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FACILE SYNTHESIS OF INDOLELACTONES USING Mn(III)-BASED OXIDATIVE SUBSTITUTION-CYCLIZATION REACTION†

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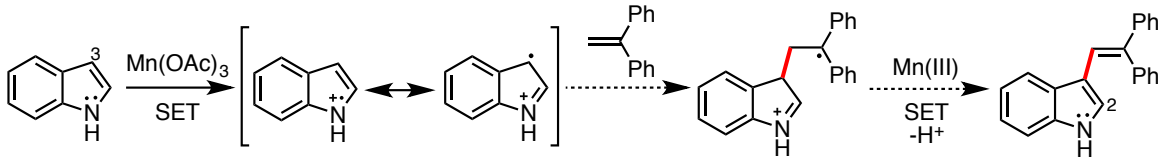
†Dedicated to Professor Kiyoshi Tomioka, Doshisha Women's College, on his 70th birthday

Abstract – Based on the oxidation of indole with $Mn(OAc)_3$ in the presence of 1,1-diarylethenes affording 3-vinyl-substituted indoles, a similar oxidation using indole-2-carboxylic acids was evaluated in order to effectively introduce the substituent group to the C-3 position of the indolecarboxylic acids. The coupling reaction followed by oxidative cyclization smoothly proceeded at room temperature in an AcOH-HCO_2H mixed solvent to give the desired indolelactones in high yields. The reaction details, the structure determination of the products and a brief reaction mechanism are described.

INTRODUCTION

Indole and its derivatives are some of the most important heterocyclic compounds in chemistry, pharmacology, physiology, and the medical and life sciences as well as material science.[1] Therefore, synthetic studies of the indoles, isolation and identification from natural sources, and pharmacological studies have been performed by many chemists. Most of the syntheses were performed according to the typical Fischer indole synthesis[2] and Fukuyama's method,[3] and the main reactions using indoles were an electrophilic substitution. The synthesized indoles are sometimes unstable because of their sensitivity to oxygen in the air and metal oxidants. However, several reactions using metal oxidants, such as $Mn(OAc)_3$ and $Mn(acac)_3$, were found in the literature,[4] which showed that the oxidative substitution occurred at the C-3-position of the indoles.[4a,e] We recently reported the synthesis of oxindoles from

N-aryl-3-oxobutanamides[5] and heterocycle-substituted indole derivatives via the Paal-Knorr strategy.[6] Especially, the oxidative cyclization of *N*-phenyl-3-oxobutanamide with $Mn(OAc)_3$ did not stop at the indolinone stage, but produced dimeric indolinones which coupled at the C-3 position.[5] Since indole is a kind of enamine and the ionization potential (IP_{calcd} 6.66 eV) is lower than that of naphthalene (*IP* 8.14 eV),[7] the indole should easily undergo a single electron-transfer (SET) oxidation with $Mn(OAc)_3$ to produce the cation radical, which could undergo a C-C bond formation with an alkene (Scheme 1). Based on this background, we commenced the reaction of the indole with 1,1-diphenylethene. Although our attempt succeeded, the reaction became complicated because the products were more reactive than the indole substrate. We then postulated that the substituent introduced to the C-3 position should be trapped by other functional groups, such as the carboxylic acid functionality, at the vicinal C-2 position to efficiently obtain the oxidative coupling product. In this paper, we describe the Mn(III)-based oxidative substitution-cyclization of indole-2-carboxylic acids with 1,1-diarylethenes, giving indolelactones, i.e., the 4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-ones. Normally, the indolelactone was prepared in four steps from γ-butyrolactone,[8] which is a very important starting substance for drugs related to the treatment of diseases of the central nervous system such as psychosis,[9] selective inhibitor agents for the aldo-keto reductase 1B1 (AKR1B1) and glucagon-like peptide-1 (GLP-1) related anti-diabetic effect,[10] antitumor agents,[11] and dopamine D_1/D_5 antagonists.[12]



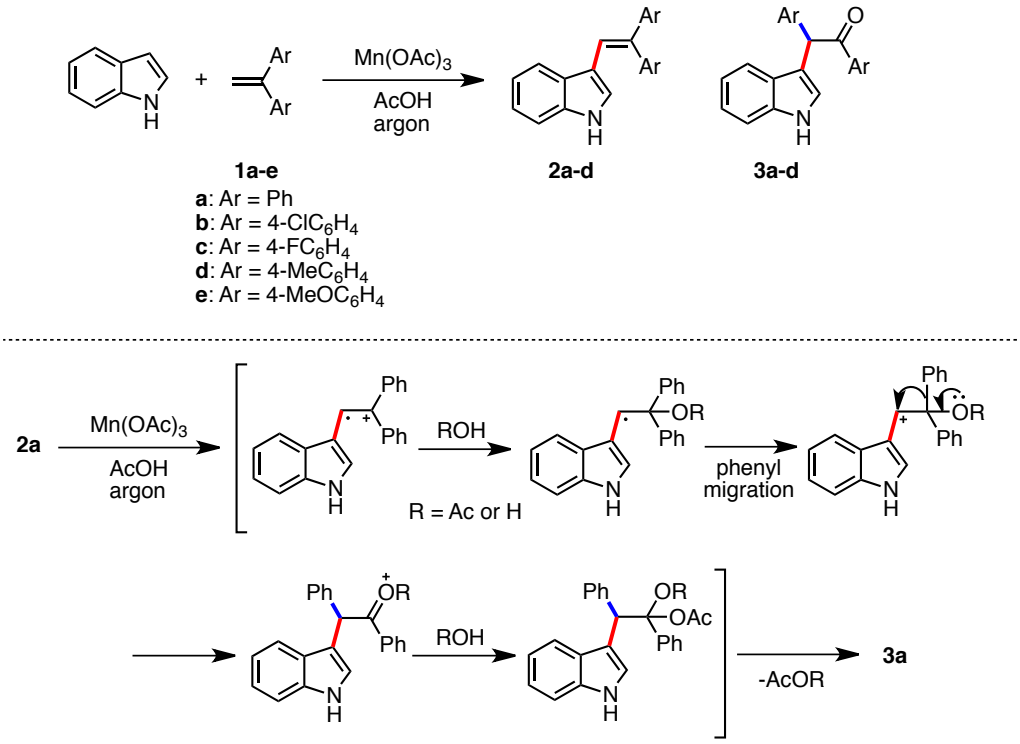
Scheme 1. Mn(III)-Based Oxidative Coupling Reaction of Indole with 1,1-Diphenylethene

RESULTS AND DISCUSSION

Reaction of Indole with 1,1-Disubstituted Alkenes

The reaction of the indole with 1,1-diphenylethene (**1a**) was carried out under various conditions. Although the reaction was complicated as expected, the desired substitution product **2a** was obtained together with the over-oxidation product **3a** in a low yield and no other characterizable materials could be isolated from the reaction mixture (Scheme 2 and Table 1, Entries 1-3). Since it was known that the electron-transfer oxidation was accelerated by adding KOAc,[13] the reaction was conducted in the presence of KOAc (2 equiv.), affording the corresponding substitution products **2a** and **3a** in the combined yield of 37% (Entry 5). However, the reaction was still complicated. A similar reaction using **1b** (Ar = 4-Cl-C_6H_4) and **1c** (Ar = 4-F-C_6H_4) gave a slightly good result (Entries 6,7). The use of **1d** (Ar =

4-Me-C_6H_4) and **1e** (Ar = 4-MeO-C_6H_4) led to a much more intractable mixture due to the low ionization potentials of **1d** and **1e** (Entries 8,9).[14] The vinylindole **2a** alternatively underwent oxidation with $Mn(OAc)_3$ (2 equiv.) to give **3a** (26%) along with the unchanged **2a** (23%) via oxidative phenyl migration (see Experimental Section).[15] Very recently, another synthetic method of the vinylindole **2a** was reported by Beller et al. by the cobalt(III)-catalyzed *reductive* C-H alkylation of indole with diphenylacetic acid and molecular hydrogen.[16]



Scheme 2. Mn(III)-Based Reaction of Indole with 1,1-Diarylethenes **1a-e**

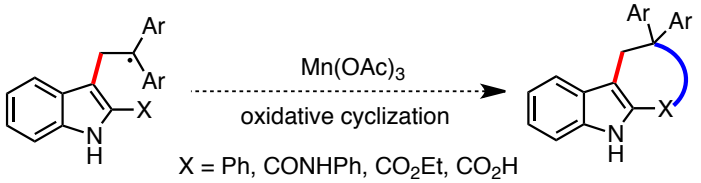
Table 1. Mn(III)-Based Reaction of Indole with 1,1-Diarylethenes **1a-e** under Various Conditions[a]

Entry	**1**/Ar	Molar ratio[b]	Temp/℃	Time/min	Product (Yield/%)[c]		Indole recov./%[d]
1	**1a**: Ph	1:1:2	100	60	**2a** (3)	**3a** (trace)	17
2	**1a**	1:1:2	reflux	10	**2a** (7)	**3a** (trace)	41
3	**1a**	1:1:4	reflux	10	**2a** (7)	**3a** (2)	-
4	**1a**	1:4:4	reflux	15	**2a** (24)	**3a** (6)	-
5	**1a**	1:4:4[e]	reflux	15	**2a** (25)	**3a** (12)	-
6	**1b**: 4-Cl-C_6H_4	1:4:4[e]	reflux	15	**2b** (37)	**3b** (7)	-
7	**1c**: 4-F-C_6H_4	1:4:4[e]	reflux	15	**2c** (30)	**3c** (20)	-
8	**1d**: 4-Me-C_6H_4	1:4:4[e]	reflux	15	**2d** (trace)	**3d** (16)	-
9	**1e**: 4-MeO-C_6H_4	1:4:4[e]	reflux	10	complex mixture		-

[a] The reaction of indole (0.5 mmol) with alkene **1** was carried out in acetic acid (15 mL) under argon.
[b] Indole:**1**:$Mn(OAc)_3$.
[c] Isolated yield based on the amount of indole used.
[d] Recovery of indole.
[e] KOAc (1 mmol) was added.

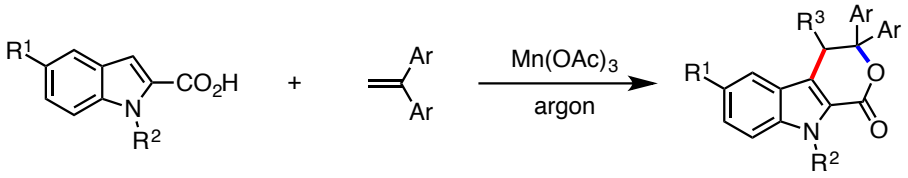
Reaction of Indoles Having a Functional Group at the C-2 Position

With these positive results in hand, we next studied the reaction using indoles having a functionality at the C-2 position in order to trap the unstable intermediates or the products as a stable cyclization product (Scheme 3). We selected phenyl, *N*-phenylcarbamoyl, ethoxycarbonyl, and carboxyl groups as the functional group and investigated the possibility of the oxidative cyclization reaction.



Scheme 3. Reaction of 3-Substituted Indoles Having Another Functionality X at the C-2 Position

The reaction of 2-phenylindole and *N*-phenyl-1*H*-indole-2-carboxamide gave an intractable mixture and no characterizable products could be isolated from the reaction mixture. A similar reaction of ethyl indole-2-carboxylate did not afford the cyclization product, but the corresponding substitution-oxidative rearrangement product (39% yield) such as **3** (see Experimental Section).[15] To our delight, the oxidation of indole-2-carboxylic acid (**4a**) with $Mn(OAc)_3$ in the presence of alkene **1a** was completed within 1.5 min, and two neutral products, indolelactone **5aa** and a small amount of the acetate **6aa**, were obtained (Scheme 4 and Table 2, Entry 1). The structure of **5aa** was determined by 1D and 2D NMR studies, and IR and elemental analyses. In the ^{1}H NMR spectrum of **5aa**, two peaks corresponding to H-3 and the



4a-e
a: R^1 = H, R^2 = H
b: R^1 = Cl, R^2 = H
c: R^1 = F, R^2 = H
d: R^1 = H, R^2 = Me
e: R^1 = H, R^2 = Et

1a-e
a: Ar = Ph
b: Ar = 4-ClC_6H_4
c: Ar = 4-FC_6H_4
d: Ar = 4-MeC_6H_4
e: Ar = 4-MeOC_6H_4

5 : R^3 = H
6 : R^3 = OAc
7 : R^3 = OCHO

Scheme 4. Reaction of Indole-2-carboxylic Acids **4a-e** with Alkenes **1a-e**

carboxylic acid of the substrate **4a** disappeared, and methylene protons (δ 4.14) and ten additional aromatic protons newly appeared. The ^{13}C NMR spectrum showed an sp^3 quaternary carbon (δ 89.0) attached to the oxygen, methylene carbon (δ 31.0) and additional aromatic carbons corresponding to two phenyl groups. The HMQC and HMBC spectra and the elemental analysis were in good agreement with

the structure of **5aa**. The acetate **6aa** was also characterized by the spectroscopic methods. In addition, the indolelactone **5aa** could be subjected to $Mn(OAc)_3$ oxidation to transform into **6aa** in 81% yield (see Experimental Section). Therefore, it was confirmed that the acetate **6aa** was an over-oxidation product of **5aa**.

Table 2. Reaction of Indole-2-carboxylic Acids **4a-e** with Alkenes **1a-e**[a]

Entry	**4**		**1**/Ar	**4**:**1**:Mn[b]	Solvent/mL	Temp/℃	Time/min	Product (Yield/%)[c]		
	R^1	R^2			AcOH:HCO_2H					
1	**4a**: H	H	**1a**: Ph	1:4:2	15:0	reflux	1.5	**5aa** (34)	**6aa** (3)	
2				1:4:4	15:0	reflux	15	**5aa** (46)	**6aa** (22)	
3				1:4:2	15:0	100	1.5	**5aa** (25)	**6aa** (trace)	
4				1:1:2	15:0	rt	240	**5aa** (11)		
5				1:4:2	15:0	rt	240	**5aa** (17)		
6				1:1:2	12:3	rt	40	**5aa** (65)		
7				1:1:2	9:6	rt	40	**5aa** (80)		
8				1:1:2	6:9	rt	40	**5aa** (84)		
9				1:1:2	3:12	rt	40	**5aa** (89)		
10				1:1:2	0:15	rt	40	**5aa** (75)		
11				1:1:2[d]	3:12	rt	25	**5aa** (92)		
12	**4b**: Cl	H	**1a**: Ph	1:1:2[d]	3:12	rt	25	**5ba** (quant)		
13	**4c**: F	H	**1a**: Ph	1:1:2[d]	3:12	rt	25	**5ca** (90)		
14	**4d**: H	Me	**1a**: Ph	1:1:2[d]	3:12	rt	25	**5da** (92)		
15	**4e**: H	Et	**1a**: Ph	1:1:2[d]	3:12	rt	25	**5ea** (83)		
16	**4a**: H	H	**1b**: 4-Cl-C_6H_4	1:1:2[d]	3:12	rt	25	**5ab** (88)		
17	**4b**: Cl	H	**1b**: 4-Cl-C_6H_4	1:1:2[d]	3:12	rt	25	**5bb** (80)		
18	**4c**: F	H	**1b**: 4-Cl-C_6H_4	1:1:2[d]	3:12	rt	25	**5cb** (89)		
19	**4a**: H	H	**1c**: 4-F-C_6H_4	1:1:2[d]	3:12	rt	25	**5ac** (92)		
20	**4b**: Cl	H	**1c**: 4-F-C_6H_4	1:1:2[d]	3:12	rt	25	**5bc** (87)		
21	**4c**: F	H	**1c**: 4-F-C_6H_4	1:1:2[d]	3:12	rt	25	**5cc** (92)		
22	**4a**: H	H	**1d**: 4-Me-C_6H_4	1:1:2[d]	3:12	rt	22	**5ad** (16)	**6ad** (3)	**7ad** (13)
23	**4a**: H	H	**1d**: 4-Me-C_6H_4	1:1:4[d]	3:12	rt	30	**5ad** (20)	**6ad** (20)	**7ad** (27)
24	**4b**: Cl	H	**1d**: 4-Me-C_6H_4	1:1:2[d]	3:12	rt	23	**5bd** (trace)	**6bd** (trace)	**7bd** (trace)
25	**4b**: Cl	H	**1d**: 4-Me-C_6H_4	1:1:4[d]	3:12	rt	30	**5bd** (2)	**6bd** (trace)	**7bd** (17)
26	**4c**: F	H	**1d**: 4-Me-C_6H_4	1:1:2[d]	3:12	rt	24	**5cd** (17)	**6cd** (trace)	**7cd** (7)
27	**4c**: F	H	**1d**: 4-Me-C_6H_4	1:1:4[d]	3:12	rt	40	**5cd** (17)	**6cd** (trace)	**7cd** (36)
28	**4a**: H	H	**1e**: 4-MeO-C_6H_4	1:1:2[d]	3:12	rt	20	complex mixture		

[a] The reaction of **4** (0.5 mmol) with **1** was carried out in solvent (15 mL) under an argon atmosphere.
[b] Molar ratio of **4**, **1**, and $Mn(OAc)_3$.
[c] Isolated yield based on the amount of indole-2-carboxylic acid **4** used.
[d] Four portions of $Mn(OAc)_3$ were successively added every 5 min.

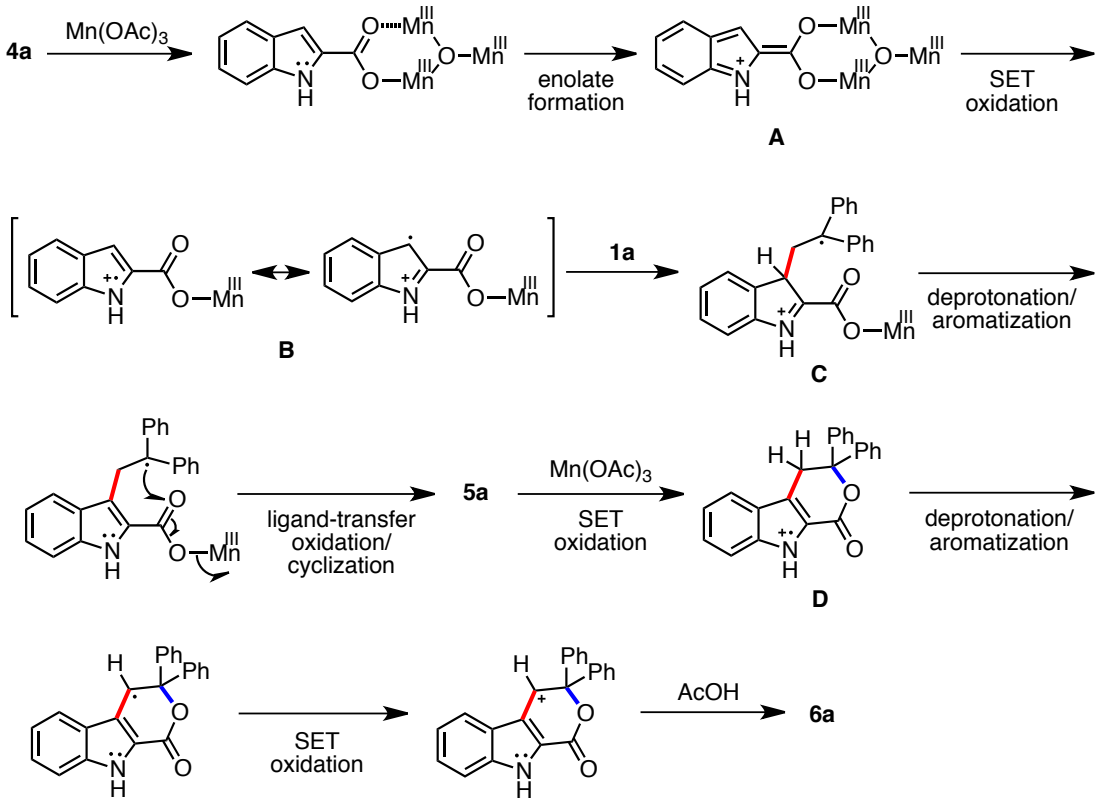
In order to suppress the formation of the over-oxidation product **6aa** and optimize the production of the indolelactone **5aa**, we examined the reaction under mild reaction conditions. When the reaction was carried out at room temperature, it took a long reaction time and was complicated (Entries 4,5). Since we recently found that the addition of HCO_2H to the $Mn(OAc)_3$ oxidation system caused activation of the

Mn(III)-enolate complex at room temperature resulting in shortening of the reaction time and increasing the product yield,[17] we next studied the reaction in the presence of HCO_2H (Entries 6-10). Gratifyingly, our prospect proved right, and the desired **5aa** was obtained in 89% maximum yield using an $AcOH/HCO_2H$ (1:4 v/v) mixed solvent (Entry 9) with no other by-product. Furthermore, the successive addition of the oxidant to the reaction mixture was more effective to produce **5aa** (Entry 11).[18]

With the optimized conditions in hand, we investigated the diversity of the reaction. Introduction of a halo group at the C-5 position (**4b** and **4c**) and protection of the indole nitrogen with an alkyl group (**4d** and **4e**) did not affect the production of the indolelactones **5** (Entries 12-15). Use of halo-substituted alkenes **1b** and **1c** also gave a similar result (Entries 16-21). However, the reaction of electron-rich alkenes **1d** and **1e** became complicated. In the case of **1d**, the indolelactones **5**, the acetates **6**, and the formates **7** were isolated in only small amounts (Entries 22-27). No characterizable products were obtained from the reaction of **1e** (Entry 28). It was considered that the oxidative radical chain reaction could not be controlled because the ionization potentials of **1d** and **1e** were lower than that of the indole-2-carboxylic acids **4** so that the electron-rich alkenes should be oxidized before **4**. It is noteworthy that the production of formates **7** was superior to that of the acetates **6** (Entries 22, 23, 25-27).

Proposed Mechanism for the Formation of the Products

It is obvious that the indole-2-caroxylic acid **4a** underwent a ligand-exchange reaction with $Mn(OAc)_3$ to



Scheme 5. Proposed Mechanism for the Formation of Indolelactone **5a** and the Acetate **6a**

produce the corresponding enolate complex **A** from the previously mentioned result of the reaction of indole-2-carboxylate which could not form the Mn(III)-enolate complex.[19] The SET oxidation of **A** gives the cation radical **B** which would add an alkene **1a** to make a C-C bond, producing another cation radical **C**. Deprotonation-aromatization followed by the ligand-transfer oxidation resulted in the indolelactone **5a**. Although **5a** is stable under the stated reaction conditions, the indolelactone **5a** would be subject to electron-transfer oxidation with excess $Mn(OAc)_3$ to form the cation radical **D**, finally affording the acetate **6a** via a similar mechanism. Especially, the further oxidation tends to occur when the reaction was conducted at elevated temperature (Table 2, Entries 1-3) and the produced indolelactones **5** were substituted by an electron-donating group (Ar = 4-Me-C_6H_4) (Table 2, Entries 22-27).

CONCLUSION

We have accomplished the facile synthesis of indolelactones **5** derived from the Mn(III)-based oxidative coupling reaction followed by cyclization of indole-2-carboxylic acids **4** with 1,1-diarylethenes **1**. Although the oxidation depends on the ionization potential of the indole substrates, 1,1-diarylethenes, and the products, the use of the AcOH/HCO_2H mixed solvent enabled the mild reaction conditions, use of a stoichiometric amount of the oxidant, and selective production of the indolelactones. We believe that the present reaction could be widely used for the synthesis of biologically important indolelactone intermediates.[9-12]

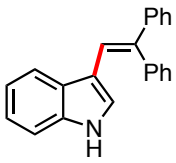
EXPERIMENTAL

Measurements. Melting points were taken using a MP-J3 Yanagimoto micromelting point apparatus and are uncorrected. The IR spectra were measured in $CHCl_3$ or KBr using a Shimadzu 8400 FT IR spectrometer and expressed in cm^{-1}. The NMR spectra were recorded using a JNM ECX 500 or AL300 FT-NMR spectrometer at 500 MHz for the ^1H and at 125 MHz for ^{13}C, with tetramethylsilane as the internal standard. The chemical shifts are reported as δ values (ppm) and the coupling constants in Hz. The following abbreviations are used for the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and brs, broad singlet for the ^1H NMR spectra. The high-resolution mass spectra and the elemental analyses were performed at the Instrumental Analysis Center, Kumamoto University, Kumamoto, Japan.

Materials. 1,1-Diarylethenes **1a-e** were prepared by the Grignard reaction of the corresponding acetophenones with arylmagnesium bromides followed by dehydration in 20% aqueous sulfuric acid.[20] Indole-2-carboxylic acid (**4a**) was purchased from Tokyo Kasei Co., Ltd., and indole and ethyl indole-2-carboxylate were from Wako Pure Chemical Ind., Ltd., and used as received. The 5-chloro- (**4b**) and 5-fluoro-indole-2-carboxylic acids (**4c**) were synthesized by saponification of the corresponding ethyl

esters which were prepared by [3,3]sigmatropic rearrangement of the arylhydrazones in the presence of polyphosphoric acid.[21-23] The 1-methyl- (**4d**) and 1-ethylindole-2-carboxylic acids (**4e**) were prepared by alkylation of ethyl 2-indolecarboxylate with alkyl iodides in the presence of sodium hydride followed by hydrolysis.[24] Manganese(II) acetate tetrahydrate, $Mn(OAc)_2$•$4H_2O$, was purchased from Wako Pure Chemical Ind., Ltd. Manganese(III) acetate dihydrate, $Mn(OAc)_3$•$2H_2O$, was prepared according to our modified method.[5] Flash column chromatography was performed on silica gel 60N (40-50 mm), which was purchased from Kanto Chemical Co., Inc., and preparative thin layer chromatography (TLC) on Wakogel B-10 and B-5F from Wako Pure Chemical Ind., Ltd. The solvents were commercially available first grade and used as received.

Reaction of Indole with 1,1-Disubstituted Alkenes 1a-e. The typical reaction of the indole was as follows. To a mixture of the indole (0.5 mmol) and alkene **1** in AcOH (15 mL), $Mn(OAc)_3$•$2H_2O$ was added. The exact molar ratio is described in Table 1. The mixture was heated at reflux temperature under argon until the Mn(III) oxidant was completely consumed. The existence of the oxidant was monitored by iodine-starch paper and the reaction time was also mentioned in Table 1 (normally 10-15 min). After completion of the reaction, the solvent was removed in vacuo and 2M HCl (30 mL) was added. The aqueous mixture was extracted with $CHCl_3$ (20 mL × 3). The combined extracts were washed with a saturated aqueous solution of $NaHCO_3$, water, dried over anhydrous magnesium sulfate, then concentrated to dryness. The residue was separated by column chromatography on silica gel eluting with $CHCl_3$/hexane (5:5 *v*/*v*), giving the desired vinylindoles **2** and indolylethanones **3** (Table 1).

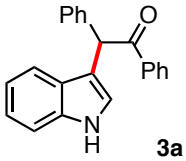


2a

3-(2,2-Diphenylvinyl)-1*H*-indole (2a)[16]: R_f = 0.82 ($CHCl_3$); yellow microcrystals (from $CHCl_3$-hexane); mp 146 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (1H, s, NH), 7.75 (1H, d, J = 6.6 Hz, arom H), 7.43-7.17 (14H, m, arom H), 6.18 (1H, d, J = 2.6 Hz, -C<u>H</u>=C<); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.8 (><u>C</u>=CH-), 141.9, 138.1, 135.0, 127.6, 113.8 (arom C), 130.0 (2C), 129.1, 128.2 (2C), 127.2, 126.7 (2C), 126.6 (2C), 123.2, 120.0, 118.5, 118.4, 111.0 (arom CH), 122.3, (-<u>C</u>H=C<); FAB HRMS (acetone/NBA): calcd for $C_{22}H_{17}N$ 295.1361 (M+H); Found 295.1370.

3-(2,2-Bis(4-chlorophenyl)vinyl)-1*H*-indole (2b): R_f = 0.50 ($CHCl_3$/hexane 4.5:5.5 v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (1H, s, NH), 7.71 (2H, d, J = 8.1 Hz, arom H), 7.46-7.20 (11H, m, arom H), 6.27 (1H, d, J = 2.2 Hz, -C<u>H</u>=C<).

3-(2,2-Bis(4-fluorophenyl)vinyl)-1*H*-indole (2c): R_f = 0.44 ($CHCl_3$/hexane 4.5:5.5 v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (1H, s, NH), 7.72-7.58 (2H, m, arom H), 7.23-6.69 (11H, m, arom H), 6.12 (1H, d, J = 2.6 Hz, -C<u>H</u>=C<).



3a

2-(1*H*-Indol-3-yl)-1,2-diphenylethan-1-one (3a): R_f = 0.25 ($CHCl_3$); brown microcrystals (from $CHCl_3$-hexane) mp 60 °C[25]; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (1H, s, NH), 8.05 (2H, d, J = 8.0 Hz, arom H), 7.49-6.89 (13H, m, arom H), 6.27 (1H, s, -CH<); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5 (C=O), 138.8, 136.8, 136.3, 126.4, 114.2 (arom C), 133.0, 129.0 (2C), 128.8 (2C), 128.6 (2C), 128.5 (2C), 127.0, 123.8, 122.3, 120.0, 118.7, 113.3 (arom CH), 50.7, (-CH<); FAB HRMS (acetone/NBA): calcd for $C_{22}H_{18}NO$ 312.1388 (M+H); Found 312.1398.

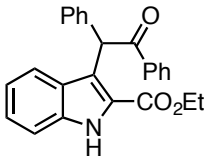
The vinylindole **2a** (77.5 mg) was dissolved in AcOH (7.5 mL) and $Mn(OAc)_3$•$2H_2O$ (134.2 mg) was added. The mixture was heated under reflux for 3 min and the work-up mentioned above was performed, giving **3a** (21.0 mg, 26%) along with the unchanged **2a** (17.7 mg, 23%).

1,2-Bis(4-chlorophenyl)-2-(1*H*-indol-3-yl)ethan-1-one (3b): R_f = 0.23 ($CHCl_3$/hexane 4.5:5.5 v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (1H, s, NH), 7.95 (2H, d, J = 8.4 Hz, arom H), 7.47-7.08 (10H, m, arom H), 6.97 (1H, d, J = 2.6 Hz, arom H), 6.27 (1H, s, -CH<).

1,2-Bis(4-fluorophenyl)-2-(1*H*-indol-3-yl)ethan-1-one (3c): R_f = 0.22 ($CHCl_3$/hexane 4.5:5.5 v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (1H, s, NH), 8.05 (2H, dd, J = 8.9, 5.2 Hz, arom H), 7.48-6.95 (11H, m, arom H), 6.19 (1H, s, -CH<).

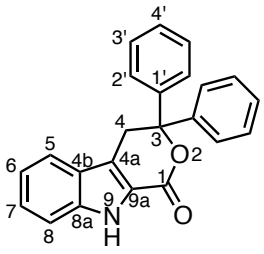
2-(1*H*-Indol-3-yl)-1,2-di-*p*-tolylethan-1-one (3d): R_f = 0.19 ($CHCl_3$/hexane 4.5:5.5 v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (1H, s, NH), 7.97 (2H, d, J = 8.1 Hz, arom H), 7.50-6.87 (11H, m, arom H), 6.23 (1H, s, -CH<).

Reaction of 2-Phenylindole, *N*-Phenyl-1*H*-indole-2-carboxmide, and Ethyl Indole-2-carboxylate with 1a. To a mixture of 2-phenylindole (96.6 mg) and 1,1-diphenylethene (**1a**) (180.3 mg) in AcOH (15 mL), $Mn(OAc)_3$•$2H_2O$ (536.2 mg) was added. The mixture was heated at reflux temperature under argon until the Mn(III) oxidant was completely consumed (for 10 min). After the work-up described above, no characterizable products were isolated. Ethyl indole-2-carboxylate (91.4 mg) and **1a** (109.6 mg) were dissolved in a mixture of AcOH (3 mL) and HCO_2H (12 mL) at room temperature under argon, and four portions of $Mn(OAc)_3$•$2H_2O$ (68.0 mg × 4) were successively added every 5 min (vide infra). After adding the oxidant, the mixture was continued to be stirred until the oxidant was consumed (total for 25 min). After the work-up, ethyl 3-(2-oxo-1,2-diphenylethyl)-1*H*-indole-2-carboxylate (71.7 mg, 39%) was isolated together with the recovery of the carboxylate unchanged (50.8 mg, 56%).[15] A similar reaction of *N*-phenyl-1*H*-indole-2-carboxmide (118.1 mg) with **1a** (90.1 mg) was carried out in AcOH/HCO_2H (3 mL/12 mL) by adding $Mn(OAc)_3$•$2H_2O$ (68.7 mg × 4) to give an intractable mixture and no characterizable materials were separated.

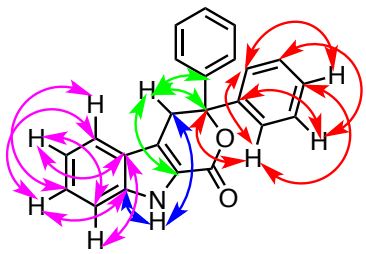


Ethyl 3-(2-Oxo-1,2-diphenylethyl)-1*H*-indole-2-carboxylate[25a]**:** R_f = 0.20 (EtOAc/hexane 2.0:8.0 v/v); colorless microcrystals (from $CHCl_3$-hexane); mp 160 °C; IR (KBr) ν 3412 (NH), 1690 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.91 (1H, s, NH), 7.97 (2H, dd, J = 7.9, 1.3 Hz, H-4), 7.52 (1H, t, J = 7.4 Hz, arom H), 7.44-7.41 (3H, m, arom H), 7.30-7.20 (7H, m, arom H), 7.18 (1H, s, -CH<), 6.95 (1H, t, J = 7.4 Hz, arom H), 4.37 (2H, m, O-C$\underline{H_2}$-CH$_3$), 1.31 (3H, t, J = 6.8 Hz, O-CH$_2$-C$\underline{H_3}$); ^{13}C NMR (125 MHz, DMSO-d_6) δ 198.5 (C=O), 162.0 (O-$\underline{C}$=O), 139.4, 136.8, 136.6, 126.5, 123.6, 119.3 (arom C), 133.2, 129.4 (2C), 128.9 (2C), 128.4 (2C), 128.3 (2C), 126.9, 124.9, 121.7, 120.4, 113.0 (arom CH), 60.9 (O-$\underline{C}$H$_2$-CH$_3$), 50.7 (-$\underline{C}$H<), 14.4 (O-CH$_2$-$\underline{C}$H$_3$); FAB HRMS (acetone/NBA): calcd for $C_{25}H_{22}NO_3$ 384.1600 (M+H). Found 384.1596.

Reaction of Indole-2-carboxylic Acids 4a-e with 1,1-Disubstituted Alkenes 1a-e. The typical oxidation of indole-2-carboxylic acids **4** was as follows. The indole-2-carboxylic acid **4** (0.5 mmol) and alkene **1** (0.5 mmol) were dissolved in a mixture of AcOH (3 mL) and HCO_2H (12 mL), and stirred at room temperature under argon. Four portions of $Mn(OAc)_3$•$2H_2O$ (0.25 mmol × 4) were then successively added every 5 min, and the mixture was continued to be stirred until the Mn(III) oxidant was completely consumed (Table 2). The existence of the oxidant was monitored by iodine-starch paper. After the work-up previously mentioned, the desired indolelactones **5**, **6**, and **7** were obtained (Table 2).

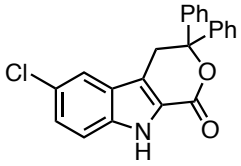


5aa



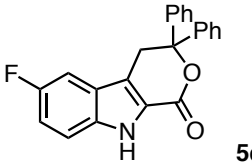
HMBC Study of **5aa**

3,3-Diphenyl-4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-one (5aa): R_f = 0.33 (EtOAc/hexane 1.5:8.5 v/v); Colorless microcrystals (from $CHCl_3$-hexane); mp 233-235 °C; IR (KBr) ν 3321 (NH), 1693 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.90 (1H, s, NH), 7.86 (1H, br.d, J = 8 Hz, H-5), 7.55 (4H, d, J = 7.4 Hz, H-2'×4), 7.38 (1H, br.d, J = 8 Hz, H-8), 7.32 (5H, t, J = 7.4 Hz, H-7 and H-3' × 4), 7.21 (2H, t, J = 7.4 Hz, H-4'), 7.15 (1H, t, J = 7.4 Hz, H-6), 4.14 (2H, s, H-4); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.4 (C-1), 144.0 (C-1' × 2), 138.4 (C-8a), 128.5 (C-3' × 4), 127.5 (C-4' × 2), 126.1 (C-7), 125.4 (C-2' × 4), 124.2 (C-4b), 122.9 (C-4a), 121.8 (C-9a), 121.2 (C-5), 120.3 (C-6), 112.9 (C-8), 89.0 (C-3), 31.0 (C-4). Anal. Calcd for $C_{23}H_{17}NO_2$: C, 81.40; H, 5.05; N, 4.13. Found: C, 81.26; H, 5.11; N, 4.09.



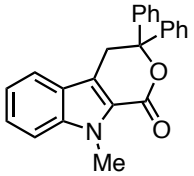
5ba

6-Chloro-3,3-diphenyl-4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-one (5ba): R_f = 0.33 (EtOAc/hexane 1.5:8.5 v/v); Colorless microcrystals (from $CHCl_3$-hexane); mp 212 °C; IR (KBr) ν 3279 (NH), 1701 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.06 (1H, s, NH), 7.91 (1H, d, J = 1.9 Hz, arom H), 7.48 (4H, d, J = 7.7 Hz, arom H), 7.35-7.27 (6H, m, arom H), 7.20 (2H, t, J = 6.7 Hz, arom H), 4.10 (2H, s, -CH_2-); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.1 (C=O), 143.8 (2C), 136.6, 125.1, 124.7, 124.2, 121.3 (arom C), 128.5 (4C), 127.5 (2C), 126.1, 125.4 (4C), 120.4, 114.5 (arom CH), 89.1 (>C<), 30.7 (-CH_2-). Anal. Calcd for $C_{23}H_{16}NO_2Cl$: C, 73.90; H, 4.31; N, 3.75. Found: C, 73.67; H, 4.37; N, 3.71.



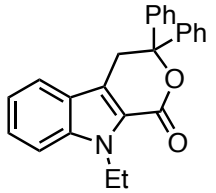
5ca

6-Fluoro-3,3-diphenyl-4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-one (5ca): R_f = 0.3 (EtOAc/hexane 1.5:8.5 v/v); Colorless microcrystals (from $CHCl_3$-hexane); mp 253 °C; IR (KBr) ν 3340 (NH), 1690 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.00 (1H, s, NH), 7.63 (1H, dd, J = 9.1, 1.9 Hz, arom H), 7.51 (4H, dd, J = 7.7, 1.9 Hz, arom H), 7.36 (1H, dd, J = 9.1, 4.8 Hz, arom H), 7.32 (4H, t, J = 7.3 Hz, arom H), 7.23-7.16 (3H, m, arom H), 4.10 (2H, s, -CH_2-); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.2 (C=O), 157.1 (d, J_{CF} = 234 Hz, arom CF), 124.2 (d, J_{CF} = 10.8 Hz, arom C), 121.7 (d, J_{CF} = 4.8 Hz, arom C), 143.8 (2C), 135.1, 124.5 (arom C), 115.0 (d, J_{CF} = 27 Hz, arom CH), 114.3 (d, J_{CF} = 13 Hz, arom CH), 105.4 (d, J = 24 Hz, arom CH), 128.5 (4C), 127.6 (2C), 125.4 (4C) (arom CH), 89.1 (>C<), 30.9 (-CH_2-); FAB HRMS (acetone/NBA): calcd for $C_{23}H_{17}NO_2F$ 358.1243 (M+H); Found 358.1244.



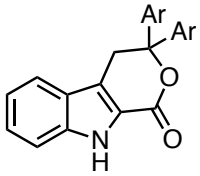
5da

9-Methyl-3,3-diphenyl-4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-one (5da): R_f = 0.34 (EtOAc/hexane 1.5:8.5 v/v); Colorless microcrystals (from $CHCl_3$-hexane); mp 178 °C; IR (KBr) ν 1717 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (1H, br. d, J = 8.6 Hz, arom H), 7.51 (4H, dd, J = 10.0, 1.9 Hz, arom H), 7.40 (1H, br. t, J = 8.6 Hz, arom H), 7.31-7.21 (8H, m, arom H), 3.94 (5H, s, -CH_2- and N-$\underline{C}H_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.1 (C=O), 143.8 (2C), 140.1, 123.6, 123.4, 121.8 (arom C), 128.6 (4C), 127.8 (2C), 126.5, 126.2 (4C), 120.9, 120.8, 110.8 (arom CH), 89.0 (>C<), 32.5 (-CH_2-), 31.3 (N-$\underline{C}H_3$); FAB HRMS (acetone/NBA): calcd for $C_{24}H_{20}NO_2$ 354.1494 (M+H); Found 354.1498.



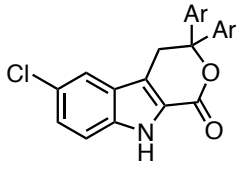
5ea

9-Ethyl-3,3-diphenyl-4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-one (5ea): R_f = 0.38 (EtOAc/hexane 1.5:8.5 v/v); Colorless microcrystals (from $CHCl_3$-hexane); mp 179 °C; IR (KBr) ν 1717 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.81 (1H, d, J = 7.7 Hz, arom H), 7.47 (5H, br. d, J = 6.5 Hz, arom H), 7.31 (1H, t, J = 7 Hz, arom H), 7.25 (4H, t, J = 7.5 Hz, arom H), 7.16-7.10 (3H, m, arom H), 4.36 (2H, q, J = 7.7 Hz, N-C$\underline{H_2}$-CH$_3$), 4.10 (2H, s, -CH$_2$-), 1.03 (3H, q, J = 7.7 Hz, N-CH$_2$-C$\underline{H_3}$); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.4 (C=O), 144.4 (2C), 139.0, 124.0, 123.1, 122.3 (arom C), 129.0 (4C), 128.0 (2C), 126.9, 125.8 (4C), 122.0, 121.0, 111.5 (arom CH), 89.1 (>C<), 39.3 (N-$\underline{C}$H$_2$-CH$_3$), 31.6 (-CH$_2$-), 15.9 (N-CH$_2$-$\underline{C}$H$_3$); FAB HRMS (acetone/NBA): calcd for $C_{25}H_{22}NO_2$ 368.1651 (M+H); Found 368.1649



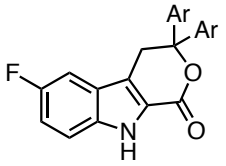
5ab: Ar = 4-ClC$_6$H$_4$

3,3-Bis(4-chlorophenyl)-4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-one (5ab): R_f = 0.4 (EtOAc/hexane 1.5:8.5 v/v); Colorless microcrystals (from $CHCl_3$-hexane); mp 229 °C; IR (KBr) ν 3288 (NH), 1705 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.98 (1H, s, NH), 7.84 (1H, dd, J = 8.5, 2.3 Hz, arom H), 7.54 (4H, dd, J = 9.0, 2.0 Hz, arom H), 7.41-7.15 (7H, m, arom H), 4.14 (2H, s, -CH$_2$-); ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.9 (C=O), 142.5 (2C), 138.5, 132.5 (2C), 124.1, 122.6, 121.6 (arom C), 128.6 (4C), 127.4 (4C), 126.3, 121.2, 120.3, 112.9 (arom CH), 88.0 (>C<), 30.7 (-CH$_2$-); FAB HRMS (acetone/NBA/NaI): calcd for $C_{23}H_{15}NO_2Cl_2Na$ 430.0378 (M+Na); Found 430.0382.



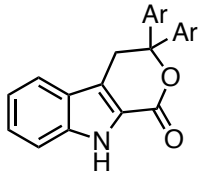
5bb: Ar = 4-ClC$_6$H$_4$

6-Chloro-3,3-bis(4-chlorophenyl)-4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-one (5bb): R_f = 0.39 (EtOAc/hexane 1.5:8.5 v/v); Colorless microcrystals (from $CHCl_3$-hexane); mp 229-230 °C; IR (KBr) ν 3327 (NH), 1713 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.13 (1H, s, NH), 7.89 (1H, d, J = 1.9 Hz, arom H), 7.48 (4H, d, J = 8.6 Hz, arom H), 7.39 (4H, d, J = 8.6 Hz, arom H), 7.35 (1H, d, J = 8.6 Hz, arom H), 7.29 (1H, dd, J = 8.6, 1.9 Hz, arom H), 4.10 (2H, s, -CH$_2$-); ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.7 (C=O), 142.3 (2C), 136.8, 132.6 (2C), 125.0, 124.9, 124.0, 121.2 (arom C), 128.7 (4C), 127.4 (4C), 126.4, 120.5, 114.7 (arom CH), 88.3 (>C<), 30.6 (-CH$_2$-). Anal. Calcd for $C_{23}H_{14}NO_2Cl_3$: C, 62.40; H, 3.19; N, 3.16. Found: C, 62.36; H, 3.35; N, 3.14.



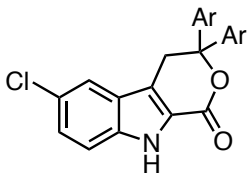
5cb: Ar = 4-ClC_6H_4

6-Fluoro-3,3-bis(4-chlorophenyl)-4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-one (5cb): R_f = 0.29 (EtOAc/hexane 1.5:8.5 v/v); Colorless microcrystals (from $CHCl_3$-hexane); mp 230 °C; IR (KBr) ν 3323 (NH), 1709 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.07 (1H, s, NH), 7.60 (1H, dd, J = 9.5, 2.0 Hz, arom H), 7.50 (4H, d, J = 8.6, arom H), 7.41- 7.36 (5H, m, arom H), 7.19 (1H, ddd, J = 9.9, 9.1, 1.9 Hz, arom H), 4.10 (2H, s, -CH_2-); ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.7 (C=O), 157.2 (d, J_{CF} = 232 Hz, arom CF), 124.1 (d, J_{CF} = 9.5 Hz, arom C), 121.5 (d, J_{CF} = 6.0 Hz, arom C), 142.4, 135.2 (2C), 132.5 (2C), 124.2 (arom C), 115.3 (d, J_{CF} = 26 Hz, arom CH), 114.3 (d, J_{CF} = 8.3 Hz, arom CH), 105.4 (d, J_{CF} = 23 Hz, arom CH), 128.6 (4C), 127.4 (4C) (arom CH), 88.2 (>C<), 30.6 (-CH_2-); FAB HRMS (acetone/NBA): calcd for $C_{23}H_{15}NO_2Cl_2F$ 426.0464 (M+H); Found 426.0443.



5ac: Ar = 4-FC_6H_4

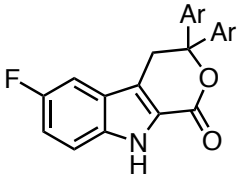
3,3-Bis(4-fluorophenyl)-4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-one (5ac): R_f = 0.3 (EtOAc/hexane 1.5:8.5 v/v); Colorless microcrystals (from $CHCl_3$-hexane); mp 207 °C; IR (KBr) ν 3292 (NH), 1709 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.95 (1H, s, NH), 7.83 (1H, d, J = 8.5 Hz, arom H), 7.54 (4H, dd, J = 8.0, 5.7 Hz, arom H), 7.39 (1H, d, J = 8.6 Hz, arom H), 7.31 (1H, t, J = 6.7 Hz, arom H),7.16-7.15 (5H, m, arom H), 4.14 (2H, s, -CH_2-); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.4 (2C, d, J_{CF} = 243 Hz, arom CF), 159.1 (C=O), 140.1(2C, d, J_{CF} = 2.4 Hz, arom C), 138.5, 124.2, 122.7, 121.8 (arom C), 127.7 (4C, d, J_{CF} = 8.4 Hz, arom CH), 115.3 (4C, d, J_{CF} = 22 Hz, arom CH), 126.2, 121.2, 120.3, 112.9 (arom CH), 88.3 (>C<), 31.2 (-CH_2-); FAB HRMS (acetone/NBA/NaI): calcd for $C_{23}H_{15}NO_2F_2Na$ 398.0969 (M+Na); Found 398.0969.



5bc: Ar = 4-FC_6H_4

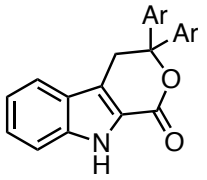
6-Chloro-3,3-bis(4-fluorophenyl)-4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-one (5bc): R_f = 0.3 (EtOAc/hexane 1.5:8.5 v/v); Colorless microcrystals (from $CHCl_3$-hexane); mp 220 °C; IR (KBr) ν 3323 (NH), 1705 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.14 (1H, s, NH), 7.92 (1H, br. s, arom H), 7.51 (4H, dd, J = 7.2, 5.7 Hz, arom H), 7.38 (1H, d, J = 8.6 Hz, arom H), 7.30 (1H, d, J = 8.6 Hz, arom H),7.16 (4H, t, J = 8.6 Hz, arom H), 4.11 (2H, s, -CH_2-); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.4 (2C, d, J_{CF} =

243 Hz, arom CF), 158.9 (C=O), 139.85 (2C, d, J_{CF} = 2.4 Hz, arom C), 136.8, 125.1, 124.9, 124.1, 121.3 (arom C), 127.8 (4C, d, J_{CF} = 8.8 Hz, arom CH), 115.4 (4C, d, J_{CF} = 22 Hz, arom CH), 126.3, 120.4, 114.6 (arom CH), 88.5 (>C<), 31.0 (-CH_2-). Anal. Calcd for $C_{23}H_{14}NO_2Cl_2F$: C, 67.41; H, 3.44; N, 3.42. Found: C, 67.26; H, 3.44; N, 3.38.



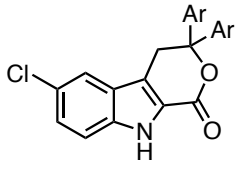
5cc: Ar = 4-FC_6H_4

6-Fluoro-3,3-bis(4-fluorophenyl)-4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-one (5cc): R_f = 0.3 (EtOAc/hexane 1.5:8.5 v/v); Colorless microcrystals (from $CHCl_3$-hexane); mp 216 °C; IR (KBr) ν 3319 (NH), 1705 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.09 (1H, s, NH), 7.63 (1H, dd, J = 9.6, 1.9 Hz, arom H), 7.54 (4H, dd, J = 8.6, 5.5 Hz, arom H), 7.41 (1H, dd, J = 8.6, 4.8 Hz, arom H), 7.20- 7.16 (5H, m, arom H), 4.11 (2H, s, -CH_2-); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.4 (2C, d, J_{CF} = 243 Hz, arom CF), 158.9 (C=O), 157.2 (d, J_{CF} = 234 Hz, arom CF), 124.1 (4C, d, J_{CF} = 9.6 Hz, arom C), 121.7 (d, J_{CF} = 6.0 Hz, arom C), 139.9 (2C), 135.2, 124.3 (arom C), 127.8 (d, J_{CF} = 8.3 Hz, arom CH), 115.4 (4C, d, J_{CF} = 22 Hz, arom CH), 115.2 (d, J_{CF} = 20 Hz, arom CH), 114.3 (d, J_{CF} = 9.6 Hz, arom CH), 105.4 (d, J_{CF} = 23 Hz, arom CH), 88.5 (>C<), 31.1 (-CH_2-); FAB HRMS (acetone/NBA): calcd for $C_{23}H_{15}NO_2F_3$ 394.1055 (M+H); Found 394.1051.



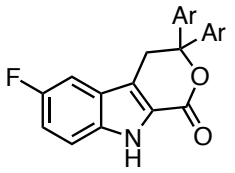
5ad: Ar = 4-MeC_6H_4

3,3-Bis(4-methylphenyl)-4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-one (5ad): R_f = 0.33 (EtOAc/hexane 1.5:8.5 v/v); Colorless microcrystals (from $CHCl_3$-hexane); mp 205 °C; IR (KBr) ν 3277 (NH), 1701 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.81 (1H, s, NH), 7.79 (1H, d, J = 7.7 Hz, arom H), 7.35-7.25 (5H, m, arom H), 7.27 (1H, t, J = 7.7 Hz, arom H), 7.11-7.06 (5H, m, arom H), 4.03 (2H, s, -CH_2-), 2.18 (6H, s, $CH_3 \times 2$); ^{13}C NMR (125 MHz, DMSO-d_6) δ 160.0 (C=O), 141.8 (2C), 138.9, 137.2 (2C), 124.8, 123.4, 122.3 (arom C), 129.5 (4C), 126.6, 125.9 (4C), 121.7, 120.7, 113.3 (arom CH), 89.6 (>C<), 31.6 (-CH_2-), 21.0 ($CH_3 \times 2$); FAB HRMS (acetone/NBA): calcd for $C_{25}H_{22}NO_2$ 368.1651 (M+H); Found 368.1659.



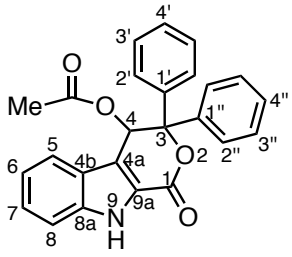
5bd: Ar = 4-MeC_6H_4

6-Chloro-3,3-bis(4-methylphenyl)-4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-one (5bd): R_f = 0.30 (EtOAc/hexane 1.5:8.5 v/v); Colorless microcrystals (from $CHCl_3$-hexane); mp 235 °C; IR (KBr) ν 3317 (NH), 1709 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.04 (1H, s, NH), 7.90 (1H, d, J = 1.4 Hz, arom H), 7.35-7.28 (5H, m, arom H), 7.27 (1H, dd, J = 8.6, 1.9 Hz, arom H), 7.08 (4H, d, J = 8.6 Hz, arom H), 4.03 (2H, s, -CH_2-), 2.18 (6H, s, CH_3 × 2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.8 (C=O), 141.6 (2C), 137.3 (2C), 137.2, 125.7, 125.2, 124.9, 121.9 (arom C), 129.5 (4C), 126.6, 125.9 (4C), 120.9, 115.0 (arom CH), 89.8 (>C<), 31.4 (-CH_2-), 21.0 (CH_3 × 2); FAB HRMS (acetone/NBA/NaI): calcd for $C_{25}H_{20}NO_2ClNa$ 424.1080 (M+Na); Found 424.1075.

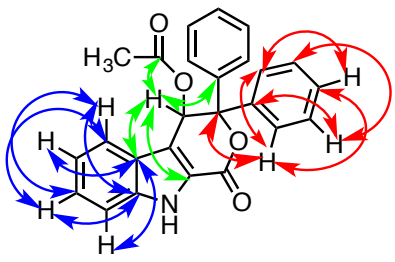


5cd: Ar = 4-MeC_6H_4

6-Fluoro-3,3-bis(4-methylphenyl)-4,9-dihydropyrano[3,4-*b*]indol-1(3*H*)-one (5cd): R_f = 0.33 (EtOAc/hexane 2.0:8.0 v/v); Colorless microcrystals (from $CHCl_3$-hexane); mp 240 °C; IR (KBr) ν 3314 (NH), 1709 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.94 (1H, s, NH), 7.58 (1H, dd, J = 9.6, 1.9 Hz, arom H), 7.34-7.31 (5H, m, arom H), 7.14 (1H, ddd, J = 9.1, 9.1, 2.9 Hz, arom H), 7.08 (4H, d, J = 8.6 Hz, arom H), 4.00 (2H, s, -CH_2-), 2.18 (6H, s, CH_3 × 2); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.9 (C=O), 157.7 (d, J_{CF} = 235 Hz, arom CF), 141.6 (2C), 137.3 (2C), 135.6, 125,1 (arom C), 124.7 (d, J_{CF} = 9.6 Hz, arom C), 122.3 (d, J_{CF} = 6.0 Hz, arom C), 129.5 (4C), 125.9 (4C) (arom CH), 115.5 (d, J_{CF} =28 Hz, arom CH), 114.7 (d, J_{CF} = 9.6 Hz, arom CH), 105.9 (d, J_{CF} = 24Hz, arom CH), 89.8 (>C<), 31.5 (-CH_2-), 21.0 (CH_3 × 2); FAB HRMS (acetone/NBA): calcd for $C_{25}H_{21}NO_2F$ 386.1556 (M+H); Found 386.1558.



6aa

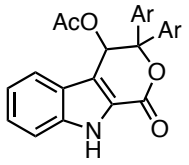


HMBC Study of **6aa**

1-Oxo-3,3-diphenyl-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-4-yl acetate (6aa): R_f = 0.30 (EtOAc/hexane 1.5:8.5 v/v); Colorless microcrystals (from $CHCl_3$-hexane); mp 232 °C; IR (KBr) ν 3290 (NH), 1743(C=O), 1717 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.42 (1H, s, NH), 7.92 (1H, br. d, J = 8 Hz, H-5), 7.56 (2H, d, J = 7.9 Hz, H-2' or H-2''), 7.52 (2H, d, J = 7.9 Hz, H-2'' or H-2'), 7.44 (1H, s, H-4), 7.40 (2H, t, J = 7.4 Hz, H-3' or H-3''), 7.36 (2H, d, J = 7.4 Hz, H-3'' or H-3'), 7.36 (1H, br. d, J = 8 Hz, H-8), 7.30 (1H, t, J = 7.5 Hz, H-7), 7.23 (1H, t, J = 7.5 Hz, H-6), 7.23 (1H, t, J = 7.5 Hz, H-4' or H-4''), 7.13 (1H, t, J = 7.5 Hz, H-4'' or H-4'), 1.65 (3H, s, Me); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.4 (AcO),

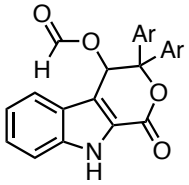
158.4 (C-1), 142.4 (C-1' or C- 1''), 140.8 (C-1'' or C-1'), 138.3 (C-8a), 124.0 (C-4b), 123.5 (C-4a), 119.2 (C-9a), 128.9 (C-3' or C-3''), 128.3 C-3'' or C-3'), 128.0 (C-4' or C-4''), 127.6 (C-4'' or C-4'), 126.6 (C-7), 125.6 (C-2' or C-2''), 125.2 (C-2'' or C-2'), 121.4 (C-5), 121.3 (C-6), 113.2 (C-8)), 90.3 (C-3), 65.0 (C-4), 20.1 (Me); FAB HRMS (acetone/NBA): calcd for $C_{25}H_{19}NO_4$ 397.1314 (M+H); Found 397.1324.

The indolelactone **5aa** (83.1 mg) was dissolved in AcOH (15 mL) and $Mn(OAc)_3$•$2H_2O$ (143.5 mg) was added. The mixture was heated under reflux for 1.5 h and the acetate **6aa** (78.9 mg, 81%) was isolated after normal work-up.



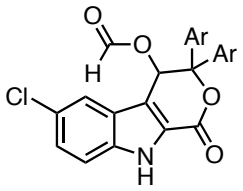
6ad: Ar = 4-MeC_6H_4

1-Oxo-3,3-bis(4-methylphenyl)-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-4-yl acetate (6ad): R_f = 0.20 (EtOAc/hexane 1.5:8.5 v/v); Colorless microcrystals (from $CHCl_3$-hexane); mp 245-249 °C; IR (KBr) ν 3290 (NH), 1745, 1717 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.38 (1H, s, NH), 7.894 (1H, dd, J = 8.5, 3.0 Hz, arom H), 7.35 (1H, s, O-CH<), 7.43-7.34 (5H, m, arom H), 7.22-7.18 (4H, m, arom H), 7.01 (2H, br. d, J = 8.5 Hz, arom H), 2.27 (3H, s, -CH_3), 2.10 (3H, s, -CH_3), 1.67 (3H, s, AcO); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.9 (AcO), 159.1 (C=O), 140.3, 138.7, 138.6, 137.8, 137.2, 124.6, 124.0, 119.7 (arom C), 129.8 (2C), 129.3 (2C), 127.0, 126.0 (2C), 125.6 (2C), 121.9, 121.7, 113.6 (arom CH), 90.9 (>C<), 65.5 (O-CH<), 21.1 (-CH_3), 20.9 (-CH_3), 20.7 (AcO); FAB HRMS (acetone/NBA/NaI): calcd for $C_{27}H_{23}NO_4Na$ 448.1525 (M+Na); Found 448.1514.



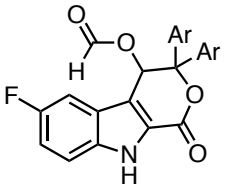
7ad: Ar = 4-MeC_6H_4

1-Oxo-3,3-bis(4-methylphenyl)-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-4-yl formate (7ad): R_f = 0.20 (EtOAc/hexane 1.5:8.5 v/v); Colorless microcrystals (from $CHCl_3$-hexane); mp 235 °C; IR (KBr) ν 3290 (NH), 1713 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.37 (1H, s, NH), 8.11 (1H, s, CHO), 7.91 (1H, d, J = 8.6 Hz, arom H), 7.50 (1H, s, O-CH<), 7.44 (2H, d, J = 7.7 Hz, arom H), 7.38-7.31 (5H, m, arom H), 7.21-7.16 (2H, m, arom H), 6.98 (2H, d, J = 7.7 Hz, arom H), 2.24 (3H, s, -CH_3), 2.07 (3H, s, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.7 (H-C=O), 158.9 (C=O), 140.4, 138.7, 138.5, 137.7, 137.3, 124.6, 124.0, 119.4 (arom C), 129.9 (2C), 129.5 (2C), 127.0, 125.8 (2C), 125.4 (2C), 121.9, 121.8, 113.6 (arom CH), 90.7 (>C<), 65.6 (O-CH<), 21.1 (-CH_3), 20.9 (-CH_3); FAB HRMS (acetone/NBA/NaI): calcd for $C_{26}H_{21}NO_4Na$ 434.1368 (M+Na); Found 434.1378.



7bd: Ar = 4-MeC_6H_4

6-Chloro-1-oxo-3,3-bis(4-methylphenyl)-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-4-yl formate (7bd): R_f = 0.22 (EtOAc/hexane 1.5:8.5 v/v); Colorless microcrystals (from $CHCl_3$-hexane); mp 221 °C; IR (KBr) ν 3300 (NH), 1717 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.60 (1H, s, NH), 8.09 (1H, s, C<u>H</u>O), 8.00 (1H, d, J = 1.9 Hz, arom H), 7.49 (1H, s, O-CH<), 7.43-7.32 (6H, m, arom H), 7.17 (2H, d, J = 7.7 Hz, arom H), 6.98 (2H, d, J = 6.8 Hz, arom H), 2.24 (3H, s, -CH_3), 2.08 (3H, s, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.7 (H-<u>C</u>=O), 158.7 (C=O), 140.3, 138.5, 137.8, 137.3, 137.0, 126.4, 125.9, 125.0, 119.1 (arom C), 129.9 (2C), 129.6 (2C), 127.1, 125.8 (2C), 125.3 (2C), 121.2, 115.4 (arom CH), 90.9 (>C<), 65.7 (O-<u>C</u>H<), 21.1 (-CH_3), 20.9 (-CH_3); FAB HRMS (acetone/NBA/NaI): calcd for $C_{26}H_{20}NO_4ClNa$ 468.0979 (M+Na); Found 468.0968.



7cd: Ar = 4-MeC_6H_4

6-Fluoro-1-oxo-3,3-bis(4-methylphenyl)-1,3,4,9-tetrahydropyrano[3,4-*b*]indol-4-yl formate (9cd): R_f = 0.21 (EtOAc/hexane 1.5:8.5 v/v); Colorless microcrystals (from $CHCl_3$-hexane); mp 222 °C; IR (KBr) ν 3285 (NH), 1717 (C=O); ^{1}H NMR (500 MHz, DMSO-d_6) δ 12.52 (1H, s, NH), 8.09 (1H, s, C<u>H</u>O), 7.66 (1H, d, J = 8.6 Hz, arom H), 7.47(1H, s, O-CH<), 7.42-7.16 (8H, m, arom H), 7.00 (2H, d, J = 6.7 Hz, arom H), 2.23 (3H, s, -CH_3), 2.08 (3H, s, -CH_3); ^{13}C NMR (125 MHz, DMSO-d_6) δ 161.7 (H-<u>C</u>=O), 158.7 (C=O), 158.2 (d, J_{CF} = 236 Hz, arom CF), 124.2 (d, J_{CF} = 10.8 Hz, arom C), 119.5 (d, J_{CF} = 4.8 Hz, arom C), 140.3, 138.5, 137.8, 137.3, 135.4, 126.1 (arom C), 116.1 (d, J_{CF} = 27.6 Hz, arom CH), 115.2 (d, J_{CF} = 8.4 Hz, arom CH), 106.2 (d, J_{CF} = 24.0 Hz, arom CH), 129.9 (2C), 129.6 (2C), 125.8(2C), 125.3 (2C) (arom CH), 90.8 (>C<), 65.7 (O-<u>C</u>H<), 21.1 (-CH_3), 20.9 (-CH_3); FAB HRMS (acetone/NBA): calcd for $C_{26}H_{20}NO_4F$ 429.1376 (M); Found 429.1357.

ACKNOWLEDGEMENTS

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