BIOMIMETIC SYNTHESIS OF INDOLE ALKALOIDS FROM AJMALINE

CHADA PHISALAPHONG

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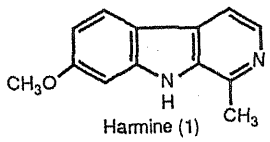
Contents

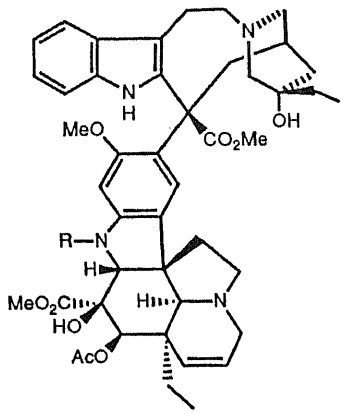
Introduction

Most of alkaloids are secondary metabolites that occur in the flowering plants (the Angiosperms). Fewer are found in animals, insects, marine organisms, and the lower plants. Among 6000 alkaloids isolated up to date, more than one-forth of them are indole alkaloids. Indole alkaloids can be divided into two main classes. The first comprises the simple alkaloids. Their structures are not uniform, having only the indole nucleus or a direct derivative of it as a common feature, e.g. harmine (**1**).

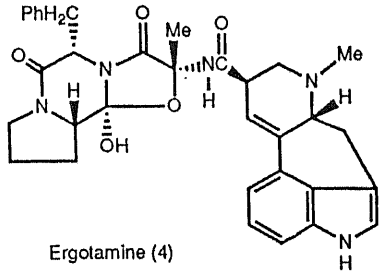


Harmine (1)

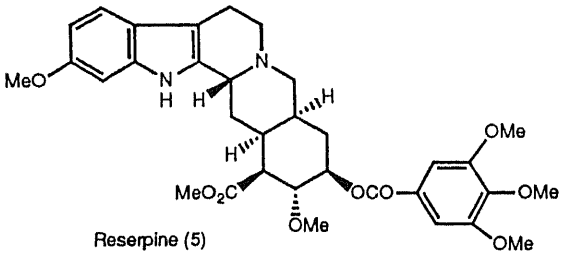
The indole alkaloids of the second class, which contain C_9 or C_{10} monoterpene moiety derived from secologanin are called "monoterpenoid indole alkaloids". These alkaloids are almost entirely distributed among three plant families: Loganiaceae, Apocynaceae, and Rubiaceae.[1)] Many of them possess biological activities. Some are in current clinical use, e.g. vincristine (**2**) and vinblastine (**3**) (anti leukemia), ergotamine (**4**) (migraine drug), reserpine (**5**) (tranquilizer and hypotensive), yohimbine (**6**) (α-blocker).



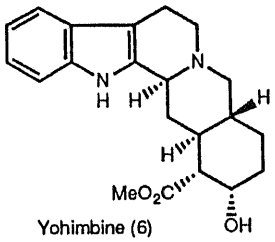
R=CHO: Vincristine (2)
R=Me: Vinblastine (3)



Ergotamine (4)

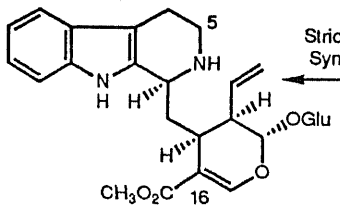


Reserpine (5)



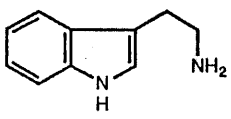
Yohimbine (6)

It is well recognized that the monoterpenoid indole alkaloids are biosynthesized through the biological transformations of strictosidine (**7**), which was derived from the condensation of tryptamime (**8**) and secologanin (**9**).[2)]

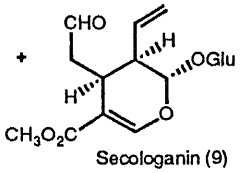


Strictosidine (7)

Strictosidine Synthase

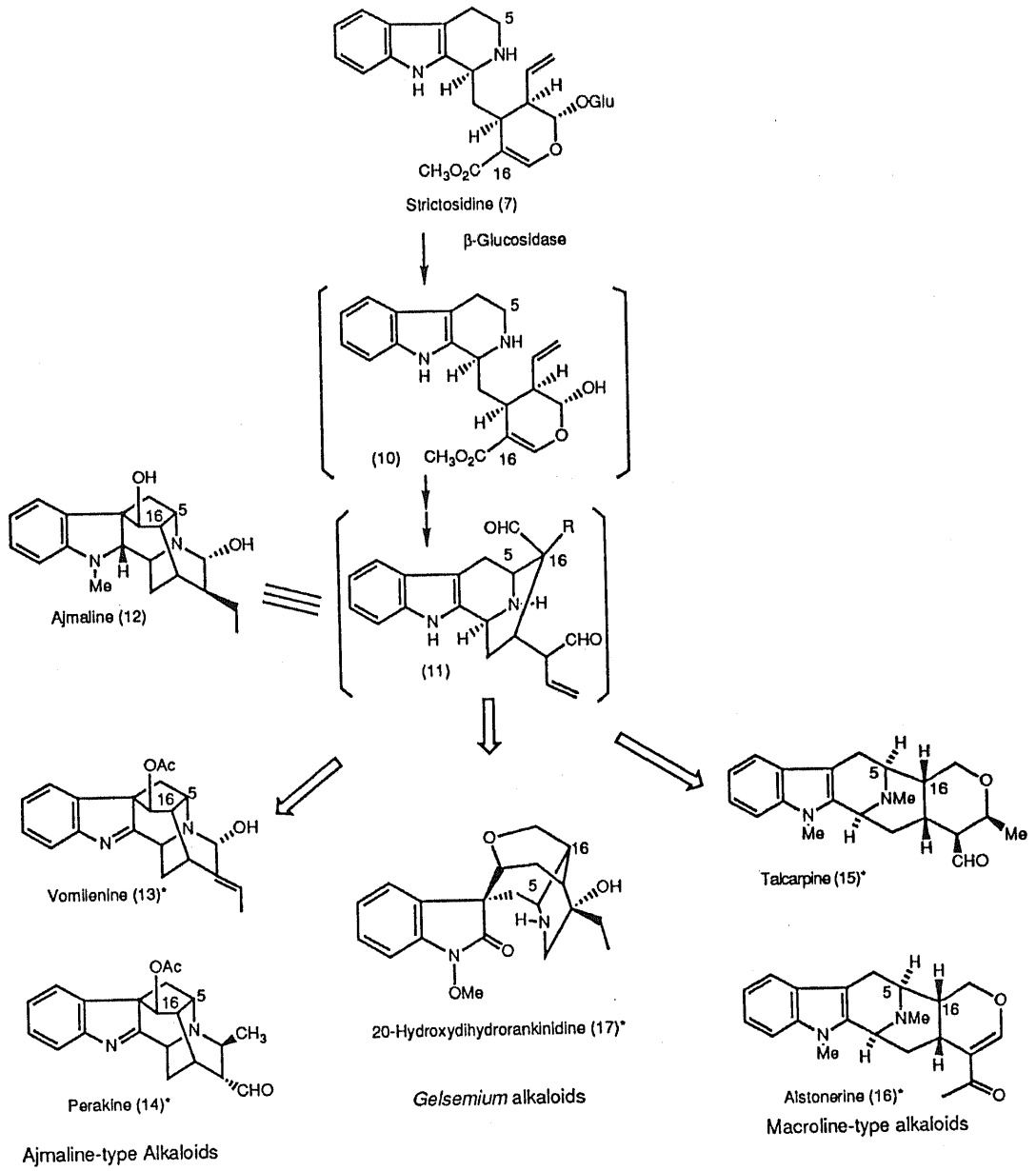


Tryptamine (8)



Secologanin (9)

Among the monoterpenoid indole alkaloids, the compounds that possess a bond between C5 and C16, such as ajmaline-type alkaloids, macroline-type alkaloids, and most of *Gelsemium* alkaloids are considered to be derived from strictosidine (7) *via* the common sarpagine



*These alkaloids were derived from ajmaline (12) by a biomimetic synthesis in this thesis.

type intermediate such as (**11**). These sarpagine-derived alkaloids were isolated from different species of plants in Loganiaceae and Apocynaceae, but not in Rubiaceae.[1)]

In order to elucidate the exact mechanism of the biosynthesis of these alkaloids and their regulation, detailed enzymatic studies and isolation and structure elucidation of all the alkaloid products are necessary. This process is complicated and time-consuming. Recently the biosynthetic studies of ajmaline/ sarpagine type alkaloids using cell-culture technique is in progress,[3)] but those of macroline-type alkaloids and *Gelsemium* alkaloids have not been done yet.

Our interest in the structures of these sarpagine-derived alkaloids, their biosynthetic pathway, and their biological activities, led us to consider a common strategy for their synthesis. By mimicking the plausible biosynthetic route and using a natural compound that has a similar structure to the biosynthetic intermediate as the starting material would provide an efficient synthetic pathway of fewer steps, and the products of higher optical purity than that of total synthesis. Thus, the synthesis of the alkaloids (**13**)-(**17**) using the commercially available ajmaline (**12**), which could be considered approximately the same as the intermediate (**11**), as the starting material was planned. Ajmaline (**12**) could be obtained in a large amount from *Rauwolfia serpentina* Benth., which is cultivated in tropical area for the main purpose of isolation of reserpine (**5**).

This thesis was undertaken in an effort to show the versatility of ajmaline (**12**) on the semisynthesis of the sarpagine-derived alkaloids and to gain more understanding of the biosynthetic pathway of these alkaloids.

The content of this thesis will be divided into 3 parts.

1) Partial synthesis of vomilenine (**13**) and perakine (**14**)

2) Biomimetic synthesis of talcarpine (**15**) and alstonerine (**16**)

3) Biomimetic synthesis of 20-hydroxydihydrorankinidine (**17**)

The introduction for each alkaloid and the purpose for its synthesis will be described in each chapter.

Chapter 1

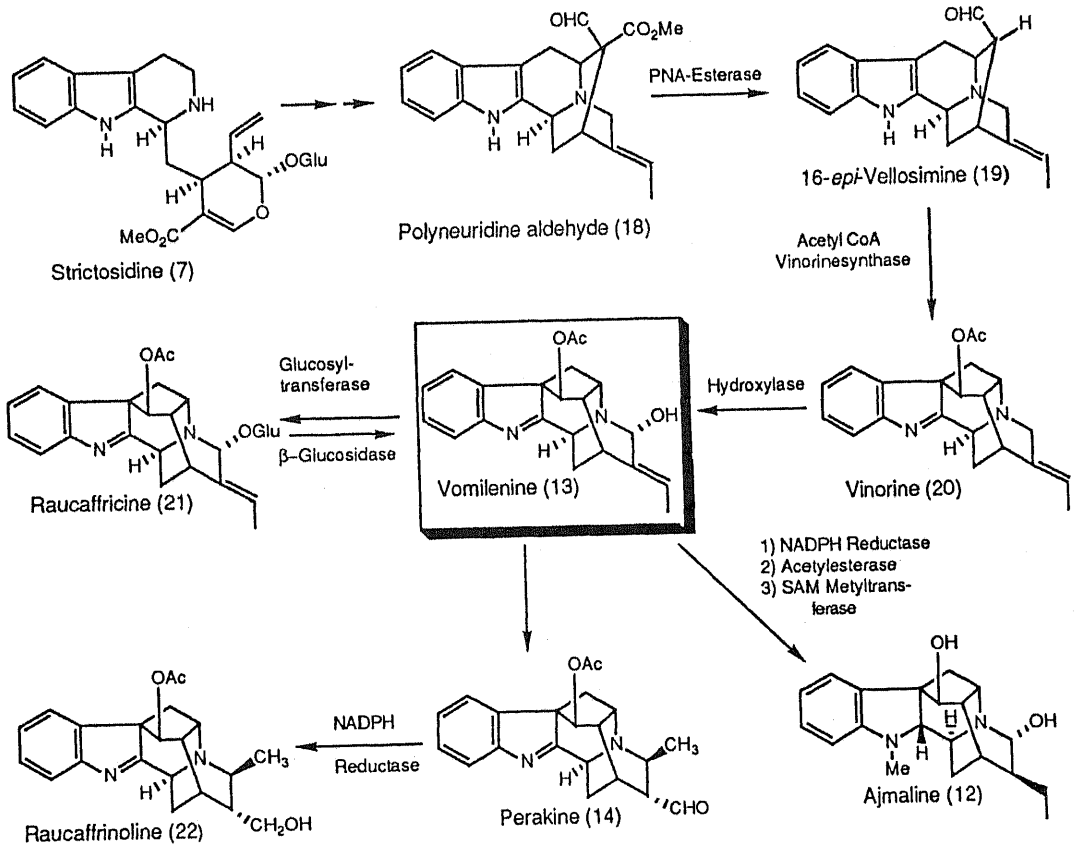
Partial Synthesis of *Rauwolfia* Alkaloids Vomilenine and Perakine.

Many plants in the genus *Rauwolfia* (Apocynaceae) have medical uses. The first report concerning the hypotensive properties of *Rauwolfia* extracts was made in 1933. Later, Muller and co-worker succeeded in isolating the alkaloid reserpine (**5**), which was shown to be the principle hypotensive and sedative ingredient of *R. serpentina* Benth. Following the isolation of reserpine (**5**) and the demonstration of its immense importance as a hypotensive and sedative drug, an intense search was made for alternative sources among the *Rauwolfia* species, particularly those which are endemic to the regious outside India.[4] This resulted in isolations of many *Rauwolfia* alkaloids. Two medically active alkaloids: yohimbine (**6**) (α-blocker) and ajmaline (**12**) (antiarrhythmia) were also isolated from *Rauwolfia* plants.

One of *Rauwolfia* alkaloids, vomilenine (**13**) was first isolated in 1957 from the roots of African species *R. vomitoria* Afz. as a minor constituent[5] and later it was found in the leaves of four New Caledonian *Rauwolfia* species, namely *R. balansae* ssp. *balansae* Boiteau, *R. balansae* ssp *schumanniana* var. *basicola* Boiteau, *R. spathulata* Boiteau, and *R. sevenetii* Boiteau,[6] and the pan-african species *R. Caffra* Sond.[7] Vomilenine (**13**) is the main alkaloid in

cultured *R. serpentina* cells,[8] the yield of (13) was 51 times more than that in differentiated plants.[8a] Recently, the important role of vomilenine (13) in the biogenesis of some *Rauwolfia* alkaloids, such as ajmaline (12), raucaffricine (21), raucaffrinoline (22), *etc.*, has been proposed, as summarized in Fig. 1-1.[3]

Fig. 1-1 Biosynthesis of Sarpagine/Ajmaline Alkaloids*



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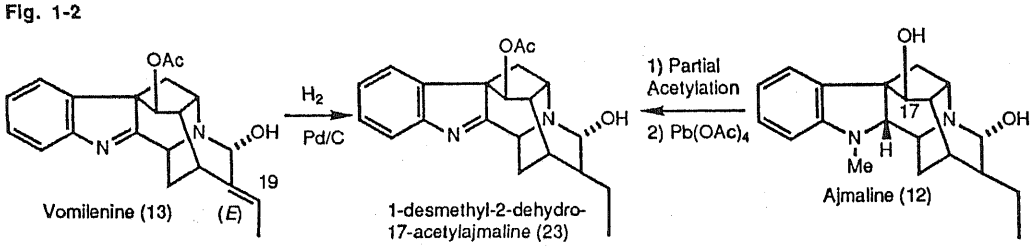
*A demonstration of this biochemical route is in progress by a co-operative research between Prof. J. Stöckigt group and our laboratory.

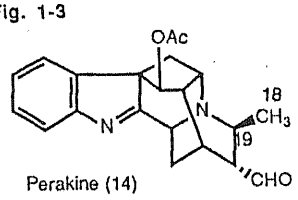
The structure of vomilenine (13) was determined by Taylor *et al.*[9] through the chemical correlation with ajmaline (12), as illustrated in Fig. 1-2. The structure of (13) then proposed had a (19*Z*) ethylidene side chain, but later, without any chemical evidence, the geometry of the C19 position was revised to (19*E*),[10] as in the common sarpagine class of indole alkaloids. However, several sarpagine-type indole alkaloids having a (19*Z*) ethylidene moiety were found in *Gardneria* and *Gelsemium* species.[11] Consequently, careful confirmation of the ethylidene configuration is needed.

Fig. 1-2

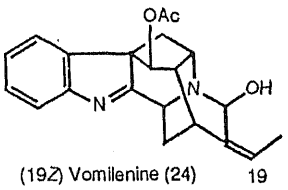


Meanwhile one of the *Rauwolfia* alkaloids, perakine (14), isolated for the first time from the aqueous-methanolic-acetic acid raffinate of *R. vomitoria*,[12] may be regarded as an artifact derived from vomilenine (13) based on the fact that treatment of (13) with hot acetic acid gave perakine (14).[9] In order to obtain chemical evidence of the configuration of the ethylidene side chain in (13) and to see the effect of the configuration of the ethylidene side chain on the thermodynamic stability, the synthesis of vomilenine (13) and (19*Z*)-vomilenine(24) from ajmaline (12) and subsequent transformation into perakine (14) were planned.

Fig. 1-3



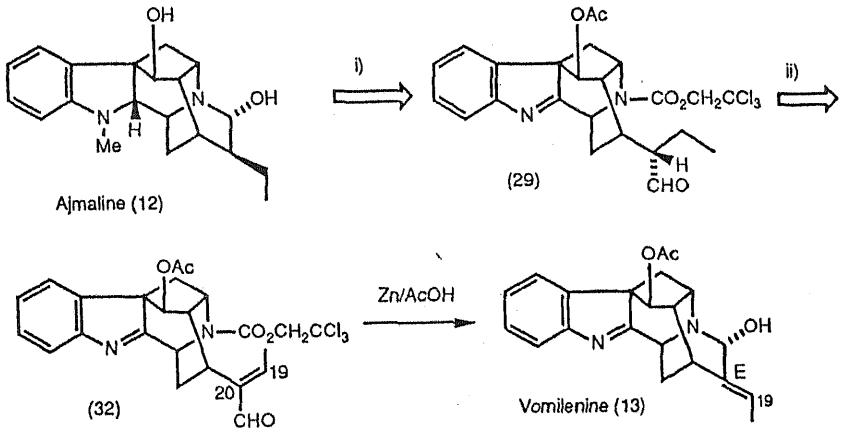
Perakine (14)



(19*Z*) Vomilenine (24)

The transformation of ajmaline (**12**) into vomilenine (**13**) involves 2 key steps: (i) generation of indolenine ring from indoline (ii) stereoselective introduction of a 19,20 double bond.

Fig. 1-4



Ajmaline (12)

(29)

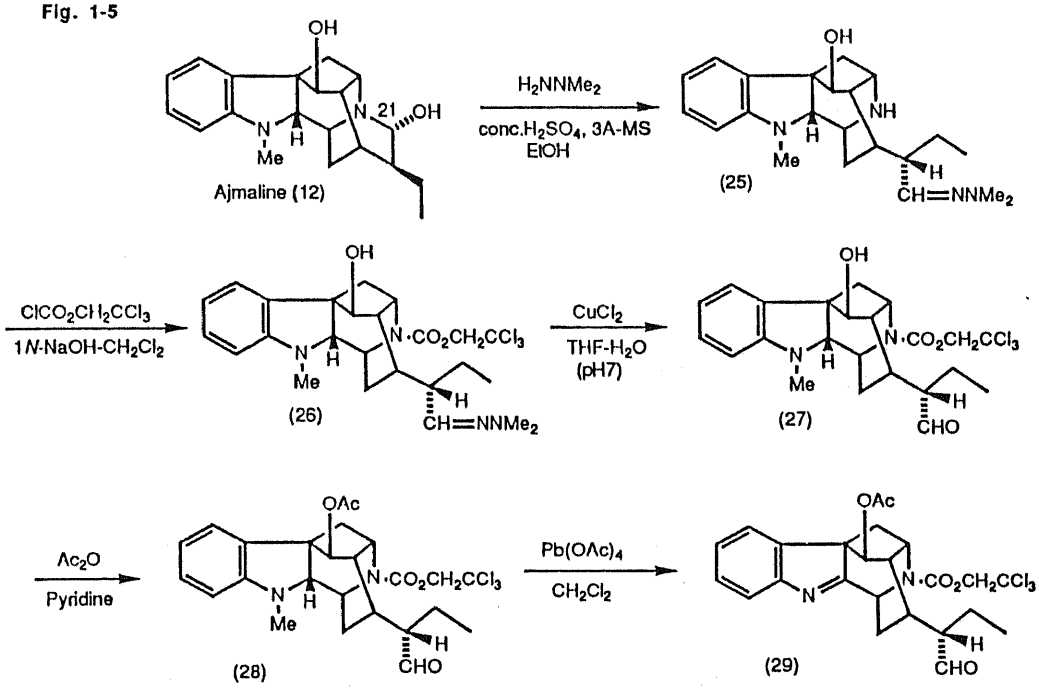
(32)

Vomilenine (13)

Initially, ajmaline (**12**) was treated with *N,N*-dimethylhydrazine (5 equiv) and a catalytic amount of H_2SO_4 in dry EtOH at reflux for 2.5 h to afford the secondary amine (**25**), that was directly converted to the carbamate (**26**) by using ββ-trichloroethyl chloroformate ($ClCO_2CH_2CCl_3$) under Schotten-Baumann conditions in 70% overall yield. On hydrolysis of the hydrazone function in (**26**) with cupric chloride ($CuCl_2$) in aqueous tetrahydrofuran (THF) at pH 7,[13] the aldehyde (**27**) was obtained in 86% yield. In the ^{1}H-NMR, (**27**) exhibited

a signal at δ 9.64 due to an aldehyde function. After acetylation of the C17 hydroxy group with acetic anhydride in pyridine, the N_a-methylindoline moiety was oxidized with 2.9 equiv of lead tetraacetate [$Pb(OAc)_4$] in dry CH_2Cl_2 at -70 °C to furnish the indolenine (**29**) in 88% yield. Compound (**29**) showed the characteristic ultraviolet (UV) absorption peaks at 210, 220, and 249 nm due to the indolenine chromophore.

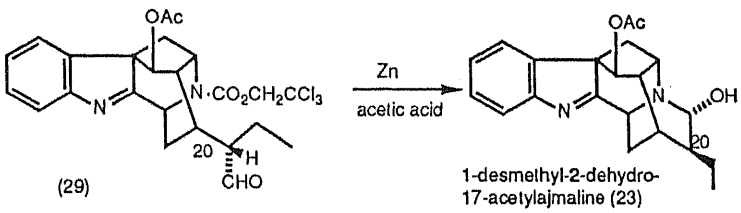
Fig. 1-5



The protecting group on N_b in (**29**) was cleaved with zinc (Zn) in AcOH at room temperature to afford 1-desmethyl-2-dehydro-17-acetylajmaline (**23**) (mp 238-242 °C); its spectral properties [mass spectrum (MS), proton (^{1}H-) and carbon-13 nuclear magnetic

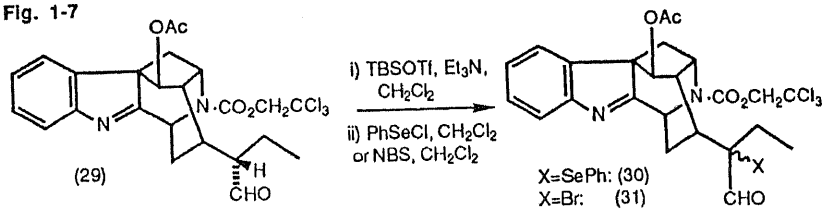
resonance (^{13}C-NMR) (Table 1-1) spectra] were in accord with those of natural (**23**).[6,14] This fact indicates that the configuration at the C20 position did not epimerize under the reaction conditions of transformation from (**12**) to (**23**) *via* the hydrazone derivative.

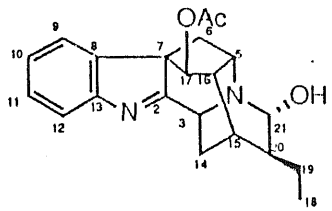
Fig. 1-6



To introduce the double bond at the 19-20 position, a bromine atom or phenylselenyl group were introduced at the C-20 position through the silyl enol ether of the aldehyde function. Thus, (**29**) was treated successively with *tert*-butyldimethylsilyltriflate (TBSOTf) and triethylamine (Et_3N) in dry CH_2Cl_2 and then with phenylselenenyl chloride (PhSeCl) or *N*-bromosuccinimide (NBS) to provide the α-substituted aldehydes (**30**) or (**31**) in 53% and 71% yields, respectively.

Fig. 1-7





1-desmethyl-2-dehydro-17-acetylajmaline (23)

Table 1-1 ^{13}C-NMR Chemical Shifts and Assignments

No.	Natural (23)	Synthetic (23)
2	183.0	183.2
3	54.8	54.8
5	49.8*	49.8*
6	37.4	37.7
7	65.1	65.1
8	136.1	136.5
9	123.7	123.8
10	125.4	125.5
11	128.7	128.8
12	121.1	121.1
13	156.6	156.4
14	27.8	27.8
15	27.5	27.6
16	47.2*	47.0*
17	78.7	78.7
18	11.9	11.9
19	26.0	26.0
20	42.0	42.0
21	87.5	87.5
-CO- (ester)	169.8	169.9
MeCO-	21.1	21.1

Solvent $CDCl_3$. Assigntments bearing the same superscript on vertical column may be interchanged.

Oxidation of (**30**) using hydrogen peroxide (H_2O_2), *m*-chloroperbenzoic acid (*m*CPBA) or sodium periodate ($NaIO_4$) resulted in the exclusive formation of the tetrasubstituted olefins as shown in Table 1-2.

Fig. 1-8

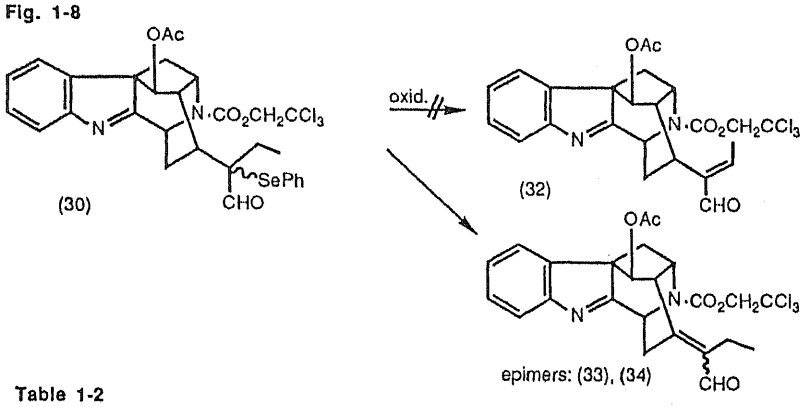


Table 1-2

Entry	Condition	(32)	(33)+(34)
1	30% H_2O_2 aq. (8.8), AcOH, 70 °C, 30min	0	29
2	mCPBA (3.0), dry CH_2Cl_2, -70 °C, 1h	0	65
3	$NaIO_4$ (1.0), MeOH-H_2O, -10 °C~ rt	0	30

Dehydrobromination of (**31**) with lithium carbonate (Li_2CO_3) in dimethylformamide (DMF) at 80 °C (Table 1-3, entry 4) afforded the desired *E*-olefin (**32**) in 26% yield accompanied with the *Z*-olefin (**35**) (21%) and tetrasubstituted olefins (**33**), (**34**) (total 18%).

Fig. 1-9

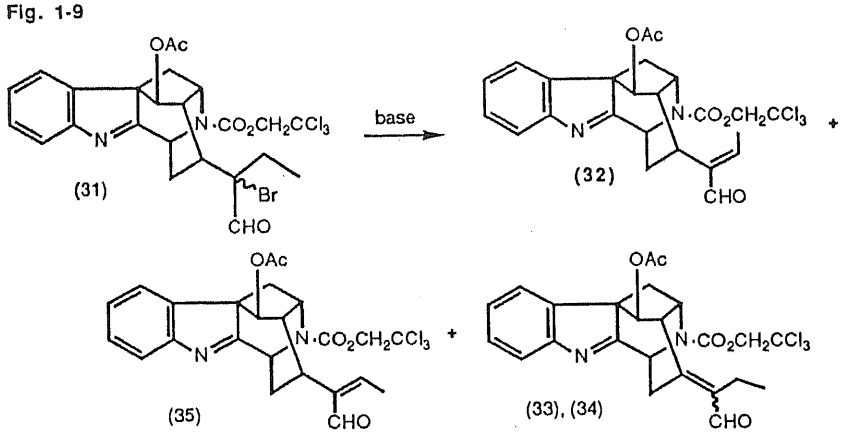


Table 1-3

Entry	Condition	(32)	(35)	(33)+(34)	Total yield
1	DBU (1.1), dry DMF, rt, overnight	3	30	18	54
2	t-BuOK (1.1), 18 Crown 6, dry toluene, rt, overnight				unknown compound
3	Li_2CO_3 (3.0), dry DMF, rt~80 °C	18	25	12	55
4	Li_2CO_3 (3.0), dry DMF, 80 °C, 4.5 h	26	21	18	65
5	Li_2CO_3 (3.0), dry DMF, 100 °C, 2 h	7	26	20	53
6	Li_2CO_3 (3.0), dry DMSO, 80 °C, 5 h	10	10	30	50
7	Li_2CO_3 (3.0), dry acetone, 80 °C, 1.2 h				no reaction

The geometry of the olefins (**32**) and (**35**) was unambiguously determined by nuclear Overhauser effect (NOE) experiments. Thus, irradiation of the C21 aldehyde proton (δ 9.39, 9.37*) in (**32**) led to enhancement (22.7%) of the C19 olefinic proton signal (δ 6.62), while 9.5% enhancement was observed between the aldehyde proton (δ 10.21, 10.16) and C-18 methyl protons (δ 2.16 and 2.17) in (**35**) (Fig. 1-10).

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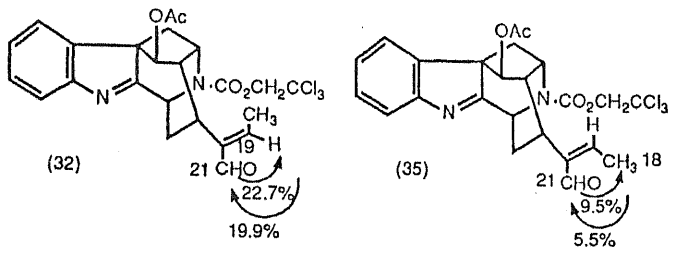
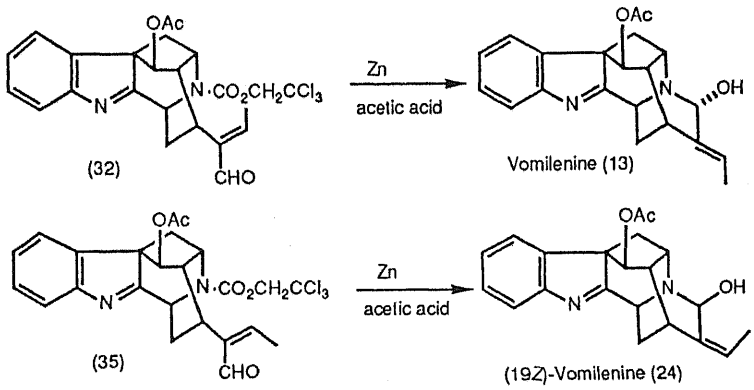
*Ajmaline derivatives possessing a carbamate function in the molecule are often shown by their ^{1}H-NMR spectra to occur as a mixture of rotation isomers.

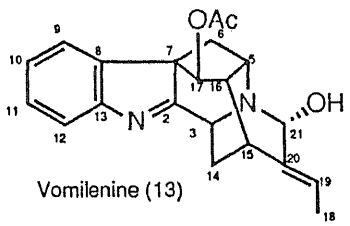
Fig. 1-10



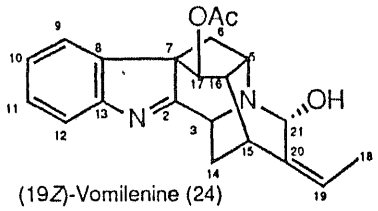
Finally, the protecting group on N_b in (**32**) was removed with Zn in AcOH at room temperature to give rise to vomilenine (**13**) in 68% yield. The ^{1}H- and ^{13}C-NMR spectra, infrared (IR) spectrum, MS and mp (189-191 °C) were identical with those of natural vomilenine (**13**). Therefore, the structure of vomilenine was concluded to be (**13**).[15] The *Z*-isomer (**35**) was also converted to the vomilenine-type compound (**24**) in 75% yield by removal of the carbamate group under the same reaction conditions.

Fig. 1-11





Vomilenine (13)



(19*Z*)-Vomilenine (24)

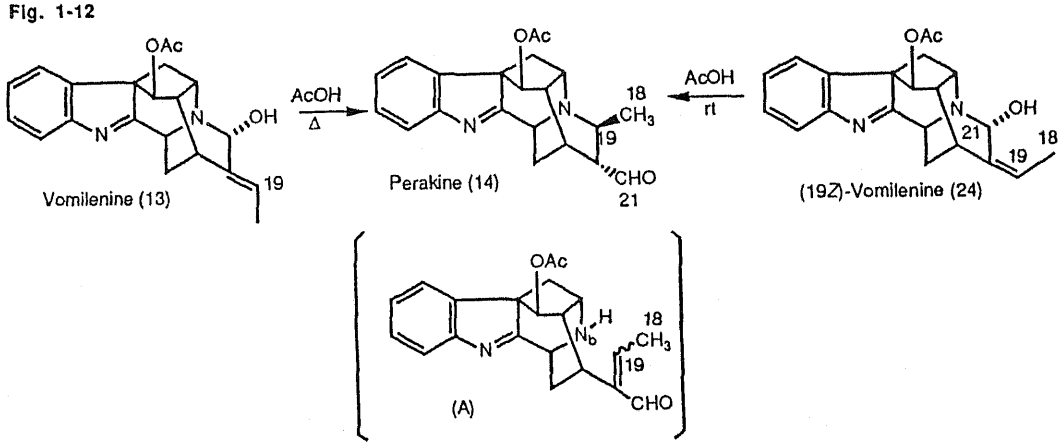
Table 1-4 ^{13}C-NMR Chemical Shifts and Assignments

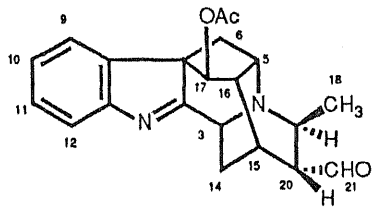
No.	Natural (13)	Synthetic (13)	(24)
2	183.6	182.3	182.9
3	54.3*	54.4*	55.5
5	50.9*	50.9*	50.6
6	36.4	36.4	37.0
7	65.1	65.2	64.3
8	136.1	136.3	136.3
9	123.9	123.8	123.8
10	125.8	125.7	125.5
11	128.9	128.8	128.7
12	121.1	121.1	121.1
13	156.3	156.4	156.4
14	26.3	26.4	26.4
15	28.2	28.4	34.4
16	49.0*	49.2*	48.6
17	77.5	77.6	77.8
18	13.0	13.0	13.0
19	119.4	119.6	122.1
20	131.0**	139.2	139.4
21	82.5	82.4	80.9
-CO- (ester)	169.7	169.9	169.9
MeCO-	21.1	21.1	21.0

Solvent $CDCl_3$. Assigntments bearing the same superscript on vertical column may be interchanged.
**This value should be revised to δ 139.2.
(Personal Correspondence with Prof. Poisson)

Next, the facility of the transformation of vomilenine (**13**) and (19*Z*)-vomilenine (**24**) into perakine (**14**) was compared. On standing of (**24**) in acetic acid at room temperature, 25% of the starting material had changed to perakine (**14**) after 17 h, and two weeks later (**24**) was completely converted to (**14**). The synthetic compound (mp 179-183 °C) exhibited spectral properties (^{1}H- and ^{13}C-NMR, IR, and MS) in accord with those of authentic perakine (**14**).[12] In contrast to the results obtained with (**24**), (**13**) was quite stable in acetic acid at room temperature (no reaction for 2 days).[9] For the conversion of vomilenine (**13**) to perakine (**24**), relatively severe conditions (reflux in AcOH) were required.[9] Interestingly, the two geometric isomers, vomilenine (**13**) and (19*Z*)-vomilenine (**24**), gave the same product, perakine (**14**). In the ^{13}C-NMR spectra, the signal of C21 in (**24**) was observed at 1.5 ppm upfield from the corresponding signal of (**13**). Therefore, probably due to the steric repulsion between the hydroxy group and/or the hydrogen on C21 and the C_{18}-methyl group in (**24**), cleavage of the amino-acetal function in (**24**) could proceed more readily than that of (**13**) and subsequent Michael-type ring closure between N_b and C19 of an intermediate (A) would furnish the thermodynamically controlled product, perakine (**14**), through epimerization at the C20 position.

Fig. 1-12


OAc
OH
N
19
Vomilenine (13)
AcOH
Δ
OAc
18
CH3
19
CHO
21
Perakine (14)
AcOH
rt
OAc
OH
21
19
18
(19Z)-Vomilenine (24)
OAc
H
Nb
18
CH3
19
CHO
(A)



Perakine (14)

Table 1-5 ^{1}H-NMR Chemical Shifts and Assignments

No.	Natural (14) (270 MHz)	Synthetic (14) (500 MHz)
3	4.19 (d, J=9.2)	4.18 (d, J=9.3)
5	3.64 (t, J=5.8)	3.63 (t, J=5.8, 6.1)
6α	1.66 (d, J=11.9)	1.65 (d, J=11.3)
6β	2.81 (dd, J=11.9, 5.2)	2.81 (dd, J=11.8, 5.0)
9	7.48 (d, J=7.3)	7.48 (dd, J=7.4, 0.5)
10	7.23 (t, J=7.3)	7.23 (td, J=7.4, 1.1)
11	7.40 (t, J=7.6)	7.40 (td, J=7.7, 1.1)
12	7.62 (d, J=7.6)	7.62 (d, J=7.7)
14α	1.78 (dd, J=15.0, 9.2)	1.76 (dd, J=15.2, 9.6)
14β	1.60 (dd, J=15.0, 5.2)	1.59 (dd, J=14.9, 5.2)
15	2.89 (t, J=4.9, 5.5)	2.88 (t, J=5.2, 5.5)
16	2.48 (t, J=6.0)	2.47 (t, 5.5)
17	4.94 (d, J=1.2)	4.94 (d, J=1.1)
18-CH_3	1.30 (3H, d, J=6.7)	1.29 (3H, d, J=6.9)
19	3.34 (qd, J=9.2, 6.7)	3.33 (qd, J=9.3, 6.6)
20	2.17 (d, J=9.2)	2.17 (d, J=~9)
21	9.85 (d, J=0.6)	9.85 (d, J=0.9)
-$OCOCH_3$	2.19 (3H, s)	2.18 (3H, s)

Solvent $CDCl_3$.

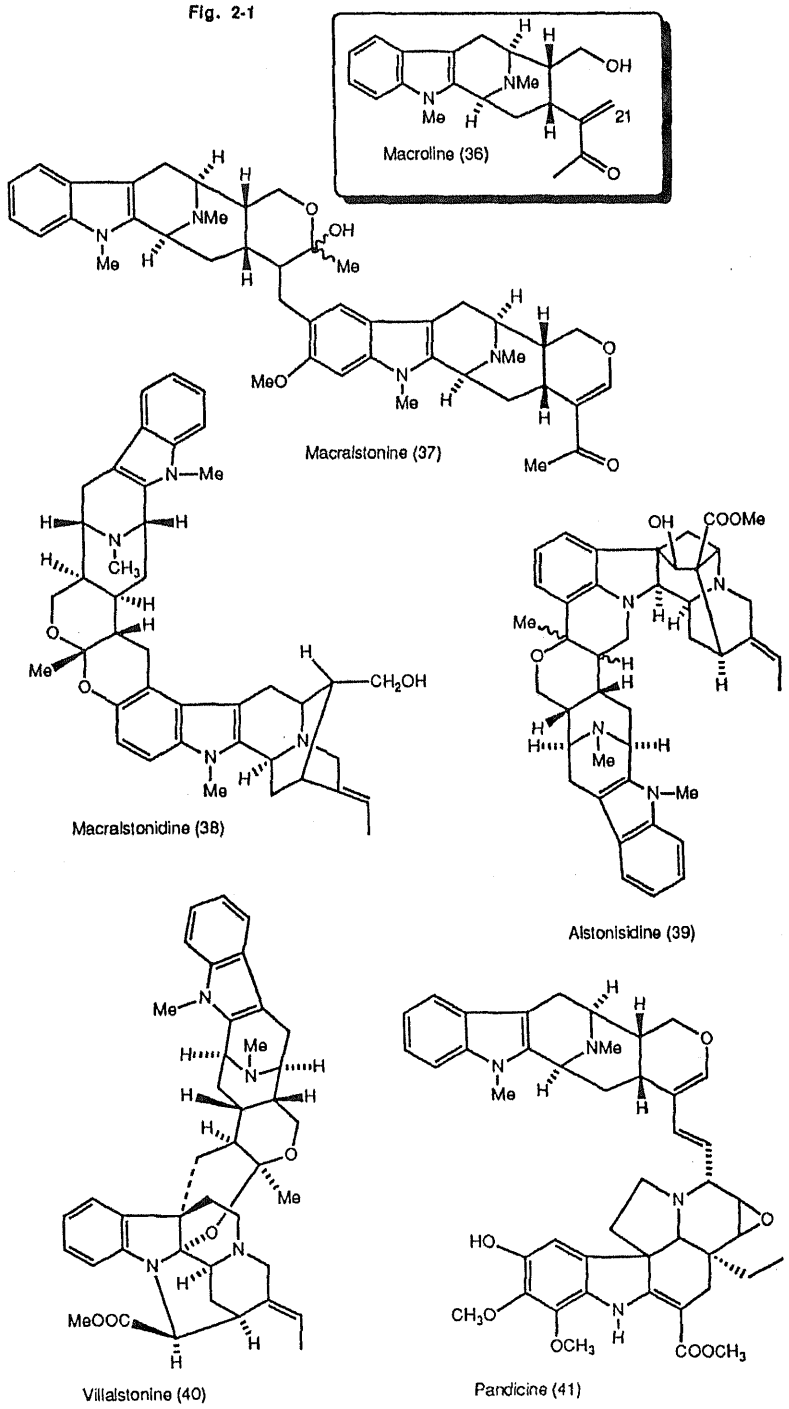
Chapter 2

Biomemetic Synthesis of Macroline-type Alkaloids: Talcarpine and Alstonerine

The Genus *Alstonia* is accompanied in the tribe Alstonieae (subfamily Plumerioideae) of the Apocynaceae by other genera which are also important sources of indole alkaloids, e.g. *Aspidosperma*, *Catharanthus*, and *Rhazya*.[16] Investigations into the constituents of *Alstonia* species were stimulated by the knowledge that in Far East extracts of *Alstonia* species were commonly used as a cure for malaria. The pharmacology of *Alstonia* extracts and of the pure alkaloids has been investigated, however so far there is no indication of any effective antimalarial activity.[17] The *Alstonia* genus appears to be divided into three defined sections as far as alkaloid content is concerned. Those containing macroline-type alkaloids belong to the Monuraspermum section. *A. muelleriana* Domin., *A. macrophylla* Wall, and *A. angustifolia* Wall are examples of the members of this section.[18] Although macroline (**36**), which features bond cleavage between the N_b and the C21 position in the sarpagine class of indole alkaloids,[19] itself has not been isolated as a natural product,[20] (**36**) is generally accepted as a biogenetic precursor of some bisindole alkaloids, such as macralstonine (**37**),[21] macralstonidine (**38**),[22]

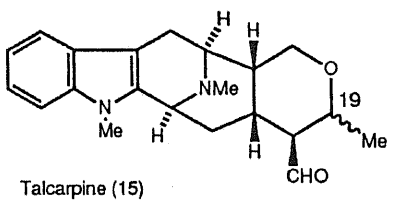
alstonisidine (39),[23] villalstonine (40),[20a, 23a, 23c, 24] and pandicine (41).[25]

Fig. 2-1

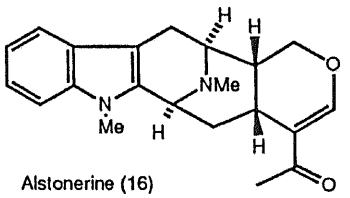


Talcarpine (**15**) and alstonerine (**16**) are monomeric macroline-type alkaloids. Talcarpine (**15**) was first isolated from the stem bark of *Pleiocarpa talbotii* Wernham in 1972[26] and later it was found in the bark of *A. macrophylla*.[27] The structure of (**15**) was elucidated by mass, UV, and ^{1}H-NMR spectroscopies and chemical correlations[28] with other macroline-type indole alkaloids, but as yet the stereochemistry at C19 remains unsettled. Alstonerine (**16**) was first isolated from the tree bark of the Australian species *A. muelleriana* in 1969[29] and later was also found in other Alstonia species.[18] The structure of alstonerine (**16**) is closely related to alstophylline (**42**), alstonisine (**43**) and the hypotensive bisindole alkaloid, macralstonine (**37**). Thus, it could be. considered to be a biogenetic precursor of these alkaloids.

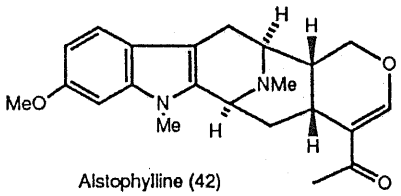
Fig. 2-2



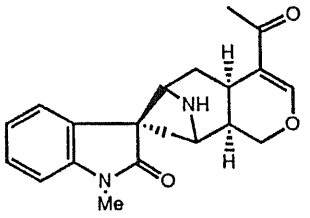
Talcarpine (15)



Alstonerine (16)



Alstophylline (42)

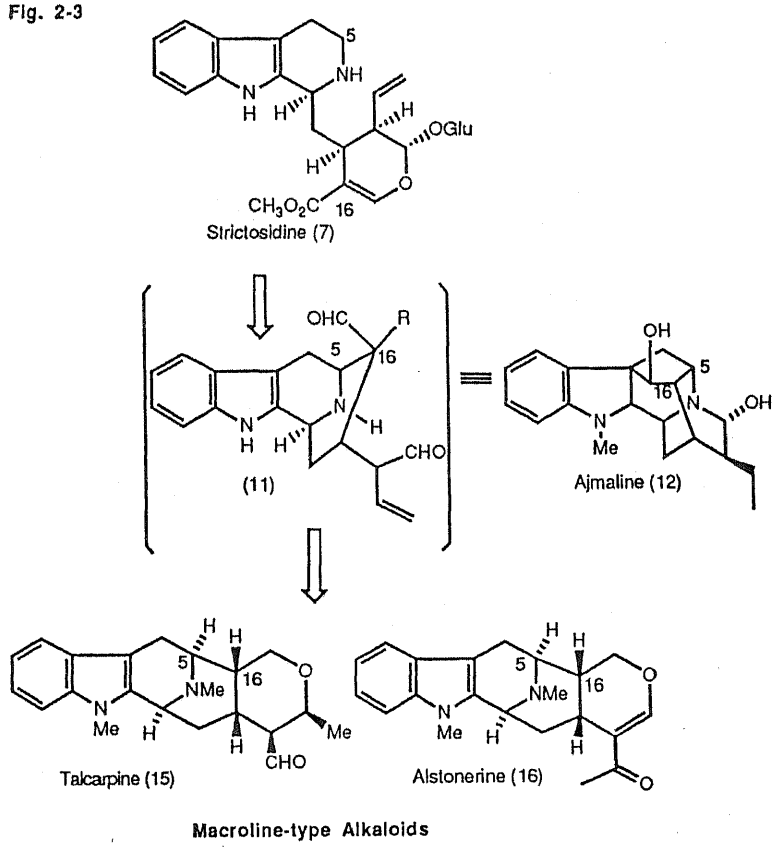


Alstonisine (43)

The exact biosynthesis of macroline-type alkaloids is still vague. Meanwhile, an elegant total synthesis of alstonerine (**16**) was quite

recently published by Cook *et al.*[30] A short and biomimetic synthesis of macroline-type alkaloids is still valuable. Also the configuration at C19 of talcarpine (**15**) was needed to be determined. On the proposal that macroline-type alkaloids should be generated from strictosidine *via* the sarpagine-type intermediate (**11**), which is considered to be chemically equivalent to ajmaline (**12**), the synthesis of talcarpine (**15**) and alstonerine (**16**) from (**12**) was planned.

Fig. 2-3

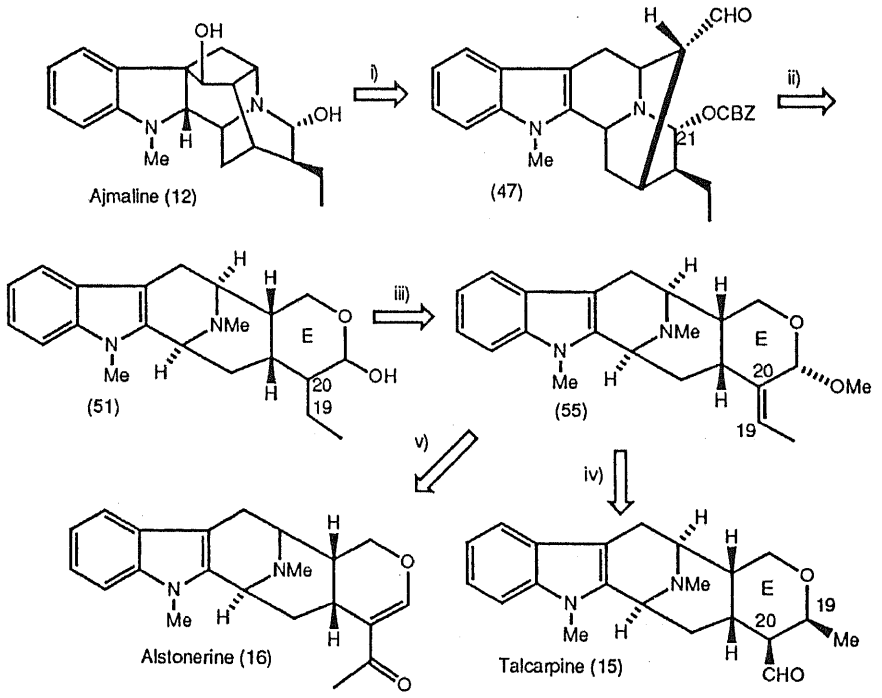


Macroline-type Alkaloids

The transformation from ajmaline (**12**) into talcarpine (**15**) and alstonerine (**16**) involves mainly five structural changes of the starting material: i) generation of indole ring from indoline and epimerization

at C16 position (**12** to **47**), ii) cleavage of N_b-C21 bond and formation of E-ring (**47** to **51**), iii) introduction of a 19-20 double bond iv) re-construction of E-ring leading to talcarpine (**15**) or v) introduction of an oxygen function to C19 bond and creation of a double bond at C20-21 leading to alstonerine (**16**).

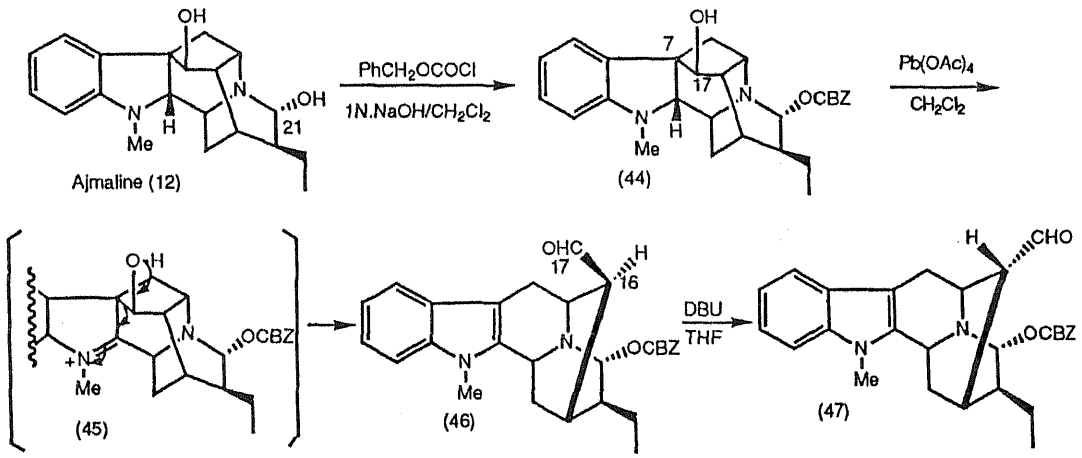
Fig. 2-4



Initially, the hydroxy function at C21 in ajmaline (**12**) was selectively protected in 87% yield with carbobenzoxy group under Schotten-Baumann condition to yield the carbonate (**44**) (mp 218-220 °C). Oxidation of the indoline moiety in (**44**) with one equiv of lead tetraacetate [$Pb(OAc)_4$][31] in dry CH_2Cl_2 generated the indole derivative (**46**) (mp 80-82 °C) in 68% yield. In the ^{1}H-NMR spectrum,

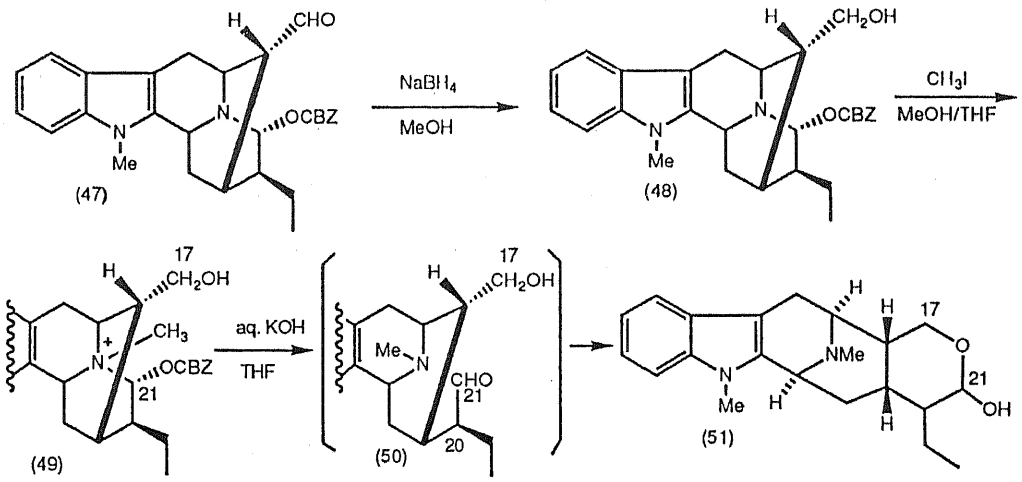
(46) exhibited a signal at δ 9.32 due to an aldehyde function. Treatment of (46) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dry THF afforded the epimeric aldehyde (47) as a result of the epimerization at the C16 position in a quantitative yield. The chemical shift of the aldehyde proton in (47) appeared at 0.38 ppm lower than that of (46) caused by the release of the shielding effect of the indole ring

Fig. 2-5



Reduction of (47) with sodium borohydride ($NaBH_4$) gave the primary alcohol (48) (mp 177-178 °C) in 90% yield. Next, quaternarization of the N_b group in (48) with methyl iodide (MeI) and successive hydrolysis of the carbonate (49) with aqueous KOH solution resulted in the formation of macroline-skeleton (51) in 92% yield from (48) *via* the cleavage between the N_b and C21 and subsequent construction of the hemiacetal ring between the primary alcohol and the C21 aldehyde group of the intermediate (50).[32]

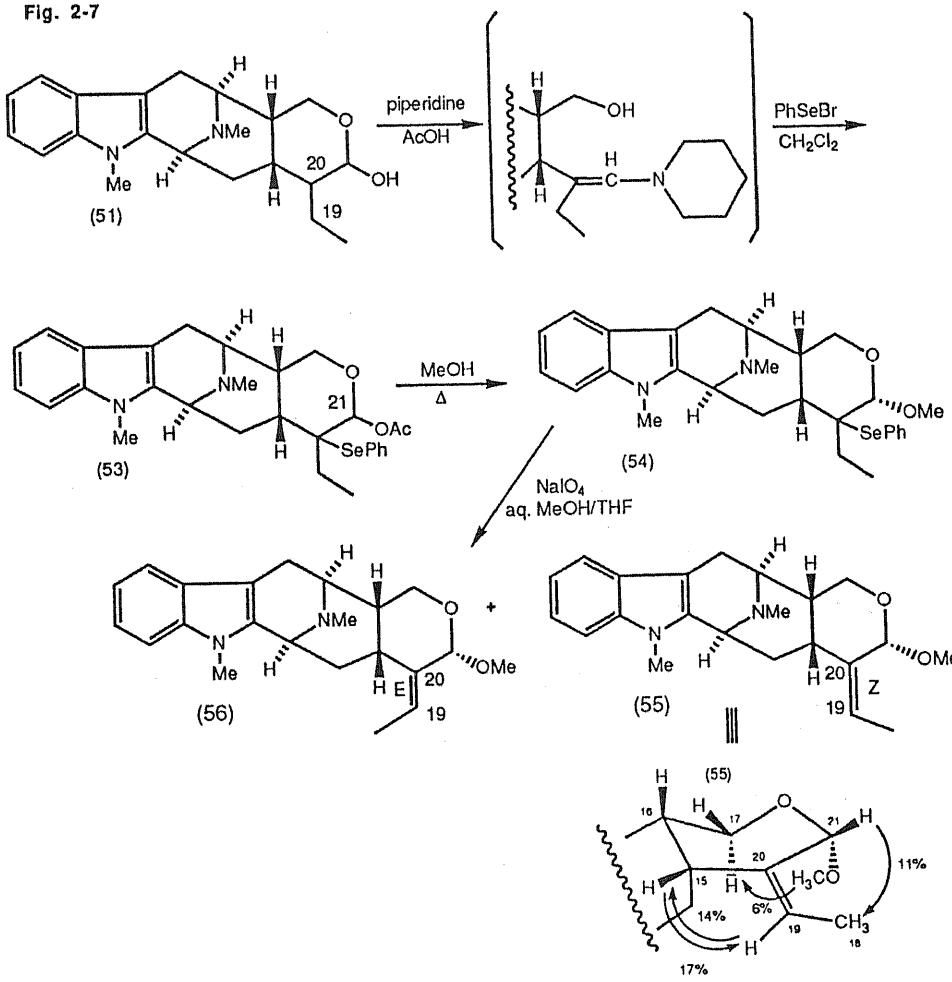
Fig. 2-6



To introduce a double bond at the C19-20 position, a phenylselenenyl group was introduced to C20 position by means of enamine method. Thus, (**51**) was heated with 5 equiv of piperidine in acetic acid and the resultant unstable enamine intermediate (**52**), which was obtained by the evaporation of the solvent and reagent under reduced pressure, was treated with phenylselenenyl bromide (PhSeBr) in dry CH_2Cl_2 under reflux condition to yield the selenenylated product (**53**), which upon recrystallization from MeOH afforded the acetal (**54**) (mp 180-181.5 °C) in 47% overall yield from (**51**). Oxidation of (**54**) with sodium periodate ($NaIO_4$) in aqueous MeOH/THF provided a mixture consisting of two olefins (**55**) and (**56**). The ^{1}H-NMR spectrum of the mixture reveals the ratio of (**55**) and (**56**) as approximately 2:1. By the careful chromatographic separation of this mixture with medium pressure liquid chromatography and by recrystallization, major isomer (**55**) was obtained as colorless prisms

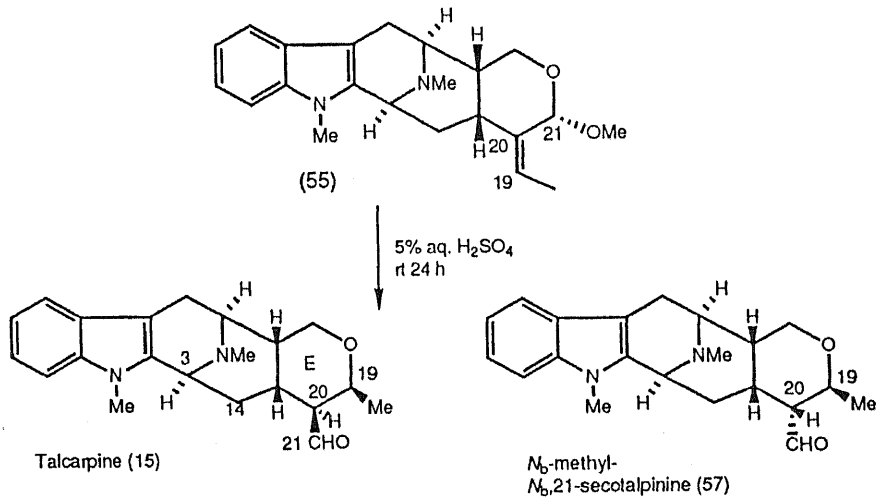
(mp 198-202 °C). NOE experiments of (**55**) made clear the stereochemistry at C19 and C21 positions. Irradiation at 21-H (δ 5.23) and olefinic proton at C19 (δ 5.15) showed the 11% and 14% enhancement of 18-H_3 (δ. 1.56) and 15-H (δ 2.26), respectively. This indicates that the geometry of the major olefin (**55**) has Z-form. As 6% enhancement was observed between methoxy signal (δ 3.43) and 17-Hα (δ 4.41), an anomeric methoxy group existed in α-orientation.

Fig. 2-7



Finally, the major isomer (**55**) was treated with 5% aqueous H_2SO_4 solution at room temperature for 26 h to furnish talcarpine (**15**) (mp 160-161 °C) and the aldehyde (**57**) in 30% and 59% yield, respectively. The properties (mp. UV, IR, MS, ^{1}H-NMR, and CD spectra) of semisynthetic compound (**15**)[33] were well consistent with the values reported in the literature.[26]

Fig. 2-8



To elucidate the configuration at C19 position in talcarpine (**15**), NOE experiments were attempted. However, the signals of 19-H and 3-H were overlapped in (**15**), so that clear information concerned with the stereochemistry at C19 could not be obtained. Then the acetyl derivative (**58**) was prepared from (**15**) (i. $NaBH_4$ in MeOH, ii. Ac_2O in pyridine) and the NOESY experiments on (**58**) was carried out. Since clear interactions between 19-H and 14-Hα and between 18-H3 and one of the protons on C21 were observed, the configuration at C19 was concluded to be *S*. Compound (**57**) obtained together with (**15**) by the

acidic treatment of (**55**) was also identical with the reported compound[26] that was derived from talpinine (**59**) by the methylation of N_b with MeI. Talcarpine (**15**) was also able to convert to (**57**) by treating with K_2CO_3 in MeOH through the epimerization at C20 position.[26] In the ^{13}C-NMR spectra, the signal due to C14 in (**15**) was observed at downfield (Δ 3.3 ppm) and, on the contrary, that of C16 was observed at upfield (Δ 3.2 ppm) than the corresponding signals of (**57**). (see Table 2-1). These phenomena can be interpreted by the γ-gauche effect of the C21 formyl group. From this NMR analysis as well as the above chemical interconversions, the configuration at C19 in talpinine (**59**) should be *S* similar to talcarpine (**15**).* NOE data of (**57**) also supported this conclusion.

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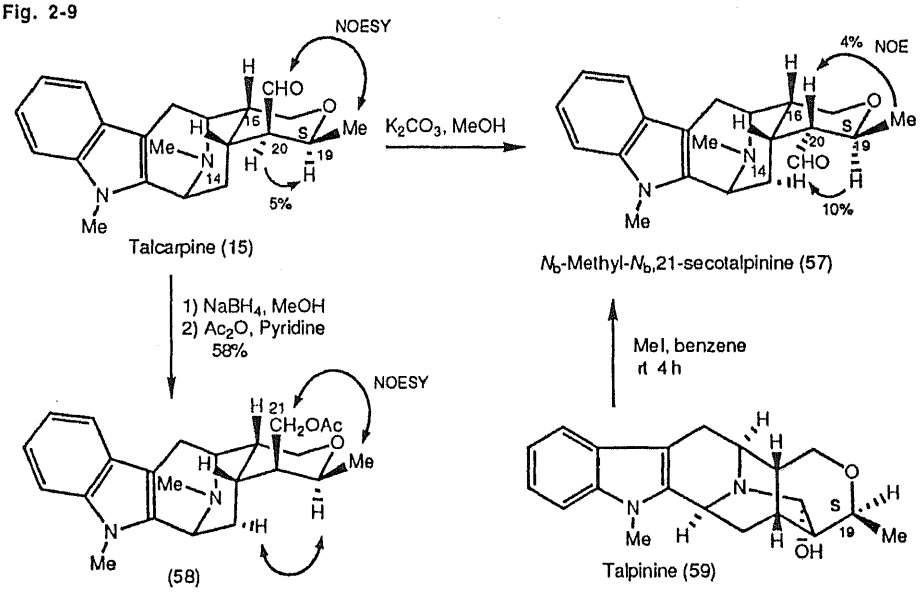
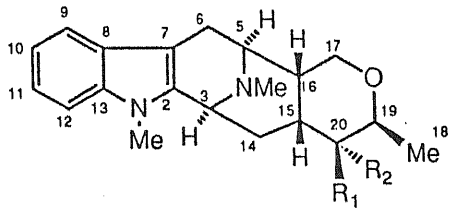
* Thus far, the stereochemistry at C19 in talpinine (59) was deduced by comparison of ^{1}H-NMR spectral data of (59) and 21-hydroxycyclolochnerine.[34]

Fig. 2-9


NOESY
CHO
Me
Me
N
14
16
20
19
S
H
5%
Talcarpine (15)
K_2CO_3, MeOH
4% NOE
10%
N_b-Methyl-N_b,21-secotalpinine (57)
1) $NaBH_4$, MeOH
2) Ac_2O, Pyridine
58%
NOESY
21
CH_2OAc
(58)
MeI, benzene
rt 4 h
Talpinine (59)
OH



R_1=CHO, R_2=H: Talcarpine (15)
R_1=H, R_2=CHO: (57)

Table 2-1 ^{13}C-NMR Chemical Shifts and Assignments

No.	Talcarpine (15)		(57)
2	132.64 (s)		132.88 (s)
3	54.50 (d)*		55.01 (d)
5	53.54 (d)		53.20 (d)
6	22.51 (t)		22.52 (t)
7	106.67 (s)		106.68 (s)
8	126.40 (s)		126.33 (s)
9	118.18 (d)		118.01 (d)
10	118.94 (d)		119.04 (d)
11	121.04 (d)		121.11 (d)
12	108.79 (d)		109.01(d)
13	137.03 (s)		137.07 (s)
14	30.08 (t)	△	26.81 (t)
15	27.02 (d)		26.20 (d)
16	39.42 (d)	△	42.60 (d)
17	68.88 (t)		67.23 (t)
18	19.22 (q)		20.32 (q)
19	54.60 (d)*		57.88 (d)
20	69.48 (d)		67.88 (d)
21	204.70 (d)		203.23 (d)
N_a-Me	29.02 (q)		29.08 (q)
N_b-Me	41.80 (q)		41.75 (q)

Meatured at 500MHz, Solvent $CDCl_3$
Assignments bearing the superscript
may be interchanged

Next task was to synthesize alstonerine (**16**) from the compound (**55**). To complete this object, introduction of an oxygen function to C19 position and creation of a double bond at C20-21 position in (**55**) were required. Hydroboration of (**55**) with borane dimethylsulfide complex provided two diastereomeric secondary alcohols (**60**) and (**61**) (mp 130-132 °C) in 27% and 26% yield, respectively, accompanied with 22% of the starting material (**55**). The stereochemistry of each alcohols (**60**) and (**61**) were determined by NOE observations as well as the mechanistic consideration of hydroboration (*cis* addition of BH_3 to the *Z*-olefin) as depicted in the Fig. 2-11. Alcohol (**60**) was subjected to Swern oxidation to yield the ketone (**62**) (mp 138-140 °C) in 70% yield. By the same oxidation procedure, (**61**) also afforded (**62**) in 57% yield (21% recovering of the starting material. The production of (**62**) from (**60**) was caused by the epimerization of the acetyl group into the stable equatorial orientation.

Fig. 2-10

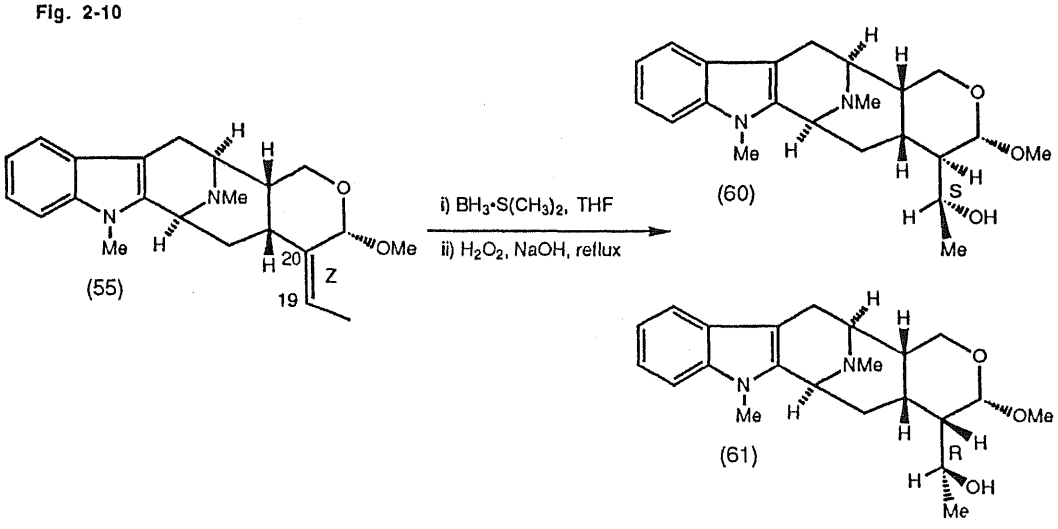
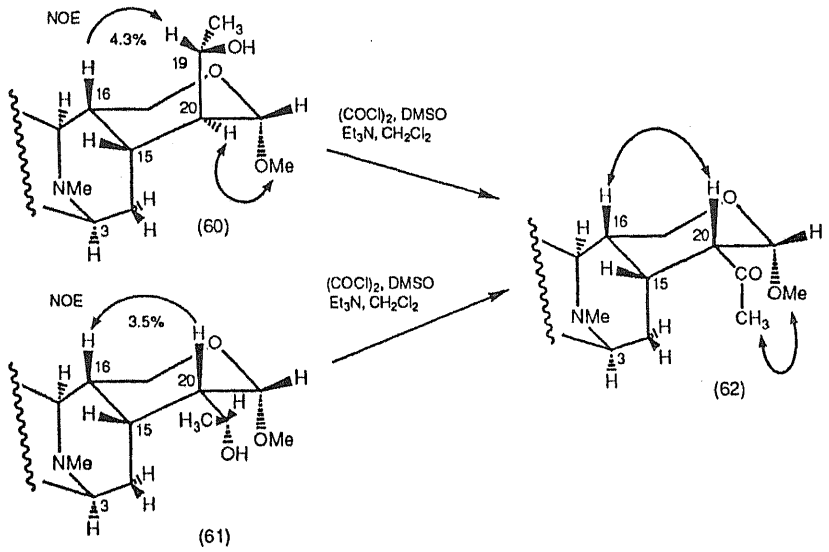
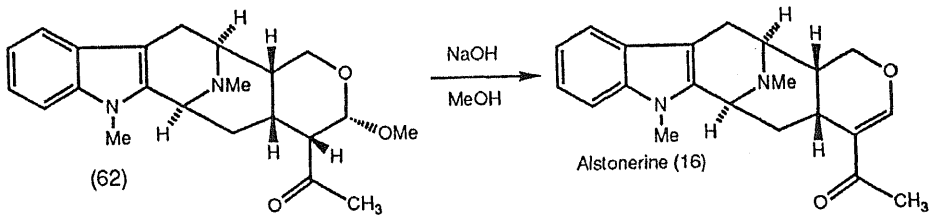


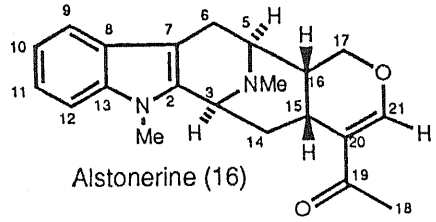
Fig. 2-11



Finally, (**62**) was treated with sodium hydroxide in MeOH to furnish alstonerine (**16**) (mp 162-164 °C) in 89% yield, which was identical with the natural compound in all respects.[29] The assignments of the chemical shifts in the ^{13}C-NMR spectrum of (**16**) in the literature[27] were revised by using 2D-NMR (^{1}H-^{1}H, and ^{13}C-^{1}H COSY) technique (see Table 2-2).[33]

Fig. 2-12





Alstonerine (16)

Table 2-2 ^{13}C-NMR Chemical Shifts and *Assignments

No.	Natural (16) 75 MHz	Synthetic (16) 125 MHz
2	137.39 (s)	133.24 (s)
3	54.02 d)	53.81 (d)
5	54.86 (d)	54.73 (d)
6	22.96 (t)	22.85 (t)
7	105.93 (s)	105.93 (s)
8	126.50 (s)	126.59 (s)
9	117.91 (d)	117.84 (d)
10	118.87 (d)	118.73 (d)
11	121.02 (d)	120.82 (d)
12	109.76 (d)	108.99 (d)
13	137.39 (s)	137.24 (s)
14	32.29 (t)	32.42 (t)
15	22.42 (d)	22.94 (d)
16	38.67 (d)	38.67 (d)
17	67.75 (t)	67.81 (t)
18	25.04 (q)	25.03 (q)
19	195.44 (s)	195.46 (s)
20	w	121.14 (s)
21	157.45 (d)	157.42 (d)
N_a-Me	29.12 (q)	29.07 (q)
N_b-Me	41.75 (q)	41.81 (q)

Solvent $CDCl_3$
w-weak, the signal could not be estabished with certainly.
* reassigned by using 2D spectrum

Chapter 3

Biomimetic Synthesis of a New *Gelsemium* Alkaloid: 20-Hydroxydihydroranki nidine

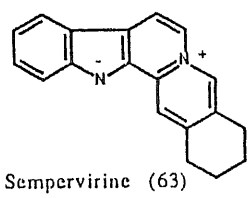
The genus *Gelsemium* (Loganiaceae) consists of three species: *Gelsemium elegans* Benth. in South-eastern Asia; *Gelsemium sempervirens* (L.) Jaume St.-Hilaire, and *Gelsemium rankinii* Small in the United States.

G. elegans is a well-known toxic plant in South-eastern Asia and is used in Chinese traditional medicine as an analgesic, antispasmodic and a remedy for certain kinds of skin ulcers. This plant is known in some parts of China as Kou-Wen and in the other parts (e.g. Guangxi Province) as Hu-Man-Teng. More recently a preparation of the total alkaloids, which consists of seven individual *Gelsemium* alkaloids (as shown by TLC) has been used as an analgesic for the palliation of various acute cancer pains, including hepatic cancer.[35)]

All of the alkaloids obtained from the species of *Gelsemium* can be divided into two main groups, indole and oxindole alkaloids. The indole alkaloids have been classified into three different skeletal types; sempervirine-, koumine-, and sarpagine-types which are of indole, indolenine, and indole nucleus, respectively. On the other hand, the oxindole alkaloids are divided into four different skeletal types; gelsemine-, humantenine-, gelsedine-, and gelselegine-types.

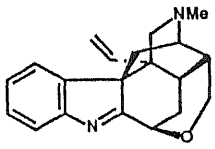
Fig. 3-1 Representative *Gelsemium* Alkaloids

[*Sempervirine-Type*]



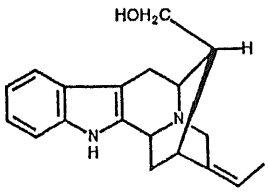
Sempervirine (63)

[*Koumine-Type*]

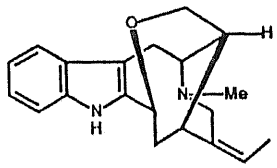


Koumine (64)

[*Sarpagine-Type*]

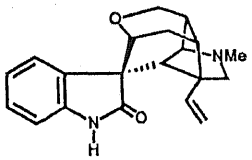


Koumidine (65)



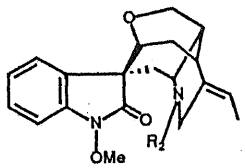
19(Z)-Anhydrovobasinediol (66)

[*Gelsemine-Type*]



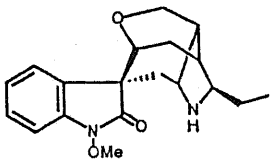
Gelsemine (67)

[*Humantenine-Type*]



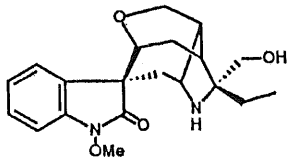
R=Me: Humantenine (68)
R=H: Rankinidine (69)

[*Gelsedine-Type*]



Gelsedine (70)

[*Gelselegine-Type*]



Gelselegine (71)

Although the transformation of [6-^{14}C] strictosidine to gelsemine (**67**) in *G. sempervirens* with 0.47% incorporation has been reported,[36] the exact biosynthetic pathway is still vague. On the basis of the structures of the isolated alkaloids, the tentative biosynthetic route of the *Gelsemium* alkaloids was proposed. Along this biosynthetic speculation, the synthesis of sarpagine-type alkaloids,[37] humantenine-type oxindole alkaloids,[38] gelsedine skeleton,[39] gelselegine skeleton,[40] and koumine (**64**)[41] was successful in our laboratory.

Although, twenty-nine N_a-methoxyoxindole alkaloids of various skeletons have been isolated from *Gelsemium* species up to date, none of them has been synthesized. Recent intensive research on the chemical components of *G. elegans* by our group and others resulted in the isolation of many new indole and oxindole alkaloids.[11b, 42] Among them, 20-hydroxydihydrorankinidine (**17**), a new humantenine-type N_a-methoxyoxindole alkaloids isolated as a minor alkaloids,[42j] is the only one that has a hydroxy at C20 position and proposed to be an important biosynthetic precusor of some other alkaloids such as gelselegine (**71**), gelsenicine (**73**), gelsedine (**70**) *via* the aziridinium intermediate (**72**) (Fig. 3-2). The proposal of the aziridinium compound as the intermediate in the synthesis of gelselegine-type alkaloids has been supported by the recent synthesis of N_a-demethoxy-11-methoxy-19(R)-hydroxygelselegine (**77**) as shown in Fig. 3-3.[40]

Fig. 3-2 Tentative biogenetic route of some *Gelsemium* alkaloids

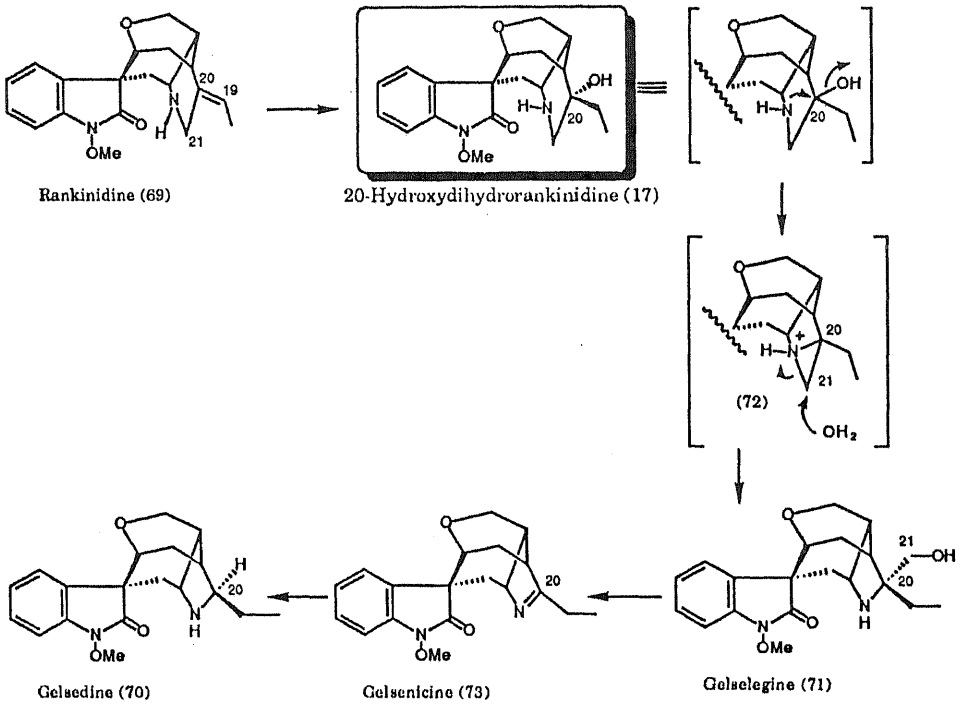
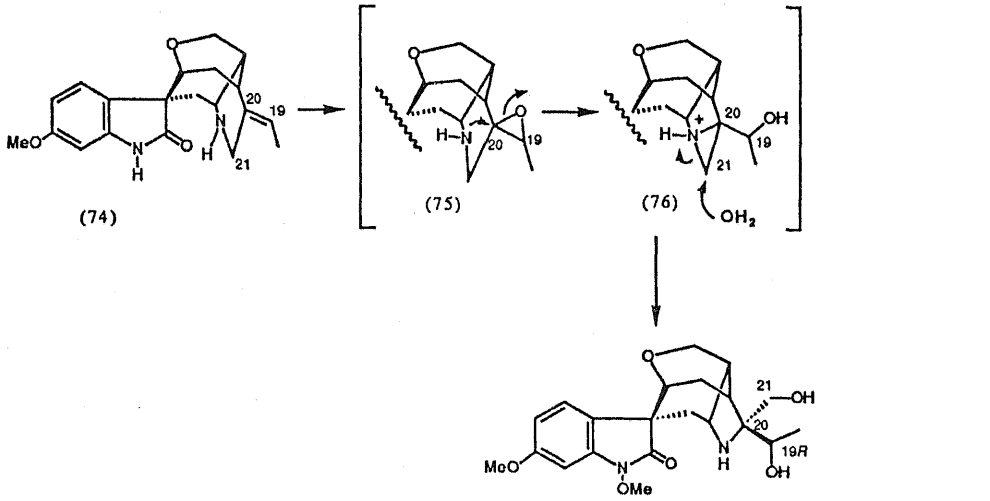


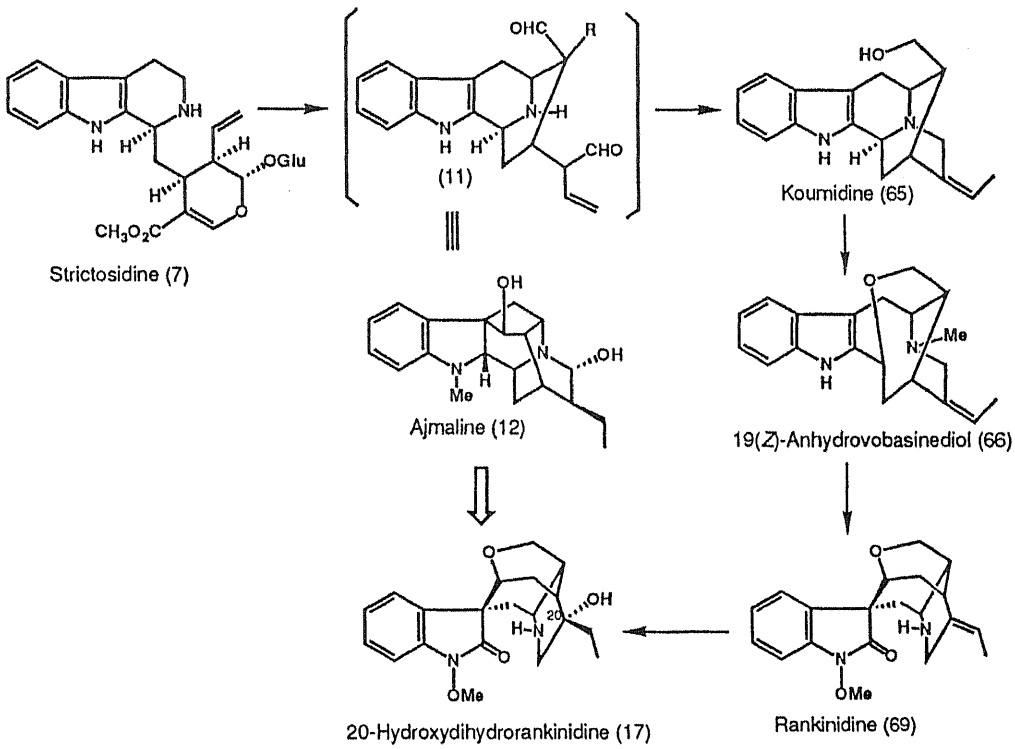
Fig. 3-3



N_a-Demethoxy-11-methoxy-19(*R*)-hydroxygelselegine (77)

The biosynthetic pathway of 20-hydroxydihydrorankinidine (**17**) was proposed as shown in Fig. 3-4.

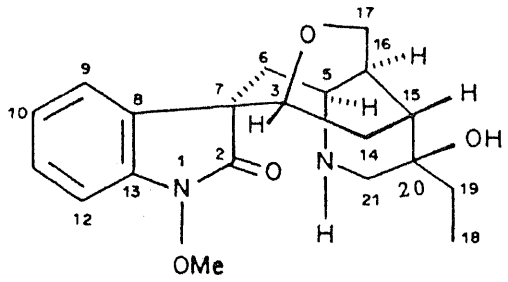
Fig. 3-4 Plausible Biosynthetic Route of 20-Hydroxydihydrorankinidine (17)



It is possible that from strictosidine (**7**), koumidine (**65**) is formed *via* the sarpagine-type intermediate (**11**). C/D ring opening would yield 19(*Z*)-anhydrovobasinediol (**66**). The transformation of (**66**) into the N_a-methoxyoxindole, rankinidine (**69**) might involve a series of more extensive alterations. Finally, the hydration of the double bond in rankinidine (**69**) would generate 20-hydroxydihydrorankinidine (**17**).

In order to prove the proposal that 20-hydroxydihydrorankinidine (**17**) is the biosynthetic intermediate of other alkaloids such as, gelselegine (**71**) and gelsenicine (**73**) by chemical transformations, an adequate amount of (**17**) was needed. Therefore, the synthesis of (**17**) from ajmaline (**12**), which could be considered approximately the same as the biosynthetic intermediate (**11**), was planned. At first the configuration at C20 of the natural 20-hydroxydihydrorankinidine was uncertain. From the molecular structure presented at that time (Fig 3-5),[43] the configuration at C20 could be considered to be either *S* or *R* form. Thus, convertion of ajmaline (**12**) to the compound having one of two possible structures of 20-hydroxydihydrorankinidine was then attempted.

Fig. 3-5



Initially, in order to liberate the masked aldehyde (C21) from the amino acetal function and to protect the N_b group as carbamate, ajmaline (**12**) was successively treated with *N*,*N*-dimethylhydrazine and a catalytic amount of H_2SO_4, carbobenzoxy chloride in 1 *N*-NaOH-CH_2Cl_2 to afford the benzyl carbamate (**78**) in 80% yield from (**12**). Hydrolysis of the hydrazone (**78**) by treatment with $CuCl_2$ in aqueous THF (pH7) gave the aldehyde (**79**) in 84% yield. Aldehyde function in (**79**) was converted to the silyl enol ether (**80**) in 71% yield by treatment

with TBSOTf and Et_3N in dry CH_2Cl_2 (Fig. 3-6). Exposure of the silyl enol ether (80) to osmium tetraoxide (OsO_4) in pyridine-THF gave α-hydroxyaldehyde (81) as a single product in 81% yield[13b]. Since the configuration of C20 position in (81) could not be determined from the spectroscopic analysis at this stage, (81) was subjected to the ring-closure between C21 and N_b position. Aldehyde group in (81) was reduced with $NaBH_4$ in MeOH to afford the diol (82) in 92% yield. Hydrogenolysis (H_2, 10% Pd/C, EtOH-AcOH) of (82) gave the amine (83) in 82% yield. The primary hydroxy group in (83) was selectively mesylated to give the D ring-closure compound (84) in 76% yield. The stereochemistry at C20 in (84) was concluded to be *R* form by the NOE experiments. Thus, the irradiation at 19-H (δ 1.83) showed the 8% enhancement of 5-H (δ 3.03), as well as the 5% enhancement of 19-H was observed when 5-H was irradiated (Fig. 3-7).

Fig. 3-6

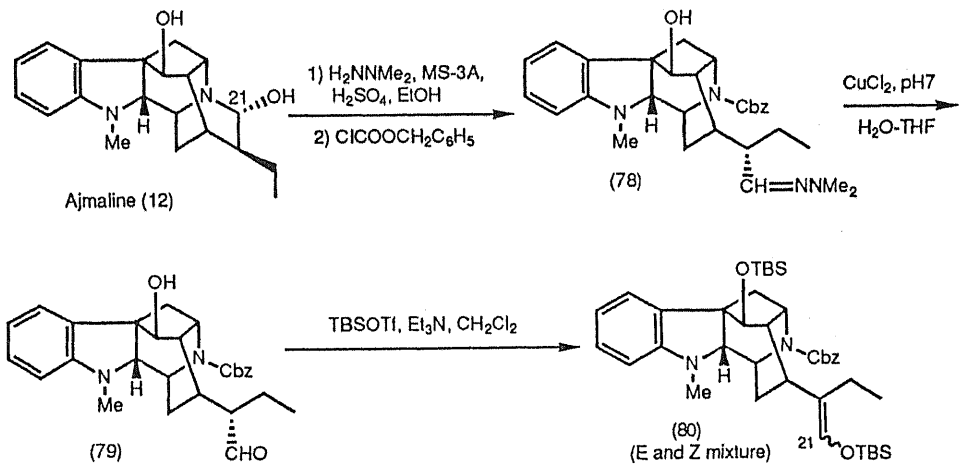
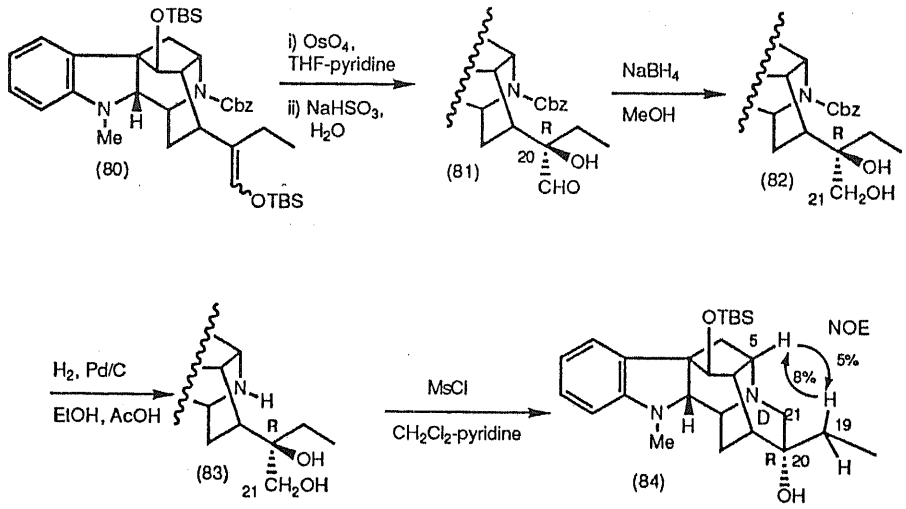
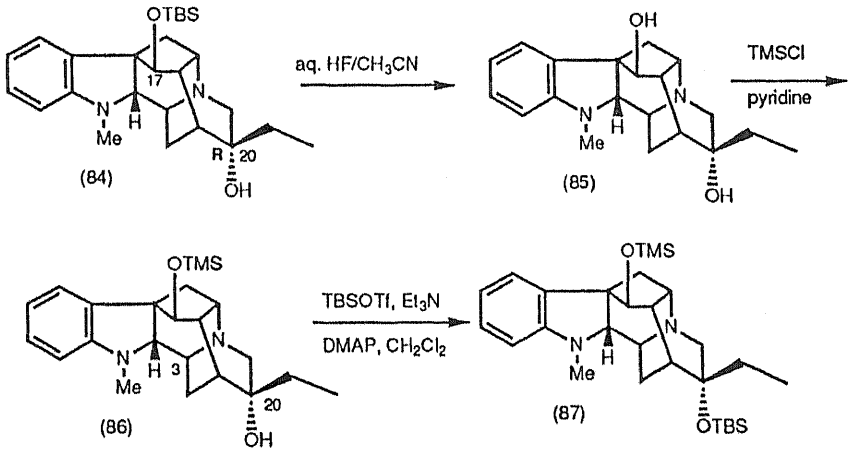


Fig. 3-7



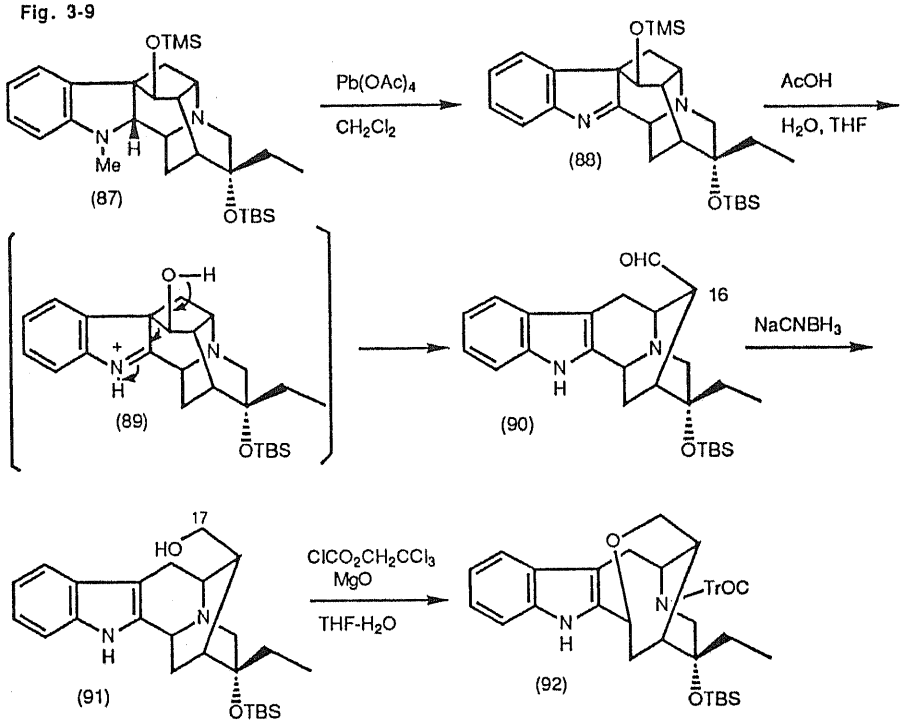
In order to prevent epimerization at C16 during the transformation from indoline to indole, a protecting group of 17-hydroxy function that could be removed under a mild condition was necessary.[13a] Thus the TBS group in (84) was substituted by TMS group. The TBS group in (84) was removed by heating (84) in aq. HF-CH_3CN (1:4) to give the diol (85) in 87% yield. Then the 17-hydroxy group was selectively protected by treatment with TMSCl in pyridine to afford (86), in 95% yield. The protection of 20-hydroxy group in (86) was also necessary in order to prevent ether-formation between the hydroxy group of C20 and C3 in the following step (see Fig. 3-10). TBS group was found to be suitable for this propose. On treatment of (86) with TBSOTf, Et_3N in dry CH_2Cl_2 in the present of 4-dimethylaminopyridine (DMAP), the disilyl derivative (87) was obtained in 96% yield.

Fig. 3-8



The indole (**91**) was prepared from the indoline (**87**) in the following way. On oxidation of N_a-methylindoline (**87**) with $Pb(OAc)_4$ (2.7 equiv) in dry CH_2Cl_2 at low temperature, the indolenine (**88**) was obtained. Without purification, (**88**) was subjected to deprotection of the 17-hydroxy group under a mild acidic condition (AcOH/THF/H_2O; 2:1:1), to give the aldehyde (**90**). In order to prevent epimerization at C16, the resultant unstable aldehyde (**90**) was immediately reduced by addition of $NaCNBH_3$ to the reaction mixture to give the alcohol (**91**) in 21% overall yield from (**87**). The low yield of this three-step reaction is probably due to the presence of the lone pair electrons of N_b which is susceptible to the oxidation with $Pb(OAc)_4$. The indole (**91**) was treated with $ClCO_2CH_2CCl_3$ in aqueous THF in the presence of a large excess of MgO to give the carbamate (**92**) in 71% yield* see next page.

Fig. 3-9



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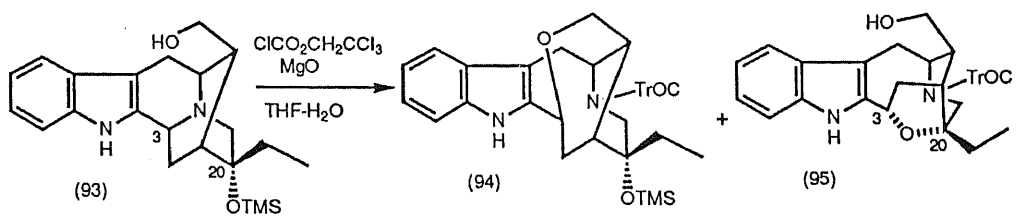
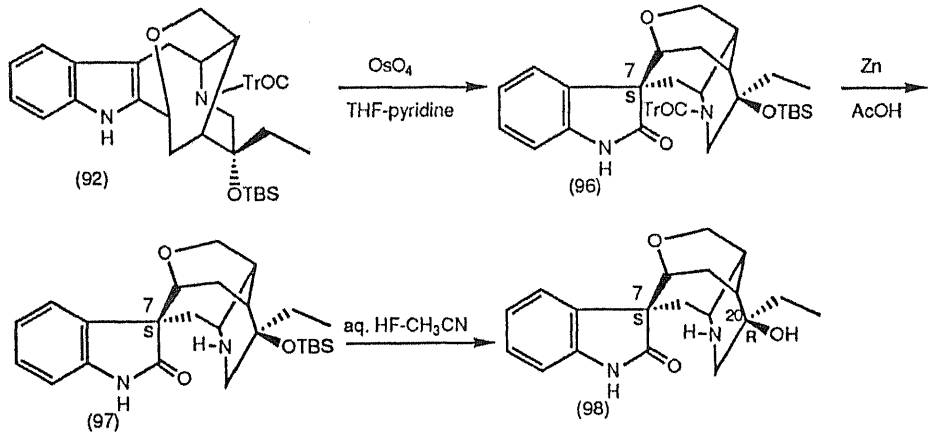
* When the TMS analogue (**93**) of (**91**) was treated with $ClCO_2CH_2CCl_3$ under the same condition, the desired product (**94**) and the byproduct (**95**) were obtained in the same amount (39% each).

Fig. 3-10



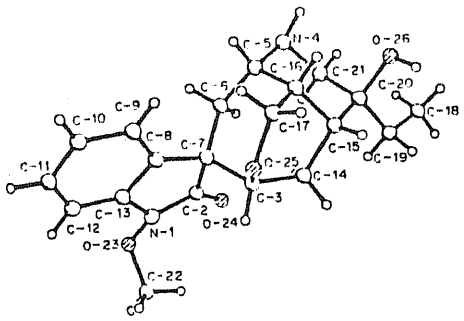
The indole (**92**) was stereoselectively converted into oxindole (**96**) in 73% yield by treatment with OsO_4 in pyridine-THF.[38] The protecting group on N_b was removed with Zn in AcOH to furnish (**97**) in 82% yield. The C7 configuration of (**97**) was confirmed to be *S* by comparison of the CD spectrum of (**97**) with that of humantenine (**68**). Finally, the TBS group was removed by heating in aqueous HF-CH_3CN to give N_a-demethoxy-20(*R*)-hydroxydihydrorankinidine (**98**) in 51% yield, accompanied with 25% of the starting material (**97**).

Fig. 3-11



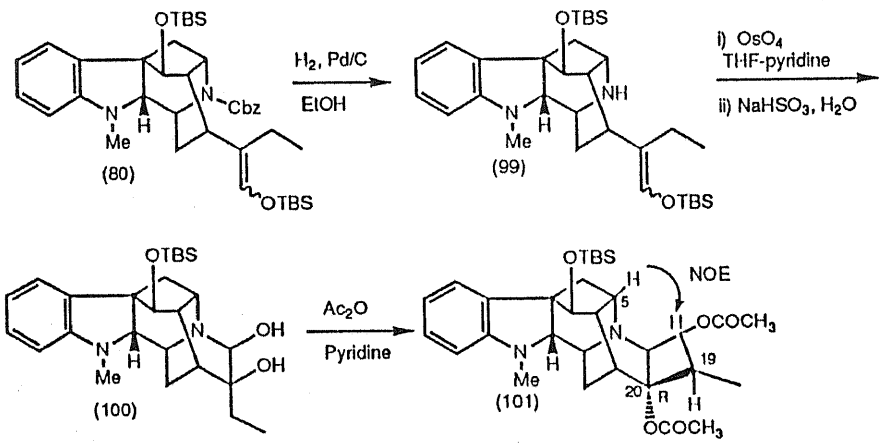
The pattern of ^{1}H-NMR spectrum of (**98**) was not similar to that of natural 20-hydroxydihydrorankinidine, which had been directly sent from Prof. Cordell. Thus, the C20 configuration of the natural 20-hydroxydihydrorankinidine was considered to be *S* form. This conclusion was confirmed by the single crystal X-ray analysis of the natural 20-hydroxydihydrorankinidine, which was published later by Cordell group[42j] as shown in Fig 3-12. Therefore, a new synthetic route for the natural 20(*S*)-hydroxydihydrorankinidine (**17**) was necessary.

Fig. 3-12



In the oxidation of the silyl enol ether (**80**) with OsO_4 that gave only the (20*R*) hydroxyaldehyde (**81**) as shown in Fig. 3-7, the selectivity of this reaction was thought to be controlled by the steric hindrance of the TBS group and the CBZ group in (**80**). In order to change the phase-selectivity of the oxidation, two less sterically constrained compounds (**99**) and (**104**) were prepared from (**80**), and the oxidation of both compounds was proceeded as shown in Fig. 3-13 and Fig. 3-14.

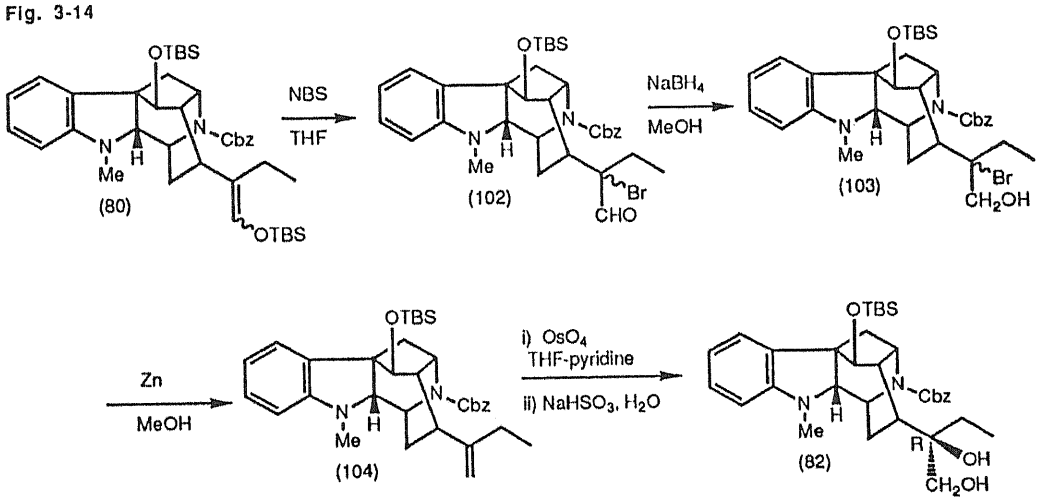
Fig. 3-13



First, the CBZ group in (**80**) was removed by hydrogenolysis (H_2, 10% Pd/C, EtOH) to give (**99**) in 41% yield. Then, (**99**) was oxidized with

OsO_4 to afford the diol (**100**) in 70% yield. In order to elucidate the C20 configuration, (**100**) was transformed into the diacetate (**101**). The differential NOE experiment between 19-H and 5-H in (**101**) suggested the undesired (20*R*) configuration.

Fig. 3-14

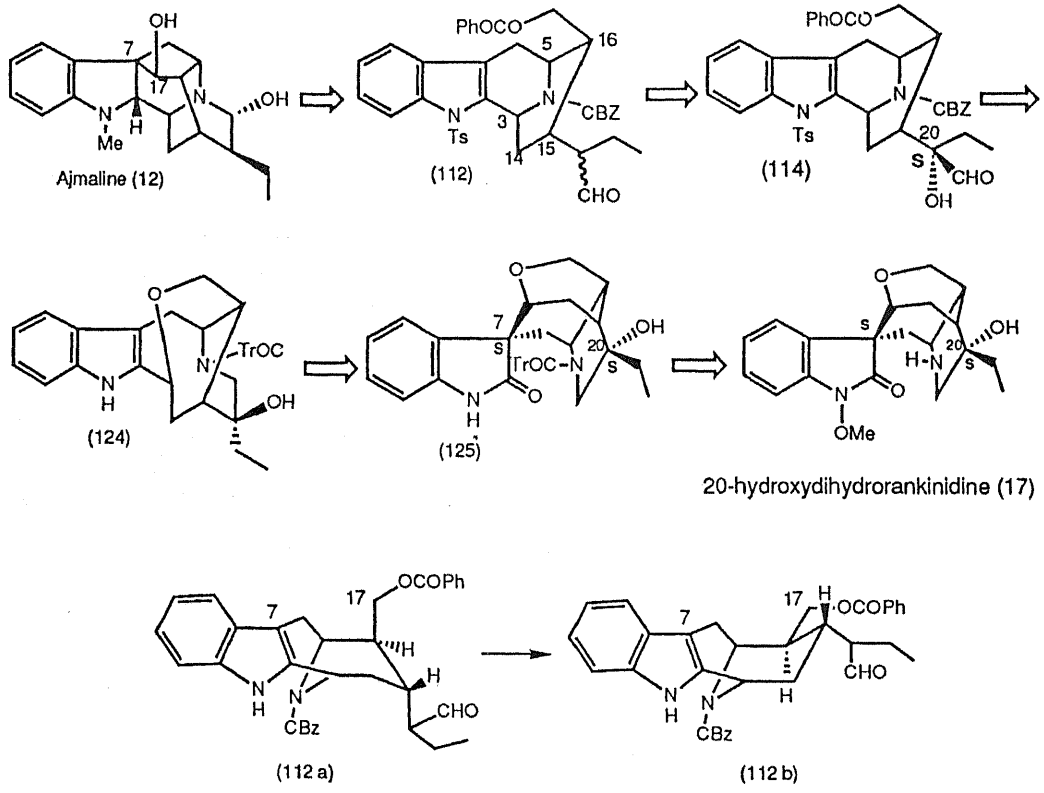


Next attempt was to synthesize (20*S*) compound from (**104**). From (**80**), a bromine atom was introduced by treatment with NBS in THF to give the α-bromoaldehyde (**102**) as an epimeric mixture in 78% yield. The aldehyde in (**102**) was reduced with $NaBH_4$ in MeOH to provide the α-bromohydrin (**103**) in 75% yield. By treatment of (**103**) with Zn in MeOH, the olefin (**104**) was obtained in 80% yield. (**104**) was subjected to oxidation with OsO_4 to give 72% yield of the (20*R*) diol (**82**), which had the identical ^{1}H-NMR spectrum to that of (**82**) obtained previously.

All of the efforts to introduce a hydroxy group in *S* manner from the indolines (**80**), (**99**), and (**104**) were failed. Thus, a new synthetic route for 20-hydroxydihydrorankinidine (**17**) was planned as shown in Fig. 3-

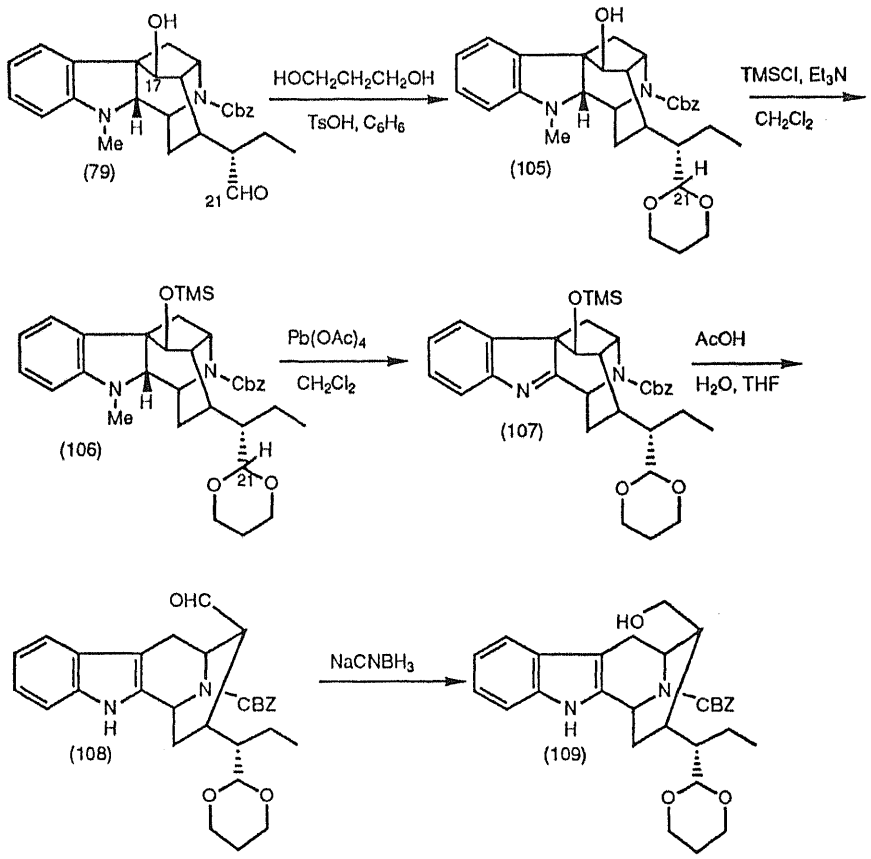
15. The key point was to cleave a bond between C17 and C7 leading to the indole compound (**112**). The change in the structure of the 6-membered ring that consists of C3, N_b, C5, C16, C15, and C14, from boat form in the indolines (**80**), (**99**), and (**104**) to chair form in the indole (**112b**) was expected to cause a change in the phase-selectivity of the OsO_4 oxidation. Other steps in the synthetic plan would follow the presumed biosynthetic lines. Thus, from sarpagine-type indole intermediate (**112**), (**17**) would be generated via C/D ring cleaved compound, oxindole, and then N_a-methoxyoxindole, respectively.

Fig. 3-15 Synthetic Plan of 20-Hydroxydihydrorankinidine (17)



Initally, the aldehyde group in (**79**) was protected as the 1,3 dioxane (**105**) in quantitative yield. (**105**) was transformed into the indole (**109**) by the following manner. 1) Protection of the hydroxy group as the trimethylsilyl ether (**106**). 2) Oxidation of the N_a-methyl indoline moiety with $Pb(OAc)_4$ leading to the indolenine (**107**). 3) Deprotection of the hydroxy group under a mild acidic condition ($AcOH/H_2O/THF$, 3:1:1) and immediate reduction of the aldehyde (**108**) with $NaCNBH_3$. The yield in each step was 97%, 76%, and 82%, respectively.

Fig. 3-16

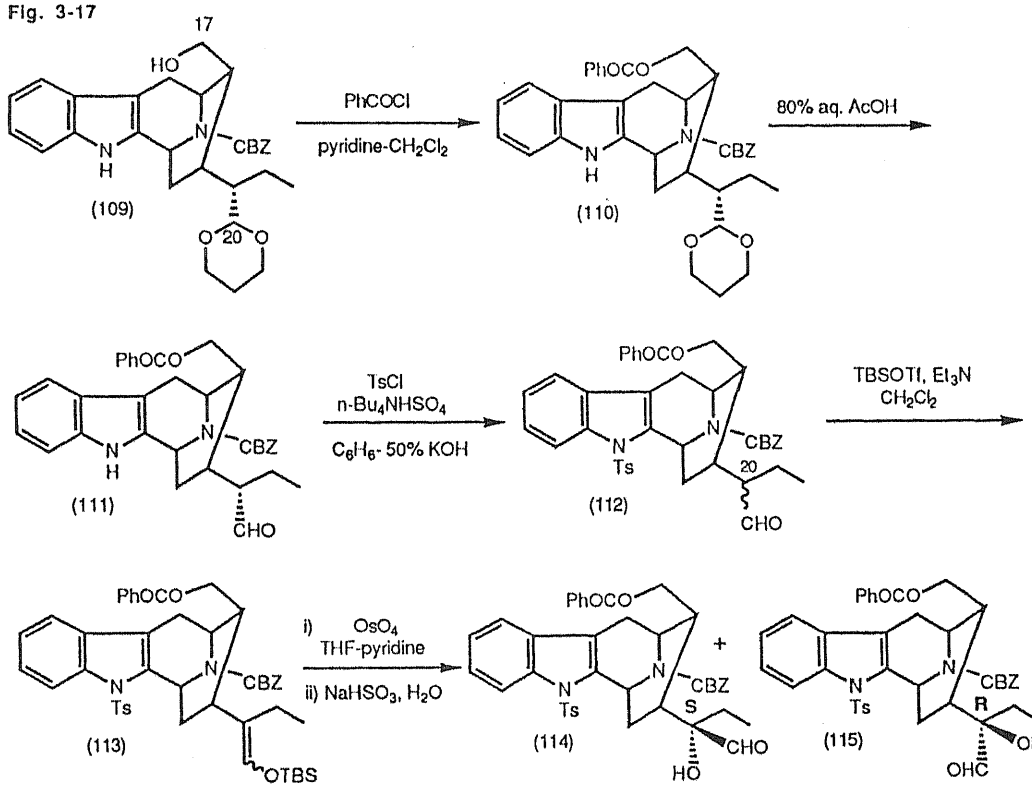


The hydroxy group in (**109**) was protected as the benzoyl ester (**110**) (PhCOCl, pyridine-CH_2Cl_2, 91% yield) before removal of the aldehyde-protecting group (80% aq. AcOH, reflux, 96% yield) in order to prevent hemiacetal formation between the C_{17}-OH and C_{21}-aldehyde functions. The indole amine in (**111**) was tosylated under a basic condition [TsCl, benzene-50% KOH, n-Bu_4NHSO_4 (cat.)] with some epimerization occured at C20 to give the epimeric mixture (**112**) in 81% yield. The aldehyde function in (**112**) was converted to the silyl enol ether (**113**) in 82% yield and then a hydroxy group was introduced into the C20 position by treatment with OsO_4 in pyridine-THF at low temperature*. Separation by medium pressure liquid chromatography gave two a-hydroxyaldehyde compounds (**114**) (mp 108-110 °C), (**115**) and the starting material (**113**) in 45, 22 and 7% yield, respectively. Since the configuration of the epimeric C20 position in (**114**) and (**115**) could not be determined from the spectroscopic analysis at this stage, both compounds were subjected to the ring-closure between the C21 and N_b position to afford compounds having a more fixed structure.

---

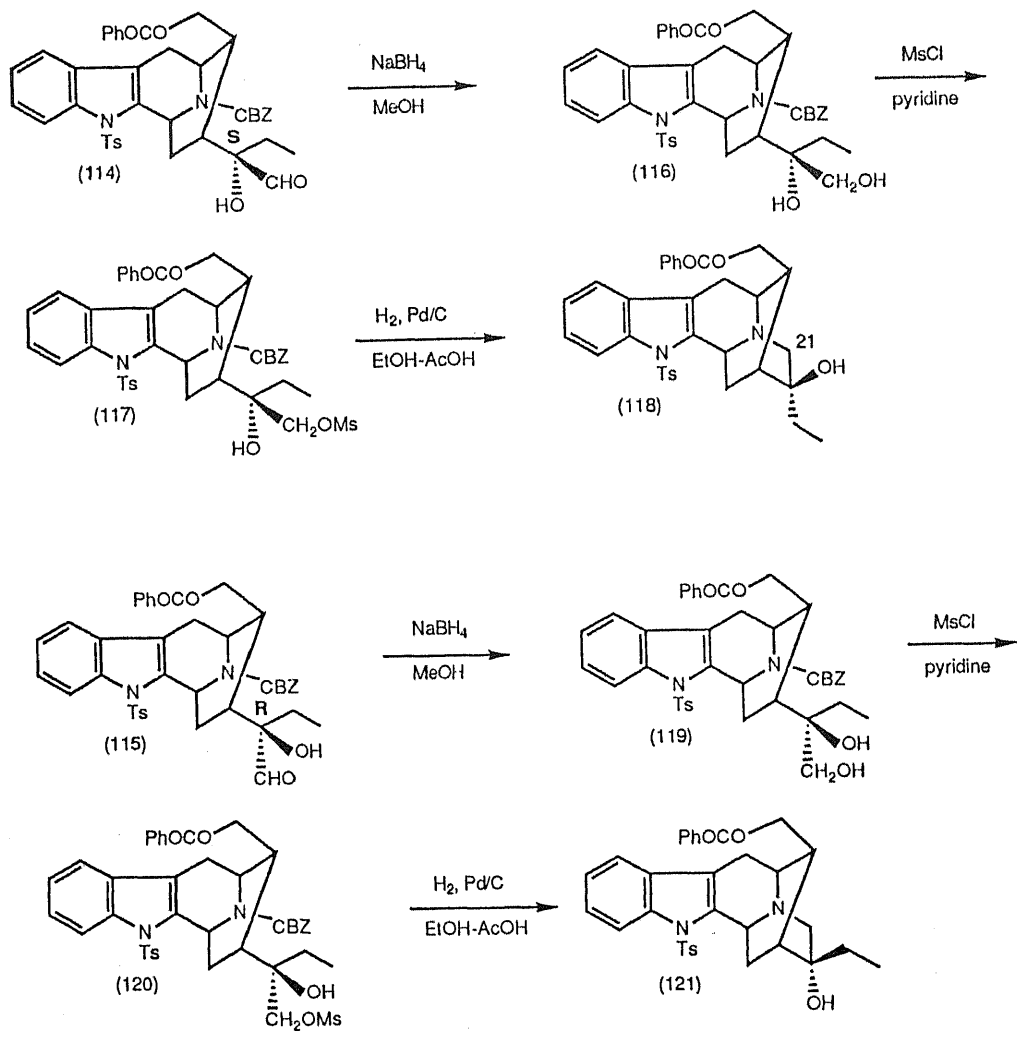
* When the N_a-tert-butoxycarbonyl analogue was treated with OsO_4 under the same condition, oxindole was obtained as the main product. The existence of the toluenesulfonyl group at N_a enabled the indole ring to resist the eletrophilic addition of OsO_4.

Fig. 3-17



The aldehyde group in the major compound (**114**) was reduced with NaBH4 to give the diol (**116**) in 83% yield. The primary hydroxy group in (**116**) was selectively mesylated (MsCl, pyridine) to give (**117**) in 100% yield. Hydrogenolysis (H_2, 10% Pd/C, EtOH-AcOH) of the carbamate (**117**) provided the ring-closure compound (**118**) in 73% yield. The minor product (**115**) was also transformed into (**121**) by the same procedure in 74% yield (Fig. 3-18).

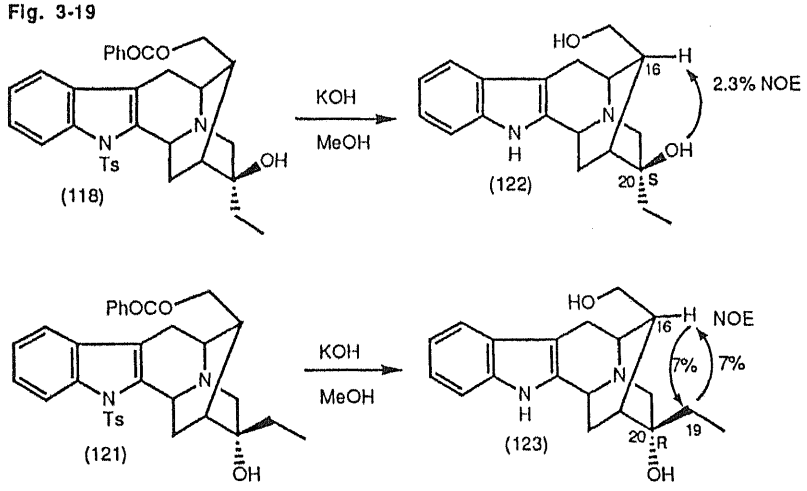
Fig. 3-18



On removal of the protecting groups under a strong basic condition (KOH, MeOH, reflux), (**118**) and (**121**) were converted to the sarpagine-type intermediates (**122**) (mp 220-222 °C), (**123**) (mp 162.5-163.5 °C) in 96% and 100% yield, respectively. The stereochemistry at C20 position of (**122**) and (**123**) was unambiguously determined by the NOE

experiments. Irradiation of the 20-OH (δ 4.15, in DMSO-D_6) in (**122**) led to enhancement (2.3%) of 16-H (δ 2.57), while 7% enhancement was observed between the 19-H_2 (δ 1.80) and 16-H (δ 2.46) in (**123**) (Fig. 3-19). This indicates that the main product from this synthetic route (**122**) has the same *S*-configuration at C20 as in the natural product (**17**).

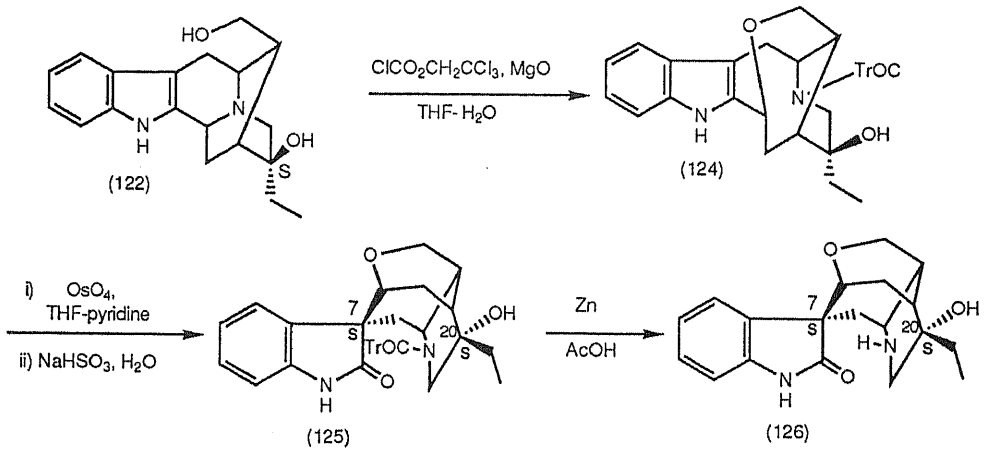
Fig. 3-19



Treatment of (**122**) with $ClCO_2CH_2CCl_3$ and MgO in aq. THF provided C/D ring-cleaved compound (**124**) in 63% yield. The indole moiety in (**124**) was oxidized with OsO_4 in THF-pyridine to give the desired (7*S*) oxindole (**125**) in 69% yield accompanied with 18% of the starting material (**124**). (**125**) showed the characteristic UV absorption peaks at 209, 252 nm due to the oxindole chromophore. To confirm the structure of (**125**), the trichloroethoxycarbonyl group in (**125**) was removed to give N_a-demethoxy-20-hydroxydihydrorankinidine (**126**) in 79% yield. The C7 configuration was confirmed by a comparison of the

CD spectrum of (**126**) with that of 20-hydroxydihydrorankinidine (**17**). As shown in Table 3-2, the ^{13}C-NMR spectrum of (**126**) is also similar to that of (**17**).

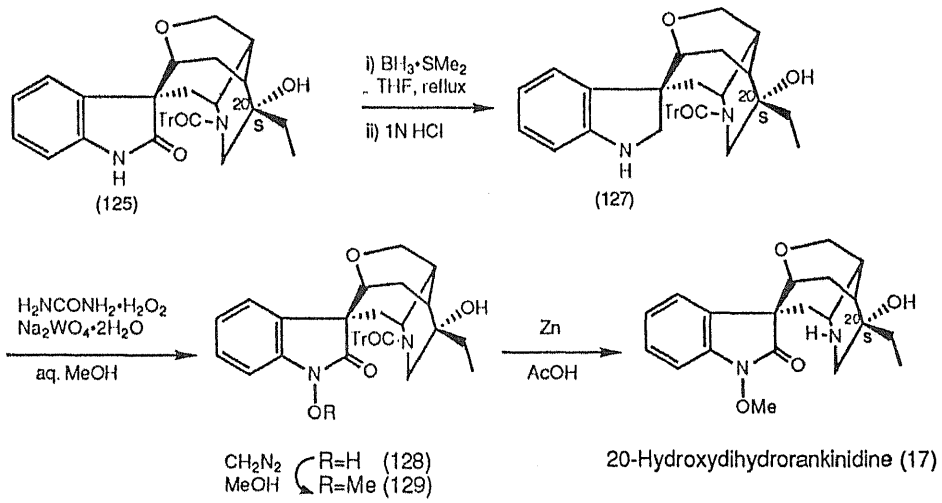
Fig. 3-20

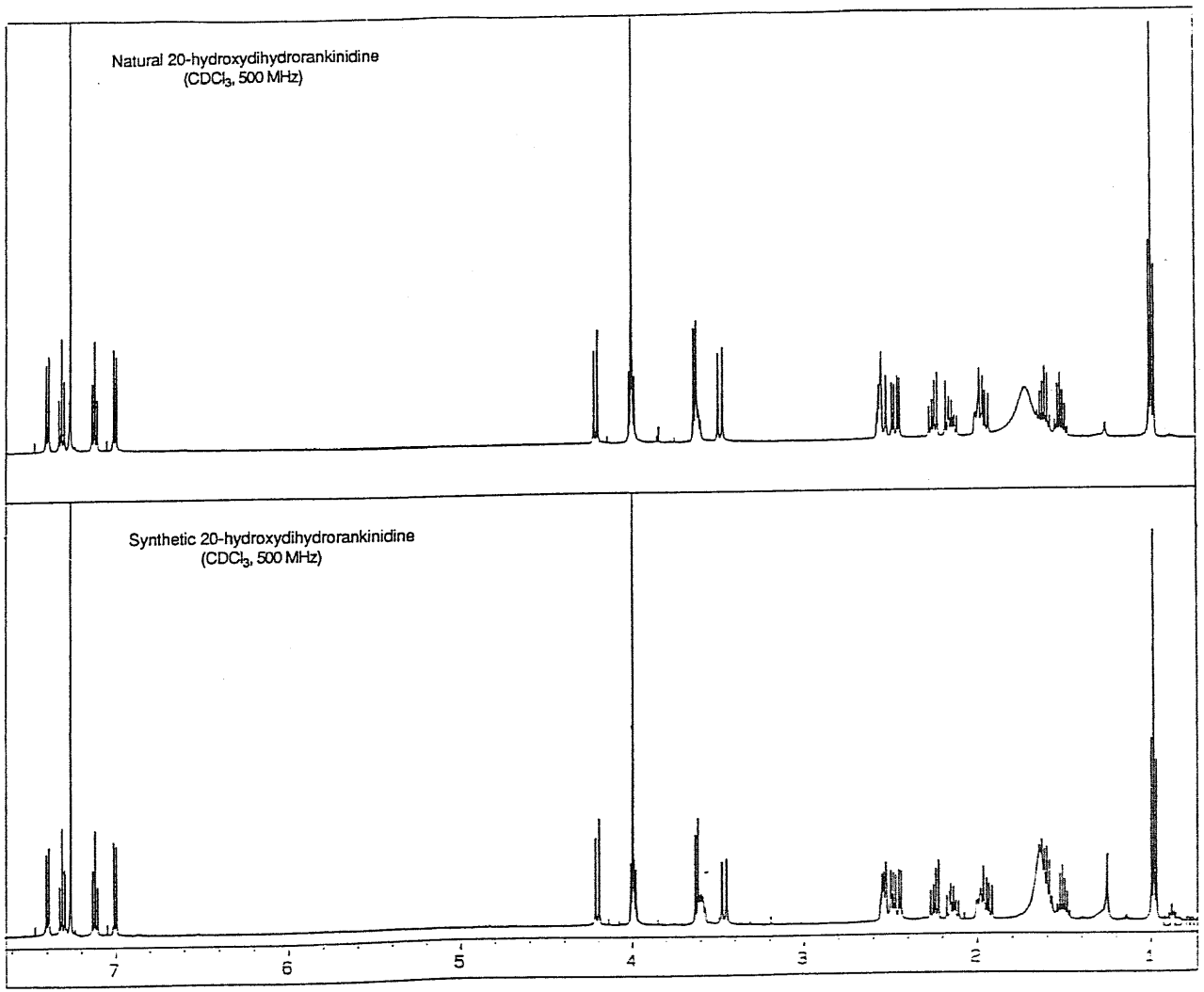


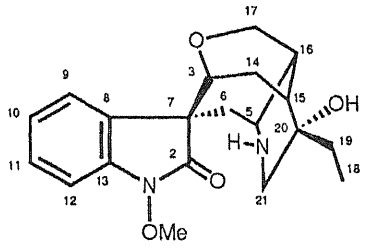
The oxindole (**125**) was converted into N_a-methoxyoxindole by a method recently investigated in our laboratory.[44] Reduction of oxindole (**125**) with borane-dimethylsulfide complex (15 equiv) in THF[45] gave the indoline (**127**) (mp 231-234 °C) in 76% yield. (**127**) showed the characteristic UV absorption peaks at 205, 243, 295 nm due to the indoline chromaphore. Oxidation of (**127**) with urea hydrogen peroxide addition compound (26 equiv) and sodium tungstate (0.3 equiv) in aq. MeOH at room temperature provided hydroxamic acid (**128**),[46] which was O-methylated with diazomethane to give the N_a-methoxyoxindole (**129**) in 55% overall yield from the indoline (**127**). In the ^{1}H-NMR spectrum, (**129**) exhibited a signal at δ 3.99, 3.98 due to N_a-methoxy group. Finally, removal of N_b protecting group in (**129**) with zinc dust in

acetic acid furnished 20-hydroxydihydrorankinidine (17) in 79% yield. Synthetic (17)[47] (mp 168-169 °C) showed spectral properties (^{1}H-NMR, ^{13}C-NMR, IR, UV, MS, CD, and m. mp) identical with those of natural product (mp 166-167 °C).[42j] Since the absolute configuration of ajmaline (12) has already been established,[31] that of (17) was chemically determined. This is the first synthesis of naturally occuring N_a-methoxyoxindole alkaloid.

Fig. 3-21




Natural 20-hydroxydihydrorankinidine
(CDCl3, 500 MHz)
Synthetic 20-hydroxydihydrorankinidine
(CDCl3, 500 MHz)
7
6
5
4
3
2
1

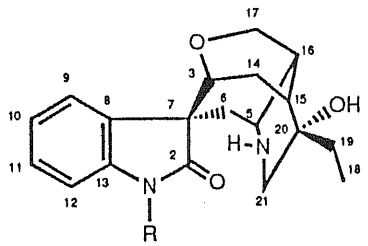


20-Hydroxydihydrorankinidine (17)

Table 3-1 ^{1}H-NMR Chemical Shifts and Assignments

No.	Natural (17) (500 MHz)	Synthetic (17) (500 MHz)
3	3.62 (d, J=7.8)	3.62 (d, J=8.1)
5	3.61 (m)	3.59 (m)
6α	1.95 (dd, J=16.1, 9.5)	1.94 (dd, J=16.1, 9.5)
6β	2.46 (dd, J=16.1, 6.6)	2.46 (dd, J=16.1, 6.6)
9	7.39 (d, J=7.6)	7.39 (d, J=7.6)
10	7.12 (td, J=7.6, 1.0)	7.12 (td, J=7.6, 1.0)
11	7.31 (td, J=7.8, 1.0)	7.31 (td, J=7.8, 1.0)
12	7.00 (dd, J=7.8, 0.5)	7.00 (dd, J=7.8, 0.5)
14α	2.25 (dd, J=14.9, 8.3)	2.25 (dd, J=14.9, 8.3)
14β	2.14 (ddd, J=14.9, 11.0, 8.3)	2.14 (ddd, J=15.1, 10.9, 8.3)
15	1.98 (m)	1.98 (m)
16	2.56 (m)	2.55 (m)
17a	4.21 (d, J=11.0)	4.21 (d, J=11.0)
17b	4.00 (dd, J=11.0, 5.6)	4.00 (dd, J=11.0, 5.6)
18	0.98 (t, J= 7.5)	0.98 (t, J=7.5)
19α	1.51 (dq, J=14.4, 7.5)	1.51 (dq, J=14.4, 7.5)
19β	1.61 (dq, J=14.4, 7.5)	1.61 (dq, J=14.4, 7.5)
21α	2.53 (dd, J=13.7, 1.4)	2.51 (br. d, J=14.8)
21β	3.48 (d, J=13.7)	3.46 (d, J=13.7)
N_a-OMe	4.00 (s)	4.00 (s)

Solvent $CDCl_3$.



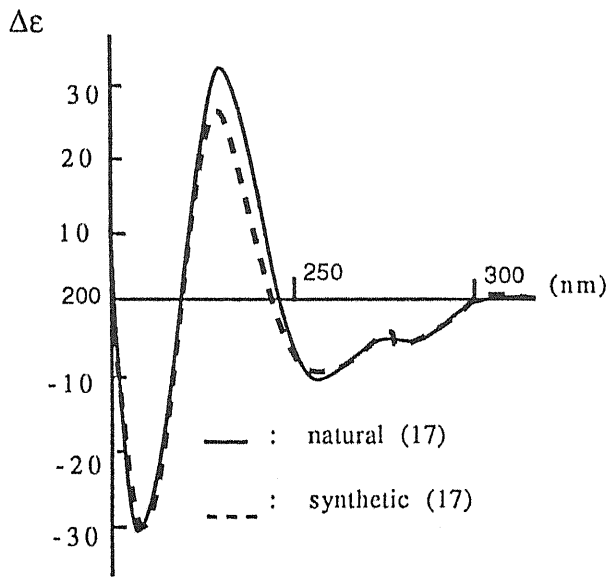
R=OMe: 20-Hydroxydihydrorankinidine (17)
R=H: N_a-demethoxy-20-hydroxydihydrorankinidine (126)

Table 3-2 ^{13}C-NMR Chemical Shifts and Assignments

No.	Natural (17)[42j] 75.6 MHz	Synthetic (17) 125 MHz	(126) 125 MHz
2	174.81	174.67	181.06
3	72.55	72.52	72.42
5	54.69	54.56	54.63
6	31.41	31.12	31.19
7	55.48	55.40	57.11
8	130.06	129.99	133.72
9	125.71	125.70	125.83
10	123.22	123.29	122.61
11	128.12	128.21	128.02
12	107.34	107.37	109.60
13	138.77	138.69	139.31
14	24.22	24.03	23.88
15	35.31	34.94	35.17
16	33.97	33.46	33.70
17	67.39	67.20	67.27
18	6.40	6.39	6.39
19	28.79	28.72	28.78
20	71.83	71.81	71.85
21	45.63	45.29	45.41
N_a-OMe	63.40	63.45	

Solvent $CDCl_3$

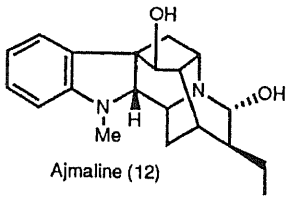
Fig. 3-22 CD curves of natural (17) and synthetic (17)



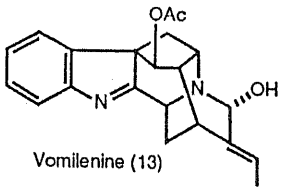
Conclusion

The results obtained from the synthetic study can be summerized as follows:

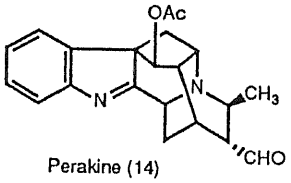
Chapter 1 Ajmaline (**12**) was chemically transformed into vomilenine (**13**) and the geometry of the ethylidene side chain in vomilenine (**13**) was proved to be (19*E*) form by the spectroscopic analysis of the intermediate. (19*Z*)-vomilenine (**24**) was also synthesized and the thermodynamic stabilitiy of vomilenine (**13**) and (19*Z*)-vomilenine (**24**) was discussed based on their transformation into perakine (**14**).



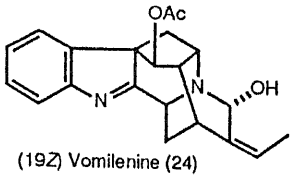
Ajmaline (12)



Vomilenine (13)



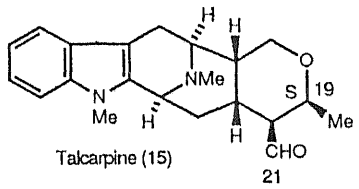
Perakine (14)



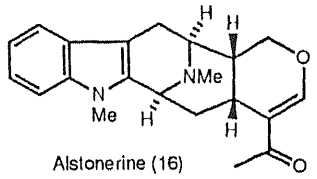
(19*Z*) Vomilenine (24)

Chapter 2 Two macroline-related indole alkaloids: talcarpine (**15**) and alstonerine (**16**) were semisynthesized from ajmaline (**12**) *via* the common intermediate (**55**). The configuration at C19 in talcarpine (**15**)

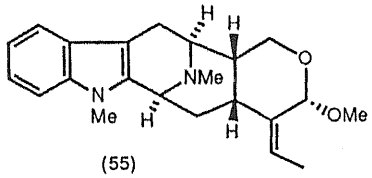
and talpinine (**59**) was elucidated to be (*S*) form by NOE data and the chemical correlation.



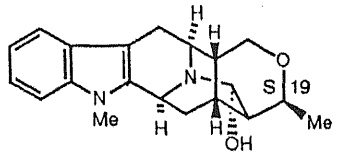
Talcarpine (15)



Alstonerine (16)

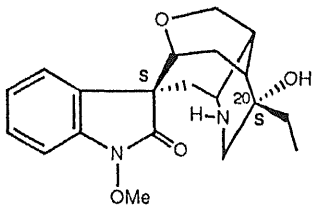


(55)



Talpinine (59)

Chapter 3 20-Hydroxydihydrorankinidine (**17**), a new and biogenetically interesting *Gelsemium* alkaloid was synthesized from ajmaline (**12**) in 22 steps. The key steps were the cleavage between C7 and C17 bonds leading to sarpagine-type intermediate before the introduction of a hydroxy group at C20 and the novel oxidative transformation of the oxindole into the N_a-methoxyoxindole derivative.



20-Hydroxydihydrorankinidine (17)

In conclusion, ajmaline (**12**) could be used as the starting material in the synthesis of the various sarpagine-derived alkaloids. Ajmaline

(**12**), because of its availability and facile transformation, remains the compound of choice as a convenient material for semisynthetic work. Furthermore, the efficient biomimetic synthesis of macroline-type alkaloids and *Gelsemium* alkaloids showed the advantage of the biomimetic semisynthesis comparing to the usual total synthesis in requiring fewer steps and providing the products of high optical purity. Thus, the biomimetic semisynthesis should be an appropriate way for transformation of compounds that are abundant in nature into minor natural products or their derivatives, which have better pharmaceutical activities and lower side effects, especially in the cases that the starting natural materials could be obtained in large amounts and in low prices.

Experimental

The melting points were determined on a Yamato MP-21 apparatus (capillary) and Yanagimoto Micro Melting Point Apparatus 1631A (hot plate). All melting points are uncorrected. The instruments used in this study were as follows; UV spectra, Hitachi U3400 spectrophotometer; IR spectra, Hitachi 260 spectrophotometer; MS, Hitachi RMU-6E and RMU-7M, JMS-AM20 (LR-EI) and JEOL JMS-HX110A spectrometers; ^{1}H- and ^{13}C-NMR spectra, JEOL JNM GX270, JEOL GSX400, JEOL GSX500, and JEOL GSX-A500 instruments with tetramethylsilane as an internal standard, chemical shifts are recorded in δ values; optical rotation, JASCO DIP-140 polarimeter; CD spectra were measured with JASCO J-500A in MeOH. Thin layer chromatography was performed on Merck precoated Silica gel 60 F_{254} plates. Column chromatography was carried out on Merck Silica gel 60 (230-400 mesh for flash chromatography) and pre-packed column [Kusano CPS-HS-221-05 (for medium pressure column chromatography)]. Abbreviations used are: singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br).

Experiments of Chapter 1

Preparation of the hydrazone (26) from ajmaline (12)

Concentrated H_2SO_4 (1 ml), *N,N*-dimethylhydrazine (6.8 ml, 89.5 mmol) and molecular sieves (3Å, 12 g) were added to a stirred suspension of ajmaline (**12**) (6.0 g, 18.38 mmol) in dry ethanol (100 ml), and the mixture was heated under reflux for 2.5 h. After evaporation of the ethanol, the reaction mixture was poured into cold 10% aqueous Na_2CO_3 solution and the whole was extracted with $CHCl_3$. The organic extract was dried over $MgSO_4$ and evaporated to give 7.5 g of residue (**25**). The resulting crude hydrazone was dissolved in CH_2Cl_2 (240 ml) and 1*N*- NaOH solution (60 ml). Then $ClCO_2CH_2CCl_3$ (3.7 ml, 26.88 mmol) was added to the vigorously stirred solution during 2 min at O °C and the mixture was stirred at room temperature for 40 min. The reaction mixture was diluted with water (100 ml) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with water, dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (AcOEt-hexane, 2:1) to give the carbamate (**26**) (7.00 g, 70%) as an amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}: 3350, 2950, 1750, 1300. UV λ_{max}^{EtOH} nm: 247, 293. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 6.45, 6.40 (1H, each d, J=7.0 Hz, *N*=CH), 4.82, 4.79 (1H, each d, J=11.9 Hz, $C\underline{H_a}H_bCCl_3$), 4.73, 4.69 (1H, each d, J=11.9 Hz, $CH_a\underline{H_b}CCl_3$), 4.48, 4.40

(1H, each dd, J=7.3, 4.0 Hz, 5-H), 4.08, 4.07 (1H, each s, 17-H), 2.76, 2.75 [9H, each s, N_a-CH_3, $N(CH_3)_2$], 0.86, 0.84 (3H, each t, J=7.3 Hz, 18-CH_3). MS m/z (%): 544 (M^++2, 24), 542 (M^+, 25), 144 (100), 113 (76).

Preparation of the aldehyde (27)

$CuCl_2$ (139 mg, 0.103 mmol) was added to a solution of (**26**) (187 mg, 0.034 mmol) in THF (4.6 ml), phosphate buffer (pH 7, 0.24 ml) and water (2.2 ml). The mixture was stirred at room temperature for 36 h and then diluted with water (10 ml) and concentrated ammonia (5 ml). The whole was extracted with $CHCl_3$ and the organic layer was washed with water, and dried over $MgSO_4$. Evaporation of the solvent gave a residue (214 mg), which was separated by flash column chromatography (AcOEt-hexane, 2:1) to afford the aldehyde (**27**) (149 mg, 86%) as an amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}: 3300, 2950, 1710, 1430, 1120. UV λ_{max}^{EtOH} nm: 247, 291. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 9.64 (1H, d, J=3.7 Hz, CHO), 4.90, 4.76 (1H, each d, J=11.9 Hz,) and 4.83, 4.65 (1H, each d, J=12.2 Hz) CH_2CCl_3, 4.68 (1H, d, J=8.6 Hz, 3-H), 4.48-4.40 (1H, m, 5-H), 4.13 (1H, s, 17-H), 2.77, 2.76 (3H, each s, N_a-CH_3), 0.86 (3H, t, J=7.3 Hz, 18-CH_3). MS m/z (%): 502 (M^++2, 17), 500 (M^+, 18), 144 (100).

Preparation of the 17-O-acetate (28)

A solution of (**27**) (618 mg, 1.23 mmol) in dry pyridine (10 ml) and acetic anhydride (4 ml) was stirred at room temperature overnight. After evaporation of the solvents, 5% aqueous Na_2CO_3 solution was added to the residue and the whole was extracted with

$CHCl_3$. The organic extract was washed with water, dried over $MgSO_4$ and evaporated. The residue was purified with flash column chromatography (AcOEt-hexane, 2:1) to give the acetate (**28**) (623 mg, 93%) as an amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}: 2960, 1710, 1430, 1240, 1120. UV λ_{max}^{EtOH} nm: 247, 293. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 9.51, 9.49 (1H, each d, J=3.4 Hz, CHO), 4.89 (1H, s, 17-H), 4.85, 4.70 (1H, each d, J=11.9 Hz) and 4.80 (1H, s) CH_2CCl_3, 4.72 (1H, d, J=8.6 Hz, 3-H), 4.46-4.39 (1H, m, 5-H), 2.774, 2.768 (3H, each s, N_a-CH_3), 2.21, 2.19 (3H, each s, $OCOCH_3$), 0.87 (3H, t, J=7.4 Hz, 18-CH_3). MS m/z(%): 544 (M^++2, 20), 542 (M^+, 20), 144 (100).

Lead tetraacetate oxidation of the indoline (28)

$Pb(OAc)_4$ was added to a stirred solution of (**28**) (915 mg, 1.68 mmol) in dry CH_2Cl_2 (20 ml) at -70 °C in the following manner: 0 min, 746 mg (1.68 mmol); 60 min, 840 mg (1.89 mmol); 135 min, 650 mg (1.47 mmol). During this period, stirring was continued at the same temperature, and after the final addition of $Pb(OAc)_4$ the reaction temperature was gradually raised to 0 °C over 1 h. The reaction mixture was diluted with CH_2Cl_2 and washed successively with 5% aqueous Na_2CO_3 solution and water. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was purified by flash column chromatography (AcOEt-hexane, 1:2) to yield the indolenine (**29**) (788 mg, 88%) as an amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}: 2950, 1720, 1420, 1220, 1120. UV λ_{max}^{MeOH} nm: 210, 220, 249. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 9.544, 9.540 (1H, each d, J=4.4 Hz, CHO), 5.46, 5.43 (1H,

each d, J=7.1 Hz, 3-H), 5.01, 4.84 (1H, each d, J=12.0 Hz, $C\underline{H_a}H_bCCl_3$), 4.76, 4.57 (1H, each d, J=12.0 Hz, $CH_a\underline{H_b}CCl_3$), 2.15, 2.14 (3H, each s, $COCH_3$), 0.88, 0.86 (3H, each t, J=7.2 Hz, 18-CH_3). MS m/z(%): 499 (M^++2-CHO, 11), 497 (M^+-CHO, 12), 167 (100).

Preparation of 1-desmethyl-2-dehydro-17-acetylajmaline (23)

Zinc dust (99 mg) was added to a solution of (**29**) (49 mg, 0.093 mmol) in acetic acid (1 ml), and the mixture was stirred at room temperature for 30 min. The reaction mixture was filtered and the filtrate was concentrated *in vacuo* and then basified by the addition of chilled 5% aqueous $NaHCO_3$ solution. The whole was extracted with $CHCl_3$. The organic extract was washed with water, and dried over $MgSO_4$. Removal of the solvent gave a residue, which was subjected to medium-pressure liquid column chromatography (MPLC) (5% MeOH-$CHCl_3$) to afford 17 mg (52%) of (**23**) as colorless prisms, mp 238-242 °C (lit,[14] 240-242 °C). IR ν_{max}^{KBr} cm^{-1}: 3300-3000, 2960, 1740, 1240. UV λ_{max}^{MeOH} nm: 219, 257. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.37 (1H, br s, OH), 5.00 (1H, s, 17-H), 4.33 (1H, d-like, J=~11 Hz, 3-H), 4.31 (1H, s, 21-H), 3.33 (1H, t, J=5.7 Hz, 5-H), 2.78 (1H, dd, J=12.0, 5.0 Hz, 6-H_β), 2.42 (1H, m, 15-H), 2.26 (1H, t, J=6.0 Hz, 16-H), 2.17 (3H, s, $COCH_3$), 1.89 (1H, dd, J=14.0, 10.1 Hz, 14-H_α), 1.74 (1H, dd, J=14.0, 5.0 Hz, 14-H_β), 1.64 (1H, d, J=12.0 Hz, 6-H_α), 1.50-1.40 (2H, m, 19-H_2), 0.98 (3H, t, J=6.6 Hz, 18-CH_3). ^{13}C-NMR (Table 1-1). MS m/z(%): 352 (M^+, 100), 324 (24), 323 (26), 169 (95). Exact MS Calcd for $C_{21}H_{24}N_2O_3$: 352.1788. Found: 352.1787.

Preparation of the α-phenylselenylaldehyde (30)

Et_3N and TBSOTf were added to a stirred solution of (**29**) (318 mg, 0.60 mmol) in dry CH_2Cl_2 (5 ml) at 0 °C as follows: 0 min, Et_3N (125 ml, 0.90 mmol) and TBSOTf (200 ml, 0.87 mmol); 45 min, Et_3N (125 ml, 0.90 mmol) and TBSOTf (200 ml, 0.87 mmol); 180 min, TBSOTf (150 ml, 0.65 mmol). Stirring was continued at the same temperature for 4 h. To this reaction mixture containing silyl enol ether, a solution of PhSeCl (116 mg, 0.60 mmol) in dry CH_2Cl_2 (2 ml) was added at -20 °C. After 2 h, a solution of PhSeCl (89 mg, 0.46 mmol) in dry CH_2Cl_2 (0.6 ml) was added at -20 °C and then the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with CH_2Cl_2 and washed with 5% aqueous Na_2CO_3 solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layer was washed with water and dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was purified by flash column chromatography (AcOEt-hexane, 2:1) and then by MPLC (1% MeOH-$CHCl_3$) to give oily (**30**) (220 mg, 53%) as a diastereomeric mixture and the starting material (**29**) (31 mg, 10%). IR ν_{max}^{CHCl3} cm^{-1}: 2970, 1720, 1420, 1320, 1220. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.70-7.20 (9H, m, arm-H). MS m/z(%): 655 (M^++2-CO, 4), 653 (M^+-CO, 4), 345(58), 343 (59), 169 (70), 168 (100), 167 (96).

Preparation of the α-bromoaldehyde (31)

Et_3N and TBSOTf were added to a stirred solution of (**29**) (92 mg, 0.174 mmol) in dry CH_2Cl_2 (1.5 ml) at 0 °C as follows: 0 min, Et_3N (37

ml, 0.27 mmol) and TBSOTf (58 ml, 0.25 mmol); 75 min, Et_3N (37 ml, 0.27 mmol) and TBSOTf (58 ml, 0.25 mmol); 180 min, TBSOTf (29 ml, 0.13 mmol). After the final addition of the reagent, the mixture was stirred at room temperature for 5 h. To this reaction mixture containing silyl enol ether, a solution of NBS (36 mg, 0.202 mmol) in dry CH_2Cl_2 (1.5 ml) was added at 0 °C, and the whole was stirred at the same temperature for 10 min. The reaction mixture was diluted with CH_2Cl_2 and washed with 5% aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was purified by MPLC (AcOEt-hexane, 1:2) to afford 75 mg (71%) of oily (**31**) as a diastereomeric mixture. IR ν_{max}^{CHCl3} cm^{-1}: 2950, 1720, 1700, 1220. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.47, 9.45, 9.42 (1H, each s, CHO), 2.19, 2.18, 2.17, 2.16 (3H, each s, $COCH_3$). MS m/z(%): 525 (M^++2-HBr, 15), 523 (M^+-HBr, 17), 345 (63), 343 (65), 169 (77), 168 (90), 167 (100), 156 (63).

Dehydrobromination of (31) with Li_2CO_3

A mixture of (**31**) (134 mg, 0.22 mmol) and Li_2CO_3 (50 mg, 0.68 mmol) in dry DMF (4 ml) was stirred at 80 °C for 4.5 h under an argon atmosphere. Then 5% aqueous $NaHCO_3$ solution was added to the reaction mixture and the whole was extracted with $CHCl_3$. The organic extract was washed with brine, dried over $MgSO_4$ and evaporated. DMF was removed in a Kugelrohr apparatus and the residue was purified by MPLC (AcOEt-hexane, 1:2) to give oily (**32**) (30

mg, 26%), oily (**35**) (25 mg, 21%), a more polar tetrasubstituted olefin (**33**) (8 mg, 7%), and a less polar tetrasubstituted olefin (**34**) (13 mg, 11%). (**32**); IR ν_{max}^{CHCl3} cm^{-1}: 3000, 1710, 1430, 1220, 1130, 1040. UV λ_{max}^{EtOH} nm: 220.2. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.39, 9.37 (1H, each s, CHO), 6.62 (1H, q, J=7.2 Hz, 19-H), 5.52, 5.49 (1H, each d, J=8.5 Hz, 3-H), 5.06, 4.98 (1H, each m, 5-H), 4.85, 4.81 (1H, each d, J=11.8 Hz, $C\underline{H_a}H_bCCl_3$), 4.76, 4.63 (1H, each d, J=11.8 Hz, $CH_a\underline{H_b}CCl_3$), 4.60, 4.59 (1H, each s, 17-H), 2.17, 2.16 (3H, each s, $COCH_3$), 2.05 (3H, d, J=6.9 Hz, 18-CH_3). MS m/z(%): 526 (M^++2, 25), 524 (M^+, 24), 498 (13), 496 (13), 345 (54), 343 (53), 169 (69), 168 (76), 167 (100). (**35**); IR ν_{max}^{CHCl3} cm^{-1}: 2940, 1715, 1680, 1430, 1220, 1130, 1040. UV λ_{max}^{EtOH} nm: 220.5. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 10.21, 10.16 (1H, each s, CHO), 6.79 (1H, qt, J=7.5, 1.3 Hz, 19-H), 5.46, 5.44 (1H, each d, J=8.5 Hz, 3-H), 4.96, 4.73 (1H, each d, J=11.9 Hz, $C\underline{H_a}H_bCCl_3$), 4.91, 4.80 (1H, each m, 5-H), 4.80 (1H, s, 17-H), 4.70, 4.53 (1H, each d, J=11.9 Hz, $CH_a\underline{H_b}CCl_3$), 2.17, 2.16 (3H, each s, $COCH_3$), 2.16, 2.14 (3H, each dd, J=7.5, 1.6 Hz, 18-CH_3). MS m/z(%): 526 (M^++2, 24), 524 (M^+, 23), 498 (13), 496 (13), 168 (82), 167 (100). (**33**); IR ν_{max}^{CHCl3} cm^{-1}: 2950, 1710, 1420, 1220. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 10.04 (1H, s, CHO), 2.21, 2.20 (3H, each s, $COCH_3$), 0.96, 0.94 (3H, each t, J=7.7 Hz, 18-CH_3). MS m/z (%): 526 (M^++2, 11), 524 (M^+, 11), 169 (100), 168 (100). (**34**); IR ν_{max}^{CHCl3} cm^{-1}: 2950, 1710, 1420, 1220, 1120 . ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 10.04, 10.03 (1H, each s, CHO), 2.18, 2.17 (3H, each s, $COCH_3$). 0.93 (3H, t, J=7.7 Hz, 18-CH_3). MS m/z (%): 526 (M^++2, 22), 524 (M^+,22), 169 (95), 168 (100)

Preparation of vomilenine (13)

Zinc dust (450 mg) was added to a solution of (**32**) (124 mg, 0.24 mmol) in acetic acid (4 ml), and the mixture was stirred at room temperature for 3 h, then filtered. The filtrate was concentrated and then basified with chilled 5% aqueous $NaHCO_3$ solution. The whole was extracted with $CHCl_3$ and the organic extract was washed with water and dried over $MgSO_4$. Evaporation of the solvent gave the residue, which was purified by MPLC (5% MeOH-$CHCl_3$) to afford 58 mg (68%) of vomilenine (**13**) as colorless prisms from AcOEt. mp 189-191 °C (lit[9] 207° C). $[\alpha]_D^{19}$ -71.6 ° (c=0.45, pyridine) (lit[9] -72 °). IR νmax^{KBr} cm^{-1}: 3300-3000, 2950, 1740, 1600, 1450, 1230. UV λmax^{MeOH} nm: 219, 260. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.06 (1H, br s, OH), 5.75 (1H, q, J=6.6 Hz, 19-H), 5.03 (1H, br s, 21-H), 4.98 (1H, s, 17-H), 4.31 (1H, dd, J=7.1, 2.8 Hz, 3-H), 3.92 (1H, t, J=5.8 Hz, 5-H), 3.28 (1H, m, 15-H), 2.77 (1H, dd, J=12.1, 4.7 Hz, 6-Hβ), 2.17 (3H, s, $COCH_3$), 1.68 (3H, d, J=6.6 Hz, 18-CH_3). ^{13}C-NMR (Table 1-4). MS m/z(%): 350 (M^+, 29), 169 (100), 43 (15). Anal. Calcd for $C_{21}H_{22}O_3N_2.1/4H_2O$: C, 71.07; H, 6.39; N, 7.89. Found: C, 70.96; H, 6.27; N, 7.82. Exact MS Calcd for $C_{21}H_{22}N_2O_3$: 350.1629. Found: 350.1627.

Preparation of (19Z)-vomilenine (24)

Zinc dust (99 mg) was added to a solution of (**35**) (42 mg, 0.08 mmol) in acetic acid (2 ml), and the mixture was stirred at room temperature for 1.5 h. A residue obtained by work-up as described above was purified by MPLC (*i*-PrOH-$CHCl_3$-hexane, 7:63:30) to give 21

mg (75%) of (**24**) as an amorphous solid and 3 mg (7%) of the starting material (**35**). IR ν_{max}^{CHCl3} cm^{-1}: 3600-3100, 2970, 1740, 1230. UV λ_{max}^{EtOH} nm: 219, 258. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.65-7.20 (4H, m, arm-H), 5.54 (1H, q like, 19-H), 5.19 (1H, s, 21-H), 4.99 (1H, s, 17-H), 2.16 (3H, s, $COCH_3$), 1.8-1.6 (3H, 18-CH_3). ^{13}C-NMR (Table 1-4). Exact MS Calcd for $C_{21}H_{22}N_2O_3$: 350.1629. Found: 350.1621.

Preparation of perakine (14) from (19Z)-vomilenine (24)

A solution of (**24**) (6 mg, 0.017 mmol) in acetic acid (0.5 ml) was stirred at room temperature under an argon atmosphere. After 17 h, a small portion of the reaction mixture was neutralized with chilled ammonia water and extracted with $CHCl_3$. The organic extract was dried over $MgSO_4$ and evaporated. The crude residue was subjected to ^{1}H-NMR measurement. The ratio of (19*Z*)-vomilenine (**24**) and perakine (**14**) was calculated from the integrals of the signals of the olefinic proton (19-H) of (**24**) and the aldehyde proton (21-H) of (**14**). The reaction mixture after 17 h contained 25% perakine (**14**) and 75% starting material (**24**). The remaining reaction mixture was stirred at the same temperature for two weeks. The ^{1}H-NMR spectrum of the crude residue obtained by the same work-up procedure as above showed the exclusive presence of perakine (**14**). The residue was crystallized from acetone-hexane to give 4 mg of colorless prisms. mp 179-182 ° C (lit[12] 183 ° C). The chromatographic behavior on TLC, as well as the IR, MS, Exact MS (Calcd for $C_{21}H_{22}N_2O_3$: 350.1629. Found: 350.1622), and ^{1}H- (Table 1-5) and ^{13}C-NMR spectra of the

semisynthetic compound were identical with those of authentic perakine (**14**). The stereochemistry at the C-19 and C-20 positions was further confirmed by the differential NOE spectrum. Irradiation of 18-H_3 (δ 1.30) in (**14**) led to enhancement of the 5-H (16%) and H-20 (15%) signals.

Experiments of Chapter 2

Preparation of the carbonate (44) from ajmaline (12)

To a vigorously stirred solution of ajmaline (12) (2.0 g, 6.13 mmol) in CH_2Cl_2 (60 ml) and aqueous 1*N*-NaOH solution (16 ml), $ClCO_2CH_2Ph$ (1.73 ml, 12.12 mmol) was added dropwise at 0 °C. After 1.5 h the reaction mixture was diluted with CH_2Cl_2 and washed with water. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with water, dried over $MgSO_4$, and then evaporated to give a residue, which was crystallized from AcOEt to afford 2.34 g of (44) as colorless prisms. 0.11 g of pure (44) was further obtained by the purification of the mother liquid with flash column chromatography (AcOEt-hexane, 2:3). Total 2.45 g (87%). mp 218-220 °C (from acetone). IR ν_{max}^{KBr} cm^{-1}: 3300(br), 2940, 1740, 1250. UV λ_{max}^{EtOH} nm: 206, 248, 291. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 5.19 and 5.17 (each 1H, d, J=12.0 Hz, $OC\underline{H}_2Ph$), 5.18 (1H, s, 21-H). MS m/z (%): 460 (M^+, 49), 326 (26), 91 (100). Anal. Calcd for $C_{28}H_{32}O_4N_2 \cdot 1/2H_2O$: C; 71.62, H; 7.08, N; 5.96, Found: C; 71.26, H; 6.79, N; 5.89.

Lead tetraacetate oxidation of the indoline (44)

To a stirred solution of (44) (2.46 g, 5.34 mmol) in dry CH_2Cl_2 (100 ml) was added $Pb(OAc)_4$ (2.0 g, 4.06 mmol) at -70 °C under nitrogen atmosphere. After 25 min the reaction mixture was diluted with $CHCl_3$ and washed with aqueous 1*N*-NaOH solution. The

aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by flash column chromatography (AcOEt-hexane, 1:2) and then crystallized from MeOH to yield 1.67 g (68%) of (**46**) accompanied with 270 mg (11%) of the starting material (**44**). (**46**): colorless needles, mp 80-82 °C. IR ν_{max}^{KBr} cm^{-1}: 2940, 1750, 1700, 1470, 1250. UV λ_{max}^{MeOH} nm: 226, 282. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 9.32 (1H, d, J=1.2 Hz, CHO), 3.59 (3H, s, *N*-CH_3). MS m/z (%): 458(M^+, 40), 182 (100), 91 (56). Anal. Calcd for $C_{28}H_{30}O_4N_2 \cdot 1/4H_2O$: C; 72.63, H; 6.64, N; 6.05. Found: C; 72.74, H; 6.63, N; 6.01.

Epimerization of (46) with DBU

A mixture of (**46**) (1.525 g, 3.31 mmol) and DBU (0.5 ml, 3.31 mmol) in dry THF (50 ml) was stirred at room temperature under argon atmosphere for 20 h. After evaporation of the solvents, the residue was purified by flash column chromatography (AcOEt-hexane, 1:2) and then by medium pressure column chromatography (MPLC) (AcOEt-hexane, 1:2) to afford 1.50 g (99%) of the epimeric aldehyde (**47**) as an amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}: 2940, 1750, 1720, 1250. UV λ_{max}^{EtOH} nm: 227, 283. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 9.70 (1H, s, CHO). MS m/z (%): 458(M^+, 40), 182 (100), 91 (52).

$NaBH_4$ reduction of the aldehyde (47)

To a stirred solution of (**47**) (206 mg, 0.45 mmol) in MeOH (7 ml) was added $NaBH_4$ (20 mg, 0.53 mmol) at room temperature. After 10 min crystalline of (**48**) was precipitated from the reaction solution. The

precipitate was filtered and washed with MeOH to afford 110 mg of (**48**). The mother liquid was concentrated and diluted with water. The whole was extracted with 5% MeOH-$CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated. The residue was crystallized from hexane to yield 67 mg of (**48**). Further purification of the mother liquid by MPLC (AcOEt-hexane, 1:2) gave 11 mg of (**48**). Totally 187 mg (90%) of (**48**) was obtained. (**48**): colorless needles. mp 177-178 °C (from hexane). IR ν_{max}^{CHCl3} cm^{-1}: 3250 (br.), 2920, 1760, 1240. UV λ_{max}^{EtOH} nm: 229, 284. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.73 and 3.67 (each 1H, dd, J=10.0, 8.0 Hz, $C\underline{H}_2OH$). MS m/z (%): 460 (M^+, 17), 326 (22), 183 (100). Anal. Calcd for $C_{28}H_{32}O_4N_2 \cdot 1/2H_2O$: C; 71.62, H; 7.08, N; 5.97. Found: C; 71.66, H; 6.94, N; 5.94.

Preparation of the macroline skeleton (51)

A mixture of 1.768 g (3.84 mmol) of (**48**) and MeI (1.2 ml, 19.28 mmol) in dry MeOH (60 ml) and dry THF (60 ml) was allowed to stand for 85 h under dark condition. A residue obtained by the removal of the solvents and reagents was dissolved in THF (75 ml) and 5% KOH solution (75 ml) and the mixture was stirred at room temperature for 1 h. After concentration of THF, the mixture was diluted with water and extracted with $CHCl_3$. The organic layer was washed with water, dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (AcOEt to 2%MeOH-AcOEt) to give 1.208 g (92%) of (**51**) as an amorphous powder (diastereomeric mixture of 2:1). IR ν_{max}^{CHCl3} cm^{-1}: 3500-3100, 2950, 1470. UV λ_{max}^{EtOH} nm: 228,

286. ^{1}H-NMR (500 MHz, $CDCl_3$) (selected data of major product) δ: 5.04 (1H, s, 21-H), 2.32 (3H, s, N_b-CH_3). MS m/z (%): 340 (M^+, 100), 224 (39), 197 (82), 60 (22). Exact MS Calcd for $C_{21}H_{28}N_2O_2$: 340.2149. Found: 340. 2147.

Phenylselenenylation of the acetal (51)

To a stirred solution of (**51**) (1.773 g, 5.21 mmol) in acetic acid (33 ml) was added 4Å molecular sieves (6 g) and freshly distilled piperidine (1.34 ml, 13.55 mmol) and the mixture was refluxed for 2 h under argon atmosphere. Molecular sieves were filtered off and acetic acid and piperidine were removed from the filtrate under reduced pressure. The residue was dissolved in dry CH_2Cl_2 (20 ml) and a solution of PhSeBr (1.490 g, 6.19mmol) in dry CH_2Cl_2 (26 ml) was added at 0 °C. The mixture was heated under reflux condition for 4 h. The reaction mixture was diluted with $CHCl_3$ and washed with aqueous 5% $NaHCO_3$ solution. The aqueous layer was extracted with $CHCl_3$ and combined organic layer was washed with water and then dried over $MgSO_4$. Removal of the solvent gave a residue, which was purified by flash column chromatography (AcOEt) and then crystallized from hot MeOH to provide 971 mg of (**54**) as colorless prisms. The mother liquid was subjected to flash column chromatography (AcOEt-hexane, 1:1) to yield 270 mg of (**54**). Totally 1.241 g (47%) of (**54**) was obtained. mp 180-181.5 °C. IR ν_{max}^{KBr} cm^{-1}: 2900, 1450, 1030. UV λ_{max}^{EtOH} nm: 223, 286. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.56-6.69 (9H, aromatic H), 4.46 (1H, s, 21-H), 3.31 (3H, s,

OCH_3). MS m/z (%): 510 (M^+, 23), 311 (100), 197 (83). Anal. Calcd for $C_{28}H_{34}O_2N_2Se$: C; 66.00, H; 6.73, N; 5.50. Found: C; 66.03, H; 6.71, N; 5.41.

Preparation of the olefins (55) and (56)

A solution of $NaIO_4$ (1.03 g, 4.82 mmol) in water (15 ml) was added to the stirred solution of (**54**) (1.63 g, 3.20 mmol) in THF (30 ml) and MeOH (30 ml) at 0 °C. The mixture was stirred at room temperature for 5 h. After filtration of the precipitate, the filtrate was concentrated and diluted with 5% $NaHCO_3$ solution. The whole was extracted with $CHCl_3$. The organic extract was washed with water, dried over $MgSO_4$, and then evaporated. The residue was subjected to flash column chromatography (AcOEt-hexane, 1:1) to give 930 mg (83%) of the mixture of (**55**) and (**56**). The ^{1}H-NMR spectrum of this fraction showed the ratio of (**55**) and (**56**) as approximately 2:1. Recrystallization of this fraction from acetone gave 533 mg (47%) of (**55**) as colorless prisms. Repeated chromatography using MPLC gave 46 mg of pure (**56**). (**55**): mp 198-202 °C. IR ν_{max}^{KBr} cm^{-1}: 2900, 1460, 1040. UV λ_{max}^{EtOH} nm: 230, 285. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.23 (1H, s, 21-H), 5.15 (1H, q, J=7.0 Hz, 19-H), 4.41 (1H, t, J=11.6 Hz, 17α-H), 3.43 (3H, s, OCH_3), 2.26 (1H, td, J=5.0, 12.6 Hz, 15-H), 1.56 (3H, d, J=7.0 Hz, 18-Me). MS m/z (%): 352 (M^+, 91), 197 (100), 170 (72). Exact MS Calcd for $C_{22}H_{28}N_2O_2$: 352.2148. Found: 352.2147. (**56**): amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}: 2950, 1470, 1105, 1040. UV λ_{max}^{EtOH} nm: 230, 285. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 5.39 (1H, q, 6.9 Hz, 19-H),

4.72 (1H, s, 21-H), 3.37 (3H, s, OCH_3), 1.23 (3H, d, J=6.9 Hz, 18-Me). MS m/z (%): 352 (M^+, 78), 197 (100), 170 (77). Exact MS Calcd for $C_{22}H_{28}N_2O_2$: 352.2148. Found: 352.2140.

Talcarpine (15) from (55)

A mixture of (**55**) (100 mg, 0.28 mmol) in aqueous 5% H_2SO_4 solution (6 ml) was stirred at room temperature for 24 h under argon atmosphere. $CHCl_3$ was added to the reaction mixture and the aqueous layer was carefully basified with 5% $NaHCO_3$ solution at 0 °C under stirring. After separation of the organic layer, the aqueous layer was extracted with $CHCl_3$. The combined organic phase was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by MPLC (2.5% MeOH-$CHCl_3$) to yield 28 mg (30%) of (**15**) and 56 mg (59%) of (**57**). (**15**): colorless prisms, mp 160-161 °C (from hexane-acetone-ether) (lit.[26] 167-169 °C). IR ν_{max}^{KBr} cm^{-1}: 2900, 1720, 1480, 1380, 740. UV λ_{max}^{MeOH} nm: 228, 285. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 9.94 (1H, d, J=3.3 Hz, CHO), 4.13 (1H, t, J=11.7 Hz, 17α-H), 3.97 (1H, br-s, 3-H), 3.97 (1H, qd, J=6.6, 2.4 Hz, 19-H), 3.89 (1H, dd, J=11.7, 4.9 Hz, 17β-H), 3.62 (3H, s, N_a-CH_3), 3.27 (1H, dd, J=16.6, 7.1 Hz, 6α-H), 2.90 (1H, d, J=7.1 Hz, 5-H), 2.49 (1H, td, J=12.9, 4.2 Hz, 14α-H), 2.45 (1H, d, J=16.6 Hz, 6β-H), 2.32 (3H, s, N_b-CH_3), 2.20 (1H, 15-H), 2.06 (1H, 16-H), 1.78 (1H, t-like, 20-H), 1.45 (1H, ddd, J=12.5, 4.4, 2.5 Hz, 14β-H), 1.30 (3H, d, J=6.6 Hz, 18-Me). ^{13}C-NMR (Table 2-1). MS m/z (%): 338 (M^+, 99), 197 (100), 70 (70). Exact MS Calcd for $C_{21}H_{26}N_2O_2$: 338.1992. Found: 338.1985. CD (c=0.237 mmol/l, MeOH, 29 °C): Δε (nm)

-14.22 (227), 0.70 (274), 0.93 (301). N_b-methyl-N_b,21-secotalpinine (**57**): colorless amorphous powder, IR ν_{max}^{CHCl3} cm^{-1}: 2950, 1720, 1470. UV λ_{max}^{MeOH} nm: 228, 285. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.41 (1H, s, CHO), 4.06 (1H, t, J=11.9 Hz, 17α-H), 3.95 (1H, s, 3-H), 3.92 (1H, qd, J=6.0, 9.9 Hz, 19-H), 3.58 (3H, s, N_a-CH_3), 2.36 (1H, m, 20-H), 2.31 (3H, s, N_b-CH_3), 1.20 (3H, d, J=6.0 Hz, 18-Me). ^{13}C-NMR (Table 2-1). MS m/z (%): 338 (M^+, 58), 197 (100), 70 (69). Exact MS Calcd for $C_{21}H_{26}N_2O_2$: 338.1992. Found: 338.1998.

Acetate (58) from talcarpine (15)

To a solution of talcarpine (**15**) (9 mg, 0.027 mmol) in MeOH (1 ml) was added $NaBH_4$ (3.6 mg, 0.096 mmol) and the mixture was stirred for 3 h at room temperature. After dilution of the reaction mixture with 5% $NaHCO_3$ solution, the whole was extracted with $CHCl_3$. The organic layer was washed with water and dried over $MgSO_4$. Removal of the solvent gave a residue, which was treated with dry pyridine (0.5 ml) and acetic anhydride (0.25 ml) at room temperature for 6 h. A residue obtained by the usual work up manner was purified by MPLC (5% MeOH-$CHCl_3$) to give 6 mg (58%) of acetate (**58**) as colorless oil. IR ν_{max}^{CHCl3} cm^{-1}: 2940, 1730, 1470, 1130. UV λ_{max}^{EtOH} nm: 230, 285. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.21 (1H, dd, J=11.3, 6.6 Hz, 21-H), 4.13 (1H, dd, J=11.3, 7.4 Hz, 21-H), 3.90 (1H, qd, J=6.9, 2.2 Hz, 19-H), 2.51 (1H, td, J=12.9, 4.1 Hz, 14α-H), 1.66 (3H, s, OCH_3), 1.14 (3H, d, J=6.6 Hz, 18-Me). MS m/z (%): 382 (M^+, 100), 268

(15), 197 (76), 183 (21), 70 (37). Exact MS Calcd for $C_{23}H_{30}N_2O_3$: 382.2254. Found: 382.2248.

Hydroboration of (55)

To a solution of (**55**) (271 mg, 0.769 mmol) in dry THF (12 ml) was added $BH_3 \cdot SMe_2$ complex in THF (0.38 ml, 3.80 mmol) at -70 °C and the mixture was allowed to stand at -20 °C for 120 h. Furthermore, $BH_3 \cdot SMe_2$ in THF (0.077 ml, 0.77 mmol) was added to the reaction mixture at -20 °C and it was left overnight at the same temperature. 3*N*-NaOH solution (5.5 ml) and 30% H_2O_2 solution (1.1 ml) were added at 0 °C and the mixture was heated at 90 °C for 1 h. The reaction mixture was diluted with water and extracted with $CHCl_3$. The organic layer was washed with water, dried over $MgSO_4$, and then evaporated. The residue was purified by MPLC (MeOH, $CHCl_3$, hexane 4:56:60) to yield 78 mg (27%) of (**60**), 74 mg (26%) of (**61**), and 59 mg (22%) of the starting material (**55**). (**60**): colorless amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}: 3600-3200, 2940, 1470, 1050. UV λ_{max}^{EtOH} nm: 229, 285. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.72 (1H, dq, J=7, 6.3 Hz, 19-H), 1.57 (1H, ddd, J=7.5, 5.0, 3.6 Hz, 20-H), 0.90 (3H, d, J=6.3 Hz, 18-Me). MS m/z (%): 370 (M^+, 100), 197 (83), 70 (56). Exact MS Calcd for $C_{22}H_{30}N_2O_3$: 370.2255. Found: 370.2262. (**61**): colorless needles, mp 130-132 °C (from ether). IR ν_{max}^{KBr} cm^{-1}: 3600-3200, 2900, 1470, 1060. UV λ_{max}^{EtOH} nm: 231, 285. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.84 (1H, dq, J=6.3, 6.3 Hz, 19-H), 1.51 (1H. td, J=6, 3.6 Hz, 20-H), 0.96 (3H, d, J=6.4 Hz, 18-Me). MS m/z (%): 370 (M^+, 100), 197 (89), 70

(54). Anal. Calcd for $C_{22}H_{30}O_3N_2 \cdot 1/2H_2O$: C; 69.63, H; 8.23, N; 7.38. Found: C; 69.65, H; 8.23, N; 7.31

Swern oxidation of the alcohol (60)

A solution of DMSO (74 ml, 1.04 mmol) in CH_2Cl_2 (0.5 ml) was added dropwise at -70 °C to a stirred solution of oxalyl chloride (54 ml, 0.634 mmol) in CH_2Cl_2 (0.5 ml). The mixture was stirred at -70 °C for 10 min. A solution of (**60**) (77 mg, 0.208 mmol) in dry CH_2Cl_2 (1 ml) was added dropwise and the mixture was stirred at -70 °C to -20 °C for 1 h. Et_3N (0.23 ml, 1.66 mmol) was added and the mixture was stirred at -20 °C to room temperature for 1 h. The reaction mixture was diluted with $CHCl_3$ and washed with 5% $NaHCO_3$ solution. The aqueous layer was extracted with $CHCl_3$. The combined organic phase was washed with water, dried over $MgSO_4$ and concentrated. The residue was subjected to MPLC (hexane-AcOEt, 1:2) to provide 54 mg (70%) of ketone (**62**) as colorless needles, mp 138-140 °C (from MeOH). IR ν_{max}^{KBr} cm^{-1}: 2950, 1705, 1470, 1040. UV λ_{max}^{EtOH} nm: 230, 285. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.06 (1H, d, J=3.6 Hz, 21-H), 2.48 (1H, dd, J=4.7, 3.6 Hz, 20-H), 1.99 (3H, s, 18-Me). MS m/z (%): 368 (M^+, 100), 197 (72), 70 (67). Anal. Calcd for $C_{22}H_{28}O_3N_2$: C; 71.71, H; 7.66, N; 7.60. Found: C; 71.66, H; 7.66, N; 7.61

Swern oxidation of (61)

Same treatment of (**61**) (45 mg, 0.121 mmol) with DMSO, oxalyl chloride, and Et_3N in dry CH_2Cl_2 afforded 26 mg (57%) of (**62**) along with 9.4 mg (21%) of the starting material. (**62**) obtained by this

reaction was identical with the sample derived form (**60**) by the comparison of their mp, TLC behavior, ^{1}H-NMR, and MS spectra.

Alstonerine (16) from (62)

A mixture of (**62**) (45.5 mg, 0.123 mmol) and NaOH (49 mg, 1.23 mmol) in MeOH (2 ml) was stirred at 0 °C for 30 min. The reaction mixture was diluted with water and extracted with $CHCl_3$. The organic phase was washed with water, dried over $MgSO_4$. Removal of the solvent gave a residue, which was purified by MPLC (0.7% MeOH-$CHCl_3$) to furnish 37 mg (89%) of alstonerine (**16**) as colorless prisms, mp. 162-164 °C (hot plate; 172-175 °C) (from ether) (lit.[29] 172-173 °C). $[\alpha]_D^{26}$ -140 ° (c=0.2, EtOH). IR ν_{max}^{KBr} cm^{-1}: 2930, 1655, 1620, 1480, 1200. UV λ_{max}^{EtOH} nm: 230, 259. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.53 (1H, s, 21-H), 4.41 (1H, t, J=11.2 Hz, 17α-H), 4.17 (1H, ddd, J=11.0, 4.1, 1.6 Hz, 17β-H), 3.87 (1H, dd, J=3.3, 3.0 Hz, 3-H). 3.65 (3H, s, N_a-CH_3), 3.09 (1H, d, J=6.9 Hz, 5-H), 3.33 (1H, dd, J=16.5, 6.9 Hz, 6α-H), 2.50 (1H, d, J=16.5 Hz, 6β-H), 2.62 (1H, dt, J=12.1, ~5 Hz, 15-H), 2.32 (3H, s, N_b-CH_3), 2.09 (3H, s, 18-Me), 2.13 (1H, ddd, J=12.9, 4.9, 3.0 Hz, 14β-H), 1.82 (1H, td, J=12.4, 4.1 Hz, 14α-H), 1.91 (1H, dt, J=12.4, 4.1 Hz, 16-H). ^{13}C-NMR (Table 2-2). MS m/z (%): 336 (M^+, 100), 197 (77), 181 (46), 170 (82). Exact MS Calcd for $C_{21}H_{24}N_2O_2$: 336.1842. Found: 336.1836.

Experiments of Chapter 3

Preparation of the carbamate (78) from ajmaline (12)

A mixture of ajmaline (12) (500mg, 1.532 mmol), *N*,*N*-dimethylhydrazine (0.58 ml, 7.634 mmol), a catalytic amout of H_2SO_4 (5 drops), molelular seives 3 Å and ethanol (10 ml) was heated under reflux for 3 h. The filtrate obtained by the filtration of molecular seives was concentrated under reduced pressure and then basified with ammonia water. The aqueous layer was extracted with $CHCl_3$ and the organic layer was washed with water, dried over $MgSO_4$, and evaporated. The residue was dissolved in 1*N*-NaOH/CH_2Cl_2=1:4 (12.5 ml) and carbobenzoxy chloride (0.25 ml, 1.751 mmol) was added to the mixture at 0 °C. The reaction mixture was vigorously stirred at room temperature for 30 min. The organic layer was seperated and the aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with water, dried over $MgSO_4$, and evaporated. The residue was separated by MPLC (AcOEt-hexane, 2:1) to give 600 mg (80%) of (**78**) as an amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}: 3400, 2950, 1690. UV λ_{max}^{EtOH} nm: 206, 246, 291. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 6.43 and 6.42 (1H, each d, J=7.4 Hz, 21-H), 5.23, 5.09 (1H, each d, J=12.8 Hz, $CH_{\underline{a}}H_bC_6H_5$), 5.21, 5.08 (1H, each d, J=12.5 Hz, $CH_aH_{\underline{b}}C_6H_5$), 2.77, 2.74, 2.73, 2.62 [9H, each s, N_a-CH_3, $N(CH_3)_2$]. MS m/z (%): 502 (M^+, 50), 358 (16), 144 (59), 91 (100).

Hydrolysis of the hydrazone (78)

$CuCl_2$ was added portionwise to a solution of (**78**) (5.340 g, 10.62 mmol) in a mixture of THF (190 ml), H_2O (25 ml), and phosphate buffer (0.05 *N*, pH7, 75 ml) at room temperature in the following manner. 0 min, 3.588g (26.69 mmol); 15.5 h, 1.686 g (12.54 mmol); 63.5 h, 428 mg (3.18 mmol). After the final addition of $CuCl_2$, the mixture was stirred at room temperature for 24 h. After evaporation of THF, the mixture was diluted ice-water and basified with conc. ammonia. The whole mixture was extracted with $CHCl_3$ and the extract was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by flash column chromatography (30-50% AcOEt-hexane) to give 4.123 g (84%) of (**79**) as an amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}: 3600, 3450, 1715, 1680, 1420. UV λ_{max}^{EtOH} nm: 205, 247, 291. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 9.61 (d,J=3.4 Hz) and 9.54.(d, J=4.3 Hz) (1H, 21-H), 2.76, 2.64 (3H, each s, N_a-CH_3). MS m/z (%): 460 (M^+, 59), 272 (41), 173 (36), 144 (47), and 91 (100). Exact MS Calcd for $C_{28}H_{32}N_2O_4$: 460.2360. Found: 460.2365.

Preparation of the silyl enol ether (80)

TBSOTf (0.24 ml, 1.045 mmol) was added to a solution of (**79**) (160 mg, 0.347 mmol) and Et_3N (0.22 ml, 1.581 mmol) in dry CH_2Cl_2 (1ml) at 0 °C and the mixture was stirred for 1.5 h. Furthur, TBSOTf (40 ml, 0.174 ml) was added to the reaction mixture at 0 °C and the mixture was sitrred at the same temperature for 1 h. A cold 5% $NaHCO_3$ solution was added to the mixture and the whole was extracted with

$CHCl_3$. The residue was separated by flash column chromatography (10% AcOEt-hexane) to give 170 mg (71%) of (**80**) as an amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}: 2950, 1690, 1100, 850. UV λ_{max} EtOH nm: 210, 248, 293. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 6.18 (1H, s, 21-H), 0.98, 0.97, 0.92, 0.90 (18 H, each s, 2 $SiBu^t$), 0.14, 0.11, 0.09, 0.06 (12 H, each s, 2 $SiMe_2$). MS m/z (%): 689 (M^+, 18), 412 (20), 236 (13), 144 (13), 91 (100).

Preparation of α-hydroxyaldehyde (81)

OsO_4 (31 mg, 0.122 mmol) was added to a stirred solution of (**80**) (76 mg, 0.110 mmol) in pyridine-THF (1:1, 2 ml), and the mixture was stirred at room temperature for 20 min. Aqueous $NaHSO_3$ solution (80 mg in H_2O 0.5 ml) was added and the mixture was stirred for 1 h at room temperature. The reaction mixture was basified with 1 *N*-Na_2CO_3 and the whole was extracted with $CHCl_3$. The extract was dried over $MgSO_4$, and evaporated. The residue was purified by MPLC (AcOEt-hexane, 1:3) to yield 53 mg (81%) of (**81**) as an amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}: 3500, 2950, 1710, 1960, 1100, 850. UV λ_{max} EtOH nm: 206, 248, 292. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 9.35, 9.32 (1H, each d, J=1.2 Hz, -CHO), 5.21, 5.11 (1H, each d, J=12.5 Hz, $C\underline{H_a}H_bC_6H_5$), 5.19, 5.07 (1H, each d, J=12.5 Hz, $CH_a\underline{H_b}C_6H_5$), 4.62, 4.48 (1H, each d, J=8.0 Hz, 3-H), 4.33, 4.27 (1H, each dd, J=7.3, 4.3 Hz, 5-H), 3.99, 3.98 (1H, each-s, 17-H), 3.65, 3.41 (1H, each s, 20-OH), 2.76, 2.60 (3H, each s, N_a-CH_3), 1.00, 0.97 (9H, each s, $SiBu^t$), 0.82, 0.76 (3H, each t, J=7.5 Hz, 18-CH_3), 0.17, 0.14, 0.13 (6H, each s, $SiMe_2$). MS m/z (%): 590 (M^+, 33), 402 (50), 287 (21), 144 (28), 91 (100).

Reduction of the aldehyde (81)

$NaBH_4$ (4 mg, 0.106 mmol) was added to a solution of (**81**) (66 mg, 0.112 mmol) in MeOH (2 ml) and the mixture was stirred at room temperature for 10 min. Acetone was added to the reaction mixture and stirring was continued for 10 min. After evaporation of the solvent, 1*N*-Na_2CO_3 was added to the mixture, and the whole was extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and evaporated. The residue was purified by open column chromatography (AcOEt-hexane, 1:1) to give 61 mg (92%) of (**82**) as an amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}: 3450, 2950, 1690, 1100, 850. UV λ_{max}^{EtOH} nm: 207, 248, 293. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 5.3~4.9 (2H, $CH_2C_6H_5$), 4.7~4.5 (1H, m, 3-H), 4.5~4.3 (1H, m, 5-H), 3.94 (1H, s, 17-H), 2.77, 2.67 (3H, each s, N_a-CH_3), 0.98, 0.97 (9H, each s, $SiBu^t$), 0.14, 0.13, 0.12 (6H, each s, $SiMe_2$). MS m/z (%): 502 (M^+, 27), 404 (29), 287 (26), 144 (27), 91 (100).

Hydrogenolysis of the carbamate (82)

Compound (**82**) (7.30 g, 12.35 mmol) in EtOH (120ml) and glacial AcOH (3 ml) was hydrogenated over 10% Pd/C (1.31 g) under 1 atm of hydrogen. After 22 h and 25 h 10% Pd/C (500 mg) was respectively added. The reaction was stopped after 27 h and the reaction mixture was filtered and concentrated. The mixture was diluted with 5% MeOH/$CHCl_3$ and the aqueous layer was basified with chilled ammonia water. After separation of the organic layer, the aqueous layer was extracted with 5% MeOH/$CHCl_3$. The combined organic

phase was dried over $MgSO_4$, and evaporated. The residue was purified by flash column chromatography (7% MeOH/$CHCl_3$) to give 4.65 g (82%) of (**83**) as an amorphous powder. IR ν_{max}^{CHCl3} cm-1: 3400 (br.), 2950, 2930, 1460, 1120, 830. UV λ_{max}^{EtOH} nm: 206, 247, 291. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.04 (1H, s, 17-H), 3.84 (1H, t-like, 5-H), 3.70 (1H, d, J=11.8 Hz, 21-H), 3.69 (1H, d, J=11.8 Hz, 21-H), 3.69 (1H, d, J=8.8 Hz, 3-H), 2.75 (3H, s, N_a-CH_3), 2.53 (1H, s, 2-H), 0.98 (9H, s, $SiBu^t$), 0.89 (3H, t, J=7.4 Hz, 18-CH_3), 0.14 (6H, s, $SiMe_2$). MS m/z (%): 458 (M^+, 12), 314 (100).

Preparation of (84) by mesylation

To a stirred solution of the diol (**83**) (3.96 g, 8.63 mmol) in dry CH_2Cl_2 (50 ml) and dry pyridine (50 ml), MsCl (0.70 ml, 9.04 mol) was added dropwise at 0 °C. The mixture was then stirred at room temperature for 3 h. Further MsCl (0.8 ml, 10.34 mmol) was added to the reaction mixture and stirring was continued at the same temperature for 2 h. The reaction mixture was concentrated under reduced pressure, diluted with $CHCl_3$, and then 5% $NaHCO_3$ solution was added. The organic layer was seperated and the aqueous layer was extracted several times with $CHCl_3$. The combined organic extract was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by flash column chromatography (5% MeOH/$CHCl_3$) to yield 2.87 g (76%) of (**84**) as an amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}: 3400 (br.), 2950, 1460, 1250, 1080, 840. UV λ_{max}^{MeOH} nm: 208, 246, 290. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.41 (1H,

s, 17-H), 3.39 (1H, d, J=9.9 Hz, 3-H), 3.03 (1H, t, J=4.4 Hz, 5-H), 2.88 (1H, d, J= 13.7 Hz, 21b-H), 2.71 (1H, d, J=13.7 Hz, 21a-H), 2.75 (3H, s, N_a-CH_3), 2.63 (1H, s, 2-H), 1.83 (1H, dq, J=14.5, 7.4 Hz, 19-H), 1.68 (1H, dq, J=14.5, 7.4 Hz, 19-H), 1.00 (3H, t, J=7.4 Hz, 18-CH_3), 0.98 (9H, s, $SiBu^t$), 0.16 (3H, s, SiMe), 0.14 (3H, s, SiMe). MS m/z (%): 440 (M^+, 73), 296 (100), 182 (45)

Desilylation of (84)

A solution of (84) (747 mg, 1.695 mmol) in CH_3CN (12 ml) and 48% aqueous HF solution (3 ml) was refluxed for 1 h. The mixture was concentrated, diluted with 5% MeOH/$CHCl_3$ and water, and then basified with chilled ammonia water. The white precipitate was filtered off and the filtrate was extracted several times with 5% MeOH/$CHCl_3$. The combined organic extract was washed with water, dried over $MgSO_4$, and evaporated, furnishing 483 mg (87%) of (**85**) as an amorphous powder which was used in the next reaction without purification. IR ν_{max}^{CHCl3} cm^{-1}: 3400 (br.), 2930, 1190, 1110, 1080. UV λ_{max}^{MeOH} nm: 203, 245, 291. ^{1}H-NMR (500 MHz, CD_3OD) δ: 4.42 (1H, s, 17-H), 3.40 (1H, d, J=9.8 Hz, 3-H), 3.07 (1H, t, J=4.9 Hz, 5-H), 2.82 (1H, d, J=13.5 Hz, 21-H), 2.65 (1H, d, J=13.5 Hz, 21-H), 2.75 (3H, s, N_a-CH_3), 2.62 (1H, s, 2-H), 1.87~ 1.67 (2H, m, 19-CH_2), 1.04 (3H, t, J=7.6 Hz, 18-CH_3). MS m/z (%): 327 (M^++1, 19), 326 (M^+, 61), 182 (100), 144 (29).

Preparation of the silyl ether (86)

To a stirred suspension of (**85**) (28 mg, 0.086 mmol) in dry pyridine (2 ml), trimethylsilyl chloride (TMSCl) (15.7 ml, 0.123 mmol) was added dropwise at 0 °C. The reaction was stirred at room temperature for 2 h. Further TMSCl (5.2 ml, 0.041 mmol) was added and stirring was continued for 30 min at the same temperature. Pyridine was removed under reduced pressure. The residue was diluted with $CHCl_3$, and washed with 5% $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$ and evaporated to give a residue (**86**) (32.6 mg, 95%), which was used in the next reaction without purification. UV λ_{max}^{MeOH} nm: 205, 248, 292. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 4.38 (1H, s, 17-H), 3.39 (1H, d, J=10.2 Hz, 3-H), 3.03 (1H, m, 5-H), 2.87 (1H, d, J= 13.8 Hz, 21-H), 2.67 (1H, d, J=13.8 Hz, 21-H), 2.75 (3H, s, N_a-CH_3), 1.00 (3H, t, J=7.3 Hz, 18-CH_3), 0.20 (9H, s, $SiMe_3$). MS m/z (%): 398 (M^+, 100), 254 (90), 144 (65).

Preparation of the disilyl ether (87)

A solution of (**86**) (93 mg, 0.233 mmol) in dry CH_2Cl_2 (2 ml) was stirred at 0 °C, and treated with Et_3N (80.4 ml, 0.577 mmol) and TBSOTf (80.4 ml, 0.350 mmol), followed by addition of 4-dimethylaminopyridine (3.6 mg, 0.03 mmol). The solution was stirred at room temperature for 1 h. Further TBSOTf (40.2 ml, 0.175 mmol) was added, and stirring was continued for 1 h at the same temperature. The mixture was diluted with $CHCl_3$, and then washed with 5% $NaHCO_3$ solution and water. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by flash column

chromatography (5% MeOH/$CHCl_3$) to afford 115 mg (96%) of (**87**) as an amorphous powder. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.38 (1H, s, 17-H), 3.38 (1H, d, J=10.2 Hz,3-H), 3.05 (1H, m, 5-H), 1.82 (1H, dq, J=14.6, 7.3 Hz, 19-H), 1.68 (1H, dq, J=14.6, 7.3 Hz,19-H), 1.00 (3H, t, J=7.3 Hz, 18-CH_3), 0.91 (9H, s, $SiBu^t$), 0.21 (9H, s, $SiMe_3$), 0.14 (3H, s, SiMe),0.11 (3H, s, SiMe).

Preparation of the indole (91)

To a stirred solution of (**87**) (52 mg, 0.101 mmol) in dry CH_2Cl_2 (1 ml) was added $Pb(OAc)_4$ (90%, 107.5 mg, 0.218 mmol) at -70 °C under the stream of nitrogen and the solution was stirred for 30 min (-70~ -5 °C). Further $Pb(OAc)_4$ (26.9 mg, 0.055 mmol) was added at -70 °C and stirring was continued (-70~ 0 °C) for 1.8 h. The reaction mixture was diluted with $CHCl_3$ and washed with 5% $NaHCO_3$ solution. The aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with water, dried over $MgSO_4$, and evaporated. The residue (36 mg) was dissolved in THF/H_2O (1:1, 0.5 ml) and acetic acid (0.5 ml) was added to the mixture at 0 °C. The reaction mixture was stirred at 0 °C. After 25 min, $NaCNBH_3$ (6.7 mg, 0.107 mmol) was introduced, and the mixture was stirred for additional 15 min at room temperature. The mixture was diluted with $CHCl_3$ and water, and basified with chilled ammonia water. The aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by MPLC (5% MeOH/$CHCl_3$) to give 9 mg (21%) of (**91**) as an amorphous

powder. UV λ_{max}^{MeOH} nm: 226, 279. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.94 (9H, s, $SiBu^t$), 0.19 (3H, s, SiMe), 0.13 (3H, s, SiMe). MS m/z (%): 426 (M^+, 39), 169 (100), 168 (92).

Preparation of the carbamate (92)

A stirred solution of (**91**) (25.8 mg, 0.061 mmol) in THF (2.0 ml) and water (0.5 ml) was treated with $ClCO_2CH_2CCl_3$ (12.5 ml, 0.091 mmol) and MgO (72.5 mg, 1.815 mmol) at 0 °C. Further $ClCOOCH_2CCl_3$ was added in a following manner: 30 min, 25 ml (0.182 mmol); 1.5 h, 38 ml (0.276 mmol); 2 h, 25 ml (0.182 mmol). The reaction mixture was stirred at room temperature for totally 2.5 h. The reaction mixture was filtered and the filtrate was added 5% $NaHCO_3$ solution. The whole was extracted with $CHCl_3$. The organic extract was washed with water, dried over $MgSO_4$ and evaporated. The residue was purified by MPLC (AcOEt-hexane, 1:4~ 1:1) to yield 26 mg (71%) of (**92**) accompanied with 4.5 mg (17%) of the starting material (**91**). (**92**): amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}: 3450, 2950, 2920, 1710, 1090, 840. UV λ_{max}^{EtOH} nm: 223, 284. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.00, 7.98 (1H, each s, N_a-H), 5.24, 5.23 (1H, each d, J=9.9 Hz, 3-H), 5.01, 4.92 (1H, each d, J=12.1 Hz, $C\underline{H_a}H_bCCl_3$), 4.66, 4.65 (1H, each d, J=12.1 Hz, $CH_a\underline{H_b}CCl_3$), 4.52 (1H, m, 5-H), 3.94, 3.91 (1H, each d, J=14.0 Hz, 21-H), 3.37, 3.33 (1H, each d, J=14.0 Hz, 21-H), 1.95 (1H, m, 19-H), 1.65 (1H, m, 19-H), 0.963, 0.957 (3H, each t, J=7.4 Hz, 18-CH_3), 0.895, 0.891 (9H, each s, $SiBu^t$), 0.17, 0.143, (3H, each s,

SiMe), 0.135, 0.99 (3H, each s, SiMe). MS m/z (%): 602 (M^++2, 52), 600 (M^+, 52), 156 (100)

Oxidation of the indole derivative (92)

To a stirred solution of (**92**) (12 mg, 0.020 mmol) in dry THF (0.4 ml) and dry pyridine (0.4 ml) was added OsO_4 (6.0 mg, 0.024 mmol) at 0 °C and the mixture was stirred at room temperature for 2 h. Aqueous $NaHSO_3$ solution (21 mg in 0.8 ml H_2O) was added and the mixture was stirred for 1 h at room temperature and 1 h at 65 °C. The reaction mixture was diluted with water and the whole was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by MPLC (AcOEt-hexane, 1:4) to afford 9.0 mg (73%) of (**96**) as an amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}: 3440, 2950, 2930, 1700, 1120, 840. UV λ_{max}^{EtOH} nm: 207, 251. ^{1}H-NMR (500 MHz, $CDCl_3$) (selected data of a main rotamer) δ: 7.50 (s, N_a-H), 4.90 (d, J=11.8 Hz, $C\underline{H}_aH_bCCl_3$), 4.57 (d, J=12.1 Hz, $CH_a\underline{H}_bCCl_3$), 4.20 (d, J=11.0 Hz, 17α-H), 1.90 (dq, J=14.8, 7.4 Hz, 19-H), 1.62 (dq, J=14.8, 7.4 Hz, 19-H), 0.94 (t, J= 7.4 Hz, 18-CH_3). MS m/z (%): 618 (M^++2, 1.8), 616 (M^+, 1.9), 561 (61), 559 (59), 146 (100)

N_b-deprotection of (96)

To a solution of (**96**) (9 mg, 0.0146 mmol) in acetic acid (0.6 ml) was added zinc dust in a following manner: 0 min, 19mg; 13 h, 19 mg; 15 h, 19 mg. The reaction mixture was stirred at room temperature for totally 17 h. The mixture was filtered. The filtrate was basified with chilled ammonia water. The whole was extracted with 2%

MeOH/$CHCl_3$. The organic extract was dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography (20% MeOH/$CHCl_3$) to give 5.3 mg (82%) of (**97**) accompanied with 0.5 mg (6%) of the starting material (**96**). (**97**): amorphous powder. UV λ_{max}^{EtOH} nm: 207, 252. ^{1}H-NMR (500MHz, $CDCl_3$) δ: 8.0 (1H, br s, N_a-H), 4.26 (1H, d, J=10.6 Hz, 17_a-H), 3.96 (1H, dd, J=10.8, 4.8 Hz, 17_b-H), 3.70 (1H, d, J=8.5 Hz, 3-H), 3.67 (1H, m, 5-H), 3.29 (1H, d, J=14.3 Hz, 21-H), 2.66 (1H, d, J=14.3 Hz, 21-H), 0.96 (3H, t, J=7.3 Hz, 18-CH_3), 0.90 (9H, s, $SiBu^t$), 0.28 (3H, s, SiMe), 0.14 (3H, s, SiMe). MS m/z (%): 442 (M^+, 7), 413 (62), 310 (100). CD (c=0.178 mmol/l, 23 °C): $[\theta]_{228}$+67000, $[\theta]_{255}$–29000, $[\theta]_{283}$–6000.

Desilylation of (97)

To a solution of (**97**) (4 mg, 0.009 mmol) in CH_3CN (0.5 ml), 48% aqueous HF solution was added dropwise at 0 °C. The reaction mixture was stirred for 30 h at room temperature and 18.5 h at 50~ 80 °C. The mixture was diluted with $CHCl_3$ and then basified with chilled ammonia water. After separation of organic layer, the aqueous layer was extracted with 3% MeOH/$CHCl_3$. The combined organic phase was dried over $MgSO_4$, and evaporated. The residue was purified by preparative TLC (15% MeOH/$CHCl_3$-NH_3) to give 1.5 mg (51%) of N_a-demethoxy-20(*R*)-hydroxy-dihydrorankinidine (**98**) and 1.0 mg (25%) of the starting material (**97**). (**98**): amorphous powder. UV λ_{max}^{EtOH} nm: 207, 251. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.6 (1H, br s, N_a-H), 4.28 (1H, d, J=10.4 Hz, 17_α-H), 3.98 (1H, dd, J= 10.4, 4.1 Hz, 17_β-

H), 3.70 (1H, d, J=7.7 Hz, 3-H), 3.58 (1H, m, 5-H), 3.04 (1H, d, J=13.5 Hz, 21-H), 2.68 (1H, d, J=15.8 Hz, 21-H), 1.9 (2H, br s, OH+ N_b-H), 1.01 (3H, t, J=7.3 Hz, 18-CH_3). Exact MS Calcd for $C_{19}H_{24}N_2O_3$: 328.1785. Found: 328.1799.

Hydrogenolysis of the carbamate (80)

Compound (**80**) (108 mg, 0.157 mmol) in EtOH (3 ml) was hydrogenated over 10 % Pd/C (100 mg) under 1 atm of hydrogen. After 2.5 h additional 10% Pd/C (100 mg) was added and the reaction was continued for 4 h. The catalyst was filtered off and the filtrate was concentrated. The residue was purified by MPLC (AcOEt- hexane, 1:6) to yield 36 mg (41%) of (**99**) and 5.7 mg (5%) of the starting material (**80**). (**99**) : amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}: 3300 (br s), 2950, 2930, 1460, 1250, 1160, 840. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.42 (1H, s, 21-H), 4.01 (1H, s, 17-H), 3.44 (1H, d, J=8.3 Hz, 3-H), 3.36 (1H, dd, J=16.8, 4.4 Hz, 5-H), 2.72 (3H, s, N_a-CH_3), 2.41 (1H, s, 2-H), 1.02 (3H, t, J=7.7 Hz, 18-CH_3). MS m/z (%): 554 (M^+, 17), 278 (60), 198 (100), 73 (58).

Osmylation of the silyl enol ether (99)

To a stirred solution of (**99**) (22.5 mg, 0.041 mmol) in dry THF (0.5 ml) and dry pyridine (0.5 ml) was added OsO_4 (11.2 mg, 0.044 mmol) at 0 °C and the reaction mixture was stirred at the same temperature for 30 min. Aqueous $NaHSO_3$ solution (42 mg in 1.0 ml H_2O) was added and the mixture was stirred for 1.5 h at room temperature. The mixture was diluted with $CHCl_3$ then 5% $NaHCO_3$ solution was added. After separation of the organic layer, the aqueous

layer was extracted with 5% MeOH/$CHCl_3$. The combined organic extract was dried over $MgSO_4$ and evaporated. The residue was purified by MPLC (10% MeOH/$CHCl_3$) to give 13 mg (70%) of (**100**) as an amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}: 3400 (br s), 2950, 1620, 1470, 1100, 840. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.37 (1H, s, 17-H), 2.77 (3H, s, N_a-CH_3), 0.96 (9H, s, $SiBu^t$), 0.16 (3H, s, SiMe), 0.14 (3H, s, SiMe). MS m/z (%): 456 (M^+, 17), 455 (18), 312 (67), 145 (100).

Acetylation of the diol (100)

A solution of (**100**) (11 mg, 0.024 mmol) and Ac_2O (68 ml, 0.722 mmol) in dry pyridine (0.5 ml) was stirred at the room temperature for 22 h. A residue obtained by the usual work up manner was purified by MPLC (AcOEt-hexane, 1:1) to afford 7 mg (54%) of (**101**) as an amorphous powder. UV λ_{max} EtOH nm: 206, 249, 289. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.57 (1H, s, 21-H), 4.40 (1H, s, 17-H), 3.62 (1H, d, J=9.9 Hz, 3-H), 3.46 (1H, t, J=6.1 Hz, 5-H), 2.74 (3H, s, N_a-CH_3), 2.64 (1H, s, 2-H), 2.10 (3H, s, OCH_3), 2.04 (3H, s, OCH_3), 0.94 (9H, s, $SiBu^t$), 0.93 (3H, t, J=7.4 Hz, 18-CH_3), 0.17 (3H, s, SiMe), 0.16 (3H, s, SiMe). MS m/z (%): 541 (M^+, 73), 456 (29), 455 (86), 428 (32), 427 (100).

Bromination of the silyl enol ether (80)

A solution of *N*-bromosuccinimide (NBS) (65 mg, 0.365 mmol) in dry THF (2.5 ml) was added dropwise to a solution of (**80**) (227 mg, 0.329 mmol) in dry THF (2.5 ml) at -22 °C and the mixture was stirred at the same temperature for 20 h. Saturated aqueous ammonium chloride solution was added and the whole was extracted with $CHCl_3$. The

organic layer was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by MPLC (AcOEt-hexane, 1:4) to yield 167 mg (78%) of (**102**) as an amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}: 1720, 1690, 1090, 840. UV λ_{max}^{EtOH} nm: 208, 248, 291. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 9.38 (d, J=0.9 Hz) and 9.31 (d, J=0.6 Hz) (1H, 21-H). MS m/z (%): 654 (M^++2, 3), 652 (M^+, 2), 386 (20) 144 (25), 91 (100).

Reduction of the aldehyde (102)

$NaBH_4$ (16.9 mg, 0.448 mmol) was added to a solution of (**102**) (266 mg, 0.407 mmol) in MeOH (6 ml) at 0 °C, and the reaction mixture was stirred at the same temperature for 30 min. Acetone was added to the mixture and stirring was continued for 10 min. Solvent was evaporated, and then $CHCl_3$ and 5% $NaHCO_3$ solution were added to the residue. The whole was extracted with $CHCl_3$. The combined organic layer was washed with water, dried over $MgSO_4$. The residue was purified by flash column chromatograghy (AcOEt-hexane, 1:2) to give 201 mg (75%) of (**103**) as an amorphous powder (unstable). IR ν_{max}^{CHCl3} cm^{-1}: 2970, 1700, 1440, 1090, 840. UV λ_{max}^{EtOH} nm: 249, 292. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.23, 5.18 (1H, each d, J=12.4 Hz, $C\underline{H_a}H_bC_6H_5$), 5.15, 4.98 (1H, each d, J=12.5 Hz, $CH_a\underline{H_b}C_6H_5$). FABMS, in m-nitrobenzylalcohol-thioglycerol m/z (%): 657 (MH^++2, 76), 656 (72), 655 (MH^+, 89), 575 (100), 574 (73).

Preparation of the olefin (104)

Zine dust (115 mg) was added to a solution of (**103**) in MeOH (1 ml). The mixture was stirred at room temperature for 1.5 h, and then

filtered. The filtrate was basified with 5% $NaHCO_3$ solution and the whole was extracted with $CHCl_3$. The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by MPLC (AcOEt-hexane, 1:6) to give 30 mg (80%) of (**104**) as an amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}: 2960, 1960, 1090, 840. UV λ_{max} EtOH nm: 204, 247, 292. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 5.17, 4.98 (each d, J=12.2 Hz) and 5.15 (s) (2H, $C\underline{H_2}C_6H_5$), 4.80 (1H, br.s, 21-H_a), 4.69 (1H, br.s, 21-H_b), 4.69, 4.60 (1H, each d, J=8.5 Hz, 3-H), 4.42, 4.37 (1H, each dd, J=7.3, 4.0 Hz, 5-H), 4.03 (1H, each t, J=1.3 Hz, 17-H), 2.78, 2.67 (3H, each s, N_a-CH_3), 1.05, 1.03 (3H, each t, J=7.3 Hz, 18-CH_3), 0.99, 0.98 (9H, each s, $SiBu^t$), 0.15, 0.14 (6H, each s, $SiMe_2$). MS m/z (%): 558 (M^+, 2), 370 (13), 144 (19), 91 (100).

Oxidation of (104)

OsO_4 (8.8 mg, 0.035 mmol) was added to a stirred solution of (**104**) (21 mg, 0.038 mmol) in dry pyridine-THF (1:1, 1 ml) at 0 °C, and the mixture was stirred at the same temperature for 45 min. Aqueous $NaHSO_3$ solution (78 mg in H_2O 1 ml) was added to the reaction mixture, and stirring was continued at room temperature for 2 h. 5% $NaHCO_3$ solution was added to the mixture, and the whole was extracted with $CHCl_3$. The organic layer was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by MPLC (AcOEt-hexane, 1:2) to yield 16 mg (72%) of (**82**). (**82**) obtained by this reaction was identical with the compound derived from (**81**) by the comparison of their ^{1}H-NMR spectra (400 MHz).

Preparation of the acetal (105)

To a stirred solution of (**79**) (682 mg, 1.48 mmol) and 1,3 propanediol (1.1 ml, 15.2 mmol) in dry benzene (14 ml) was added p-toluenesulfonic acid monohydrate (84.5 mg, 0.44 mmol) and the reaction mixture was refluxed for 1 h. The residue obtained by the evaporation of benzene was diluted with $CHCl_3$ and the mixture was basified with 5% $NaHCO_3$ solution. The aqueous layer was extracted with $CHCl_3$. The combined organic extract was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by flash column chromatography (3% MeOH/$CHCl_3$) to give 767 mg (100%) of (**105**) as an amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}: 2900, 1690, 1430, 1105. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.25, 5.20 (1H, each d, J=12.6 Hz, $C\underline{H_a}H_bC_6H_5$), 5.12, 5.02 (1H, each d, J=12.6 Hz, $CH_a\underline{H_b}C_6H_5$), 4.64, 4.59 (1H, each d, J=9.7 Hz, 3-H), 4.62, 4.59 (1H, each d, J=2.0 Hz, 21-H), 4.55~ 4.50 (1H, m, 5-H), 2.77, 2.64 (3H, each s, N_a-CH_3), 2.45, 2.38 (1H, each s, 2-H), 0.91, 0.87 (3H, each t, J=7.5 Hz, 18-CH_3). MS m/z (%): 519 (18), 518 (M^+, 45), 91 (100). Exact MS calcd for $C_{31}H_{38}O_5N_2$: 518.2781. Found 518.2780.

O-silylation of (105)

Et_3N (8.3 ml, 0.0597 mol) and TMSCl (6.1 ml, 0.0477 mol) were added dropwise to a stirred solution of (**105**) (20.6 g, 0.0397 mol) at 0 °C. The mixture was stirred at the same temperature for 1 h and at room temperature for 2.5 h. Further Et_3N (6.0 ml, 0.0431 mol) and TMSCl (6.1 ml, 0.0477 mol) were added dropwise to the reaction mixture at 0

°C, and stirring was continued for 1 h. The reaction mixture was diluted with $CHCl_3$ and washed with 5% $NaHCO_3$ solution. The aqueous layer was extracted with $CHCl_3$ and the combined organic extract was washed with water and dried over $MgSO_4$. The residue was purified by flash column chromatograpy (AcOEt-hexane, 1:4) to yield 22.7 g (97%) of (**106**) as an amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}: 2900, 1690, 1430, 1110, 1080, 840. UV λ_{max}^{EtOH} nm: 248, 292. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.23, 5.19 (1H, each d, J=12.7 Hz, $CH_{\underline{a}}H_bC_6H_5$), 5.12, 5.02 (1H, each d, J=12.7 Hz, $CH_a\underline{H_b}C_6H_5$), 4.64, 4.55 (1H, each d, J=8.6 Hz, 3-H), 4.63, 4.60 (1H, each d, J=1.4 Hz, 21-H), 4.49 (1H, dd, J=7.4, 4.4 Hz, 5-H), 3.96, 3.94 (1H, each s, 17-H), 2.76, 2.64 (3H, each s, N_a-CH_3), 2.43, 2.37 (1H, each s, 2-H), 0.92, 0.87 (3H, each t, J=7.5 Hz, 18-CH_3), 0.201, 0.196 (9H, each s, $SiMe_3$). MS m/z (%): 590 (M^+, 41), 446 (66), 91 (100). Exact MS calcd for $C_{34}H_{46}O_5N_2Si$: 590.3176. Found 590.3171.

Lead tetraacetate oxidation of the indoline (106)

To a stirred solution of (**106**) (709 mg, 1.20 mmol) in dry CH_2Cl_2 (16 ml) was added $Pb(OAc)_4$ (90%, 2.01 g, 4. 08 mmol) at -70 °C under the stream of nitrogen and the solution was stirred for 1 h (-70~ -60 °C). Further $Pb(OAc)_4$ (1.34 g, 2.72 mmol) was added at -70°C and stirring was continued for 2 h (-70~ -10 °C). The reaction mixture was diluted with $CHCl_3$ and washed with 5% $NaHCO_3$ solution. The aqueous layer was extracted with $CHCl_3$. The combined organic layer was washed with water, dried over $MgSO_4$, and evaporated. The

residue was purified by flash column chromatography (AcOEt-hexane, 1:3) to afford 522 mg (76%) of (**107**) as an amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}: 2910, 1690, 1110, 840. UV λ_{max}^{EtOH} nm: 209, 256. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.31, 5.25 (1H, each d, J=8.8 Hz, 3-H), 5.22, 5.16 (1H, each d, J=12.4 Hz, $CH_aH_bC_6H_5$), 5.06, 5.03 (1H, each d, J=12.4 Hz, $CH_aH_bC_6H_5$), 4.94 (1H, t-like, 5-H), 4.64, 4.60 (1H, each s, 21-H), 3.55, 3.53 (1H, each s, 17-H), 0.87, 0.86 (3H, each t, J=7.4 Hz, 18-CH_3), 0.00, -0.01 (9H, each s, $SiMe_3$). MS m/z (%): 574 (M^+, 42), 91 (100).

Preparation of the indole (109)

A solution of (**107**) (522 mg, 0.908 mmol) in AcOH/THF/H_2O (3:1:1, 10 ml) was stirred at 0 °C for 50 min. $NaCNBH_3$ (57 mg, 0.908 mmol) was added to the solution and stirring was continued at the same temperature for 30 min. The reaction mixture was diluted with water and basified with chilled ammonia water and the whole was extracted with $CHCl_3$. The organic layer was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by flash column chromatography (AcOEt-hexane, 2:3) to give 376 mg (82%) of (**109**) as an amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}: 3460, 1690, 1110. UV λ_{max}^{EtOH} nm: 226, 281. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.85, 7.68 (1H, each s, N_a-H), 5.44, 5.33 (1H, each s, 3-H), 5.17, 5.07 (1H, each d, J=12.4 Hz) and 5.16 (1H, s) $CH_2C_6H_5$, 4.89, 4.82 (1H, each t, J=~5 Hz, 5-H), 4.304, 4.297 (1H, each s, 21-H), 0.93 (3H, t, J=7.4 Hz, 18-CH_3). MS

m/z (%): 504 (M^+, 60), 91 (100), 87 (90). Exact MS calcd for $C_{30}H_{36}O_5N_2$: 504.2624. Found 504.2618.

O-benzoylation of (109)

To a stirred solution of (**109**) (1.263 g, 2.50 mmol) in dry CH_2Cl_2/pyridine (1:1, 25 ml), benzoyl chloride (0.58 ml, 5.00 mmol) was added dropwise at 0 °C. The mixture was stirred at room temperature for 1.2 h. The reaction mixture was basified with chilled saturated $NaHCO_3$ solution and the whole was extracted with $CHCl_3$. The combined organic layer was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by flash column chromatography (AcOEt-hexane, 1:8) to give 1.393 g (91%) of (**110**) as an amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}: 3450, 1680, 1270, 1100. UV λ_{max}^{EtOH} nm: 226, 274. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 8.0~ 7.1(14 H, m, arm-H). MS m/z (%): 608 (M^+, 54), 169 (27), 105 (35), 91 (100). Exact MS calcd for $C_{37}H_{40}O_6N_2$: 608.2887. Found 608.2888.

Hydrolysis of the acetal (110)

The solution of (**110**) (1.383 g, 2.27 mmol) in 80% AcOH/H_2O (30 ml) was stirred at 75 °C for 1.5 h. The mixture was diluted with H_2O and $CHCl_3$, and then basified with chilled ammonia water. Layers were seperated and the aqueous layer was extracted with $CHCl_3$. The combined organic extract was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by flash column chromatograghy (0.5% MeOH/$CHCl_3$) to yield 1.200 g (96%) of (**111**) as an amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}: 3450, 1720, 1690, 1270,

1100. UV λ_{max}^{EtOH} nm: 226, 274. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.36, 9.33 (1H, each s, 21-H). MS m/z (%): 550 (M^+, 42), 105 (80), 91 (100). Exact MS calcd for $C_{34}H_{34}O_5N_2$: 550.2468. Found 550.2466.

N_a-tosylation of the indole (111)

To a stirred solution of (**111**) (170 mg, 0.309 mmol) in benzene (4 ml) and 50% KOH solution (2 ml), n-Bu_4NHSO_4 (21.0 mg, 0.062 mmol) and p-$CH_3C_6H_4SO_2Cl$ (117.8 mg, 0.618 mmol) were added. The resulting mixture was vigorously stirred at room temperature for 1 h. The mixture was diluted with water and the whole was extracted with $CHCl_3$. The organic extract was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified with MPLC (AcOEt-hexane, 1:4) to afford 177 mg (81%) of (**112**) as an amorphous powder (diastereomeric mixture). IR ν_{max}^{CHCl3} cm^{-1}: 2960, 1720, 1690, 1280, 1180, 1110. UV λ_{max}^{EtOH} nm: 223. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.71, 9.54, 9.46, 9.42 (1H, each d, CHO), 8.0~ 6.8 (18H, m, arm-H), 6.28, 6.24, 6.18, 6.14 (1H, each br. s, 3-H), 5.26~ 5.12 (2H, m, $C\underline{H_2}C_6H_5$), 5.03, 4.95, 4.92, 4.85 (1H, each t-like, 5-H), 2.30, 2.21 (3H, each s, $C_6H_4C\underline{H_3}$). MS m/z (%): 704 (M^+, 11), 105 (35), 91 (100).

Preparation of the silyl enol ether (113)

TBSOTf (170.8 ml, 0.742 mmol) was added to a solution of (**112**) (131 mg, 0.186 mmol) and Et_3N (155.2 ml, 1.116 mmol) in dry CH_2Cl_2 (4 ml) at 0 °C and the mixture was refluxed for 2 h. Further TBSOTf (50.0 ml, 0.218 mmol) was added to the reaction mixture at 0 °C and the mixture was heated at reflux for 1 h. $CHCl_3$ and 5% $NaHCO_3$

solution were added to the mixture. After separation of the organic layer, the aqueous layer was extracted with $CHCl_3$. The combined organic phase was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by MPLC (AcOEt-hexane, 1:7) to give 125 mg (82%) of (**113**) as an amorphous powder (diastereomeric mixture). IR ν_{max}^{CHCl3} cm^{-1}: 2950, 2930, 1690, 1280, 1180, 840. UV λ_{max}^{EtOH} nm: 257. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.26, 6.16 (1H, each br.s, 3-H), 6.16, 6.02 (1H, each s, 21-H), 5.27~ 5.15 (2H, m, $C\underline{H_2}C_6H_5$), 5.05, 4.95 (1H, each s, 5-H), 2.30, 2.29, 2.20, 2.19 (3H, each s, $C_6H_4C\underline{H_3}$), 1.00 (3H, t, J=7.3 Hz, 18-CH_3), 0.84, 0.45 (9H, each s, $SiBu^t$), -0.01, -0.03, -0.17 (6H, each s, $SiMe_2$). FABMS, in *m*-nitrobenzylalcohol-thioglycerol m/z (%): 819 (MH^+, 8), 664 (78), 91 (100).

Osmylation of the silyl enol ether (113)

To a stirred solution of (**113**) (63.3 mg, 0.077 mmol) in dry THF (1 ml) and dry pyridine (1 ml) was added OsO_4 (21.6 mg, 0.085 mmol) at -10 °C and the reaction temperature was gradually raised to 5 °C over 2 h. Aqueous $NaHSO_3$ solution (161 mg in 2 ml H_2O) was added and the mixture was stirred at room temperature for 17 h. The reaction mixture was diluted with $CHCl_3$ and washed successively with 5% $NaHCO_3$ solution and water. The organic layer was dried over $MgSO_4$, and evaporated to give a residue, which was purified by MPLC (AcOEt-hexane, 1:4) to yield 24.8 mg (44.5%) of (**114**) and 12.4 mg (22.2%) of (**115**) accompanied with 4.7 mg (7.4%) of the starting material. (**114**): colorless prisms, mp 108-110 °C (from benzene). IR

ν_{max}^{CHCl3} cm^{-1}: 1720, 1690, 1270, 1170, 1110. UV λ_{max}^{MeOH} nm: 223. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.69, 9.66 (1H, each s, CHO), 6.29, 6.18 (1H, each s, 3-H), 5.24, 5.16 (1H, each d, J=12.6 Hz, $C\underline{H_a}H_bC_6H_5$), 5.19, 5.11 (1H, each d, J=12.6 Hz, $CH_a\underline{H_b}C_6H_5$), 5.03, 4.94 (1H, each t, J=5.5 Hz, 5-H), 4.63, 4.61 (1H, each dd, J=8.0, 4.7, 17-H), 4.32, 4.28 (1H, each-dd, J=11.9, 10.1, 17-H), 2.31, 2.21 (3H, each s, $C_6H_4C\underline{H_3}$), 0.66 (3H, m, 18-CH_3). MS m/z (%): 720 (M^+, 5), 168 (15), 105 (36), 91 (100). Anal. Calcd for $C_{41}H_{40}N_2O_8S$: C, 68.32; H, 5.59; N, 3.87. Found: C, 68.38; H, 5.68; N, 3.70. (**115**): amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}: 1720, 1690, 1270, 1170, 1110. UV λ_{max}^{EtOH} nm: 223. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 9.33, 9.29 (1H, each s, CHO), 6.30, 6.20 (1H, each br.s, 3-H), 5.24, 5.17 (1H, each d, J=12.7 Hz, $C\underline{H_a}H_bC_6H_5$), 5.21, 5.13 (1H, each d, J=12.7 Hz, $CH_a\underline{H_b}C_6H_5$), 4.90, 4.81 (1H, each t, J=5.4 Hz, 5-H), 2.31, 2.21 (3H, each s, $C_6H_4C\underline{H_3}$), 1.70 (1H, m, 19-H), 1.55 (1H, m, 19-H), 0.67, 0.66 (3H, each t, J=7.4 Hz, 18-CH_3). MS m/z (%): 720 (M^+, 2.3), 168 (14), 105 (26), 91 (100).

Reduction of the aldehyde (114)

To a stirred solution of (**114**) (16 mg, 0.022 mmol) in MeOH (0.5 ml) was added $NaBH_4$ (0.9 mg, 0.024 mmol) at 0 °C and the mixture was stirred at the same temperature for 30 min. The reaction was diluted with $CHCl_3$ and washed with 5% $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was purified by MPLC (AcOEt-hexane, 1:1) to yield 13.2 mg (83%) of (**116**) as an amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}: 1700,

1280, 1180, 1120. UV λ_{max}^{EtOH} nm: 223. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.22, 6.12 (1H, each s, 3-H), 5.24~ 5.06 (3H, $C\underline{H_2}C_6H_5$+17-H), 5.04, 4.96 (1H, each t, J=5.7 Hz, 5-H), 4.25, 4.21 (1H, each dd, J=12.1, 11.0 Hz, 17-H), 3.84 (1H, br.d, 21-H), 3.54, 3.53 (1H, each d, J=10.0 Hz, 21-H), 2.31, 2.23 (3H, each s, $C_6H_4C\underline{H_3}$), 0.59 (3H, t, J=7.2 Hz, 18-CH_3). FABMS, in thioglycerol-glycerol m/z (%): 723 (MH^+, 36), 185 (100).

Mesylation of the diol (116)

To a stirred solution of the diol (**116**) (4.21 g, 5.82 mmol) in dry pyridine (80 ml), MsCl (0.63 ml, 8.15 mmol) was added dropwise at 0 °C. The mixture was then stirred at room temperature for 45 min. The reaction mixture was concentrated under reduced pressure, diluted with $CHCl_3$, then 5% $NaHCO_3$ solution was added. Layers were seperated and the aqueous layer was extracted several times with $CHCl_3$. The combined organic extract was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by flash column chromatography (MeOH-$CHCl_3$-hexane, 1:9:10) to yield 4.66 g (100%) of (**117**) as an amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}: 2920, 1695, 1170. UV λ_{max}^{MeOH} nm: 223. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 3.12 (3H, s, SO_2CH_3), 2.31, 2.20 (3H, each s, $C_6H_4C\underline{H_3}$), 0.62 (3H, t, J=7.3 Hz, 18-CH_3). FABMS, in thioglycerol-glycerol m/z (%): 801 (MH^+, 7.5), 185 (100)

Hydrogenolysis of the carbamate (117)

Compound (**117**) (110 mg, 0.137 mmol) in EtOH (3.0 ml) and glacial AcOH (0.3 ml) was hydrogenated over 10% Pd/C (150 mg)

under 1 atm of hydrogen for 4 h. The reaction mixture was filtered and the filtrate was evaporated to give a residue, which was dissolved in CH_2Cl_2 (3.0 ml). Water (1ml) and chilled ammonia water (1 ml) were added to the CH_2Cl_2 solution and the mixture was stirred for 20 h at room temperature. The reaction mixture was extracted with $CHCl_3$. The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by MPLC (AcOEt-hexane, 13:2) to afford 57 mg (73%) of (**118**) as an amorphous powder accompanied with 14 mg (13%) of the starting material. IR ν_{max}^{CHCl3} cm^{-1}: 2930, 1720, 1280, 1180. UV λ_{max}^{EtOH} nm: 223. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.47 (1H, d, J=7.6 Hz, 3-H), 4.16 (1H, dd, J=11.0, 7.6 Hz, 17-H), 4.03 (1H, dd, J=11.3, 7.3 Hz, 17-H), 3.74 (1H, dd, J=9.8, 4.0 Hz, 5-H), 2.30 (3H, s, $C_6H_4C\underline{H_3}$), 1.89 (1H, dq, J=14.7, 7.4 Hz, 19-H), 1.75 (1H, dq, J=14.7, 7.4 Hz, 19-H), 1.01 (3H, t, J=7.4 Hz, 18-CH_3). MS m/z (%): 570 (M^+, 12), 449 (53), 415 (100), 168 (70). Exact MS calcd for $C_{33}H_{34}O_5N_2S$: 570.2189. Found 570.2203.

Reduction of aldehyde (115)

To a stirred solution of (**115**) (18 mg, 0.25 mmol) in MeOH (0.5 ml) was added $NaBH_4$ (1.1 mg, 0.029 mmol) at 0 °C and the mixture was stirred at the same temperature for 30 min. The reaction was diluted with $CHCl_3$ and washed with 5% $NaHCO_3$ solution. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was purified by MPLC (AcOEt-hexane, 1:2) to afford 16.5 mg (91%) of (**119**) as an amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}: 2930,

1695, 1450, 1280, 1170, 1110. UV λ_{max}^{EtOH} nm: 223. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.23, 6.13 (1H, each s, 3-H), 5.23, 5.15 (1H, J=12.6 Hz, $C\underline{H}_aCH_bC_6H_5$), 5.18, 5.10 (1H, J=12.6 Hz, $CH_aC\underline{H}_bC_6H_5$), 5.07, 4.99 (1H, each t, J=4.5 Hz, 5-H), 4.99, 4.94 (1H, each dd, J=12.6, 4.7 Hz, 17-H), 4.27, 4.21 (1H, each t, J=12.2 Hz, 17-H), 3.93, 3.90 (1H, each d, J=9.3 Hz, 21-H), 3.66, 3.60 (1H, each d, J=9.3 Hz, 21-H), 2.31, 2.21 (3H, each s, $C_6H_4C\underline{H}_3$), 0.95, 0.94 (3H, each t-like, 18-CH_3). FABMS, in *m*-nitrobenzylalcohol-glycerol m/z (%): 723 (MH^+, 50), 185 (100).

Mesylation of the diol (119)

MsCl (0.48 ml, 6.23 mmol) was added dropwise to a stirred solution of the diol (**119**) (2.81 g, 2.89 mmol) in dry pyridine (60 ml) at 0 °C. The mixture was then stirred at room temperature for 1.3 h. The reaction mixture was concentrated under reduced pressure, diluted with $CHCl_3$, and then 5% $NaHCO_3$ solution was added. Layers were seperated and the aqueous layer was extracted several times with $CHCl_3$. The combined organic extract was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by flash column chromatography (MeOH-$CHCl_3$-hexane, 1:9:10) to yield 3.12 g (100%) of (**120**) as an amorphous powder. IR ν_{max}^{CHCl3} cm-1: 2930, 1695, 1170. UV λ_{max}^{MeOH} nm: 223. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 2.76 (3H, s, SO_2CH_3), FABMS, in thioglycerol-glycerol m/z (%): 801 (MH^+, 26), 185 (100)

Hydrogenolysis of the carbamate (120)

Compound (**120**) (3.12 g, 3.89 mmol) in EtOH (100 ml) and glacial AcOH (10 ml) was hydrogenated over 10% Pd/C (2 g) under 1 atm of hydrogen. After 18 h and 22 h 10% Pd/C (1 g) was respectively added and the reaction was continued for totally 23.5 h. The reaction mixture was filtered and concentrated. The mixture was diluted with $CHCl_3$ (60 ml), water (30 ml) and basified with ammonia water (30 ml). The resulting mixture was stirred for 13 h. Layers were separated and the aqueous layer was extracted several times with $CHCl_3$. The combined organic extract was washed with water, dried over $MgSO_4$, and evaporated to give a residue, which was purified by flash column chromatography (MeOH-$CHCl_3$-hexane, 1:4:5) to afford 1.79 g (80%) of (**121**). IR ν_{max}^{CHCl3} cm^{-1}: 2930, 1720, 1280, 1180. UV λ_{max} EtOH nm: 224. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.65 (1H, dd, J=10.0, 4.0 Hz, 3-H), 4.28 (1H, dd, J=10.9, 7.0 Hz, 17-H), 3.95 (1H, dd, J=11.0, 8.5 Hz, 17-H), 3.50~ 3.45 (1H, m, 5-H), 3.05 (2H, s, 21-CH_2), 2.31 (3H, s, $C_6H_4C\underline{H_3}$), 1.85~ 1.75 (2H, m, 19-CH_2), 0.97 (3H, t, J=7.4 Hz, 18-CH_3). FABMS, in *m*-nitrobenzylalcohol m/z (%): 571 (MH^+, 100), 449 (19), 415 (36), 154 (41).

Preparation of the diol (122)

To a solution of (**118**) (530 mg, 0.929 mmol) in MeOH (18 ml) was added KOH (1.77 g, 31.55 mmol) at room temperature. The reaction mixture was heated at reflux for 3.5 h, cooled to room temperature, and then diluted with MeOH. CO_2 gas was passed through the mixture for 30 min. MeOH was evaporated, and then 10%

MeOH/$CHCl_3$ was added to the dry residue. The resulting mixture was filtered, the filtrate was concentrated and passed through open column chromatography (20% MeOH/$CHCl_3$). The main fraction was further purified by MPLC (15% MeOH/$CHCl_3$) to yield 279 mg (96%) of (**122**). (**122**): colorless needles, mp 220-222 °C (from AcOEt-MeOH). IR ν_{max}^{KBr} cm^{-1}: 3580, 3460, 2920, 1450, 1000, 750. UV λ_{max} EtOH nm: 226, 281. ^{1}H-NMR (500 MHz, $CDCl_3$+2 drops of CD_3OD) δ: 3.89 (1H, dd, J=10.5, 3.2 Hz, 3-H), 3.70 (1H, dt, J=7.1, 3.9 Hz, 5-H), 3.56 (1H, dd, J=10.5, 6.3 Hz, 17-H), 3.17 (1H, dd, J=10.5, 9.0 Hz, 17-H), 3.02 (1H, d, J=14.4 Hz, 21β-H), 2.84 (1H, d, J=14.6 Hz, 21α-H), 2.73 (1H, m, 16-H), 1.93 (1H, t-like, 15-H), 1.86 (1H, m, 14α-H), 1.79 (1H, dq, J=14.8, 7.4 Hz, 19-H), 1.65 (1H, dq, J=14.6, 7.3 Hz, 19-H), 1.62 (1H, dt, J=14.0, 3.8 Hz, 14β-H), 0.98 (3H, t, J=7.3 Hz, 18-CH_3). (500 MHz, DMSO-D_6) 10.64 (br. s, *N*-H) 4.15 (1H, br. s, 21-OH), 4.07 (1H, t, J=4.7 Hz, 17-OH), 3.75 (1H, m, 3-H), 3.44 (1H, dd, J=10.7, 5.6 Hz, 5-H), 3.26 (1H, ddd, J=10.7, 7.1, 5.1 Hz, 17-H), 2.88 (1H, ddd, J=10.2, 8.0, 4.4 Hz, 17-H), 2.85 (1H, d, J=15.8 Hz, 6-H), 2.77 (1H, d, J=14.2 Hz, 21-H), 2.71 (1H, d, J=14.2 Hz, 21-H), 2.63 (1H, dd, J=15.4, 5.9 Hz, 6-H), 2.57 (1H, br. q, J=8.8 Hz, 16-H), 1.75~1.70 (2H, m, 15-H, 14α-H), 1.67 (1H, dq, J=14.4, 7.3 Hz, 19-H), 1.54 (1H, dq, J=14.6, 7.5 Hz, 19-H), 1.36 (1H, ddd, J=13.4, 4.4, 3.2 Hz, 14β-H), 0.87 (3H, t, J=7.5 Hz, 18-CH_3). MS m/z (%): 312 (M^+, 44), 169 (100), 168 (83). 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.

Preparation of diol (123)

To a solution of (**121**) (80 mg, 0.140 mmol) in MeOH (1.5 ml) was added KOH (280 mg, 4.99 mmol) at room temperature. The reaction mixture was heated at reflux for 1.3 h, cooled to room temperature, and diluted with MeOH. CO_2 gas was passed through the mixture for 30 min. MeOH was evaporated and 10% EtOH/$CHCl_3$ was then added to the dry residue. The resulting mixture was filtered, the filtrate was concentrated and passed through open column chromatograghy (30% MeOH/$CHCl_3$). The main fraction was further purified by crystallization from acetone to give 44 mg (100%) of (**123**). (**123**): colorless needles, mp 162.5-163.5 °C (from acetone-MeOH). IR ν_{max}^{CHCl3} cm^{-1}: 3400, 2930, 1450, 980, 840, 740. UV λ_{max}^{EtOH} nm: 226, 280. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.08 (1H, dd, J=10.7, 3.1 Hz, 3-H), 3.53 (1H, dd, J=11.0, 6.6 Hz, 17-H), 3.47 (1H, dd, J=~11, ~6 Hz, 5-H), 3.17 (1H, dd, J=11.0, 8.2 Hz, 17-H), 3.01 (1H, dd, J=15.9, 0.5 Hz, 6-H), 2.99 (1H, J=13.9 Hz, 21-H), 2.90 (1H, d, J=14.0 Hz, 21-H), 2.90 (1H, dd, J=16.2, 5.2 Hz, 6-H), 2.46 (1H, tt, J=10.7, 2.0 Hz, 16-H), 2.28 (1H, m, 14β-H), 1.94 (1H, dd, J=5.5, 3.0 Hz, 15-H), 1.80 (2H, m, 19-H_2), 1.49 (1H, dt, J=13.5, 3.5 Hz, 14α-H), 1.01 (3H, t, J=7.4 Hz, 18-CH_3). MS m/z (%): 313 (37), 312 (M^+, 99), 311 (43), 169 (90), 168 (100). Exact MS (FAB, positive, in *m*-nitrobenzylalcohol) Calcd for $C_{19}H_{25}O_2N_2$: 313.1916. Found: 313.1903.

Preparation of the carbamate (124)

To a stirred solution of (**122**) (450 mg, 1.44 mmol) in H_2O-THF (3:1, 20 ml) at 0 °C, $ClCO_2CH_2CCl_3$ (6.0 ml, 43.20 mmol), MgO (4.5 g,

111.63 mmol) were added in three equal portions at 0 h, 1 h and 2.5 h. After each addition the reaction mixture was warmed to room temperature. After the final addition the mixture was stirred for 5 h, and then filtered. The filtrate was diluted with $CHCl_3$ and washed with 5% $NaHCO_3$ solution. The aqueous layer was extracted with $CHCl_3$. The combined organic extract was washed with water, dried over $MgSO_4$, and evaporated. The residue was purified by MPLC (AcOEt-hexane, 1:1) to give 440 mg (63%) of (**124**) as an amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}: 3480, 2940, 1710, 1100, 820. UV λ_{max} ^{EtOH} nm: 222, 284. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 5.03, 4.87 (1H, each d, J=12.0 Hz, $C\underline{H_a}H_bCCl_3$), 4.76, 4.66 (1H, each d, J=12.0 Hz, $CH_a\underline{H_b}CCl_3$). MS m/z (%): 488 (M^++2, 15), 486 (M^+, 15), 197 (20), 180 (30), 168 (76), 156 (100), 130 (57), 95 (80). Exact MS Calcd for $C_{22}H_{25}O_4N_2{}^{35}Cl_3$: 486.0880. Found: 486.0890.

Osmylation of the indole (124)

To a stirred solution of (**124**) (22.5 mg, 0.046 mmol) in dry THF-pyridine (1:1, 1ml) was added OsO4 (14.1 mg, 0.056 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 1.2 h. Aqueous $NaHSO_3$ solution (96 mg in H_2O) was added and the mixture was heated at 70 °C for 1.2 h. The mixture was diluted with $CHCl_3$, then 5% $NaHCO_3$ solution was added. After separation of the organic layer, the aqueous layer was extracted with $CHCl_3$. The combined organic extract was dried over $MgSO_4$ and evaporated. The residue was purified by MPLC (acetone:hexane:$CHCl_3$, 1:3:6) to give 16 mg

(69%) of (**125**) and 4 mg (18%) of the starting material (**124**). IR ν_{max}^{CHCl3} cm^{-1}: 3430, 2950, 1705, 1120. UV λ_{max}^{EtOH} nm: 209, 252. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.94, 7.89 (1H, each s, N_a-H), 4.91, 4.89 (1H, each t, J=4.9 Hz, 5-H), 4.82, 4.79 (1H, each d, J=11.9 Hz, $C\underline{H}_aH_bCCl_3$), 4.70, 4.68 (1H, each d, J=11.9 Hz, $CH_a\underline{H}_bCCl_3$), 4.29, 4.27 (1H, each d, J=10.7 Hz, 17α-H), 4.07, 4.04 (1H, each dd, J=11.0, 5.5 Hz, 17β-H), 3.92, 3.89 (1H, each d, J=8.1 Hz, 3-H), 3.81, 3.73 (1H, each d, J=15.0 Hz, 21-H), 1.67 (1H, dq, J=15.0, 7.3 Hz, 19-H), 1.57 (1H, dq, J=15.0, 7.3 Hz, 19-H), 1.01 (3H, t, J=7.3 Hz, 18-CH_3). FABMS, in *m*-nitrobenzylalcohol-thioglycerol m/z (%): 505 (MH^++2, 15), 504 (14), 503 (MH^+, 16), 502 (M^+, 12), 487 (37), 485 (32), 391 (15), 262 (20), 154 (100). Exact MS Calcd for $C_{22}H_{25}O_5N_2{}^{35}Cl_3$: 502.0829. Found: 502.0825.

Preparation of N_a-demethoxy-20-hydroxydihydrorankinidine (126)

Zinc dust (170 mg) was added to a solution of (**125**) (33 mg, 0.0655 mmol) in acetic acid (1 ml) and the mixture was stirred at room temperature for 3 h. Further zinc dust (70 mg) was added to the mixture, and the reaction mixture was stirred for 2 h, then diluted with $CHCl_3$. The mixture was basified with chilled ammonia water. The whole was extracted with $CHCl_3$ and the organic extract was washed with brine solution and dried over $MgSO_4$. Evaporation of the solvent gave the residue, which was purified by open column chromatography (30% MeOH/$CHCl_3$) to give 17 mg (79%) of (**126**) as an amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}: 3440, 2930, 1705, 1620, 1470. UV λ_{max}^{EtOH} nm: 207, 250. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.38 (1H,

d, J=7.0 Hz, 9-H), 7.22 (1H, td, J=7.5, 1.2 Hz, 11-H), 7.07 (1H, td, J=7.5, 1.0 Hz, 10-H), 6.87 (1H, d, J=7.6 Hz, 12-H), 4.22 (1H,d, J=11.0 Hz, 17α-H), 3.99 (1H, dd, J=11.0, 5.4 Hz, 17β-H), 3.65 (1H, m, 5-H), 3.65 (1H, d, J=8.1 Hz, 3-H), 3.49 (1H, d, J=13.7 Hz, 21β-H), 2.6 (1H, m, 21α-H, 16-H), 2.48 (1H, dd, J=15.3, 6.6 Hz, 6β-H), 2.26 (1H, dd, J=14.9, 8.0 Hz, 14α-H), 2.11 (1H, ddd, 15.1, 10.9, 8.0 Hz,14β-H), 1.99 (1H, m, 15-H), 1.61 (1H, dq, J=14.4, 7.3 Hz, 19-H), 1.51 (1H, dq, J=14.4, 7.3 Hz, 19-H), 0.98 (3H, t, J=7.3 Hz, 18-CH_3). ^{13}C-NMR (Table 3-2). MS m/z (%): 328 (M^+, 65), 311 (44), 299 (47), 182 (87), 117 (100). Exact MS (FAB, positive, in *m*-nitrobenzylalcohol) Calcd for $C_{19}H_{25}O_2N_2$: 329.1866. Found: 329.1873. CD (c=0.305 mmol/l, MeOH, 20 °C): Δε (nm) 8.80 (227), -4.31 (255), -1.36 (285).

Reduction of the oxindole (125)

To a solution of (**125**) (64.4 mg, 0.129 mmol) in dry THF (1.5 ml) was added BH_3•SMe_2 complex in THF (0.20 ml, 2.0 mmol) at 0 °C and the mixture was heated under reflux for 3.2 h. THF was evaporated and MeOH (2 ml) and 1 *N*-HCl (4 ml) was added to the residue. The resulting mixture was stirred at room temperature. The mixture was basified with chilled ammonia water. The whole was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by MPLC (AcOEt-hexane, 1:1) to yield 48.6 mg (76%) of (**127**) a colorless needles, mp 231-234 °C (from acetone). IR ν_{max}^{CHCl3} cm^{-1}: 3370, 1710, 1130. UV λ_{max} EtOH nm: 205, 243, 295 nm. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.8 (1H, m, 5-H), 4.802, 4.799 (1H,

each d, J=12.0 Hz, $CH_aH_bCCl_3$), 4.77, 4.74 (1H, each d, J=12.0 Hz, $CH_aH_bCCl_3$), 4.26, 4.25 (1H, each d, J=11.0 Hz, 17α-H), 4.0~3.9 (2H, m, 17β-H, 21-H), 3.23 (1H, each d, J=8.6 Hz, 2-H), 3.20 (1H, d, J=8.8 Hz, 2-H), 3.21, 3.10 (1H, each d, J=14.4 Hz, 21-H), 2.65, 2.60 (1H, each q, J=~5 Hz, 16-H). MS m/z (%): 490 (M^++2, 16), 488 (M^+, 16), 342 (35), 340 (36), 168 (44), 133 (100), 131 (99.98), 130 (99.90), 118 (100), 117 (99.98). Anal. Calcd for $C_{22}H_{27}N_2O_4Cl_3$: C, 53.95; H, 5.56; N, 5.72. Found: C, 53.95; H, 5.64; N, 5.38.

Preparation of the N_a-methoxyoxindole (129)

$H_2NCONH_2 \cdot H_2O_2$ (55 mg, 0.572 mmol) and $Na_2WO_4 \cdot 2H_2O$ (2.8 mg, 0.0086 mmol) were added to a solution of (**127**) (14 mg, 0.0286 mmol) in MeOH:H_2O (10:1) at 0 °C and the mixture was stirred for 3.5 h at room temperature. Further $H_2NCONH_2 \cdot H_2O_2$ (16 mg, 0.169 mmol) was added at 0 °C, and the reaction mixture was stirred for 1 h. The mixture was diluted with water, and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and evaporated to give 14 mg of the residue. The resulting hydroxamic acid (**128**) was dissolved in MeOH (0.1 ml) and CH_2N_2 in ether solution (excess) was added. The mixture was stirred at room temperature for 30 min. The reaction was diluted with $CHCl_3$ and washed with 5% aqueous $NaHCO_3$ solution. The aqueous layer was extracted with $CHCl_3$ and the combined organic extract was dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was purified by MPLC (3% MeOH/$CHCl_3$) to give 8.7 mg (55%) of (**129**) as an amorphous powder. IR ν_{max}^{CHCl3} cm^{-1}:

2940, 1720, 1400, 1120. UV λ_{max}^{EtOH} nm: 208, 256. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 4.89, 4.88 (1H, each t, J=~9 Hz, 5-H), 4.84, 4.79 (1H, each d, J=12.0 Hz, $CH_{\underline{a}}H_bCCl_3$), 4.72, 4.69 (1H, each d, J=12.0 Hz, $CH_a\underline{H_b}CCl_3$), 4.27, 4.25 (1H, each d, J=10.9 Hz, 17α-H), 4.07, 4.05 (1H, each d, J=11.2 Hz, 17β-H), 3.99, 3.98 (3H, each s, N_a-OMe), 3.91, 3.72 (1H, each-d, J=16.9 Hz, 21-H), 3.66, 3.65 (1H, each d, J=~17 Hz, 21-H), 2.76, 2.68 (1H, each q, J=~5 Hz, 16-H), 1.02, 1.01 (3H, each t, J=7.6 Hz, 18-CH_3). MS m/z (%): 534 (M^++2, 17), 532 (M^+, 18), 358 (12), 356 (18), 176 (56), 175 (48), 144 (100), 133 (78), 131 (75), 116 (71), 95 (57). Exact MS Calcd for $C_{23}H_{27}O_6N_2{}^{35}Cl_3$: 532.0934. Found: 532.0933.

Preparation of 20-hydroxydihydroranki nidine (17)

Zinc dust (232 mg) was added to a solution of (**129**) (36 mg, 0.065 mmol) in acetic acid (1 ml) and the mixture was stirred at room temperature for 4 h. Further zinc dust (88 mg) was added to the mixture, and the reaction mixture was stirred for 1 h, then diluted with $CHCl_3$. The mixture was basified with chilled ammonia water. The whole was extracted with $CHCl_3$ and the organic extract was washed with brine solution and dried over $MgSO_4$. Evaporation of the solvent gave the residue, which was purified by flash column chromatography (15% MeOH/$CHCl_3$) to give 18.4 mg (79%) of 20-hydroxydihydroranki nidine (**17**) as colorless needles, mp 179-180 °C (hot plate) (lit.[42j]173-174 °C). By capillary method, synthetic (**17**), 168-169 °C; natural (**17**); 166-167 °C, mixed (**17**), 166-168 °C. IR ν_{max}^{CHCl3} cm^{-1}: 2900, 1720, 1435, 1210, 1080, 760. UV λ_{max}^{EtOH} nm: 207, 253.

^{1}H-NMR (Table 3-1). ^{13}C-NMR (Table 3-2). MS m/z (%): 358 (M^+, 44), 341 (31), 340 (25), 329 (31), 327 (27), 309 (42), 182 (100). Exact MS (FAB, positive, in *m*-nitrobenzylalcohol) Calcd for $C_{20}H_{27}O_4N_2$: 359.1971. Found: 359.1978. CD (c=0.296 mmol/l, MeOH, 24 °C): $\Delta\varepsilon$ (nm) 25.15 (226), -8.77 (255), -4.82 (281), -4.52 (285) (Fig.3-22).

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