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Total Syntheses of Drimane-Type Sesquiterpenoids Enabled by a Gold-Catalyzed Tandem Reaction

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Supporting Information

ABSTRACT: Development of a gold-catalyzed tandem reaction of 1,7-diynes with both internal and external nucleophiles was realized, which constructed five chemical bonds, two rings, and two stereogenic centers in a single step. Based on the novel cascade transformation, we achieved a unified strategy toward the stereoselective total syntheses of C-15 oxygenated drimane-type sesquiterpenoids and their analogues, which provided the natural products kuehneromycin A, antrocin, anhydromarasmone, and marasmene as a proof-of-concept study.

In our continuous efforts toward the total syntheses of biologically active natural products, we attempt to prepare both known compounds and their analogues more efficiently than realized through existing approaches to enable an enhanced exploitation of their structure−activity relationships.[1] Special attention has been paid to novel synthetic strategies and methodologies that could lead to a modular and concise approach that is predisposed for further medicinal chemistry optimization if necessary.[2] To showcase the intertwined nature of synthetic strategies and methodologies, we describe herein a new cascade reaction allowing the collective syntheses[3] of several drimane-type sesquiterpenoids.

Drimane-type sesquiterpenoids are a large group of natural products possessing a variety of remarkable biological activities.[4] Many members are oxygenated at C-15 and have a characteristic [6-6-5] tricyclic system (Figure 1). For instance, kuehneromycin A (**1**) and mniopetal F inhibit the reverse transcriptase of some RNA viruses, including HIV-1.[5] We are particularly interested in antrocin (**2**), a metabolite originally reported by Chiang et al. in 1995,[6] which has recently been identified as a selective and novel inhibitor of Akt/mTOR signaling in metastatic breast cancer MDA-MB-231 cells.[7] The structural complexity of these sesquiterpenoids is increased by incorporating another ring system, leading to anhydromarasmone (**3**) and marasmene (**4**), which are metabolites isolated from *Marasmius oreades* featuring a [6-6-5-5] tetracyclic skeleton.[8] The molecular complexity also increases rapidly by substituting the core skeleton, culminating in the complicated left-wing fragment of azadirachtin.[9]

The conventional synthetic method toward these sesquiterpenoids has focused on applying an intramolecular Diels−Alder reaction to construct the tricyclic core structure.[10] Aiming at an alternative synthetic strategy that could readily reach analogues of these promising natural products, we recognized that the key intermediate **A** would give rise to **1**−**4** straightforwardly with minimum functional group manipulation. We further envisioned that **A** could be accessed from 1,7-diyne **C** through a tandem reaction involving the sequential nucleophilic addition of alkynes (Figure 1). High alkynophilicity and good functional group compatibility make gold catalysts a good choice for this cascade transformation.[11]

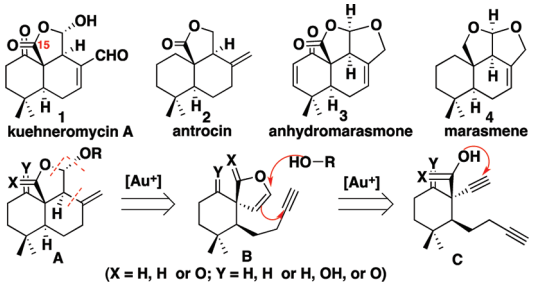

Figure 1. Synthetic analysis of C-15 oxygenated drimane-type sesquiterpenoids.

It was reported that strategic placement of multiple alkynes and nucleophiles could result in sequential alkyne activation to accomplish various cascade reactions.[12] In our scenario, 5-*endo*-dig addition of oxygen to an alkyne leads to a polarized olefin functionality, which functions as the nucleophile in the following 6-*exo*-dig cyclization (Figure 1, **B**). The reaction will be terminated by an external nucleophile (e.g., alcohol), affording tricyclic compound **A** as the final product.

As a model system for this envisioned tandem transformation, racemic diyne acid **5**[13] was subjected to the cationic gold catalyst either in the absence or in the presence of *p*-nitrobenzylic alcohol at room temperature. To our delight, **6** and **7** were isolated, respectively (Table 1, entries 1 and 2). When **6** was again subjected to the gold catalyst in the presence of *p*-nitrobenzylic alcohol, it afforded tricyclic **7** (Table S1). It is notable that the reaction leading to **6** was much faster than the formation of **7**, indicating that the 6-*exo*-dig cyclization[14] is the rate-determining step in the tandem reaction. It was further observed that tris(*p*-trifluoromethylphenyl)phosphine, a less-electron-donating ligand than triethylphosphine, resulted in a decreased yield of **7**,

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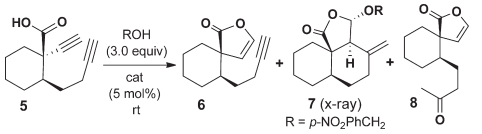
Table 1. Optimization of the Cascade Cyclization Conditions for Synthesizing Tricyclic Lactone 7[a]



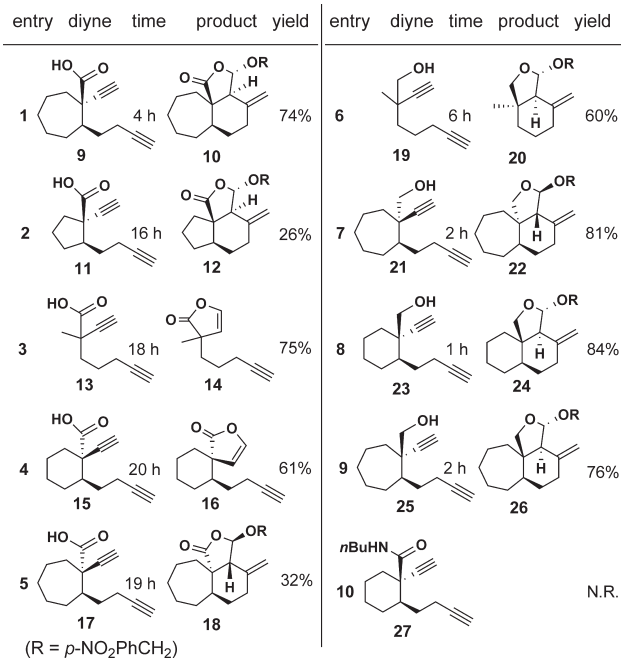
entry	catalyst	conditions[a]	yield, %[b] 6	7	8
1	$(Et_3P)AuCl/AgSbF_6$[c]	CH_2Cl_2, 10 min	70	0	0
2	$(Et_3P)AuCl/AgSbF_6$	CH_2Cl_2, 5 h	0	62	0
3	$(p\text{-}CF_3C_6H_4)_3PAuCl\ AgSbF_6$	CH_2Cl_2, 1.5 h	0	45	0
4	$(^tBu_3P)AuCl/AgSbF_6$	CH_2Cl_2, 2 h	0	77	0
5	IMes)AuCl/$AgSbF_6$	CH_2Cl_2, 12 h[d]	72	9	0
6	**(IPr)AuCl/$AgSbF_6$**	**CH_2Cl_2, 0.8 h**	**0**	**86**	**0**
7	(IPr)AuCl/$AgBF_4$	CH_2Cl_2, 5 h	0	43	0
8	(IPr)AuCl/$AgNTf_2$	CH_2Cl_2, 10 h	0	62	0
9	(IPr)AuCl/AgOTf	CH_2Cl_2, 1 h	0	10	0
10	(IPr)AuCl/$AgSbF_6$	toluene, 0.8 h	0	60	0
11	(IPr)AuCl/$AgSbF_6$	MeCN, 12 h	0	0[a]	0
12	(IPr)AuCl/$AgAgSbF_6$	THF, 6 h	0	0	76
13	$NaAuCl_4 \cdot H_2O$	CH_2Cl_2, 6 h[d]	83	9	0
14	$AgSbF_6$	CH_2Cl_2, 12 h	0	0[e]	0
15	$(Tf)_2NH$[f]	CH_2Cl_2, 12 h	0	0[e]	0

[a] [**5**] = 0.05 M (0.13 mmol), 3 equiv of *p*-nitrobenzylic alcohol. Products are racemic. [b] Isolated yields after column chromatography. [c] Without alcohol. [d] Substrate **5** was consumed completely within 1 h. [e] Substrate **5** was recovered. [f] 10 mol % $(Tf)_2NH$.

while tri-*tert*-butylphosphine increased the yield to 77% (entries 3 and 4). Intriguingly, two carbene ligands provided **6** and **7** as the major product respectively, with 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene giving the best result (entries 5 and 6).[15] Investigation of the counterion effect revealed that $AgBF_4$, AgOTf, and $AgNTf_2$ led to a decreased yield compared to $AgSbF_6$ (entries 7−9). The use of different solvents also could affect the reaction, as shown by the decreased yields of **7** in toluene, THF, and acetonitrile (entries 10−12). Presumably, the 6-*exo*-dig cyclization (Figure 1, **B**) is not favorable in THF; therefore, intermolecular addition of alcohol to the alkyne yields **8** as the major product. As a gold(III) catalyst, $NaAuCl_4$ only slightly promoted the second cyclization and afforded **6** as the major product in 6 h (entry 13). Neither $AgSbF_6$ nor the Brønsted acid Tf_2NH catalyzed any cyclization, both leading to the recovery of starting material **5** (entries 14 and 15). Among these reactions, **7** was obtained as a single diastereomer, the structure of which has been determined unambiguously by X-ray crystallography.

The scope of the cascade reaction was further explored with a variety of substrates using the optimum conditions identified in Table 1 (entry 6). Table 2 summarizes variations in 1,7-diyne that affect the outcome of the reaction. Diynes **9** and **11** produced the corresponding [7-6-5] tricycle **10** and [5-6-5] tricycle **12**, respectively, though **12** was obtained in a lower yield (entries 1 and 2). In contrast, linear diyne **13** did not give rise to any identifiable cascade cyclization product but instead afforded **14** in 75% yield, even after a longer reaction time (entry 3). The reaction of diyne **15**, which is the diastereomer of **5**, afforded 61%

Table 2. Scope of Diynes in the Gold-Catalyzed Cascade Reaction[a]



[a] Conditions: diyne (0.1−0.2 mmol, 0.05 M), *p*-nitrobenzylic alcohol (3 equiv), [(IPr)AuCl]/$AgSbF_6$ (5 mol %), CH_2Cl_2, rt. Diynes and products are racemic and isolated in >20:1 diastereomeric ratio, except **11** (dr = 10:1).

yield of **16** in 20 h, also sparing the second alkyne (entry 4). Though diyne **17** provided the cascade cyclization product **18**, the reaction yield was significantly lower than that of its diastereomer **9** (entry 5). These results indicate that the cycloalkane scaffold, as well as the *trans* relationship between two alkynes, might be important for the second cyclization (6-*exo*-dig). We envisioned that the challenging second cyclization could be facilitated by increasing the nucleophilicity of the polarized olefin resulting from the first cyclization (5-*endo*-dig), which could be realized by reducing the carboxylic acid to a primary alcohol. Consistent with this notion, diynes **19** and **21** respectively gave cascade cyclization products **20** and **22** in a much higher yield compared to the carboxylic acid counterparts **13** and **17** (entries 6 and 7). However, when diynes **23** and **25** were subjected to the cascade reaction, **24** and **26** were formed with similar efficiency compared to **7** and **10**, respectively (entries 8 and 9). Intriguingly, the [(IPr)AuCl]/$AgSbF_6$ catalytic system failed to effect any reaction of amide **27**, simply resulting in recovery of the starting material (entry 10).

To investigate the scope of external nucleophiles, we focused on two diynes, **5** and **23**, which are envisioned to deliver antrocin analogues with a [6-6-5] tricyclic skeleton if successfully implemented (Table 3). It turned out that phenol and sulfonamide are suitable external nucleophiles for the reaction with substrate **5** (entries 1 and 2), but neither indole nor aniline provided the desired tricyclic product. In comparison, diyne **23** reacted with methanol and carbon-based nucleophiles (including allylsilane, trimethoxybenzene, and indole) to give the corresponding cascade cyclization products in synthetically useful yields (entries 3−6). Similarly, diyne **21** afforded tricycle **34** in 81% yield with indole

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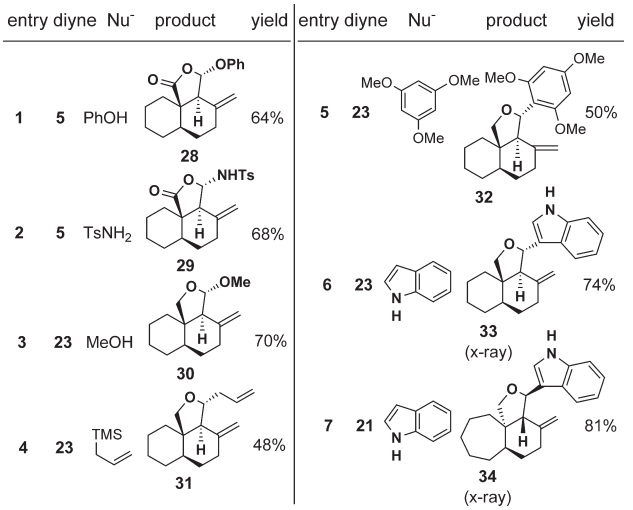
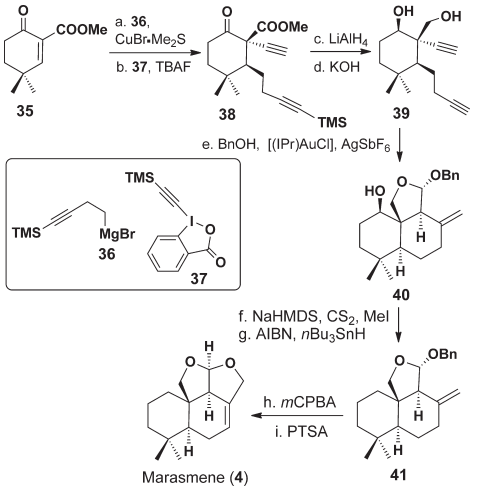
Table 3. Scope of External Nucleophiles in the Gold-Catalyzed Cascade Reaction[a]



[a] Conditions: diyne (0.1−0.2 mmol, 0.05 M), nucleophile (3 equiv), [(IPr)AuCl]/$AgSbF_6$ (5 mol %), CH_2Cl_2, rt, 1−20 h (see the Supporting Information). Diynes and products are racemic and isolated in >20:1 diastereomeric ratio.

Scheme 1. Total Synthesis of Marasmene (4)[a]

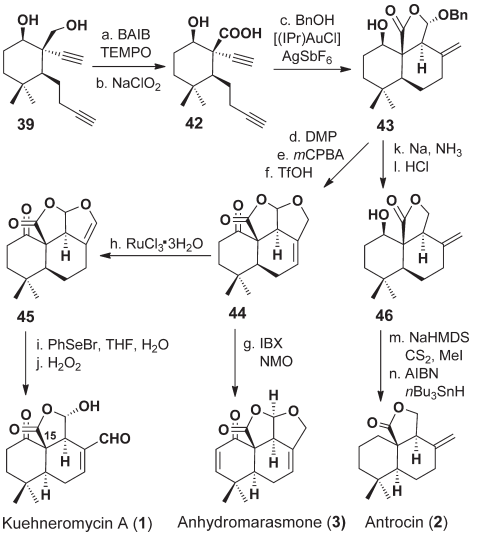


[a] Reagent and conditions: (a) **36** (2.5 equiv), CuBr·Me_2S (0.3 equiv), THF, −78 °C; (b) **37** (1.4 equiv), TBAF/THF (1.4 equiv), −40 °C, 58% over two steps; (c) $LiAlH_4$ (4.0 equiv), THF, rt, 87%; (d) KOH (5.0 equiv), THF/MeOH/H_2O, reflux, 95%; (e) BnOH (3 equiv), [(IPr)AuCl]/$AgSbF_6$ (5 mol %), CH_2Cl_2, rt, 96%; (f) NaHMDS (1.5 equiv), CS_2 (3 equiv), MeI (7 equiv), THF, rt; (g) nBu_3SnH (4.0 equiv), AIBN (0.1 equiv), toluene, 110 °C, 95% over two steps; (h) *m*CPBA (2.0 equiv), CH_2Cl_2, rt, 95%; (i) PTSA (1.2 equiv), $CHCl_3$, 50 °C, 58%.

as the external nucleophile (entry 7; structures of **33** and **34** have been confirmed by X-ray crystallography).

After establishing the gold-catalyzed tandem reaction, we moved toward the total syntheses of various interested drimane-type sesquiterpenoids (Scheme 1). Conjugated addition of Grignard reagent **36** to known cyclohexenone **35**,[16] followed by treatment with hypervalent iodine reagent **37**,[17] assembled two alkynes on the cyclohexyl skeleton to give **38** in 58% overall

Scheme 2. Total Syntheses of Sesquiterpenoids 1−3[a]



[a] Reagent and conditions: (a) TEMPO (0.7 equiv), BAIB (1.2 equiv), CH_2Cl_2, rt; (b) $NaClO_2$ (8.0 equiv), 2-methylbutene, CH_2Cl_2, rt, 51% over two steps; (c) BnOH (3.0 equiv), [(IPr)AuCl]/$AgSbF_6$ (5 mol %), CH_2Cl_2, rt, 54%; (d) Dess−Martin periodinane (1.5 equiv), $NaHCO_3$ (3.0 equiv), CH_2Cl_2, rt, 95%; (e) *m*CPBA (3.0 equiv), CH_2Cl_2, rt, 96%; (f) TfOH (2.0 equiv), CH_2Cl_2, −25 °C, 65%; (g) IBX (15.0 equiv), NMO (15.0 equiv), DMSO, 85 °C, 60%; (h) $RhCl_3 \cdot 3H_2O$ (0.5 equiv), EtOH, reflux, 81%; (i) PhSeBr (2.0 equiv), THF/H_2O, rt; (j) H_2O_2/H_2O, CH_2Cl_2, rt, 43% in two steps; (k) Na, NH_3, THF, −78 °C; (l) HCl, MeOH, 50 °C, 71% in two steps; (m) NaHMDS (1.5 equiv), CS_2 (3.0 equiv), MeI (7.0 equiv), THF, rt; (n) nBu_3SnH (2.0 equiv), AIBN (0.1 equiv), toluene, 110 °C, 78% over two steps.

yield with >20:1 diastereoselectivity. The cyclization precursor, diyne **39**, was obtained by the reduction and desilylation of **38**. Gratifyingly, with benzylic alcohol as the external nucleophile, the gold-catalyzed cascade reaction of **39** gave tricyclic compound **40** in 96% yield as a single diastereomer,[18] while the presence of the secondary alcohol group did not interfere with the reaction. The secondary alcohol then underwent Barton reduction in 95% yield over a two-step sequence. Epoxidation of the olefin in **41** with *m*CPBA followed by one-pot acid-catalyzed epoxide-opening and intramolecular transacetalization gave marasmene (**4**) in 55% yield.

Encouraged by this result, we proceeded to make **1**−**3** (Scheme 2). Selective oxidation of the primary alcohol in diol **39** to an aldehyde, followed by further oxidation, afforded carboxylic acid **42**, which underwent the aforementioned gold-catalyzed cascade cyclization to give the crucial intermediate tricyclic **43** in 54% yield. Subsequent oxidations, epoxide-opening and intramolecular transacetalization similar to those in synthesizing **4**, provided tetracyclic compound **44**, which had been achieved en route toward anhydromarasmone (**3**).[10f] Alternatively, introduction of a double bond conjugated to the ketone could also be achieved by IBX oxidation, which gave **3** in 60% yield. At this stage, we anticipated that kuehneromycin A (**1**) could also be synthesized from **44**. Olefin isomerization of **44** following conditions reported by Jauch and co-workers provided **45** in 81% yield.[10f] The vinyl ether moiety was set ready for oxidation using PhSeBr,[19] after which treatment with hydrogen peroxide gave rise to **1** in moderate yield over two steps. Last, we carried out the synthesis of antrocin (**2**) by executing a sequence

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of reductions of **43**. Interestingly, we found that the ketal in **43** could be reduced under Birch reduction conditions, and subsequent acid-catalyzed lactonization furnished **46** in 71% yield over two steps. Eventually, straightforward Barton reduction of **46** led to **2** in 78% yield. The ^{1}H NMR and ^{13}C NMR spectra of the synthesized sesquiterpenoids **1**−**4** (racemic) are identical to the published data of naturally occurring compounds.[5,6,8,10a]

In summary, we have developed a unified strategy for the syntheses of drimane-type sesquiterpenoids based on an enabling gold-catalyzed tandem reaction under mild conditions. This strategy has not only accomplished the first total syntheses of antrocin (**2**) and marasmene (**4**) but also provided an efficient approach to access analogues of biologically active drimane-type sesquiterpenoids. The mechanism of the tandem reaction, especially the 6-*exo*-dig cyclization followed by external nucleophilic attack, deserves further investigation. Preparation of enantiopure **38**, which is contemplated to automatically lead to enantioselective syntheses of **1**−**4**, is underway and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures, compound characterization data, and CIFs for **7**, **33**, and **34**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) See the Supporting Information for preparation of **5** and other diynes.

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