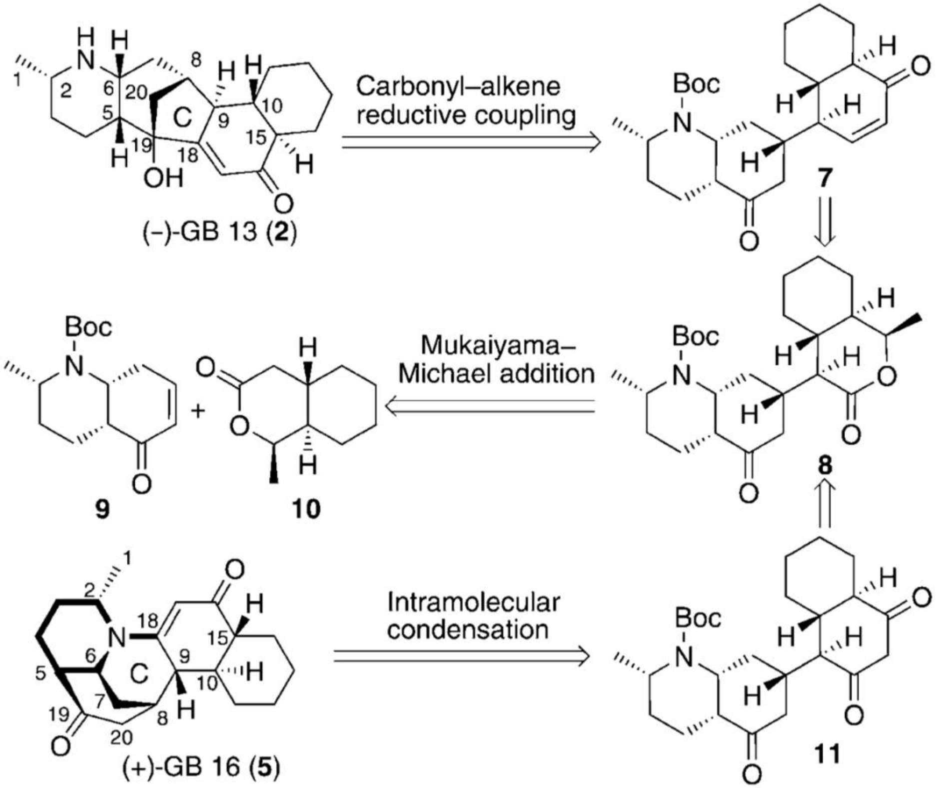
Movassaghi, M.; Tjandra, M.; Qi, J. *J. Am. Chem. Soc.* **2009**, *131*, 9648

Movassaghi, M.; Hunt, D. K.; Tjandra, M. *J. Am. Chem. Soc.* **2006**, *128*, 8126

Synthetic Strategy



(–)-GB 13 (**2**)

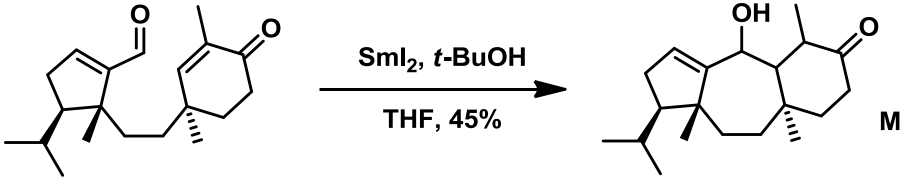


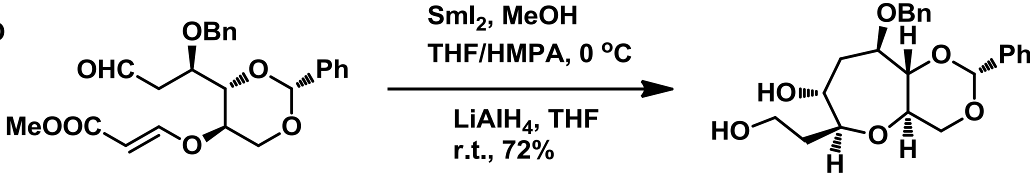
Ma Group(2010)

- ***Formation of C ring at late stage***

Featured Reactions

Carbonyl-alkene reductive coupling

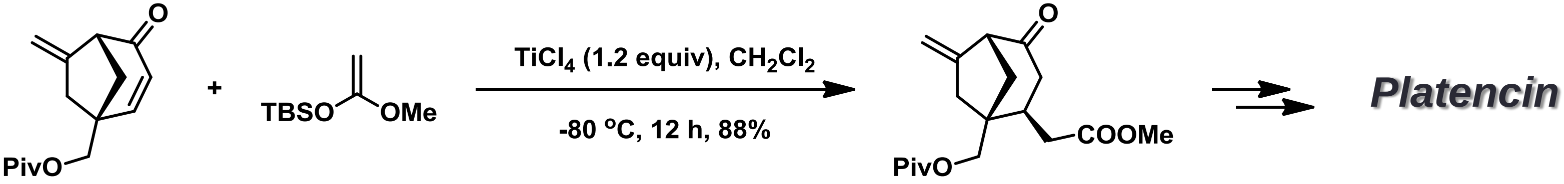




Nguyen, T. M.; Lee, D. *Tetrahedron Lett.* **2002**, *43*, 4033

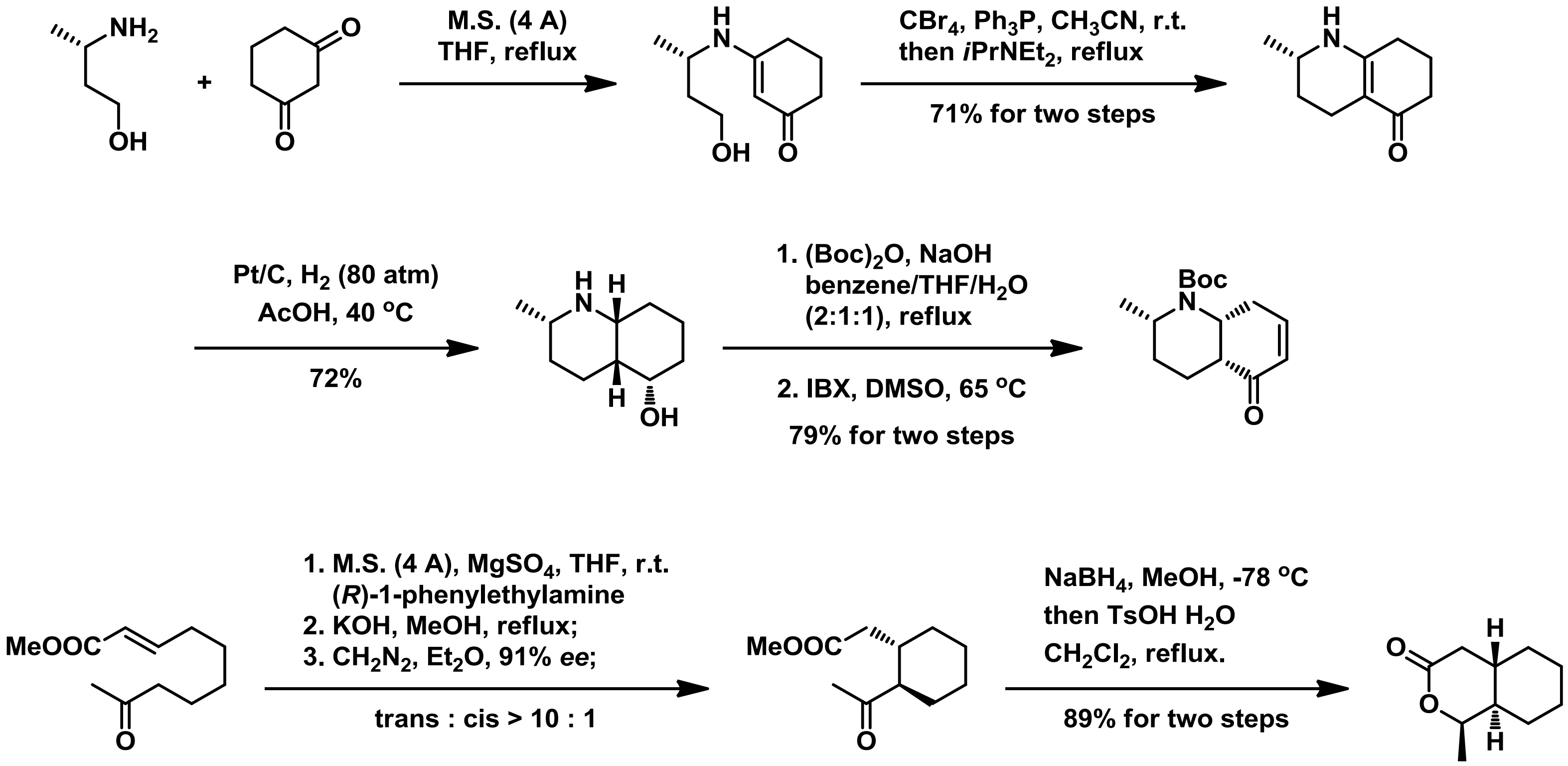
Takakura, H.; Noguchi, K.; Sasaki, M.; Tachibana K. *Angew. Chem. Int. Ed.* **2001**, *40*, 1090.

Mukaiyama Michael addition

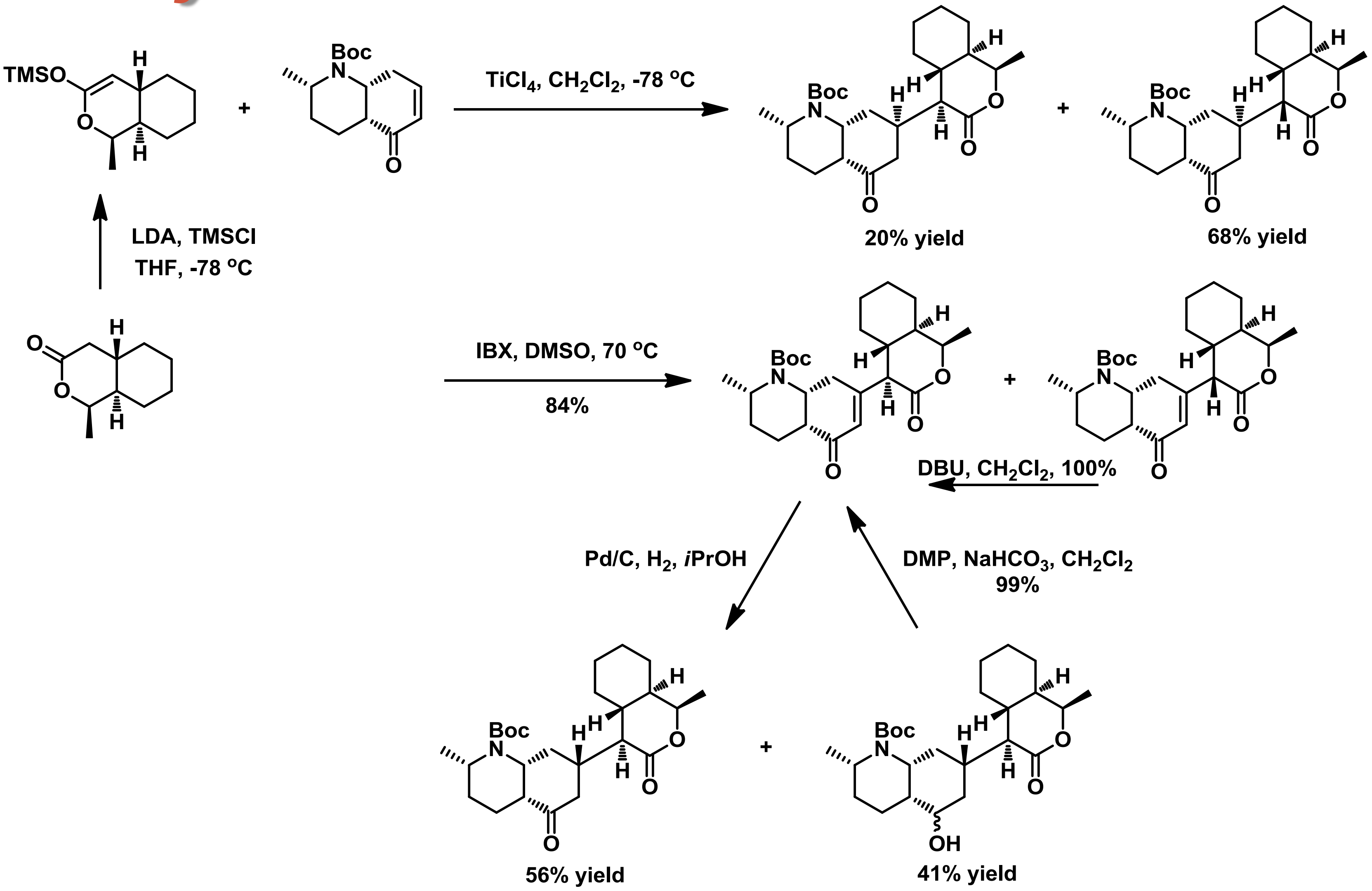


Narasaka, K.; Soai, K.; Mukaiyama, T. *Chem. Lett.* **1974**, 1223.
Varseev G. N.; Maier, M. E. *Angew. Chem. Int. Ed.* **2009**, *48*, 3685.

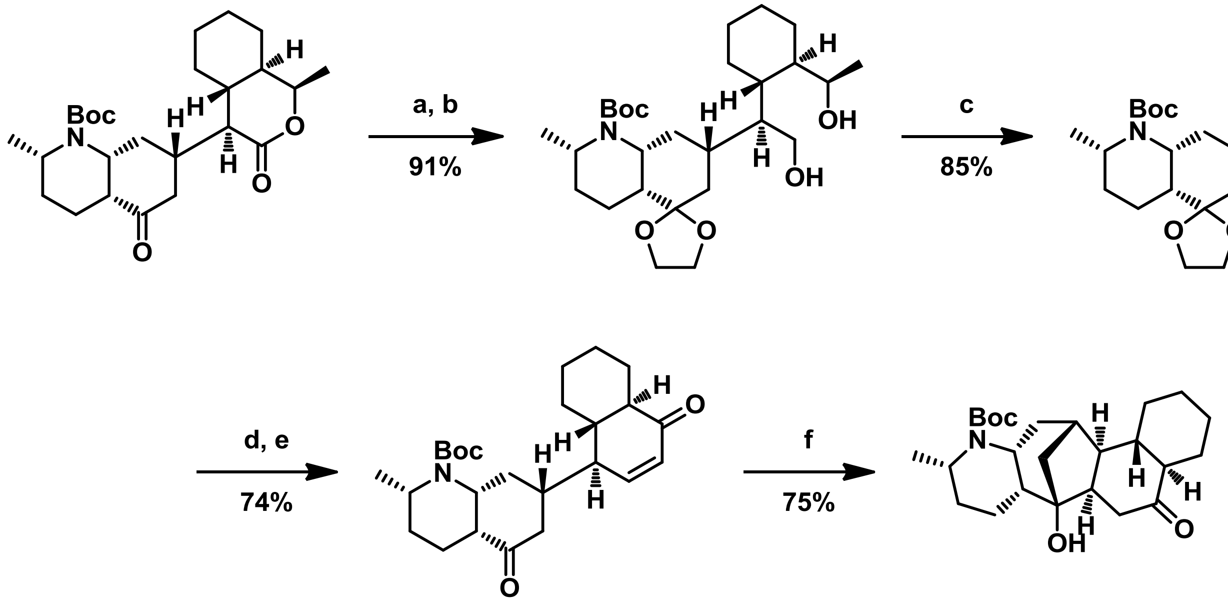
Synthesis of Coupling Partner

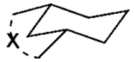


Mukaiyama Michael Addition

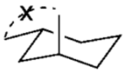


Carbonyl-alkene Reductive Coupling

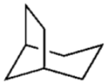




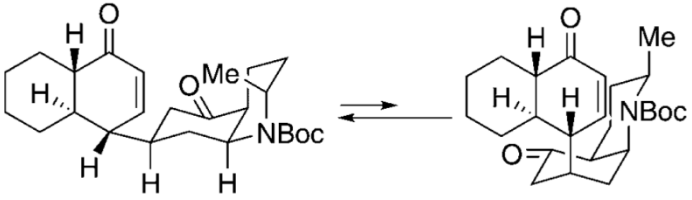
1,3-diequatorial connection



1-axial-3-equatorial connection



1,3-diaxial connection



conformation A

conformation B

a) glycol, $TsOH \cdot H_2O$, toluene, Dean-Stark;

b) $LiAlH_4$, THF, 0 °C to r.t.;

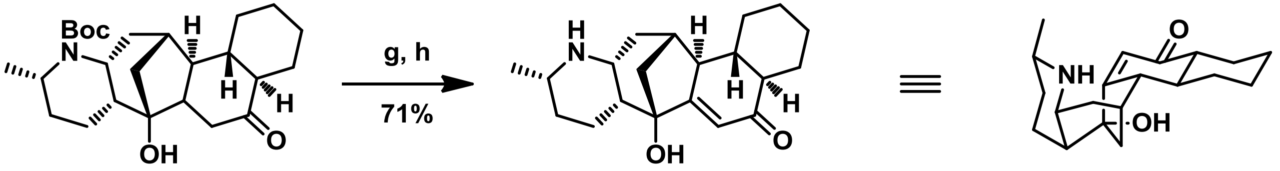
c) $(CF_3CO)_2O$, DMSO, DBU, CH_2Cl_2, -78 °C to r.t.;

d) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, r.t.;

e) $TsOH \cdot H_2O$, acetone, H_2O, reflux, 4 days;

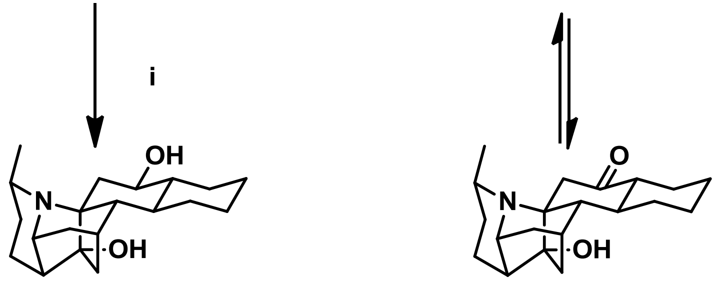
f) SmI_2, THF, reflux, then DMP

End Game



(-)-GB 13

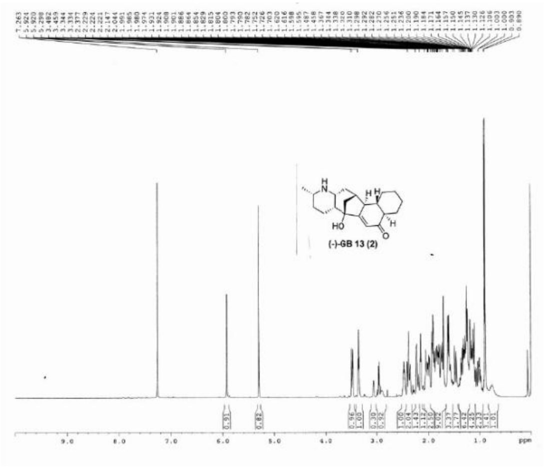
(-)-GB 13



Himgaline

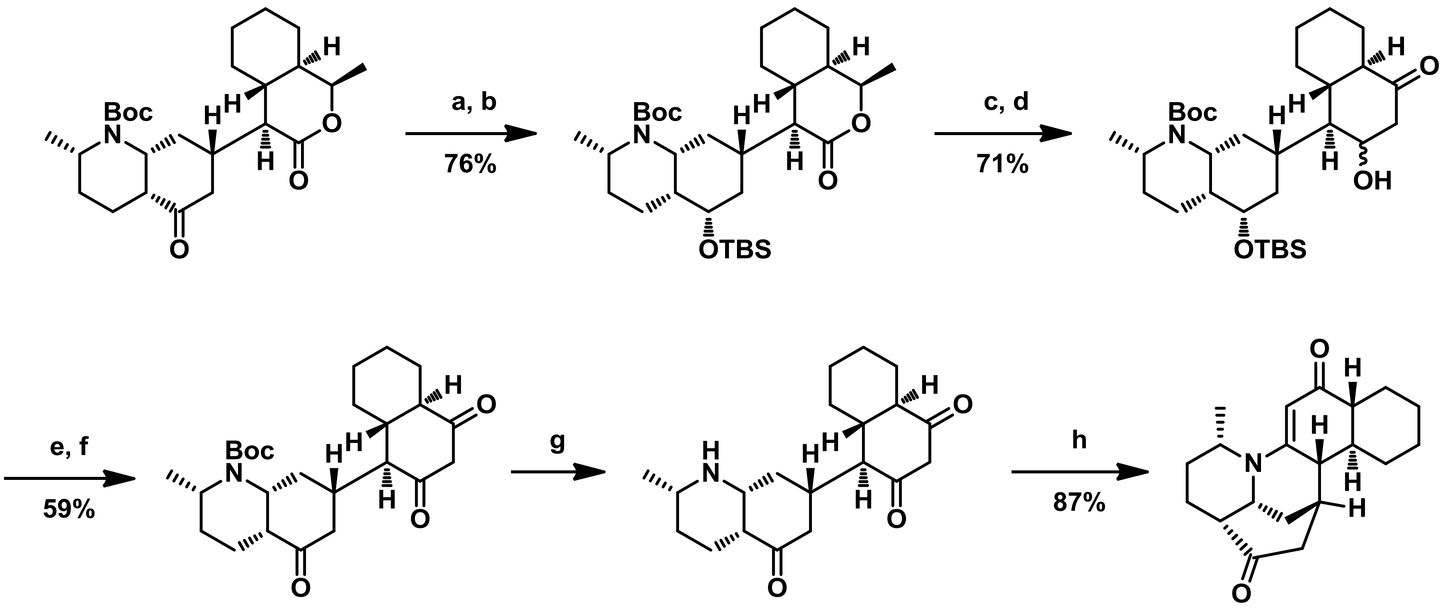
16-oxohimgaline

g) IBX, DMSO, 70 °C;
h) CF_3CO_2H, CH_2Cl_2; then NaOH;
i) HOAc, CH_3CN; then $NaBH(OAc)_3$.

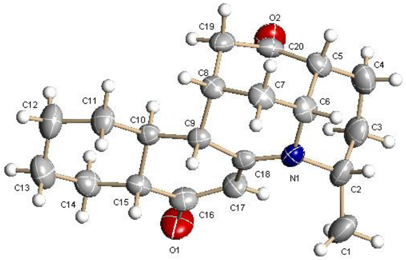


- *19 steps 6% yield*

Synthesis of (+)-GB 16



a) $NaBH_4$, MeOH/THF (1:1), -78 °C; b) TBSCl, imidazole, DMAP, DMF, r.t;
c) $LiAlH_4$, THF, r.t.; d) $(CF_3CO)_2O$, DMSO, DBU, CH_2Cl_2, -78 °C to r.t.;
e) HF, CH_3CN, -20 °C; f) PCC, CH_2Cl_2, r.t.;
g) CF_3CO_2H, CH_2Cl_2, r.t.; h) toluene, NaOAc, Dean-Stark.



Conclusion

- ***A novel and convergent route for the asymmetric synthesis of alkaloid (-)-GB 13***
- ***19 linear steps (overall yield of 6.1%) from commercially available starting material***
- ***Mukaiyama-Michael addition and carbonyl–alkene reductive coupling mediated by SmI_2***
- ***Using an advanced intermediate from (-)-GB 13 synthesis as a starting material, achieved the first total synthesis of (+)-GB 16***