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SYNTHESIS OF NAPHTH[3,2,1-*cd*]INDOLE BY HECK CYCLIZATION OF 2-METHOXYCARBONYL-3-BENZOYLINDOLES

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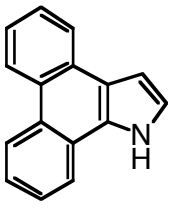
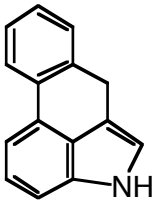
Abstract - Reaction of 1-benzylindole-2,3-dicarboxylic anhydride with 1,3-dimethoxybenzene in the presence of titanium(IV) chloride gave the corresponding 3-(2,4-dimethoxybenzoyl)indole-2-carboxylic acid as the sole product. This carboxylic acid could be converted to naphth[3,2,1-*cd*]indole.

We have shown that reaction of 1-benzylindole-2,3-dicarboxylic anhydride (**1**)[1] with anisoles in the presence of titanium(IV) chloride gave 3-benzoyl-1-benzylindole-2-carboxylic acids, which were converted to the corresponding 3-benzoylindoles[2] and quinones.[3] Jones reported that pyrrolo[9,10-*b*]phenanthrene was a potential antitumor agent.[4] Naphth[3,2,1-*cd*]indole, the isomer of pyrrolo[9,10-*b*]phenanthrene, was synthesized by Kornet from a Friedel-Crafts cyclization of 4-phenylindole-3-carboxamide as a potent pharmacological active indole derivative, but the synthetic method incurs some limitations.[5] Herein, we show the synthesis of a naphth[3,2,1-*cd*]indole derivative by a Friedel-Crafts reaction of **1** with 3-bromoanisole and 1,3-dimethoxybenzene, followed by Heck cyclization.



Pyrrolo[9,10-*b*]phenanthrene

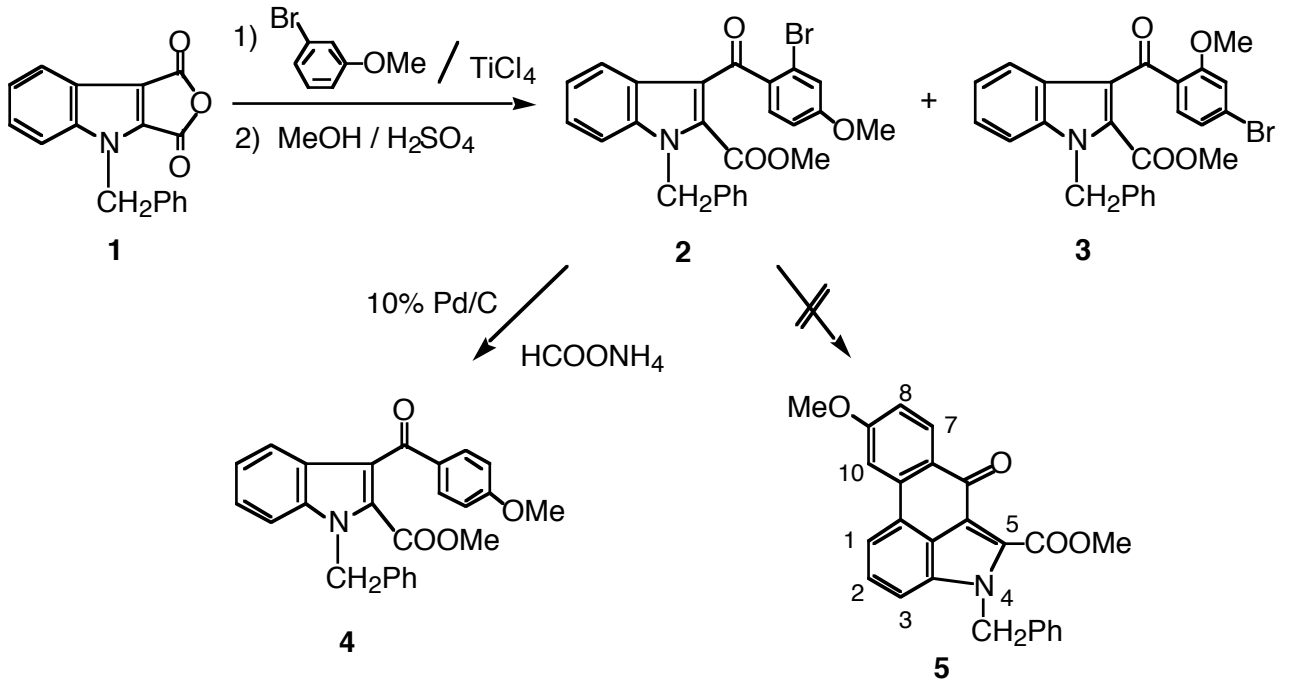


Naphth[3,2,1-*cd*]indole

Reaction of 1-benzylindole-2,3-dicarboxylic anhydride (**1**)[1] with 3-bromoanisole in the presence of 2 equivalents of titanium(IV) chloride, followed by treatment with methanol and a small amount of sulfuric acid gave a mixture of methyl 1-benzyl-3-(2-bromo-4-methoxybenzoyl)- (**2**) and methyl 1-benzyl-3-(4-bromo-2-methoxybenzoyl)indole-2-carboxylate (**3**) in 45% and 38% yields, respectively. **2** was converted to methyl 1-benzyl-3-(4-methoxybenzoyl)indole-2-carboxylate (**4**) by catalytic hydrogenation

over 10% palladium on activated carbon in the presence of ammonium formate in hot methanol in 88% yield in order to determine the structure of **2**. Several efforts were made to isolate naphth[3,2,1-*cd*]indole-6-one (**5**) from **2** by a Heck reaction ($(Ph_3P)_4Pd$) or under radical conditions (Bu_3SnH, 2,2'-azobisisobutyronitrile (AIBN)), but the results attained under various conditions were less than satisfactory. (Scheme 1)

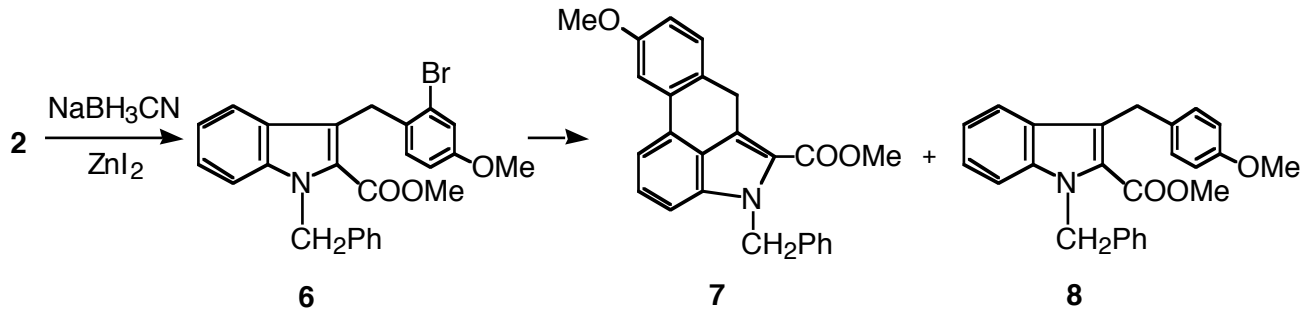
Scheme 1



1 **2** **3** **4** **5**

Reduction of 2-bromo-4-methoxybenzoyl derivative (**2**) with sodium cyanoborohydride in the presence of zinc iodide[6] provided the corresponding benzyl derivative (**6**). **6** was heated with Bu_3SnH in the presence of AIBN to provide the debrominated compound (**8**) in 44% yield, but **7** was not isolated. However, treatment of **6** with $(Ph_3P)_4Pd$ as a catalyst in the presence of potassium acetate in hot 1,4-dioxane gave naphth[3,2,1-*cd*]indole derivative (**7**) in 74% yield. (Scheme 2, Table 1)

Scheme 2



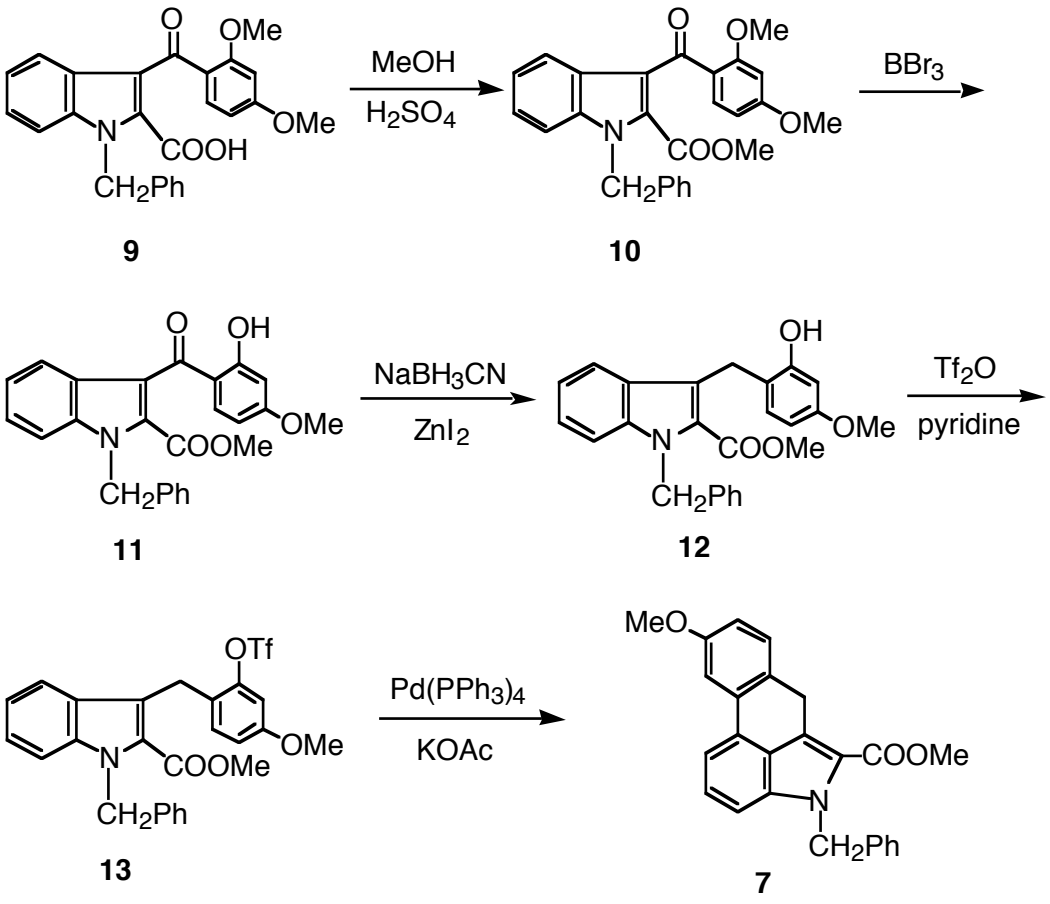
6 **7** **8**

Table 1

Entry	Reagent	Solvent	Time	Yield(%) 7	8
1	Bu_3SnH, AIBN	toluene	5 h	-	44
2	$Pd(PPh_3)_4$, KOAc	dioxane	30 h	74	-

Next, treatment of 3-(2,4-dimethoxybenzoyl)-1-benzylindole-2-carboxylic acid (**9**),[2] prepared from reaction of anhydride (**1**) with 1,3-dimethoxybenzene, with PCl_5, followed by MeOH gave methyl 1-benzyl-3-(2,4-dimethoxybenzoyl)indole-2-carboxylate (**10**) as a single product in 80% yield. Demethylation of **10** with boron tribromide afforded **11** (84%) and subsequent reduction of **11** with $NaBH_3CN$ in the presence of ZnI_2 provided methyl 1-benzyl-3-(2-hydroxy-4-methoxybenzyl)indole-2-carboxylate (**12**)(99%), which was converted by treatment with trifluoromethanesulfonic anhydride in pyridine to trifluoromethanesulfonate (**13**) in 91% yield. In a similar manner to that for the synthesis of naphth[3,2,1-*cd*]indole derivative (**7**) from **6**, the **13** could be converted to **7** in 82% yield by treatment with $(Ph_3P)_4Pd$ as a catalyst .

Scheme 3



EXPERIMENTAL

Melting points were determined on a Yanagimoto micromelting 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. The IR spectra were recorded with a JASCO FT/IR-7000 spectrophotometer. The high MS 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). Tetrahydrofuran (THF) was distilled from sodium and benzophenone prior to use.

Methyl 3-(2-Bromo-4-methoxybenzoyl)-1-benzylindole-2-carboxylate (2) and Methyl 3-(4-Bromo-2-methoxybenzoyl)-1-benzylindole-2-carboxylate (3)

To a solution of 1-benzylindole-2,3-dicarboxylic anhydride (**1**)[1] (1.25 g, 4.5 mmol) and 3-bromoanisole (2.85 mL, 22.5 mmol) in CH_2Cl_2 (23 mL) was added titanium(IV) chloride (22.5 mL of a 1 M CH_2Cl_2 solution, 22.5 mmol) and the mixture was stirred for 2 h at rt. Water was added to the reaction mixture and the mixture was extracted with $CHCl_3$: MeOH (10 : 1). The combined extracts were washed with water and dried over Na_2SO_4, then concentrated under reduced pressure to give a solid. The solid was purified by column chromatography ($CHCl_3$: methanol = 10 : 1) to afford an inseparable mixture of 3-(2-bromo-4-methoxybenzoyl)-1-benzylindole-2-carboxylic acid and 3-(4-bromo-2-methoxybenzoyl)-1-benzylindole-2-carboxylic acid (1.53 g, 73%) as a solid.

A solution of the mixture of the two carboxylic acids (1.12 g, 2.4 mmol) and sulfuric acid (3.3 mL) in dry MeOH (33 mL) was refluxed for 4 h. The mixture was neutralized with aqueous 5% $NaHCO_3$ solution, extracted with CH_2Cl_2. The extracts were washed with water, dried over sodium sulfate, and evaporated off to give a residue, which was chromatographed (*n*-hexane : ethyl acetate =10 : 1) to afford methyl 3-(2-bromo-4-methoxybenzoyl)-1-benzylindole-2-carboxylate (**2**) (0.71 g, 45%) and methyl 3-(4-bromo-2-methoxybenzoyl)-1-benzylindole-2-carboxylate (**3**) (0.60 g, 38%).

2; mp 141-142°C (AcOMe). IR (Nujol) 1721, 1639 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.42 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 5.64 (2H, s, C*H*$_2$Ph), 6.84 (1H, dd, *J* = 8.5, 2 Hz, H-5'), 7.06-7.12 (2H, m, aromatic protons), 7.20-7.42 (8H, m, aromatic protons), 7.91-7.97 (1H, m, H-4). *Anal.* Calcd for $C_{25}H_{20}NO_4Br$: C, 62.77; H, 4.21; N, 2.93. Found: C, 62.72; H, 4.33; N, 3.03.

3; mp 196-198°C (AcOMe). IR (Nujol) 1709, 1638 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.36 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 5.61 (2H, s, C*H*$_2$Ph), 7.05-7.38 (9H, m, aromatic protons), 7.41 (1H, d, *J* = 8 Hz, H-6'), 7.96-8.01 (1H, m, H-4). *Anal.* Calcd for $C_{25}H_{20}NO_4Br$: C, 62.77; H, 4.21; N, 2.93. Found: C, 62.56; H, 4.29; N, 2.94.

Methyl 3-(4-Methoxybenzoyl)-1-benzylindole-2-carboxylate (4)

A suspension of methyl 3-(2-bromo-4-methoxybenzoyl)-1-benzylindole-2-carboxylate (**2**) (48 mg, 0.1 mmol), ammonium formate (38 mg, 0.6 mmol), and 10% palladium-carbon (8 mg) in MeOH (2 mL) was refluxed for 4 h. The catalyst was removed by filtration through Celite and the filtrate was evaporated off. The residue was purified by chromatography (*n*-hexane : CH_2Cl_2 = 1 : 1) to give methyl 3-(4-methoxybenzoyl)-1-benzylindole-2-carboxylate (**4**) (35 mg, 88%) as a white solid, mp 173-174°C (acetone). IR (Nujol) 1702, 1658 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.41 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 5.79 (2H, s, C*H*$_2$Ph), 6.90-7.43 (10H, m, aromatic protons), 7.68-7.73 (1H, m, H-4), 7.80-7.87 (2H,

m, aromatic protons). *Anal.* Calcd for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 4.10. Found: C, 80.85; H, 5.75; N, 4.15.

Methyl 3-(2-Bromo-4-methoxybenzyl)-1-benzylindole-2-carboxylate (6)

A suspension of methyl 3-(2-bromo-4-methoxybenzoyl)-1-benzylindole-2-carboxylate (**2**) (143 mg, 0.3 mmol), zinc iodide (144 mg, 0.45 mmol), and sodium cyanoborohydride (145 mg, 2.25 mmol) in dichloroethane (1 mL) was stirred for 3 h. The insoluble material was removed by filtration through Celite and the filtrate was evaporated off. The residue was purified by chromatography (*n*-hexane : AcOEt = 5 : 1) to give methyl 3-(2-bromo-4-methoxybenzyl)-1-benzylindole-2-carboxylate (**6**) (124 mg, 89%) as a white solid, mp 116-117°C (*n*-hexane-AcOMe). IR (Nujol) 1708 cm^{-1}; ^{1}H-NMR ($CDCl_3$) □: 3.74 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.51 (2H, s, CH_2), 5.82 (2H, s, C*H*$_2$Ph), 6.62 (1H, dd, *J* = 8.5, 2.5 Hz, H-5'), 6.71(1H, d, *J* = 8.5 Hz, H-6'), 7.01-7.40 (9H, m, aromatic protons), 7.55 (1H, d, *J* = 8 Hz, aromatic proton). *Anal.* Calcd for $C_{25}H_{22}NO_3Br$: C, 64.66; H, 4.78; N, 3.02. Found: C, 64.64; H, 4.77; N, 3.00.

Attempt to Synthesis of Methyl 4-Benzyl-9-methoxynapht[3,2,1-*cd*]indole-5-carboxylate (7) by Radical Cyclization: Methyl 3-(4-Methoxybenzyl)-1-benzylindole-2-carboxylate (8)

To a refluxing solution of methyl 3-(2-bromo-4-methoxybenzyl)-1-benzylindole-2-carboxylate (**6**) (46 mg, 0.1 mmol) in toluene (2.5 mL) was added a solution of tri-*n*-butyltin hydride (30 □L, 0.01 mmol) and AIBN (8 mg, 0.05 mmol) in toluene (0.5 mL) over 10 min by using syringe pump under argon and the reaction mixture was refluxed for 1 h. A further portion of tri-*n*-butyltin hydride (30 □L, 0.01 mmol) and AIBN (8 mg, 0.05 mmol) in toluene (0.5 mL) was added to the solution over 20 min and the reaction mixture was refluxed for a further 4 h. 8% Potassium fluoride aqueous solution was added to the solution and the mixture was stirred for 1 h at rt. The aqueous mixture was extracted with ether. The extracts were washed with water, dried over sodium sulfate, and evaporated off to give a residue, which was purified by preparative thin-layer chromatography (*n*-hexane : benzene = 1 : 3) to provide methyl 3-(4-methoxybenzyl)-1-benzylindole-2-carboxylate (**8**) (17 mg, 44%), mp 132-133°C (*n*-hexane-AcOMe). IR (Nujol) 1712, cm^{-1}; ^{1}H-NMR ($CDCl_3$) □: 3.75 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 4.44 (2H, s, CH_2), 5.78 (2H, s, C*H*$_2$Ph), 6.74-6.81 (2H, m, aromatic protons), 6.99-7.36 (10H, m, aromatic protons), 7.66 (1H, br d, *J* = 8 Hz, H-4). *Anal.* Calcd for $C_{25}H_{23}NO_3$: C, 77.90; H, 6.01; N, 3.64. Found: C, 79.92; H, 6.01; N, 3.58.

Methyl 4-Benzyl-9-methoxynaphth[3,2,1-*cd*]indole-5-carboxylate (7) from 6

A suspension of methyl 3-(2-bromo-4-methoxybenzyl)-1-benzylindole-2-carboxylate (**6**) (37 mg, 0.08 mmol), potassium acetate (8 mg, 0.08 mmol), and tetrakis(triphenylphosphine)palladium (0) (15 mg, 0.012 mmol) in dry dioxane (2 mL) was refluxed for 30 h under argon. Water was added to the reaction mixture and the mixture was extracted with CH_2Cl_2. The extracts were washed with water, dried over sodium sulfate, and evaporated off to give a residue, which was purified by chromatography (*n*-hexane : ethyl acetate = 20 : 1) to provide methyl 4-benzyl-9-methoxynaphth[3,2,1-*cd*]indole-5-carboxylate (**7**) (23 mg, 74%), mp 162-164°C (AcOEt). IR (Nujol) 1705 cm^{-1}; ^{1}H-NMR ($CDCl_3$) □: 3.90 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 4.44 (2H, s, CH_2), 5.81 (2H, s, C*H*$_2$Ph), 6.88 (1H, dd, *J* = 9, 3 Hz, H-8), 7.06-7.47

(9H, m, aromatic protons), 7.53 (1H, d, J = 3 Hz, H-9). *Anal.* Calcd for $C_{25}H_{21}NO_3$: C, 78.31; H, 5.52; N, 3.36. Found: C, 78.27; H, 5.58; N, 3.30.

Methyl 3-(2,4-Dimethoxybenzoyl)-1-benzylindole-2-carboxylate (10)

To a suspension of 3-(2,4-dimethoxybenzoyl)-1-benzylindole-2-carboxylic acid (**9**)[2] (1.25 g, 3 mmol) in dry benzene (30 mL) was added phosphorus pentachloride (1.25 g, 6 mmol). The mixture was stirred for 4 h at rt, then dry MeOH (6 mL) was added to the solution under ice-cooling. The reaction mixture was made alkaline by 5% $NaHCO_3$ solution and extracted with ether. The extracts were washed with water, dried over sodium sulfate, and evaporated off to give a residue, which was chromatographed (*n*-hexane : ethyl acetate = 2 : 1) to afford methyl 3-(2,4-dimethoxybenzoyl)-1-benzylindole-2-carboxylate (**10**) (1.03 g, 80%), mp 133-134°C (AcOEt). IR (Nujol) 1706, 1639 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.40 (3H, s, OCH_3), 3.66 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 5.67 (2H, s, CH_2Ph), 6.46 (1H, d, , J = 2 Hz, H-3'), 6.51 (1H, dd, J = 8.5, 2 Hz, H-5'), 7.05-7.38 (8H, m, aromatic protons), 7.60 (1H, d, J = 8.5 Hz, H-6'), 7.83-7.89 (1H, m, H-4). *Anal.* Calcd for $C_{26}H_{23}NO_5$: C, 72.71; H, 5.40; N, 3.26. Found: C, 72.65; H, 5.39; N, 3.20.

Methyl 3-(2-Hydroxy-4-methoxybenzoyl)-1-benzylindole-2-carboxylate (11)

To a solution of methyl 3-(2,4-dimethoxybenzoyl)-1-benzylindole-2-carboxylate (**10**) (858 mg, 2 mmol) in CH_2Cl_2 (20 mL) was added boron tribromide (2 mL of a 1 M CH_2Cl_2 solution, 2 mmol) and the mixture was stirred for 45 min under ice-cooling. Water was added to the reaction mixture and the mixture was extracted with CH_2Cl_2. 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 : ethyl acetate = 10 : 1) to afford methyl 3-(2-hydroxy-4-methoxybenzoyl)-1-benzylindole-2-carboxylate (**11**) (701 mg, 84%), mp 160-161°C (AcOEt). IR (Nujol) 1713, 1616 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.59 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 5.84 (2H, s, CH_2Ph), 6.34 (1H, dd, J = 9, 2 Hz, H-5'), 6.53 (1H, d, J = 2 Hz, H-3'), 6.99-7.45 (8H, m, aromatic protons), 7.31 (1H, d, J = 9 Hz, H-6'), 7.60 (1H, br d, J = 8 Hz, H-4), 12.79 (1H, s OH). *Anal.* Calcd for $C_{25}H_{21}NO_5$: C, 72.28; H, 5.09; N, 3.37. Found: C, 72.21; H, 5.12; N, 3.33.

Methyl 3-(2-Hydroxy-4-methoxybenzyl)-1-benzylindole-2-carboxylate (12)

Sodium cyanoborohydride (189 mg, 3 mmol) and zinc iodide (383 mg, 1.2 mmol) was added to a solution of methyl 3-(2-hydroxy-4-methoxybenzoyl)-1-benzylindole-2-carboxylate (**11**)(166 mg, 0.4 mmol) in 1,2-dichloroethane (4 mL) and the mixture was stirred for 4 h at rt. The insoluble material was removed by filtration through Celite and the filtrate was evaporated off. The residue was purified by column chromatography (*n*-hexane : ethyl acetate = 10 : 1) to afford methyl 3-(2-hydroxy-4-methoxybenzyl)-1-benzylindole-2-carboxylate (**12**) (158mg, 99%), mp 153-155°C (AcOEt). IR (Nujol) 3274, 1675 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.72 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 4.37 (2H, s, CH_2), 5.61 (2H, s, CH_2Ph), 6.39-6.46 (2H, m, aromatic protons), 6.96-7.34 (7H, m, aromatic protons), 7.80 (1H, s, OH), 7.83 (1H, br d, J = 8 Hz, aromatic proton). *Anal.* Calcd for $C_{25}H_{23}NO_4$: C, 74.80; H, 5.77; N, 3.49. Found: C, 74.72; H, 5.74; N, 3.46. M-456

Methyl 3-(2-Trifluoromethanesulfonyloxy-4-methoxybenzyl)-1-benzylindole-2-carboxylate (13)

To a solution of methyl 3-(2-hydroxy-4-methoxybenzyl)-1-benzylindole-2-carboxylate (**12**) (1.20 g, 3 mmol) in pyridine (30 mL) was added trifluoromethanesulfonic anhydride (1.90 g, 6.6 mmol) and the mixture was stirred overnight at rt. Water was added to the reaction mixture and the mixture was extracted with ether. The combined extracts were washed with water, 5% HCl, then water, dried over Na_2SO_4, and filtered. The solvent was concentrated under reduced pressure to give a residue, which was purified by column chromatography (*n*-hexane : ethyl acetate = 10 : 1) to afford methyl 3-(2-trifluoromethanesulfonyloxy-4-methoxybenzyl)-1-benzylindole-2-carboxylate (**13**) (1.46 g, 91%), mp 131-133°C (*n*-hexane). IR (Nujol) 1712 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.76 (3H, s, OCH_3), 3.77 (3H, s, OCH_3), 4.51 (2H, s, CH_2), 5.83 (2H, s, CH_2Ph), 6.68 (1H, dd, *J* = 9, 3 Hz, H-5'), 6.81 (1H, d, *J* = 9 Hz, H-6'), 6.83 (1H, d, *J* = 3 Hz, H-3'), 7.00-7.59 (9H, m, aromatic protons). *Anal.* Calcd for $C_{26}H_{22}NO_6F_3S$: C, 58.76; H, 4.17; N, 2.64. Found: C, 58.75; H, 4.15; N, 2.54.

Methyl 4-Benzyl-9-methoxynaphth[3,2,1-*cd*]indole-5-carboxylate (7) from 13

A suspension of methyl 3-(2-trifluoromethanesulfonyloxy-4-methoxybenzyl)-1-benzylindole-2-carboxylate (**13**) (800 mg, 1.5 mmol), potassium acetate (152 mg, 1.5 mmol), and tetrakis(triphenylphosphine)-palladium(0) (520 mg, 0.45 mmol) in dry dioxane (30 mL) was refluxed for 21 h under argon. Water was added to the reaction mixture and the mixture was extracted with CH_2Cl_2. The extracts were washed with water, dried over sodium sulfate, and evaporated off to give a residue, which was purified by chromatography (*n*-hexane : ethyl acetate =10 : 1) to provide methyl 4-benzyl-9-methoxynaphth[3,2,1-*cd*]indole-5-carboxylate (**7**) (474 mg, 82%).

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