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Au(I)-Catalyzed Ring Expanding Cycloisomerizations: Total Synthesis of Ventricosene

Steven G. Sethofer, Steven T. Staben, Olivia Y. Hung, and F. Dean Toste*

Department of Chemistry, University of California, Berkeley, Berkeley, California 94720-1460

fdtoste@berkeley.edu

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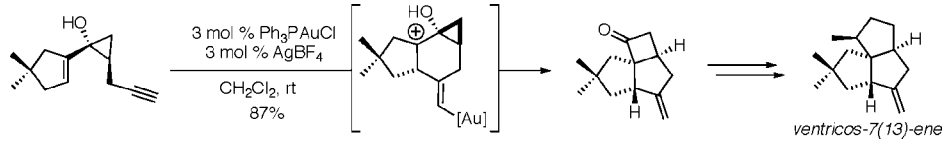
ABSTRACT



The gold(I)-catalyzed cycloisomerization of enynes containing an embedded cyclopropane unit leads selectively to the formation of ring systems containing the cyclopropylmethyl cation. A subsequent Wagner−Merwein shift provides diastereomerically pure fused cyclobutanes. The utility of this methodology for the rapid assembly of polycyclic ring systems is illustrated by the total synthesis of the angular triquinane ventricosene.

Transition-metal-catalyzed cycloisomerization reactions offer an efficient means of entry to highly functionalized ring systems from acyclic starting materials.[1] Cycloisomerizations catalyzed by π-acids such as gold(I) are thought to proceed through a carbocationic intermediate which may be stabilized by electron donation from the catalyst.[2] Functionalization of the gold(I)−carbenoid contributor to these delocalized cations has been the focus of a number of recent investigations from this laboratory[3] and others.[4] We were interested in the possibility for interception of positive charge density on carbon by strain-release driven skeletal rearrangements. The cyclopropylmethyl cation was an appealing model for this proposed transformation on account of its well-known ring expansion chemistry[5] and the potential to utilize the remaining strain energy of the cyclobutanone products in subsequent transformations.[6] Thus, the sequential enyne cycloisomerization/ring expansion could constitute an expedient entry into polycyclic ring systems.[7]

Both alkylidenecyclopropanes and vinylcyclopropanes could be conceived of as precursors to the cyclopropylmethyl cation in the context of intramolecular cycloisomerization with a suitably tethered alkyne. For example, enyne cycloisomerization of an alkylidenecyclopropane would lead to a spirocyclic cyclopropylmethyl cation bearing a vinylogous

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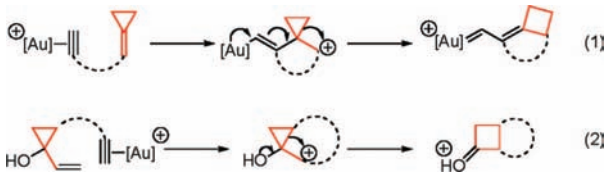
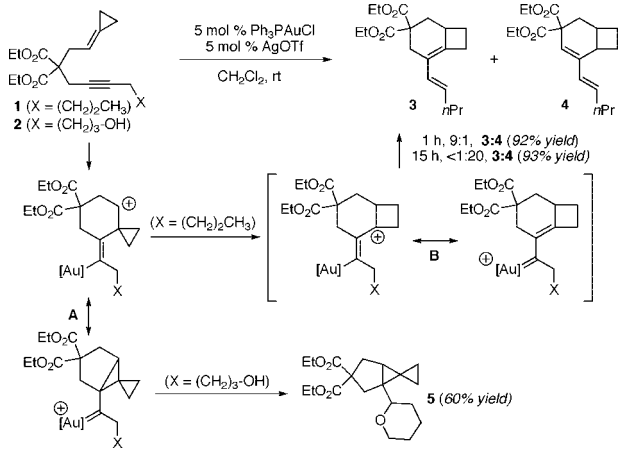
gold substituent. In this case, σ-bond migration may be aided by electron donation from gold (eq 1). Alternatively, cyclization of a vinylcyclopropanol onto a gold(I)−alkyne complex generates a carbocation poised to undergo a semipinacol rearrangement, leading to cyclobutanone products (eq 2).[8]



To evaluate the hypothesis outlined in eq 1, enyne **1** was treated with 5 mol % of Ph_3PAuCl and 5 mol % of AgOTf, leading to a 9:1 mixture of dienes **3** and **4** within 1 h (Scheme 1). Allowing the reaction to run for 15 h provides a greater

Scheme 1. Cycloisomerization of Alkylidenecyclopropanes

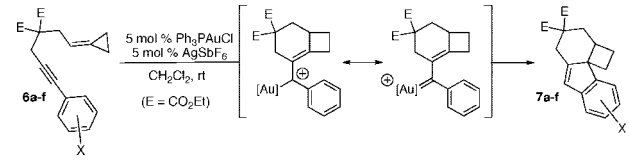


proportion of the less strained diene **4**, suggesting isomerization of the initial product **3** was occurring under the reaction conditions.

A proposed mechanism for this reaction is outlined in Scheme 1. In contrast to the 5-*exo*-dig or 6-*endo*-dig cyclizations typically observed in gold-catalyzed cycloisomerizations of 1,6-enynes, the rearrangement of **1** is initiated by a 6-*exo*-dig addition of the alkylidenecyclopropanes. The reversal in selectivity of the cyclization is presumably driven by the formation of a cyclopropylcarbinyl cation (**A**) that may be further stabilized through backbonding from gold. Methylene cyclobutene **3**, generated by a 1,2-hydrogen shift onto the cation or gold carbenoid (**B**), is formed as the kinetic product which isomerizes to the thermodynamically more stable diene **4**. In support of a mechanism involving alkyne rather than cyclopropane activation,[9] gold-catalyzed cycloisomerization of alcohol **2** results in selective formation of pyran **5** in 60% yield. In this case, intramolecular addition of the pendant alcohol to gold-stabilized cation **A** occurred faster than cyclopropane ring opening.

On the basis of this mechanistic hypothesis, we anticipated that the gold(I)-stabilized allyl cation would participate in a Nazarov-type electrocyclization.[10,4e] We were pleased to find that treatment of phenylacetylene **6a** with cationic gold(I) provides access to tetracycle **7a** as a single diastereomer, accompanied by the formation of a benzylic all-carbon quaternary center (Table 1). An evaluation of several aryl-

Table 1. Cyclization of Aryl Ynylidenecyclopropanes[a]



entry	substrate	X	time (h)	yield
1	**6a**	H	1.25	75%[a]
2	**6b**	2-Me	1.5	75%
3	**6c**	2-I	1.25	91%
4	**6d**	4-Me	14	35%[b]
5	**6e**	3,5-Me	1	44%[a]
6	**6f**	3,5-Cl	1.25	86%

[a] Reagents and Conditions: substrate (0.25 M in CH_2Cl_2). [b] Reagents and Conditions: $(4\text{-}CF_3Ph)_3PAuCl$, AgOTf.

substituted ynylidenecyclopropanes was carried out. The reaction was found to tolerate alkyl substituents (entries 2, 4, and 5) as well as halogen-substituted arenes (entries 3 and 6). The best result was obtained with the sterically hindered *ortho*-iodo substrate **6c**, giving the tetracyclic product **7c** in 91% yield (entry 3). Notably, the reaction of **6c** catalyzed by (*R*)-xylSDP$(AuCl)_2$/$AgSbF_6$ afforded **7c** with 82% ee (eq 3).[11]

An alternative approach to the generation of the cyclopropylmethyl cation involves the cyclization of enynes bearing an internal cyclopropanol unit. We foresaw the necessity for *cis*-disubstituted cyclopropanol substrates to

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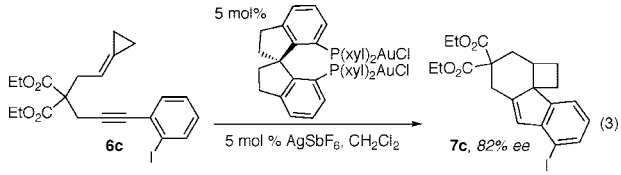
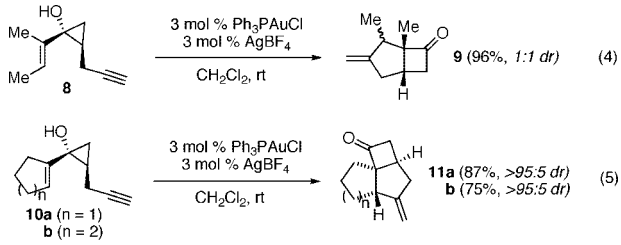
(11) Other bisphosphine ligands afforded the product with lower selectivities (e.g. SEGPHOS (59% ee), DTBMSEGPHOS (53% ee), SYNPHOS (53% ee), DUANPHOS (37% ee), BINAP (20% ee)).

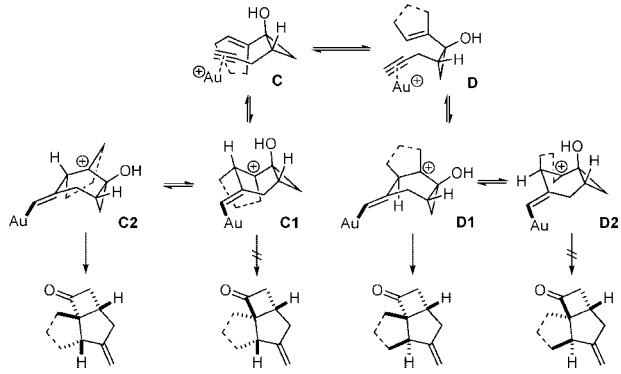


maintain proximity between the unsaturated side chains needed for cycloisomerization to proceed. Thus, in accord with the hypothesis presented in eq 2, *cis*-disubstituted cyclopropanol **8** was treated with 3 mol % of Ph_3PAuBF_4, leading to bicyclic ketone **9** in 96% yield (eq 4). Moreover, gold(I)-catalyzed cycloisomerization of cyclic olefin substrates **10a** and **b** provided diastereomerically pure angular tricyclic systems **11a** and **b** in good yields (eq 5).



A stereochemical analysis for the gold(I)-catalyzed reactions is presented in Scheme 2. Initial cyclization through

Scheme 2. Stereochemical Analysis of Cyclopropanol Cycloisomerization

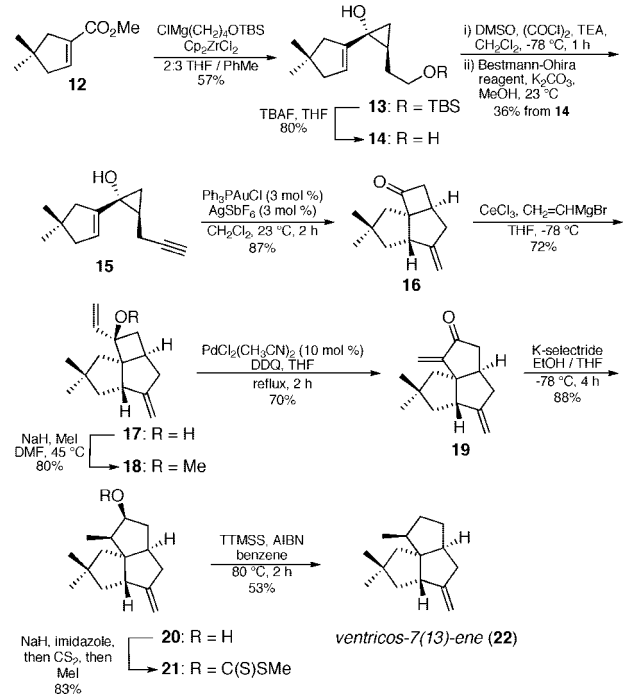


two boat conformers leads to intermediates **C1** or **D1**. A semipinacol shift through conformer **C1** and **D2** does not occur as it would produce high energy *trans*-cyclobutanones. Therefore, gold(I)-catalyzed cyclization of **8** proceeds nonselectively through **C2** and **D1** both of which lead to *cis*-cyclobutanones. On the other hand, with cyclic alkenes such as **10a**, reaction through **C2** is disfavored as the transition state would resemble a high-energy *trans*-diquinane. We therefore propose that the observed high selectivity observed for the cycloisomerization of cyclic olefins **10a/b** to **11a/b** results from a selective semipinacol shift (through **D1**).

On the basis of these results, we envisioned that the tandem cyclization/semipinacol rearrangement could provide a novel approach to the angular triquinane ring system found in a wide range of sesquiterpene natural products. More specifically, we sought to apply the gold-catalyzed cycloisomerization to generate the angular tricyclic ring system, hindered all-carbon quaternary center, and remote *exo*-methylene of ventricos-7(13)-ene (**22**),[12] a novel triquinane containing an unprecedented rearranged pentalenene skeleton.

Our synthesis begins with the Kulinkovich cyclopropanation[13] of commercially available ester **12**[14] (Scheme 3).

Scheme 3. Synthesis of Ventricos-7(13)-ene **22**



While a variety of titanium(IV) reagents resulted in low yields for this reaction, the use of the less oxophillic zirconocene dichloride afforded vinylcyclopropanol **13** in 57% yield. Desilylation of this material with TBAF furnished diol **14** in good yield. Alkyne **15** was prepared from **14** in a two-step oxidation/alkynylation sequence in 36% overall yield. The modest yield is attributable to the tendency of the intermediate aldehyde to undergo intramolecular attack of the vinylcyclopropanol on the pendant carbonyl group.[15] Gold(I)-catalyzed reaction of **15** proceeded smoothly at room temperature to furnish cyclobutanone **16** in 87% yield as a single diastereomer. At this point, completion of the natural product entails ring expansion to the angular triquinane ring

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(14) Alternatively, this material could be prepared by a route previously reported in the literature. See Supporting Information.

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system, establishment of the methyl-bearing chiral center, and the removal of the single heteroatom that has served to control the key ring-expansion reactions. To this end, we anticipated palladium(II)-catalyzed oxidative ring expansion[16] of cyclobutanol **17**, produced from the reaction of **16** with vinylmagnesium bromide in the presence of $CeCl_3$, would provide *exo*-methylene cyclopentanone **19**. However, treatment of **17** with catalytic $PdCl_2(MeCN)_2$ and either benzoquinone or DDQ in THF resulted in a 4:1 mixture of products in favor of migration of the less substituted C−C bond. On the basis of recent work on a related system,[17] we examined the ring expansion of the corresponding methyl ether **18** and were delighted to obtain only the desired enone **19** in 70% yield when the reaction was run in refluxing THF for 3 h.

The reduction of **19** was accomplished using K-selectride in a mixture of ethanol and THF at −78 °C,[18] providing alcohol **20** as a single diastereomer. With the hydrocarbon skeleton of ventricosene fully assembled, we turned our attention to the deoxygenation of **20**. Conversion of this material to the corresponding tosylate failed under several conditions, and reduction of the mesylate was accompanied by significant amounts of intractable elimination products. We found that Barton−McCombie reduction of xanthate ester **21** provided **22**, whose spectra were identical with that of the isolated natural product.[12] The use of tris(trimethylsilyl)silane[19] (TTMSS) as the hydride source proved critical: the silane byproducts could be removed by treatment of the reaction mixture with TBAF, whereas we were unable to adequately purify the natural product when using the conventional organotin hydride reagent.

In conclusion, we have developed two new gold-catalyzed ring-expanding enyne cycloisomerization reactions that allow for rapid preparation of complex polycyclic ring systems. In the first, alkylidenecyclopropanes are used as a regiocontrolling element with latent ring-strain reactivity. In contrast to much of transition-metal chemistry of alkylidenecyclopropanes,[9] the use of cationic gold(I) allows for pathways that proceed selectively via alkyne activation. This concept was extended to the development of a pinacol-terminated enyne cycloisomerization of vinyl cyclopropanols. Finally, the first total synthesis of (±)-ventricos-7(13)-ene (**22**), completed in 11 steps from ester **12**, illustrates the ever-increasing utility of gold-catalyzed enyne cycloisomerizations as a tool for the rapid construction of complex structures.[20]

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Supporting Information Available: Experimental procedures and compound characterization data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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