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Total synthesis of conolidine and apparicine

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ABSTRACT

A total synthesis of indole alkaloids, (±)-conolidine and (±)-apparicine, was accomplished via a gold(I)-catalyzed 6-*exo*-*dig* cyclization to construct a piperidine ring bearing an exocyclic (*E*)-ethylidene appendage.

Introduction

During our chemical and pharmacological studies of analgesic indole alkaloids derived from plant resources,[1] we have found that mitragynine derivatives, such as MGM-9[2] and MGM-16,[3] exhibited potent antinociceptive activity through the opioid receptors (Fig. 1). Bohn et al. have disclosed the unique analgesic activity[4] of conolidine (**1**),[5] a C5-nor stemmadenine-type indole alkaloid isolated from *Tabernaemontana* species. Although they revealed that **1** was a non-opioid analgesic, they were unable to elucidate the mechanism of action. These findings have motivated us to develop an efficient method for the synthesis of C5-nor stemmadenine-type alkaloids and their derivatives, and to elucidate the exact mechanism of action of **1**. In this Letter, we report the total synthesis of

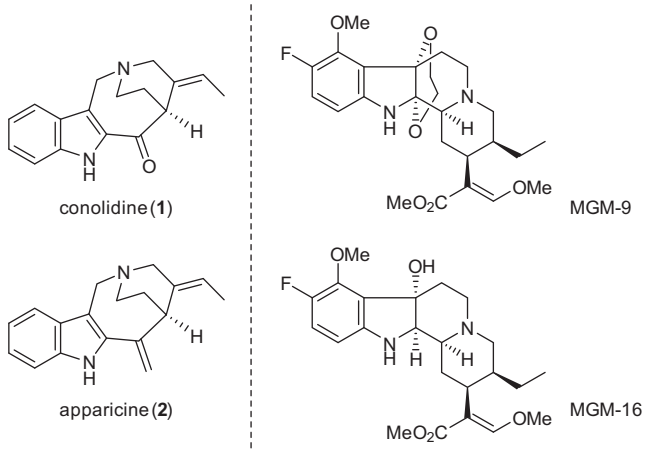
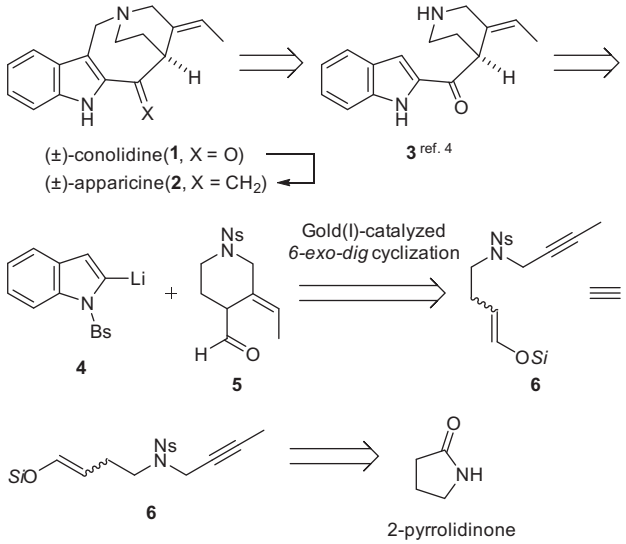


Figure 1. C5-nor stemmadenine-type indole alkaloids and mitragynine derivatives.



Scheme 1. Retrosynthetic analysis of (±)-**1** and (±)-**2**.

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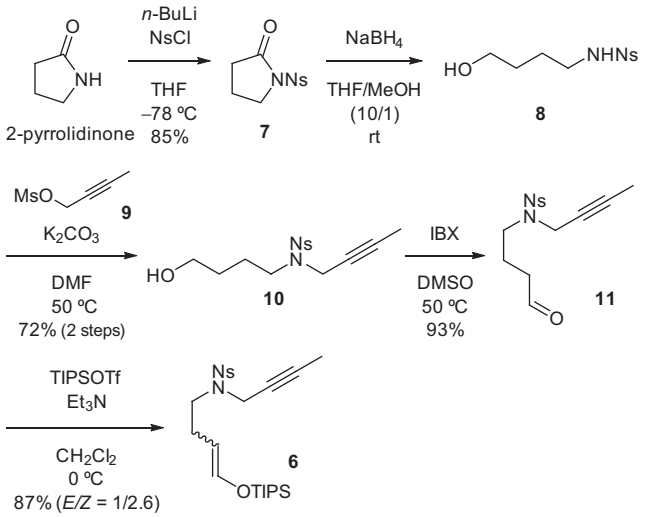


Scheme 2. Synthesis of silyl enol ether **6**.

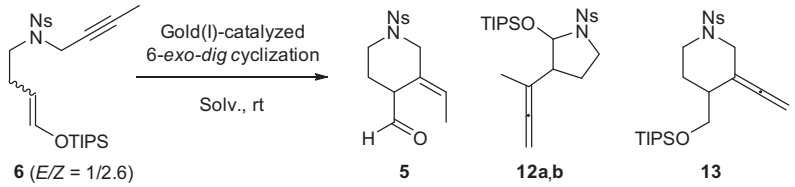
(±)-**1**, which features a gold(I)-catalyzed 6-*exo-dig* cyclization reaction for the construction of a piperidine ring bearing an exocyclic (*E*)-ethylidene appendage. We also describe the transformation of **1** into (±)-apparicine (**2**).[6]

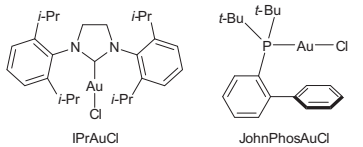
Results and discussion

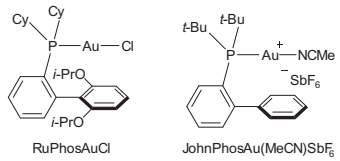
Our retrosynthetic analysis of (±)-**1** and (±)-**2** is shown in Scheme 1. Key compound **3**, a known Micalizio's intermediate[4] for the synthesis of **1**, would be obtained by coupling indole unit **4** with piperidine unit **5**. We had anticipated that the gold(I)-catalyzed cyclization reaction of alkynyl silyl enol ethers **6**[7] would be feasible for the construction of the (*E*)-ethylidene moiety embedded in **5**.[8] To the best of our knowledge, the gold(I)-catalyzed 6-*exo-dig* cyclization of silyl enol ethers having an *internal* alkynyl group has not been reported so far.[9,10] In this context, we have been interested in the potential application of this cyclization to the synthesis of the (*E*)-ethylidene appendage. Requisite substrate **6** would be prepared from commercially available 2-pyrrolidinone in a few steps.

Our synthesis commenced with the preparation of sulfonamide **7** (Scheme 2). Treatment of 2-pyrrolidinone with 2-nitrobenzenesulfonyl chloride[11] and *n*-butyllithium gave nitrobenzenesulfonamide **7** in 85% yield,[12] which was further converted into alcohol **8** by reduction with sodium borohydride in a mixture of THF and methanol (10/1). Successive treatment of alcohol **8** with alkylating reagent **9**[13] afforded internal alkyne **10** in 72% yield from **7**. IBX oxidation of **10** produced aldehyde **11** in 93% yield. Treatment of aldehyde **11** with TIPSOTf in the presence of Et_3N gave alkynyl silyl enol ether **6** as a mixture of geometrical isomers (*E*/*Z* = 1/2.6) in 87% yield.

Table 1
Results of gold(I)-catalyzed 6-*exo-dig* cyclization







Entry	Conditions			Products (%)			
	Au cat. (mol %)	Ag cat. (mol %)	Solv. (0.2 M)	**5**	**12a,b**	**13**	**11**
1	Ph_3PAuCl (5)	$AgBF_4$ (5)	CH_2Cl_2/H_2O (10:1)	20	–	–	42
2	IPrAuCl (5)	$AgBF_4$ (5)	CH_2Cl_2/H_2O (10:1)	52	34	–	–
3	RuPhosAuCl (5)	$AgBF_4$ (5)	CH_2Cl_2[a]	57	14	–	–
4	JohnPhosAuCl (5)	$AgBF_4$ (5)	CH_2Cl_2/H_2O (10:1)	61	34	–	–
5	JohnPhosAuCl (5)	$AgBF_4$ (5)	CH_3CN/H_2O (10:1)	4	5	–	34
6	JohnPhosAu(MeCN)SbF_6 (5)	–	CH_2Cl_2[a]	61	4	7	–
7	JohnPhosAu(MeCN)SbF_6 (5)	–	CH_2Cl_2[b]	17	19	49	–
8	JohnPhosAu(MeCN)SbF_6 (2)	–	CH_2Cl_2[c]	67	29	–	–

[a] 1.5 equiv water was added as proton source.
[b] No water was added.
[c] 1.2 equiv water was added and the reaction was conducted at 0 °C.