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Total Syntheses of Ellipticine Alkaloids and their Amino Analogues

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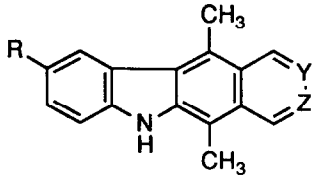
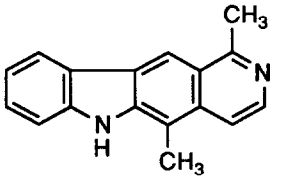
ABSTRACT: Staudinger reaction of **9** with triphenylphosphine gave 2,4-dihydropyrrolo[3,4-*b*]indole **10**. Treatment of **10** with di-*tert*-butyl dicarbonate and 4-dimethylaminopyridine gave **11**. Diels-Alder reaction of **11** with 3,4-pyridyne gave cycloadducts **12** and **13**, which were converted into ellipticine **1** and isoellipticine **2**. New amino analogues of ellipticine **27** and **28** were also synthesized by this new route.

The ellipticine family of alkaloids ellipticine **1**, 9-methoxyellipticine **3**, and olivacine **4** possess pronounced anticancer activity.[1] Since their isolation[2] the synthesis of ellipticine alkaloids and derivatives has been extensively investigated. While several reviews on the subject appeared with the emphasis on the different aspects,[3] new and efficient synthesis of ellipticine **1**, or the more potent new derivatives, are still highly desirable.[4] Recently Gribble reported the Diels-Alder approach to ellipticine **1** using furo[3,4-*b*]indole as the diene part.[5] Moody described the synthesis of ellipticine using the Diels-Alder reaction of pyrano[3,4-*b*]indol-3-one with pyridyne.[6] In our study of the ellipticine synthesis, we reported the synthesis and Diels-Alder reactions of 2,4-dihydropyrrolo[3,4-*b*]indole ring system.[7] We now report the application of this Diels-Alder reaction toward the total syntheses of ellipticine **1**, isoellipticine **2** and new amino analogues **27** and **28**.



1 R = H, Y = N, Z = CH
2 R = H, Y = CH, Z = N
3 R = OCH_3, Y = N, Z = CH



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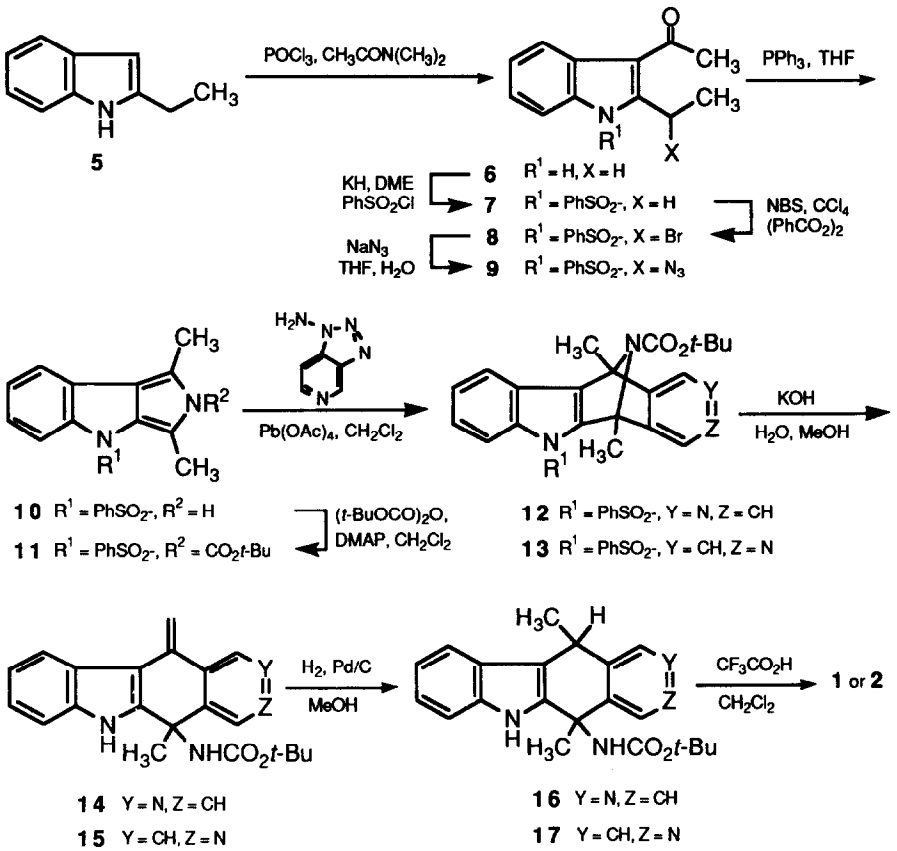
RESULTS AND DISCUSSION

The syntheses of ellipticine **1** and isoellipticine **2** were carried out as shown in Scheme I. Acetylation of 2-ethylindole **5** with *N,N*-dimethylacetamide and phosphorus oxychloride gave **6** (90%).[8] Treatment of **6** with potassium hydride and then phenylsulfonyl chloride in dimethoxyethane afforded **7** (76%). Bromination of **7** with *N*-bromosuccinimide and dibenzoyl peroxide gave bromide **8** (82%). Bromide **8** was then allowed to react with sodium azide in aqueous tetrahydrofuran to give azido compound **9** (95%).

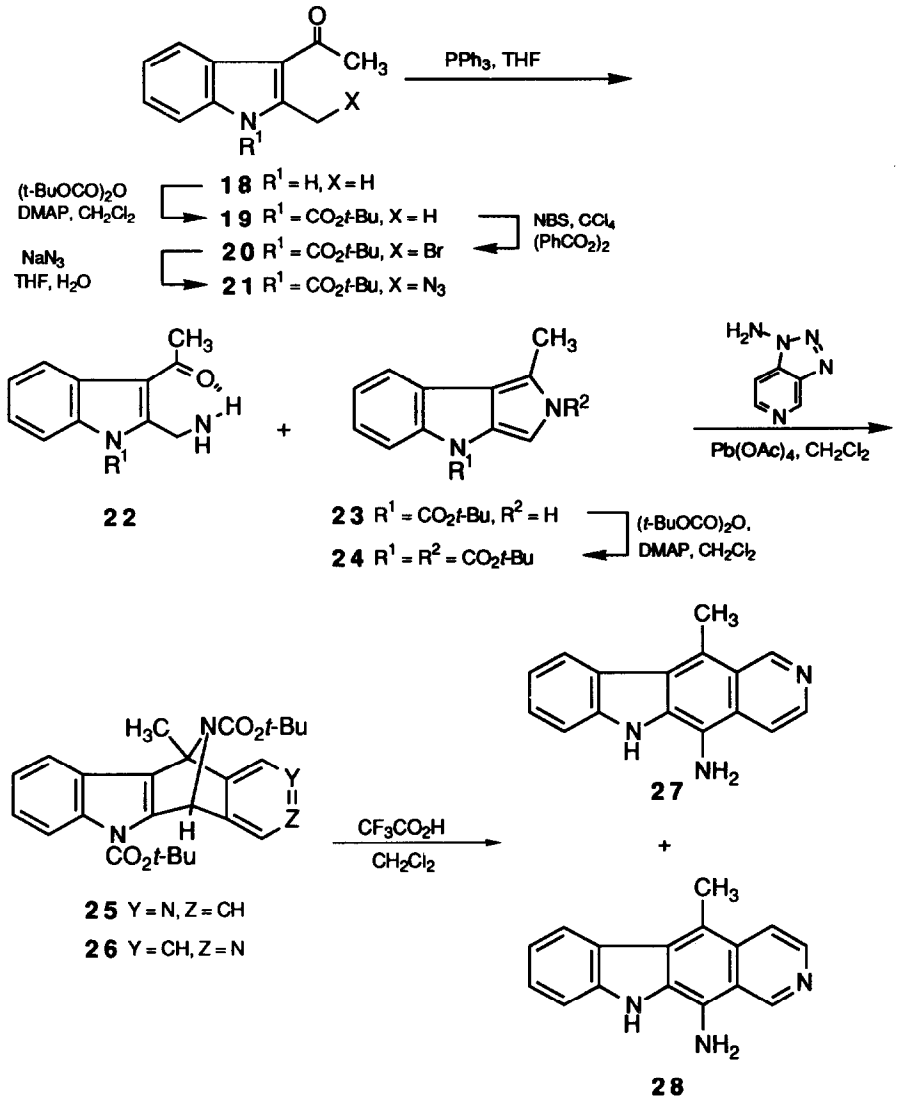
Scheme I



A Staudinger reaction[9] of **9** with triphenylphosphine produced dihydropyrrolo[3,4-*b*]indole **10** (90%). Reaction of **10** with di-*tert*-butyl dicarbonate and 4-dimethylaminopyridine gave **11** (90%).[10] Diels-Alder reaction of **11** with 3,4-pyridyne, generated from 1-aminotriazolo[4,5-*c*]pyridine with lead tetraacetate,[11] afforded cycloadducts **12** and **13** (62% in a 55:45 ratio). Treatment of the mixture **12** and **13** with sodium hydroxide in refluxing aqueous methanol gave **14** (35%) and **15** (39%). Intermediates **14** and **15** were separated and hydrogenated separately, using 5% palladium on carbon as the catalyst, to give **16** (80%) and **17** (83%), respectively. Treatment of **16** and **17** with trifluoroacetic acid in dichloromethane afforded ellipticine **1**

(85%) and isoellipticine **2** (78%) respectively. Data (^{1}H NMR, MS, IR, UV, mp) of **1** were identical with that of an authentic sample.[12] Data of **2** were identical with the reported data.[5]

Scheme II



We then applied this new approach for the preparation of new amino analogues of ellipticine, **27** and **28**, Scheme II. Reaction of **18**[8] with di-*tert*-butyl dicarbonate and 4-dimethylaminopyridine gave **19** (95%). NBS bromination of **19** gave bromide **20** (99%). Treatment of **20** with sodium azide in aqueous THF gave azido compound **21** (96%). A Staudinger reaction of **21** with triphenylphosphine produced pyrrolo[3,4-*b*]indole **23** (87%) and amino ketone **22** (11%). Amino ketone **22** was stable, and did not cyclize to **23** at room temperature. Compound **23** was reacted with di-*tert*-butyl dicarbonate and 4-dimethylaminopyridine to afford

24 (93%). Diels-Alder reaction of **24** with 3-pyridyne gave **25** and **26** in 65% total yield. The mixture of **25** and **26** was then treated with trifluoroacetic acid in dichloromethane to give the new ellipticine analogues 5-amino-5-demethylellipticine **27** and 5-amino-5-demethylisoellipticine **28** (60%). Compounds **27** and **28** were separated by silica gel chromatography and characterized.

In summary, we have described a new route for the syntheses of ellipticine alkaloids based on the Diels-Alder reactions of 2,4-dihydropyrrolo[3,4-*b*]indoles with 3-pyridyne. This method also provides an efficient entry to the preparation of new amino analogues of ellipticine. The anticancer activity of new amino analogues **27** and **28** is currently under investigation.

Experimental Section

General. ^{1}H NMR spectra were recorded on a Varian EM-390, JEOL HX-100 or a Bruker AM-400 spectrometer. ^{13}C NMR spectra were recorded on a Bruker AM-400 spectrometer. Mass spectra refer to the electron impact mass spectra and were recorded on a JEOL TMS-D-100 mass spectrometer. High-resolution mass spectra were recorded on a JEOL HX-110 mass spectrometer. IR spectra were recorded on a Perkin-Elmer 781 spectrometer, UV spectra were recorded on a Perkin-Elmer Lambda 5 UV-VIS spectrometer. Melting points were determined with a Büchi 530 melting point apparatus and were uncorrected. Flash column chromatography was performed as follows: silica gel, Merck No. 7736 Kieselgel 60H, was placed in a sintered glass funnel packed dry. Solvent was flushed through the silica gel under a water aspirator vacuum. The compound was then deposited with a minimal amount of solvent and eluted with solvent under a water aspirator vacuum. Ether and tetrahydrofuran (THF) were distilled from potassium/sodium metal under a nitrogen atmosphere with benzophenone ketyl as the indicator. All reactions were conducted under a nitrogen atmosphere. Elemental analyses were performed by the Microanalytical Laboratory of NSC Regional Instrumentation Center operated by Department of Chemistry, National Cheng Kung University, Tainan, Taiwan.

1-(Phenylsulfonyl)-2-ethyl-3-indolyl Methyl Ketone (7). To a suspension of potassium hydride (863 mg, 21.6 mmol) in dry dimethoxyethane (20 mL) was added a solution of **6** (4.0 g, 21.4 mmol) in dimethoxyethane (80 mL) dropwise at -78°C The reaction mixture was then warmed to 0°C and stirred for 1 h at room temperature. This solution was then added to a solution of phenylsulfonyl chloride (3.953 g, 22.5 mmol) and imidazole (68 mg, 1.0 mmol) in dimethoxyethane (30 mL) at -78°C. The mixture was warmed to room temperature and stirred for 15 h. Water (100 mL) was added. The mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). Concentration and silica gel flash column chromatography (hexane-dichloromethane; 2:1) gave the title compound **7** (5.32 g, 76%). Recrystallization (hexane and ethyl acetate mixture) gave colorless needles, mp 92-93°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (t, J = 7.3 Hz, 3 H), 2.63 (s, 3 H), 3.35 (q, J = 7.3 Hz, 2 H), 7.31-7.55 (m, 5 H), 7.76-7.87 (m, 3 H) 8.25-8.27 (m, 1 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 15.2 (q), 20.8 (t), 32.0 (q), 114.9 (d), 120.2 (s), 120.8 (d), 124.4 (d), 124.7 (d), 126.3 (d, two carbons), 127.2 (s), 129.5 (d, two carbons), 134.1 (d), 136.0 (s), 139.0 (s), 149.3 (s), 195.5 (s); IR ($CHCl_3$) 1660 cm^{-1}; MS *m/z* (relative intensity) 327 (M^+, 45), 263 (3), and 186 (100). Anal. Calcd for $C_{18}H_{17}NO_3S$: C, 66.04; H, 5.23; N, 4.28. Found: C, 66.07; H, 5.25; N, 4.26.

1-(phenylsulfonyl)-2-(1-bromoethyl)-3-indolyl Methyl Ketone (8). To a solution of **7** (4.239

g, 13.0 mmol) in carbon tetrachloride (50 mL) was added *N*-bromosuccinimide (2.524 g, 14.2 mmol) and dibenzoyl peroxide (20 mg). The reaction mixture was heated at reflux for 4 h. After being cooled to room temperature, the solid suspension was removed by filtration. The filtrate was diluted with dichloromethane (100 mL), and washed with sodium bicarbonate solution (5%, 50 mL) and then brine (50 mL). The solution was dried ($MgSO_4$) and concentrated. Silica gel flash column chromatography (hexane-ethyl acetate; 7:1) gave **8** (4.732 g, 90%). Recrystallization (ethyl acetate and hexane mixture) gave colorless needles, mp 97-98°C; ^1H NMR (400 MHz, $CHCl_3$) 2.08 (d, 3 H, J = 7.2 Hz), 2.68 (s, 3 H), 6.32 (q, 1 H, J = 7.2 Hz), 7.29-7.57 (m, 6 H), 7.84-7.86 (m, 2 H), and 8.17-8.20 (m, 1 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) 26.4 (q), 32.6 (q), 37.3 (d), 115.5 (d), 120.1 (d), 124.7 (d), 125.6 (s), 126.4 (d), 126.8 (d, two carbons), 127.1 (s), 129.6 (d, two carbons), 134.5 (d), 135.7 (s), 138.6 (s), 139.8 (s), and 199.5 (s); IR ($CHCl_3$) 1690 cm^{-1}; MS *m/z* (relative intensity) 407 (M^++2, 3), 405 (M^+, 3), 326 (100), 263 (13), 220 (3), and 184 (53). Anal. Calcd for $C_{18}H_{16}BrNO_3S$: C, 53.21; H, 3.97; N, 3 45. Found: C, 53.26; H, 4.00; N, 3.45.

1-(phenylsulfonyl)-2-(1-azidoethyl)-3-indolyl Methyl Ketone (9). To a solution of **8** (1.703 g, 4.2 mmol) in tetrahydrofuran (25 mL) and water (25 mL) was added sodium azide (820 mg, 12.6 mmol). The reaction mixture was stirred at room temperature for 4 h, and then extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine (50 mL) and dried ($MgSO_4$). Concentration and silica gel flash column chromatography (hexane-ethyl acetate; 7:1) gave **9** (1.47 g, 95%). Recrystallization (hexane and ethyl acetate mixture) gave colorless crystals, mp 66-67°C ; ^1H NMR (400 MHz, $CDCl_3$) δ 1.76 (d, 3 H, J = 6.8 Hz), 2.63 (s, 3 H), 5.70 (q, 1 H, J = 6.8 Hz), 7.27-7.57 (m, 6 H), 7.75-7.77 (m, 2 H), and 8.20 (d, 1 H, J = 8.5 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.1 (q), 32.6 (q), 54.0 (d), 115.2 (d), 119.9 (d), 124.2 (s), 124.6 (d), 125.8 (d), 126.2 (d, two carbons), 126.8 (s), 129.5 (d, two carbons), 134.4 (d), 136.0 (s), 138.4 (s), 139.1 (s), and 198.7 (s); IR ($CHCl_3$) 2120, 1690 cm^{-1}; MS *m/z* 368 (M^+, 1), 340 (M^+-28, 2), 325 (12), 275 (25), 233 (5), and 199 (100).

4-(phenylsulfonyl)-1,3-dimethyl-2,4-dihydropyrrolo[3,4-*b*]indole (10). To a solution of **9** (323 mg, 0.88 mmol) in dry tetrahydrofuran (10 mL) was added triphenylphosphine (460 mg, 1.8 mmol) and stirred at room temperature for 8 h. Concentration and silica gel flash column chromatography (hexane-ethyl acetate; 5:1) gave **10** (267 mg, 94%). Recrystallization (hexane and ethyl acetate mixture) gave colorless needles, mp 198-199°C dec; ^1H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3 H), 2.58 (s, 3 H), 7.14-7.59 (m, 8 H), 7.70 (br s, 1 H), and 8.07-8.09 (m, 1 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 12.3 (q), 12.5 (q), 108.4 (s), 114.0 (s), 116.0 (s), 116.6 (d), 119.4 (d), 124.0 (d), 124.2 (d), 126.5 (s), 126.6 (s), 126.9 (d, two carbons), 128.5 (d, two carbons), 133.0 (d), 136.9 (s), and 143.4 (s); IR ($CHCl_3$) 3450, 1650 cm^{-1}; UV ($CHCl_3$) υ_{max} 308 (ε 5771), 247 nm (15337);MS *m/z* (relative intensity) 324 (M^+, 67), 183 (100). Anal. Calcd for $C_{18}H_{16}N_2O_2S$: C, 66.65; H, 4.97; N, 8.64; S, 9.88. Found: C, 66.50; H, 4.98; N, 8.63; S, 9.97.

4-(phenylsulfonyl)-2-(*tert*-butoxycarbonyl)-1,3-dimethyl-2,4-dihydropyrrolo[3,4-*b*]indole (11). To a solution of **10** (475 mg, 1.5 mmol) in dichloromethane (5 mL) was added di-*tert*-butyldicarbonate (639 mg, 2.9 mmol) and 4-dimethylaminopyridine (179 mg, 1.5 mmol). The reaction mixture was stirred at room temperature for 30 min. Water (50 mL) was added. The mixture was extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Silica gel flash column chromatography (hexane-ethyl acetate; 10:1) gave **11** (546 mg, 88%). Recrystallization (hexane and ethyl acetate mixture) gave flaky crystals, mp 171-172°C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.63 (s, 9 H), 2.49 (s, 3 H), 2.78 (s, 3 H), 7.12-7.51 (m, 8 H), and 8.06 (d, 1 H, J = 8.0 Hz); ^{13}C NMR (100.6 MHz,

$CDCl_3$) δ 14.3 (q), 15.0 (q), 28.0 (q), 84.2 (s), 114.8 (s), 117.7 (d), 119.3 (s, two carbons), 120.4 (d), 124.9 (d), 125.70 (d), 125.74 (s), 127.1 (d, two carbons), 128.5 (d, two carbons), 129.8 (s), 133.2 (d), 136.4 (s), 145.3 (s), 150.7 (s); IR ($CHCl_3$) 1730 cm^{-1}; UV ($CHCl_3$) υ_{max} 251 nm (ε 13915); MS *m/z* 424 (M^+, 39),368 (100), 324 (48), 227 (56), and 183 (81).Anal. Calcd for $C_{23}H_{24}N_2O_4S$: C, 65.08; H, 5.70; N, 6.60; S, 7.55. Found: C, 65.03; H, 5.72; N, 6.62; S, 7.41.

6-(Phenylsulfonyl)-12-(*tert*-butoxycarbonyl)-5,11-imine-5,11-dimethyl-5,11-dihydro-6*H*-pyrido[4,3-*b*]carbazole (12) and 10-(Phenylsulfonyl)-12-(*tert*-butoxycarbonyl)-5,11-imine-5,11-dimethyl-5,11-dihydro-10*H*-pyrido[3,4-*b*]carbazole (13). To a mixture of **11** (163 mg, 0.39 mmol) and 1-aminotriazolo[4,5-*c*]pyridine (80 mg, 0.59 mmol) in dichloromethane (5 mL) was added a solution of lead tetraacetate (264 mg, 0.59 mmol) in dichloromethane (5 mL) dropwise at 5°C. The reaction mixture was stirred at room temperature for 1 h and then filtered through a short pad of Celite. The filtrate was then diluted with dichloromethane (100 mL), and washed with sodium bicarbonate solution (10%, 30 mL), brine (30 mL), and then dried ($MgSO_4$). Concentration and silica gel flash column chromatography (hexane-ethyl acetate; 2:1) gave a mixture of **12** and **13** (126 mg, 65%, **12**: **13** = 45: 55), which were not separated. Data for the mixture of **12** and **13**; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9 H), 2.40, 2.45, 2.52, and 2.57 (four s, 6 H), 7.04-7.50, 7.89-7.98 and 8.25-8.40 (m, 12 H); IR ($CHCl_3$) 1705 cm^{-1}; MS *m/z* (relative intensity) 501 (M^+, 100), 445 (10), 400 (99), 386 (10),337 (12), 322 (15), 304 (23), 260 (95), 246 (12). Anal. Calcd for $C_{28}H_{27}N_3O_4S$: C, 67.05; H, 5.43; N, 8.38, S, 6.39. Found: C, 67.25; H, 5.46; N, 8.37; S, 6.13.

5-(*N*-*tert*-Butoxycarbonylamino)-5-methyl-11-methylene-5,11-dihydro-6*H*-pyrido[4,3-*b*]carbazole (14) and 11-(*N*-*tert*-Butoxycarbonylamino)-11-methyl-5-methylene-5,11-dihydro-10*H*-pyrido[3,4-*b*]carbazole (15). To a solution of the mixture of **12** and **13** (120 mg, 0.24 mmol) in methanol (1 mL) and tetrahydrofuran (2 mL) was added 50% potassium hydroxide aqueous solution (1 mL). The reaction mixture was stirred at 50°C for 30 min. After cooling to room temperature, 10% hydrochloric acid was added slowly to give a weakly basic solution (pH = 8). The reaction mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. Silica gel flash column chromatography (hexane-ethyl acetate; 1:1) gave **14** (31 mg) and **15** (32 mg). Data for compound **14**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.14 (s, 9 H), 1.85 (s, 3 H), 5.65 (br s,1 H), 5.94 (s, 1 H), 5.99 (s, 1 H), 7.20-7.26 (m, 2 H), 7.38-7.40 (m, 1 H), 7.51 (d, 1 H, *J* = 5.41 Hz), 7.98 (d, 1 H, *J* = 6.9 Hz), 8.58 (d, 1 H, *J* = 5.4 Hz), 9.25 (s, 1 H), and 9.40 (br s, 1 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) 28.0 (CH_3 x 3), 30.9 (CH_3), 53.4 (C), 77.0 (C), 80.9 (C), 105.2 (CH_2), 108.7 (C), 111.6 (CH), 119.3 (CH), 120.7 (CH), 120.9 (CH), 122.8 (CH), 124.6 (C),128.7 (C), 133.0 (C), 137.0 (C), 139.1 (C),146.4 (CH), 148.6 (CH), and 155.5 (C); IR ($CHCl_3$) 3450, 3370, 1700, 1630 cm^{-1}; UV ($CHCl_3$) υ_{max} 242 nm (ε 15000), 201 nm (ε 5300); MS *m/z* (relative intensity) 361 (M^+, 100), 305 (72), 290 (35), 246 (59), 245 (47), 244 (95). Data for Compound **15**, ^1H NMR (400 MHz, $CDCl_3$: DMSO-d_6; 10:1) δ 0.6-1.5 (two br s, 9 H), 1.77 (s, 3 H), 5.95 (s, 1 H), 5.98 (s, 1 H), 6.56 (br s, 1 H), 7.16-7.23 (m, 2 H), 7.44-7.46 (m, 1 H), 7.78 (d, 1 H, *J* = 5.2 Hz), 7.94 (d, 1 H, *J* = 7.2 Hz), 8.51 (d, 1 H, *J* = 5.2 Hz), 8.90 (s, 1 H), and 10.78 (br s, 1 H); ^{13}C NMR (100.6 MHz, $CDCl_3$: DMSO-d_6; 10:1) δ 26.8 (CH_3), 31.4 (CH_3 x 3), 51.1 (C), 77.2 (C), 78.1 (C), 104.4 (CH_2), 106.3 (C), 110.9 (CH), 116.0 (CH), 119.2 (CH), 120.9 (CH), 123.5 (C), 132.9 (C), 136.2 (C), 139.3 (C), 139.9 (C), 146.4 (CH), 147.3 (CH), and 153.5 (C); IR ($CHCl_3$) 3420, 3380, 1700 cm^{-1}; UV ($CHCl_3$) υ_{max} 242 nm (ε 11000); MS *m/z* (relative intensity) 361 (M^+, 73), 305 (52), 290 (31), 276

(11), 260 (11), 246 (42), 245 (50), and 244 (100). HRMS Calcd for $C_{22}H_{23}N_3O_2$ 361.1790, found 361.1783.

5-(*N-tert*-Butoxycarbonylamino)-5,11-dimethyl-5,11-dihydro-6*H*-pyrido[4,3-*b*]carbazole (16). A solution of **14** (30 mg, 0.083 mmol) and 5% palladium on carbon (4 mg) in methanol (3 mL) was hydrogenated at 1 atm for 1 h at room temperature. Filtration with Celite, concentration, and silica gel chromatography (hexane-ethyl acetate; 2:1) gave **16** (24 mg, 80%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 9 H), 1.70 (d, 3 H, *J* = 6.8 Hz), 2.03 (s, 3 H), 4.40 (q, 1 H, *J* = 6.8 Hz), 5.36 (br s, 1 H), 7.12-7.24 (m, 2 H), 7.42 (d, 1 H, *J* = 8.0 Hz), 7.54 (d, 1 H, *J* = 5.1 Hz), 7.68 (d, 1 H, *J* = 7.8 Hz), 8.52 (d, 1 H, *J* = 5.1 Hz), 8.74 (s, 1 H), and 9.39 (br s, 1 H); IR ($CHCl_3$) 3420, 1704 cm^{-1}; UV ($CHCl_3$) υ_{max} 263 (ε 9216), 245 nm (9430); MS *m/z* (relative intensity) 363 (M^+, 83), 348 (5), 307 (41), 292 (50), and 246 (100).

11-(*N-tert*-Butoxycarbonylamino)-5,11-dimethyl-5,11-dihydro-10*H*-pyrido[3,4-*b*]carbazole (17). Compound **15** was hydrogenated under same condition as that of **14** to give **17** (26 mg, 83%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9 H), 1.69 (d, 3 H, *J* = 7.0 Hz), 2.14 (s, 3 H), 4.33 (q, 1 H, *J* = 7.0 Hz), 5.38 (br s, 1 H), 7.13-7.26 (m, 2 H), 7.37 (d, 1 H, *J* = 5.1 Hz),7.45 (d, 1 H, *J* = 8.0 Hz), 7.67 (d, 1 H, *J* = 7.8 Hz), 8.52 (d, 1 H, *J* = 5.1 Hz), 8.94 (s, 1 H), and 9.65 (br s, 1 H); IR ($CHCl_3$) 3425, 1700 cm^{-1}; UV ($CHCl_3$) υ_{max} 244 nm (ε 6278); MS *m/z* 363 (relative intensity) (M^+, 100), 348 (11), 307 (38), 292 (83), 246 (74).

Ellipticine 1. To a solution of **16** (22 mg, 0.06 mmol) in dichloromethane (1 mL) was added trifluoroacetic acid (0.1 mL). The reaction mixture was stirred at room temperature for 20 min. Water (4 mL) and saturated sodium carbonate solution (10 mL) were added. The mixture was extracted with ethyl acetate (25 mL x 4). The combined organic layers were dried ($MgSO_4$) and concentrated. Silica gel flash column chromatography (hexane-ethyl acetate-methanol; 20:40:1) gave ellipticine **1** (13 mg, 85%). Recrystallization from methanol gave yellow needles, mp 313-315°C dec. (lit.[2] mp 311-315°C dec.); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.76 (s, 3 H), 3.22 (s, 3 H), 7.23-7.26 (m, 1 H, *J* = 7.2 Hz), 7.50-7.57 (m, 2 H), 7.88 (d, 1 H, *J* = 6.0 Hz), 8.35 (d, 1 H, *J* = 8.0 Hz), 8.41 (d, 1 H, *J* = 6.0 Hz), 9.67 (s, 1 H), 11.37 (s, 1 H); MS *m/z* (relative intensity) 246 (M^+, 100).

Isoellipticine 2. Compound **17** (25.6 mg, 70.5 mmol) was treated with trifluoroacetic acid under the same condition as that of **16** to give isoellipticine **2** (14 mg, 78%). Recrystallization with methanol gave yellow needles, mp 275-278°C dec. (lit.[13] mp 270-286°C dec.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.94 (s, 3 H), 3.19 (s, 3 H), 7.30-7.33 (m, 1 H), 7.51-7.57 (m, 2 H), 8.05 (d, 1 H, *J* = 6.0 Hz), 8.17 (br s, 1 H), 8.41 (d, 1 H, *J* = 8.0 Hz), 8.50 (d, 1 H, *J* = 6.0 Hz), 9.61 (s, 1 H); MS *m/z* (relative intensity) 246 (M^+, 100).

1-(*tert*-Butoxycarbonylamino)-2-methyl-3-indolyl Methyl Ketone (19). Using the same procedure as the preparation of **11**, starting material **18** (2.41 g, 13.9 mmol) was converted into **19** (3.6 g, 95%). Recrystallization (hexane and ethyl acetate mixture) gave colorless crystals: mp 73.5-74.5°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, 1 H, *J* = 6.2 Hz and 0.3 Hz), 7.91 (dd, 1 H, *J* = 6.0 and 0.3 Hz), 7.31-7.29 (m, 2 H), 2.89 (s, 3 H), 2.66 (s, 3 H), 1.71 (s, 9 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 196.1 (s), 149.9 (s), 143.8 (s), 135.4 (s), 126.6 (s), 124.0 (d), 123.6 (d), 120.4 (d), 119.8 (s), 115.0 (d), 85.1 (s), 32.0 (q), 28.1 (q, 3 carbons), 15.4 (q); IR ($CHCl_3$): 2990, 1740, 1650 cm^{-1}; MS *m/z* 363 (relative intensity) 273 (M^+, 69), 217 (100), 173 (41), 57 (71). Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.32; H, 7.00; N, 5.17.

1-(*tert*-Butoxycarbonyl)-2-bromomethyl-3-indolyl Methyl Ketone (20). Using the same

procedure as the preparation of **8**, compound **19** (3.29 g, 12.1 mmol) was converted into **20** (4.2 g, 99%). Recrystallization (hexane and ethyl acetate mixture) gave colorless crystals: mp 103.5-104.0°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, 1 H, J = 8.0 Hz), 7.87 (d, 1 H, J = 7.7 Hz), 7.39-7.30 (m, 2 H), 5.37 (s, 2 H), 2.73 (s, 3 H), 1.73 (s, 9 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 196.0 (s), 149.1 (s), 140.3 (s), 136.4 (s), 125.9 (s), 125.7 (d), 124.1 (d), 121.0 (d), 120.6 (s), 115.8 (d), 86.3 (s), 32.1 (q), 27.9 (q, 3 carbons), 23.6 (t); IR ($CHCl_3$): 1750, 1660 cm^{-1}; MS *m/z* 353 (M^++2, 32), 351 (M^+, 32), 297 (25), 295 (25), 253 (30), 251 (40), 216 (71), 172 (71), 57 (100); Anal. Calcd for $C_{16}H_{18}BrNO_3$: C, 54.56; H, 5.15; N, 3.98. Found: C, 54.41; H, 5.19; N, 4.00.

1-(*tert*-Butoxycarbonyl)-2-azidomethyl-3-indolyl Methyl Ketone (21). Using the same procedure as the preparation of **9**, compound **20** (3.85 g, 10.9 mmol) was converted into **21** (3.29 g, 96%). Recrystallization (hexane and ethyl acetate mixture) gave colorless crystals: mp 58.0-58.5°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, 1 H, J = 8.2 Hz), 7.78 (d, 1 H, J = 7.7 Hz), 7.41-7.32 (m, 2 H), 5.08 (s, 2 H), 2.72 (s, 3 H), 1.72 (s, 9 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 195.8 (C), 149.1 (C), 138.1 (C), 135.9 (C), 125.6 (C), 125.4 (CH), 123.9 (CH), 121.8 (CH), 120.8 (CH), 115.7 (CH), 86.1 (C), 45.0 (CH_2), 32.0 (CH_3), 27.8 (CH_3 x 3); IR ($CHCl_3$): 2100, 1740, 1660 cm^{-1}; MS *m/z* 314 (M^+, 5), 229 (6), 186 (40), 185 (26), 171 (13), 57 (100); Anal. Calcd for $C_{16}H_{18}N_4O_3$: C, 61.14; H, 5.77; N, 17.82. Found: C, 61.17; H, 5.75; N, 17.85.

1-(*tert*-Butoxycarbonyl)-2-aminomethyl-3-indolyl Methyl Ketone (22) and 1-(*tert*-Butoxycarbonyl)-1-methyl-2,4-dihydropyrrolo[3,4-*b*]indole (23). Using the same procedure as the preparation of **10**, compound **21** (513 mg, 1.6 mmol) was converted into **22** (49 mg, 11%) and **23** (383 mg, 87%). Compound **22** was recrystallized (hexane and ethyl acetate mixture) to give colorless crystals: mp 178.0-178.5°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.38 (br s, 1 H), 7.85 (d, 1 H, J = 7.8 Hz), 7.33 (d, 1 H, J = 7.9 Hz), 7.26-7.19 (m, 2 H), 6.06 (br t, 1 H), 4.71 (d, 2 H, J = 6.3 Hz), 2.73 (s, 3 H), 1.41 (s, 9 H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 195.7 (C), 157.2 (C), 144.6 (C), 134.7 (C), 126.0 (C), 122.7 (CH), 122.0 (CH), 120.3 (CH), 114.1 (C), 112.1 (CH), 80.1 (C), 37.7 (CH_2), 31.3 (CH_3), 28.4 (CH_3 x 3); IR 3440, 1690, 1640 cm^{-1}; MS *m/z* 288 (M^+, 79), 232 (100), 189 (17). Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99; N, 9.72. Found: C, 66.60; H, 6.98; N, 9.69. Data for **23**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 and 7.90 (two br s, 2 H), 7.56 (d, 1 H, J = 7.9 Hz), 7.24-7.15 (m, 2 H), 6.77 and 6.45 (two br s, 1 H), 2.46 (s, 3 H), 1.68 (br s, 9 H); IR ($CHCl_3$): 3440, 1710 cm^{-1}; MS *m/z* (relative intensity) 270 (M^+, 56), 214 (100), 170 (44); HRMS Calcd for $C_{16}H_{18}N_2O_2$: 270.1368, found: 270.1382.

2,4-Di-*tert*-butoxycarbonyl-1-methyl-2,4-dihydropyrrolo[3,4-*b*]indole (24). Using the same procedure as the preparation of **11**, compound **23** (242 mg, 0.9 mmol) was converted into **24** (308 mg, 93%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (br s, 1 H), 7.65 (d, 1 H, J = 7.5 Hz), 7.31-7.17 (m, 2 H), 7.04 (br s, 1 H), 2.75 (s, 3 H), 1.68 (s, 9 H), 1.63 (s, 9 H); IR ($CHCl_3$): 1720 cm^{-1}; MS *m/z* (relative intensity) 370 (M^+, 22), 258 (100), 57 (69); HRMS Calcd for $C_{21}H_{26}N_2O_4$ 370.1892, found 370.1887.

6,12-Di-*tert*-butoxycarbonyl-5,11-imine-5-methyl-5,11-dihydro-6*H*-pyrido[4,3-*b*]carbazole (25) and 10,12-Di-*tert*-butoxycarbonyl-5,11-imine-11-methyl-5,11-dihydro-6*H*-pyrido[3,4-*b*]carbazole (26). Using the same procedure as the preparation of **12** and **13**, compound **24** (305 mg, 0.82 mmol) was converted into **25** and **26** (241 mg, 1:1, 65%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 and 8.38 (two s, 1 H), 8.26-8.23 (m, 1 H), 8.09 (br s, 1 H), 7.50-7.45 (m, 1 H), 7.26-7.14 (m, 3 H), 6.21 and 6.15 (two s, 1 H), 2.54 and 2.49 (two s, 3 H), 1.74 (s, 9 H), 1.43 (s, 9 H); IR ($CHCl_3$) 1720 cm^{-1};

MS *m/z* 477 (M^+, 31), 346 (46), 291 (69), 247 (77), 246 (100), 57 (62); HRMS Calcd for $C_{26}H_{29}N_3O_4$ 477.2158, found 477.2153.

5-Amino-11-methyl-6*H*-pyrido[4,3-*b*]carbazole (27) and 11-Amino-5-methyl-10*H*-pyrido[3,4-*b*]carbazole (28). To a solution of **25** and **26** (1.01 g, 2.15 mmol) in dichloromethane (6 mL) was added trifluoroacetic acid (2 mL). The reaction mixture was stirred at room temperature for 20 min. and then was added sodium bicarbonate solution to pH 10. The aqueous solution extracted with ethyl acetate (4 x 50 mL). The combined organic layers were combined and washed with brine (50 mL) and dried (Na_2SO_4). Concentration and silica gel column chromatography ($CHCl_3$: CH_3OH; 10:1) gave **27** and **28** (335 mg, 60%). Compounds **27** and **28** were seperated and isolated by further silica gel column chromatography ($CHCl_3$: CH_3OH; 10:1). Data for **27**: ^1H NMR (400 MHz, $CDCl_3$ and DMSO-d_6 mixture) δ 10.72 (s, 1 H), 9.64 (s, 1 H), 8.38-8.36 (m, 2 H), 7.80 (d, 1 H, J = 6.0 Hz), 7.50-7.49 (m, 2 H), 7.27-7.25 (m, 1 H), 4.92 (br s, 2 H), 3.25 (s, 3 H); MS *m/z* 247 (M^+, 100); HRMS Calcd for $C_{16}H_{13}N_3$ 247.1109, found 247.1107. Data for **28**: ^1H NMR (400 MHz, DMSO-d_6) δ 11.15 (s, 1 H), 9.64 (s, 1 H), 8.38 (d, 1 H, J = 8.0 Hz), 8.25 (d, 1 H, J = 6.0 Hz), 7.99 (d, 1 H, J = 6.0 Hz), 7.59 (d, 1 H, J = 8.0 Hz), 7.52 (dd, 1 H, $J_1 = J_2 = 7.2$ Hz), 7.23 (dd, 1 H, $J_1 = J_2 = 7.6$ Hz), 6.15 (br s, 2 H), 3.03 (s, 3 H); MS *m/z* 247 (M^+, 100); HRMS Calcd for $C_{16}H_{13}N_3$ 247.1109, found 247.1107.

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