CHEMICAL CONVERSION OF GARDNERINE INTO KOUMIDINE BY INVERTING THE ETHYLIDENE SIDE CHAIN WITH PALLADIUM CATALYST

Hiromitsu TAKAYAMA and Shin-ichiro SAKAI*

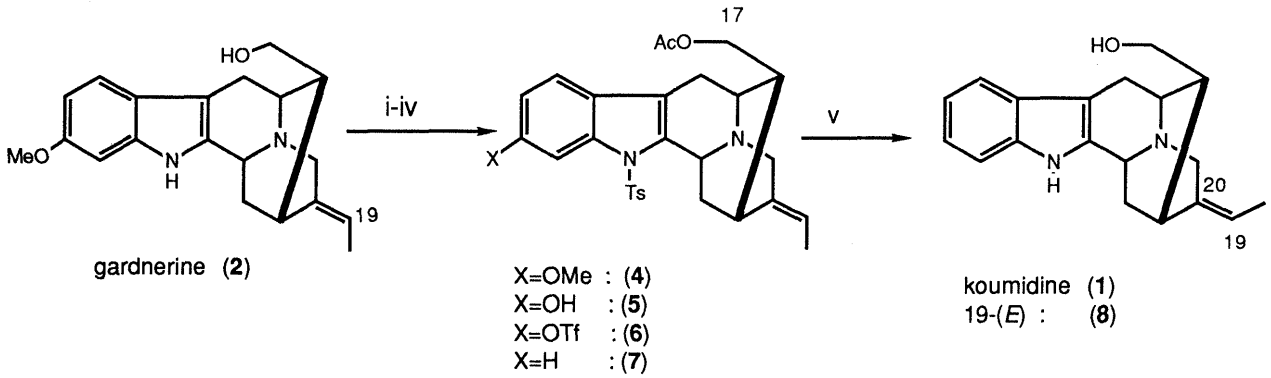
Faculty of Pharmaceutical Sciences, Chiba University, 1-33 Yayoi-cho, Chiba 260, Japan

A minor *Gelsemium* alkaloid, koumidine (**1**), was synthesized from gardnerine (**2**) by the demethoxylating the indole ring and the inverting the configuration of the ethylidene side chain with palladium catalyst.

KEYWORDS *Gelsemium* alkaloid; koumidine; 19-(*E*)-koumidine; gardnerine; chemical conversion; olefin inversion; palladium catalyst

Koumidine (**1**), a minor constituent of *Gelsemium elegans* Benth., was first isolated by a Chinese group[1] and the structure, which had an unusual 19-(*Z*) ethylidene side chain compared with that of the conventional sarpagine class of indole alkaloids, was revised by us[2] and the Cordell group.[3] Koumidine (**1**) is considered to be one of the important biosynthetic intermediates of some *Gelsemium* alkaloids, such as 19-(*Z*)-taberpsychine, humantenine, koumine, gelsemine, etc.[4] During course of studies on the biomimetic synthesis of *Gelsemium* alkaloids,[5, 6] we needed a large quantity of koumidine (**1**). Recently we established the synthetic route of koumidine (**1**) from ajmaline in 15 steps.[7] However, a more concise way to get (**1**) was highly required. Therefore, we have developed a synthesis of koumidine (**1**) from gardnerine (**2**), which was readily obtainable from *Gardneria nutans*.[8] The transformation involves two structural changes of the starting material (**2**): 1) removing the methoxy group from the aromatic ring and 2) inverting the 19-(*E*) ethylidene side chain to 19-(*Z*) form. Here we report an efficient alternative synthesis of koumidine (**1**) that features the inversion of the ethylidene side chain assisted by palladium catalyst.

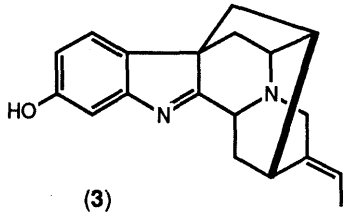
The first attempt to cleave the methyl ether on the indole ring of gardnerine (**2**) using sodium thioethoxide in dimethyl formamide (DMF) gave the abnormal indolenine derivative (**3**). Demethylation of the aryl methyl ether was cleanly achieved by applying Fujita's procedure[9] to the N_a-tosyl derivative (**4**), which was prepared in 98% yield from 17-O-acetylgardnerine by treatment with *p*-toluenesulfonyl chloride in an aqueous 50% KOH and benzene (1:1) solution in the presence of tetra-*n*-butylammonium hydrogensulfate. The reaction of (**4**) with aluminum chloride (4 eq.) in ethanethiol and dry CH_2Cl_2 at -18°C for 3 h afforded the desired phenolic compound (**5**) [mp 248-255°C (dec.)] in 91% yield. Next we used the palladium catalyzed triethylammonium formate reduction of aryl triflate to deoxygenate phenol.[10] Triflate (**6**), prepared in 97% yield from (**5**) with trifluoromethanesulfonic anhydride and triethylamine in dry CH_2Cl_2, was treated with 0.2 eq. of palladium acetate, 0.4 eq. of 1,1'-bis(diphenylphosphino)ferrocene (DPPF), triethylamine, and formic acid in DMF at 60°C for 2 h to produce deoxygenated compound (**7**) in 98% yield. Reductive deprotection of N_a-tosyl and 17-O-acetyl group in (**7**) with lithium aluminum hydride in THF (reflux, 6 h) gave rise to 19-(*E*)-koumidine (**8**), mp 170-172°C, in 95% yield. The structure of (**8**) was confirmed by the comparison of the spectroscopic data (^1H and ^{13}C-NMR, IR, and MS) with those of koumidine (**1**). On the other hand, by treating (**7**) at room temperature for 50 h with a large excess of magnesium (turnings) in dry methanol in the presence of a 0.1 eq. of palladium chloride and 0.2 eq. of triphenylphosphine, deprotection and the inversion of the configuration of the double bond proceeded simultaneously to afford koumidine (**1**) as the major product (48% yield) along with the isomer (**8**) (34% yield) and 19,20-dihydrokoumidine (7% yield). Semisynthetic koumidine (**1**), mp 200-201°C, had spectral properties (^1H-NMR, IR, UV, and MS) in accord with those of a natural sample. Palladium catalyst, phosphine ligand, magnesium, and methanol altogether is essential for the olefin inversion reaction. The plausible mechanism of this reaction would involve the metal hydride 1, 2 addition/β-hydride elimination process.[11] The optimization of the reaction condition of palladium-catalyzed olefin inversion and its application to the indole alkaloid synthesis are in progress in this laboratory.



gardnerine (**2**)

X=OMe : (**4**)
X=OH : (**5**)
X=OTf : (**6**)
X=H : (**7**)

koumidine (**1**)
19-(*E*) : (**8**)



(**3**)

Reagents and conditions
i, Ac_2O, pyridine, r.t., 8 h, 97%; TsCl, n-Bu_4NHSO_4, 50%KOH-benzene, r.t., 3 h, 98%.
ii, $AlCl_3$, EtSH, CH_2Cl_2, -18°C, 3 h, 91%.
iii, $(CF_3SO_2)_2O$, Et_3N, CH_2Cl_2, -20°C, 10 min, 97%.
iv, $Pd(OAc)_2$, DPPF, Et_3N, HCOOH, DMF, 60°C, 2 h, 98%.
v, Mg, $PdCl_2$, PPh_3, MeOH, r.t., 50 h, 48% (1), 34% (8).

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