Tetrahedron Letters, Vol.31, No.9, pp 1287-1290, 1990
Printed in Great Britain

0040-4039/90 $3.00 + .00
Pergamon Press plc

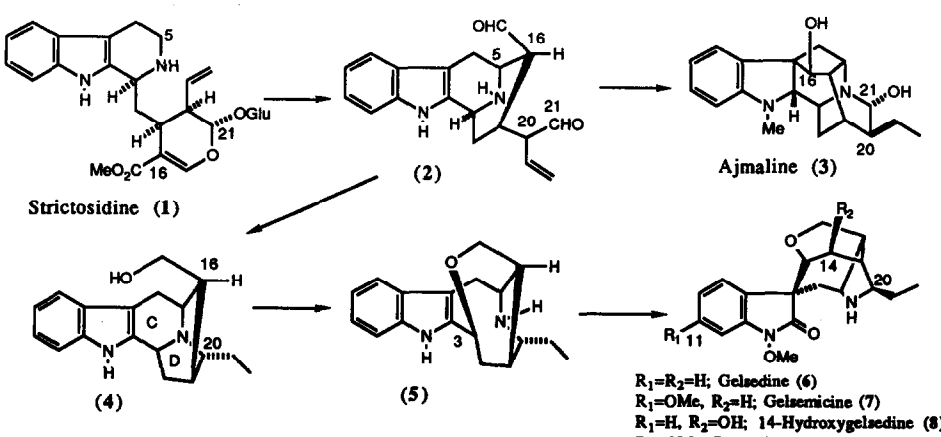
SYNTHETIC STUDIES ON GELSEDINE ALKALOIDS-I: STEREOSELECTIVE PREPARATION OF HYPOTHETICAL BIOGENETIC INTERMEDIATES, D-NORSARPAGINE TYPE COMPOUNDS FROM AJMALINE.

Hiromitsu Takayama, Masato Horigome, Norio Aimi, and Shin-ichiro Sakai*

Faculty of Pharmaceutical Sciences, Chiba University, 1-33, Yayoi-cho, Chiba, 260 Japan

Summary: D-Norsarpagine type compound (**4**) and its C/D ring-opening derivative (**22**), which were corresponding to the hypothetical biogenetic intermediate for gelsedine (**6**), were prepared from ajmaline (**3**) *via* the deformylation (C_{21}) and the construction of five-membered D ring having an α-ethyl group on C_{20} position.

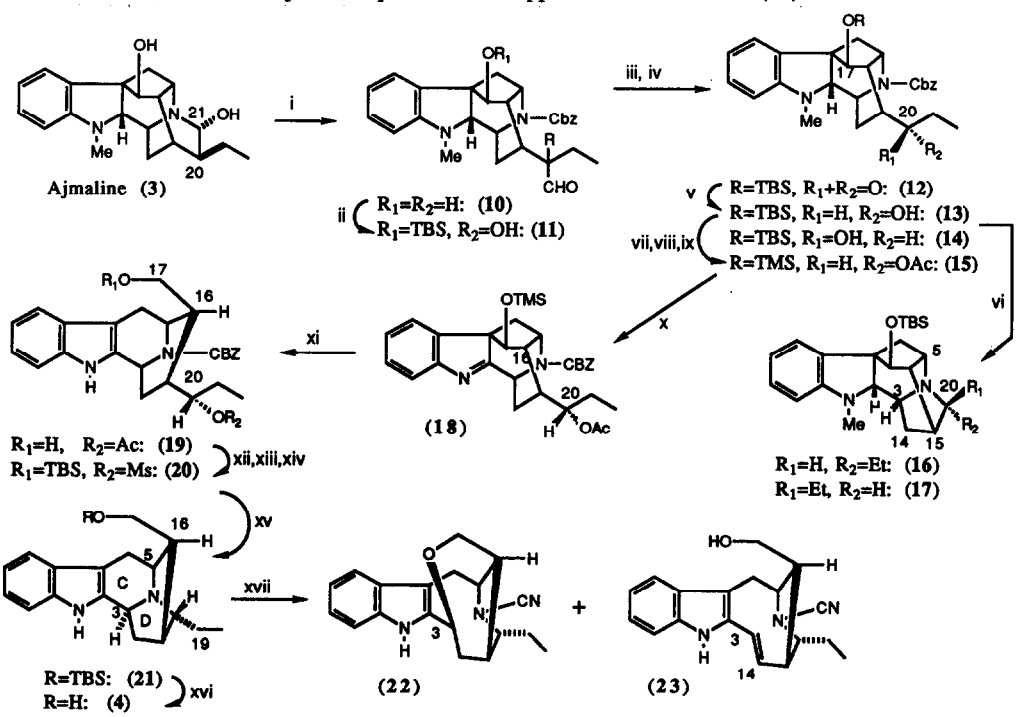
The genus *Gelsemium* is well known to contain indole alkaloids of various skeletal type.[1] Among them, gelsedine-type alkaloids such as gelsedine (**6**), gelsemicine (**7**), 14-hydroxygelsedine (**8**), and 14-hydroxygelsemicine (**9**), have a unique D-norsarpagine type oxindole skeleton. Biogenetically, these alkaloids would be generated from strictosidine (**1**) by the release of C_{21}-aldehyde carbon from the common intermediate (**2**) for usual indole alkaloids and subsequent ring closure between N_b and C_{20} position. Thus generated hypothetical intermediate, D-norsarpagine type indole compound (**4**) would be converted to the C/D ring-opening compound (**5**), and then transformed into gelsedine series *via* the successive oxidative rearrangement to oxindole and oxidation on N_a, C_{11} and/or C_{14}.[2a] (Scheme I) As part of our program on the chemical studies on *Gelsemium* alkaloids,[2] we planed the synthesis of gelsedine type compounds along the above biogenetic speculation. We chose commercially available ajmaline as a starting material, which could be considered to be a synthetic equivalent approximately with the biogenetic intermediate (**2**). Here we report the first construction of D-norsarpagine type indole compound (**4**) and its C/D ring-opening derivative (**22**), that are the plausible and important biogenetic intermediates of gelsedine alkaloids.



Scheme I: A Biogenetic Speculation of Gelsedine-type Alkaloids

Our first task was removing the C_{21} aldehyde carbon from ajmaline (**3**). Masked aldehyde existing as amino acetal function in (**3**) was converted to the aldehyde (**10**) in 64% overall yield by the three steps operations, *i.e.* formation of *N,N*-dimethylhydrazone, protection of the liberated N_b as benzyl carbamate under Schotten-Baumann condition, and hydrolysis of the hydrazone with $CuCl_2$ (pH 7). Aldehyde function in (**10**) was converted to the silyl enol ether in 71% yield by treatment with two equivalents of *tert*-butyldimethylsilyl (TBS) trifluoromethanesulfonate (triflate), and then hydroxy group was introduced into the α-position of aldehyde in 81% yield by exposure of silyl enol ether to osmium tetroxide (OsO_4) in pyridine-THF. Attempts at the direct introduction of the hydroxy group at C_{20} position in (**10**) by using the MoO_5-Py-HMPA complex oxidation of lithium enolate were unsuccessful. Aldehyde group in (**11**) was reduced with $NaBH_4$ in MeOH and the C-C bond in the resultant glycol system was cleaved with $NaIO_4$ in MeOH to yield the C_{20}-keto compound (**12**) in 76% overall yield from (**11**). (**12**), mp 173-175°C, showed two intensive absorption at 1700 and 1690 cm^{-1} in the IR spectrum. The carbonyl group at C_{20} was reduced with $NaBH_4$ in MeOH at rt to give two diastereomers (**13**) and (**14**) in the ratio of 1.5:1. In order to determine the configuration at C_{20} of these alcohols, ring closure between C_{20} and N_b was performed, respectively. Each alcohols (**13**) and (**14**) were converted to mesylate and then subjected to the hydrogenolysis to give the tertiary amines (**16**) and (**17**). The stereochemistry at C_{20} in (**16**) and (**17**) were concluded by the spectroscopic analysis, as follows. In the ^{13}C-nmr spectra[3], the signal due to C_5 of compound (**16**) was observed at downfield (5.8ppm) and, on the contrary, that of C_{14} was observed at upfield (4.9ppm) than the corresponding signal of the C_{20}-epimer (**17**). This phenomena can be reasonably interpreted in terms of γ-gauche effect due to α-ethyl group on C_{20} in (**16**). Differential NOE experiments also supported the configuration of the C_{20} position in both compounds. Thus, irradiation of C_{20}-H (δ 2.97) in (**16**) led to enhancement (21%) of C_5-H, indicating that the ethyl group lies anti to C_5-H. On the other hand, in (**17**) 6% and 7% enhancements were observed between C_{20}-H (δ 2.85) and C_{14}-H and C_3-H, respectively. From these results, compound (**16**) had the desired configuration at C_{20} for the synthesis of gelsedines. In general, the reaction between the amine and the secondary mesylate proceeds in inversion of the configuration on the alcoholic carbon. Therefore, the alcohol (**13**) has *S* configuration at C_{20} position. Next, we attempted the stereoselective reduction of the C_{20}-carbonyl function in (**12**) to obtain the C_{20} (*S*)-alcohol (**13**) preferentially. Although the desired alcohol (**13**), mp 170-173°C, was obtained diasteroselectively (100%) by reduction with L-selectride, the isolated yield was not so good (60%). Then, we employed $NaBH_4$ reduction in *iso*-propanol/H_2O/CH_2Cl_2 at -20°C to afford (**13**) and (**14**) in the ratio of 3.7:1 in a quantitative isolated yield. The (*R*)-alcohol (**14**) was converted to the (*S*)-isomer by repeating the oxidation (Swern method)-reduction ($NaBH_4$ at -20°C) sequence. Attempts at direct inversion at C_{20} in (**14**) by Mitsunobu procedure was unsuccessful. Next requirement of this work was the transformation of indoline moiety to the indole. We initially attempted the lead tetraacetate [$Pb(OAc)_4$] oxidation[4] of (**16**) to introduce the indolenine function, however, probably owing to the susceptibility of N_b in five membered ring toward oxidating reagents, decomposed product was obtained. Then we changed the order of synthetic sequence as follows; 1) preparation of indole ring starting from (**13**), 2) construction of five membered D ring. After the acetylation of C_{20} hydroxy group in (**13**), the TBS ether on C_{17} hydroxy group was substituted for trimethylsilyl (TMS) ether to afford (**15**) in 95% overall yield from (**13**). On oxidation of N_a-methyl indoline (**15**) with $Pb(OAc)_4$ in CH_2Cl_2 at -70°C, indolenine derivative (**18**) was obtained in 68% yield. (**18**) exhibited the characteristic indolenine absorption [208, 221(s), 228(s), 253 nm] in the UV spectrum. The TMS ether in (**18**) was cleaved in AcOH/THF/H_2O (3:1:1) at rt and after the evaporation of the solvent at same temperature under reduced

pressure, the resultant unstable aldehyde was immediately reduced with $NaBH_4$ in MeOH at 0°C to give the indole (**19**) in 80% yield without the epimerization at C_{16}. After the protection of the primary alcohol in (**19**) as TBS ether, acetate was converted to mesylate (**20**), which upon hydrogenolysis (Pd/C, H_2, EtOH/AcOH) provided D-norsarpagine derivative (**21**), mp 244-246°C, in 66% yield by ring closure between N_b and C_{20} position. The stereochemistry at C_{16} and C_{20} position were unambiguously determined by the differential NOE spectra of (**21**). Thus, the irradiation of the C_{16}-H (δ 2.46) led to enhancement (9% and 7%) of the C_5-H (δ 3.74) and C_{20}-H (δ 3.05), respectively. Furthermore, 7% enhancement was observed between the C_3-H (δ 4.24) and C_{19}-H_2 (δ 1.63 and 1.53). Finally, by removing the TBS ether in (**21**) with *n*-$Bu_4N^+F^-$ in THF, D-norsarpagine type indole compound (**4**), mp 269-270°C, which might be an important hypothetical biogenetic intermediate for gelsedine alkaloids, was obtained in 90% yield. Next we attempted the C/D ring cleavage of (**4**), that would be led to the following biogenetic intermediate (**5**), in Scheme I. Under the reaction condition ($ClCO_2CH_2Ph$, MgO, H_2O/THF) for cleaving the C/D ring of usual indole alkaloids having six membered D-ring,[2e] (**4**) gave the undesired carbamates[5] as the major products. (**4**) also resisted the cleavage of C/D ring under Harley-Mason's condition (Ac_2O).[6] Eventually, on treatment of (**4**) with BrCN and MgO in benzene under reflux condition, desired cleaved product (**22**) was obtained in 48% yield accompanying with the 2-vinyl derivative (**23**). The 500MHz ^{1}H-NMR spectrum of (**22**) showed the characteristic signal of C_3-H as a doublet (δ 5.10, J=4.5Hz), and other spectroscopic data also supported the structure of (**22**).



Reagents and conditions: i, H_2N-NMe_2, cat.H_2SO_4, 3A-MS, EtOH; CBZ-Cl, 1N-NaOH/CH_2Cl_2, 80% from (3). ;$CuCl_2$, aq. THF(pH7), 80%. ii, $TBSOSO_2CF_3$, Et_3N, CH_2Cl_2, 71%; OsO_4, THF-Py., $NaHSO_3$ aq, 81%. iii, $NaBH_4$, MeOH, 92%. iv, $NaIO_4$, MeOH, 83%. v, L-Selectride, THF, -70°C, (13) 60%, or $NaBH_4$, *iso*-Propanol/H_2O/CH_2Cl_2,-20°C, (13) 78%, (14) 21%. vi, MsCl, Py, then H_2, Pd-C, AcOH, EtOH, 83% (16) from (13), 48% (17) from (14). vii, Ac_2O-Py., 96%. viii, n-Bu_4NF, THF, quant. ix, $TMSOSO_2CF_3$, CH_2Cl_2, 90%. x, $Pb(OAc)_4$, CH_2Cl_2, -70°C, 68%. xi, AcOH-THF-H_2O then $NaBH_4$, MeOH, 80%. xii, $TBSOSO_2CF_3$, Et_3N, CH_2Cl_2, 80%. xiii, 5% aq.KOH/MeOH, 90%. xiv, MsCl, Et_3N, DMAP, CH_2Cl_2, 93%. xv, H_2, Pd-C, AcOH, EtOH, 66%. xvi, n-Bu_4NF, THF, 90%. xvii, BrCN, MgO, benzene, (22) 48%, (23) 30%

In conclusion, we succeeded for the first time in the stereoselective construction of D-norsarpagine type compounds (**4**) and (**22**), which supported chemically our proposal of the biosynthetic route of gelsedine type alkaloids. Further efforts on the biomimetic synthesis of gelsedine alkaloids from (**4**) and (**22**) are in progress in our laboratory.

Acknowledgement

This study was supported by a Grant-in-Aid (No. 01470136) from the Ministry of Education, Science and Culture, Japan, which is gratefully acknowledged.

References and Notes

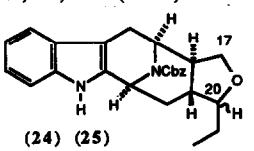
1) Z. J. Liu and R. R. Lu, "*The Alkaloids*", vol. **33**, ed. by A. Brossi, Academic Press, New York, 1988, Chapter 2.

2) (a) D. Ponglux, S. Wongseripipatana, S. Subhadhirasakul, H. Takayama, M. Yokota, K. Ogata, C. Phisalaphong, N. Aimi, and S. Sakai, *Tetrahedron*, **44**, 5075 (1988); (b) S. Sakai, S. Wongseripipatana, D. Ponglux, M. Yokota, K. Ogata, H. Takayama, and N. Aimi, *Chem. Pharm. Bull.*, **35**, 4668 (1987); (c) D. Ponglux, S. Wongseripipatana, H. Takayama, K. Ogata, N. Aimi, and S. Sakai, *Tetrahedron Lett.*, **29**, 5395 (1988); (d) S. Sakai, E. Yamanaka, M. Kitajima, M. Yokota, N. Aimi, S. Wongseripipatana, and D. Ponglux, *Tetrahedron Lett.*, **27**, 4585 (1986); (e) H. Takayama, K. Masubuchi, M. Kitajima, N. Aimi, and S. Sakai, *Tetrahedron*, **45**, 1327 (1989); (f) H. Takayama, M. Kitajima, S. Wongseripipatana, and S. Sakai, *J. Chem. Soc., Perkin Commun.*, **1989**, 1075; (g) H. Takayama and S. Sakai, *Chem. Pharm. Bull.*, **37**, 2256 (1989); (h) H. Takayama, M. Kitajima, and S. Sakai, *Heterocycles*, in press.

3) ^{13}C-NMR δ in $CDCl_3$: (**16**); 78.0 (C2), 54.8 (C3), 68.2 (C5), 31.7 (C6), 55.4 (C7), 134.1 (C8), 123.2 (C9), 119.0 (C10), 127.0 (C11), 109.2 (C12), 153.7 (C13), 34.4 (C14), 42.2 (C15), 51.3 (C16), 76.9 (C17), 11.7 (C18), 20.1 (C19), 78.6 (C20), 34.4 (N-Me), -4.49 and -4.26 (Si-Mex2), 18.1 and 26.0x3 (^{t}Bu), (**17**); 78.3 (C2), 53.5 (C3), 62.4 (C5), 30.6 (C6), 54.7 (C7), 134.0 (C8), 123.3 (C9), 119.1 (C10), 127.0 (C11), 109.2 (C12), 153.7 (C13), 39.3 (C14), 42.6 (C15), 52.3 (C16), 77.2 (C17), 12.1 (C18), 21.8 (C19), 80.2 (C20), 34.3 (N-Me), -4.45 and -4.28 (Si-Mex2), 18.1 and 26.0x3 (^{t}Bu).

4) M. F. Bartlett, B. F. Lambert, and W. I. Taylor, *J. Am. Chem. Soc.*, **86**, 729 (1964).

5) The structure of carbamates (**24**) and (**25**) produced by the N_b-C_{20} fission and ring closure between C_{17}-OH and C_{20} position were determined by the spectroscopic analysis and the derivatization from (**20**).



(**24**) (**25**)

6) G. H. Foster, J. Harley-Mason, and W. R. Waterfield, *J. Chem. Soc., Chem. Commun.*, **1967**, 21.

(Received in Japan 10 January 1990)