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

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Date: 2017/06/19

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- 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

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

Synthesis of Key Intermediate 7

1. A SPh

a) NaH, DMF, 2, 80%
b) mCPBA, DCM, then CaCO₃, Toluene, reflux 81%

2. Ts

3. A Ts

TiCl₄, Allyl-TMS DCM, -78 °C to rt 85%

4. Ts

OsO₄, NMO 86%

5. Ts

6. OH

a) TBSCI, Imidazole
b) AcOH, H₂O/THF 69%

7. Ts

a) MsCl, DMAP
b) tBuOK, THF 67%
Synthesis of Key Intermediate 8

7

a) NaBH₄, MeOH
b) TBSOTf, Et₃N
c) TBAF, THF

69%

8

a) PCC, Celite
b) HF·Py, THF

77%

9
Synthesis of Key Intermediate 13

\[ 8 \xrightarrow{a) \text{BH}_3\cdot\text{Me}_2\text{S}} 10 \xrightarrow{t\text{BuOK, Toluene}} 11 \]

\[ 10 \xrightarrow{\text{b) PCC, 4 Å MS}} 65\% \]

\[ 10 \xrightarrow{\text{d.r.} = 2:1} \]

\[ 12 \xrightarrow{\text{Burgess reagent}} 80\% \xrightarrow{\text{H}_2, \text{Pd/C}} 88\% \]

\[ 12 \xrightarrow{\text{13}} \]

A synthesis pathway is shown with intermediates labeled 8, 10, 11, 12, and 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

13 → a) NaBH₄
     b) MOMCl

14 → a) TBAF
     b) PCC, 4 Å MS

15 → Na-Naph then HCHO
     NaBH₃CN, 62%

16 → a) LDA, Cl(Ph)S=N°Bu
     b) 10% HCl (aq)

17 → (-)-magellanine

13 → 14 → 15 → 16 → (-)-magellanine
Mukaiyama Method

Dehydro Diels-Alder Reaction (DDA)

Dehydro Diels-Alder Reaction (DDA)

18 \[\text{[LAuNCMe]}\text{SbF}_6\]
PhMe, rt, 16h

19a \[\text{TIPS}O\]
19b \[\text{TIPS}O\]
19c \[\text{TIPS}O\]

L1
L2
L3
L4
L5
L6

Ar = 3,5-CF₃C₆H₃
## Dehydro Diels-Alder Reaction (DDA)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Loading (mol %)</th>
<th>19a:19b:19c&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
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<td>L1</td>
<td>2.5</td>
<td>6:6:1</td>
<td>98</td>
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<td>6:6:1</td>
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<td>6:6:1</td>
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<tr>
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<td>0.1</td>
<td>6:6:1</td>
<td>18</td>
</tr>
<tr>
<td>5&lt;sup&gt;b&lt;/sup&gt;</td>
<td>L1</td>
<td>1</td>
<td>13:0:1</td>
<td>98</td>
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<td>6&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>12:0:1</td>
<td>98</td>
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<td>7&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>1</td>
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<tr>
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<td>Ph&lt;sub&gt;3&lt;/sub&gt;PAuNTf&lt;sub&gt;2&lt;/sub&gt;</td>
<td>1</td>
<td>&gt; 20:0:1</td>
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<tr>
<td>10&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>1</td>
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<td>49</td>
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<tr>
<td>11&lt;sup&gt;b&lt;/sup&gt;</td>
<td>L6</td>
<td>1</td>
<td>&gt; 20:0:1</td>
<td>98 (96)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture using mesitylene as internal standard.  
<sup>b</sup> One equivalent of CSA was added to the reaction mixture only after all the starting material was consumed.  
<sup>c</sup> Isolated yield.
Dehydro Diels-Alder Reaction (DDA)

\[
\text{TIPSO}^+ R^1 R^2 \xrightarrow{[L^6\text{AuNCMe}]\text{SbF}_6 (1 \text{ mol}\%)} \text{PhMe, 16h then CSA (1 equiv)}} \text{TIPSO}^+ R^1 R^2
\]

\[\text{E} = \text{CO}_2\text{Et}\]

79% yield 61% yield 91% yield 81% yield

93% yield 93% yield 86% yield, d.r. = 1:1 89% yield

[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]SbF6. [d] No addition of CSA.
Proposed Retrosynthesis

\[ \text{N} \quad \text{OH} \quad \text{H} \quad \text{H} \quad \text{O} \quad 
\]

[190x478]Proposed Retrosynthesis

\[ \text{TsN} \quad \text{TIPSO} \quad \text{E E} \quad \text{Au(I)-DDA} \quad \text{1,4-addition} \quad \text{E} = \text{CO}_2\text{Et} \]

\[ \text{E} = \text{CO}_2\text{Et} \]

\[ \text{Oxidation/Aldol} \quad \text{Mitsunobu/Diels-Alder} \]

\[ \text{HO} \quad \text{24} \quad \text{+} \quad \text{TsNH} \quad \text{23} \quad \text{\textit{Mitsunobu/Diels-Alder}} \quad \text{\textit{Oxidation/Aldol}} \]

\[ \text{20} \quad \text{21} \quad + \quad \]

\[ \text{22} \quad \text{TsN} \]

\[ \text{24} \quad \text{23} \quad \text{22} \]
Synthesis of Key Intermediate 29

24

TsNH

HO

TMAD, TBP,
then 150 °C
70%

[gram scale]

25

d.r. = 1:1

22

a) OsO₄, NMO, NaIO₄

b) Piperidine, HOAc

[gram scale]

26

E = CO₂Et

20

[L₆AuNCMe][SbF₆] (1 mol%)

then CSA, 91%

[gram scale]

27

28

a) TBAF, 60 °C, then, LiOH 140 °C
b) DMP, DCM
80%

80%

84%

29

PtO₂, H₂
Synthesis of Key Intermediate 33

29

$^{1}$PrC(O)Cl, NMM, Et$_3$N, Toluene, 0°C

30

LED(365 nm), O$_2$

31 (29%)

32 (26%)

DIAD, HCO$_2$H, Ph$_3$P then LiOH

31 (59%)

31

Na, C$_{10}$H$_8$, THF then HOAc, CH$_2$O

74%

32

LDA, TMSCl then Cl(Ph)S=N^tBu HCl

(+/-)-magellanine
Radical Oxidative Decarboxylation

Summary

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


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

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 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.
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.