Tetrahedron Vol. 47, No. 8, pp. 1383-1392, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00
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AN EFFICIENT SYNTHETIC PATHWAY TO THE MACROLINE-TYPE INDOLE ALKALOIDS, TALCARPINE AND ALSTONERINE FROM AJMALINE.

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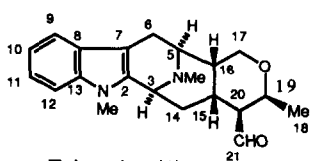
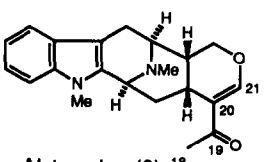
(*Received in Japan* 18 *October* 1990)

Abstract---Ajmaline (**6**) was transformed into two macroline-related indole alkaloids, talcarpine (**1**) and alstonerine (**2**) *via* the common synthetic intermediate (**13**). The stereochemistry at C19 position in talcarpine (**1**) and talpinine (**5**) were elucidated by NOE experiments and the chemical correlations.

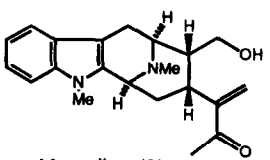
Talcarpine (**1**) and alstonerine (**2**) fall under macroline-type alkaloid, which features bond cleavage between the N_b and the C21 position in the sarpagine class of indole alkaloids.[1] Although macroline (**3**)[2] itself has not been isolated from nature, (**3**) is generally accepted as a biogenetic precursor of some bisindole alkaloids, such as macralstonine (**4**),[3] macralstonidine,[4] alstonisidine,[5] villalstonine,[2a,5a,5c,6] and pandicine.[7] Talcarpine (**1**) was first isolated from *Pleiocarpa talbotii* Wernham in 1972.[8] The structure of (**1**) was elucidated by mass, UV, and ^{1}H-NMR spectroscopies and chemical correlations[9] with other macroline-type indole alkaloids, but as yet the stereochemistry at C19 remains unsettled. For the pharmacological study on these uncommon macroline-related indole alkaloids including the dimeric indole alkaloids, it was thus desirable to develop an efficient synthetic sequence. Meanwhile, an elegant total synthesis of



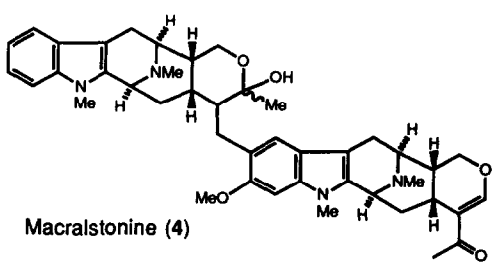
Talcarpine (1)



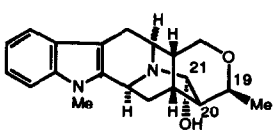
Alstonerine (2) [18]



Macroline (3)



Macralstonine (4)



Talpinine (5)

Fig. 1

alstonerine (**2**) was quite recently published by Cook *et al.*[10] Here we would like to report our unique and valuable synthetic route to talcarpine (**1**) and alstonerine (**2**) from readily obtainable compound, ajmaline (**6**).[11] We also describe the determination of the stereochemistries at C19 position in talcarpine (**1**) and talpinine (**5**), which have been indistinct since their isolation.

The transformation from ajmaline (**6**) into talcarpine (**1**) involves mainly three structural changes of the starting material: 1) generation of indole ring from indoline and epimerization at C16 position (**6** to **9**), 2) cleavage of N_b-C21 bond and formation of *E*-ring (**10** to **11**), 3) introduction of a 19-20 double bond and re-construction of *E*-ring leading to talcarpine (**1**). Initially, the hydroxy function at C21 in ajmaline (**6**) was selectively protected in 87% yield with carbobenzoxy group under Schotten-Baumann condition to yield the carbonate (**7**) (mp 218-220°C). Oxidation of the indoline moiety in (**7**) with one equiv of lead tetraacetate [$Pb(OAc)_4$][12] in dry CH_2Cl_2 generated the indole derivative (**8**) (mp 80-82°C) in 68% yield. In the ^{1}H-NMR spectrum, (**8**) exhibited a signal at δ9.32 due to an aldehyde function. Treatment of (**8**) with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dry THF afforded the epimeric aldehyde (**9**) as a result of the epimerization at the C16 position in a quantitative yield. The chemical shift of the aldehyde proton in (**9**) appeared at 0.38 ppm lower than that of (**8**) caused by the release of the shielding effect of the indole ring. Reduction of (**9**) with sodium borohydride ($NaBH_4$) gave the primary alcohol (**10**) (mp 177-178°C) in 90% yield. Next, quaternarization of the N_b group in (**10**) with methyl iodide (MeI) and successive hydrolysis of the carbonate with aqueous KOH solution resulted in the formation of macroline-skeleton (**11**) in 92% yield *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.[13] To introduce a double bond at C19-20 position, a phenyl selenenyl group was introduced to C20 position by means of enamine method. Thus, (**11**) was heated with 5 equiv of piperidine in acetic acid and the resultant unstable enamine intermediate, which was

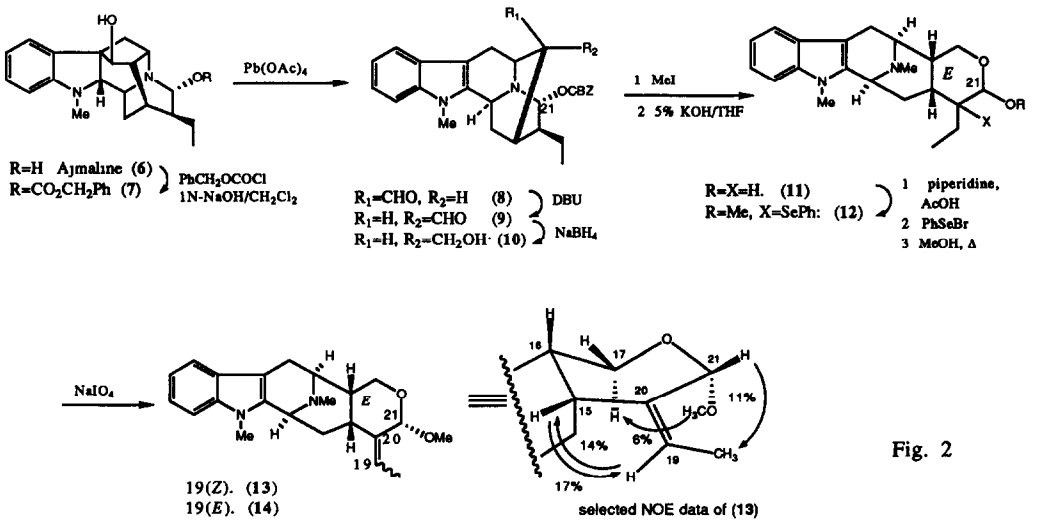


Fig. 2

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 products, which upon recrystallization from MeOH afforded the acetal (**12**) (mp. 180-181.5°C) in 47% overall yield from (**11**). Oxidation of (**12**) with sodium periodate ($NaIO_4$) in aqueous MeOH/THF provided a mixture consisting of two olefins (**13**) and (**14**). The ^{1}H-NMR spectrum of the mixture reveals the ratio of (**13**) and (**14**) as approximately 2:1. By the careful chromatographic separation of these mixture with medium pressure liquid chromatography and by recrystallization, major isomer (**13**) was obtained as colorless prisms (mp. 198-202°C). NOE experiments of (**13**) 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 (**13**) 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. Finally, the major isomer (**13**) was treated with 5% aqueous H_2SO_4 solution at room temperature for 26 h to furnish talcarpine (**1**) (mp. 160-161°C) and the aldehyde (**15**) in 30% and 59% yield, respectively. The property (mp. UV, IR, MS, ^{1}H-NMR, and CD spectra) of semisynthetic compound (**1**) were well consistent with the values reported in the literature.[8] To elucidate the configuration at C19 position in talcarpine (**1**), NOE experiments were attempted. However, the signals of 19-H and 3-H were overlapped in (**1**), so that clear information concerned with the stereochemistry at C19 could not be obtained. Then we prepared the acetyl derivative (**16**) from (**1**) (i. $NaBH_4$ in MeOH, ii. Ac_2O in pyridine) and carried out the NOESY experiments on (**16**). Since clear interactions between 19-H and 14-Hα and between 18-H_3 and one of the protons on C21 were observed, the configuration at C19 was concluded to be *S*. Compound (**15**) obtained together with (**1**) by the acidic treatment of (**13**) was also identical with the reported compound,[8] that was derived from talpinine (**5**) by the methylation of N_b with MeI. Talcarpine (**1**) was also able to convert to (**15**) by treating with K_2CO_3 in MeOH through the epimerization at C20 position. In the ^{13}C-NMR spectra, the signal due to C14 in (**1**) 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 (**15**). (see Table) These phenomena can be interpreted by the γ-gauche effect of the C21 formyl group. From these NMR analysis as well as the above chemical interconversions, the configuration at C19 in talpinine (**5**) should be *S* similar to talcarpine (**1**).[14] NOE data of (**15**) also supported this conclusion.

We turned our attention to the synthesis of alstonerine (**2**)[15] by utilizing the synthetic intermediate (**13**) into talcarpine (**1**). To complete this object, introduction of an oxygen function to C19 position and creation of a double bond at C20-21 position in (**13**) were required. Hydroboration of (**13**) with borane dimethylsulfide complex provided two diastereomeric secondary alcohols (**17**) and (**18**) (mp. 130-132°C) in 27% and 26% yield, respectively, accompanied with 22% of the starting material. The stereochemistry of each alcohols (**17**) and (**18**) 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.4. Alcohol (**17**) was subjected to Swern oxidation to yield the ketone (**19**) (mp. 138-140°C) in 70% yield. By the same oxidation procedure, (**18**) also afforded (**19**). The production of (**19**) from (**17**) was caused by the

epimerization of the acetyl group into the stable equatorial orientation. Finally, (19) was treated with sodium hydroxide in MeOH to furnish alstonerine (2) (mp. 162-164°C) in 89% yield, which was identical with natural compound in all respects.[15] The assignments of the chemical shifts in the ^{13}C-NMR spectrum of (2) in the literature[16] were revised by using 2D-NMR (^{1}H-^{1}H, and ^{13}C-^{1}H COSY) technique (see Table).

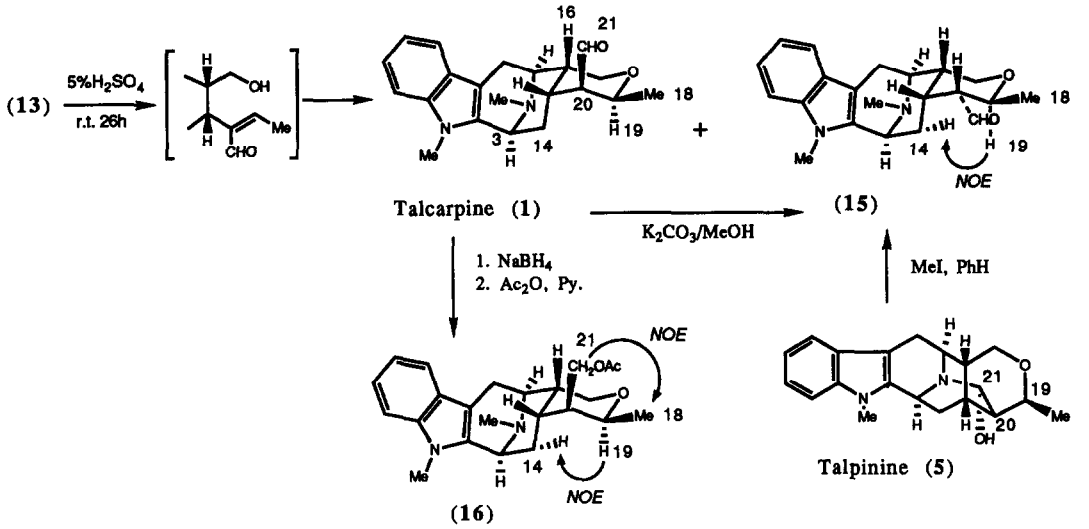


Fig. 3

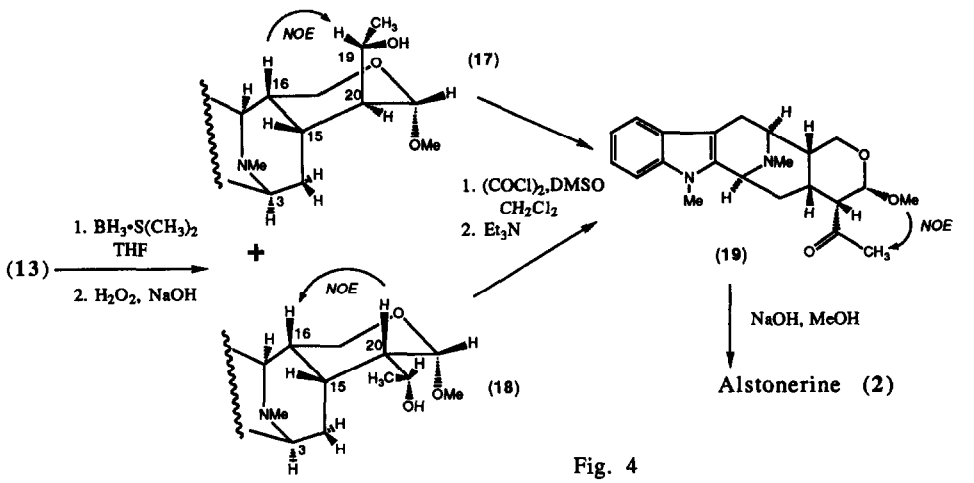


Fig. 4

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

No.	Talcarpine (1)		(15)	Alstonerine (2)[a]
2	132.64(s)		132.88(s)	133.24(s)
3	54.50(d)*		55.01(d)	53.81(d)
5	53.54(d)		53.20(d)	54.73(d)
6	22.51(t)		22.52(t)	22.85(t)
7	106.67(s)		106.68(s)	105.93(s)
8	126.40(s)		126.33(s)	126.59(s)
9	118.18(d)		118.01(d)	117.84(d)
10	118.94(d)		119.04(d)	118.73(d)
11	121.04(d)		121.11(d)	120.83(d)
12	108.79(d)		109.01(d)	108.99(d)
13	137.03(s)		137.07(s)	137.24(s)
14	30.08(t)	Δ	26.81(t)	32.42(t)
15	27.02(d)		26.20(d)	22.95(d)
16	39.42(d)	Δ	42.60(d)	38.57(d)
17	68.88(t)		67.23(t)	67.81(t)
18	19.22(q)		20.32(q)	25.03(q)
19	54.60(d)*		57.88(d)	195.46(s)
20	69.48(d)		67.88(d)	121.14(s)
21	204.70(d)		203.23(d)	157.42(d)
N(a)-Me	29.02(q)		29.08(q)	29.07(q)
N(b)-Me	41.80(q)		41.75(q)	41.81(q)

Measured at 125MHz, Solvent $CDCl_3$. Assignments bearing the superscript may be interchanged. a: revised the assignments in the literature 16) by using C-H COSY spectrum.

Experimental

All melting points were determined on a Yamato MP-21 apparatus and 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 spectrometers; ^{1}H- and ^{13}C-NMR spectra, JEOL JNM GX270, JEOL GSX400, and JEOL GSX500 instruments in $CDCl_3$ with tetramethylsilane as an internal standard, chemical shifts are recorded in δ values; optical rotation, JASCO DIP-140 polarimeter; CD spectrum was measured with JASCO J-500A in MeOH. Thinlayer chromatography was performed on Merck precoated Silicagel 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).

Preparation of carbonate (7) from ajmaline (6)

To a vigorously stirred solution of ajmaline (6) (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 (7) as colorless prisms. 0.11 g of pure (7) 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). IRν_{max}^{KBr} cm^{-1}: 3300(br), 2940, 1740, 1250. UVλ_{max}^{EtOH} nm: 206, 248, 291. ^{1}H-NMR (270 MHz) δ: 5.19 and 5.17 (each 1H, d, J=12.0 Hz, OC$\underline{H}_2$Ph), 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 indoline (7)

To a stirred solution of (7) (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 (8) accompanied with 270 mg (11%) of the starting material (7). (8): colorless needles, mp. 80-82°C. IRν_{max}^{KBr} cm^{-1}: 2940, 1750, 1700, 1470, 1250. UVλ_{max}^{MeOH} nm: 226, 282. ^{1}H-NMR (270 MHz) 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 (8) with DBU

A mixture of (8) (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 (9) as an amorphous powder. IRν_{max}^{CHCl3} cm^{-1}: 2940, 1750, 1720, 1250. UVλ_{max}^{EtOH} nm: 227, 283. ^{1}H-NMR (270 MHz) δ: 9.70 (1H, s, CHO). MS m/z (%): 458(M^+, 40), 182 (100), 91 (52).

$NaBH_4$ reduction of aldehyde (9)

To a stirred solution of (9) (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 (10) was precipitated from the reaction solution. The precipitate was filtered and washed with MeOH to afford 110 mg of (10). 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 (10). Further purification of the mother liquid by MPLC (AcOEt-hexane, 1:2) gave 11 mg of (10). Totally 187 mg (90%) of (10) was obtained. (10): colorless needles. mp. 177-178°C (from hexane). IRν_{max}^{CHCl3} cm^{-1}: 3250 (br.), 2920, 1760, 1240. UVλ_{max}^{EtOH} nm: 229, 284 ^{1}H-NMR (500 MHz) δ: 3.73 and 3.67 (each 1H, dd, J=10.0, 8.0 Hz, C$\underline{H}_2$OH). 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 (11)

A mixture of 1.768 g (3.84 mmol) of (10) 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 (**11**) as an amorphous powder (diastereomeric mixture of 2:1). $IR\nu_{max}^{CHCl3}$ cm^{-1}: 3500-3100, 2950, 1470. $UV\lambda_{max}^{EtOH}$ nm: 228, 286. ^{1}H-NMR (500 MHz) (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 acetal (11)

To a stirred solution of (**11**) (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, 13.55mmol) 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 (**12**) as colorless prisms. The mother liquid was subjected to flash column chromatography (AcOEt-hexane, 1:1) to yield 270 mg of (**12**). Totally 1.241 g (47%) of (**12**) was obtained. mp. 180-181.5°C. $IR\nu_{max}^{KBr}$ cm^{-1}: 2900, 1450, 1030. $UV\lambda_{max}^{EtOH}$ nm: 223, 286. ^{1}H-NMR (500 MHz) 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 olefins (13) and (14)

A solution of $NaIO_4$ (1.03 g, 4.82 mmol) in water (15 ml) was added to the stirred solution of (**12**) (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 (**13**) and (**14**). The 1H-NMR spectrum of this fraction showed the ratio of (**13**) and (**14**) as approximately 2:1. Recrystallization of this fraction from acetone gave 533 mg (47%) of (**13**) as colorless prisms. Repeated chromatography using MPLC gave 46 mg of pure (**14**). (**13**): mp. 198-202°C. $IR\nu_{max}^{KBr}$ cm^{-1}: 2900, 1460, 1040. $UV\lambda_{max}^{EtOH}$ nm: 230, 285. ^{1}H-NMR (500 MHz) 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. (**14**): amorphous powder. $IR\nu_{max}^{CHCl3}$ cm^{-1}: 2950, 1470, 1105, 1040. $UV\lambda_{max}^{EtOH}$ nm: 230, 285. ^{1}H-NMR (270 MHz) 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 (1) from (13)

A mixture of (**13**) (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 (**1**) and 56 mg (59%) of (**15**). (**1**): colorless prisms mp. 160-161°C (from hexane-acetone-ether) (lit.[8] 167-169°C). IRν_{max}^{KBr} cm^{-1}: 2900, 1720, 1480, 1380, 740. UVλ_{max}^{MeOH} nm: 228, 285. ^{1}H-NMR (400 MHz) 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) 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 (**15**): colorless amorphous powder, IRν_{max}^{CHCl3} cm^{-1}: 2950, 1720, 1470. UVλ_{max}^{MeOH} nm: 228, 285. ^{1}H-NMR (500 MHz) 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) 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 (16) from talcarpine (1)

To a solution of talcarpine (**1**) (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 (**16**) as colorless oil. IRν_{max}^{CHCl3} cm^{-1}: 2940, 1730, 1470, 1130. UVλ_{max}^{EtOH} nm: 230, 285. ^{1}H-NMR (500 MHz) 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 (13)

To a solution of (**13**) (271 mg, 0.769 mmol) in dry THF (12 ml) was added $BH_3.SMe_2$ 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, $BH_3.SMe_2$ 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 (**17**), 74 mg (26%) of (**18**), and 59 mg (22%) of the starting material (**13**). (**17**): colorless amorphous powder. IRν_{max}^{CHCl3} cm^{-1}: 3600-3200, 2940, 1470, 1050. UVλ_{max}^{EtOH} nm: 229, 285. ^{1}H-NMR (500 MHz) 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. (**18**): colorless needles, mp. 130-132°C (from ether). $IR\nu_{max}^{KBr}$ cm^{-1}: 3600-3200, 2900, 1470, 1060. $UV\lambda_{max}^{EtOH}$ nm: 231, 285. ^{1}H-NMR (500 MHz) 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 alcohol (17)

A solution of DMSO (74 μl, 1.04 mmol) in CH_2Cl_2 (0.5 ml) was added dropwise at -70°C to a stirred solution of oxalyl chloride (54 μl, 0.634 mmol) in CH_2Cl_2 (0.5 ml). The mixture was stirred at -70°C for 10 min. A solution of (**18**) (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 (**19**) as colorless needles, mp. 138-140°C (from MeOH). $IR\nu_{max}^{KBr}$ cm^{-1}: 2950, 1705, 1470, 1040. $UV\lambda_{max}^{EtOH}$ nm: 230, 285. ^{1}H-NMR (500 MHz) 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 (18)

Same treatment of (**18**) (45 mg, 0.121 mmol) with DMSO, oxalyl chloride, and Et_3N in dry CH_2Cl_2 afforded 26 mg (57%) of (**19**) along with 9.4 mg (21%) of the starting material. (**19**) obtained by this reaction was identical with the sample derived form (**17**) by the comparison of their mp., TLC behavior, ^{1}H-NMR, and MS spectra.

Alstonerine (2) from (19)

A mixture of (**19**) (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 (**2**) as colorless prisms. mp. 162-164°C (hot plate; 172-175 °C) (from ether) (lit.[15] 172-173°C). $[\alpha]_D^{26}$ -140° (c=0.2, EtOH). $IR\nu_{max}^{KBr}$ cm^{-1}: 2930, 1655, 1620, 1480, 1200. $UV\lambda_{max}^{EtOH}$ nm: 230, 259. ^{1}H-NMR (500 MHz) 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). 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.

Acknowledgment

The authors wish to thank the members of Chemical Analysis Center of Chiba University for the measurement of NMR, MS and elemental analysis.

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