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A First Synthesis of 20-Hydroxydihydrorankinidine, a New Oxindole Alkaloid from *Gelsemium elegans* Benth.

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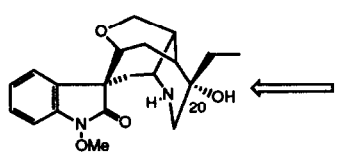
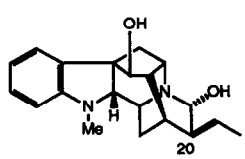
Abstract: Starting with ajmaline (**2**), the first synthesis of a new and biogenetically interesting *Gelsemium* alkaloid, 20-hydroxydihydrorankinidine (**1**), was achieved.

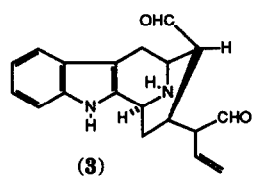
Chemical studies on the Chinese medicinal plant, *Gelsemium elegans* Benth. have continued for many decades.[1] In the last few years, numerous new indole and oxindole alkaloids were isolated from this plant by us and other researchers.[2] Our interest in the relationship of various skeletons of *Gelsemium* alkaloids has led us to consider their biogenetic pathway and investigate our proposal by chemical transformations. We have already succeeded in the biomimetic syntheses of some alkaloids.[3] Twenty-nine of the N_a-methoxy oxindole alkaloids of various types have been isolated from this plant thus far. Among them, 20-hydroxydihydrorankinidine (**1**), a new humantenine-type alkaloid isolated in 1991,[4] is the only one that has a hydroxy group at the C-20 position and is proposed to be an important biogenetic processor of some alkaloids, such as gelselegine, gelsenicine and gelsedine via the aziridinium intermediate.[2b, 3g] In order to prove this proposal by chemical transformation, an adequate amount of **1** is needed. Therefore, we planned the synthesis of **1** from commercially available ajmaline (**2**), which could be considered approximately the same as a hypothetical biogenetic intermediate (**3**) in this type of alkaloid.[5] We report here the twenty-two-step synthesis of **1** from **2**, which contains a novel oxidative transformation of the oxindole alkaloid into the N_a-methoxyoxindole derivative. This is the first synthesis of a naturally occurring N_a-methoxy oxindole alkaloid.



20-Hydroxydihydrorankinidine (**1**)



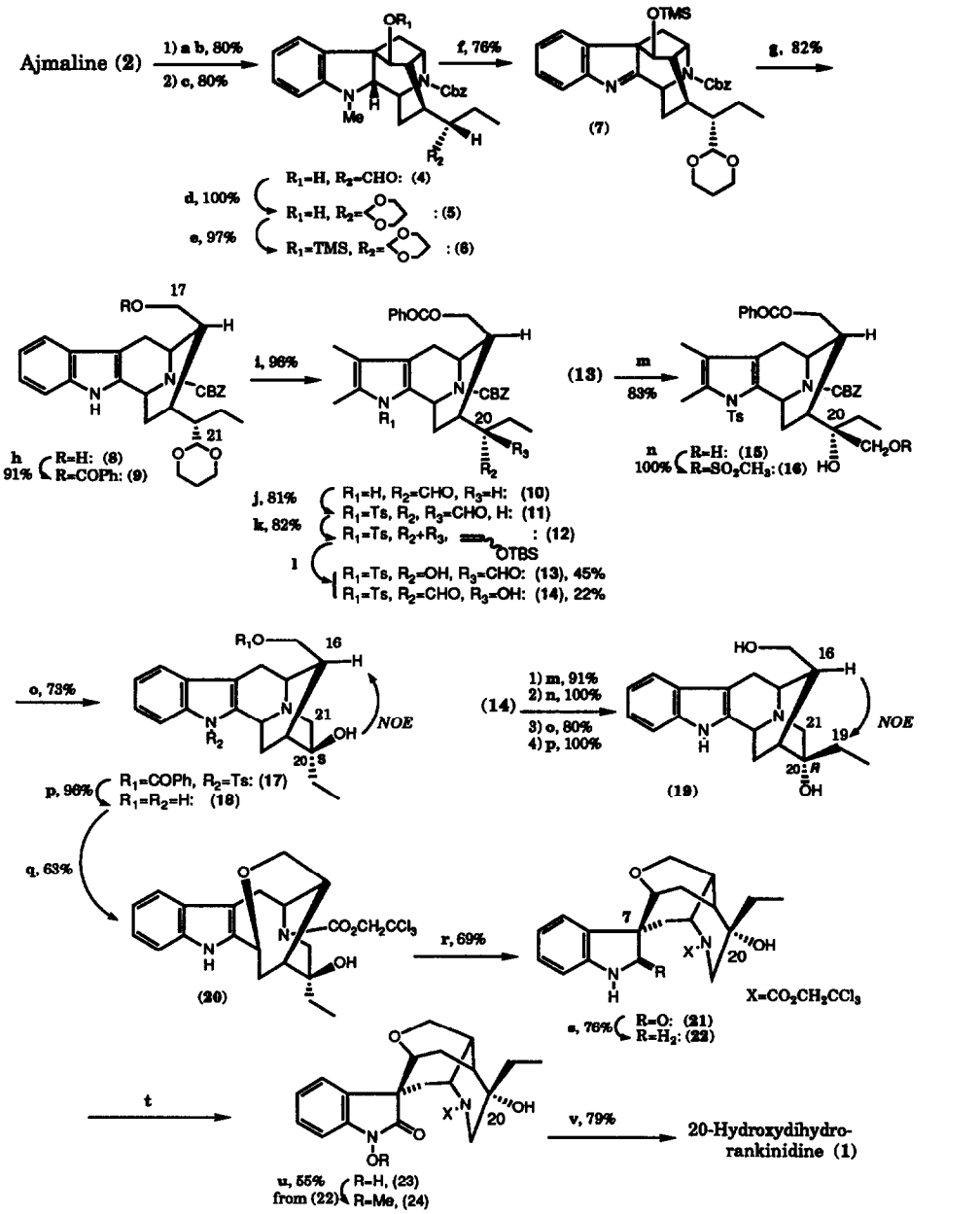
Ajmaline (**2**)



(**3**)

Initially, in order to liberate the masked aldehyde and secondary amine, ajmaline (**2**) was converted to the carbamate (**4**) in three steps by a method developed in our laboratory.[6] The aldehyde group in **4** was protected as the 1,3-dioxane (**5**), which was transformed into the indole (**8**) by the following procedure. 1) Protection of the hydroxy group as a trimethylsilyl ether. 2) Oxidation of N_a-methyl indoline with $Pb(OAc)_4$ leading to indolenine (**7**). 3) Deprotection of the hydroxy group, followed by fragmentation under mildly acidic conditions. 4) Immediate reduction of the resultant aldehyde with $NaCNBH_3$. The hydroxy group in **8** was protected as the benzoyl ester (**9**) before removal of the aldehyde-protecting group in order to prevent hemiacetal formation between the C_{17}-OH and C_{21}-aldehyde functions. The indole amine in **10** was tosylated under a basic conditions accompanied with some epimerization occurring at C-20 to produce the epimeric mixture **11**. The aldehyde function in **11** was converted to silyl enol ether (**12**), and then a hydroxy group was introduced at the C-20 position by treatment of **12** with OsO_4 in pyridine-THF at low temperature.[7] Separation by medium pressure liquid chromatography yielded two α-hydroxyaldehydes (**13** and **14**) and the starting material (**12**) in 45, 22 and 7% yields, respectively. Because the configuration of the epimeric C-20 position in **13** and **14** could not be determined from the spectroscopic analysis at this stage, the major isomer (**13**) was subjected to ring-closure between the C-21 and N_b position. The aldehyde group in **13** was reduced with $NaBH_4$ and the resultant primary hydroxy group in **15** was selectively mesylated to produce **16**. Hydrogenolysis of the carbamate (**16**) provided the ring-closure compound (**17**), which was then converted to the sarpagine-type key intermediate (**18**)[8] by removal of the protecting groups under strong basic conditions. The minor product (**14**) was also transformed into the epimeric sarpagine-type compound (**19**)[8] by the same procedure. The stereochemistry at the C-20 position in **18** and **19** was unambiguously determined by the NOE experiment.[8] The major product (**18**) showed the same *S*-configuration at the C-20 position as in the natural product (**1**). Treatment of **18** with trichloroethylchloroformate and MgO in aq. MeOH provided the C/D ring-cleaved compound (**20**). The indole moiety in **20** was stereoselectively converted by oxidation with OsO_4 in THF-pyridine to the oxindole (**21**), which had the desired C7(*S*) configuration. The lactam in **21** possessed a humantenine-skeleton which was chemoselectively reduced with borane-dimethylsulfide complex in THF to produce the indoline (**22**), which was then converted to N_a-methoxy oxindole under the conditions recently investigated in our laboratory.[9] Thus, oxidation of **22** with the urea hydrogen peroxide addition compound and sodium tungstate in aq. MeOH at room temperature provided hydroxamic acid (**23**),[10] followed by *O*-methylation with diazomethane to yield the N_a-methoxyoxindole (**24**) in an overall yield of 55% from the amine (**22**). Finally, removal of the N_b protecting group in **24** with activated zinc in acetic acid provided 20-hydroxydihydrorankinidine (**1**). Synthetic **1**, mp. 179-180°C, showed spectral properties (^{1}H-NMR, ^{13}C-NMR, IR, UV, MS and CD) identical with those of the natural product.

In conclusion, we have produced a new *Gelsemium* alkaloid (**1**) in a stereoselective manner utilizing a biogenetically patterned synthesis [*ie.*, a hypothetical biogenetic intermediate (≈ajmaline)→sarpagine-type indole alkaloid → C/D-ring cleavaged compound → rearrangement



Reagents: a) H_2N-NMe_2, cat.H_2SO_4, 3Å-MS, EtOH. b) CBZ-Cl, 1N-NaOH/CH_2Cl_2. c) $CuCl_2$, aq. THF (pH7). d) $HOCH_2CH_2CH_2OH$, TsOH, benzene, reflux. e) TMSCl, Et_3N, CH_2Cl_2. f) $Pb(OAc)_4$, CH_2Cl_2, -70~ -10°C. g) AcOH-THF-H_2O, 0°C; $NaCNBH_3$. h) PhCOCl, CH_2Cl_2-pyridine. i) 80%AcOH, reflux. j) p-$CH_3C_6H_4SO_2Cl$, n-Bu_4NHSO_4, benzene-50%KOH. k) TBSOTf, Et_3N, CH_2Cl_2. l) OsO_4, THF-pyridine, -10~ 0°C. m) $NaBH_4$, MeOH. n) MsCl, pyridine. o) H_2, 10%Pd/C, AcOH, EtOH. p) KOH, MeOH, reflux. q) $ClCO_2CH_2CCl_3$, MgO, aq. THF. r) OsO_4, THF-pyridine. s) BH_3•SMe_2, THF, reflux. t) H_2NCONH_2•H_2O_2, Na_2WO_4, aq. MeOH. u) CH_2N_2, MeOH. v) Zn, AcOH.

to the oxindole → N_a-methoxylation]. Because the absolute configuration of ajmaline has already been established, that of 1 was chemically determined.

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References and Notes

1. a) Liu, Z. J.; Lu, R. R. *Gelsemium* alkaloids. in "*The Alkaloid*", Vol. 33, ed. by A. Brossi, Academic Press, New York, **1988**. b) Takayama, H.; Sakai, S. Recent advances in the chemistry of *Gelsemium* alkaloids. in "*Studies in Natural Product Chemistry*", ed. by A. Rahman, Elsevier, Amsterdam, in press.
2. a) Ponglux, D.; Wongseripipatana, S.; Takayama, H.; Ogata, K.; Aimi, N,; Sakai, S. *Tetrahedron Lett.*, **1988**, *29*, 5395, and references cited therein. b) Lin, L. Z.; Cordell, G. A.; Ni, C. Z.; Clardy, J. *Phytochemistry*, **1990**, *29*, 3013. c) Lin, L. Z.; Cordell, G. A.; Ni, C. Z.; Clardy, J. *Phytochemistry*, **1991**, *30*, 679, and references cited therein.
3. a) Sakai, S.; Yamanaka, E.; Kitajima, M.; Yokota, M.; Aimi, N.; Wongseripipatana, S.; Ponglux, D. *Tetrahedron Lett.*, **1986**, *27*, 4585. b) Takayama, H.; Kitajima, M.; Wongseripipatana, S.; Sakai, S. *J. Chem. Soc., Perkin Trans. 1*, **1989**, 1075. c) Takayama, H.; Masubuchi, K.; Kitajima, M.; Aimi, N.; Sakai, S. *Tetrahedron*, **1989**, *45*, 1327. d) Takayama, H.; Kitajima, M.; Sakai, S. *Heterocycles*, **1990**, *30*, 325. e) Takayama, H.; Odaka, H.; Aimi, N.; Sakai, S. *Tetrahedron Lett.*, **1990**, *31*, 5483. f) Kitajima, M.; Takayama, H.; Sakai, S. *J. Chem. Soc., Perkin Trans. 1*, **1991**, 1773. g) Takayama, H.; Kitajima, M.; Ogata, K.; Sakai, S. *J. Org. Chem.*, **1992**, *57*, 4583.
4. Lin, L. Z.; Cordell, G. A.; Ni, C. Z.; Clardy, J. *Phytochemistry*, **1991**, *30*, 1311.
5. Takayama H.; Sakai, S. *J. Synth. Org. Chem. Jpn.*, **1990**, *48*, 876.
6. Takayama, H.; Horigome, M.; Aimi, N.; Sakai, S. *Tetrahedron Lett.*, **1990**, *31*, 1287.
7. When the N_a-*tert*-butoxycarbonyl analogue was treated with OsO_4 under the same condition, oxindole was obtained as the main product. The existence of the toluenesulfonyl group at N_a enabled the indole ring to resist the electrophilic addition of OsO_4.
8. (**18**): mp. 220-222°C, Anal. Calcd for $C_{19}H_{24}N_2O_2$: C; 73.05, H; 7.74, N; 8.97, Found: C;72.88, H; 7.71, N; 8.67. EI-MS m/z (%); 312 (M^+, 44%), 169 (100), 168 (83). ^{1}H-NMR (500 MHz, in DMSO-d_6) δ: 4.15 (1H, br s, 20-OH), 4.07 (1H, t, *J*=4.7 Hz, 17-OH), 2.77 and 2.71 (each 1H, d, *J*=14.2 Hz, 21-H), 2.57 (1H, br q, *J*=8.8Hz, 16-H). Irradiation of the 20-OH proton led to enhancement (2.3%) of the proton at C-16. (**19**): mp. 162.5-163.5°C, Anal. (FAB-HRMS) Calcd for $C_{19}H_{25}N_2O_2$ (M+H), 313.1916, Found: 313.1903. EI-MS m/z (%); 312 (M^+, 99%), 169 (90), 168 (100). ^{1}H-NMR (500 MHz, in CD_3OD) δ: 2.99 and 2.90 (each 1H, d, *J*=14.0 Hz), 2.46 (1H, tt, *J*=10.7, 2.0 Hz, 15-H), 1.80 (2H, m, 19-H_2). Irradiation of the C-16 proton led to enhancement (7.2%) of one of the protons at C-19.
9. Takayama, H.; Seki, N.; Kitajima, M.; Aimi, N.; Sakai, S. *Natural Product Lett.* in press.
10. Murahashi, S.; Oda, T.; Sugahara, T.; Masui, Y. *J. Org. Chem.* , **1990**, *55*, 1744.

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