The first and simple synthesis of indole alkaloid, bipolaramide

THE FIRST AND SIMPLE SYNTHESIS OF INDOLE ALKALOID, BIPOLARAMIDE[1]

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Abstract----The first and simple total synthesis of bipolaramide was achieved in 31% overall yield from (2*S*)-2,3-dihydroindole-2-carboxylic acid in three (or two) steps. Derivatives of bipolaramide having halogen, alkenyl, nitro, or azido substituents were also prepared.

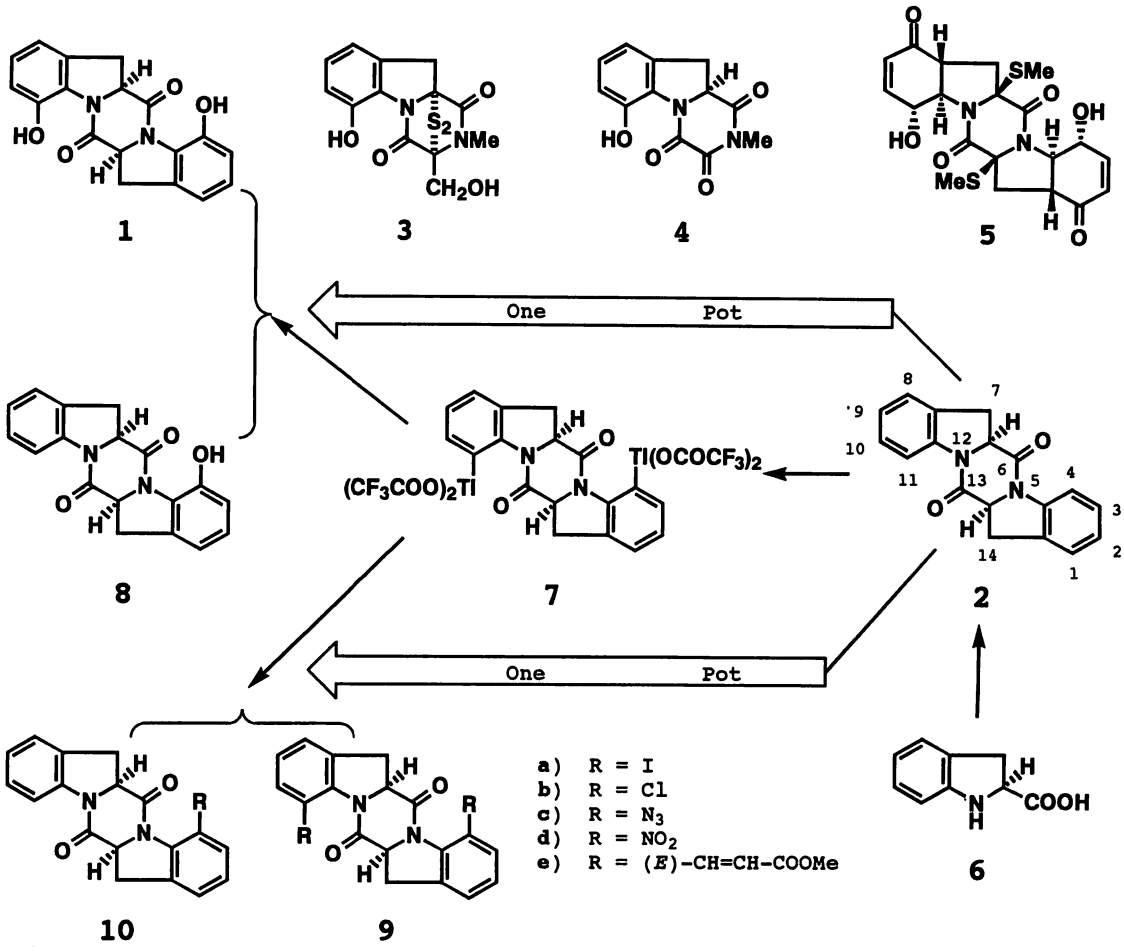
Bipolaramide ((-)-**1**), isolated from cultures of *Bipolaris sorokiniana* in 1985 by Steyn and co-workers,[2] has attracted our attention due to its interesting structure having (6a*S-cis*)-6a,7,13a,14-tetrahydropyrazino[1,2-*a*:4,5-*a*']diindole-6,13-dione ((-)-**2**) as a mother skeleton. Many structurally related indole alkaloids are reported, such as dehydrogliotoxin[3] (**3**), dioxopiperazinoindole[4] (**4**), and exserohilone[5] (**5**).

Total syntheses of these alkaloids could be attained, if we had a suitable reaction which realized direct functionalization at the 4 and 11 positions of (-)-**2**. To meet this requirement, we have created novel reactions[6] which enable C-Tl bond to transform into various C-heteroatom[6a-e] and C-C[6f] bond utilizing thallium chemistry. Here we report a successful application of our reaction to the first and simple total synthesis of (-)-**1**. The originality rate[7] of the alkaloid synthesis is 67%. We also describe the syntheses of derivatives having halogen, alkenyl, nitro, or azido substituents in place of the hydroxy groups at the 4 and 11 positions of (-)-**1**.

Commercially available (2*S*)-2,3-dihydroindole-2-carboxylic acid ((-)-**6**) was derived to (6a*S-cis*)-6a,7,13a,14-tetrahydropyrazino[1,2-*a*:4,5-*a*']diindole-6,13-dione ((-)-**2**) in 76% yield, using 1,3-dicyclohexylcarbodiimide (DCC) in tetrahydrofuran (THF) at room temperature (Scheme 1). The next reaction of (-)-**2** with thallium tris(trifluoroacetate)[8] (TTFA) in trifluoroacetic acid (TFA) afforded dithallated compound ((-)-**7**) in 66% yield. Subsequent treatment of (-)-**7** with cupric sulfate pentahydrate[6a] ($CuSO_4 \cdot 5H_2O$) in dimethylformamide (DMF) and water (1:1, v/v) at 132°C produced (-)-**1** and monohydroxylated compound ((-)-**8**) in 62% and 5% yields, respectively. In a simple one-pot reaction by the sequential treatment of (-)-**2** with TTFA in TFA, followed by treatment with $CuSO_4 \cdot 5H_2O$, (-)-**1** was prepared in 35% overall yield, together with a 5% yield of (-)-**8**. The synthetic (-)-**1** was identical with bipolaramide in every respects.

Treatment of (-)-**7** with potassium iodide (KI) in H_2O afforded diiodo compound ((-)-**9a**) in 20% yield. In an one-pot pro-

Scheme 1



cedure, (-)-**9a** was also obtained in 29% overall yield from (-)-**2** together with a 16% yield of monoiodo compound ((-)-**10a**). An attempt to improve the yield of (-)-**9a** by reacting (-)-**7** with cuprous iodide (CuI) and I_2[6b] in DMF resulted in a poor yield (16%). On the other hand, introduction of chlorine was achieved by reacting (-)-**7** with cupric chloride[6c] ($CuCl_2$) in DMF, affording the dichloro compound ((-)-**9b**) in 78% yield. By the one-pot procedure from (-)-**2**, (-)-**9b** was obtained in 46% overall yield together with a 3% yield of the monochloro compound ((-)-**10b**). In addition, azido and nitro groups were introduced successfully. Treatment of (-)-**7** with CuI and sodium azide[6e] (NaN_3) in DMF afforded (-)-**9c** and (-)-**10c** in 64% and 5% yields, respectively, while the reaction of (-)-**7** with $CuSO_4 \cdot 5H_2O$ and sodium nitrite[6e] ($NaNO_2$) produced (-)-**9d** in 21% yield.

The thallation-palladation method[6f] was also applied to the syntheses of alkenylated derivatives of (-)-**1**. Thus, the reaction of (-)-**7** with methyl acrylate in the presence of a catalytic amount of palladium acetate ($Pd(OAc)_2$) in DMF

produced the dialkenylated compound ((-)-**9 e**) and the monoalkenylated compound ((-)-**10 e**) in 30% and 34% yields, respectively. Alternatively, (-)-**9 e** and (-)-**10 e** were prepared by one-pot procedure from (-)-**2** in 13% and 24% overall yields, respectively.

In conclusion, we could demonstrate that development of a suitable reaction makes shorten the synthesis of target compound. Searching for new pharmacologically active compounds, further efforts to produce various derivatives of (-)-**1** are in progress.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (Ir) spectra were determined with a Shimadzu IR-420 spectrophotometer, and proton nuclear magnetic resonance (^{1}H-nmr) spectra with a JEOL JNM FX100S spectrometer with tetramethylsilane as an internal standard. Mass spectra (Ms) were recorded on a Hitachi M-80 spectrometer. Preparative thin-layer chromatography was performed on Merck Kieselgel GF_{254} (Type 60)(SiO_2). Column chromatography was performed on silica gel (SiO_2, 100-200 mesh, from Kanto Chemical Co. Inc.) throughout the present study.

(6a*S-cis*)-6a,7,13a,14-Tetrahydropyrazino[1,2-*a*:4,5-*a*']diindole-6,13-dione ((-)-2) ---------- DCC (2.782 g, 13.5 mmol) was added to the solution of commercially available (2*S*)-2,3-dihydroindole-2-carboxylic acid (1.000 g, 6.13 mmol, $[\alpha]_D^{20}$ -13.3° (c=0.30, MeOH)) in THF (150 ml) and the mixture was stirred at room temperature for 1 h. Precipitates were filtered off and the filtrate was evaporated under reduced pressure to leave an oil, which was subjected to column chromatography on SiO_2 with CH_2Cl_2 as an eluent to give (-)-**2** (680.0 mg, 76%). mp 270-271°C (colorless needles, recrystallized from CH_2Cl_2-MeOH). $[\alpha]_D^{23}$ -3.49° (c=0.601, $CHCl_3$). Ir (KBr): 1680, 1605, 1484, 1407, 744 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 3.41 (2H, dd, *J*=16.6 and 10.7 Hz), 3.80 (2H, dd, *J*=16.6 and 8.8 Hz), 4.96 (2H, dd, *J*=10.7 and 8.8 Hz), 6.94-7.40 (6H, m), 7.96-8.22 (2H, m). *Anal.* Calcd for $C_{18}H_{14}N_2O_2$: C, 74.40; H, 4.76; N, 9.59. Found: C, 74.47; H, 4.86; N, 9.65.

(6a*S-cis*)-4,11-Di[bis(trifluoroacetoxy)thallio]-6a,7,13a,14-tetrahydropyrazino[1,2-*a*:4,5-*a*']diindole-6,13-dione ((-)-7) ------- A solution of TTFA in TFA[9] (0.88 M, 10.0 ml, 8.79 mmol) was added to the solution of (-)-**2** (1.062 g, 3.66 mmol) in TFA (10.0 ml) and the mixture was stirred at room temperature (25°C) for 12 h. Precipitates were collected and washed with small amount of TFA, and then with 1,2-dichloroethane to remove a trace amount of TFA. After drying *in vacuo*, (-)-**7** (2.785 g, 66%) was obtained and this sample was used without further purification. mp 198°C (decomp., pale yellow powders). $[\alpha]_D^{22}$ -82.7° (c=0.208, DMSO). Ir (KBr): 1674, 1428, 1205, 1128, 815, 800, 719 cm^{-1}.

Bipolaramide ((-)-1) and (6a*S-cis*)-4-hydroxy-6a,7,13a,14-tetrahydropyrazino[1,2-*a*:4,5-*a*']diindole-6,13-dione ((-)-8). a) From (-)-7 -------- $CuSO_4 \cdot 5H_2O$ (1.109 g, 4.44 mmol) was added to a solution of (-)-**7** (509.9 mg, 0.444 mmol) in DMF (15 ml) and H_2O (15 ml), and the mixture was stirred at 132°C for 3 h. After evaporation of the solvent under reduced pressure, a mixture of benzene-acetone (9:1, v/v) and brine were added to

the resultant residue and well shaked. Insoluble materials were filtered off and organic layer was separated. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was repeatedly subjected to column chromatography on SiO_2 with benzene-acetone (9:1, v/v) as an eluent to give bipolaramide ((-)-**1**) (89.3 mg, 62%) and (-)-**8** (7.0 mg, 5%) in the order of elution. (-)-**1**: mp 299-301°C [colorless needles, recrystallized from acetone, (lit.,[2] mp 296-297°C). Depression of mp of admixture was not observed]. $[\alpha]_D^{22}$ -203° (c=0.286, acetone) [lit.,[2] $[\alpha]_D$ -210° (c=1.0, acetone)]. Ir (KBr): 1648, 1602, 1473, 1431, 1257, 1139 cm^{-1}. ^{1}H-Nmr (DMSO-d_6) δ: 3.36 (2H, dd, *J*=16.0 and 10.0 Hz), 3.56 (2H, dd, *J*=16.0 and 9.8 Hz), 5.44 (2H, br t, *J*=9.5 Hz), 6.70 (2H, br d, *J*=7.6 Hz), 6.78 (2H, br d, *J*=7.6 Hz), 7.06 (2H, t, *J*=7.6 Hz), 11.20 (2H, s). *Anal.* Calcd for $C_{18}H_{14}N_2O_4$: C, 67.08; H, 4.38; N, 8.69. Found: C, 67.26; H, 4.31; N, 8.94. The above data, ^{13}C-nmr data, and tlc behavior of the synthetic (-)-**1** were identical with those of natural product. (-)-**8**: mp 226-227°C (colorless needles, recrystallized from acetone). $[\alpha]_D^{26}$ -127° (c=0.251, $CHCl_3$). Ir (KBr): 1684, 1648, 1603, 1478, 1406, 780, 752 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 3.37 (1H, dd, *J*=17.0 and 10.5 Hz), 3.43 (1H, dd, *J*=17.0 and 10.5 Hz), 3.75 (1H, dd, *J*=17.0 and 9.3 Hz), 3.78 (1H, dd, *J*=17.0 and 9.3 Hz), 4.94 (1H, br t, *J*=10.0 Hz), 5.04 (1H, br t, *J*=10.0 Hz), 6.75 (2H, br t, *J*=6.7 Hz), 6.88-7.35 (4H, m), 7.95-8.14 (1H, m), 11.08 (1H, s). Ms *m/z*: 306 (M^+). *Anal.* Calcd for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.61; N, 9.14. Found: C, 70.67; H, 4.57; N, 9.23.

b) From (-)-2 ------ One pot procedure: A solution of TTFA in TFA (0.88 M, 0.48 ml, 0.425 mmol) was added to the solution of (-)-**2** (51.3 mg) in TFA (1.0 ml) and the whole was stirred at room temperature for 12 h. After evaporation of the solvent under reduced pressure, DMF (8.0 ml) was added to the resultant residue. To this solution, $CuSO_4 \cdot 5H_2O$ (441.7 mg, 1.77 mmol) was added and the mixture was stirred at 135°C for 3 h. After the same work-up and separation as described above, (-)-**8** (2.7 mg, 5%) and (-)-**1** (19.7 mg, 35%) were obtained.

(6a*S-cis*)-4-Iodo- ((-)-10a) and -4,11-diiodo-6a,7,13a,14-tetrahydropyrazino[1,2-*a*:4,5-*a'*]diindole-6,13-dione ((-)-9a). a) From (-)-7 ---- A solution of KI (586.8 mg, 3.53 mmol) in H_2O (10.0 ml) was added to a suspension of (-)-**7** (202.9 mg, 0.177 mmol) in H_2O (2.0 ml). After stirring at room temperature for 1 h, the whole was extracted with CH_2Cl_2-MeOH (95:5, v/v). The extract was washed subsequently with 10% aq. sodium thiosulfate, brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was subjected to preparative thin layer chromatography on SiO_2 with $CHCl_3$ as a developing solvent. Extraction with CH_2Cl_2-MeOH (95:5, v/v) from the band having Rf value of 0.48-0.27 afforded (-)-**9a** (19.7 mg, 20%). In this case, (-)-**10a** was not formed. (-)-**9a**: mp 266-267°C (colorless needles, recrystallized from CH_2Cl_2). $[\alpha]_D^{23}$ -514.9° (c=0.255, $CHCl_3$). Ir (KBr): 1671, 1442, 1430, 1387, 1089, 763 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 3.45 (4H, d, *J*=9.5 Hz), 5.20 (2H, t, *J*=9.5 Hz), 6.91 (2H, dd, *J*=7.8 and 7.6 Hz), 7.29 (2H, dd, *J*=7.6 and 1.0 Hz), 7.73 (2H, dd, *J*=7.8 and 1.0 Hz). Ms *m/z*: 542 (M^+). *Anal.* Calcd for $C_{18}H_{12}N_2O_2I_2$: C, 39.88; H, 2.23; N, 5.17. Found: C, 39.88; H, 2.14; N, 5.16.

b) From (-)-7 ---- I_2 (67.9 mg, 0.535 mmol) and CuI (67.9 mg, 0.357 mmol) were added to a solution of (-)-**7** (204.7 mg, 0.178 mmol) in DMF (5.0 ml). After stirring at room temperature for 1 h, CH_2Cl_2-MeOH (95:5, v/v) was added and insoluble materials were filtered off through short column of SiO_2. The filtrate was washed subsequently with 10% aq. sodium thiosulfate, brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was purified as described in the above procedure **a** to give (-)-**9a** (15.0 mg, 16%).

c) From (-)-2 ------ One pot procedure: A solution of TTFA in TFA (0.88 M, 0.80 ml, 0.706 mmol) was added to the solution of (-)-**2** (85.3 mg, 0.294 mmol) in TFA (1.0 ml) and the mixture was stirred at room temperature for 12 h.

After evaporation of the solvent under reduced pressure, H_2O (2.0 ml) was added to the resultant residue. To this emulsion, a solution of KI (976.5 mg, 5.88 mmol) in H_2O (10.0 ml) was added and the mixture was stirred at room temperature for 1 h. CH_2Cl_2-MeOH (95:5, v/v) was added to the reaction mixture and insoluble materials were filtered off. Separated organic layer was washed subsequently with 10% aq. sodium thiosulfate, brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was subjected to column chromatography on SiO_2 with $CHCl_3$-hexane (9:1, v/v) as an eluent to give (-)-**10a** (19.5 mg, 16%) and (-)-**9a** (46.1 mg, 29%) in the order of elution. (-)-**10a**: mp 238-239°C (decomp., colorless needles, recrystallized from AcOEt). $[\alpha]_D^{23}$ -470.7° (c=0.15, $CHCl_3$). Ir (KBr): 1687, 1663, 1479, 1433, 1393, 828, 767 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 3.13-3.93 (4H, m), 5.09 (1H, dt, *J*=10.0 and 1.1 Hz), 5.10 (1H, dt, *J*=10.0 and 1.1 Hz), 6.86 (1H, dd, *J*=8.0 and 7.6 Hz), 7.25 (1H, dd, *J*=7.6 and 1.2 Hz), 7.41-7.75 (3H, m), 7.73 (1H, dd, *J*=8.0 and 1.0 Hz), 7.85 (1H, d, *J*=8.0 Hz). *Anal.* Calcd for $C_{18}H_{13}N_2O_2I$: C, 51.94; H, 3.15; N, 6.73. Found: C, 52.00; H, 2.95; N, 6.49.

(6a*S*-*cis*)-4-Chloro- ((-)-10b) and -4,11-dichloro-6a,7,13a,14-tetrahydropyrazino[1,2-*a*:4,5-*a'*]-diindole-6,13-dione ((-)-9b). a) From (-)-7 ------- Anhydrous $CuCl_2$ (231.9 mg, 1.72 mmol) was added to a solution of (-)-**7** (198.0 mg, 0.172 mmol) in DMF (5.0 ml) and the mixture was stirred at 122°C for 5 h. After evaporation of the solvent under reduced pressure, a mixture of CH_2Cl_2-MeOH (95:5, v/v) and brine were added and well shaked. Insoluble materials were filtered off and organic layer was separated. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was subjected to column chromatography on SiO_2 with $CHCl_3$-hexane (9:1, v/v) as an eluent to give (-)-**10b** (3.8 mg, 7%) and (-)-**9b** (48.5 mg, 78%) in the order of elution. (-)-**10b**: mp 245-246°C (colorless needles, recrystallized from CH_2Cl_2-MeOH). $[\alpha]_D^{25}$ -301.5° (c=0.202, $CHCl_3$). Ir (KBr): 1700, 1673, 1602, 1393, 758 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 3.11-3.87 (4H, m), 4.92-5.20 (2H, m), 6.86-7.29 (6H, m), 7.96-8.12 (1H, m). Ms *m/z*: 326 and 324 (M^+). *Anal.* Calcd for $C_{18}H_{13}N_2O_2Cl$: C, 66.57; H, 4.03; N, 8.63. Found: C, 66.43; H, 3.91; N, 8.56. (-)-**9b**: mp 304-306°C (decomp., colorless needles, recrystallized from MeOH-$CHCl_3$). $[\alpha]_D^{24}$ -470.2° (c=0.258, $CHCl_3$). Ir (KBr): 1695, 1679, 1596, 1380, 1102, 907, 768 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 3.37 (2H, dd, *J*=16.1 and 9.0 Hz), 3.59 (2H, dd, *J*=16.1 and 10.7 Hz), 5.26 (2H, dd, *J*=10.7 and 9.4 Hz), 7.00-7.39 (6H, m). Ms *m/z*: 362, 360, and 358 (M^+). *Anal.* Calcd for $C_{18}H_{12}N_2O_2Cl_2$: C, 60.19; H, 3.37; N, 7.80. Found: C, 60.35; H, 3.10; N, 7.94.

b) From (-)-2 ------- One pot procedure: A solution of TTFA in TFA (0.88 M, 0.59 ml, 0.520 mmol) was added to the solution of (-)-**2** (62.8 mg, 0.217 mmol) in TFA (1.0 ml) and the mixture was stirred at room temperature for 12 h. After evaporation of the solvent under reduced pressure, DMF (5.0 ml) was added to the resultant residue. To this solution, anhydrous $CuCl_2$ (291.2 mg, 2.17 mmol) was added and the whole was stirred at 134°C for 5 h. After the same work-up and separation as described above, (-)-**10b** (1.9 mg, 3%) and (-)-**9b** (36.4 mg, 46%) were obtained.

(6a*S*-*cis*)-4-Azido- ((-)-10c) and -4,11-diazido-6a,7,13a,14-tetrahydropyrazino[1,2-*a*:4,5-*a'*]-diindole-6,13-dione ((-)-9c) ------ CuI (1.407 g, 7.38 mmol) was added to a solution of (-)-**7** (2.120 g, 1.84 mmol) and NaN_3 (720.4 mg, 11.0 mmol) in DMF (50.0 ml) and the mixture was stirred at 79°C for 2 h. After evaporation of the solvent under reduced pressure, a mixture of CH_2Cl_2-MeOH (95:5, v/v) and brine were added and well shaked. Insoluble materials were filtered off and organic layer was separated. The organic layer was washed subsequently with 10% aq. sodium thiosulfate, brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was subjected to column chromatography on SiO_2 with $CHCl_3$ as an eluent to give (-)-**10c** (29.6 mg, 5%) and (-)-**9c**

(439.8 mg, 64%) in the order of elution. (-)-**9c**: mp 179°C (decomp., pale brown powder, recrystallized from $CHCl_3$-MeOH). $[\alpha]_D^{25}$ -527.7° (c=0.20, $CHCl_3$). Ir (KBr): 2115, 1683, 1605, 1475, 1453, 1395, 1303, 794 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 3.34 (2H, dd, *J*=16.4 and 9.5 Hz), 3.57 (2H, dd, *J*=16.4 and 10.7 Hz), 5.23 (2H, t, *J*=10.7 and 9.5 Hz), 6.90-7.33 (6H, m). Ms *m/z*: 372 (M^+). *Anal.* Calcd for $C_{18}H_{12}N_8O_2$: C, 58.06; H, 3.25; N, 30.09. Found: C, 57.88; H, 3.19; N, 30.04. (-)-**10c**: mp 188-190°C (decomp., pale orange needles, recrystallized from CH_2Cl_2-MeOH). $[\alpha]_D^{19}$ -340.9° (c=0.176, $CHCl_3$). Ir (KBr): 2120, 1687, 1667, 1599, 1395, 755 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 3.37 (1H, dd, *J*=16.0 and 10.0 Hz), 3.43 (1H, dd, *J*=16.0 and 10.0 Hz), 3.66 (1H, dd, *J*=16.0 and 10.0 Hz), 3.81 (1H, dd, *J*=16.0 and 10.0 Hz), 5.12 (2H, br t, *J*=10.0 Hz), 6.82-7.36 (6H, m), 8.08 (1H, br d, *J*=8.0 Hz). Ms *m/z*: 331 (M^+). *Anal.* Calcd for $C_{18}H_{13}N_5O_2$: C, 65.25; H, 3.95; N, 21.14. Found: C, 64.95; H, 3.80; N, 20.86.

(6a*S*-*cis*)-4,11-Dinitro-6a,7,13a,14-tetrahydropyrazino[1,2-*a*:4,5-*a*']diindole-6,13-dione ((-)-9d) ------ $NaNO_2$ (579.3 mg, 8.39 mmol) was added to a solution of (-)-**7** (200.8 mg, 0.175 mmol) and $CuSO_4 \cdot 5H_2O$ (786.1 mg, 3.14 mmol) in DMF (10.0 ml) and the mixture was stirred at 100°C for 1 h. After evaporation of the solvent under reduced pressure, a mixture of CH_2Cl_2-MeOH (95:5, v/v) and brine were added and well shaked. Insoluble materials were filtered off and organic layer was separated. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was subjected to preparative thin layer chromatography on SiO_2 with CH_2Cl_2 as a developing solvent. Extraction with CH_2Cl_2-MeOH (95:5, v/v) from the band having Rf value of 0.52-0.43 afforded (-)-**9 d** (14.0 mg, 21%). mp 327-338°C (decomp., colorless needles, recrystallized from CH_2Cl_2-MeOH). $[\alpha]_D^{23}$ -1479.5° (c=0.151, CH_2Cl_2). Ir (KBr): 1703, 1681, 1609, 1544, 1529, 1464, 1399, 1369, 1326, 1225, 1118, 801, 733 cm^{-1}. ^{1}H-Nmr (DMSO-d_6) δ: 3.34 (2H, dd, *J*=16.0 and 10.0 Hz), 3.56 (2H, dd, *J*=16.0 and 10.0 Hz), 5.58 (2H, t, *J*=10.0 Hz), 7.34 (2H, t, *J*=7.8 Hz), 7.67 (2H, d, *J*=7.8 Hz), 7.71 (2H, d, *J*=7.8 Hz). Ms *m/z*: 380 (M^+). *Anal.* Calcd for $C_{18}H_{12}N_4O_6$: C, 56.85; H, 3.18; N, 14.73. Found: C, 57.06; H, 2.94; N, 14.58.

(6a*S*-*cis*)-4-((*E*)-2-Methoxycarbonylvinyl)- ((-)-10e) and -4,11-di((*E*)-2-methoxycarbonylvinyl)-6a,7,13a,14-tetrahydropyrazino[1,2-*a*:4,5-*a*']diindole-6,13-dione ((-)-9e). a) From (-)-7 ------ $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) was added to a solution of (-)-**7** (319.8 mg, 0.279 mmol) and freshly distilled methyl acrylate (143.9 mg, 1.67 mmol) in DMF (8.0 ml) and the mixture was stirred at 136°C for 3 h. $CHCl_3$-MeOH (95:5, v/v) was added to the reaction mixture and insoluble materials were filtered off. The filtrate was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave an oil, which was subjected to column chromatography on SiO_2 with $CHCl_3$ as an eluent to give recovery of (-)-**7** (11.5 mg, 14%), (-)-**10 e** (35.9 mg, 34%), and (-)-**9 e** (38.8 mg, 30%) in the order of elution. (-)-**10 e**: mp 272-273°C (colorless needles, recrystallized from CH_2Cl_2-MeOH). $[\alpha]_D^{26}$ -406.7° (c=0.195, $CHCl_3$). Ir (KBr): 1720, 1673, 1484, 1407, 754 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 3.16-3.90 (4H, m), 3.79 (3H, s), 5.12 (2H, t, *J*=10.0 Hz), 6.27 (1H, d, *J*=15.9 Hz), 6.94-7.52 (6H, m), 7.99 (1H, d, *J*=15.9 Hz), 8.00-8.12 (1H, m). Ms *m/z*: 374 (M^+). *Anal.* Calcd for $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.53; H, 4.82; N, 7.65. (-)-**9 e**: mp 194-195°C (colorless plates, recrystallized from CH_2Cl_2-MeOH). $[\alpha]_D^{28}$ -487.6° (c=0.178, $CHCl_3$). Ir (KBr): 1705, 1679, 1631, 1389, 1277, 1165 cm^{-1}. ^{1}H-Nmr ($CDCl_3$) δ: 3.45 (4H, d, *J*=10.0 Hz), 3.79 (6H, s), 5.26 (2H, t, *J*=10.0 Hz), 6.34 (2H, d, *J*=15.9 Hz), 6.98-7.38 (4H, m), 7.49 (2H, dd, *J*=7.1 and 2.0 Hz), 7.88 (2H, d, *J*=15.9 Hz). Ms *m/z*: 458 (M^+). *Anal.* Calcd for $C_{26}H_{22}N_2O_6 \cdot 1/2H_2O$: C, 66.80; H, 4.96; N, 5.99. Found: C, 66.54; H, 4.74; N, 6.11.

b) From (-)-2 -------- One pot procedure: A solution of TTFA in TFA (0.88 M, 0.72 ml, 0.637 mmol) was added to a solution of (-)-**2** (77.0 mg, 0.266 mmol) in TFA (1.0 ml) and the mixture was stirred at room temperature for 12 h. After evaporation of the solvent under reduced pressure, DMF (5.0 ml) was added to the resultant residue. To this solution, a solution of freshly distilled methyl acrylate (137.2 mg, 1.59 mmol) and $Pd(OAc)_2$ (11.9 mg, 0.053 mmol) in DMF (1.0 ml) was added and the mixture was stirred at 127°C for 3 h. After the same work-up and separation as described above, (-)-**10e** (23.8mg, 24%) and (-)-**9e** (16.0 mg, 13%) were obtained.

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