The First and Biomimetic Construction of the New Skeleton of Gelselegine-Type Oxindole Alkaloids

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Summary: Starting from a sarpagine-type indole alkaloid **8**, the first and biomimetic construction of a new skeletal type of *Gelsemium* alkaloid, N_a-demethoxy-11-methoxy-19(*R*)-hydroxygelselegine (**13**), was stereoselectively achieved via a biogenetically hypothetical aziridine intermediate **12**.

During chemical studies of the *Gelsemium* alkaloids found in *Gelsemium elegans* Benth.,[1] which has been used as a medicinal plant in southeastern Asia,[2] we became interested in the novel structure of the new alkaloids, 11-methoxy-19(*R*)-hydroxygelselegine (**1**) and gelselegine (**2**).[3] These alkaloids are a new skeletal type of oxindole alkaloid having a hydroxymethyl group at the C20 position, meaning that the C21 carbon is rearranged to the exo position on the D ring. Biogenetically, the alkaloid **1** might be derived from the corresponding sarpagine-type indole alkaloid **3** through oxidative transformation of the C/D ring cleaved compound **4** into the humantenine-type oxindole **5**, formation of epoxide **6** at C19-20 position, rearrangement to the aziridinium intermediate such as **7**, and then ring opening by the attack of water at the C21 position in **7**. Numerous recent efforts on the synthesis of the structurally complex *Gelsemium* alkaloids[4] prompt us to disclose the first synthesis of the gelselegine skeleton, which presents chemical evidence for the already mentioned biogenetic speculation.

Initially, the sarpagine-type indole alkaloid, gardnerine (**8**),[5] having the (19*E*) configuration, was treated with β,β,β-trichloroethyl chloroformate in the presence of magnesium oxide in aqueous THF to afford the product of C/D ring cleavage. This compound was then subjected to osmium tetraoxide (OsO_4) oxidation (2 equiv) in pyridine–THF at room temperature to yield the oxindole **9** in 78% yield. The stereoselectively obtained oxindole **9** had the natural (7*S*) configuration, as confirmed by a comparison of its CD spectrum with that of natural humantenine-type alkaloids.[1i,6] The stereospecific transformation of the indole into the natural (7*S*) oxindole might proceed via a pinacol-type rearrangement of a C2–C7 diol intermediate generated by the attack of OsO_4 from the less hindered α-side of the indole moiety. This transformation would be closely related to the enzymatically oxidative transformation of indole alkaloids in plants. The diol function at C19–C20 in **9** (the stereochemistry was deduced afterwards from the reaction mechanisms for conversion of **9** to **12**, whose structure was determined by X-ray analysis, vide infra) was converted to the epoxide **10** (1. MsCl, Et_3N in CH_2Cl_2, 2. K_2CO_3 in MeOH) in 76% overall yield. Using this procedure, we could obtain the epoxide having the same relative stereochemistry between the C19 and C20 positions as that derived by the direct epoxidation of the (19*Z*) ethylidene side chain in *Gelsemium* alkaloids such as **5**. Removal of the N_b protecting group in **10** with zinc in AcOH gave secondary amine **11** in 95% yield. The differential NOE experiment between H19 and H15 suggested the desired (19*R*) configuration. The amine–epoxide **11** was then heated in dioxane at 120 °C for 11 h to give aziridine **12** (mp 243–248 °C) in 60% yield, whose structure, including the stereochemistry at C19 and C20, was established by single-crystal X-ray analysis.[7] Attempts to open the aziridine using aqueous sulfuric acid or perchloric acid were unsuccessful. However, treatment of **12** with trifluoroacetic acid in THF at 85 °C for 1 h furnished N_a-demethoxy-11-methoxy-(19*R*)-hydroxygelselegine (**13**) (mp 279–283 °C) in 81% yield by regioselective ring opening at C21. The ^{1}H- and

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(7) Compound **12** crystallized from acetone in the orthorhombic, space group $P2_12_12_1$ ($z = 4$) with unit cell parameters $a = 15.1440$ (37) Å, $b = 17.7214$ (53) Å, $c = 6.5336$ (22) Å, and $D_{calcd} = 1.350$ g/cm^3. A total of 1510 reflections were observed using graphite-monochromated Cu Kα radiation (2θ values in the range of 3–120°). The structure was solved by direct methods using the computer program MULTAN and was refined by the full-matrix least-squares method. The final R value is 0.0546. Specific details of the diffraction analysis along with tables of atomic coordinates, bond lengths and angles, and thermal parameters have been submitted as supplementary material.

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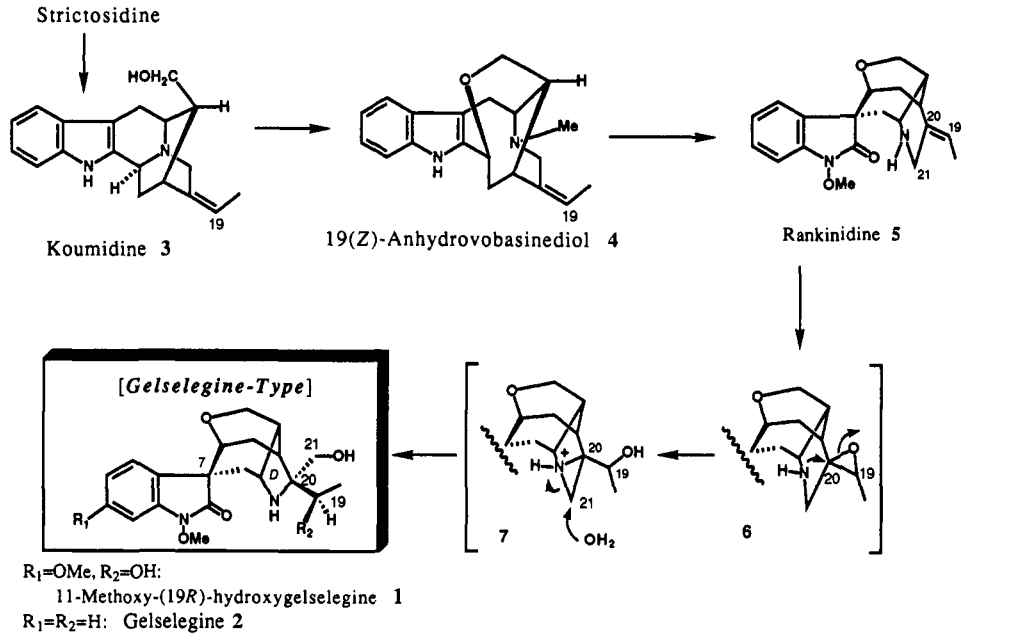
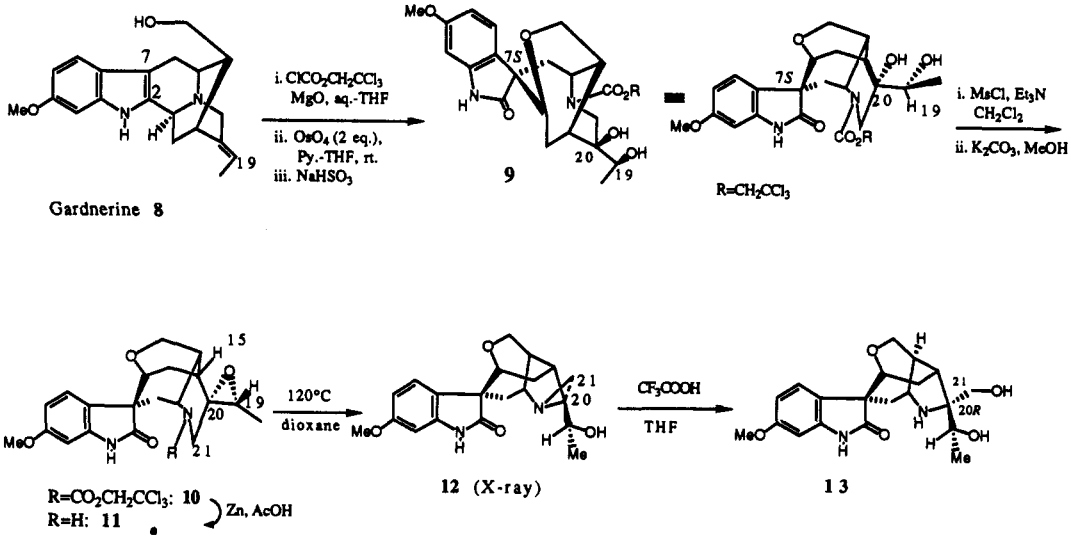
Scheme I. A Biogenetic Hypothesis for the Gelselegine-Type Alkaloids



Scheme II



^{13}C-NMR spectra of **13**[8] strongly resembled that of natural **1** except for the signals of the N_a-methoxy part in the oxindole moiety. Comparison of the CD spectrum of **13**[9] with that of **1** confirms the absolute configuration of the new alkaloid **1**. In this manner, we succeeded for the first time in the stereoselective construction of the gelselegine skeleton using the biogenetic hypothesis.

Supplementary Material Available: Experimental details, characterization data, ^{1}H NMR spectra, and X-ray data (19 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(8) Data: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.26 (d, 1 H, J = 8.3 Hz, H-9), 6.59 (dd, 1 H, J = 8.4 and 2.3 Hz, H-10), 6.43 (d, 1 H, J = 2.2 Hz, H-12), 4.65 (q, 1 H, J = 6.4 Hz, H-19), 4.31 (dd, 1 H, J = 11.2 and 3.7 Hz, H-17), 4.26 (d, 1 H, J = 10.7 Hz, H-17), 3.78 (m, 1 H, H-5), 3.78 (s, 3 H, OMe), 3.71 (d, 1 H, J = 11.2 Hz, H-21), 3.59 (d, 1 H, J = 6.1 Hz, H-3), 3.53 (d, 1 H, J = 11.2 Hz, H-21), 2.80 (m, 1 H, H-16), 2.47 (m, 1 H, H-15), 2.42 (d, 1 H, J = 15.8 Hz, H-14), 2.17 (m, 1 H, H-14), 2.13 (dd, 1 H, J = 15.6 and 4.1 Hz, H-6), 2.02 (dd, 1 H, J = 16.0 and 2.3 Hz, H-6), 1.41 (d, 3 H, J = 6.3 Hz, H_3-18); ^{13}C NMR ($CDCl_3$, 125.65 MHz) δ 182.2 (C-2), 75.4 (C-3), 59.9 (C-5), 33.1 (C-6), 58.7 (C-7), 127.6 (C-8), 125.7 (C-9), 107.4 (C-10), 160.0 (C-11), 97.1 (C-12), 140.1 (C-13), 22.5 (C-14), 36.3 (C-15), 38.7 (C-16), 63.3 (C-17), 18.9 (C-18), 67.7 (C-19), 69.8 (C-20), 62.1 (C-21), 55.5 (OMe).

(9) CD, $\Delta\epsilon$ nm (c = 0.27 mmol/L, MeOH, 21 °C): −19.9 (215), +20.9 (235), −6.64 (263). The absolute configuration of gardnerine **8** has been established: Sakai, S.; Kubo, A.; Hamamoto, T.; Wakabayashi, M.; Takahashi, K.; Ohtani, Y.; Haginiwa, J. *Tetrahedron Lett.* **1969**, 1489–1492.