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SYNTHETIC STUDIES ON GELSEDINE ALKALOIDS-II: FIRST CONSTRUCTION OF GELSEDINE SKELETON (N_a-DESMETHOXYGELSEMICINE) FROM GARDNERINE BASED ON THE ALTERNATIVE BIOGENETIC SPECULATION.

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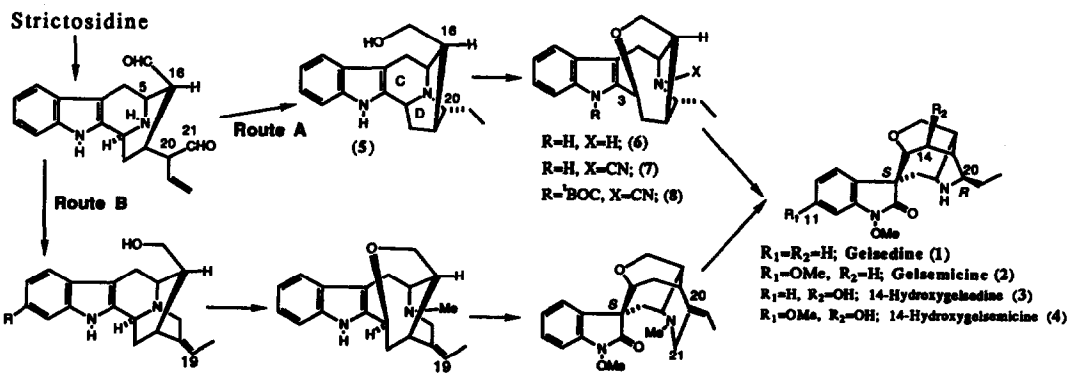
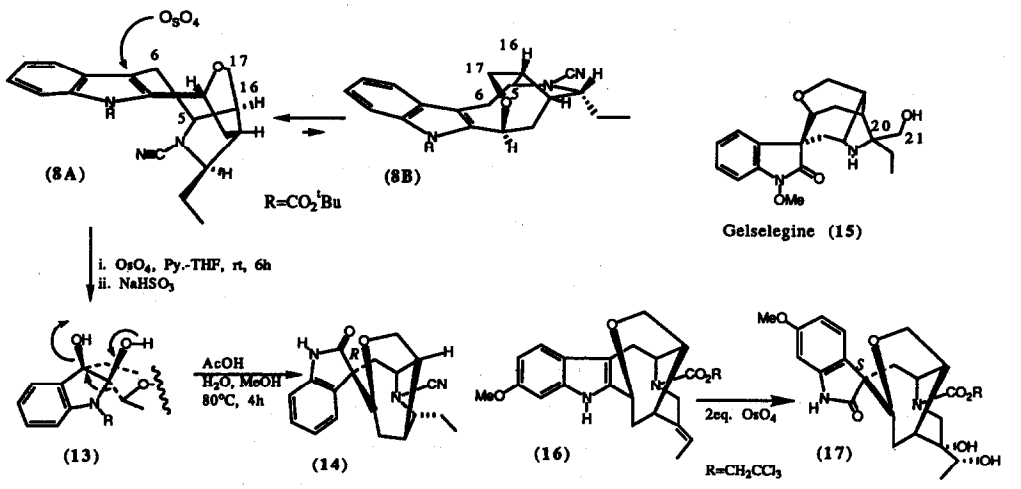
Summary: On the basis of the new biogenetic proposal of gelsedine-type alkaloids involving the humantenine-type oxindole alkaloids as the intermediates, gardnerine (**10**) was converted into N_a-desmethoxygelsemicine (**30**) in a highly stereoselective manner.

As described in the previous publication,[1] gelsedine-type alkaloids (**1**)-(**4**), one of the member of the structurally complex *Gelsemium* alkaloids,[2] were considered to be generated from strictosidine through *D*-norsarpagine type compounds by the release of C_{21} carbon in the early stage of the biogenesis (Route A in Scheme 1). Along this speculation, we recently synthesized *D*-norsarpagine type compounds (**5**) and (**7**).[3] To achieve the biomimetic synthesis of gelsedine alkaloids, we attempted the conversion of the *C/D* ring-opening compound (**7**) into oxindole derivative. Treatment of N_a-BOC derivative (**8**)[4] successively with osmium tetroxide (OsO_4) in pyridine/THF and then with AcOH/MeOH/H_2O at 80°C gave the oxindole (**14**) as the sole product in 70% overall yield from (**8**). However, the CD spectrum of (**14**)[5] demonstrated that (**14**) had the opposite configuration at the spiro C7 position compared with that of natural oxindoles. The stereochemical course of this oxidation-rearrangement reaction was speculated as follows, assuming that, in the transition state (**8**) took the folded conformation A rather than the extended conformation B (Scheme 2) from careful ^{1}H-NMR analysis of (**8**).[6] OsO_4 might attack to the double bond in the indole part of (**8**) from less hindered β-side to generate the diol (**13**). Subsequent treatment of this intermediate with aqueous acetic acid provided oxindole (**14**) having C7(*R*) configuration *via* stereospecific pinacol-type rearrangement.[7] Formation of the C7(*R*) isomer from (**8**) by use of OsO_4 oxidation is contrast to the results obtained from the reaction of humantenine-type alkaloids.[8] Thus, the *C/D* ring-opening compound (**16**)[9] derived from the compound having six membered *D*-ring gave the oxindole (**17**) with C7(*S*) configuration by using the same oxidative reagent (Scheme 2).



Scheme 1



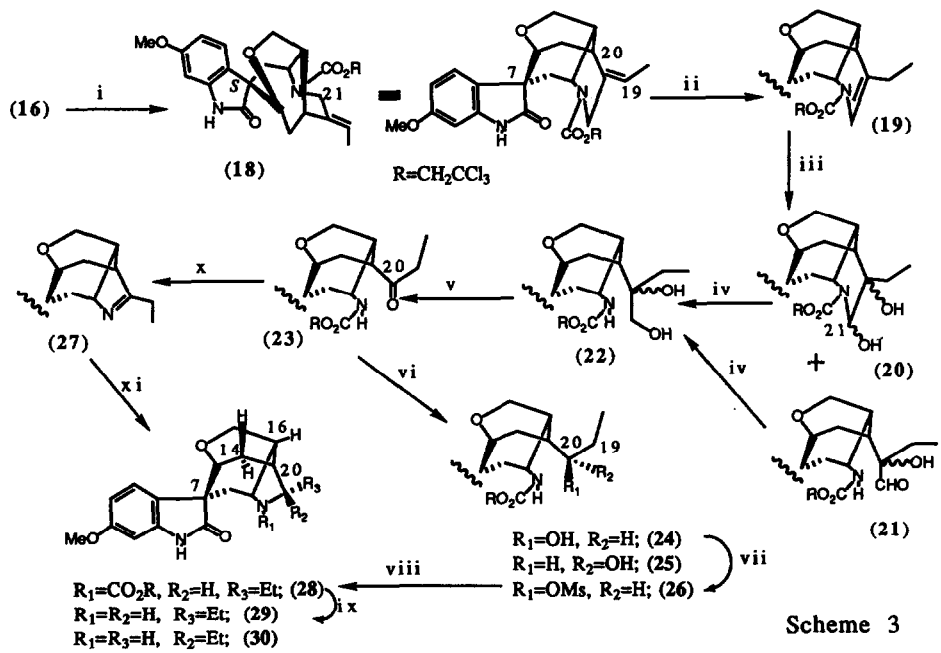
Scheme 2

These knowledge from the chemical reactions as well as the appearance of a new *Gelsemium* alkaloid (**15**)[10] led us to consider the possibility of the alternative biogenetic pathway of gelsedine-type alkaloids. Thus, enzymatic oxidation of sarpagine-type indole alkaloids, such as koumidine (**9**) and 19-(*Z*)-anhydrovobasinediol (**11**)[11] would first serve the humantenine-type oxindole alkaloid (**12**) having C7(*S*) configuration, and subsequent ring contraction of the nine membered ring through the elimination of the C_{21} carbon would furnish gelsedine-type alkaloids (Route **B** in Scheme 1). We therefore changed our synthetic strategy of gelsedine alkaloids along the second biogenetic speculation starting with one of the sarpagine-type alkaloid, gardnerine (**10**).

The *C/D* ring cleaved compound (**16**) readily available from (**10**) by treating with ββββ-trichloroethyl chloroformate ($ClCO_2CH_2CCl_3$) in THF was subjected to OsO_4 oxidation (1 equiv.) at -70°C for 1.5h (Scheme 3). The reaction proceeded stereoselectively to yield the oxindole (**18**) possessing C7(*S*) configuration in 52% yield, accompanied with the 19,20-diol derivative (**17**) (19%) and the recovered starting material (18%). The stereochemistry at C_7 was confirmed by the CD spectrum.[5] As a clue of the removal of C_{21} carbon in order to construct the eight membered ring, we utilized the double bond at $C_{19,20}$ position in (**18**). Treatment of (**18**) with trimethylsilyl chloride (TMSCl) and sodium iodide (NaI) in acetonitrile at rt for 10 min resulted in the olefin migration[12] to provide the enecarbamate (**19**)(δ 6.52, s, 21-H) in 95% yield. Oxidation of the double bond in (**19**) with OsO_4 afforded the diol (**20**)(δ 5.65, d, J=2.4Hz, +D_2O → s, 21-H) and the aldehyde (**21**)(δ 9.46, CHO) in 84% and 15% yield, respectively. Reduction of (**20**) and (**21**) respectively gave the same diol derivative (**22**). The C_{21} carbon was removed in 97% yield by the oxidative cleavage of the glycol system in (**22**) with sodium periodate ($NaIO_4$) in MeOH. The resultant ketone in (**23**) was reduced with sodium borohydride ($NaBH_4$) to give two diastereomers (**24**) and (**25**) in 79% and 20% yield, respectively. As the configuration of the epimeric C_{20} position in (**24**) and (**25**) could not be determined from the spectroscopic analysis at this stage, the major isomer (**24**) was subjected to the ring closure between the C_{20} and N_b position. The mesylate (**26**) prepared from (**24**) in 59% yield was treated with sodium hydride (NaH) in dry THF to yield the carbamate (**28**). The protecting group in (**28**) was removed with Zn in AcOH to afford the secondary amine (**29**) (mp 242-243°C) in 84% yield from (**26**). The stereochemistry at the C_{20} position in (**29**) was determined by the differential nuclear Overhauser effect (NOE) experiments. Irradiation of H-20 (δ 3.03, t, J=7.4Hz) led to

enhancement (4.2%) of 14-Hα (δ 2.01, br. d, J=15.1Hz). This indicates that the configuration at C_{20} in (**29**) is opposite to that of natural gelsedine series. Then, we modified the synthetic pathway in order to obtain the eight membered cyclic amine having the desired C_{20}(*R*) configuration. Treatment of (**23**) with Zn in AcOH gave the imine (**27**) in 88% yield. (**27**) showed the definite absorption at 1630 cm^{-1} due to C=N function. The catalytic reduction (PtO_2/H_2)[13] of (**27**) afforded stereospecifically the desired amine (**30**) (mp 248°C) in 98% yield. The stereochemistry at the C_{20} position was unambiguously determined by the comparison of ^{13}C-NMR spectra[14] and NOE experiments. By irradiation at one of the 19-H_2 (δ 1.72, m) and 20-H (δ 2.94, m) in (**30**), 4.5% and 5.9% enhancement of 14-Hα (δ 2.20, br. d, J=15.4Hz) and 16-H (δ 2.46, quint. like J 4.5Hz) were observed, respectively. Furthermore, in the ^{13}C-NMR spectra the signal of C_{14} in (**30**) was observed at upfield (8.9 ppm) than the corresponding signal of the diastereomer (**29**), due to the γ-gauche effect of the ethyl group. The ^{1}H-NMR spectrum (500MHz) of (**30**) resembled well that of gelsedine (**1**) except for the signals of oxindole moiety. Other physical and spectroscopic data (elemental analysis, Mass, IR, UV, and CD[5] spectra) also supported the structure of N_a-desmethoxygelsemicine (**30**).

In conclusion, we succeeded for the first time in the stereoselective synthesis of gelsedine skeleton along the alternative biogenetic hypothesis, which originated from the interesting observation that the stereochemical course of the oxidative reaction between the two *C/D* ring-opening derivatives of sarpagine-type alkaloids having nine membered ring and ten membered ring were completely reversed.



Scheme 3

Reagents and conditions: i, 1*equiv*. OsO_4, Py. THF, -70°C, 1.5h, then $NaHSO_3$ aq., 52%. ii, TMSCl, NaI, MeCN, rt, 10min, 95%. iii, OsO_4, Py. THF, -12°C, 2.5h, (**20**) 84%, (**21**) 15%. iv, $NaBH_4$, MeOH, rt, 20min, 99%. v, NaIO4, aq. MeOH, rt, 15h, 97%. vi, $NaBH_4$, MeOH, rt, 30min, (**24**) 79%, (**25**) 20%. vii, MsCl, Et_3N, cat.DMAP, dry CH_2Cl_2, rt, 2h, 59%. viii, NaH, dry THF, 0°C, 1.5h. ix, Zn, AcOH, rt, 27h, 84% from (**24**). x, Zn, AcOH, rt, 3h, 88%. xi, PtO_2, H_2, EtOH, rt, 1h, 98%.

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References and Notes

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2) Z. J. Liu and R. R. Lu, "*The Alkaloids*", vol. **33**, ed. by A. Brossi, Academic Press, New York, 1988, Chapter 2.

3) H. Takayama, M. Horigome, N. Aimi, and S. Sakai, *Tetrahedon Lett.*, **31**, 1287 (1990).

4) Direct osmylation of (**7**) did not produce the corresponding diol or oxindole derivatives, but the 7-hydroxyindolenine through the dehydration between N_a-H and C_2-hydroxy group of the osmylation product. To avoid the elimination of water, N_a function in (**7**) was protected as *t*-butylcarbamate (BOC).

5) CD spectral data in MeOH: (**14**)(c=0.37mmol/l) $[\theta]_{307}0$, $[\theta]_{284}$+11300, $[\theta]_{273}$+8600, $[\theta]_{254}$+45200, $[\theta]_{243}0$, $[\theta]_{228}$-86100, $[\theta]_{219}0$, $[\theta]_{208}$+154800. (**18**) (c=0.17mmol/l) $[\theta]_{300}0$, $[\theta]_{265}$-5900, $[\theta]_{260}$-5900, $[\theta]_{247.6}0$, $[\theta]_{236.8}$+14400, $[\theta]_{230.6}0$, $[\theta]_{216.4}$-150800. (**30**)(c=0.27mmol/l) $[\theta]_{298}0$, $[\theta]_{263.6}$-25400, $[\theta]_{249.2}0$, $[\theta]_{234.6}$+83500, $[\theta]_{225}0$, $[\theta]_{212.8}$-97000.

6) The experimental data obtained from the ^{1}H-NMR spectrum of (**8**), especially the J values ($J_{5H\text{-}6H\alpha}$=6.3Hz, $J_{5H\text{-}6H\beta}$=0Hz, $J_{16H\text{-}17H\alpha}$=$J_{16H\text{-}17H\beta}$=2.2Hz) were well consistent with the calculated values from the Dreiding model studies of (**8**) which took the conformer **A**.

7) N_b-CBZ (benzyloxycarbonyl) derivative of (**8**) also afforded the oxindole having the same absolute configuration at the C_7 position by the same procedure.

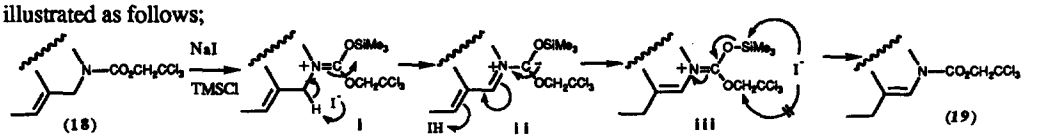
8) H. Takayama, K. Masubuchi, M. Kitajima, N. Aimi, and S. Sakai, *Tetrahedron*, **45**, 1327 (1989).

9) In contrast to (**8**), compound (**16**) was presumed to take the extended conformation from the MO calculation of the similar compound; see H. Takayama, M. Kitajima, and S. Sakai, *Heterocycles*, **30**, 325 (1990).

10) L. Z. Lin and G. A. Cordell, Abstract paper of Thirtieth Annual Meeting of the American Society of Pharmacognosy, P4, **1989**.

11) H. Takayama, M. Kitajima, S. Wongseripipatana, and S. Sakai, *J. Chem. Soc. Perkin Trans. I*, **1989**, 1075.

12) A plausible mechanism of the olefin migration (**18** to **19**) *via* the conjugate immonium intermediates was illustrated as follows;



13) J. S. Yang and Y. W. Chen, *Yaoxue Xuebao*, **18**, 104 (1983).

14) ^{13}C-NMR δ in $CDCl_3$: (**29**); 181.4 (C2), 75.2 (C3), 59.8 (C5), 34.9 (C6), 58.3 (C7), 128.5 (C8), 125.8 (9), 107.2 (C10), 159.9 (C11), 96.6 (C12), 140.0 (C13), 29.9 (C14)*, 38.8 (C15), 36.7 (C16), 63.4 (C17), 11.8 (C18), 29.1 (C19)*, 68.9 (C20), 55.5 (OCH_3). (**30**); 182.3 (C2), 75.0 (C3), 59.3 (C5), 33.5 (C6), 58.6 (C7), 127.8 (C8), 125.7 (C9), 107.5 (C10), 160.0 (C11), 96.9 (C12), 140.5 (C13), 21.0 (C14)**, 41.0 (C15), 34.3 (C16), 63.6 (C17), 11.8 (C18), 20.9 (C19)**, 65.0 (C20), 55.5 (OCH_3). Signals bearing the same superscript may be interchangeable.

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