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Biomimetic chemical transformation from simple indole alkaloids to *Gelsemium* alkaloids

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Abstract: Based on a biogenetic speculation, many skeletally varied *Gelsemium* alkaloids having highly strained polycyclic structures were synthesized starting from the relatively simple sarpagine-type indole alkaloids, ajmaline and *Gardneria* bases.

Chemical studies on the toxic plant, *Gelsemium elegans* Benth., which was the origin of the Chinese folk medicine "Kou-Wen", have continued for many decades (1). In the last few years, numerous new indole and oxindole alkaloids were isolated from this native Thailand plant by us as well as from Chinese *G. elegans* by other researchers (2). Our interest in the relationship of the various skeletons of the *Gelsemium* alkaloids has led us to consider the biogenetic pathway of more than forty of these alkaloids. They can be classified into five groups, such as the sarpagine-, koumine-, humantenine-, gelsedine-, and gelsemine-type, based on their skeletal types. Based on this hypothetical biogenetic route, we next planned the chemical synthesis of these structurally unique alkaloids starting from relatively simple indole alkaloids.

I: Sarpagine-Type Alkaloids

Among the six sarpagine-type indole alkaloids, a new compound, 19(*Z*)-anhydrovobasinediol (**6**), which was plausibly a pivotal biogenetic intermediate for several types of *Gelsemium* alkaloids, would be formed *via* a hypothetical intermediate (**1**) from strictosidine. A commercially available alkaloid, ajmaline (**2**), could be considered almost the same as the hypothetical intermediate (**1**). First, we then planned the synthesis of new alkaloids (**4** and **6**). Ajmaline was converted to the 19(*Z*)-olefin compound (**3**) *via* several steps and then the indoline moiety was transformed to the indole nucleus to afford koumidine (**4**). The *C*/*D* ring-opening of (**4**) followed by reduction of the N_b-carbamate gave 19(*Z*)-anhydrovobasinediol (**6**) (3).

II: Koumine-Type Alkaloids

Koumine (**8**), having a novel cage structure, would be biogenetically generated *via* the intramolecular coupling between the C_7 and C_{20} positions in 18-hydroxyanhydrovobasinediol (**7**) (4). This final stage was chemically accomplished by using a *Gardneria* alkaloid (**5**) (5). Removing the methoxy group from the indole ring in (**5**) and *C*/*D* ring cleavage followed by $LiAlH_4$ reduction gave a key compound (**7**). By generation both of an indole anion with NaH and an allylic cation on the C_{20} position with a Pd° catalyst, the 18-*O*-acetyl derivative of **7** gave koumine (**8**) in good yield.

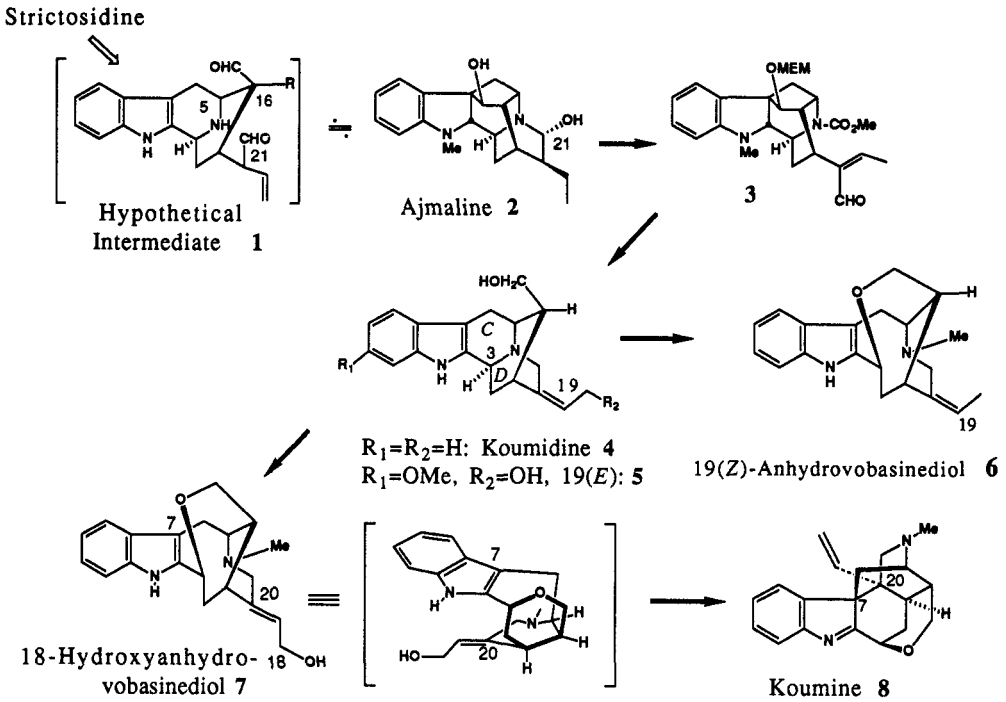

Fig. 1

III: Humantenine-Type Alkaloids

Biogenetically, humantenine-type oxindole alkaloids such as **14** and **15** would be generated from the sarpagine-type compounds through a rearrangement to oxindole and introduction of an oxygen function onto the N_a group. The first task for the synthesis of humantenine-type alkaloids, namely, the stereoselective rearrangement of indoles into the $C_7(S)$ oxindole (**11**) was achieved using OsO_4 oxidation of the pyrrole part in the *C*/*D* ring-opening compound (**10**) (6). By applying this method, a new natural product, N_a-demethoxyrankinidine (**12**), was prepared from koumidine (**4**) (7). The second requirement was the synthesis of the N_a-methoxyoxindole moiety, which is one of the characteristics of many *Gelsemium* alkaloids. We found that oxidation of the indoline derivatives (**13**), which were prepared by reduction of oxindoles, with hydrogen peroxide in the presence of a catalytic amount of sodium tungstate and subsequent treatment with CH_2N_2 afforded the desired N_a-methoxyoxindoles (8). Using this procedure, a principle *Gelsemium* alkaloid, gelsemine, could be converted to a minor

base, gelsevirine (8b). An indole alkaloid, gardnerine (**9**), was successively transformed to a humantenine-type alkaloid, humantenirine (**15**), *via* the *C/D* ring-opening, stereoselective rearrangement to oxindole, olefin inversion, and introduction of an N_a-methoxy function (8b). Furthermore, (**15**) was converted to a new type alkaloid, 11-methoxygelsemamide (**16**) (9), by treatment with NaOMe in MeOH under reflux conditions.

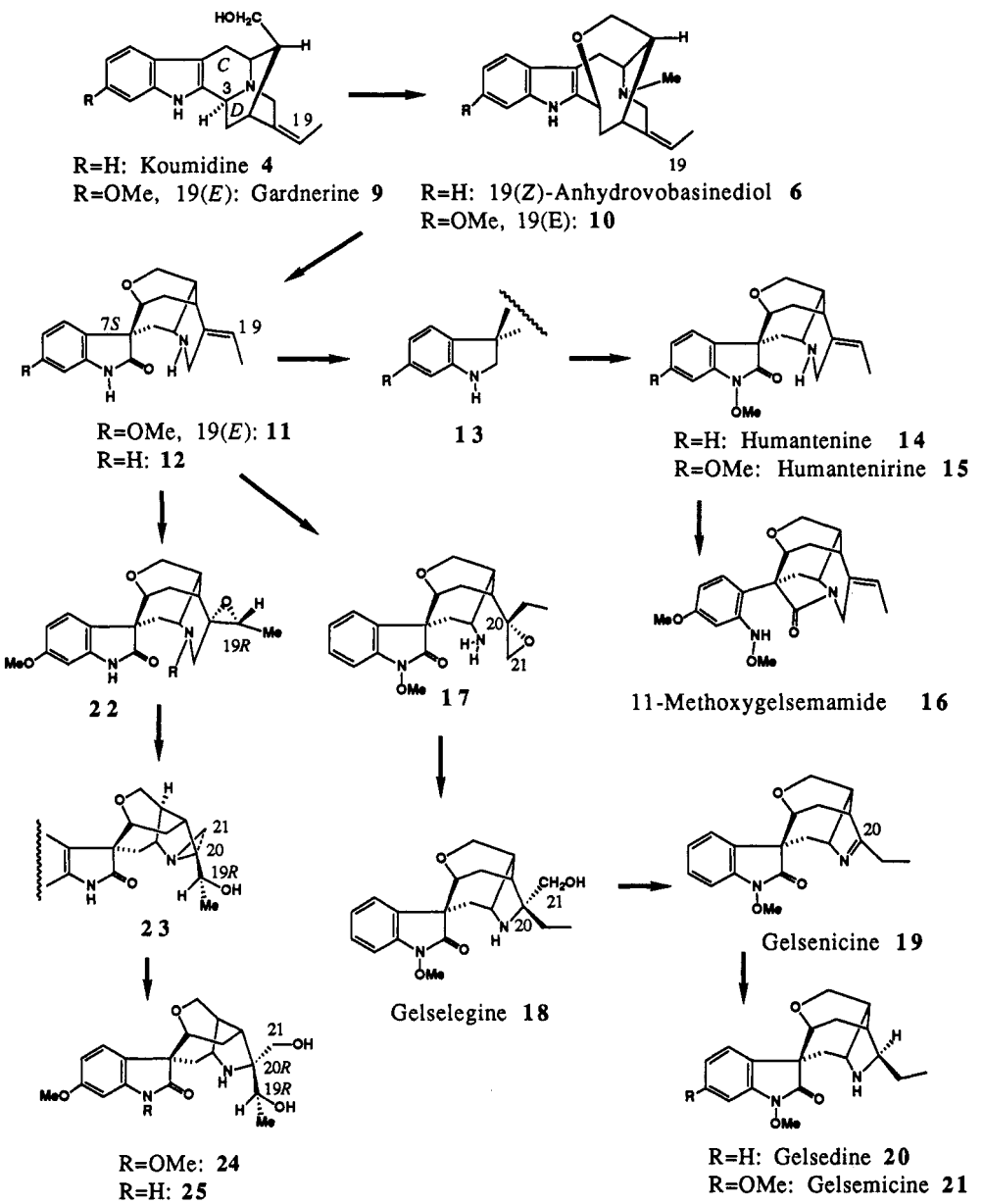

Fig. 2

IV: Gelselegine- and Gelsedine-Type Alkaloids

New type of oxindole alkaloids, gelselegines (**18** and **24**)(10), have a hydroxymethyl group at the C_{20} position, meaning that the C_{21} carbon rearranged to the *exo* position on the *D*-ring of the humantenine-type alkaloids. Also, gelsedines (**19-21**) would be biogenetically derived from **18** by losing the C_{21} carbon (11). We successfully synthesized gelselegine (**18**) and gelsedines (**19-21**) from gardnerine (**9**) by applying this biogenetic speculation. The crucial step in this synthesis was the construction of the gelselegine skeleton from the epoxy-amine intermediate (**17**). The C_{21} carbon in **18** was oxidatively cleaved with $NaIO_4$ to yield gelsenicine (**19**), which was further converted to gelsedine (**20**) by catalytic reduction. Another gelsedine group alkaloid, gelsemicine (**21**), was also synthesized from gardnerine (**9**) under almost the same process. Starting with **9**, the biomimetic construction of another member of the gelselegine group having a 19(*R*) hydroxy function (**25**) was also achieved *via* a biogenetically hypothetical epoxy-amine and aziridine intermediates (**22** and **23**) (12).

In conclusion, we have succeeded in the synthesis of many classes of *Gelsemium* alkaloids having a highly strained polycyclic skeleton starting from relatively simple indole alkaloids by incorporating chemo-, regio-, and stereoselective reactions into the biomimetic procedure.

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