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Synthesis of dl-Vincadifformine, dl-Eburcine and dl-3-Epieburcine. Introduction of Methoxycarbonyl Function to C(3)-Position of Aspidosperma Skeleton

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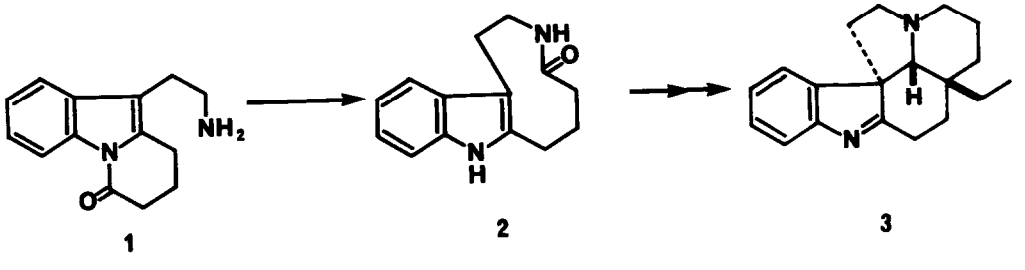
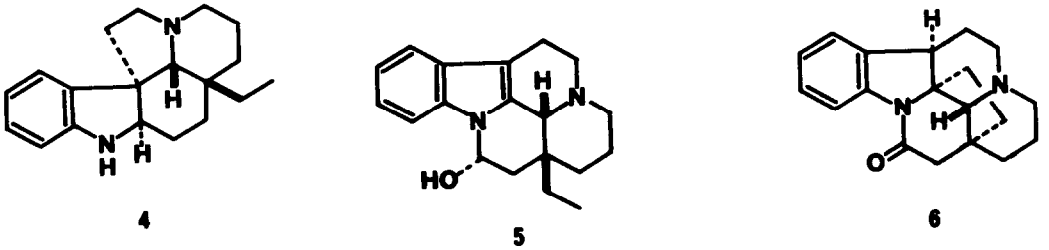
Abstract - Vincadifformine (7), eburcine (15) and 3-epieburcine (16) in racemic forms have been synthesized from 1,2-dehydroaspidospermidine (3) by introduction of methoxycarbonyl group to C(3)-position of aspidosperma skeleton.

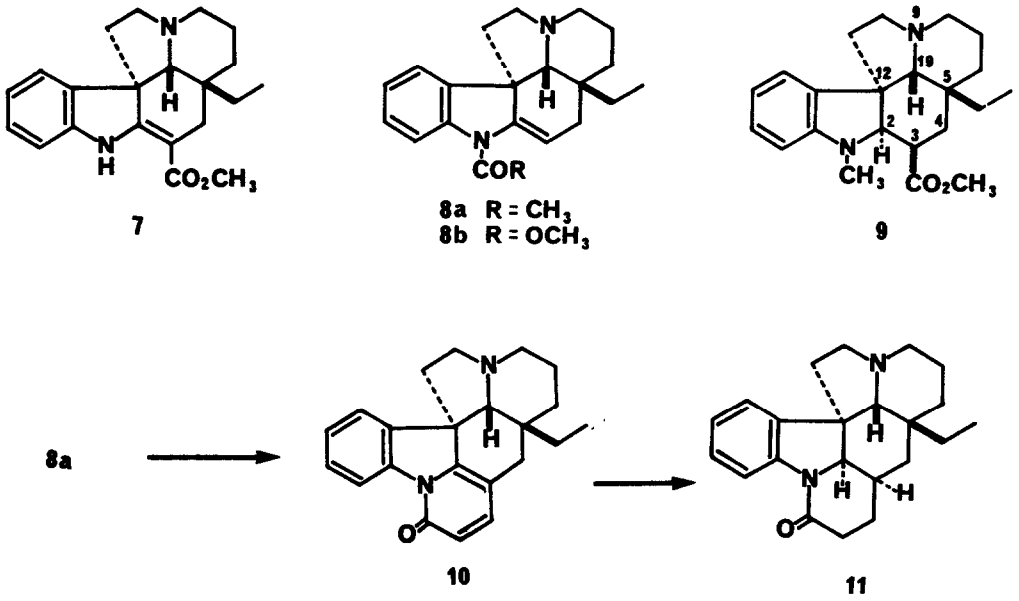
On application to the syntheses of aspidosperma alkaloids through a common intermediate 2, prepared by the new photoisomerization of 1-acylindole 1,[1] 1,2-dehydroaspidospermidine (3) and aspidospermidine (4) in racemic form were synthesized, which also constituted the formal syntheses of the other related alkaloids such as eburnamine (5)[2] and strempeliopine (6)[3] by known effective chemical conversions. In this paper, we describe the further extention of our work to the syntheses of dl-vincadifformine (7),[4] dl-eburcine (15),[5] and dl-3-epieburcine (16).[5]





A number of highly functionalized aspidosperma alkaloids possess a methoxycarbonyl group at C(3) position of general aspidosperma skeleton. (For numbering of a general formula (9)). As was reported from this laboratory in the previous paper,[1] the alkaloid 3 efficiently obtained by our method was proved to be easily unattainable by the other methods and synthetically important for stragetic arrangement. In connection with this line, recent two elegant methods to introduce a methoxycarbonyl group to C(3)-position of aspidosperma skeleton urged us to disclose our results independently realized.

Photorearrangements of N-methoxycarbonyl group on 2,3-dehydroaspidosperma skeleton to C(3)-position were made by Wenkert with the desethyl series.[6] On the other hand, Overman[7] achieved the direct C(3)-methoxycarbonylation of lithio indolenine. Our method includes Vilsmier-Haack reaction of the enamide (8b) to provide important unsaturated aldehyde 12 in good yield. The total syntheses of the titled alkaloids were completed from 12.

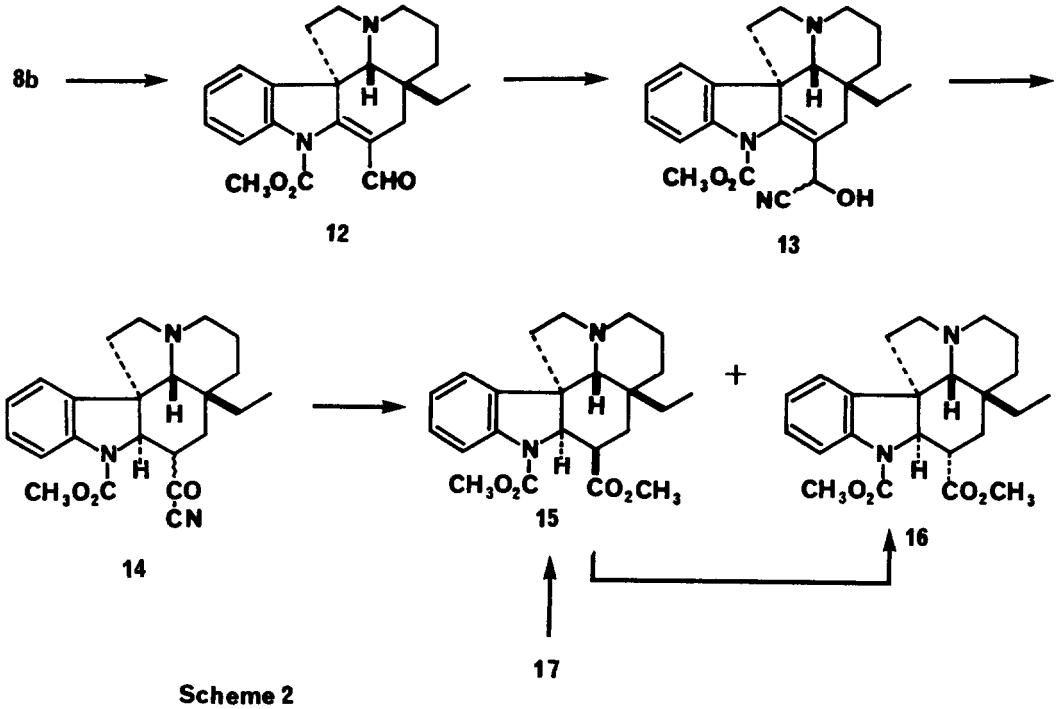


Scheme 1

Vilsmeier-Haack reaction of 1-acetyl-2,3-dehydroaspidospermidine (8a)[8] provided the unanticipated pyridone 10 as an unstable oil in 49% yield. To confirm the structure, 10 was hydrogenated over Raney-nickel to provide 11 as a sole product. The coupling constant (4.0 Hz) of H(2) with H(3) in 11 showed that these protons are in cis configuration. On account of steric hindrance of the axial ethyl group, hydrogenation could be supposed to have occurred from the opposite side of the substituent. It is suggested that Vilsmeier-Haack reaction occurred at acetyl methyl group or at C(3)-position, followed by intramolecular cyclization. On the other hand, formylation of carbamate 8b which was prepared from 3 ($ClCOOCH_3$, Et_3N) under the same conditions afforded 3-formyl derivative 12 in 94% yield. Oxidation of 12 by Corey's procedure[9] (MnO_2, NaCN, MeOH / CH_3COOH) gave the saturated ester 15 in poor yield. To clarify the reaction mechanism, 12 was treated with sodium cyanide in methanolic acetic acid to give eburcine (15) and 3-epieburcine (16) in 36% and 10% yield, respectively.
Although the mechanism of this unusual reaction is not clear yet, it might be assumed that the process shown in Scheme 2 should be plausible. The initially

formed unsaturated cyanohydrin 13 might be assumed to be α-oxonitrile 14, which was reacted with methanol to provide the correspoonding methyl ester.

Since the authentic samples of these alkaloids, 15 and 16,[5] were not available, the stereochemistry at C(2) and C(3) was determined as follows. Catalytic hydrogenation of 1-methoxycarbonylvincadifformine (17) affoded 15 exclusively. None of the other stereoisomers was detected among the reaction products. Epimerization of 15 under basic condition (MeONa-MeOH, reflux, 1h) followed by esterification gave 16 in 56% yield as a main product accompanied by a trace of



Scheme 2

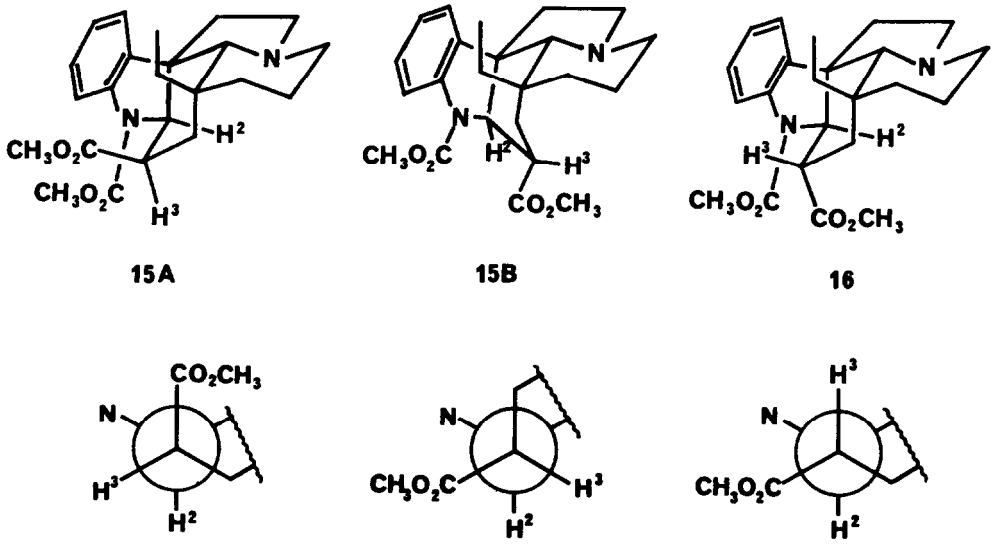


Fig. 1

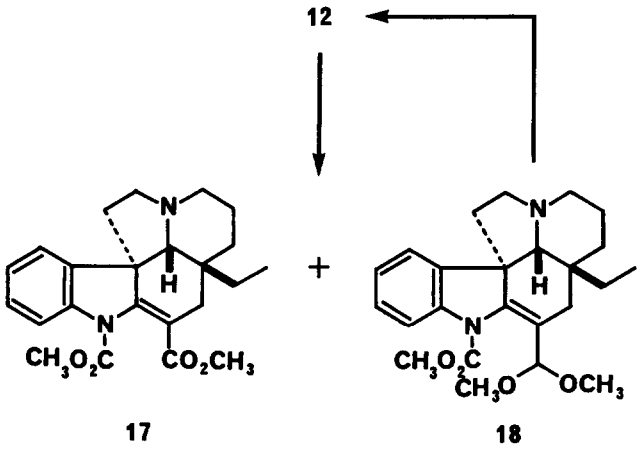
15, the results of which are comparable with the assigned structures and parallel to Olivier's observations.[5] The facts that the hydrogenation of 17 afforded 15 suggest a cis configuration of protons at C(2) and C(3), in which molecule the axial methoxycarbonyl group epimerized smoothly under basic conditions to the thermodynamically more stable equatorial configuration to give 16.

In the ^{1}H NMR spectra, the signals of H(2) and H(3) in 15 appeared at 4.53 (d, J = 2.9 Hz) and 4.34 (ddd, J = 10.0, 7.0, 2.9 Hz), respectively. On the other hand, the corresponding protons of 16 were observed at 4.50 (brd, J = 8.0 Hz) and 2.48 (brm)[10]. The orientation of the carbomethoxy group should be explainable by the coupling constant of H(2). Both of the conformers 15 (15A and 15B) should have smaller coupling constant compared with that of 16 as shown in Fig I. The unusually lower field shift of H(3) of 15 owing to the nitrogen lone pair effect[11] suggested that the conformation 15B would be more reasonable than 15A. Table I summarizes the ^{13}C NMR chemical shifts for 15, 16 and 1-methyl-2,3-dehydrovincadifformine (9).[12] The significant differences of chemical shifts were observed on C(3) and C(19). On compound 15, C(3) was shielded to an extent of 5.3 ppm and C(19) was deshielded by 5.5 ppm on being compared with those of 16. Also the chemical shifts of 15 were parallel to the reported value of 9 which should have the same stereochemistry on C(2) and C(3). It is strongly suggested that the conformation of 15 is in a boat form 15B to reduce 1,3-diaxial interactions between carbomethoxy and ethyl groups.

Table I. ^{13}C NMR Chemical Shifts of 15, 16 and 9

	15	16	9[a]
C(2)	69.4	68.3	75.5[a]
C(3)	38.4	43.7	37.9
C(4)	28.5	27.3	27.5
C(5)	35.9	35.6	33.4
C(19)	75.5	70.0	76.1[b]
C(12)	52.8	---[c]	52.4

a) reference (12)
b) signals may be interchanged.
c) signals unrecorded.



Scheme 3

The unsaturated aldehyde 12 was oxidized with sodium chlorite[13] followed by esterification and acetalization[14] to provide 1-methoxycarbonylvincadifformine (17) and dimethyl acetal 18 in 36% and 27% yield, respectively. The acetal 18 was converted to 12 in nearly quantitative yield. Attempted oxidation of 12 using the other oxidants, (Ag_2O, Pt/O_2, Jones reagent, SeO_2) gave none of the desired products. Saponification of carbamate 17 (MeONa-MeOH, reflux 15 min) gave vincadifformine (7) in 58% yield. The melting point, infrared spectrum in chloroform solution, 200 MHz ^{1}H NMR, mass spectra of the synthesized 7 were identical with the reported values[4] of the authentic specimen, thus establishing our method to be effective for the present purpose.

Experimental section

Melting points were determined on a Yamato M-P melting point apparatus and were uncorrected. Infrared spectra were recorded on JASCO IRA-2 diffraction grating spectrometer and ultraviolet spectra were measured on Hitachi ESP-3T, or Shimazu UV-240 spectrophotometers. Mass spectra were taken on JEOL-D300 spectrometer. ^{1}H NMR spectra were determined on JEOL FX-100 (100 MHz) or JEOL FX-200 (200 MHz) spectometers. ^{13}C NMR spectra were taken at 50.10 MHz with JEOL FX-200 spectrometer. ^{1}H and ^{13}C NMR chemical shifts were reported in ppm down field from internal tetramethylsilane on δ scale. ^{1}H NMR coupling constants (J) were recorded in Hertz, and abbreviations used were as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. These same abbriviations were used to denote the multiplicities in off-resonance ^{13}C NMR spectra. Column chromatographic separations were performed on Merck silica gel (70-325 mesh ASTM). Preparative TLC were carried out on Merck silica gel GF_{254} (Type 60) or Merck alumina GF_{254} (Type 60/E). Tetrahydrofuran was distilled from sodium benzophenone ketyl. All reactions were run under an argon atmosphere. Diisopropylamine and dimethylformamide were distilled over calcium-hydride.

2,3-Dehydro-1,3-(1-oxo-2-propeno)aspidospermidine (10)

To a ice cooled solution of 8a (60 mg, 0.186 mmol) in dimethylformamide (1 ml) was added dropwise phosphoryl chloride (0.2 ml, 2.17 mmol). The mixture was stirred at room temperature for 2h and diluted with methylene chloride (2 ml). The reaction was quenched by the addition of water (2 ml) at 0°C. After basification with 10% sodium hydroxide (4 ml), the resulting mixture was extracted with methylene chloride (2 x 20 ml). The extracts were washed with brine, dried over sodium sulfate, and concentrated. The residue was purified by preparative TLC (alumina, hexane : ethyl acetate = 4 : 1) gave 10 (31 mg, 49%) as unstable oil: IR ($CHCl_3$) 2780, 2700, 1665, 1615, 1590, 1575, 1535 cm^{-1}; MS m/e 332 (M^+), 124 (base peak); ^{1}H NMR ($CDCl_3$) δ 0.35-0.70 (m, 5H), 1.22-1.46 (m, 1H), 1.46-1.70 (m, 1H), 1.70-2.14 (m, 5H), 2.40-2.82 (m, 3H), 3.00 (t, 1H, J = 7.5 Hz), 3.19 (d, 2H, J = 14.7 Hz), 6.46 (d, 1H, J = 9.0 Hz), 7.15 (d, 1H, J = 9.0 Hz), 7.26-7.52 (m, 3H), 8.58 (d, 1H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 6.7 (q), 21.9 (t), 29.0 (t), 30.1 (t), 32.9 (t), 40.4 (s), 44.8 (t), 50.5 (t), 51.9 (t), 54.0 (s), 72.9 (d), 111.8 (s), 117.6 (d), 119.4 (d), 121.2 (d), 126.0 (d), 128.0 (d), 140.5 (s), 140.7 (d), 141.3 (s), 153.5 (s), 162.1 (s).

1,3-(1-oxo-propano)aspidospermidine (11)

Pyridone 10 (30 mg, 0.090 mmol) was dissolved in ethanol (1 ml) and hydroganated over Raney Nickel (W 2) (50 mg) for 72h at ordinary pressure. After removal of the catalyst, the filtrate was concentrated. The crude residue was purified by preparative TLC (alumina, hexane : ethyl acetate = 3 : 1) affoded colorless solid, which was recrystallized from hexane - ethanol to give 11 (17 mg, 56%) as colorless needles: mp 143 - 144°C; IR ($CHCl_3$) 2780, 2720, 1635, 1590 cm^{-1}; MS m/e 336 (M^+), 307, 124 (base peak); ^{1}H NMR ($CDCl_3$) δ 0.35 (t, 3H, J = 7.3 Hz), 0.66 (ABX type, 2H, J = 15.0, 8.0, 2.4 Hz), 1.0-2.1 (m, 11H), 2.26 (dd, 1H, J = 20.0, 9.6 Hz), 2.58 (dd, 2H, J = 10.0, 3.4 Hz), 2.9-3.20 (m, 2H), 3.85 (d, 1H, J = 3.9 Hz), 7.05-7.32 (m, 3H), 8.18 (d, 1H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 7.6 (q), 22.1 (t), 25.7 (t), 25.8 (d), 28.6 (t), 29.8 (t), 34.3 (t), 35.8 (t), 42.1 (t), 51.7 (s), 52.7 (t), 53.7 (t), 71.0 (d), 75.6 (d), 117.1 (d), 123.3 (d), 124.2 (d), 127.9 (d), 138.4 (s), 142.5 (s), 168.3 (s); Anal. calcd for $C_{22}H_{28}N_2O$: C, 78.52; H, 8.39; N; 8.33. Found: C, 78.37; H,8.41; N, 8.19; high resolution mass spectrum, calcd for $C_{22}H_{28}N_2O$ 336.2198; found: 336.2203.

1-Methoxycarbonyl-2,3-dehydroaspidospermidine (8b)

A mixture of 1,2-dehydroaspidospermidine (3) (86 mg, 0.307 mmol) and methyl chloroformate (0.3 ml, 3.88 mmol) in dry tetrahydrofuran was stirred at room temperature for 1h. To this solution was added triethylamine (0.73 ml, 5.23 mmol) at 0°C and the mixture was stirred at room temperature for 1h. The precipitated salt was removed by filtration. After removal of the solvent, the residue was recrystallized from ethanol to give 8b (98 mg, 94%) as colorless prisms: mp 104-105°C; IR ($CHCl_3$) 2760, 2700, 1710, 1675, 1600 cm^{-1}; MS m/e 338 (M^+), 309, 253, 124 (base peak); ^{1}H NMR ($CDCl_3$) δ 0.59 (t, 3H, J = 7.0 Hz), 1.06-1.30 (m, 2H), 1.4-1.90 (m, 6H), 2.07 (ddd, 1H, J = 11.7, 11.3, 6.8 Hz), 2.12 (dd, 1H, J = 12.0, 3.0 Hz), 2.28-2.45 (m, 2H), 2.74 (dd, 1H, J = 16.0, 2.7 Hz), 2.91 (t, 1H, J = 8.0 Hz), 3.17 (brd, 1H, J = 10.7 Hz), 3.91 (s, 3H), 5.89 (dd, 1H, J = 8.3, 2.4 Hz), 7.06 (t, 1H, J = 7.0 Hz), 7.14-7.28 (m, 2H), 7.83 (d, 1H, J = 8.3 Hz); Anal. calcd for $C_{21}H_{26}N_2O_2$: C, 74.53; H, 7.74; N, 8.28. Found: C, 74.69; H, 7.61; N, 8.47.

1-Methoxycarbonyl-2,3-dehydro-3-formylaspidospermidine (12)

To a ice cold solution of urethane 8b (101 mg, 0.30 mmol) in dimethylformamide (4 ml) was added dropwise phosphoryl chloride (1.25 ml, 13.4 mmol). The reaction mixture was stirred at room temperature for 63h. The reaction was quenched by the addition of 10% sodium hyroxide (10 ml) at 0°C and extracted with ethyl acetate (2 x 20 ml). The extracts were combined and washed with brine, dried

over magnesium sulfate. After removal of the solvent, residue was purified by chromatography (silica gel, hexane : ethyl acetate = 3 : 1) gave 12 (102 mg, 94%) as an unstable colorless foam: IR ($CHCl_3$) 2780, 2720, 1720, 1665, 1650, 1605 cm^{-1}; MS m/e 366 (M^+), 337, 124 (base peak); ^1H NMR ($CDCl_3$) δ 0.57 (t, 3H, J = 7.1 Hz), 0.6-3.24 (m, 15H), 7.65 (dd, 1H, J = 8.6, 1.3 Hz), 9.99 (s, 1H).

Eburcine (15) and 3-epieburcine (16)

To a solution of aldehyde 12 (66 mg, 0.180 mmol) in methanol (6 ml) was added sodium cyanide (200 mg, 4.08 mmol) and acetic acid (70 µl), 1.22 mmol). The mixture was stirred at room temperature for 27h. After evaporation of the solvents, water (5 ml) was added to the residue. The separated oil was extracted with methylene chloride (2 x 30 ml) and the extracts were combined, washed with brine, dried over sodium sulfate. After removal of the solvent, the residue was purified by preparative TLC (silica gel, hexane : ethyl acetate = 3 : 1) to give 15 (26 mg, 36%) as an amorphous solid: Rf = 0.37; IR ($CHCl_3$) 2780, 2730, 1720, 1700, 1600 cm^{-1}; UV (EtOH) λmax 243, 284, 290 (sh) nm; MS m/e 398 (M^+), 312, 124 (base peak); ^1H NMR ($CDCl_3$) δ 0.44 (t, 3H, J = 7.3 Hz), 0.60-0.96 (m, 2H), 1.06 (ddd, 1H, J = 13.2, 5.0 Hz), 1.38-1.76 (m, 5H), 1.78-1.98 (m, 2H), 1.98-2.36 (m, 3H), 3.02 (brd, 1H, J = 10.0 Hz), 3.15 (t, 1H, J = 7.0 Hz), 3.76 (s, 3H), 3.80 (s, 3H), 4.34 (ddd, 1H, J = 10.0, 7.0, 2.9 Hz), 4.53 (d, 1H, J = 2.9 Hz), 7.07 (t, 1H, J = 8.0 Hz), 7.15-7.32 (m, 2H), 7.77 (d, 1H, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 7.7 (q), 22.0 (t), 28.5 (t), 33.6 (t), 34.7 (t), 35.9 (s), 38.4 (d), 41.5 (t), 51.5 (q), 52.1 (t), 52.6 (q), 52.8 (s), 53.2 (t), 69.4 (d), 75.5 (d), 115.5 (d), 123.2 (d, 2C), 128.1 (d), 137.3 (s), 143.0 (s), 154.7 (s), 174.9 (s); high resolution mass spectrum, calcd for $C_{23}H_{30}N_2O_4$ 398.2175; found 398.2190; and 16 (7 mg, 10%) as an amorphous solid: Rf = 0.17; IR ($CHCl_3$) 2780, 2730, 1720, 1700, 1600 cm^{-1}; UV (EtOH) λmax 245, 284 nm; MS m/e 398 (M^+), 312, 124 (base peak); ^1H NMR ($CDCl_3$) δ 0.65 (t, 3H, J = 7.3 Hz), 0.8-2.6 (m, 9H), 2.96-3.28 (m, 2H), 3.72 (s, 3H), 3.80 (brs, 3H), 4.50 (brd, 1H, J = 8.0 Hz), 7.07 (t, 1H, J = 7.9 Hz), 7.12-7.36 (m, 2H), 7.86 (br, 1H); ^{13}C NMR ($CDCl_3$) 6.9 (q), 21.6 (t), 27.3 (t), 30.5 (t), 34.1 (t), 35.6 (s), 39.9 (t), 43.7 (d), 51,8 (q), 52.3 (t), 52.7 (q), 53.5 (t), 68.3 (d), 70.0 (d), 116.7 (d), 122.4 (d), 123.6 (d), 127.7 (d), 138.1 (s), 140.0 (s), 153.9 (s), 174.9 (s).

Isomerization of eburcine (15)

To a solution of 15 (26 mg, 0.065 mmol) in methanol (2 ml) was added 10% sodium hydroxide (2 ml) and the mixture was refluxed for 1h. After removal of the solvent, the residue was acidified (pH 2) by 10% hydrochloric acid and treated with excess ethereal diazomethane solution. The mixture was basified by sodium bicarbonate and extracted with methylene chloride (2 x 15 ml). Chromatographic separation (alumina, hexane : ethyl acetate = 5 : 1) afforded 16 (14.6 mg, 56%). Trace of 15 was detected on TLC.

Catalytic reduction of 1-Methoxycarbonylvincadifformine (17)

A sample of 17 (6 mg, 0.015 mmol) in methanol (1 ml) was hydrogenated over Raney-Nickel (W 2) at ordinary pressure for 24h. The catalyst was removed by filtration and the filtrate was concentrated to give an colorless amorphous 15 (4 mg). The TLC behavior and NMR spectrum were identical with authentic eburcine (15).

1-Methoxycarbonylvincadifformine (17) and 1-Methoxycarbonyl-2,3-dehydro-3-dimethoxy-methylaspidospermidine (18)

To a solution of aldehyde 12 (103 mg, 0.281 mmol) in tert-butanol (6.5 ml) and 2-methyl-2-butene (1.4 ml, 13.2 mmol) was added dropwise a solution of sodium chlorite (40 mg, 0.44 mmol) and sodium phosphate, monobasic monohydrate (52 mg, 0.33 mmol) in water (0.4 ml). The mixture was stirred at 30°C for 16h and concentrated. The crude residue was dissolved in methanol (3 ml) and methyl orthoformate (3 ml). The mixture was stirred in the presence of catalytic amount of concentrated hydrochloric acid for 0.5h. The reaction mixture was treated with excess ethereal diazomethane at 0°C. After removal of the solvent, the residue was chromatographed on silica gel (hexane : ethyl acetate = 3 : 1) to obtain 17 (40 mg, 36%): mp 118-120°C (recrystallized from ethanol); IR (Nujol) 2780, 2730, 1725, 1715, 1605 cm^{-1}; UV (EtOH) λ max 243, 268 nm; MS m/e 396 (M^+), 124 (base peak); ^1H NMR ($CDCl_3$) δ 0.57 (t, 3H, J = 7.4 Hz), 0.6-0.82 (m, 1H), 1.02-1.36 (m, 2H), 1.50-1.94 (m, 4H), 2.02 (dd, 1H, 16.4, 1.8 Hz), 2.09 -2.47 (m, 4H), 2.93 (t, 1H, J = 7.0 Hz), 3.04 (d, 1H, 16.4 Hz), 3.04-3.22 (m, 1H), 3.78 (s, 3H), 3.83 (s, 3H), 7.10 (dt, 1H, J = 7.4, 1.2 Hz), 7.17-7.38 (m, 2H), 7.84 (d, J = 8.4 Hz); Anal calcd for $C_{23}H_{28}N_2O_4$: C, 69.68; H, 7.12; N, 7.07. Found: C,69.72; H, 7.25; N, 7.16; and 18 (31 mg, 27%): mp 122-124 °C (recrystallized from ethanol); IR (Nujol) 2770, 2720, 1715, 1700 (sh), 1600 cm^{-1}; UV (EtOH) λmax 240, 277, 283 (sh) nm; MS m/e 412 (M^+), 397, 381, 124 (base peak); ^1H NMR ($CDCl_3$) δ 0.58-0.78 (m, 4H), 0.90-1.30 (m, 2H), 1.46-1.94 (m, 4H), 2.02 (dd, 1H, J = 16.2, 1.3 Hz), 2.08-2.37 (m, 4H), 2.63 (d, 1H, J = 16.2 Hz), 2.88-3.02 (m, 1H), 3.03-3.24 (m, 1H), 3.19 (s, 3H), 3.52 (s, 3H), 3.90 (s, 3H), 7.12 (t, 1H, J = 7.4 Hz), 7.18-7.35 (m, 2H), 7.66 (d, 1H, J = 8.0 Hz); Anal. calcd for $C_{24}H_{32}N_2O_4$: C, 69.88; H, 7.82; N, 6.79. Found: C, 69.94; H, 7.94; N, 6.73.

Deacetalization of 18

A solution of 18 (31 mg, 0.075 mmol) and catalytic amount of p-toluene sulfonic acid in acetone (4 ml) was allowed to stand at room temperature for 115h. After removal of the reagents, the residue was basified with 10% potassium carbonate (2 ml) and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate. After removal of the solvent, the residue was purified by chromatography (silica gel, hexane : ethyl acetate = 3 : 1) gave 12 (26 mg, 93%), which was superimposable on the authentic sample.

Vincadifformine (7)

A solution of 17 (8.9 mg, 0.022 mmol) in 10% methanolic sodium methoxide (1 ml) was refluxed for 15 min. After being cooled, the reaction mixture was poured onto ice-water (5 ml) and extracted with methylene chloride (2 x 15 ml). The extracts were washed with brine, dried over sodium sulfate and concentrated on a evaporator. The residue was purified by preparative TLC (silica gel, Hexane : ethyl acetate = 4 : 1) gave 7 (4.4 mg, 58%) as colorless needels: mp 124-126 °C (recrystallized from ethanol),(lit.[2] 124-125°C); IR ($CHCl_3$) 3370, 2930, 2850, 2770, 2700, 1665, 1605, cm^{-1}; UV (EtOH) λmax 226, 299, 328 nm; MS m/e 338 (M^+), 124 (base peak); ^1H NMR ($CDCl_3$) δ 0.50-0.74 (m, 4H), 0.82-1.10 (m, 1H), 1.12-1.36 (m, 1H), 1.42-2.66 (m, 8H), 2.29 (d, 1H, J = 15.5 Hz), 2.74 (d, 1H, J = 15.5 Hz), 2.94 (t, 1H, J = 7.2 Hz), 3.14 (brd, 1H, J = 11 Hz), 6.84 (d, 1H, J = 7.9 Hz), 7.91 (t, 1H, J = 7.5 Hz), 7.08-7.30 (m, 2H), 8.96 (brs, 1H), high resolution mass spectrum, calcd for $C_{21}H_{26}N_2O_2$ 338.1996; found 338.1995.

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