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Formal Synthesis of (+)-Laurencin via a Gold(I)-Catalyzed Intramolecular Dehydrative Alkoxylation

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ABSTRACT: 8-Membered cyclic ethers are found in a wide range of natural products; however, they are challenging synthetic targets due to enthalpic and entropic barriers. The gold(I)-catalyzed intramolecular dehydrative alkoxylation of *ω*-hydroxy allylic alcohols was explored to stereoselectively construct α,α′-*cis*-oxocenes and applied in a formal synthesis of (+)-laurencin. The gold(I)-catalyzed intramolecular dehydrative alkoxylation may constitute an alternative method for the synthesis of molecular building blocks and natural products that contain highly functionalized 8-membered cyclic ethers.

A number of areas associated with human health including natural products synthesis, pharmaceutical development, and chemical biology depend on reliable and efficient methods for the synthesis of a chemically diverse range of molecular building blocks and sub-structures. For this reason, the development of general and selective carbon-carbon and carbon-heteroatom bond-forming reactions, particularly those suited for application in complex molecular systems, has the potential to positively impact these diverse and important areas of research.

8-Membered cyclic ethers are highly abundant in structurally or biologically intriguing natural products (Figure 1). As a consequence, these 8-membered cyclic ethers have fueled synthetic efforts to develop novel methodologies.[1] However, despite prolonged interest in the area, effective methods for the stereoselective synthesis of 8-membered cyclic ethers are limited most notably with respect to catalytic methods. Thus, there remains a great need to develop catalytic and stereoselective methods for 8-membered cyclic ether synthesis that are applicable in structurally complex natural product synthesis.

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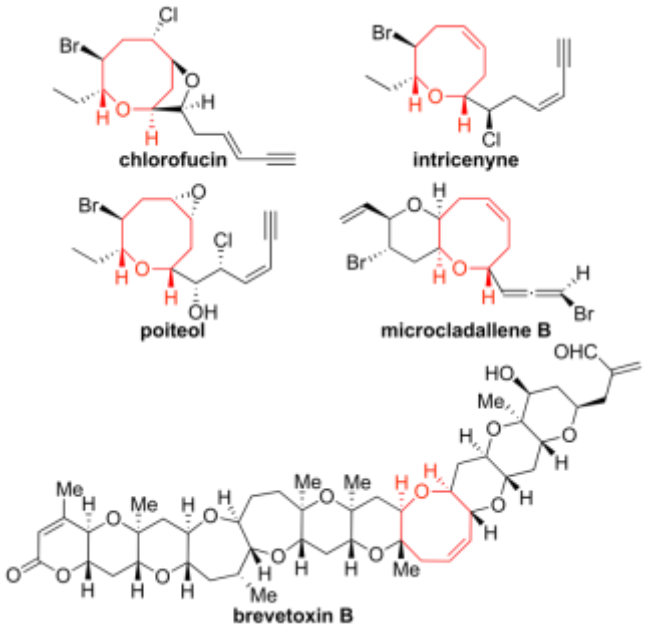

Figure 1. Examples of naturally occurring 8-membered cyclic ethers.

The use of soluble gold complexes as catalysts for organic reactions has become increasingly popular over the past decade.[2] Early work in this area focused on the application of gold(III) halides as catalysts, but effort has increasingly shifted toward cationic gold(I) complexes, which display excellent chemoselectivity and functional group compatibility. Over the past several years, these cationic gold(I) complexes have emerged as particularly active catalysts for the regio- and stereoselective functionalization of C=C bonds with carbon and heteroatom nucleophiles[3] to form carbocycles, heterocycles, and hetero-functionalized building blocks from readily available starting materials via highly atom-economical transformations.[4] Included among these transformations is the formation of cyclic ethers through the gold(I)-catalyzed hydroalkoxylation of allenes[3b, 5] or dehydrative alkoxylation of allylic alcohols.[6] However, application of these methods to the synthesis of medium-sized cyclic ethers remains underexplored[7] and only a few reports of the synthesis of an 8-membered cyclic ether via gold catalysis have been disclosed.[8] Herein, we describe our investigation of the gold(I)-catalyzed intramolecular dehydrative alkoxylation of *ω*-hydroxy allylic alcohols for the stereoselective preparation of α,α′-*cis*-oxocenes and application of the method in a stereoselective formal synthesis of (+)-laurencin (**1**, Figure 2).

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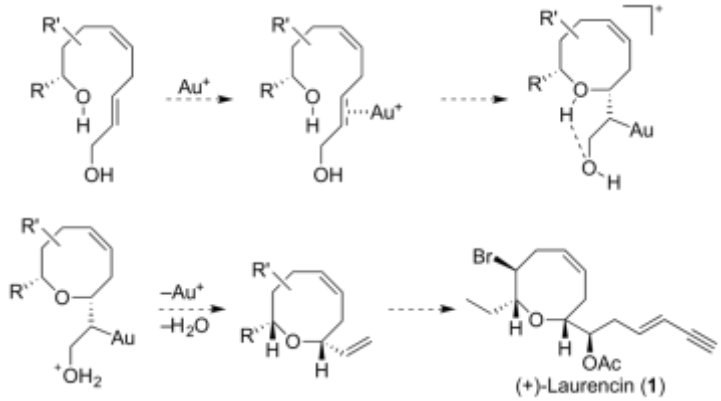

Figure 2. The gold(I)-catalyzed intramolecular dehydrative alkoxylation approach to a stereoselective synthesis of (+)-laurencin (**1**).

Since oxocenes containing a 4,5- or 5,6-*cis* double bond or a functional group that can be derived from a double bond are abundant in nature, initial studies to test the feasibility of the gold(I)-catalyzed intramolecular dehydrative alkoxylation for a stereoselective oxocene synthesis were completed with both monoallylic diols **2a** and **2b** possessing 4,5- and 5,6-*cis*-olefin, respectively (Table 1).[9] Initially, **2a** and **2b** were subjected to (JohnPhos)AuCl (5 mol%) and AgOTs (5 mol%) in dioxane at 25 °C for 24 h. Unfortunately, no product formation was observed. After increasing the temperature to 100 and 50 °C, respectively, only trace amounts of a new product were detected (entries 1 and 2). Changing the catalyst combination to IPrAuCl and $AgClO_4$ did not show any improvement in reactivity at 25 °C; however, increasing the temperature to 50 °C gave the desired oxocenes **3a** and **3b**, respectively, as single diastereomers (entries 3 and 4). The gold(I)-catalyzed intramolecular dehydrative alkoxylation stereoselectively provided the α,α′-*cis*-oxecene **3b**[10] through the more favorable conformation **2b-B** and involved the outer sphere attack of the nucleophile on a catalyst π-complex. Prolonged reaction time did not show complete consumption of the substrate in either case. Exchanging Ph_3PAuCl for IPrAuCl yielded a complex reaction mixture and microwave irradiation did not show any significant change in isolated yield (entries 5 and 6).

Table 1. Synthesis of α,α′-*cis*-Oxecenes via the Gold(I)-Catalyzed Intramolecular Dehydrative Alkoxylation.

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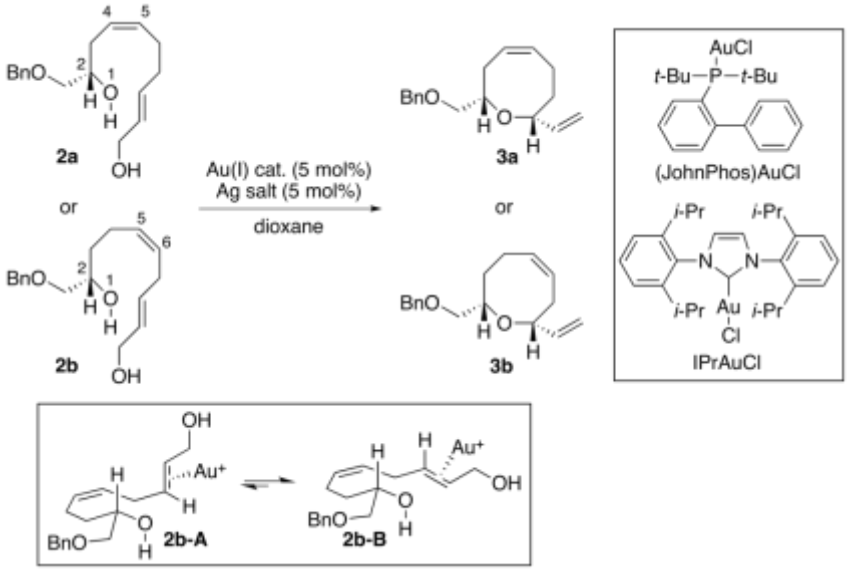

Entry	Substrate	Gold Catalyst	Silver Salt	Temp [°C]	Time [h]	Product (yield [%])
1	**2a**	(JohnPhos)AuCl	AgOTs	25–100	96	trace
2	**2b**	(JohnPhos)AuCl	AgOTs	25–50	96	trace
3	**2a**	IPrAuCl	$AgClO_4$	25–50	144	**3a** (18)[a]
4	**2b**	IPrAuCl	$AgClO_4$	25–50	144	**3b** (37)[a]
5	**2a**	Ph_3PAuCl	$AgClO_4$	25–80	48	complex mixture
6	**2a**	IPrAuCl	$AgClO_4$	50 μW	50	**3a** (17)[a]

[a] >20:1 *dr*

Since the active gold catalyst is formed *in situ* and it has been established that the silver salt counteranion can significantly affect its reactivity,[11] various silver salts were examined (Table 2). Based on the preliminary studies, optimization of the silver salt was accomplished with 10 mol% of IPrAuCl at 50 °C for 48 h. No reaction was observed with AgOTs and AgOAc (entries 1 and 2) and reactivity increased in the order of $AgAsF_6$, $AgBF_4$, $AgSbF_6$ and AgOTf, yielding up to 50% α,α′-*cis*-oxocene **3b**. In order to rule out an acid-catalyzed mechanism, **2b** was subjected to HOTf (10 mol%) in dioxane at 50 °C for 48 h. The reaction resulted in roughly 62% conversion of **2b** with the desired oxocene **3b** comprising around 6% of the reaction mixture. This result clearly suggested that the cyclization reaction is not dependent on acid-catalysis, but is dependent on gold(I)-catalysis. $AgClO_4$ gave a lower yield (entry 7) under these conditions in comparison to AgOTf. Interestingly, reducing the catalyst loading to 5 mol% gave a higher yield of **3b** (28%, entry 8). Reducing the temperature to 30 °C also resulted in a similar increase in isolated yield (22%, entry 9). Unfortunately, this trend was not applicable to the most reactive silver salt, AgOTf, and significantly lower yields were obtained (entries 10 and 11). Various solvents were also screened; however, dioxane remained the most advantageous choice (entries 12–17).

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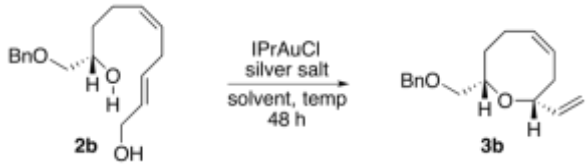
Table 2. Screening of Silver Salts and Solvents for the Gold(I)-Catalyzed Intramolecular Dehydrative Alkoxylation.



Entry	Silver Salt [mol%]	Catalyst Loading [mol%]	Solvent	Temp [°C]	Yield (%)[a]
1	AgOTs (10)	10	dioxane	50	no reaction
2	AgOAc (10)	10	dioxane	50	no reaction
3	$AgAsF_6$ (10)	10	dioxane	50	18
4	$AgBF_4$ (10)	10	dioxane	50	32
5	$AgSbF_6$ (10)	10	dioxane	50	35
6	AgOTf (10)	10	dioxane	50	50
7	$AgClO_4$ (10)	10	dioxane	50	8
8	$AgClO_4$ (5)	5	dioxane	50	28
9	$AgClO_4$ (10)	10	dioxane	30	22
10	AgOTf (5)	5	dioxane	50	32
11	AgOTf (10)	10	dioxane	30	29
12	AgOTf (10)	10	toluene	50	24
13	AgOTf (10)	10	CH_3CN	50	trace
14	AgOTf (10)	10	THF	50	14
15	AgOTf (10)	10	acetone	50	17
16	AgOTf (10)	10	CH_2Cl_2	50	trace
17	AgOTf (10)	10	EtOAc	50	trace

[a] >20:1 *dr*

Having screened the silver salt, catalyst loading, solvent, and temperature, the 5,6-*cis*-olefin containing monoallylic diol **2b** was subjected to IPrAuCl (10 mol%) and AgOTf (10 mol%) in dioxane at 50 °C for 48 h to afford the desired α,α′-*cis*-oxocene **3b** in 50% yield (entry 6).[12] These model studies suggested that the gold(I)-catalyzed intramolecular dehydrative alkoxylation of *ω*-hydroxy allylic alcohols can be used to stereoselectively construct α,α′-*cis*-oxocenes.[13,14]

Encouraged by the potential of the gold(I)-catalyzed dehydrative alkoxylation for the stereoselective synthesis of α,α′-*cis*-oxocenes, we embarked on a stereoselective formal synthesis

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of (+)-laurencin (**1**, Figure 3). (+)-Laurencin (**1**) was isolated from *Laurencia glandulifera*, collected at Oshoro Bay (Hokkaido, Japan), by Irie *et al.* in 1965.[15] Key structural features of (+)-laurencin (**1**), which were established through several reports,[16] include a 3,4,7,8-tetrahydro-2*H*-oxocin core, a bromine atom as well as ethyl and 1-acetoxyhex-3-en-5-ynyl groups. Although **1** possesses only moderate activity as a drug metabolism inhibitor,[17] its preparation has been extensively studied due to its unique structural features.[18,19,20]

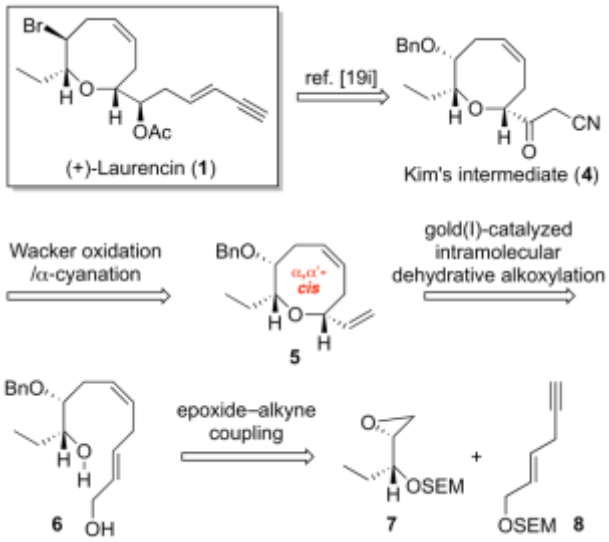

Figure 3. Retrosynthetic plan for (+)-laurencin (**1**).

As illustrated in our retrosynthetic plan (Figure 3), (+)-laurencin (**1**) could be prepared from the α-cyano ketone **4** following the known procedures.[19i] The α-cyano ketone **4** would be obtained from the α,α′-*cis*-oxocene **5** via the Wacker oxidation and subsequent α-cyanation. We envisioned the α,α′-*cis*-oxocene **5** would be accessed from the *ω*-hydroxy allylic alcohol **6** via the key gold(I)-catalyzed intramolecular alkoxylation. The coupling of epoxide **7** and alkyne **8** would provide **6** for the gold(I)-catalyzed intramolecular alkoxylation.

The synthesis began with preparation of the SEM-protected α-hydroxyepoxide **7** from the tosylate **9** (Scheme 1). The CuI-mediated coupling of **9**, which was prepared from (4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-dimethanol,[21] and CH_3Li followed by debenzylation provided the alcohol **10** in 92% overall yield for two steps. Treatment of **10** with *p*-TsCl and acetonide deprotection of the resulting tosylate under acidic conditions gave the diol **11** in 91% overall yield for two steps. An initial two-step sequence in which epoxidation was achieved using K_2CO_3 and $MeOH/CH_2Cl_2$ followed by treatment of the crude epoxide with NaH and SEMCl was somewhat successful, giving the desired SEM-protected α-hydroxyepoxide **7** in 10% yield. However, there were several drawbacks to this procedure, including prolonged reaction time for the epoxidation and the potential volatility of the intermediate epoxide. It was hypothesized that the epoxidation and SEM protection could be achieved in a single step using NaH as the base for both purposes, hence eliminating the long reaction time for epoxidation and handling of the volatile epoxide prior to protection. As depicted in Scheme 1, treatment of **11** with excess NaH and SEMCl gave **7** directly in 82% isolated yield.

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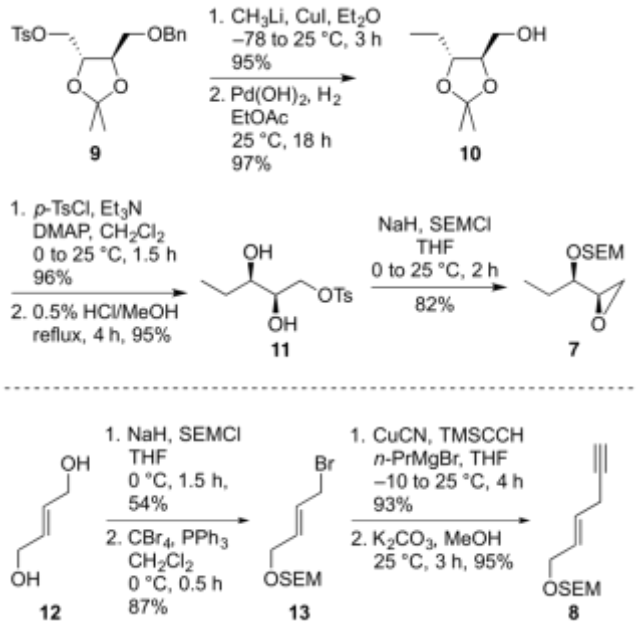
Scheme 1. Preparation of epoxide and alkyne.



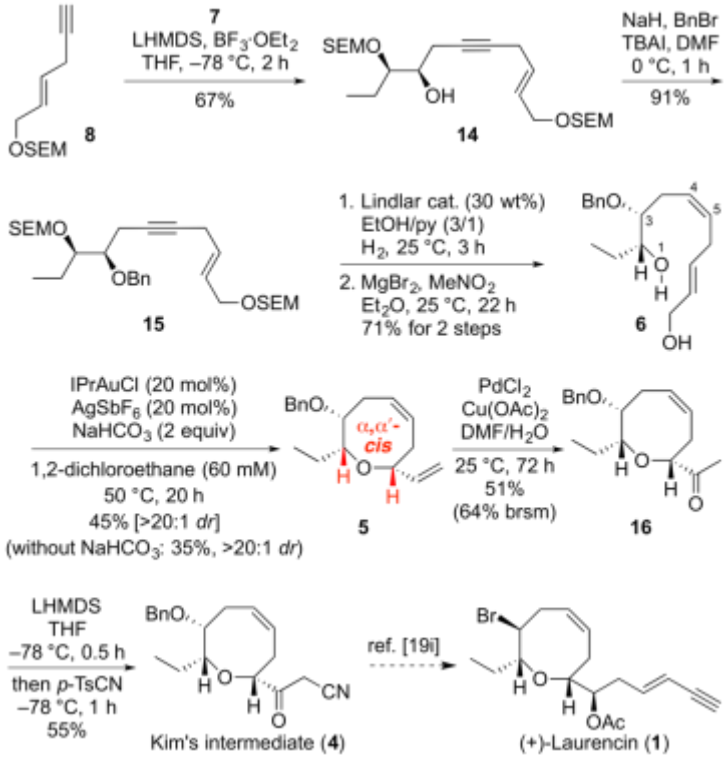
For the synthesis of the terminal alkyne **8**, we converted commercially available (*E*)-2-butene-1,4-diol (**12**) to **13** via mono-SEM protection followed by bromination (Scheme 1). The CuBr-mediated coupling of **13** and TMS-acetylene followed by TMS deprotection gave the desired terminal alkyne **8** in 88% overall yield for two steps.

With both fragments in hand, the epoxide–alkyne coupling reaction was attempted (Scheme 2). After examining several conditions, the coupling of alkyne **8** and epoxide **7** via lithiation followed by transmetalation proceeded smoothly to afford the homopropargylic alcohol **14** in 67% yield.[22] The benzylation of **14** in the presence of TBAI gave the benzyl ether **15** in 91% yield. Lindlar hydrogenation followed by bis-SEM deprotection afforded the *ω*-hydroxy allylic alcohol **6** in 71% for two steps. With the key substrate in hand, we turned our attention to the gold(I)-catalyzed intramolecular alkoxylation for preparation of the α,α′-*cis*-oxocene core of **1**. When the optimized conditions from the model studies were applied to the key cyclization of **6**, the desired α,α′-*cis*-oxocene **5** was obtained in 35% yield as a single diastereomer.[23] Based on reports of gold(I)-catalyzed reactions "buffered" by bases such as $NaHCO_3$ and $CaCO_3$, it was hypothesized that use of $NaHCO_3$ to maintain the pH might suppress potential side reaction and increase the yield of the cyclization reaction. We found that treatment of **5** with IPrAuCl (20 mol%), $AgSbF_6$ (20 mol%), and $NaHCO_3$ in 1,2-dichloroethane at 50 °C yielded the desired α,α′-*cis*-oxocene **5** in 45% yield as a single diastereomer. The isolated yield of **6** still suffered due to competing reaction pathways such as 4,5-*cis*-double bond isomerization and dimerization, but the gold(I)-catalyzed intramolecular dehydrative alkoxylation proceeded with excellent stereoselectivity (>20:1 *dr*). Moreover, the reaction is catalytic and complementary to existing synthetic methods for 8-membered cyclic ethers.

To complete the formal synthesis of (+)-laurencin (**1**), a two-step sequence of Wacker oxidation and α-cyanation was employed. The Wacker oxidation of **5** gave the desired methyl ketone **16** in 51% yield (64% brsm), a moderate yield resulting from competitive aldehyde formation (~10%). Treatment of **16** with LHMDS and *p*-TsCN yielded the known Kim's α-cyano

ketone **4**[19i] in 55% yield. The spectral data of **4** were in good agreement with those in literature, which constitutes a formal synthesis of (+)-laurencin (**1**).

Scheme 2. Formal synthesis of (+)-laurencin (**1**) via the gold(I)-catalyzed intramolecular dehydrative alkoxylation of *ω*-hydroxy allylic alcohol.



In summary, the gold(I)-catalyzed intramolecular dehydrative alkoxylation of *ω*-hydroxy allylic alcohols was explored for the stereoselective synthesis of α,α′-*cis*-oxocenes and applied in a formal synthesis of (+)-laurencin (**1**). The α,α′-*cis*-oxocene core of (+)-laurencin (**1**) was stereoselectively constructed from the readily available epoxide **7** and alkyne **8** via gold(I)-catalyzed intramolecular dehydrative alkoxylation. We expect that the gold(I)-catalyzed intramolecular dehydrative alkoxylation would be broadly applicable in stereoselective synthesis of 8-membered cyclic ethers as well as other types of medium-sized cyclic ethers.

Supporting Information

General experimental procedures including spectroscopic and analytical data along with copies of ^{1}H and ^{13}C NMR spectra.

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The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript.

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[9] Procedures for the preparation of **2a** and **2b** can be found in the Supporting Information.

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