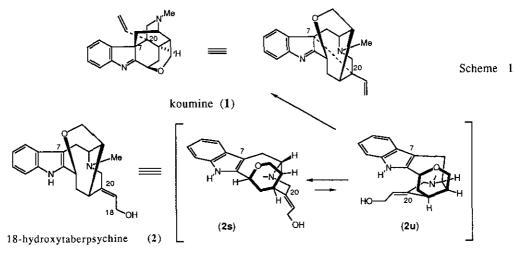
## **BIOMIMETIC SYNTHESIS OF KOUMINE BY THE PALLADIUM-CATALYZED INTRAMOLECULAR COUPLING REACTION OF 18-HYDROXYTABERPSYCHINE (18-HYDROXYANHYDROVOBASINEDIOL)**†

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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).

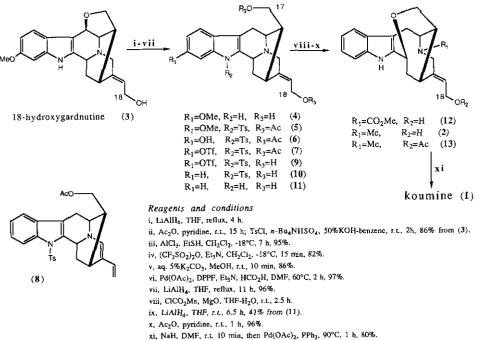
From the Chinese toxic medicinal plant Kou-Wen or Hu-Mang-Teng (*Gelsemium elegans* Benth), more than 30 indole alkaloids were isolated.<sup>1-7</sup> Most of these may be classified into six different structure types, *i.e.* gelsemine-type, gelsedine-type, humantenine-type, sarpaginetype, sempervirine-type,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



† Dedicated to the memory of Professor Tetsuji Kametani.

Hydroxytaberpsychine (2) could take two conformational isomers (2s) and (2u). Carboncarbon bond formation between C<sub>7</sub> and C<sub>20</sub> could happen via the overlapping of  $\pi$ -orbital in the conformer (2u). From the calculation by the MNDO method,<sup>16</sup> conformer (2s) ( $\Delta H_f = 12.3$ kcal/mol) is more stable than (2u) ( $\Delta H_f = 17.8$  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*.<sup>17</sup>

18-Hydroxygardnerine (4), obtained from (3) by lithium aluminum hydride (LiAlH<sub>4</sub>) reduction, was acetylated with acetic anhydride in pyridine and then tosylated with ptoluenesulfonyl chloride in an aqueous 50% KOH/benzene (1:2) solution in the presence of tetra-n-butylammonium hydrogensulfate to afford Na-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<sub>2</sub>Cl<sub>2</sub><sup>18</sup> 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<sub>2</sub>Cl<sub>2</sub>, was treated with 0.2 eq. of palladium acetate [Pd(OAc)<sub>2</sub>], 0.4 eq. of 1.1'-bis(diphenylphosphino)ferrocene (DPPF), triethylamine, and formic acid in DMF<sup>19</sup> 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<sub>2</sub>CO<sub>3</sub> 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<sub>a</sub>-tosyl group in (10) with LiAlH<sub>4</sub> 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-H2O in



the presence of magnesium oxide and the resulting carbamate (12) was reduced with LiAlH4 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<sub>7</sub> and C<sub>20</sub> positions using (11). As intermolecular coupling reaction between  $\beta$ -position in indole and allylic acetates assisted with palladium catalyst has been reported,<sup>20</sup> 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)<sub>2</sub> 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 (<sup>1</sup>H-nmr, uv, High resolution ms, and cd) in accord with those of natural koumine.

## ACKNOWLEDGEMENT

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