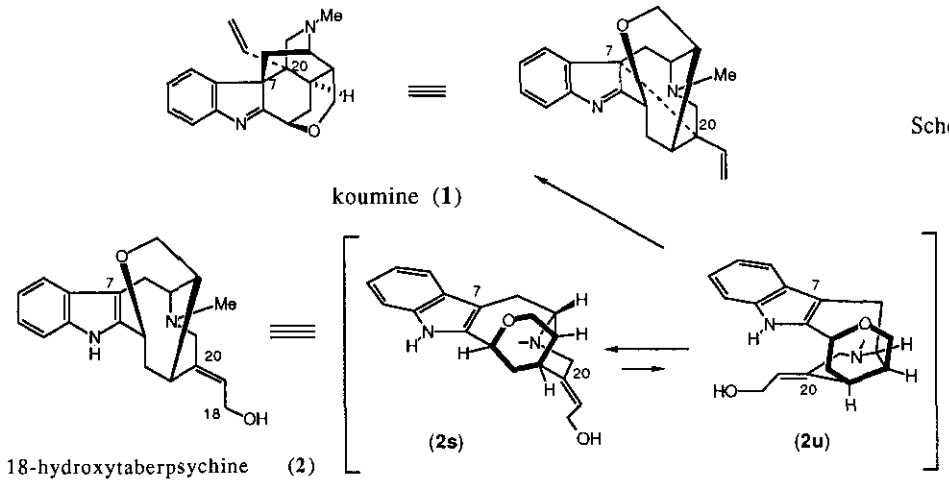
BIOMIMETIC SYNTHESIS OF KOUMINE BY THE PALLADIUM-CATALYZED INTRAMOLECULAR COUPLING REACTION OF 18-HYDROXYTABERPSYCHINE (18-HYDROXYANHYDROVOBASINEDIOL)†

Hiromitsu Takayama, Mariko Kitajima, and Shin-ichiro Sakai*

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

Abstract--A principal *Gelsemium* alkaloid, koumine (**1**) was synthesized from 18-hydroxygardnutine (**3**) *via* the demethoxylation from the indole ring and the palladium-catalyzed cyclization between C_7 and C_{20} of the hypothetical biogenetic intermediate, 18-hydroxytaberpsychine (**2**).

From the Chinese toxic medicinal plant Kou-Wen or Hu-Mang-Teng (*Gelsemium elegans* Benth), more than 30 indole alkaloids were isolated.[1-7] Most of these may be classified into six different structure types, *i.e.* gelsemine-type, gelsedine-type, humantenine-type, sarpagine-type, sempervirine-type, and koumine-type.[1] Among them, koumine (**1**) has especially unique cage structure. Biogenetically, koumine (**1**) would generate *via* the intramolecular coupling between C_7 and C_{20} positions in unnatural 18-hydroxytaberpsychine (**2**).[4,8](Scheme 1) As part of our program on the chemical studies on the Gelsemium alkaloids,[9-12] we were interested to achieve chemically this final stage in the biosynthesis of koumine (**1**). Koumine (**1**) was already synthesized from taberpsychine by treatment with $SeO_2/H_2O_2/H_3O^+$.[13, 14] However, this crucial step proceeded in 25% yield under very restricted reaction conditions. Then, we chose 18-hydroxytaberpsychine (**2**) as the substrate of the biomimetic transformation into koumine (**1**) in order to develop a more efficient coupling reaction between C_7 and C_{20}.[15] 18-

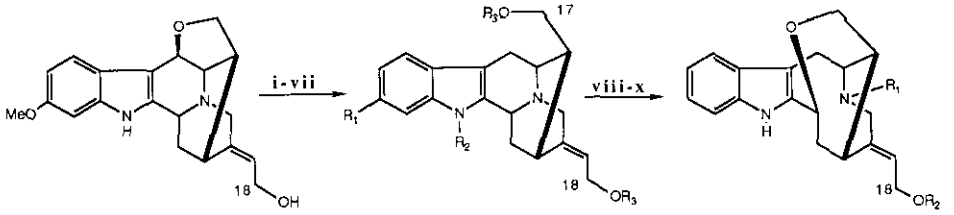


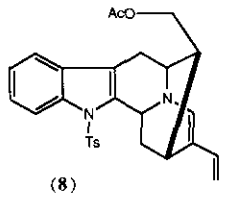
Scheme 1

† Dedicated to the memory of Professor Tetsuji Kametani.

Hydroxytaberpsychine (**2**) could take two conformational isomers (**2s**) and (**2u**). Carbon-carbon bond formation between C_7 and C_{20} could happen *via the overlapping of π-orbiral in the* conformer (**2u**). From the calculation by the MNDO method,[16] conformer (**2s**) (ΔHf=12.3 kcal/mol) is more stable than (**2u**) (ΔHf=17.8 kcak/mol). However, energic difference is only 5.5 kcal/mol so that facile conformational change from (**2s**) to (**2u**) could be expected. Initially, we focused on the synthesis of 18-hydroxytaberpsychine (**2**), a hypothetical intermediate in the final stage of the biosynthesis of koumine (**1**), from 18-hydroxygardnutine (**3**), which was easily obtained from *Gardneria nutans*.[17]

18-Hydroxygardnerine (**4**), *obtained from* (**3**) by *lithium* aluminum hydride ($LiAlH_4$) reduction, was acetylated with acetic anhydride in pyridine and then tosylated with *p*-toluenesulfonyl chloride in an aqueous 50% KOH/benzene (1:2) solution in the presence of tetra-*n*-butylammonium hydrogensulfate to afford N_a-tosyl derivative (**5**) in 86% overall yield from (**3**). Removing the methoxy group from the indole nucleus was achieved by the three steps operations, *i.e.* demethylation of the aryl methyl ether, trifluoromethanesulfonylation of the resultant phenol, and reductive deoxygenation assisted with palladium catalyst. The *reaction of* (**5**) with aluminum chloride (4 eq.) in ethanethiol and dry CH_2Cl_2[18] at -18°C for 7 h gave the phenolic compound (**6**) in 95% yield. Triflate (**7**), prepared in 82% yield from (**6**) with trifluoromethanesulfonic anhydride and triethylamine in dry CH_2Cl_2, was treated with 0.2 eq. of palladium acetate [$Pd(OAc)_2$], 0.4 eq. of 1.1'-bis(diphenylphosphino)ferrocene (DPPF), triethylamine, and formic acid in DMF[19] at 60°C for 2 h to produce undesired *dienic compound* (**8**). In order to prevent the side reaction caused by the contact of palladium catalyst with allylic ester group, dialcohol (**9**), which was prepared in 86% yield from (**7**) by partial hydrolysis (aq. 5% K_2CO_3 in MeOH at r.t. for 10 min.), was subjected to the deoxygenation under the same reaction conditions to yield (**10**) in 97% yield. Reductive deprotection of N_a-tosyl group in (**10**) with $LiAlH_4$ in THF gave rise to 18-hydroxy-11-demethoxygardnerine (**11**), mp 292-295°C (acetone) in 96% yield. (**11**) was treated with methyl chloroformate in THF-H_2O in





(**8**)

Reagents and conditions

i, $LiAlH_4$, THF, reflux, 4 h.
ii, Ac_2O, pyridine, r.t., 15 h; TsCl, *n*-Bu_4NHSO_4, 50%KOH-benzene, r.t., 2h, 86% from (3).
iii, $AlCl_3$, EtSH, CH_2Cl_2, -18°C, 7 h, 95%.
iv, $(CF_3SO_2)_2O$, Et_3N, CH_2Cl_2, -18°C, 15 min, 82%.
v, aq. 5%K_2CO_3, MeOH, r.t., 10 min, 86%.
vi, $Pd(OAc)_2$, DPPF, Et_3N, HCO_2H, DMF, 60°C, 2 h, 97%.
vii, $LiAlH_4$, THF, reflux, 11 h, 96%.
viii, $ClCO_2Me$, MgO, THF-H_2O, r.t., 2.5 h.
ix, *$LiAlH_4$, THF, r.t., 6.5 h, 41% from (11).*
x, Ac_2O, pyridine, r.t., 1 h, 96%.
xi, NaH, DMF, r.t. 10 min, then $Pd(OAc)_2$, PPh_3, 90°C, 1 h, 80%.

the presence of magnesium oxide and the resulting carbamate (**12**) was reduced with $LiAlH_4$ in THF at r.t. to furnish 18-hydroxytaberpsychine (**2**) in 41% overall yield from (**11**). Having obtained the hypothetical precursor, 18-hydroxytaberpsychine (**2**), in our hand, we next attempted intramolecular coupling reaction between C_7 and C_{20} positions using (**11**). As intermolecular coupling reaction between β-position in indole and allylic acetates assisted with palladium catalyst has been reported,[20] we applied this method to the intramolecular coupling reaction of 18-O-acetyl derivative (**13**), which was derived from (**2**) in 96% yield by treating with acetic anhydride in pyridine. Into the indole anion prepared from (**13**) by treating with sodium hydride in DMF at r.t. was added 0.1 eq. of $Pd(OAc)_2$ and 0.5 eq. of triphenylphosphine and the mixture was stirred for 1 h at 80-90°C. After purification with silicagel column chromatography, koumine (**1**) was obtained in 80% yield. The synthetic koumine (**1**), mp 164-165°C, no depression of mixed mp., had spectral properties (^{1}H-nmr, uv, High resolution ms, and cd) in accord with those of natural koumine.

ACKNOWLEDGEMENT

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