Literature Report

A 11-Steps Total Synthesis of Magellanine through a Gold(I)-Catalyzed Dehydro Diels-Alder Reaction

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Checker: Cong Liu

Date: 2017/06/19

McGee, P.; Bétournay, G.; Barabé, F.; Barriault, L.
Angew. Chem. Int. Ed. **2017**, *56,* 6280-6283.

Contents

- Introduction
- Total synthesis of (-)-magellanine by Yang
- Total synthesis of (+/-)-magellanine by Barriault
- Summary

CV of Louis Barriault

Position: Full Professor

in University of Ottawa

Education:

1993 B. Sc., University of Sherbrooke

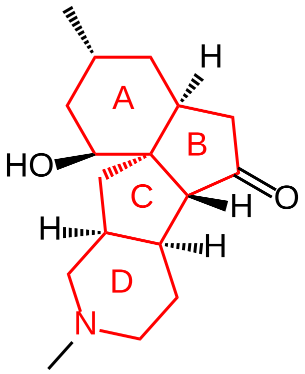
1997 Ph. D., Chemistry, University of Sherbrooke

1999 Postdoctoral Fellow, Ohio State University

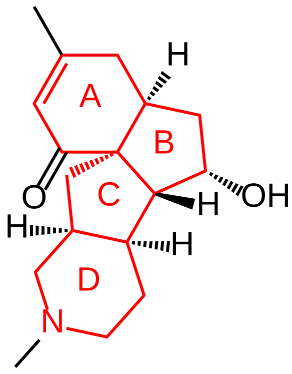
2000 Assistant Professor, University of Ottawa

2010 Full Professor, University of Ottawa

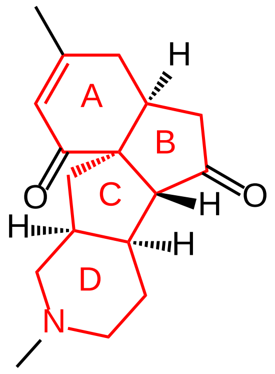
Lycopodium Alkaloids



Paniculatine

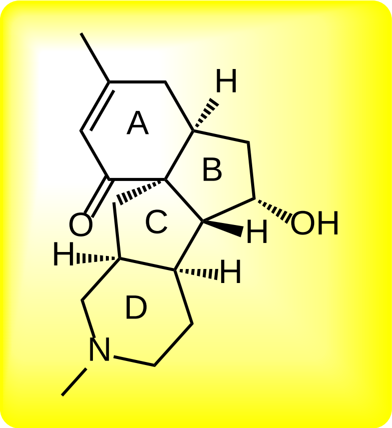


Magellanine



Magellaninone

Magellanine

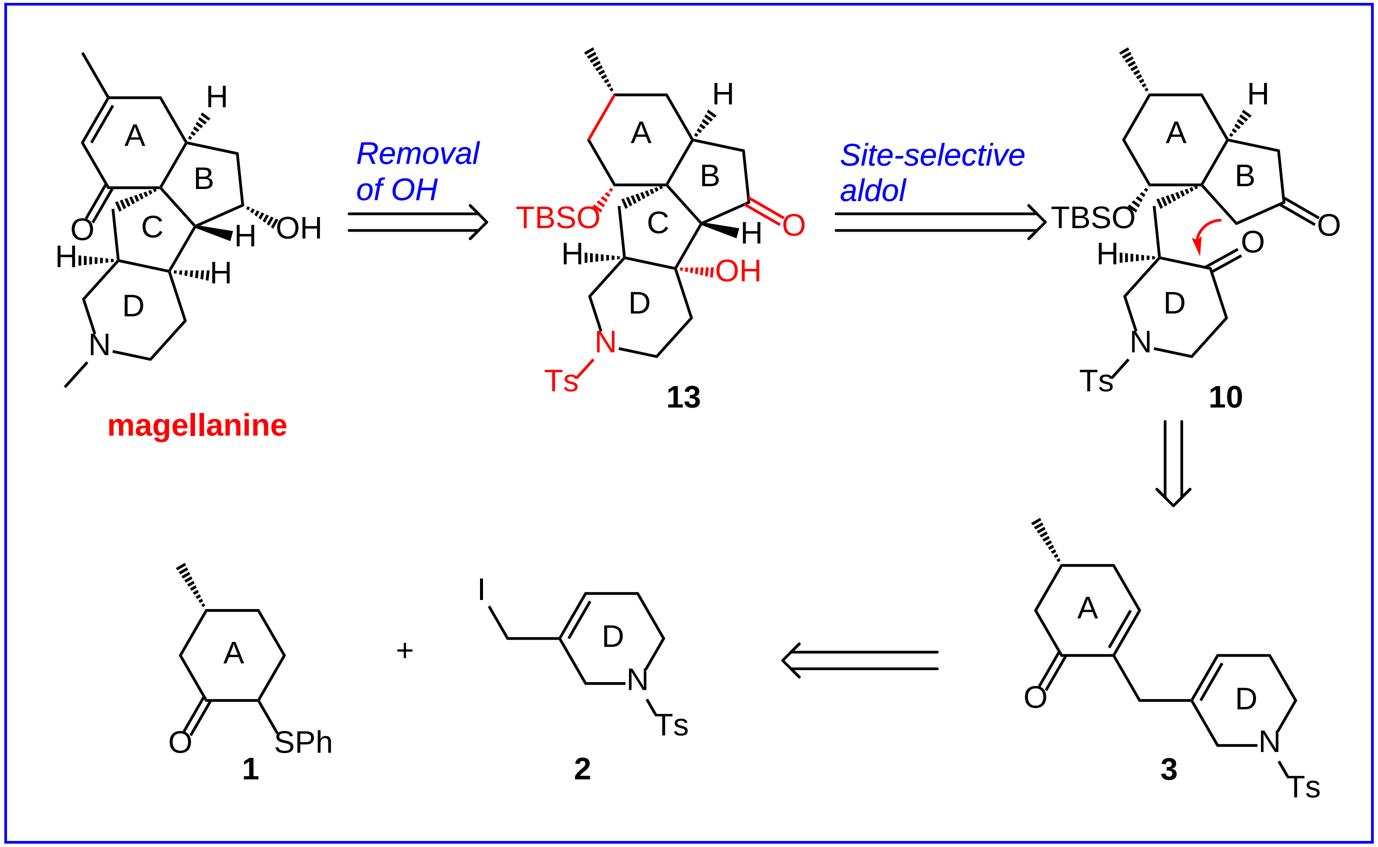


Magellanine

Lycopodium
石松

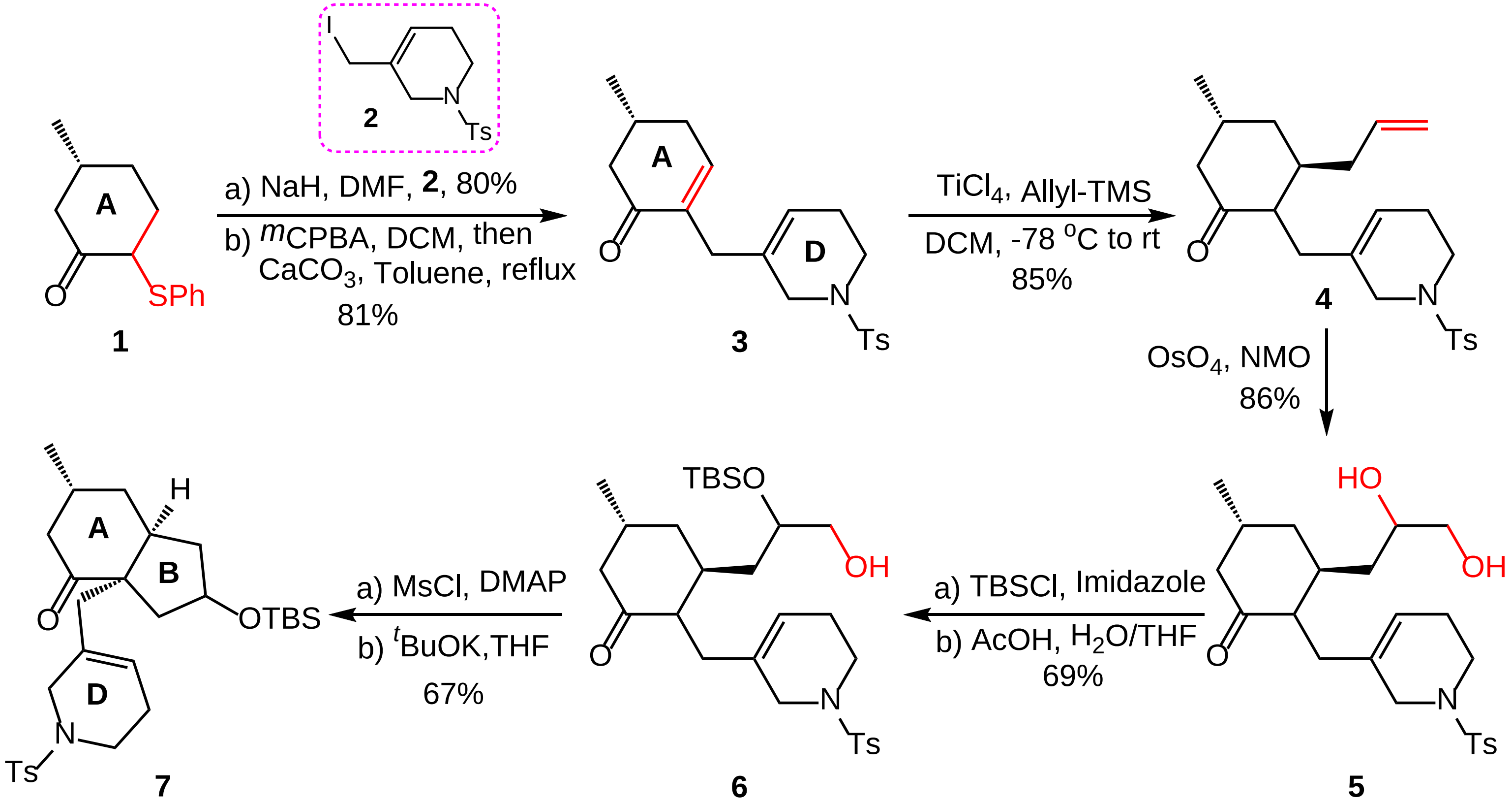
- Isolated from *Lycopodium magellanicum* in 1976
- Treatment of Alzheimer's disease and myasthenia gravis
- Six contiguous stereocenters, polycyclic framework

Proposed Retrosynthesis

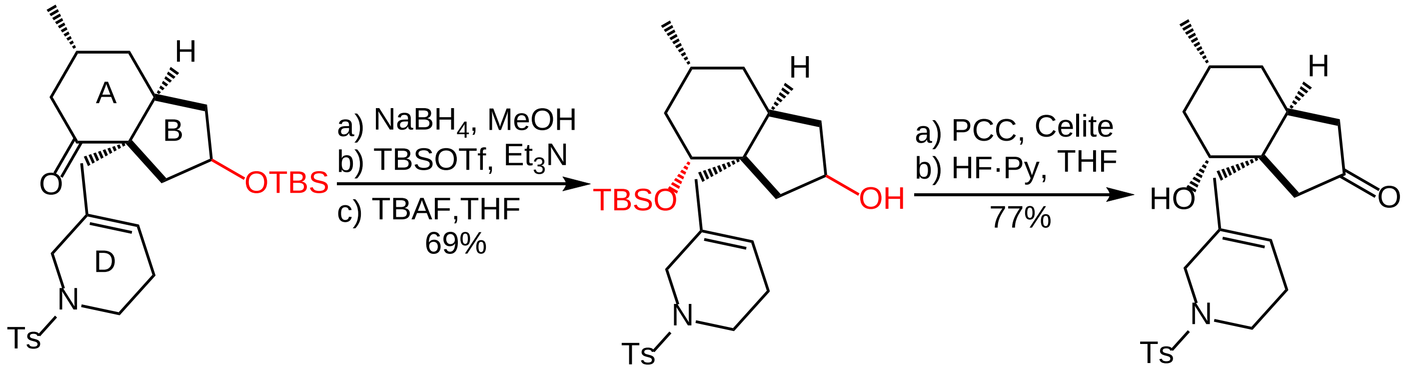


Yang, Y.-R. *et al. Org. Lett*. **2014**, *16*, 5612.

Synthesis of Key Intermediate 7

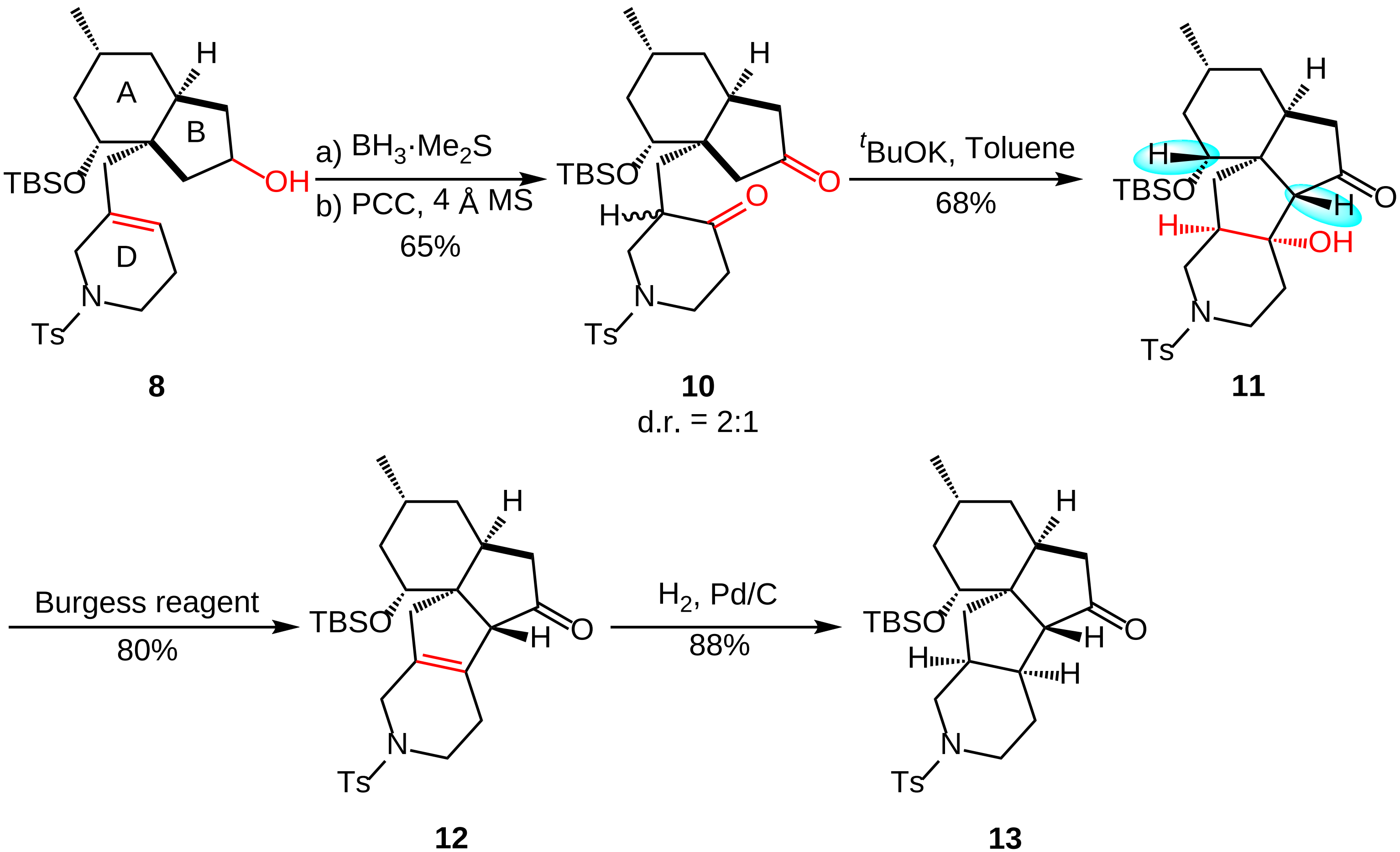


Synthesis of Key Intermediate 8



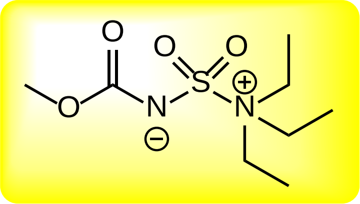
7 8 9

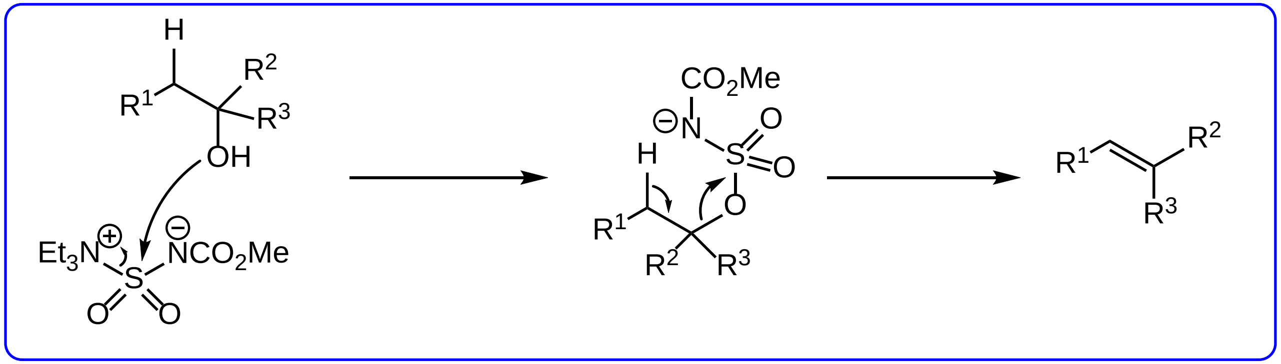
Synthesis of Key Intermediate 13



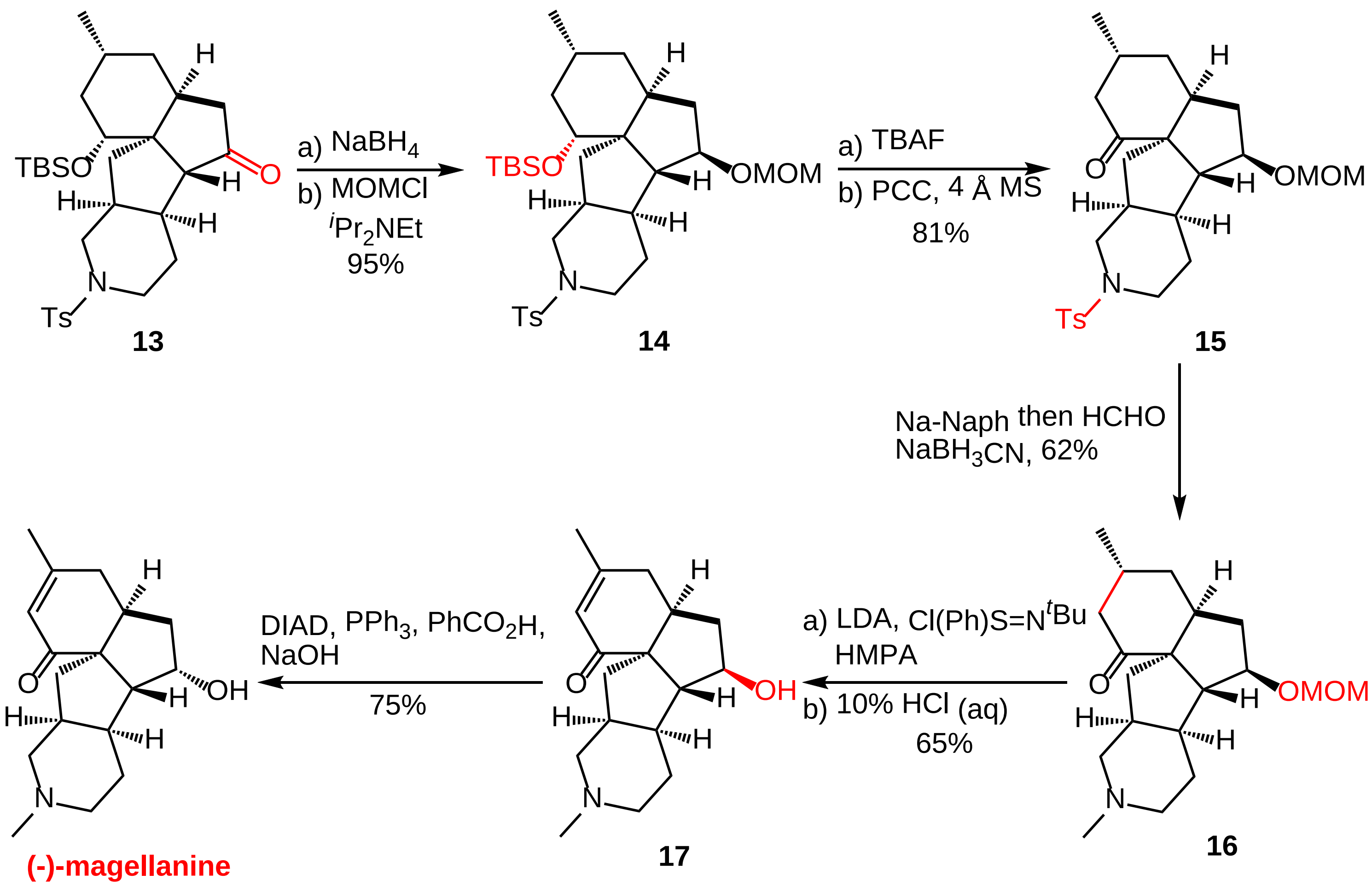
Burgess Reagent

It is used to convert secondary and tertiary alcohol with an adjacent proton into alkenes. Primary alcohols do not work well. The reagent is soluble in common organic solvents and alcohol dehydration takes place with *syn* elimination through an intramolecular elimination reaction.

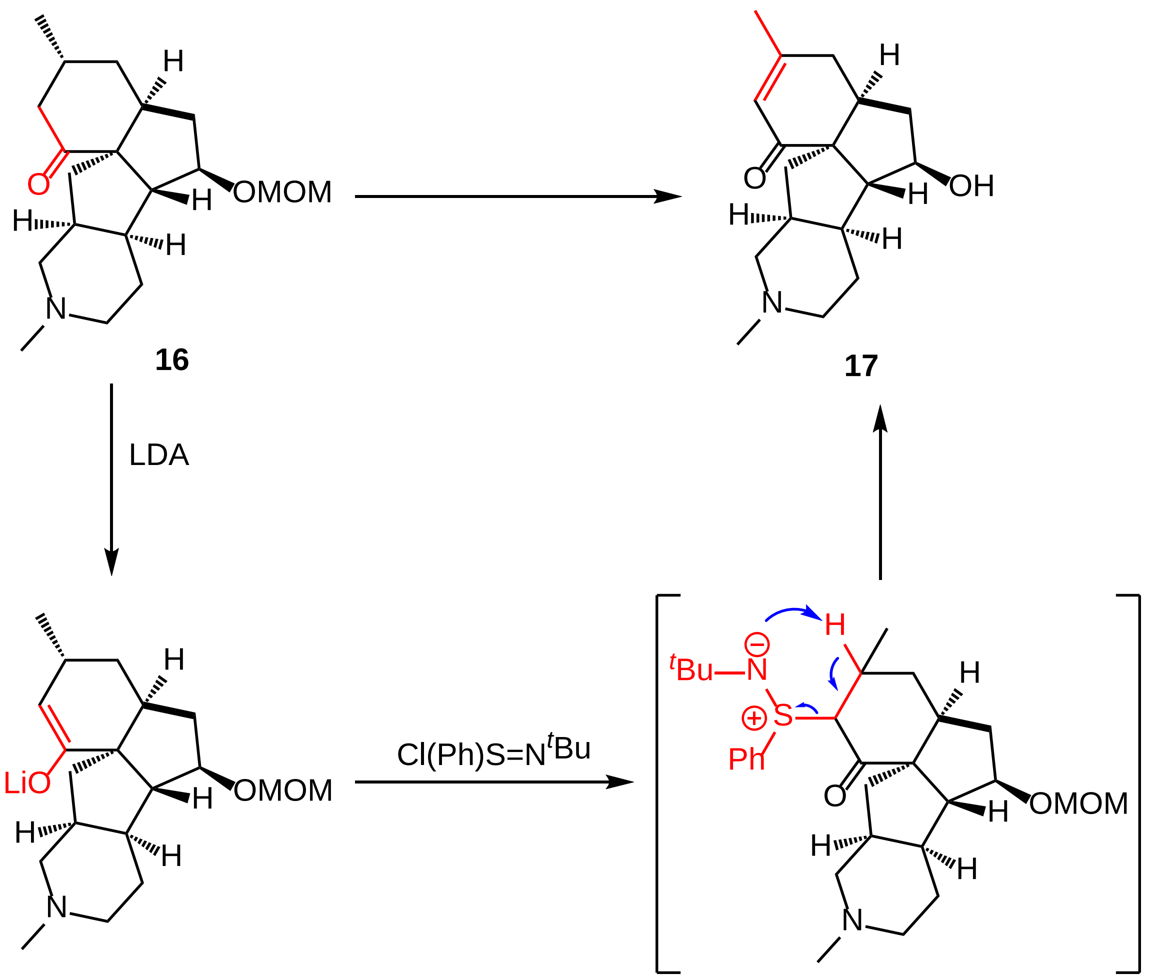




Synthesis of Magellanine

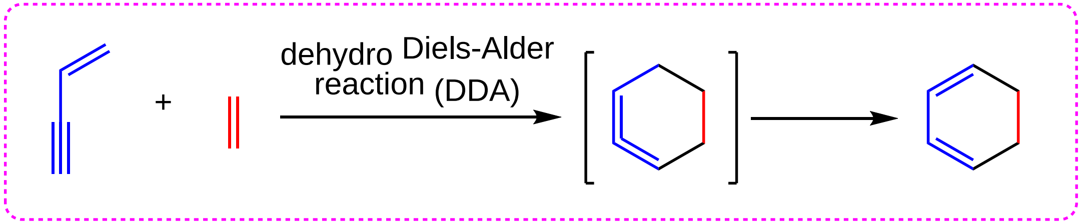


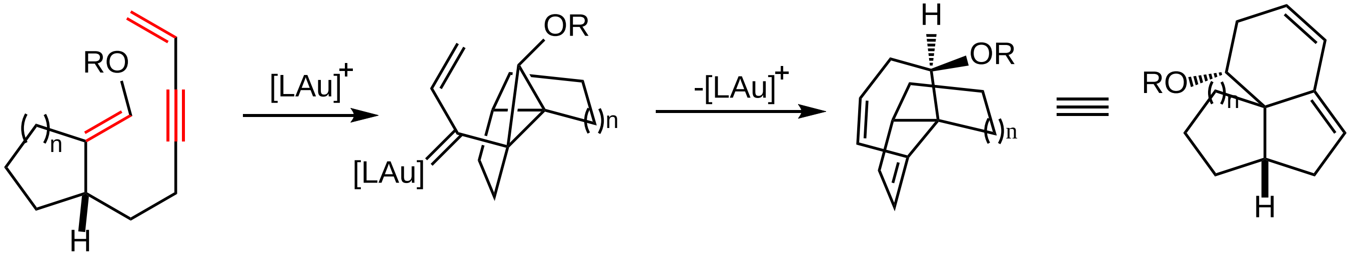
Mukaiyama Method



Mukaiyama, T. et al. *Chem. Lett.* **2000**, 1250.

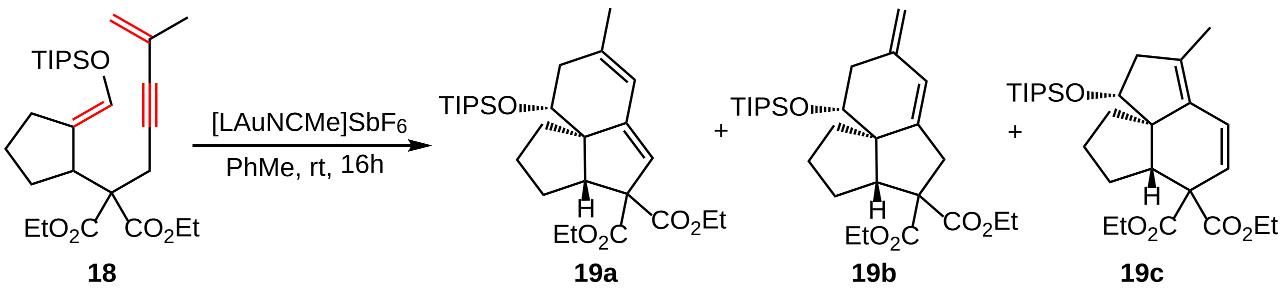
Dehydro Diels-Alder Reaction (DDA)

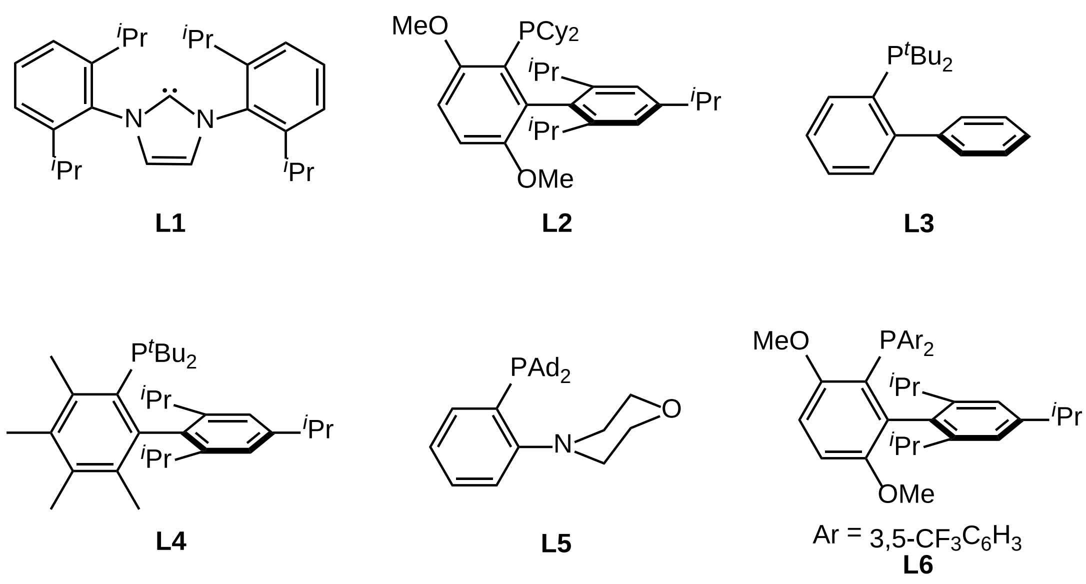




Barriault, L. *et al. Angew. Chem. Int. Ed*. **2017**, *56*, 6280.

Dehydro Diels-Alder Reaction (DDA)



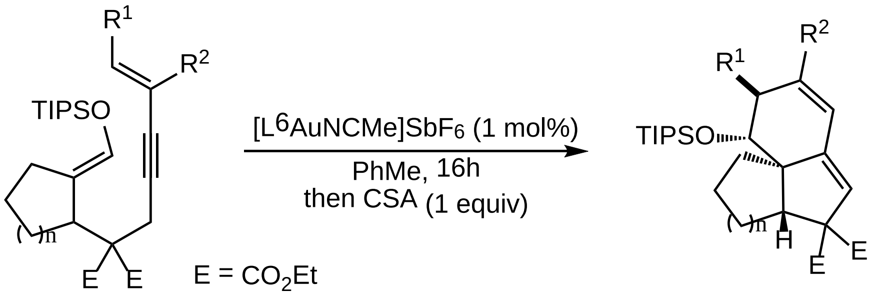


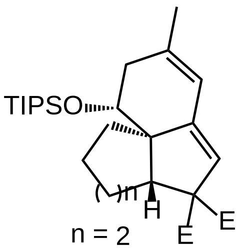
Dehydro Diels-Alder Reaction (DDA)

Entry	Ligand	Loading (mol %)	19a:19b:19c[a]	Yield (%)[a]
1	L1	2.5	6:6:1	98
2	L1	1.0	6:6:1	98
3	L1	0.5	6:6:1	51
4	L1	0.1	6:6:1	18
5[b]	L1	1	13:0:1	98
6[b]	L2	1	12:0:1	98
7[b]	L3	1	9:0:1	98
8[b]	L4	1	5:0:1	98
9[b]	$Ph_3PAuNTf_2$	1	> 20:0:1	68
10[b]	L5	1	> 20:0:1	49
11[b]	L6	1	> 20:0:1	98 (96)[c]

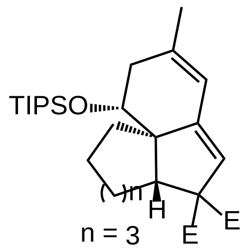
[a] Determined by ^{1}H NMR analysis of the crude reaction mixture using mesitylene as internal standard. [b] One equivalent of CSA was added to the reaction mixture only after all the starting material was consumed. [c] Isolated yield .

Dehydro Diels-Alder Reaction (DDA)

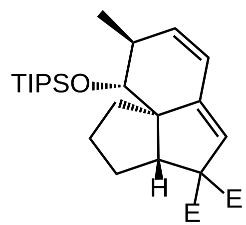




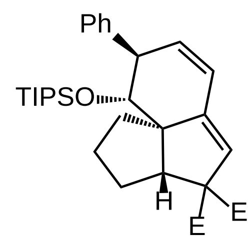
79% yield



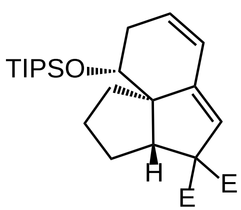
61% yield



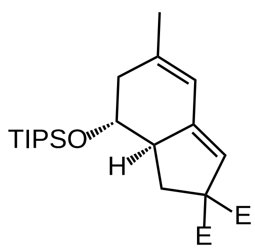
91% yield



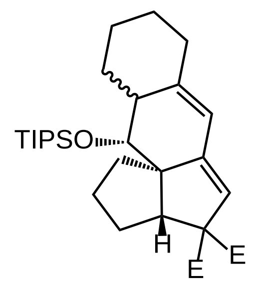
81% yield[b]



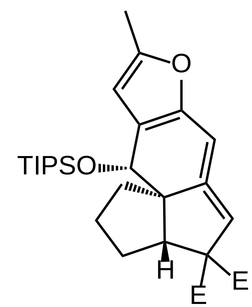
93% yield[c]



93% yield[c]



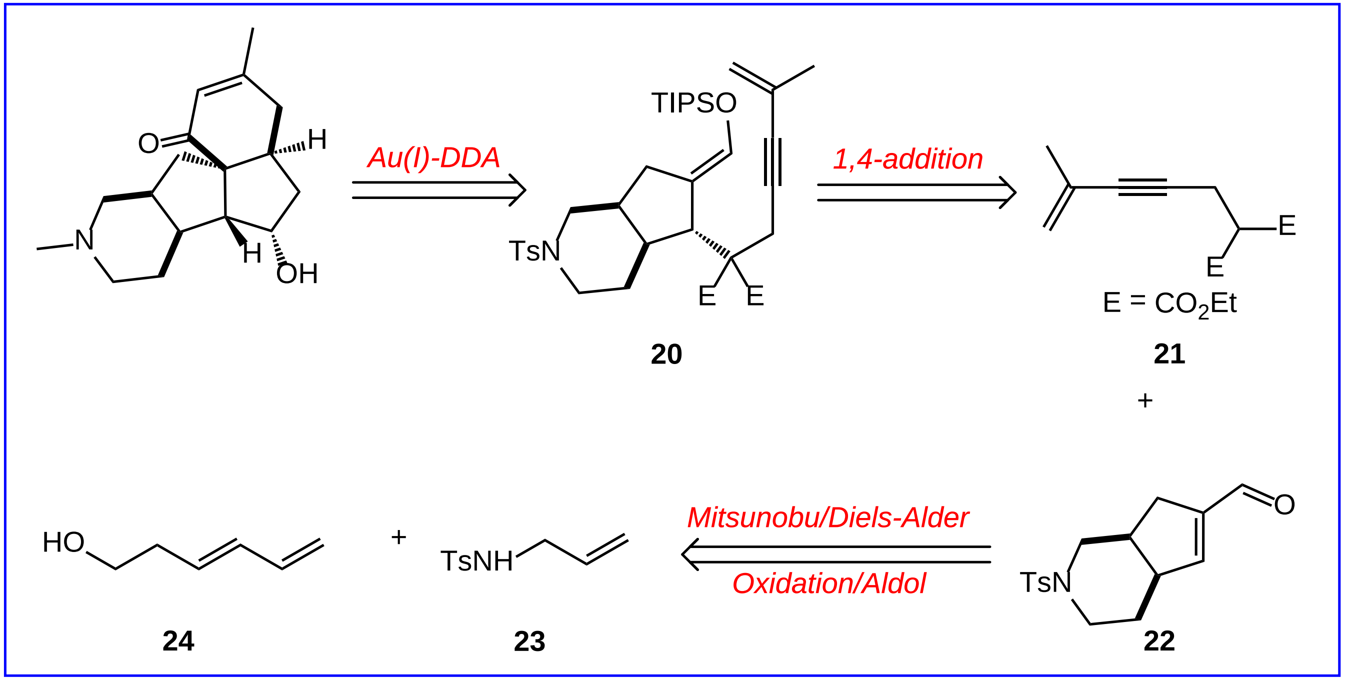
86% yield, d.r. = 1:1[b]



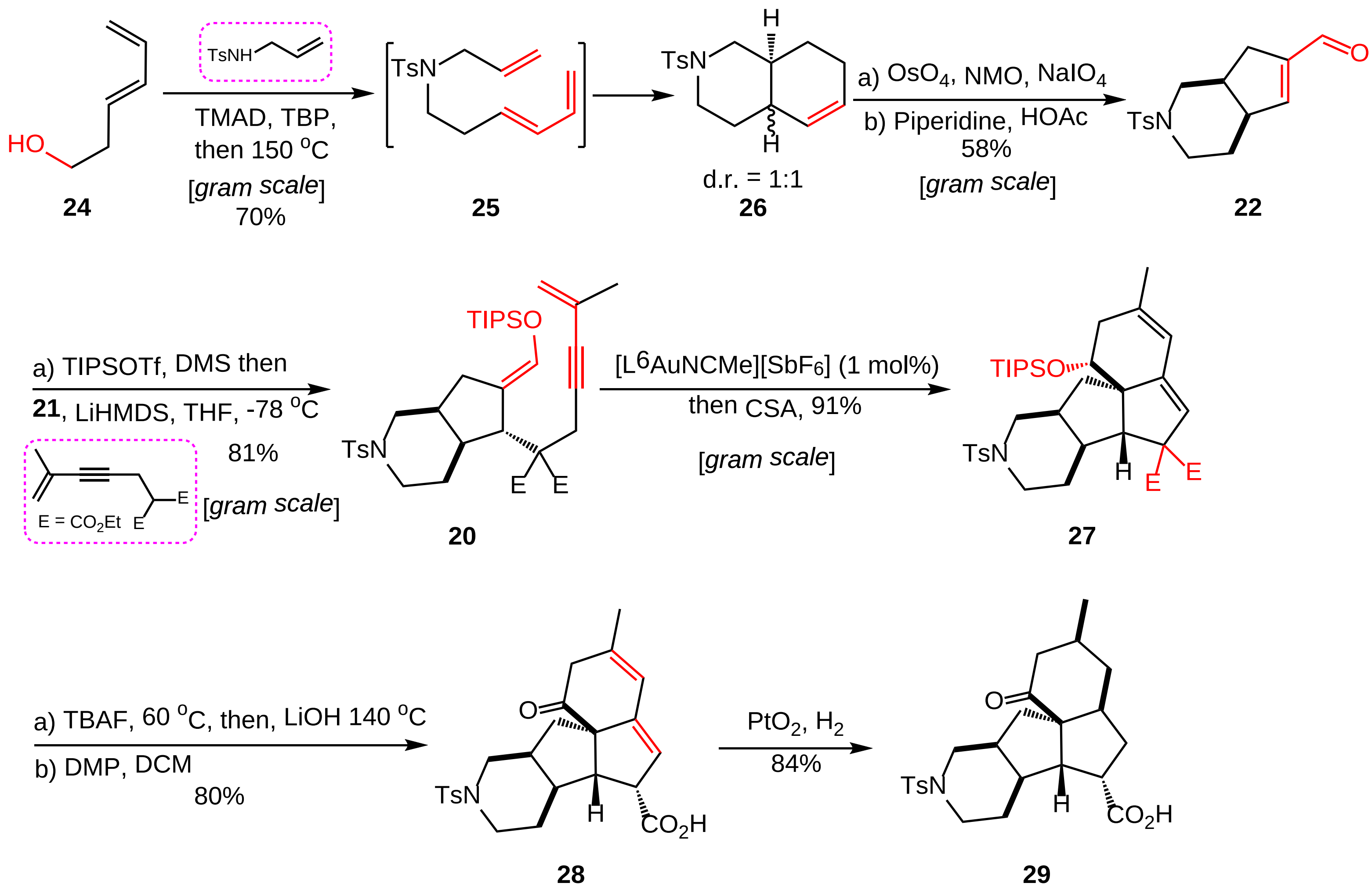
89% yield[b,d]

[a] Isolated yields, ratio 5-exo/6-endo and d.r. > 20:1. **[b]** Reaction run using 2 mol% of catalyst. **[c]** Reaction run using 1 mol% of [L1AuNCMe]SbF_6. **[d]** No addtion of CSA.

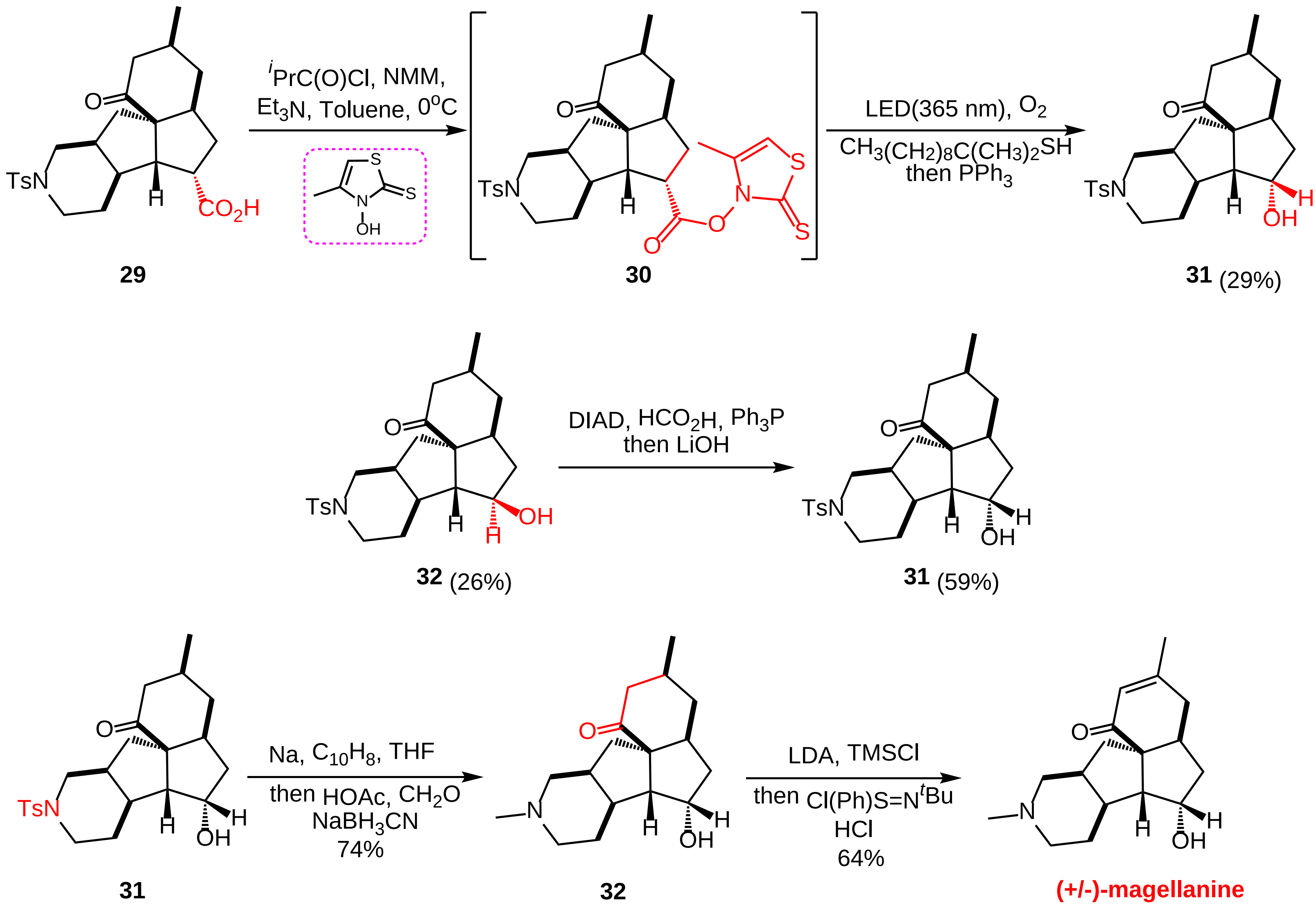
Proposed Retrosynthesis



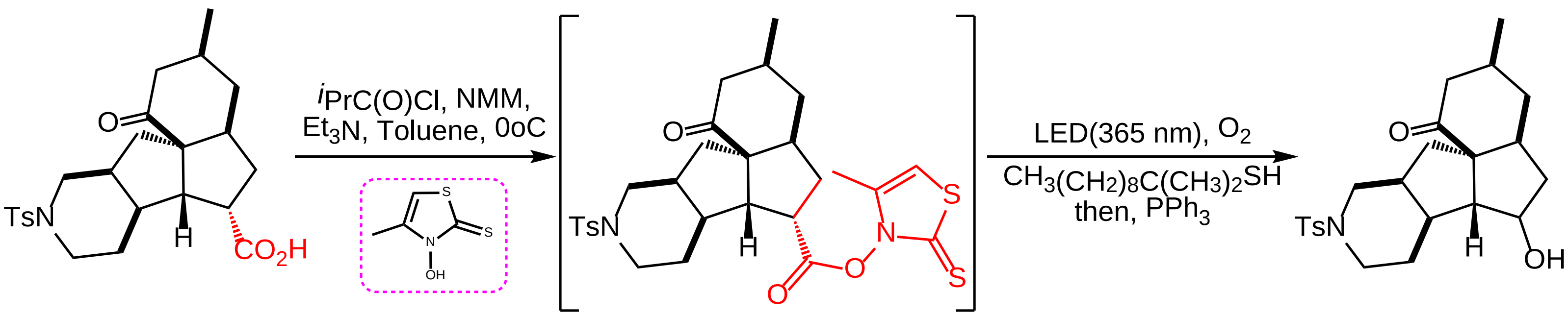
Synthesis of Key Intermediate 29

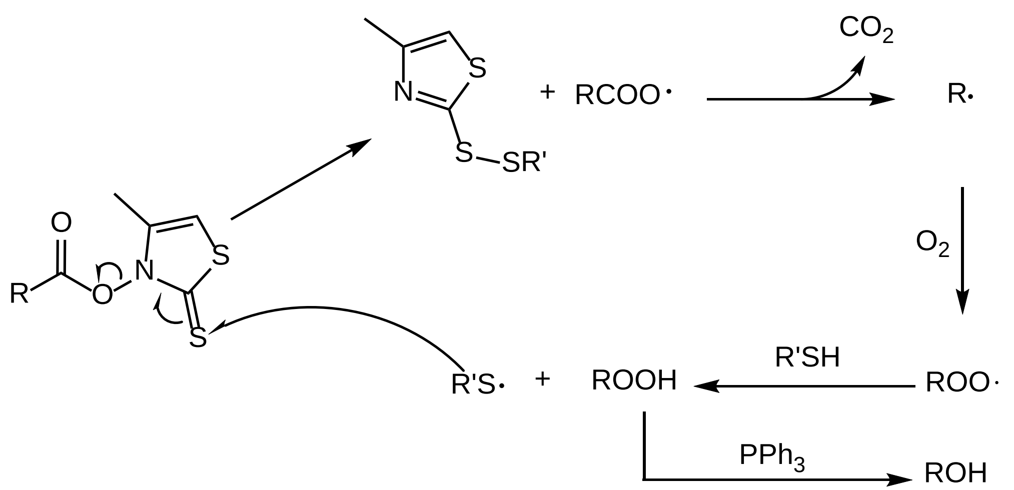


Synthesis of Key Intermediate 33



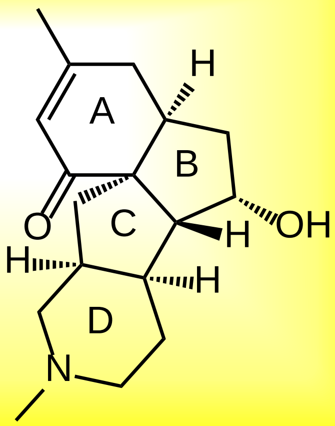
Radical Oxidative Decarboxylation





Zard, S. Z. *et al*. *Tetrahedron* **1998**, *54*, 6751.

Summary



- 27 steps, 1.1% overall yield
- Aldol cyclization
- Dehydration through Burgess reagent

Yang, Y.-R. *et al. Org. Lett*. **2014**, *16*, 5612.

- 11 steps, 2.7% overall yield
- Au-catalyzed cycloaddition
- Radical oxidative decarboxylation

Barriault, L. *et al. Angew. Chem. Int. Ed*. **2017**, *56*, 6280.

The First Paragraph

The development of new transformations for the efficient synthesis of architecturally complex scaffolds via operationally simple and practical protocols is of paramount importance. In this regard, the specific affinity of cationic gold complexes for π-system and their ability to stabilize neighboring cationic charges have stimulated the development of efficient and reliable methods for the construction of C-C bonds.

The First Paragraph

The cycloaddition between an enyne and a olefin known as the dehydro Diels–Alder reaction (DDA) is a expedient process for the synthesis of cyclohexadienes and related carbocycles. While the thermal DDA reaction is well documented, the use of transition metals to catalyze this reaction remains marginal.

The Last Paragraph

In conclusion, we have developed an innovative and operationally facile methodology for the formation of carbocycles via a gold(I)-catalyzed cycloaddition. This reaction gives access to various complex angular fused-ring systems in high diastereoselectivities. The practicality of this Au-catalyzed transformation was validated in the total synthesis of (+/-)-magellanine 7 which was accomplished in only 11 steps from alcohol 18, one of the shortest total syntheses known to date. Further applications of this transformation in natural product synthesis are currently ongoing and will be reported in due course.