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

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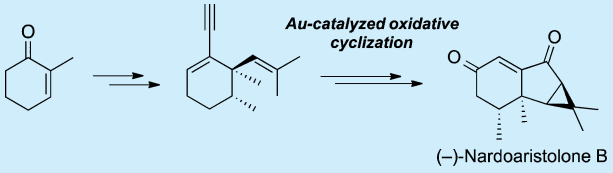
Supporting Information

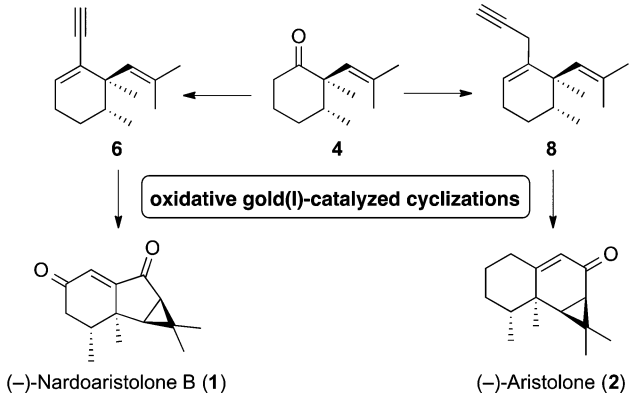
ABSTRACT: The first enantioselective total synthesis of (−)-nardoaristolone B is accomplished by the implementation of an enantio- and diastereoselective copper(I)-catalyzed conjugate addition/enolate trapping sequence and a gold(I)-catalyzed oxidative cyclization (intermolecular oxidant), employed for 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 Toste[10] and Zhang[11,12] could offer direct access to this family of compounds from cyclohexanone **4** as the common intermediate. 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.

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



Although the conjugate methylation of 2-methyl-2-cyclohexenone proceeded satisfactorily at −35 °C,[5b] the subsequent α-alkylation proved to be challenging using methallyl bromide. However, employing methallyl iodide under high concentration and using 1:1 mixture of HMPA/THF before addition of MeLi 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 $RhCl_3{\cdot}xH_2O$ (5 mol %) in ethanol at 75 °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 $Pd(PPh_3)_2Cl_2$ (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 (**PNO5**) and $IPrAuNTf_2$ as catalyst in 1,2-dichloroethane ($(CH_2Cl)_2$) at 80 °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

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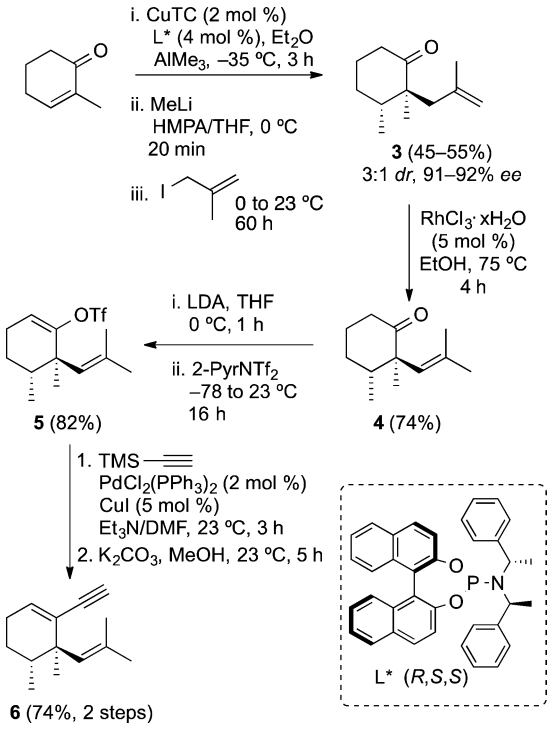
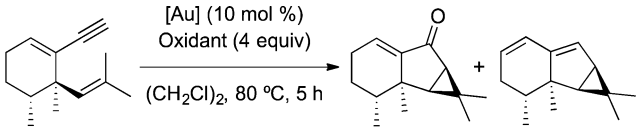
Scheme 2. Synthesis of 1,5-Enyne 6



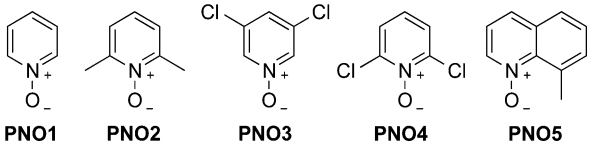
screened (Table 1, entries 3 and 11).[13,14] Interestingly, using isomeric 2,6-dichloropyridine *N*-oxide (**PNO4**) led exclusively to diene **9** (Table 1, entry 4), whereas a complex mixture was obtained under standard cycloisomerization conditions in the absence of any oxidant (Table 1, entry 6). 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]

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



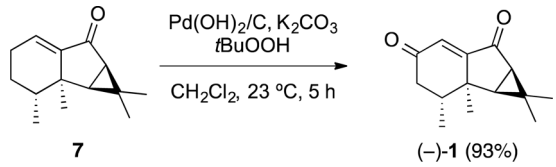
entry	[Au]	oxidant	yield of 7/9[a,b] (%)
1	IPrAuNTf$_2$	**PNO1**	31/5
2	IPrAuNTf$_2$	**PNO2**	20/36
3	IPrAuNTf$_2$	**PNO3**	74/15
4	IPrAuNTf$_2$	**PNO4**	0/55
5	IPrAuNTf$_2$	**PNO5**	20/25
6	IPrAuNTf$_2$	none	complex mixture
7	(JohnPhos)AuCl/AgNTf$_2$	**PNO3**	43/15
8[c]	*t*BuXPhosNTf$_2$	**PNO3**	18/15
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

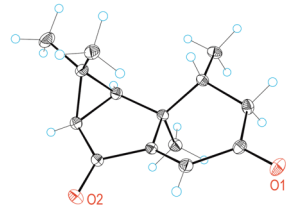
[a]Yields determined by ^{1}H NMR analysis of the crude mixture using diphenylmethane as internal standard. [b]Full conversion of starting material was observed unless otherwise stated. [c]13% unreacted starting material were also visible. [d]5 mol % of catalyst; Ar = 2,4-(*t*Bu)$_2$C$_6$H$_3$. [e]Isolated yield.



With the optimal conditions in hand, we performed an oxidative cyclization in the presence of only 5 mol % of IPrAuNTf$_2$ 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*-BuOOH[16] (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(PPh$_3$)$_4$ 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 IPrAuNTf$_2$ as catalyst.[15] Although (−)-aristolone (**2**) was

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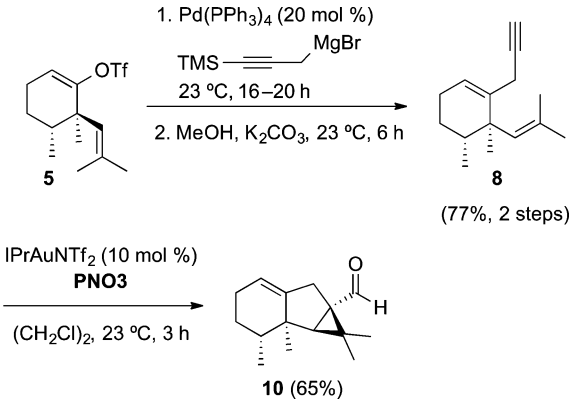
Scheme 4. Synthesis and Fate of 1,6-Enyne 8



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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Author Contributions

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Notes

The authors declare no competing financial interest.

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(13) See the Supporting Information for a comprehensive survey of conditions.

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(17) CCDC 1037494 (**1**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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