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SYNTHESIS OF 3-METHOXYELLIPTICINE AND ELLIPTICINE BY FRIEDEL-CRAFTS REACTION OF INDOLE-2,3-DICARBOXYLIC ANHYDRIDE AND SELECTIVE DEMETHYLATION

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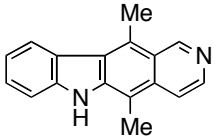
Abstract - Reaction of 1-benzylindole-2,3-dicarboxylic anhydride with 2,4,6-trimethoxypyridine in the presence of a Lewis acid gave 1-benzyl-3-(2,4,6-trimethoxynicotinoyl)indole-2-carboxylic acid as the sole product in high yield, which could be changed to 1-benzyl-3-(2,4,6-trimethoxynicotinoyl)indole. 1-Benzyl-3-(2,4,6-trimethoxynicotinoyl)indole was converted to 3-methoxy-ellipticine and ellipticine by selective demethylation and triflation of the methoxy group.

Antitumor pyridocarbazole alkaloid ellipticine, isolated from the leaves of *Ochrasia elliptica*[1] and many of its derivatives showed potent antitumor activities.[2,3] A large number of useful syntheses of ellipticine have been developed.[4] We also have shown a new synthetic method of ellipticine by using a reaction of indole-2,3-dicarboxylic anhydride with (3-bromo-4-pyridyl)triisopoxytitanium[5] or 4-lithio-3-bromo-pyridine,[6] but in this reaction a severe dry condition was required. Recently, we reported a novel synthesis of 3-(4-methoxybenzoyl)indoles by a reaction of 1-benzylindole-2,3-dicarboxylic anhydride (**1**) with anisoles in the presence of a Lewis acid[7] and its application to the synthesis of olivacine.[8]



ellipticine

In this paper we show in detail a simple and useful synthesis of 3-methoxyellipticine and ellipticine by regioselective Friedel-Crafts reaction of 1-benzylindole-2,3-dicarboxylic anhydride with 2,4,6-trimethoxypyridine.

Reaction of 1-benzylindole-2,3-dicarboxylic anhydride (**1**)[9] (1 equivalent) with 4-methoxypyridine (**2a**) or 2,4-dimethoxypyridine (**2b**) (1 equivalent) in CH_2Cl_2 in the presence of titanium chloride (IV) (2 equivalents) at room temperature resulted in recovery of the starting material (Entries 1, 2), but with 2,4,6-trimethoxypyridine (**2c**)[10] gave 1-benzyl-3-(2,4,6-trimethoxyisonicotinoyl)indole-2-carboxylic acid (**3c**) in 25% yield (Entry 3). Many attempts to attain **3c** under various conditions were less than satisfactory (Entries 4, 5). However, treatment of **1** (1 equivalent) with **2c** (2 equivalents) in the presence of titanium chloride(IV) (3 equivalents) afforded **3c** in 98% yield (Entry 6). In a similar manner, **3d** was obtained from **1** and 2,6-dimethoxypyridine (**2d**) (Entry 7) (Scheme 1) (Table 1). The carboxylic acid (**3c**) was converted to ketone (**4**) by treatment with copper chromite in hot quinoline (180°C) in 94% yield.

Scheme 1

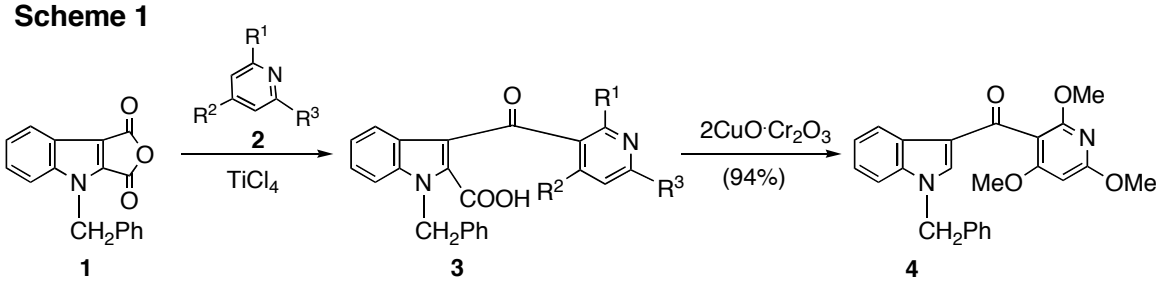


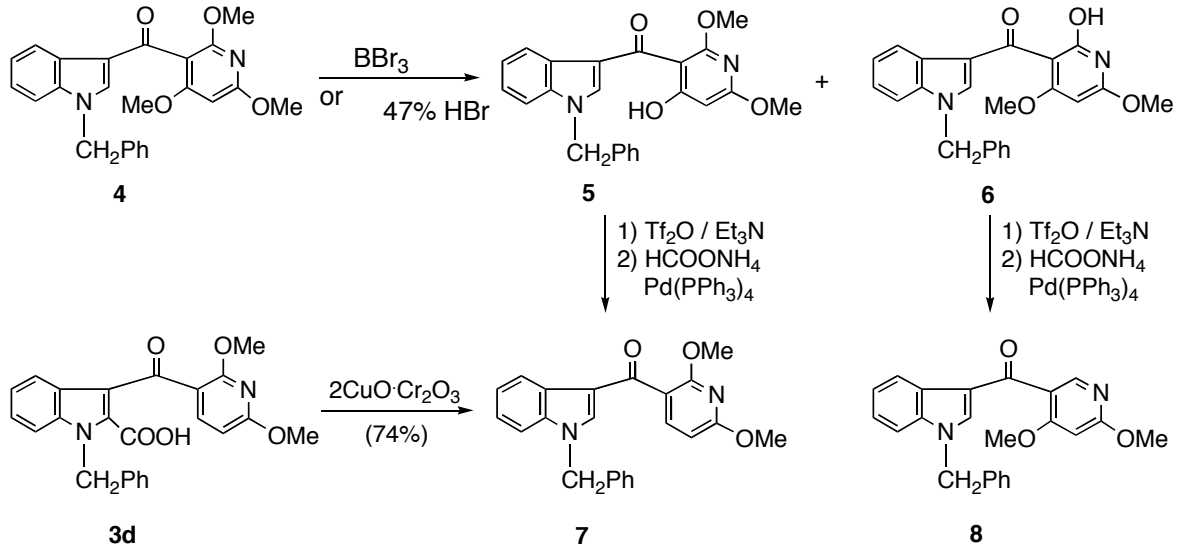
Table 1

Entry	**2**	R^1	R^2	R^3	**2** (Equiv.)	$TiCl_4$ (Equiv.)	Yield (%)
1	a	H	OMe	H	1	2	recovered
2	b	OMe	OMe	H	1	2	recovered
3	c	OMe	OMe	OMe	1	2	25
4	c	OMe	OMe	OMe	1	4	mixture
5	c	OMe	OMe	OMe	2	2	26
6	c	OMe	OMe	OMe	2	3	98
7	d	OMe	H	OMe	2	3	75

Treatment of ketone (**4**) with boron tribromide gave a mixture of 4-hydroxy (**5**) and 2-hydroxy derivative (**6**) in 37% and 47% yields, respectively, but a mixture of **4** and 47% hydrobromic acid in acetic acid

warmed to 50°C to provided **6** in 93% yield as the sole product. Reaction of the 4-hydroxy derivative (**5**) with triflic anhydride (Tf_2O) in the presence of triethylamine gave the corresponding triflate, which could be changed to 2,6-dimethoxy compound (**7**) by reduction with ammonium formate in the presence of 10% Pd-C in hot methanol in 92% yield. In a similar manner, **6** was led to 2,4-dimethoxy compound (**8**) in 82% yield. **7** was also obtained by decarboxylation of the carboxylic acid (**3d**) in the presence of copper chromite in quinoline (170-180°C) in 74% yield. (Scheme 2)

Scheme 2

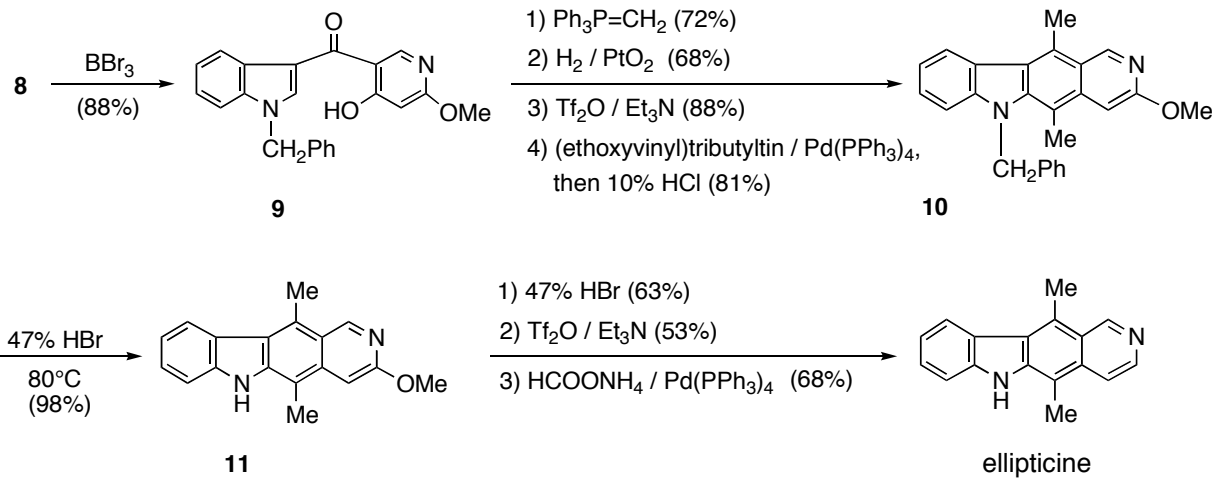


Selective demethylation of the 4-methoxy group of **8** was performed by treatment with boron tribromide to provide 4-hydroxy compound (**9**) in 88% yield, which was changed by reaction with $Ph_3P{=}CH_2$ and catalytic reduction in the presence of PtO_2, followed by treatment with Tf_2O in the presence of triethylamine to give the corresponding triflate. The triflate was reacted with (1-ethoxyvinyl)tributyltin in the presence of tetrakis(triphenylphosphine)palladium (0) ($Pd(PPh_3)_4$) in refluxing toluene to provide the ethoxyvinyl compound, which was treated with 10% hydrochloric acid in tetrahydrofuran to give 6-benzyl-3-methoxyellipticine (**10**) in 81% yield.

Debenzylation of **10** was performed by treatment with 47% hydrobromic acid at 80°C to provide 3-methoxyellipticine (**11**) (98%). When **11** was treated with boron tribromide at room temperature for 24 h, **11** was recovered, but reaction of **11** with hot 47% hydrobromic acid in acetic acid gave 3-hydroxy-ellipticine in 63% yield. Triflation of 3-hydroxyellipticine was performed by treatment with Tf_2O in the presence of triethylamine to provide the corresponding triflate and subsequent hydrogenation of the

triflate with ammonium formate in the presence of $Pd(PPh_3)_4$ in hot methanol afforded ellipticine[5] in 68% yield. (Scheme 3)

Scheme 3



EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. The ^{1}H-NMR spectra were determined on a JEOL JNM-GSX 270 spectrometer using tetramethylsilane as an internal standard and $CDCl_3$ as solvent. The IR spectra were recorded with a JASCO FT/IR-7000 spectrophotometer. The high MS spectra were recorded on a JOEL JMS-HX100 spectrometer. Column chromatography was performed on E. Merck silica gel 60 (70-230 mesh or 230-400 mesh). Thin-layer (TLC) and preparative thin-layer chromatography (PLC) were performed on E. Merck silica gel 60 F_{254}. Tetrahydrofuran (THF) was distilled from sodium and benzophenone prior to use. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride prior to use.

Reaction of 1-Benzylindole-2,3-dicarboxylic Anhydride (1) with Methoxypyridines (2): General procedure

1-Benzyl-3-(2,4,6-trimethoxynicotinoyl)indole-2-carboxylic Acid (3c)

To a solution of 1-benzylindole-2,3-dicarboxylic anhydride (**1**)[9] (4.16 g, 15 mmol) and 2,4,6-trimethoxypyridine (**2c**)[10] (5.07 g, 30 mmol) in dichloromethane (60 mL) was added 1.0 M titanium (IV) chloride in dichloromethane solution (45 mL, 45 mmol) and the mixture was stirred for 18 h at rt. Water was added to the reaction mixture and the mixture was extracted with dichloromethane. The combined extracts were washed with water and dried over Na_2SO_4, then concentrated under reduced

pressure. The residue was purified by column chromatography on silica gel ($CHCl_3$: MeOH = 10 : 1) to give 1-benzyl-3-(2,4,6-trimethoxynicotinoyl)indole-2-carboxylic acid (**3c**) (6.58 g, 98%), mp 164-168°C (from *n*-hexane-acetone). IR (Nujol) ν: 1723, 1596 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.65 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 4.01 (3H, s, OCH_3), 6.02 (1H, s, H-5'), 6.02 (2H, s, C*H*$_2$Ph), 7.08-7.34 (8H, m, aromatic protons), 7.46 (1H, d, *J* = 8.0 Hz, H-4). *Anal.* Calcd for $C_{22}H_{22}N_2O_6$: C, 67.26; H, 4.97; N, 6.27. Found: C, 67.19; H, 4.95; N, 6.34.

1-Benzyl-3-(2,6-dimethoxynicotinoyl)indole-2-carboxylic Acid (3d)

Using a procedure similar to that described for the preparation of **3c**, **3d** (75%) was obtained from **1**, mp 157-159 °C (from *n*-hexane-acetone). IR ($CHCl_3$) ν: 1716, 1592 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.77 (3H, s, OCH_3), 4.04 (3H, s, OCH_3), 6.07 (2H, s, C*H*$_2$Ph), 6.44 (1H, d, *J* = 8.0 Hz, H-5'), 7.00-7.36 (8H, m, aromatic protons), 7.47 (1H, d, *J* = 8.0 Hz, H-4'), 7.84 (1H, d, *J* = 8.0 Hz, H-4). HRMS *m/z* (M^+) calcd for $C_{24}H_{20}N_2O_2$, 416.1372. Found 416.1350.

1-Benzyl-3-(2,4,6-trimethoxynicotinoyl)indole (4)

A mixture of 1-benzyl-3-(2,4,6-trimethoxynicotinoyl)indole-2-carboxylic acid (**3c**) (3.70 g, 8.3 mmol) and copper chromite (0.33 g) in quinoline (83 mL) was heated at 180°C for 0.5 h and the insoluble material was removed by filtration through Celite. Water was added to the filtrate and the mixture was extracted with $CHCl_3$. The combined extracts were washed with water, then with 5% hydrochloric acid and water. The solution was dried over Na_2SO_4 and evaporated off to give a residue, which was purified by column chromatography (*n*-hexane : AcOEt = 2 : 1) to yield 1-benzyl-3-(2,4,6-trimethoxynicotinoyl)indole (**4**) (3.10 g, 94%), mp 175-176 °C (from AcOEt). IR (Nujol) ν: 1625 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.71 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 5.30 (2H, s, C*H*$_2$Ph), 5.95 (1H, s, H-5'), 7.08-7.35 (8H, m, aromatic protons), 7.51 (1H, s, H-2), 8.31-8.37 (1H, m, H-4). *Anal*. Calcd for $C_{24}H_{22}N_2O_4$: C, 71.63; H, 5.51; N, 6.96. Found: C, 71.60; H, 5.50; N, 7.03.

Demethylation of 1-Benzyl-3-(2,4,6-trimethoxynicotinoyl)indole (4)

1. By Boron Tribromide

To a solution of 1-benzyl-3-(2,4,6-trimethoxynicotinoyl)indole (**4**) (20 mg, 0.05 mmol) in dichloromethane (2 mL) was added 1.0 M boron tribromide in dichloromethane solution (0.6 mL, 0.06 mmol) at 0°C and the mixture was stirred for 2 h. Water was added to the reaction mixture and the mixture was neutralized with saturated sodium hydrogen carbonate solution. The solution was extracted with dichloromethane and the combined extracts were washed with water and dried over Na_2SO_4, then

concentrated under reduced pressure. The residue was purified by column chromatography on silica gel ($CHCl_3$: MeOH = 10 : 1) to give 1-benzyl-3-(4-hydroxy-2,6-dimethoxynicotinoyl)indole (**5**) (7 mg, 37%) and 1-benzyl-3-(2-hydroxy-4,6-dimethoxynicotinoyl)indole (**6**) (9 mg, 47%).

5; IR ($CHCl_3$) ν: 1623 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.65 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 5.33 (2H, s, C*H*$_2$Ph), 5.95 (1H, s, H-5'), 7.16-7.40 (8H, m, aromatic protons), 7.72 (1H, s, H-2), 8.19 (1H, m, H-4), 12.58 (1H, s, OH).

6; mp 240-242°C (from MeOH). IR ($CHCl_3$) ν: 1634 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.51 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 5.34 (2H, s, C*H*$_2$Ph), 5.83 (1H, s, H-5'), 7.16-7.40 (8H, m, aromatic protons), 7.62 (1H, s, H-2), 8.14 (1H, m, H-4). *Anal.* Calcd for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21. Found: C, 71.20; H, 5.25; N, 7.22.

2. By 47% Hydrobromic Acid in Acetic Acid

A mixture of **4** (404 mg, 1 mmol), 47% hydrobromic acid (5 mL) and acetic acid (2 mL) was heated at 50°C for 8 h and the reaction mixture was neutralized by saturated sodium hydrogen carbonate solution. The solution was extracted with $CHCl_3$. The combined extracts were washed with water and dried over Na_2SO_4, then concentrated under reduced pressure to give a residue, which was purified by column chromatography ($CHCl_3$: MeOH = 30 : 1) to yield **6** (362 mg, 93%).

1-Benzyl-3-(2,6-dimethoxynicotinoyl)indole (7)

1. In the Presence of Copper Chromite in Hot Quinoline

A mixture of 1-benzyl-3-(2,6-dimethoxynicotinoyl)indole-2-carboxylic acid (**3d**) (710 mg, 1.7 mmol) and copper chromite (0.68 mg) in quinoline (17 mL) was heated at 180°C for 1 h and the insoluble material was removed by filtration through Celite. Water was added to the filtrate and the mixture was extracted with $CHCl_3$. The combined extracts were washed with water, then with 5% hydrochloric acid and water. The solution was dried over Na_2SO_4 and evaporated off to give a residue, which was purified by column chromatography (*n*-hexane : AcOEt = 3 : 2) to yield 1-benzyl-3-(2,6-dimethoxynicotinoyl)indole (**7**) (469 mg, 74%).

2. By Reduction of the Triflate with Ammonium Formate in the Presence of $Pd(PPh_3)_4$

Triflic anhydride (0.016 mL, 0.096 mmol) was added to a mixture of 1-benzyl-3-(4-hydroxy-2,6-dimethoxynicotinoyl)indole (**5**) (30 mg, 0.08 mmol) and triethylamine (0.027 mL, 0.8 mmol) in dichloromethane (1 mL) and the mixture was stirred for 1 h at rt. Water was added to the reaction

mixture and the mixture was extracted with dichloromethane. The combined extracts were washed with water and dried over Na_2SO_4, then concentrated under reduced pressure to give a residue (35 mg).

A suspension of the residue (31 mg, 0.06 mmol)), ammonium formate (23 mg, 0.36 mmol), and $Pd(PPh_3)_4$ (13 mg, 0.012 mmol) in MeOH (1 mL) was refluxed for 2 h. Water was added to the reaction mixture and the mixture was extracted with $CHCl_3$. The combined extracts were washed with water and dried over Na_2SO_4, then concentrated under reduced pressure to give a residue, which was purified by column chromatography (*n*-hexane : AcOEt = 5 : 1) to afford **7** (18 mg, 92%), mp 178°C (from AcOEt); IR ($CHCl_3$) ν: 1619 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.89 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 5.33 (2H, s, C*H*$_2$Ph), 6.36 (1H, d, *J* = 8.0 Hz, H-5'), 7.10-7.36 (8H, m, aromatic protons), 7.53 (1H, s, H-2), 7.78 (1H, d, *J* = 8 Hz, H-4'), 8.35-8.41 (1H, m, H-4). *Anal*. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52. Found: C, 74.19; H, 5.49; N, 7.58.

1-Benzyl-3-(4,6-dimethoxynicotinoyl)indole (8)

Triflic anhydride (0.81 mL, 4.8 mmol) was added to a mixture of 1-benzyl-3-(2-hydroxy-4,6-dimethoxynicotinoyl)indole (**6**) (1.56 g, 4.0 mmol) and triethylamine (1.1 mL, 8.0 mmol) in dichloromethane (20 mL) and the mixture was stirred for 1 h at rt. Water was added to the reaction mixture and the mixture was extracted with $CHCl_3$. The combined extracts were washed with water and dried over Na_2SO_4, then concentrated under reduced pressure to give a residue, which was purified by column chromatography (*n*-hexane : AcOEt = 3 : 2) to yield 1-benzyl-3-(4,6-dimethoxy-2-trifluoromethanesulfonyloxynicotinoyl)indole (1.97 g, 94%). IR (Nujol) ν: 1627 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.80 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 5.32 (2H, s, C*H*$_2$Ph), 6.30 (1H, s, H-5'), 7.12-7.35 (8H, m, aromatic protons), 7.52 (1H, s, H-2), 8.37-8.41 (1H, m, H-4).

A suspension of 1-benzyl-3-(4,6-dimethoxy-2-trifluoromethanesulfonyloxynicotinoyl)indole (2.08 g, 4.0 mmol), ammonium formate (1.51 g, 24 mmol), and $Pd(PPh_3)_4$ (0.93 g, 0.8 mmol) in MeOH (20 mL) was refluxed for 2 h. Water was added to the reaction mixture and the mixture was extracted with $CHCl_3$. The combined extracts were washed with water and dried over Na_2SO_4, then concentrated under reduced pressure to give a residue, which was purified by column chromatography (*n*-hexane : AcOEt = 2 : 1) to afford 1-benzyl-3-(4,6-dimethoxynicotinoyl)indole (**8**) (1.28 g, 85%), mp 161-162°C (from *n*-hexane-AcOEt). IR (Nujol) ν: 1624 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.80 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 5.33 (2H, s, C*H*$_2$Ph), 6.29 (1H, s, H-5'), 7.10-7.36 (8H, m, aromatic protons), 7.53 (1H, s, H-2), 8.20 (1H, s,

H-2'), 8.41-8.47 (1H, m, H-4). *Anal*. Calcd for $C_{23}H_{20}N_2O_3$: C, 74.18; H, 5.41; N, 7.52. Found: C, 74.15; H, 5.39; N, 7.55.

1-Benzyl-3-(4-hydroxy-6-methoxynicotinoyl)indole (9)

To a suspension of 1-benzyl-3-(4,6-dimethoxynicotinoyl)indole (**8**) (781 mg, 2.1 mmol) in dichloromethane (11 mL) was added 1.0 M boron tribromide in dichloromethane solution (3.7 mL, 3.7 mmol) at -20°C and the mixture was stirred for 2 h. Water was added to the reaction mixture. The mixture was neutralized with saturated sodium hydrogen carbonate solution, extracted with dichloromethane, and the combined extracts were washed with water and dried over Na_2SO_4, then concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (*n*-hexane : AcOEt = 5 : 1) to give 1-benzyl-3-(4-hydroxy-6-methoxynicotinoyl)indole (**9**) (658 mg, 88%), mp 148-149°C (from *n*-hexane-AcOEt). IR ($CHCl_3$) ν: 1628 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.98 (3H, s, OCH_3), 5.41 (2H, s, C*H*$_2$Ph), 6.33 (1H, s, H-2'), 7.12-7.40 (8H, m, aromatic protons), 7.78 (1H, s, H-2), 8.27-8.34 (1H, m, H-4), 8.71 (1H, s, H-2'), 12.67 (1H, s, OH). *Anal*. Calcd for $C_{22}H_{18}N_2O_3$: C, 73.73; H, 5.06; N, 7.82. Found: C, 73.72; H, 5.11; N, 7.83.

6-Benzyl-3-methoxyellipticine (10)

A solution of 1-benzyl-3-(4-hydroxy-6-methoxynicotinoyl)indole (**9**) (644 mg, 1.8 mmol) in THF (9 mL) was added to a solution of methylenetriphenylphosphorane [prepared from methyltriphenylphosphonium bromide (1.90 g, 5.4 mol) and 1.56 M *n*-butyllithium in *n*-hexane solution (3.5 mL, 5.4 mmol) in THF (9 mL) at rt] at 0°C under argon and the mixture was stirred for 4 h. The reaction mixture was acidified with saturated ammonium chloride solution and extracted with $CHCl_3$. The organic extracts were washed with water, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography (*n*-hexane : AcOEt = 1 : 2) to give 1-(1-benzyl-3-indolyl)-1-(4-hydroxy-6-methoxy-3-pyridinyl)ethene (461 mg, 72%) as a white solid. IR ($CHCl_3$) ν: 3472, 1625 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.93(3H, s, OCH_3), 5.27 (2H, s, C*H*$_2$Ph), 5.32 (2H, d, *J*= 1.3 Hz, C=C*H*$_2$), 6.28 (1H, s, H-5'), 7.04 (1H, s, H-2), 7.05-7.36 (8H, m, aromatic protons), 7.78 (1H, m, H-4), 8.05 (1H, s, H-2').

A suspension of 1-(1-benzyl-3-indolyl)-1-(4-hydroxy-6-methoxy-3-pyridinyl)ethene (461 mg, 1.29 mmol) and platinum(IV) oxide (46 mg) in EtOH (7 mL) was stirred for 6 h under hydrogen. The catalyst was removed by filtration through Celite and the filtrate was evaporated off. The residue was purified by column chromatography ($CHCl_3$: MeOH = 20 : 1) to yield 1-(1-benzyl-3-indolyl)-1-(4-

hydroxy-6-methoxy-3-pyridinyl)ethane (314 mg, 68%) as a pale yellow solid. IR ($CHCl_3$) ν: 3422 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.63 (3H, d, *J* = 7.2 Hz, CH_3), 3.71 (3H, s, OCH_3), 4.60 (1H, q, *J* = 7.2 Hz, Ar-C*H*(CH_3)-Ar), 5.26 (2H, s, C*H*$_2$Ph), 6.10 (1H, s, H-5'), 6.92-7.43 (8H, m, aromatic protons), 7.44-7.54 (1H, br s, OH).

Triflic anhydride (0.161 mL, 0.96 mmol) was added to a mixture of 1-(1-benzyl-3-indolyl)-1-(4-hydroxy-6-methoxy-3-pyridinyl)ethane (286 mg, 0.8 mmol) and triethylamine (0.233 mL, 1.6 mmol) in dichloromethane (20 mL) and the mixture was stirred for 1 h at -78°C. Water was added to the reaction mixture and the mixture was extracted with $CHCl_3$. The combined extracts were washed with water and dried over Na_2SO_4, then concentrated under reduced pressure to give a residue, which was purified by column chromatography (*n*-hexane : AcOEt = 5 : 1) to yield 1-(1-benzyl-3-indolyl)-1-(6-methoxy-4-trifluoromethanesulfonyloxy-3-pyridinyl)ethane (345 mg, 88%). IR (Nujol) ν: 1622 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.65 (3H, d, *J* = 7.2 Hz, CH_3), 3.81 (3H, s, OCH_3), 4.62 (1H, q, *J* = 7.2 Hz, Ar-C*H*(CH_3)-Ar), 5.24 (2H, s, C*H*$_2$Ph), 6.81 (1H, s, H-5'), 6.94-7.46 (8H, m, aromatic protons).

A mixture of 1-(1-benzyl-3-indolyl)-1-(6-methoxy-4-trifluoromethanesulfonyloxy-3-pyridinyl)ethane (167 mg, 0.34 mmol), (1-ethoxyvinyl)tributyltin (0.115 mL, 0.34 mmol), diisopropylethylamine (0.071 mL, 0.41 mmol), lithium chloride (43 mg, 1.0 mmol), and $Pd(PPh_3)_4$ (20 mg, 0.017 mmol) in toluene (4 mL) was refluxed for 2 h under argon. The insoluble material was filtered off and the filtrate was concentrated to give a residue. A mixture of the residue and 10% hydrochloric acid (3 mL) in THF (3 mL) was stirred for 16 h at rt. The reaction mixture was neutralized by addition of 5% sodium hydrogen carbonate solution and extracted with $CHCl_3$. The organic extracts were washed with water, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography ($CHCl_3$) to give 6-benzyl-3-methoxyellipticine (**10**) (100 mg, 81%) as a greenish yellow solid, mp 229-230°C (from AcOEt). IR ($CHCl_3$) ν: 1614 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 2.74 (3H, s, CH_3), 3.26 (3H, s, CH_3), 4.00 (3H, s, OCH_3), 5.86 (2H, s, C*H*$_2$Ph), 7.08-7.53 (7H, m, aromatic protons), 8.34 (1H, d, *J* = 8.0 Hz, H-10), 9.48 (1H, s, H-1). *Anal*. Calcd for $C_{25}H_{22}N_2O$: C, 81.94; H, 6.05; N, 7.65. Found: C, 81.92; H, 6.10; N, 7.61.

3-Methoxyellipticine (11)

A solution of 6-benzyl-3-methoxyellipticine (**10**) (84 mg, 0.23 mmol) in 47% hydrobromic acid (3 mL) and acetic acid (3 mL) was heated at 80°C for 15 min. Water was added to the reaction mixture and the precipitated solid was collected by filtration to give 3-methoxyellipticine (**11**) (62 mg, 98%) as an

orange solid, mp >300°C (from MeOH). IR ($CHCl_3$) ν: 1614 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 2.74 (3H, s, CH_3), 3.24 (3H, s, CH_3), 4.09 (3H, s, OCH_3), 7.20-7.58 (4H, m, aromatic protons), 8.33 (1H, d, *J* = 8.0 Hz, H-10), 9.47 (1H, s, H-1), 11.32 (1H. br s, NH). *Anal*. Calcd for $C_{18}H_{16}N_2O$: C, 78.23; H, 5.84; N, 10.14. Found: C, 78.21; H, 5.79; N, 10.08.

Ellipticine

A solution of 3-methoxyellipticine (**11**) (17 mg, 0.06 mmol) in 47% hydrobromic acid (1 mL) and acetic acid (1 mL) was refluxed for 28 h. Water was added to the reaction mixture and the precipitated solid was collected by filtration to give 3-hydroxyellipticine (10 mg, 63%). ^{1}H-NMR (DMSO-d_6) δ: 2.64 (3H, s, CH_3), 3.17 (3H, s, CH_3), 7.01 (1H, s, H-4), 7.16-7.52 (3H, m, aromatic protons), 8.26 (1H, d, *J* = 8.0 Hz, H-10), 9.27 (1H, s, H-1), 11.10 (1H. br s, NH).

Triflic anhydride (0.06 mL, 0.036 mmol) was added to a mixture of 3-hydroxyellipticine (8.0 mg, 0.03 mmol) and triethylamine (0.083 mL, 0.06 mmol) in dichloromethane (0.5 mL) and the mixture was stirred for 1 h at 0°C. Water was added to the reaction mixture and the mixture was extracted with $CHCl_3$. The combined extracts were washed with water and dried over Na_2SO_4, then concentrated under reduced pressure to give a residue, which was purified by PLC ($CHCl_3$) to yield 3-trifluoromethanesulfonyloxyellipticine (6.4 mg, 53%). ^{1}H-NMR ($CDCl_3$) δ: 2.65 (3H, s, CH_3), 3.11 (3H, s, CH_3), 7.28-7.61 (3H, m, Ar), 7.65 (1H, s, H-4), 8.02 (1H. br s, NH), 8.29 (1H, d, *J* = 8.0 Hz, H-10), 9.29 (1H, s, H-1).

A suspension of 3-trifluoromethanesulfonyloxyellipticine (6.0 mg, 0.015 mmol), ammonium formate (5.7 mg, 0.09 mmol), and $Pd(PPh_3)_4$ (3.5 mg, 0.003 mmol) in MeOH (1 mL) was refluxed for 5 h. Water was added to the reaction mixture and the mixture was extracted with $CHCl_3$. The combined extracts were washed with water and dried over Na_2SO_4, then concentrated under reduced pressure to give a residue, which was purified by PLC ($CHCl_3$) to give ellipticine[5] (2.5 mg, 68%), mp >300 °C (from MeOH). ^{1}H-NMR (DMSO-d_6) δ: 2.80 (3H, s, CH_3), 3.27 (3H, s, CH_3), 7.22-7.33 (1H, m, aromatic protons), 7.49-7.61 (2H, m, aromatic protons), 7.91 (1H, d. *J* = 6.0 Hz, H-4), 8.36 (1H, d, *J* = 8.0 Hz, H-10), 8.43 (1H, d, *J* = 6 Hz, H-3), 9.69 (1H, s, H-1), 11.25 (1H, s, NH). HRMS *m/z* (M^+) calcd for $C_{17}H_{14}N_2$: 246.1157. Found: 246.1185.

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