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BROMINATION OF DIMETHYL 1-SUBSTITUTED INDOLE-2,3-DICARBOXYLATES

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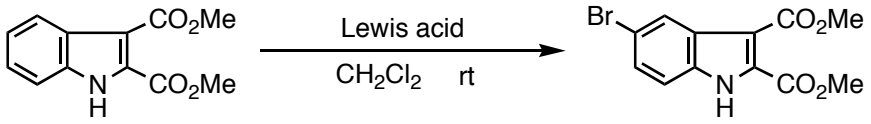
Abstract – Treatment of dimethyl indole-2,3-dicarboxylate with pyridinium hydrobromide perbromide or bromine in the presence of Lewis acid gave dimethyl 5-bromoindole-2,3-dicarboxylate as the sole product. In a similar manner, dimethyl 1-benzyl- and 1-benzenesulfonyl-indole-2,3-dicarboxylates provided a mixture of the corresponding 5-bromoindole and 6-bromoindole derivatives. However, methyl 1-trifluoromethanesulfonylindole-2,3-dicarboxylate gave methyl 6-bromo-1-trifluoromethanesulfonylindole-2,3-dicarboxylate as a major product.

Bromoindole alkaloids have been isolated as secondary metabolites of marine organisms, such as sponges, tunicates, and so on, which are promising sources of new biologically active molecules.[1] Moreover, a bromo group is a useful functional group, which could be converted to various groups by Heck-type reaction in the presence of a palladium catalyst. We have reported that dimethyl indole-2,3-dicarboxylates and indole-2,3-dicarboxylic anhydrides were useful synthons in the synthesis of pratosine,[2] hippadine,[2] murrayaquinone-A,[3] ellipticine,[4-6] olivacine,[7] and caulersin.[8] However, there are many indole alkaloids, having a substituent on the benzene ring of the indole skeleton, especially a bromo group at the 5- and 6-psition of the indole ring.[1,9-11] Chae reported that bromination of dimethyl indole-2,3-dicarboxylate (**1a**) by bromine in the presence of sodium acetate in acetic acid gave dimethyl 5-bromoindole-2,3-dicarboxylate (**2a**) as the sole product, but the influence of the substituents on the indole nitrogen in bromination of **1a** was not examined.[12] In this paper, we show bromination of dimethyl 1-substituted indole-2,3-dicarboxylates (**1**) and enhancement of their utility as a synthon.

Reaction of dimethyl indole-2,3-dicarboxylate (**1a**) with pyridinium hydrobromide perbromide (PHPB)(1 equiv.) in the presence of titanium (IV) chloride, aluminum (III) chloride, or tin (IV) chloride in dichloromethane at room temperature gave dimethyl 5-bromoindole-2,3-dicarboxylate (**2a**) in 43%, 62%, 60% yield, respectively, as the sole product, but other isomers of monobromoindole derivative were not isolated. (Entries 1-3) Treatment of **1a** with PHPB (3 equiv.) in the presence of tin (IV) chloride afforded **2a** in 71% yield. (Entry 4) When **1a** was reacted with bromine (4 equiv.) in the presence of tin (IV) chloride **2a** was afforded in 77% yield, (Entry 5) but a complex mixture was obtained in hot

1,2-dichloroethane for 30 min. (Entry 6)(Table 1)

Scheme 1



1a **2a**

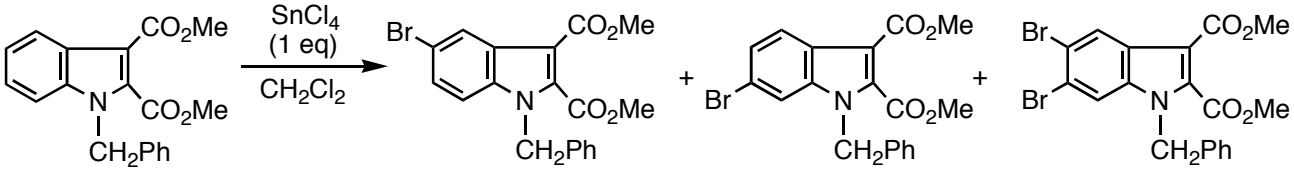
Table 1. Bromination of dimethyl indole-2,3-dicarboxylate (**1a**)

Entry		Lewis acid (5 eq)	Time	Yield (%)
1	PHPB (1 eq)	$TiCl_4$	1 d	43
2	PHPB (1 eq)	$AlCl_3$	1 h	62
3	PHPB (1 eq)	$SnCl_4$	1 d	60
4	PHPB (3 eq)	$SnCl_4$	4 h	71
5	Br_2 (4 eq)	$SnCl_4$	1 h	77
6*	Br_2 (4 eq)	$SnCl_4$	0.5 h	-

* Hot 1,2-dichloroethane was used as a solvent.

Next, we examined the bromination of dimethyl 1-benzylindole-2,3-dicarboxylate (**1b**). Treatment of **1b** with PHPB in the presence of tin (IV) chloride (1 equiv.) in dichloromethane provided a mixture of dimethyl 5-bromo- (**2b**) and 6-bromo-indole-2,3-dicarboxylate (**3b**) in 70% and 23% yields, respectively. (Entry 1) When **1b** was reacted with NBS or bromine, similar results were obtained. (Entries 2, 3) However, dimethyl 5,6-dibromoindole-2,3-dicarboxylate (**4b**) was isolated quantitatively as a single isomer by reaction of **1b** with bromine in hot dichloromethane, but other isomers of dimethyl dibromoindole-2,3-dicarboxylates were not found. (Entry 4) (Table 2)

Scheme 2



1b **2b** **3b** **4b**

Table 2. Bromination of dimethyl 1-benzylindole-2,3-dicarboxylate (**1b**)

Entry		Condition		Yield(%) **2b**	**3b**	**4b**
1	PHPB (1 eq)	rt	3 h	70	23	-
2	NBS (1 eq)	rt	1 d	80	20	-
3	Br_2 (2 eq)	-20 °C	1 d	73	15	7
4	Br_2 (2 eq)	reflux	10 min	-	-	quant

We examined the bromination of dimethyl 1-benzenesulfonyl- (**1c**) and 1-trifluoromethanesulfonyl-indole-2,3-dicarboxylate (**1d**), having electron-withdrawing substituents on the indole nitrogen. Reaction of **1c** (R=Ph) with PHPB (1 equiv.) in the presence of tin (IV) chloride (5 equiv.) in dichloromethane provided a mixture of dimethyl 5-bromo- (**2c**) and 6-bromo-indole-2,3-dicarboxylate (**3c**) in 40% and 51% yields, respectively. (Entry 1) When **1c** was treated with NBS (1 equiv.), a similar result was obtained, but treatment of **1c** with NBS (3 equiv.) or bromine (4 equiv.) gave dimethyl 5,6-dibromoindole-2,3-dicarboxylate (**4c**) exclusively. (Entries 2-4) When **1d** was treated with PHPB at room temperature, the starting material was recovered. (Entry 5) However, reaction of **1d** with bromine or NBS in hot 1,2-dichloroethane yielded a mixture of 6-bromoindole-2,3-dicarboxylate (**4d**) as a major product and 5-bromoindole-2,3-dicarboxylate (**3d**) as a minor product, but 5,6-dibromoindole derivative (**4d**) was not isolated. (Entries 6, 7) (Table 3)

Scheme 3

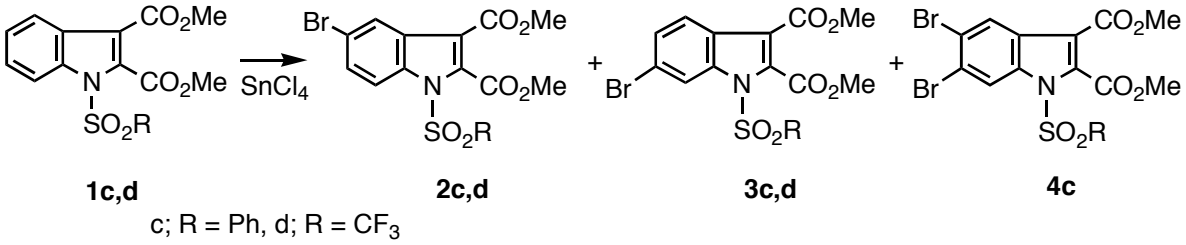
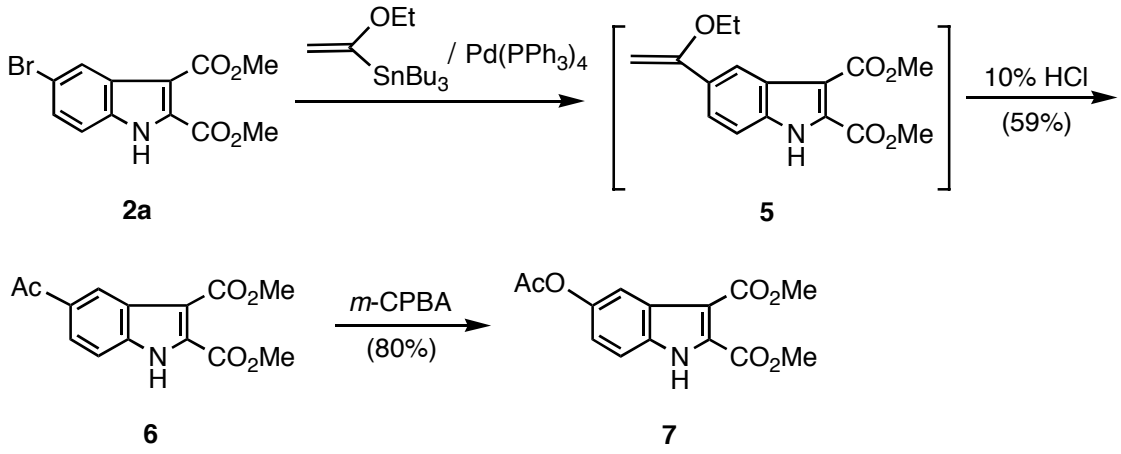


Table 3. Bromination of methyl 1-benzenesulfonyl- (**1c**) and 1-trifluoromethanesulfonyl-indole-2,3-dicarboxylate (**1d**)

						Yield(%)		
Entry	R		$SnCl_4$	Solvent	Condition	**2**	**3**	**4**
1	Ph	PHPB (1 eq)	5 eq	CH_2Cl_2	rt 2h	40	51	-
2	Ph	NBS (1 eq)	1 eq	$(CH_2Cl)_2$	reflux 0.5h	43	33	5
3	Ph	NBS (3 eq)	1 eq	$(CH_2Cl)_2$	reflux 3h	-	-	68
4	Ph	Br_2 (4 eq)	1 eq	$(CH_2Cl)_2$	reflux 2h	-	-	93
5	CF_3	PHPB (1 eq)	3 eq	$(CH_2Cl_2$	rt 24h	-	-	-
6	CF_3	Br_2 (4 eq)	1 eq	$(CH_2Cl)_2$	reflux 9h	23	45	-
7	CF_3	NBS (2 eq)	1 eq	$(CH_2Cl)_2$	reflux 10h	29	49	-

Finally, we examined a conversion of the bromine group in dimethyl 5-bromoindole-2,3-dicarboxylate (**2a**) to an acetoxy group. Reaction of **2a** with tributyl(1-ethoxyvinyl)tin in the presence of $Pd(PPh_3)_4$ in hot toluene provided ethoxyvinyl compound (**5**), which was treated with 10% HCl in tetrahydrofuran to give dimethyl 5-acetylindole-2,3-dicarboxylate (**6**) in 59% yield. Baeyer-Villiger oxidation was performed by treatment of **6** with *m*-chloroperbenzoic acid (MCPBA) in the presence of sodium hydrogen carbonate in dichloromethane to afford dimethyl 5-acetoxyindole-2,3-dicarboxylate (**7**) in 80% yield.

Scheme 4



2a **5** **6** **7**

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).

Dimethyl 1-Benzyindole-2,3-dicarboxylate (1b)

A mixture of dimethyl indole-2,3-dicarboxylate (**1a**)(303 mg, 1.3 mmol), benzyl bromide (155 μL, 1.3 mmol), and K_2CO_3 (179 mg, 1.3 mmol) in MeCN (13 mL) was refluxed for 1 h. The insoluble material was filtered off through Celite and the filtrate was concentrated to afford a residue, which was purified by column chromatography on SiO_2 (*n*-hexane : AcOEt = 5 : 1) to give dimethyl 1-benzylindole-2,3-dicarboxylate (**1b**) (414 mg, 99%) as a white solid, mp 100-101°C (MeOH) (lit.,[13] 102°C). *Anal.* Calcd for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33. Found: C, 70.59; H, 5.32; N, 4.29.

Dimethyl 1-Benzenesulfonyindole-2,3-dicarboxylate (1c)

A mixture of **1a** (2.00 g, 8.6 mmol), benzenesulfonyl chloride (1.70 mL, 13 mmol), and K_2CO_3 (1.80 g, 13 mmol) in MeCN (21 mL) was refluxed for 1 h. The insoluble material was filtered off through Celite and the filtrate was concentrated to provide a residue, which was purified by column chromatography on SiO_2 (*n*-hexane : $CHCl_3$ = 1 : 5) to give dimethyl 1-benzenesulfonylindole-2,3-dicarboxylate (**1c**)[14] (2.50 g, 78%) as a white solid, mp 138-139°C (MeOH). *Anal.* Calcd for $C_{18}H_{15}NO_6S$: C, 57.90; H, 4.05; N, 3.76. Found: C, 57.83; H, 4.09; N, 3.81.

Dimethyl 1-Trifluoromethanesulfonyindole-2,3-dicarboxylate (1d)

To a mixture of **1a** (9.32 g, 40 mmol) and trifluoromethanesulfonic anhydride (7.40 mL, 44 mmol) in CH_2Cl_2 (100 mL) was added a solution of Et_3N (8.40 mL, 60 mmol) in CH_2Cl_2 (20 mL) at 0° C and the reaction mixture was stirred for 2h. Water was added to the reaction mixture and the mixture was extracted with CH_2Cl_2, washed with water, and dried over Na_2SO_4. The extracts were concentrated under

reduced pressure to afford a residue, which was purified by column chromatography on SiO_2 (*n*-hexane : AcOEt = 20 : 1) to give dimethyl 1-trifluoromethanesulfonylindole-2,3-dicarboxylate (**1d**) (11.9 g, 82%) as a white solid, mp 76-77°C (*n*-hexane). *Anal*. Calcd for $C_{13}H_{10}NO_6F_3S$: C, 42.74; H, 2.76; N, 3.84. Found: C, 42.76; H, 2.81; N, 3.85.

Bromination of Dimethyl Indole-2,3-dicarboxylates (1): General Procedure

Dimethyl 5-Bromondole-2,3-dicarboxylate (2a)

To a mixture of dimethyl indole-2,3-dicarboxylate (**1a**) in CH_2Cl_2 or 1,2-dichloroethane (5 mL) was added 1M Ti (IV) Cl_4 in CH_2Cl_2 solution, Al (III) Cl_3, or 1M Sn (IV) Cl_4 in CH_2Cl_2 solution, then PHPB, bromine or NBS and the reaction mixture was stirred at rt or refluxed. Water was added to the mixture and the mixture was extracted with CH_2Cl_2. The extracts were washed with water, dried over Na_2SO_4, and concentrated under reduced pressure to afford a residue, which was purified by preparative thin-layer chromatography on SiO_2 (*n*-hexane : AcOEt = 5 : 1) to give dimethyl 5-bromoindole-2,3-dicarboxylate (**2a**) as a solid. These reaction conditions and results were shown in Table 1.

2a; mp 166-171°C (MeOH) (lit.,[12] 176-177°C). IR (Nujol) ν: 3234, 1697, 1666 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.99 and 4.00 (6H, s, 2 x $COOCH_3$), 7.32 (1H, dd, *J* = 9, 0.5 Hz, H-7), 7.46 (1H, dd, *J* = 9, 2 Hz, H-6), 8.23 (1H, d, *J* = 2 Hz, H-4), 9.39 (1H, br s, NH). ^{13}C-NMR ($CDCl_3$) δ: 163.51, 161.08, 133.91, 131.28, 127.56, 127.29, 123.60, 114.97, 108.30, 52.69, 51.58. *Anal*. Calcd for $C_{12}H_{10}NO_4Br$: C, 46.18; H, 3.23; N, 4.49. Found: C, 46.16; H, 3.23; N, 4.42.

Dimethyl 1-Benzyl-5-bromoindole-2,3-dicarboxylate (2b), Dimethyl 1-Benzyl-6-bromoindole-2,3-dicarboxylate (3b), and Dimethyl 1-Benzyl-5,6-dibromoindole-2,3-dicarboxylate (4b)

Using a procedure similar to that described for preparation of **2a**, **2b**, **3b**, and **4b** was obtained from **1b** and separation of **2b**, **3b**, and **4b** was performed by preparative thin-layer chromatography on SiO_2 (*n*-hexane : AcOEt = 5 : 1). These results were shown in Table 2.

2b; mp 74-75°C (ether). IR (Nujol) ν: 1733, 1707 cm^{-1}. ^{1}H-NMR ($CDCl_3$) *δ*: 3.91, 3.94 (6H, s, 2x$COOCH_3$), 5.42 (2H, s, CH_2Ph), 7.04-7.11 (2H, m, arom), 7.23-7.33 (3H, m, arom), 7.17 (1H, d, *J* = 8.5 Hz, H-7), 7.37 (1H, dd, *J* = 8.5, 2 Hz, H-6), 8.29 (1H, d, *J* = 2 Hz, H-4). *Anal*. Calcd for $C_{19}H_{16}NO_4Br$: C, 56.73; H, 4.01; N, 3.48. Found: C, 56.81; H, 4.10; N, 3.34.

3b; mp 116°C (MeOH). IR (Nujol) ν: 1737, 1708 cm^{-1}. ^{1}H-NMR ($CDCl_3$) *δ*: 3.89, 3.92 (6H, s, 2x$COOCH_3$), 5.41 (2H, s, CH_2Ph), 7.04-7.11 (2H, m, arom), 7.23-7.34 (3H, m, arom), 7.38 (1H, dd, *J* = 8.5, 2 Hz, H-5), 7.47 (1H, d, *J* = 2 Hz, H-7), 8.00 (1H, d, *J* = 8.5 Hz, H-4). *Anal*. Calcd for $C_{19}H_{16}BrNO_4$: C, 56.73; H, 4.01; N, 3.48. Found: C, 56.79; H, 4.08; N, 3.60.

4b; mp 133-134°C (MeOH). IR (Nujol) ν: 1724, 1711 cm^{-1}. ^{1}H-NMR ($CDCl_3$) *δ*: 3.90, 3.93 (6H, s, 2x$COOCH_3$), 5.38 (2H, s, CH_2Ph), 7.04-7.10 (3H, m, arom), 7.24-7.32 (3H, m, arom), 7.60 (1H, s, H-7), 8.42 (1H, s, H-4). *Anal*. Calcd for $C_{19}H_{15}NO_4Br_2$: C, 47.43; H, 3.14; N, 2.91. Found: C, 47.50; H, 3.20; N, 2.93.

Dimethyl 1-Benzenesulfonyl-5-bromoindole-2,3-dicarboxylate (2c), Dimethyl 1-Benzenesulfonyl-6-bromoindole-2,3-dicarboxylate (3c), and Dimethyl 1-Benzenesulfonyl-5,6-dibromoindole-2,3-dicarboxylate (4c)

Using a procedure similar to that described for preparation of **2a**, **2c**, **3c**, and **4c** was obtained from **1c** and

separation of **2c**, **3c**, and **4c** was performed by preparative thin-layer chromatography on SiO_2 (*n*-hexane : AcOEt = 10 : 1). These results are shown in Table 3.

2c; mp 130-131°C (MeOH). IR ($CHCl_3$) ν: 1742, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) *δ*: 3.93, 4.11 (6H, s, 2x$COOCH_3$), 7.48-7.64 (4H, m, arom, H-6), 7.88 (1H, dd, *J* = 8.5, 0.5 Hz, H-7), 8.04-8.08 (2H, m, arom), 8.25 (1H, dd, *J* = 2, 0.5 Hz, H-4). *Anal.* Calcd for $C_{18}H_{14}NO_6BrS$: C, 47.80; H, 3.12; N, 3.19. Found: C, 47.78; H, 3.18; N, 3.19.

3c; mp 178-178.5°C (MeOH). IR ($CHCl_3$) ν: 1739, 1719 cm^{-1}. ^{1}H-NMR ($CDCl_3$) *δ*: 3.91, 4.10 (6H, s, 2x$COOCH_3$), 7.47 (1H, dd, *J* = 8.5, 2 Hz, H-5), 7.50-7.66 (3H, m, arom), 7.97 (1H, dd, *J* = 8.5, 0.5 Hz, H-4), 8.06-8.10 (2H, m, arom), 8.19 (1H, dd, *J* = 2, 0.5 Hz, H-7). *Anal.* Calcd for $C_{18}H_{14}NO_6BrS$: C,47.80; H, 3.12; N, 3.10. Found: C, 47.85; H, 3.18; N, 3.06.

4c; mp 187-188°C ($CHCl_3$-MeOH). IR ($CHCl_3$) ν: 1732, 1717 cm^{-1}. ^{1}H-NMR ($CDCl_3$) *δ*: 3.92, 4.11 (6H, s, 2x$COOCH_3$), 7.54-7.65 (3H, m, arom), 8.05-8.08 (2H, m, arom), 8.32 (1H, s, H-4 or 7), 8.37 (1H, s, H-7 or H-4). *Anal.* Calcd for $C_{18}H_{13}NO_6Br_2S$: C, 40.70; H, 2.47; N, 2.64. Found: C, 40.66; H, 2.46; N, 2.67.

Dimethyl 5-Bromo-1-trifluoromethanesulfonylindole-2,3-dicarboxylate (2d) and Dimethyl 6-Bromo-1-trifluoromethanesulfonylindole-2,3-dicarboxylate (3d)

Using a procedure similar to that described for preparation of **2a**, **2d** and **3d** was obtained from **1c** and separation of **2d** and **3d** was performed by preparative thin-layer chromatography on SiO_2 (CH_2Cl_2). These results are shown in Table 3.

2d; mp 85.5-86°C (MeOH). IR ($CHCl_3$) ν: 1750, 1728 cm^{-1}. ^{1}H-NMR ($CDCl_3$) *δ*: 3.97, 4.03 (6H, s, 2x$COOCH_3$), 7.62 (1H, dd, *J* = 9, 2 Hz, H-6), 7.97 (1H, d, *J* = 9 Hz, H-7), 8.19 (1H, dd, *J* = 2, 0.5 Hz, H-4). *Anal*. Calcd for $C_{18}H_{14}NO_6BrS$: C, 47.80; H, 3.12; N, 3.19. Found: C, 47.78; H, 3.18; N, 3.19.

3d; mp 93.5-94°C (MeOH). IR (Nujol) ν: 1745, 1723 cm^{-1}. ^{1}H-NMR ($CDCl_3$) *δ*: 3.96, 4.02 (6H, s, 2x$COOCH_3$), 7.62 (1H, dd, *J* = 8.5, 2 Hz, H-5), 8.08 (1H, d, *J* = 8.5 Hz, H-4), 8.09 (1H, d, *J* = 2 Hz, H-7). *Anal*. Calcd for $C_{18}H_{14}NO_6BrS$: C, 47.80; H, 3.12; N, 3.10. Found: C, 47.85; H, 3.18; N, 3.06.

Dimethyl 5-Acetylindole-2,3-dicarboxylate (6)

A mixture of dimethyl 5-bromoindole-2,3-dicarboxylate (**2a**) (125 mg, 0.4 mmol), tetrakis(triphenylphosphine)palladium(0) (12 mg, 0.01 mmol), and tributyl(1-ethoxyvinyl)tin (270 μL, 0.8 mmol) in toluene (1 mL) was refluxed for 1h under argon and the reaction mixture was evaporated under reduced pressure. 20% potassium fluoride (2 mL) and ether (3 mL) were added to the residue and the mixture was stirred for 2h, then extracted with ether, washed with water, and dried over Na_2SO_4. The extracts were concentrated under reduced pressure to afford a residue, which was dissolved in 10% HCl (1 mL) and THF (2 mL) and the mixture was stirred for 1h. The reaction mixture was diluted with water and extracted with $CHCl_3$. The extracts were washed with water, dried over Na_2SO_4, and concentrated under reduced pressure to afford a residue, which was purified by column chromatography on SiO_2 (*n*-hexane : AcOEt = 2 : 1) to give **6** (65 mg, 59%), mp 169-170°C (*n*-hexane-AcOEt). IR (Nujol) ν: 3626, 1735, 1712, 1679 cm^{-1}. ^{1}H-NMR ($CDCl_3$) *δ*: 2.70 (3H, s, $COCH_3$), 4.02, 4.03 (6H, s, 2x$COOCH_3$), 7.49 (1H, dd, *J* = 8.5, 1 Hz, H-7), 8.05 (1H, dd, *J* = 8.5, 2 Hz, H-6), 8.70 (1H, d, *J* = 2 Hz, H-4), 9.41 (1H, s, NH). *Anal*. Calcd for $C_{14}H_{13}NO_5$: C, 61.09; H, 4.76; N, 5.09. Found: C, 61.10; H, 4.77; N, 5.11.

Dimethyl 5-Acetoxyindole-2,3-dicarboxylate (7)

To a solution of dimethyl 5-acetylindole-2,3-dicarboxylate (**6**) (28 mg, 0.1 mmol) in CH_2Cl_2 was added $NaHCO_3$ (21 mg, 0.25 mmol) and MCPBA (37 mg, 0.15 mmol) and the mixture was stirred for 3d. Water was added to the reaction mixture and the mixture was extracted with $CHCl_3$. The extracts were washed with water, dried over Na_2SO_4, and concentrated under reduced pressure to provide a residue, which was purified by preparative thin-layer chromatography on SiO_2 (*n*-hexane : AcOEt = 1 : 1) to give **7** (23 mg, 80%) as colorless oil.

IR (Nujol) ν: 3304, 1763, 1726, 1684 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.32 (3H, s, $COOCH_3$), 3.97, 3.99 (6H, s, 2x$COOCH_3$), 7.08 (1H, dd, J = 9, 2 Hz, H-6), 7.37 (1H, d, J = 9 Hz, H-7), 7.76 (1H, d, J = 2 Hz, H-4), 9.56 (1H, s, NH). HRMS (EI) *m/z*: calcd for $C_{14}H_{13}NO_6$: 291.0743. Found: 291.0733.

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