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Total Synthesis of (−)-Rhazinilam and Formal Synthesis of (+)-Eburenine and (+)-Aspidospermidine: Asymmetric Cu-Catalyzed Propargylic Substitution

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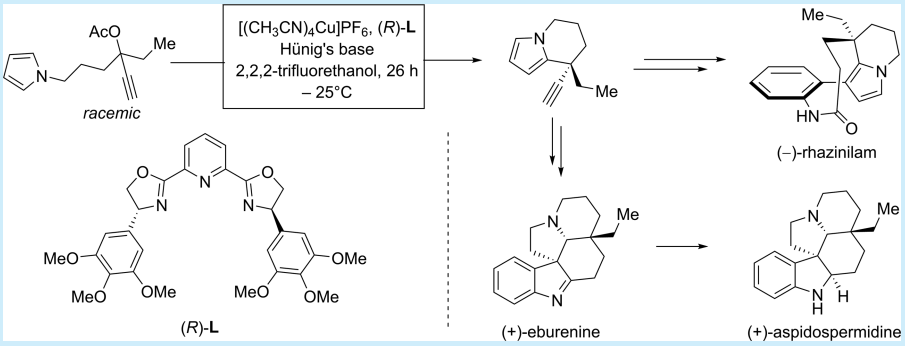
Supporting Information



ABSTRACT: A total synthesis of (−)-rhazinilam and formal syntheses of (+)-eburenine and (+)-aspidospermidine that rely on a copper(I)-catalyzed asymmetric propargylic substitution as the key step are reported. A salient feature of the reaction is the asymmetric construction of a quaternary stereocenter in high yield and enantiomeric excess.

The monoterpene indole alkaloid (−)-rhazinilam (**1**) was originally isolated from the plant species *Rhazya stricta*, which grows wild in the desert regions of Iraq, Saudi Arabia, and Yemen as well as northwestern regions of the Indian subcontinent.[1] Biological studies of **1** revealed cytotoxic activity toward various cancer cell lines in the low micromolar range in vitro,[2] where it was shown to inhibit microtubule assembly and disassembly as well as the formation of abnormal tubulin spirals.[3,4] Accordingly, (−)-rhazinilam (**1**) has been recognized as a lead compound for the development of new antitumor agents. Structurally, this natural product contains a nine-membered lactam fused to a 5,6,7,8-tetrahydroindolizine possessing a quaternary stereocenter.

The unique structure of rhazinilam (**1**), coupled with its potent biological activity, sparked interest within the synthetic community. In the early 1970s, Smith and co-workers disclosed the first total synthesis of (±)-rhazinilam.[5a] To date, various approaches toward the synthesis of rhazinilam (**1**) have been reported in the literature.[5−7] Within these approaches, the stereocontrolled formation of the quaternary center has typically represented a key challenge.[6,8] Complex structures such as these compel researchers to develop novel strategies and methods for their construction. In previous asymmetric syntheses of (−)-rhazinilam, the stereoselective formation of the quaternary center was achieved by nucleophilic attack of a pyrrole on various electrophilic sites (Figure 1A). Nelson and co-workers reported a Au(I)-catalyzed addition of pyrrole to an enantioriched allene,[6b] and Banwell and co-workers employed chiral amine organocatalysis to effect conjugate addition of a pyrrole.[6c] Herein we report the development of an intramolecular Cu-catalyzed asymmetric propargylation using a pyrrole as a C-nucleophile and its application to the total

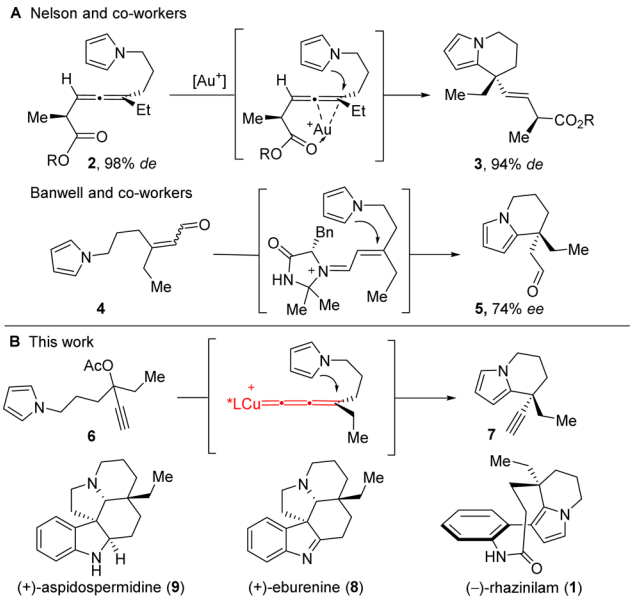


Figure 1. Structure and syntheses of (−)-rhazinilam (**1**).

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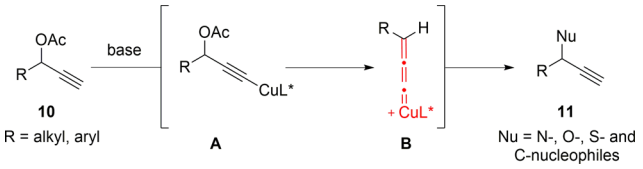
synthesis of (−)-rhazinilam (**1**) and formal syntheses of (+)-eburenine (**8**) and (+)-aspidospermidine (**9**) (Figure 1B).

Recently, asymmetric Cu-catalyzed substitution reactions of racemic propargyl alcohol derivatives have attracted considerable attention (Scheme 1).[9] Several classes of nucleophiles,

Scheme 1. Copper-Catalyzed Propargylic Substitution

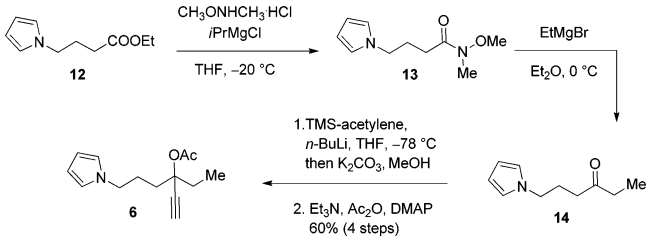


including alcohols, amines, and sulfides, have been used to efficiently generate propargylic stereocenters with high levels of enantioselectivity.[10] These reactions exploit the ability of copper acetylides **A**, generated from terminal propargylic alcohol derivatives, to form copper allenylidenes **B**, which are electrophilic at the carbon γ to the copper center. Indeed, modifying copper with chiral ligands renders the subsequent γ-attack enantioselective, thus generating the corresponding optically active substitution products. Success has also been found using C-nucleophiles, yet the extension of this class of nucleophiles to substrates leading to quaternary centers still remains limited. The sole report was by Nishibayashi in 2016, wherein an intermolecular asymmetric Cu-catalyzed indole propargylation was developed using racemic tertiary trifluoromethylated propargylic esters.[11]

We saw the chemistry of copper allenylidenes as an opportunity to design a synthetic approach to (−)-rhazinilam that centers on a novel intramolecular Cu-catalyzed propargylation of a pyrrole as the asymmetry-generating step in the route (Figure 1B). This strategy would allow the highly efficient construction of the 5,6,7,8-tetrahydroindolizine core while preserving an alkyne as a useful functional group handle.

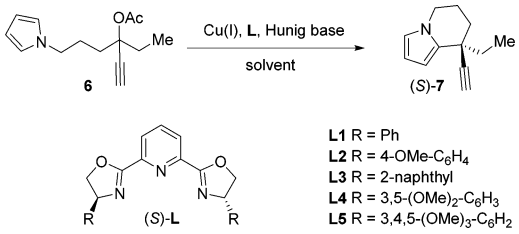
Cyclization precursor **6** was easily synthesized in four steps from known pyrrole **12** as shown in Scheme 2.[12] With **6** in hand, we began screening reaction conditions for the planned Cu-catalyzed asymmetric propargylation substitution.

Scheme 2. Synthesis of Cyclization Precursor 6



Initially, the combination of $(CuOTf)_2{\cdot}C_6H_6$ and a series of PyBOX ligands, which were previously reported to effectively act as ligands in Cu-catalyzed enantioselective propargylic amination, were tested (Table 1).[10a,b] An initial solvent and base screening revealed that MeOH and Hünig's base were optimal. Furthermore, experiments employing **L1**−**L5** allowed the desired bicyclic alkyne **7** to be obtained in high yield, yet only moderate levels of enantioselectivity were observed. Phenyl-substituted oxazoline **L1** resulted in a moderate e.r. of 71:29 (entry 4). When the electron density of the ligand was increased by methoxy substitution of the aromatic ring, alkyne

Table 1. Optimization of the Reaction Conditions[a]



entry	L	[Cu][b]	solvent[c]	t (h)	yield (%)[d]	e.r.
1	(*S*)-**L1**	A	toluene	24	47	–
2	(*S*)-**L1**	A	THF	24	36	–
3	(*S*)-**L1**	A	acetone	10	55	60:40
4	(*S*)-**L1**	A	MeOH	12	86	71:29
5	(*S*)-**L2**	A	MeOH	12	83	76:24
6	(*S*)-**L3**	A	MeOH	10	78	80:20
7	(*S*)-**L4**	A	MeOH	10	87	68:32
8	(*S*)-**L5**	A	MeOH	10	84	82:18
9	(*S*)-**L5**	B	MeOH	10	95	82:18
10	(*S*)-**L5**	C	MeOH	10	92	81:19
11	(*S*)-**L5**	B	TFE	8	95	86:14
12[e]	(*S*)-**L5**	B	TFE	26	89	90:10
13[e,f]	(*R*)-**L5**	B	TFE	26	90	11:89

[a]Reaction conditions: [Cu] (5 mol %) and ligand (10 mol %) in the solvent (0.1 M) from −8 to 0 °C. [b]A: $(CuOTf)_2{\cdot}C_6H_6$; B: $[(CH_3CN)_4Cu]PF_6$; C: $[(CH_3CN)_4Cu]BF_4$. [c]THF = tetrahydrofuran; TFE = 2,2,2-trifluoroethanol. [d]Isolated yields. [e]At −25 °C for 26 h. [f](*R*)-**7** was obtained as the major enantiomer.

7 was isolated in 83% yield with 76:24 e.r. (entry 5). These promising results prompted us to further modify the substitution pattern of the oxazoline. Hence, naphthyl-substituted ligand **L3** and trimethoxy-substituted ligand **L5** were synthesized and tested. Slightly higher selectivity was achieved with ligand **L3** (entry 6), and to our delight, alkyne **7** was isolated in 84% yield with 82:18 e.r. when **L5** was employed (entry 8). The use of different copper sources such as $[(CH_3CN)_4Cu]PF_6$ and $[(CH_3CN)_4Cu]BF_4$ provided slightly higher yields in the reaction (entries 9 and 10). Importantly, we noted that the enantioselectivity of the reaction could be slightly improved by switching to 2,2,2-trifluoroethanol as the solvent at −25 °C. Under these conditions, bicyclic alkyne **7** was obtained in 89% yield with 90:10 e.r. (entry 12). It should be noted that the use of activating groups other than acetate, such as propargylic carbonates, did not lead to any further improvement in the yield or e.r. The corresponding free propargylic alcohol did not show any reactivity under the optimized conditions and led only to recovery of the starting material.

With the optimized conditions in hand, our focus turned toward the completion of the synthesis of (−)-rhazinilam. As shown in Scheme 3, deprotonation of alkyne **7** and subsequent trapping with ethyl chloroformate followed by hydrogenation using Adam's catalyst afforded ester **15** in 75% yield. To our surprise, the use of standard peptide coupling reagents to convert the free acid to amide **16** failed because of the high nucleophilicity of the pyrrole and instead led to acylation at C3 of the pyrrole. However, the condensation of **15** with 2-iodoaniline could be effected in 97% yield using $AlMe_3$.

With this material in hand, we turned our attention to the formation of the nine-membered lactam **18**. In earlier syntheses, Trauner and co-workers demonstrated that the

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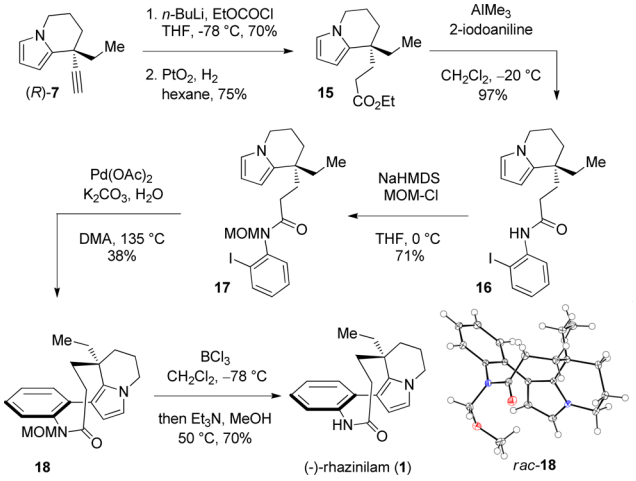
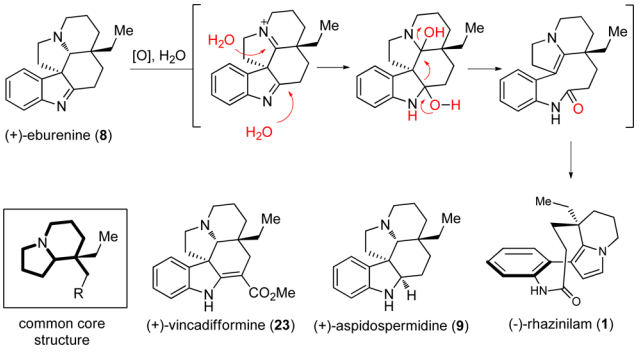
Scheme 3. Completion of the Total Synthesis of (−)-Rhazinilam



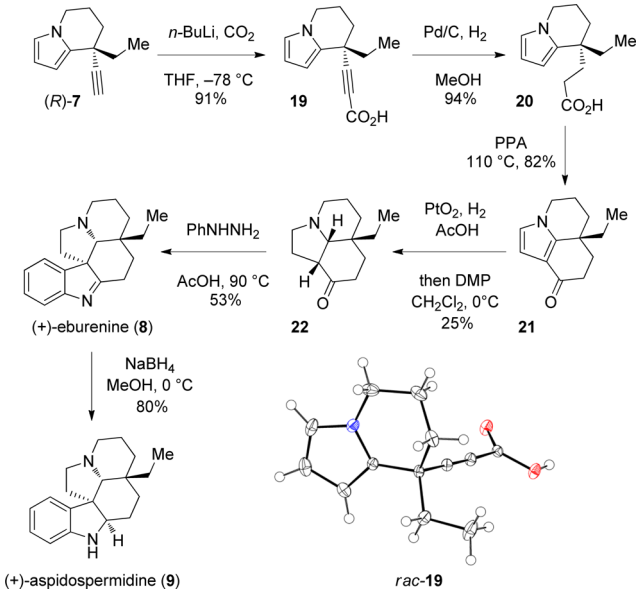
formation of similar macrocycles could be achieved by Pd-catalyzed biaryl coupling.[5d,13] In line with these reports, **16** was protected, giving **17** in 71% yield. However, Trauner's conditions led to isolation of the desired product in only 10% yield. Extensive screening studies were necessary to achieve the formation of lactam **18** by palladium catalysis. The highest yield of **18** (38%) was obtained using catalytic $Pd(OAc)_2$ with K_2CO_3 and DMA as the base and solvent, respectively. Furthermore, it was found that the addition of H_2O (10 equiv) was crucial for this reaction to proceed, while the use of phosphine ligands to modify Pd had minimal effect on the reaction outcome. Deprotection occurred upon exposure to BCl_3 at −78 °C in CH_2Cl_2, affording (−)-rhazinilam (**1**) in six steps from alkyne **7**. The spectroscopic data of the synthetic material matched those of the natural product. Comparison of the optical rotation of the synthetic material to that of the natural product enabled the configurational assignment of the copper-catalyzed transformation of propargylic ester **6** to indolizine **7**.

(−)-Rhazinilam (**1**) has been recognized as the oxidative degradation product of (+)-eburenine (**8**) and shares a common central structural feature of aspidosperma alkaloids (Scheme 4).[5a] In order to further exploit the novel Cu-catalyzed propargylic substitution, we turned our attention toward the synthesis of (+)-aspidospermidine (**9**) (Scheme 5). Lithiation of alkyne **7** with *n*-BuLi and quenching with CO_2 afforded acid **19** in excellent yield (91%). Subsequent hydrogenation using Pd/C converted alkynoic acid **19** to its

Scheme 4. Biosynthesis of (−)-Rhazinilam



Scheme 5. Formal Syntheses of (+)-Eburenine and (+)-Aspidospermidine



saturated analogue **20**, which readily engaged in an intramolecular Friedel−Crafts acylation upon treatment with polyphosphoric acid (PPA) to form tricyclic ketone **21**. Reduction with PtO_2 and H_2 followed by treatment with DMP provided pyrrolidine **22** as a single diastereomer in 25% yield over two steps. Tricycle **22** was also prepared by Banwell, yet that group was not successful in converting it to **9**.[14] However, we found that Fischer indolization could be used to obtain **8** in 53% yield. Reduction of the indoline moiety gave (+)-aspidospermidine (**9**) in 80% yield. Moreover, **8** can be converted to (+)-vincadifformine (**23**) and other related alkaloids via known procedures.[15]

In summary, we have developed an efficient asymmetric copper-catalyzed intramolecular substitution of propargylic acetate with pyrrole to enable rapid and asymmetric access to 5,6,7,8-tetrahydroindolizines bearing an all-carbon quaternary stereocenter. The utility of this copper-catalyzed asymmetric propargylic substitution was exemplified by a concise total synthesis of (−)-rhazinilam (**1**). Additionally, formal syntheses of (+)-eburenine (**8**) and (+)-aspidospermidine (**9**) were achieved from alkyne **7**, demonstrating the versatility of this approach. We are currently focusing on the expansion of this transformation in order to access other highly substituted propargylic products in an asymmetric fashion.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b02619.

Experimental procedures and full spectroscopic data for all new compounds (PDF)
Crystallographic data for *rac*-**18** (CIF)
Crystallographic data for *rac*-**19** (CIF)

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Notes

The authors declare no competing financial interest.

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