Natural Products

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Protecting-Group-Free Total Synthesis of (−)-Rhazinilam and (−)-Rhazinicine using a Gold-Catalyzed Cascade Cyclization**

*Kenji Sugimoto, Kazuki Toyoshima, Shiori Nonaka, Kenta Kotaki, Hirofumi Ueda, and Hidetoshi Tokuyama**

(−)-Rhazinilam (**1**), isolated from various Apocynaceae species, originally from *Rhazya stricta* Decaisne, is a member of the Aspidosperma class of alkaloids (Figure 1).[1,2] This compound interferes with tubulin polymerization and dynamics. Because of its significant biological

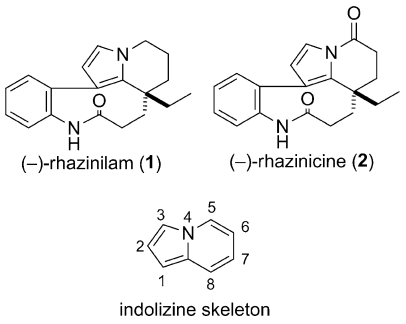
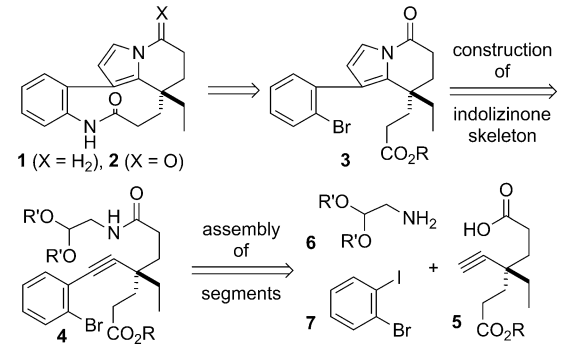


Figure 1. (−)-Rhazinilam (**1**), (−)-rhazinicine (**2**), and an indolizine skeleton.

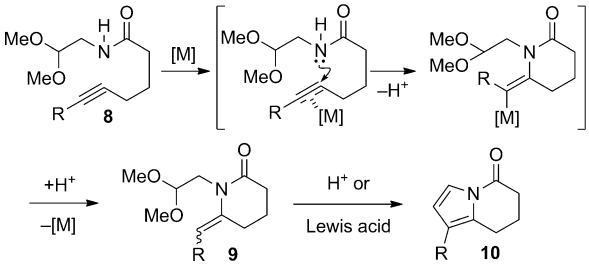
effects, (−)-rhazinilam (**1**) and its congeners such as (−)-rhazinicine (**2**)[3] have been recognized as lead compounds for new antitumor agents.[4] In addition to its interesting biological activity, its unique structure, with a nine-membered lactam ring fused to its 5,6,7,8-tetrahydroindolizine skeleton and a quaternary carbon center, has received considerable attention as a synthetic target and provided an attractive platform for demonstrating the utility of novel synthetic methodologies and tactics.[5] We describe herein a total synthesis of (−)-rhazinilam (**1**) and the first total synthesis of (−)-rhazinicine (**2**) using a facile construction of the highly substituted indolizinone by a newly developed gold-catalyzed cascade cyclization reaction.

Our retrosynthetic analysis of **1** and **2** is outlined in Scheme 1. The nine-membered lactam ring would be formed



Scheme 1. Retrosynthetic analysis of **1** and **2**.

at the final stage of the synthesis. We planned to construct the bicyclic indolizinone skeleton **3** by double cyclization of the acyclic precursor **4**. Our working hypothesis for the sequential cyclization via an enamide is depicted in Scheme 2, and starts



Scheme 2. Working hypothesis for formation of 5-indolizinone.

from an intramolecular nucleophilic addition of a nitrogen atom to the alkyne activated by a π-philic metal catalyst, such as a gold or platinum complex, in a 6-*exo*-dig fashion.[6–8] Then, cyclization of the resultant enamide **9** to the terminal acetal moiety and subsequent aromatization should provide the indolizinone **10**.[9] The fully elaborated acyclic compound **4**, a substrate for the sequential reactions, would be readily prepared by assembling three segments, **5**–**7**, by amide formation and Sonogashira coupling (Scheme 1).[10]

At the outset of our research, we tested the working hypothesis using the ynamide **11a** as a substrate, which was prepared by condensation of commercially available 5-hexynoic acid and aminoacetaldehyde dimethylacetal and subsequent Sonogashira coupling[10] with iodobenzene. The results obtained by the treatment of **11a** with various π-philic metal catalysts are summarized in Table 1. Disappointingly,

[*] Dr. K. Sugimoto, K. Toyoshima,[+] S. Nonaka,[+] K. Kotaki, Dr. H. Ueda, Prof. Dr. H. Tokuyama
Graduate School of Pharmaceutical Sciences, Tohoku University
Aoba 6-3, Aramaki, Aoba-ku, Sendai 980-8578 (Japan)
E-mail: tokuyama@mail.pharm.tohoku.ac.jp

[+] These authors contributed equally to this work.

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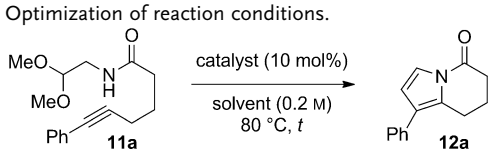
Table 1: Optimization of reaction conditions.



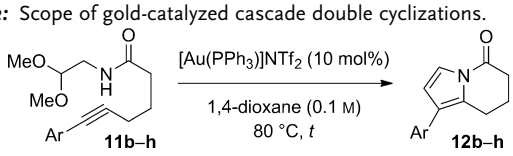
Entry	Catalyst[a]	Solvent	t [h]	Yield [%]
1	AuCl	$ClCH_2CH_2Cl$	24	–
2	$AuCl_3$	$ClCH_2CH_2Cl$	24	–
3	$[Au(PPh_3)Cl]$	$ClCH_2CH_2Cl$	24	–
4	AuCl, AgOTf	$ClCH_2CH_2Cl$	8	–
5	$[Au(PPh_3)Cl]$, AgOTf	$ClCH_2CH_2Cl$	7	20
6	$[Au(PPh_3)Cl]$, $AgNTf_2$	$ClCH_2CH_2Cl$	2.5	20
7	$[Au(PPh_3)]NTf_2$	$ClCH_2CH_2Cl$	11	50
8	$[Au(PPh_3)]NTf_2$	1,4-dioxane[b]	11	69
9	[(Cy-JohnPhos)Au]NTf_2	1,4-dioxane[b]	11	64

[a] CuI or $PdCl_2$ did not give **12a**. [b] Concentration of **11a** was 0.1 M. Tf = trifluoromethanesulfonyl.

the initial trials using AuCl, $AuCl_3$, $[Au(PPh_3)Cl]$, or a combination of AuCl with AgOTf[11] in 1,2-dichloroethane at 80 °C resulted in formation of neither enamide nor the indolizinone **12a** (entries 1–4). Surprisingly, when we heated **11a** with $[Au(PPh_3)Cl]$ in the presence of AgOTf, the reaction did not stop at the enamide stage, but the expected sequential processes proceeded all the way to the bicyclic product **12a** in one pot, albeit in low yield (entry 5). Using a combination of $[Au(PPh_3)Cl]$ and $AgNTf_2$[8a,12] improved the conversion rate but the yield still remained at 20% (entry 6). After extensive experimentations, we found that the preformed $[Au(PPh_3)]NTf_2$[12] catalyzed the cascade process more effectively to provide **12a** in 50% yield (entry 7). Eventually, yield of **12a** was improved to 69% by heating a mixture of $[Au(PPh_3)]NTf_2$ (10 mol%) and **11a** in 1,4-dioxane (0.1 M; entry 8).[13] The catalyst with a bulky ligand[14] gave **12a** in a comparable yield (entry 9).

Encouraged by these promising results, we then investigated the scope of the gold-catalyzed cascade for the synthesis of substituted indolizinones (Table 2). Ynamides having various substituents such as methyl, Cbz-protected amino, methoxy, and bromo groups on the *para* position of the benzene ring, uneventfully gave the corresponding cyclization products in low to good yields (entries 1–4). A substrate

Table 2: Scope of gold-catalyzed cascade double cyclizations.

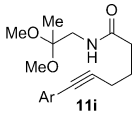
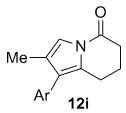
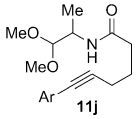
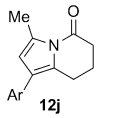
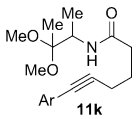
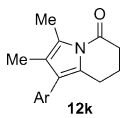


Entry	Substrate	Product	t [h]	Yield [%]
1	**11b** (Ar = 4-MeC_6H_4)	**12b**	7.5	59
2	**11c** (Ar = 4-$CbzHNC_6H_4$)	**12c**	11.5	67
3[a]	**11d** (Ar = 4-$MeOC_6H_4$)	**12d**	25	23
4	**11e** (Ar = 4-BrC_6H_4)	**12e**	10.5	59
5	**11f** (Ar = 2-BrC_6H_4)	**12f**	18	60
6	**11g** (Ar = 4-$O_2NC_6H_4$)	**12g**	15	92
7	**11h** (Ar = 3-$O_2NC_6H_4$)	**12h**	15	79

[a] $[Au(PPh_3)]NTf_2$ (20 mol%) was used. Cbz = benzyloxycarbonyl.

having an *ortho*-bromo group also gave the desired product in a comparable yield (entry 5). Interestingly, nitro-substituted substrates, especially at the a *para*-substituted benzene ring, showed remarkable reactivity, thus affording the corresponding 1-aryl indolizinone in good to almost quantitative yields (entries 6 and 7).[15] Furthermore, this methodology is feasible for the synthesis of multisubstituted indolizinones (Table 3). Thus, reactions of the ynamides **11i–k**, which were readily prepared by introduction of amine segments derived from glycine or alanine in a few steps, furnished the corresponding 1,2-, 1,3-, or 1,2,3-substituted indolizinones in good yields (entries 1–3).

Table 3: Construction of multisubstituted indolizinones.[a]

Entry	Substrate[b]	Product	t [h]	Yield [%]
1	 11i	 12i	4	65
2[c]	 11j	 12j	22.5	85
3[d]	 11k	 12k	5	50

[a] Reaction conditions: $[Au(PPh_3)]NTf_2$ (10 mol%), ynamide (0.1 M) in 1,4-dioxane, 80 °C. [b] Ar = 4-nitrophenyl. [c] Used $[Au(PPh_3)]NTf_2$ (20 mol%). [d] Used $[Au(PPh_3)]NTf_2$ (20 mol%) at 100 °C.

The successful establishment of the highly efficient cascade construction of multisubstituted indolizinones prompted us to undertake synthetic studies on (−)-rhazinilam (**1**) and (−)-rhazinicine (**2**) by using this methodology as a key step.

Our synthesis commenced with preparation of the fully functionalized ynamide **13** having the requisite all-carbon atoms to synthesize **1** and **2** (Scheme 3). Thus, construction of the quaternary stereocenter was accomplished by using the diastereoselective Michael reaction as reported by d'Angelo et al.,[16] using a chiral enamine intermediate derived from 2-ethylcyclohexanone (**14**) and (*S*)-1-phenethylamine to obtain the ketoester **15**. After conversion of **15** into the epoxyketone **16** in a three-step sequence, Eschenmoser–Tanabe-type fragmentation was effected by conversion of **16** into a semicarbazone and subsequent oxidative fragmentation under the reaction conditions reported by Warkentin et al.[17] to give aldehyde with a terminal acetylene.[18] The aldehyde was oxidized by Pinnick oxidation[19] to provide the carboxylic acid **17**. Finally, condensation with aminoacetaldehyde dimethylacetal and subsequent Sonogashira coupling with 2-bromoiodobenzene furnished the key ynamide **13**.

With the fully elaborated ynamide **13** in hand, the stage was now set for the crucial cascade double cyclization. However, we were disappointed to find that reaction under the established optimal reaction conditions resulted in only 28% yield of the desired indolizinone **18** and formation of

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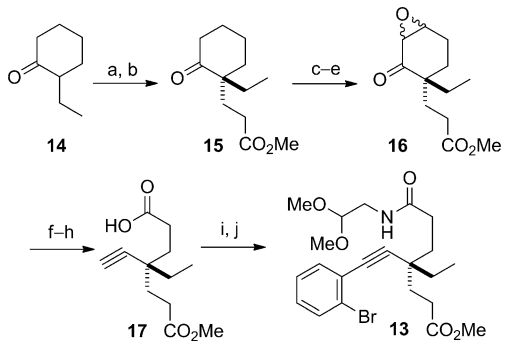
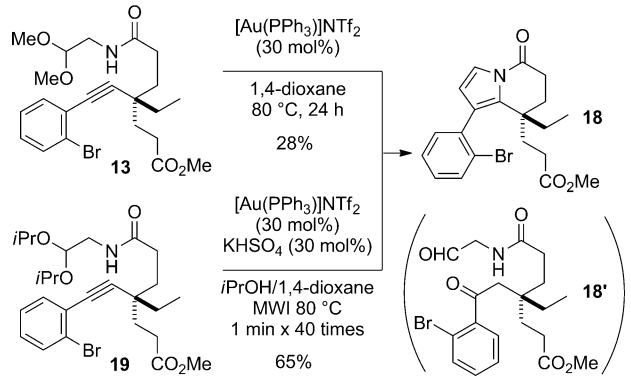


Scheme 3. Preparation of the ynamide **13**. Reagents and conditions: a) (*S*)-(−)-1-phenethylamine, toluene, reflux, 18 h. b) Methyl acrylate, RT, 7 d; then AcOH, MeOH/H_2O (3:5), RT, 3 h, 83% (2 steps), >99% *ee*. c) TMSCl, Et_3N, DMF, 100°C, 46 h. d) DDQ, 2,6-lutidine, toluene, RT, 4 d, 80% (2 steps). e) 37% aq. H_2O_2, 20% NaOH aq., MeOH, 0°C, 0.5 h, 92%. f) Semicarbazide hydrochloride, NaOAc·3H_2O, MeOH/H_2O (2:1), RT, 10 h. g) $Pb(OAc)_4$, CH_2Cl_2, −10°C, 2 h. h) $NaClO_2$, NaH_2PO_4·2H_2O, 2-methyl-2-butene, *t*BuOH/H_2O (3:1), 0°C, 2 h, 69% (3 steps). i) Aminoacetoaldehyde dimethylacetal, EDCI, HOBt, DMAP, CH_2Cl_2, RT, 3 h, 81%. j) 2-Bromoiodobenzene, [Pd-(PPh_3)$_2$$Cl_2$] (3 mol%), CuI (6 mol%), Et_3N, DMF, 50°C, 2 h, 88%. DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone, DMAP = 4-(dimethylamino)pyridine, DMF = *N*,*N*-dimethylformamide, EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, HOBt = 1-hydroxybenzotriazole, TMS = trimethylsilyl.

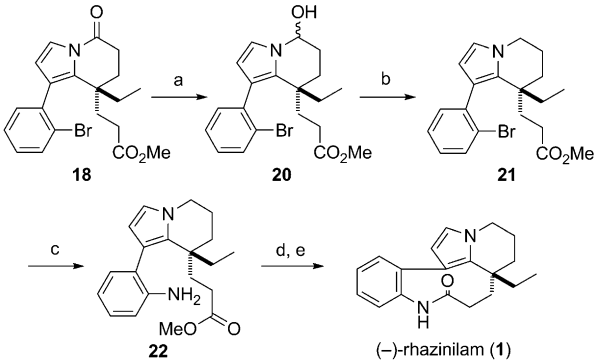
a substantial amount of the ketoaldehyde **18′** (Scheme 4). The low yield could be due to the steric bulkiness of the quaternary carbon center adjacent to the triple bond, which slows the initial cyclization step and causes decomposition of the acetal. Then, conversion of the triple bond into the ketone may have occurred by gold-catalyzed methanolysis. We reasoned that the undesired conversion of the triple bond would be suppressed by use of an acetal substrate derived from a sterically demanding alcohol. Thus, we prepared the diisopropyl acetal **19** and subjected it to the same reaction conditions. The generation of **18′** was suppressed, however, we did not observe significant improvement in the yield of **18** (33%). Expecting acceleration effects both on the first and the second cyclization steps, we then examined microwave irradiation and additives. After extensive optimization, we eventually found that reaction with irradiation of microwave



Scheme 4. Construction of 5-indolizinone by gold-catalyzed cascade cyclization. MWI = microwave irradiation.

intermittently (one minute × 40 intervals) in the presence of catalytic $KHSO_4$ in 2-propanol and 1,4-dioxane provided the desired indolizinone **18** in satisfactory yield.

Having successfully constructed the highly substituted indolizinone core by the cascade reaction, we then focused on the formation of the nine-membered lactam ring to complete a total synthesis of (−)-rhazinilam (Scheme 5). Because of a highly reactive nature toward nucleophiles,[20] the *N*-acyl



Scheme 5. Total synthesis of (−)-rhazinilam (**1**). Reagents and conditions: a) $NaBH_4$, $CeCl_3$·7H_2O, MeOH, 0°C, 2 h. b) $NaBH_3CN$, AcOH, MeCN, RT, 2 h, 80% (2 steps). c) NaN_3, CuI (2 equiv), MeHN-$(CH_2)_2$NHMe (3 equiv), DMSO, 100°C, 48 h, 64%. d) KOH, MeOH, RT, 30 min; aq. HCl. e) EDCI, HOBt, CH_2Cl_2, RT, 8 h, 76% (2 steps). DMSO = dimethyl sulfoxide.

pyrrole functionality was initially reduced in a stepwise manner by Luche conditions and subsequent $NaBH_3CN$ reduction in acidic media to give **21**. The aryl bromide **21** was then converted into aniline **22** by a one-pot copper-mediated reaction via an aryl azide.[21] Finally, saponification of the ester and subsequent lactamization furnished (−)-rhazinilam (**1**). All the properties of synthetic **1** were identical to published data.[2]

In contrast to (−)-rhazinilam (**1**), it was a difficult challenge to construct the nine-membered lactam ring of (−)-rhazinicine (**2**) and leave the highly reactive *N*-acyl pyrrole functionality untouched. Thus, the copper-mediated conversion into aniline resulted in decomposition of **18**. Even under mild saponification conditions using LiOH in THF, the ring opening of the six-membered lactam ring occurred to afford a dicarboxylic acid with loss of chirality. The requisite conversion of the methyl ester **18** to the corresponding carboxylic acid was best effected by treatment with TMSI.[22] Then, the resultant carboxylic acid was converted into an amide by activation with CDI and subsequent treatment with ammonium hydroxide. Gratifyingly, crucial formation of the nine-membered lactam ring proceeded by copper-mediated intramolecular amidation[23] to furnish (−)-rhazinicine (**2**; Scheme 6). The physical and spectral properties, including optical rotation of synthetic **2**, were identical to those reported for the natural product.[3]

In summary, we have achieved a total synthesis (−)-rhazinilam (**1**) and the first asymmetric total synthesis of (−)-rhazinicine (**2**) by using the efficient construction of the per-substituted indolizinone core though a gold-catalyzed cascade

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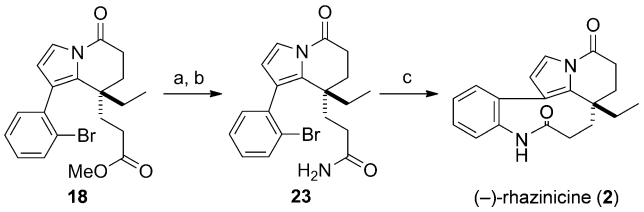

Scheme 6. Total synthesis of (−)-rhazinicine (**2**). Reagents and conditions: a) TMSI (5 equiv), $CHCl_3$, 80 °C, 12 h, 94 %. b) CDI (1.2 equiv), THF, RT, 2 h; NH_4OH, RT, 83 %. c) CuI (5 equiv), CsF (5 equiv), $MeHN(CH_2)_2NHMe$ (5.15 equiv), xylene, 150 °C, 120 h, 61 %. CDI = 1,1′-carbonyldiimidazole.

reaction of linear substrates. The mild reaction conditions for the construction of the indolizinone core and the nine-membered lactam ring allowed us to achieve these protecting-group-free total syntheses.[24] We have also demonstrated the scope and generality of this cascade reaction for synthesis of highly substituted indolizinones. Further applications of this gold-catalyzed cascade reaction for the construction of other heterocyclic skeletons are currently under investigation, and will be reported in due course.

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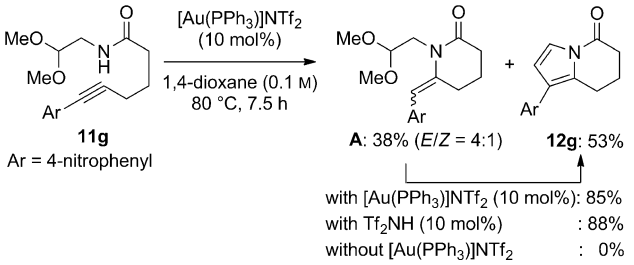

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