

Enantioselective Total Synthesis of (–)-Nardoaristolone B via a Gold(I)-Catalyzed Oxidative Cyclization

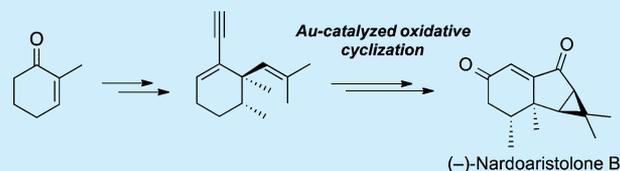
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S Supporting Information

ABSTRACT: The first enantioselective total synthesis of (–)-nardoaristolone B is accomplished by the implementation of an enantio- and diastereoselective copper(I)-catalyzed conjugate addition/enolate trapping sequence and a gold(I)-catalyzed oxidative cyclization (intermolecular oxidant), employed for the first time in total synthesis.



Nardoaristolone B (**1**) was isolated in 2013 from *Nardostachys chinensis* Batal, a plant of the genus *Nardostachys* endemic of the Himalayan mountains.¹ The synthesis of the racemic mixture has been recently reported.² Closely related sesquiterpene (–)-aristolone (**2**) was isolated much earlier, in 1955, from the roots of *Aristochia debilis*³ and has been synthesized in racemic form by various research groups.⁴ Nardoaristolone B (**1**) exhibits protective activity on the injury of neonatal rat cardiomyocytes.

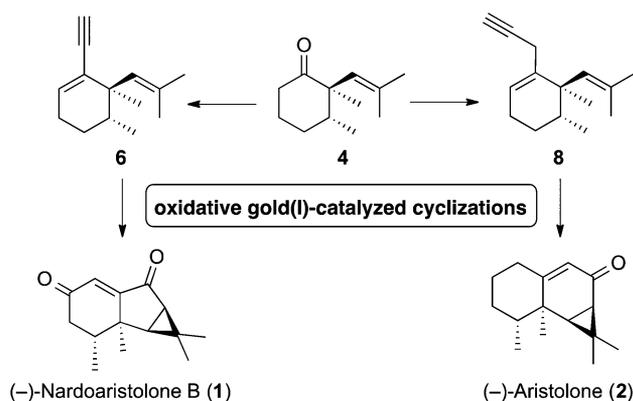
We were intrigued by the possibility of accessing **1** and other members of the aristolone family by combining the highly efficient Cu(I)-catalyzed asymmetric conjugate addition/ α -alkylation cascade of α,β -unsaturated cyclic ketones developed by the groups of Alexakis and Cramer^{5–8} with the Au(I)-catalyzed oxidative cyclization of enynes recently discovered by Liu (Scheme 1).⁹ This last method, based on the gold(I)-catalyzed oxidative functionalization of alkynes pioneered by Toste¹⁰ and Zhang^{11,12} could offer direct access to this family of compounds from cyclohexanone **4** as the common inter-

mediate. Here we report the first enantioselective total synthesis of nardoaristolone B (**1**) and additional studies on the scope of the Au(I)-catalyzed oxidative cyclization of 1,6-enynes.

Although the conjugate methylation of 2-methyl-2-cyclohexenone proceeded satisfactorily at $-35\text{ }^{\circ}\text{C}$,^{5b} the subsequent α -alkylation proved to be challenging using methyl iodide. However, employing methyl iodide under high concentration and using 1:1 mixture of HMPA/THF before addition of MeI led to trisubstituted cyclohexanone **3** in 45–55% yield (Scheme 2). Employing the optimal chiral phosphoramidite ligand as reported by Alexakis,^{5a} the reaction proceeded with 91–92% enantiomeric excess and 3:1 dr. Careful purification by standard column chromatography allowed us to isolate **3** in essentially pure form (>30:1 dr). The isomerization of *exo*-olefin **3** into the corresponding trisubstituted *endo*-alkene **4** was not trivial, and a range of conditions was screened.¹³ Fortunately, the use of $\text{RhCl}_3 \cdot x\text{H}_2\text{O}$ (5 mol %) in ethanol at $75\text{ }^{\circ}\text{C}$ led to the desired *endo*-olefin **4** in 74% yield. The conversion of cyclohexanone **4** into enol triflate **5** was performed under standard conditions (82% yield). Sonogashira cross-coupling of **5** with trimethylsilyl acetylene employing $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (2 mol %) and CuI (5 mol %) in a DMF/ Et_3N mixture, followed by methanolysis of the TMS group led to 1,5-enyne **6** in satisfactory yield (74% over two steps) (Scheme 2).

Pleasingly, 1,5-enyne underwent the desired gold(I)-catalyzed oxidative cyclization using 8-methylquinoline *N*-oxide (PNOS) and IPrAuNTf_2 as catalyst in 1,2-dichloroethane ($(\text{CH}_2\text{Cl})_2$) at $80\text{ }^{\circ}\text{C}$,⁹ albeit with low isolated yield (20%, along with 25% of the simply cycloisomerized enyne **9**). Careful scrutiny of conditions revealed that the choice of the oxidant was crucial in order to favor the desired oxidative cyclization over the cycloisomerization. Thus, 3,5-dichloropyridine *N*-oxide (PNO3) proved to be superior to all the other *N*-oxides

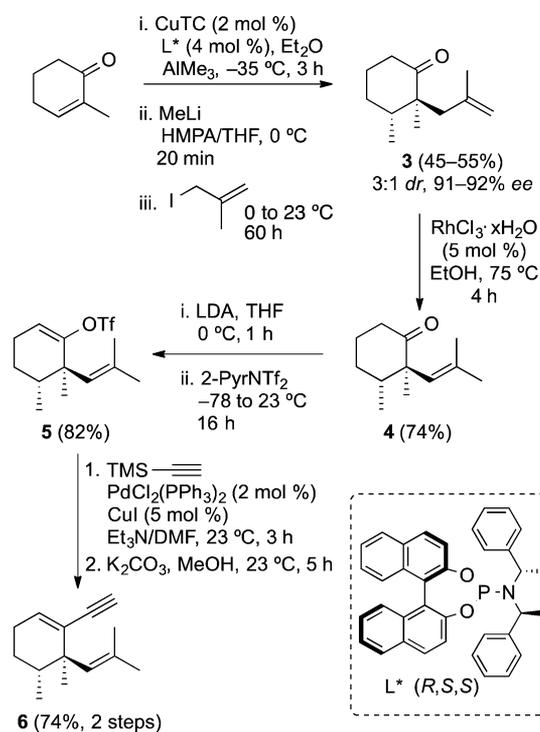
Scheme 1. Synthetic Plan toward Enantioenriched (–)-Nardoaristolone B and (–)-Aristolone



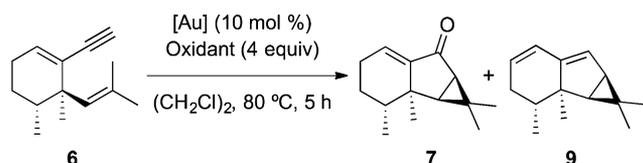
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Scheme 2. Synthesis of 1,5-Enyne 6

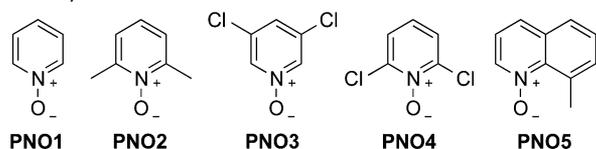


screened (Table 1, entries 3 and 11).^{13,14} Interestingly, using isomeric 2,6-dichloropyridine *N*-oxide (**PNO4**) led exclusively to diene **9** (Table 1, entry 4), whereas a complex mixture was

Table 1. Screening of Conditions for the Gold(I)-Catalyzed Oxidative Cyclization of **6**

entry	[Au]	oxidant	yield of 7/9 ^{a,b} (%)
1	IPrAuNTf ₂	PNO1	31/5
2	IPrAuNTf ₂	PNO2	20/36
3	IPrAuNTf ₂	PNO3	74/15
4	IPrAuNTf ₂	PNO4	0/55
5	IPrAuNTf ₂	PNO5	20/25
6	IPrAuNTf ₂	none	complex mixture
7	(JohnPhos)AuCl/AgNTf ₂	PNO3	43/15
8 ^c	<i>t</i> BuXPhosNTf ₂	PNO3	18/15
9	[(ArO) ₃ P]AuCl/AgNTf ₂	PNO3	55/2
10	IMesAuNTf ₂	PNO3	55/2
11	IPrAuNTf ₂ ^d	PNO3	74 (74) ^e /15

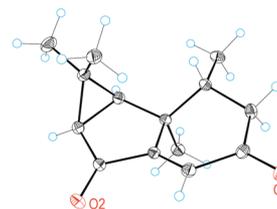
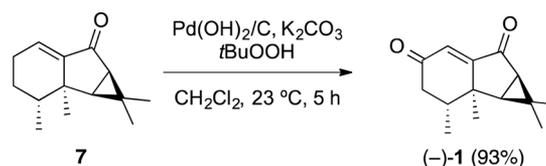
^aYields determined by ¹H NMR analysis of the crude mixture using diphenylmethane as internal standard. ^bFull conversion of starting material was observed unless otherwise stated. ^c13% unreacted starting material were also visible. ^d5 mol % of catalyst; Ar = 2,4-(*t*Bu)₂C₆H₃. ^eIsolated yield.



obtained under standard cycloisomerization conditions in the absence of any oxidant (Table 1, entry 6). The competitive formation of cycloisomerization product **9**, along with **7**, in these reactions suggests that both products result from a common cyclopropyl gold(I) intermediate.¹⁵ However, the alternative mechanism involving an earlier oxidation of the terminal alkyne to form an α -oxo gold(I) carbene intermediate that leads to **7** by intramolecular cyclopropanation, in parallel with a simple gold(I)-catalyzed cycloisomerization, cannot be excluded.⁹

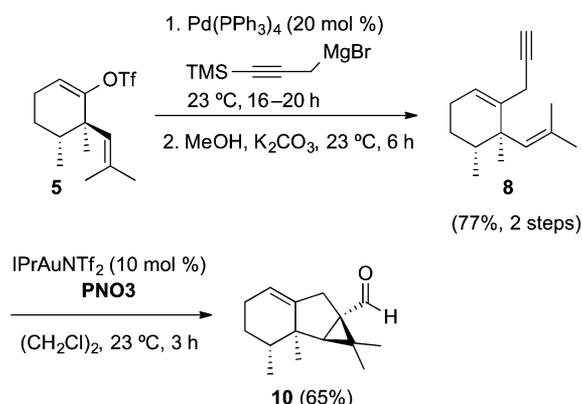
With the optimal conditions in hand, we performed an oxidative cyclization in the presence of only 5 mol % of IPrAuNTf₂ and 3,5-dichloropyridine *N*-oxide. The desired product **7** was isolated in good yield (74%) along with 15% of cycloisomerized product **9**. The last step consisted in the allylic oxidation, which was accomplished in high yield (93%) using a Pd-catalyzed radical oxidation in the presence of Pearlman's catalyst (Pd(OH)₂/C) and *t*-BuOOH¹⁶ (Scheme 3). The

Scheme 3. Last Step in the Synthesis of (–)-Nardoaristolone B



spectroscopic data are in excellent agreement with the ones reported for the isolated compound and further support for the structure was obtained by X-ray diffraction analysis.¹⁷

Having accomplished the first total synthesis of nardoaristolone B, we were very keen on applying our strategy to a higher enyne in order to gain access to the core of the aristolone family of natural products. Our synthetic effort first involved the conversion of key intermediate enol triflate **5** into the corresponding 1,6-enyne **8**. Although the direct Kumada cross-coupling of **5** with propargylmagnesium bromide in the presence of various Pd- or Ni-based catalysts did not take place, we uncovered an unprecedented Kumada cross-coupling of TMS-protected propargylmagnesium bromide with enol triflates. This coupling proceeded smoothly on our model system (4-*tert*-butylcyclohexanone-derived enol triflate) employing only 2 mol % of Pd(PPh₃)₄ and 2 equiv of freshly prepared Grignard reagent.¹³ However, the cross-coupling was significantly slower on **5** and 20 mol % of Pd complex as well as 4 equiv of Grignard reagent were necessary to obtain full conversion at 23 °C. Under these conditions, the cross-coupling of **5** proceeded smoothly to afford **8** in 77% yield after methanolysis of the TMS group (Scheme 4). This substrate was then treated under a variety of conditions in order to prepare aristolone; however all attempts resulted in the formation of 6a-formyl-6-deoxonardoaristolone **10** in 65% yield when employing IPrAuNTf₂ as catalyst.¹⁵ Although (–)-aristolone (**2**) was

Scheme 4. Synthesis and Fate of 1,6-Enyne **8**

not prepared via our original strategy, the preparation of enantioenriched cyclohexanone **4** constitutes a formal synthesis of (–)-**2**, since racemic **2** has already been prepared from (±)-**4** in five steps.^{4b}

Under all the conditions examined, the gold(I)-catalyzed reaction of 1,6-enyne **8** proceeded exclusively by the 6-*exo-dig* mode. It is interesting that this result is in contrast to that observed in the reaction 1-ethynyl-2-allylbenzene, which yielded a 6-membered ring ketone by a 6-*endo-dig* oxidative cyclization.⁹ This different behavior can be ascribed to the different substitution pattern of the alkene, which usually controls the outcome in gold(I)-catalyzed cycloisomerizations of 1,6-enynes.¹⁸

In conclusion, we have developed the first enantioselective synthesis of (–)-nardoaristolone B (**1**) in seven steps and 14–17% overall yield. Our expedient strategy, by implementation of an enantio- and diastereoselective conjugate addition/enolate alkylation and the first example of a gold(I)-catalyzed oxidative cyclization of enynes in total synthesis, is perfectly suited for the rapid preparation of analogues of this natural product.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for compounds **1** and **3–10** as well as the X-ray crystal structure of **1**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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