<u>LETTERS</u>

Asymmetric Total Synthesis of Sarpagine-Related Indole Alkaloids Hydroxygardnerine, Hydroxygardnutine, Gardnerine, (*E*)-16-*epi*-Normacusine B, and Koumine

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Supporting Information

ABSTRACT: Sarpagine-related indole alkaloids (-)-hydroxygardnerine, (+)-hydroxygardnutine, (-)-gardnerine, (+)-(E)-16-*epi*-normacusine B, and (-)-koumine were divergently synthesized via a common intermediate possessing a piperidine ring with an exocyclic (E)-ethylidene side chain, which was constructed by a gold(I)-catalyzed 6-*exo-dig* cyclization strategy.

We have recently developed a stereoselective gold(I)catalyzed 6-*exo-dig* cyclization reaction of silyl enol ether having an internal alkyne, which affords a piperidine derivative with an exocyclic (*E*)-ethylidene side chain (Figure 1), and



Figure 1. Gold(I)-catalyzed 6-*exo-dig* cyclization reaction and structures of gardnerine (1), hydroxygardnerine (2), hydroxygardnutine (3), and (E)-16-*epi*-normacusine B (4).

accomplished the total synthesis of conolidine and apparicine by using this product.¹ The piperidine ring with an exocyclic (*E*)-ethylidene side chain exists in many sarpagine-type monoterpenoid indole alkaloids² isolated from several genera, such as *Gardneria, Rauwolfia, Alstonia,* and *Gelsemium.*³ Gardnerine (1),⁴ one of the representative sarpagine-type indole alkaloids, was utilized for biomimetic chemical transformation into several *Gelsemium* alkaloids,⁵ such as gelsenicine,^{5a} des- N_a -methoxyhumantenirine,^{5b} 11-methoxy-19(*R*)-hy-



droxygelselegine,^{5c,d} and gelselegine.^{5a} Further, the partial synthesis of koumine⁶ and 11-methoxykoumine was achieved by the chemical conversion of natural hydoxygardnerine (2)⁷ in our laboratory.⁸ The total synthesis of several sarpagine-type alkaloids was accomplished by Cook's group, using mainly tryptophan derivatives as the starting material.^{2b,9} Herein we report an asymmetric total synthesis of sarpagine-related alkaloids, which involves the first total synthesis of (-)-hydroxygardnerine (2), (+)-hydroxygardnutine (3),⁴ and (-)-koumine (34) with natural absolute configuration¹⁰ by applying the gold-catalyzed 6-exo-dig cyclization reaction.

Our retrosynthetic analysis of sarpagine-type alkaloids gardnerine (1), (-)-hydroxygardnerine (2), and (+)-(E)-16-*epi*-normacusine B (4)¹¹ is shown in Scheme 1. Alkaloids 1, 2, and 4 and compound 5 are obtained from tricyclic ketone 6, which could be a common intermediate for the divergent synthesis of various sarpagine-type alkaloids, by manipulation of the indole nucleus having various substituents on the benzene part and preservation/removal of the allylic hydroxyl group.

The piperidine ring with an (*E*)-ethylidene side chain in tricyclic ketone **6** could be constructed by the gold(I)-catalyzed 6-*exo-dig* cyclization of alkynyl silyl enol ether 7. Silyl enol ether 7 would be derived by alkylation of keto amine **8**, which could be synthesized from known (+)-9-azabicyclo[3.3.1]nonane-2,6-diol derivative **9**.¹²

Employing azabicyclononane 9, which was prepared from 1,5-cyclooctadiene in four steps, as the starting material, we initially prepared alkynyl silyl enol ether 10 for use as the substrate in the gold(I)-catalyzed cyclization (Scheme 2). Swern oxidation of 9 and subsequent partial reduction of the resultant diketone by treatment with BH_3 ·THF gave monoalcohol 11. After acetylation of the hydroxyl group in 11 and deprotection of the benzyl group in acetate 12, the resultant

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Scheme 1. Retrosynthetic Analysis of Alkaloids 1, 2, and 4



Scheme 2. Synthesis of Alkynyl Silyl Enol Ethers 10 and 19



keto amine 8 was alkylated with alkyne 13 in the presence of K_2CO_3 in MeCN to afford alkyne ketone 14. The primary alcohol in 14 was protected by MOM ether, and treatment of ketone 15 with TIPSOTf in the presence of Et_3N in CH_2Cl_2 gave alkynyl silyl enol ether 10.

Next, we carried out the gold(I)-catalyzed cyclization of alkynyl silyl enol ether **10** (Scheme 3). Treatment of **10** with Au catalyst **16**¹³ (10 mol %) and AgBF₄ (10 mol %) in MeCN-H₂O (10:1) at 80 °C gave the desired 6-exo-dig-cyclized product **17** in 50% yield, together with undesired 7-endo-dig cyclized product **18** in 32% yield. To improve the selectivity of the cyclization mode, i.e., 6-exo-dig vs 7-endo-dig, the protecting group of alcohol in the alkyne part was changed from MOM to a bulky trityl group. Alkynyl silyl enol ether **19**

Scheme 3. Gold(I)-Catalyzed 6-Exo-Dig Cyclization of Alkynyl Silyl Enol Ethers 10 and 19



having a trityl ether was prepared from 12 via alkylation of 8 with alkyne 20 and silyl enol etherification of 21. As expected, the gold(I)-catalyzed cyclization of 19 with Au catalyst 16 (3 mol %) and AgBF₄ (3 mol %) in MeCN-H₂O at 80 °C gave predominantly *6-exo-dig*-cyclized product 22 in 85% yield along with 7-endo-dig-cyclized product 23 in 15% yield.

Thus, obtained cyclized product 22 was deacetylated, and the C1 unit corresponding to C-17 was introduced by treating ketone 24 with Tebbe reagent in the presence of pyridine in THF in 72% yield (Scheme 4). Swern oxidation of exo olefinic compound 25 followed by deprotection of the trityl group in 26 gave ketone 27, the substrate for the indole synthesis.



Next, we turned our attention to the synthesis of gardnerine $(1)^{14}$ and hydroxygardnerine (2) (Scheme 5). After protection of allyl alcohol in ketone 27 with an acetyl group, Fischer indole synthesis of ketone 28 with phenylhydrazine 29 in the presence of pyridine HCl in pyridine¹⁵ was conducted to give desired 11-methoxyindole 30 in 79% yield together with 9methoxy isomer in 15% yield. The regio- and diastereoselective introduction of a hydroxyl group at the C-17 position was achieved by hydroboration of 30 by 9-BBN followed by oxidation¹⁴ in 67% yield. Finally, deprotection of the benzyl group on N₂ in **31** by the Birch reduction at -78 °C gave hydroxygardnerine (2) in 63% yield. When the Birch reduction was carried out at -30 °C, gardnerine (1) was selectively obtained in 77% yield via deoxygenation at C-18 position and debenzylation.¹⁰ Hydroxygardnerine (2) was oxidized with DDQ in THF^{16} to afford hydroxygardnutine (3).

Scheme 5. Synthesis of Gardnerine (1), Hydroxygardnerine (2), and Hydroxygardnutine (3)



According to the above-mentioned procedure, ketone 27 was converted into (E)-16-*epi*-normacusine B $(4)^{17}$ having a nonsubstituted indole A ring in three steps: indole synthesis by using 1-benzyl-1-phenylhydrazine; hydroboration/oxidation of indole 32; and the Birch reduction of 33 at -30 °C to yield 4 (Scheme 6). On the other hand, the Birch reduction of 33 at -78 °C selectively afforded 5 in 90% yield. Then, using compound 5, the synthesis of (-)-koumine (34) was achieved in four steps according to a previously reported method⁸ that featured the C/D ring opening of 5 to give 35 and the intramolecular coupling reaction between C-7 and C-20 positions in 37 using palladium catalysis.

In conclusion, we have succeeded in the asymmetric total synthesis of sarpagine-related indole alkaloids, including the first total synthesis of (-)-hydroxygardnerine (2), (+)-hydroxygardnutine (3), and (-)-koumine (34) with natural absolute configuration. The divergent synthesis of sarpagine-type compounds features the gold(I)-catalyzed 6-exo-dig cyclization to furnish a piperidine ring having an exocyclic (E)-ethylidene side chain, the construction of an indole nucleus having various substituents on the benzene ring, and the preservation/removal of the allylic hydroxyl group by temperature control in the Birch reduction. Further synthetic study of other sarpagine-related alkaloids is underway in our laboratory.





ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-glett.6b00661.

Experimental procedures for the preparation of compounds 1-5, 8, 10-12, 14, 15, 17-28, and 30-37 and ¹H and ¹³C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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