REACTION OF 1-BENZYLINDOLE-2,3-DICARBOXYLIC ANHYDRIDE WITH WITTIG REAGENTS

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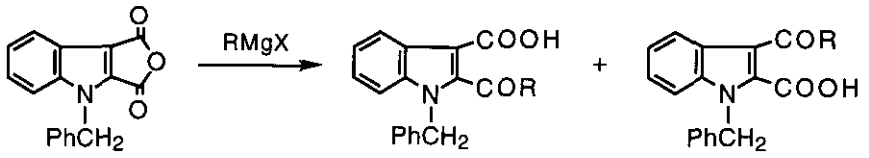
Abstract - Reaction of 1-benzylindole-2,3-dicarboxylic anhydride with methylenetriphenylphosphorane ($Ph_3P=CH_2$) and carbethoxymethylenetriphenylphosphorane ($Ph_3P=CHCOOEt$) gave [2-(3-carboxyindol-2-yl)-2-oxoethylidene]triphenylphosphorane derivatives, which were converted to cyclopenta[*b*]indol-3-ones after decarboxylation and treatment with aldehydes. On the other hand, the anhydride reacted with carbethoxyethylidenetriphenylphosphorane ($Ph_3P=C(Me)COOEt$) to afford a mixture of two enol lactones.

We have shown that 1-benzylindole-2,3-dicarboxylic anhydride (**1**) is a useful synthon in the synthesis of natural products, murrayaquinone-A[1] and ellipticine.[2] Recently, we have reported that the reaction of **1** with phenylmagnesium bromide and methylmagnesium bromide gave 2-acylindole-3-carboxylic acids (**2**) as a sole product because a carbonyl group at the 2-position in **1** is more reactive toward Grignard reagents than a carbonyl group at the 3-position. Therefore, reactivity of the carbonyl group in **1** is governed by the nitrogen in an indole. However, the reaction of **1** with *tert*-butylmagnesium chloride afforded a mixture of **2** and 3-acylindole-2-carboxylic acid (**3**) due to the steric hindrance.[3]

Scheme 1



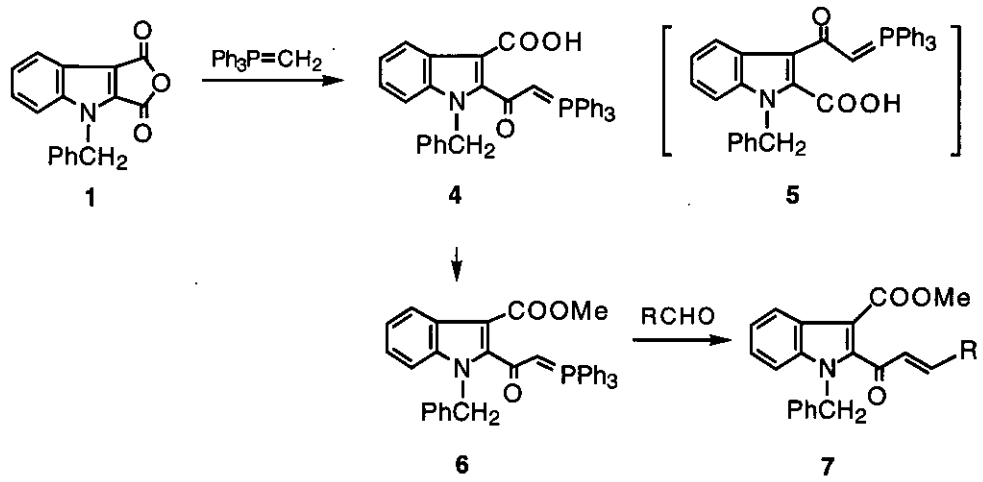
1 **2** **3**

In the reaction of substituted phthalic anhydrides[4] with Wittig reagents, the products were controlled by steric and electronic factors.[5] However, in the reaction of pyridine-2,3-dicarboxylic anhydride[6] and pyridine-3,4-dicarboxylic anhydride[7] with $Ph_3P=CHCOOBu^t$, a nitrogen in the pyridine plays a significant

role in providing the product. In this paper, we report the reactivity of **1** toward Wittig reagents and a simple synthesis of cyclopenta[*b*]indoles.[8]

Reaction of 1-benzylindole-2,3-dicarboxylic anhydride (**1**) with $Ph_3P{=}CH_2$ gave a ylide (**4**) in 92% yield, but its isomer (**5**) was not isolated. Esterification of **4** by using methanol and 1-methyl-2-chloropyridinium iodide[9] yielded a corresponding methyl ester (**6**) in 71% yield. Treatment of the ylide (**6**) with benzaldehyde in refluxing mesitylene gave an α,β-unsaturated ketone (**7a**) in 55% yield. In a similar manner, **7b** and **7c** were effected in 84% and 30% yields, respectively. **6** also reacted with acetaldehyde at room temperature to afford **7d** in 31% yield, but with ketones the starting material was recovered.

Scheme 2



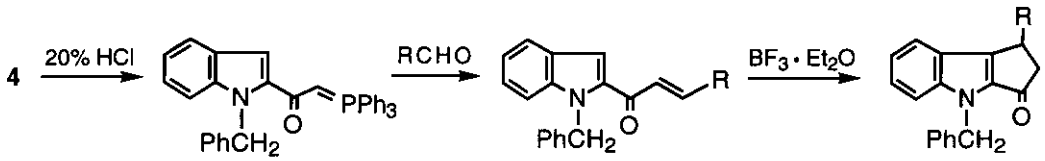
1 **4** **5** **6** **7**

Table 1

7	R	time (h)	yield(%)
a	Ph	11	55
b	4-NO_2-Ph	3	84
c	4-MeO-Ph	30	30
d	Me	6	31

The structure of the ylide (**4**) was determined as follows: treatment of **4** with 20% hydrochloric acid gave a ylide (**8**)(74%), which reacted with benzaldehyde and acetaldehyde to give α,β-unsaturated ketones (**9a**) and (**9b**) in 97% and 88% yields, respectively. The (*E*) stereochemisty about the carbon-carbon bond in **9a** was assigned on the basis of the large coupling constants (16 Hz) between the olefinic protons, but the stereochemistry of **9b** was unclear. In ^{1}H-NMR, the proton of the 4-position (δ 7.60-7.79) in **9a** appeared in higher field compared with the proton (δ 8.24-8.27) in **7a**. Acid treatment of **9a** and **9b** with boron trifluoride etherate yielded cyclopenta[*b*]indol-3-ones (**10a**) and (**10b**) in 96% and 98% yields, respectively.

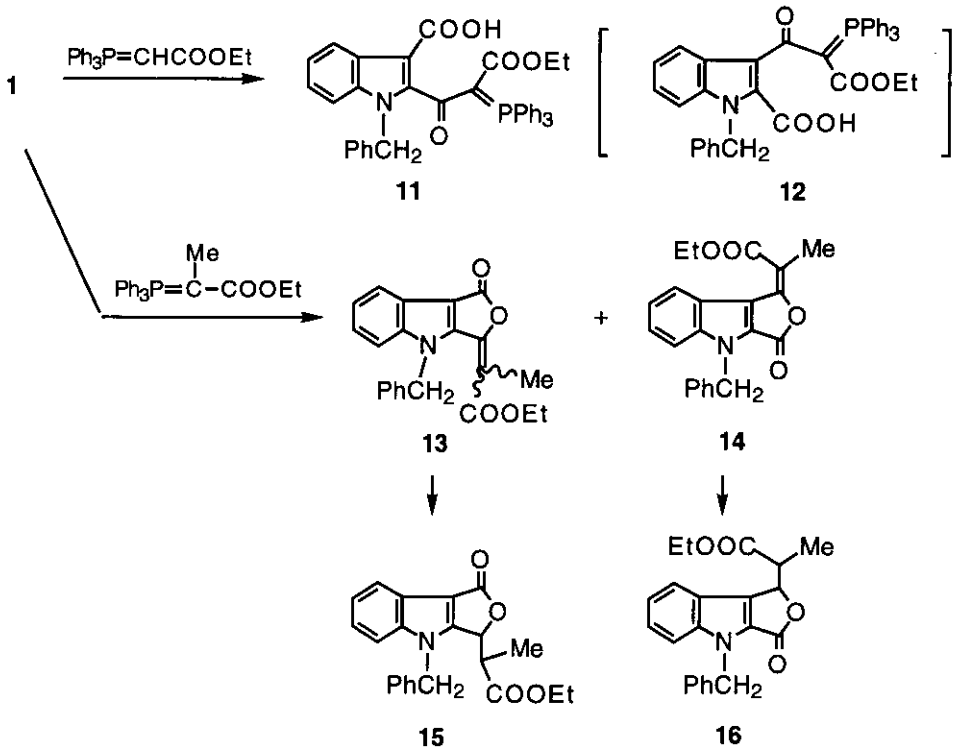
Scheme 3



a: R = Ph, b: R = Me

A stabilized ylide (Ph_3P=CHCOOEt) reacted with a carbonyl group at the 2-position in **1** to give a ylide (**11**)(83%), which was converted by treatment with 20% hydrochloric acid to the ylide (**8**) in 89% yield, but its isomer (**12**) was not found. However, reaction of **1** with Ph_3P=C(Me)COOEt gave a mixture of two enol lactones (**13**) and (**14**) in 60% and 32% yields, respectively. **13** and **14** were converted to lactones (**15**) and (**16**) by catalytic hydrogenation over 5% palladium on activated carbon in 93% and 90% yields, respectively. The stereochemistry about the carbon-carbon bond in **14** was assigned on the basis that the proton of the 8-position (δ 8.24) in **14** appeared in lower field compared with the proton (δ 7.66) in **16**.[5] **13** was obtained as a single isomer, but its stereochemistry was ambiguous.

Scheme 4



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. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride prior to use.

[2-(1-Benzyl-3-carboxyindol-2-yl)-2-oxoethylidene]triphenylphosphorane (4)

A solution of 1-benzylindole-2,3-dicarboxylic anhydride (**1**)(0.83 g, 3 mmol) in THF (30 mL) was added to a solution of methylenetriphenylphosphorane [prepared from methyltriphenylphosphonium bromide (3.24 g, 9.1 mmol) and *n*-butyllithium (5.8 mL of a 1.56 M *n*-hexane solution, 9 mmol) at rt for 20 min] in THF (15 mL) at 0°C and the mixture was stirred for 1 h. The reaction mixture was acidified with 10% hydrochloric acid and extracted with CH_2Cl_2. The organic extracts were washed with water, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography ($CHCl_3$: MeOH = 50 : 1) to give **4** (1.53 g, 92%) as a pale yellow solid: mp 192-193°C (*n*-hexane-$CHCl_3$). IR (nujol) 1679, 1500 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 5.76 (2H, s, C*H*$_2$Ph), 7.09-7.64 (26H, m, aromatic protons), 8.62-8.68 (1H, m, H-4). HRMS *m/z* (M^+) calcd for $C_{36}H_{29}NO_3P$: 554.1885. Found: 554.1887.

[2-(1-Benzyl-3-methoxycarbonylindol-2-yl)-2-oxoethylidene]triphenylphosphorane (6)

To a solution of **4** (1.44 g, 2.6 mmol) and triethylamine (0.90 mL, 6.5 mmol) in MeOH (0.32 mL, 7.9 mmol) and CH_2Cl_2 (26 mL) was added 2-chloro-1-methylpyridinium iodide (0.73 g, 2.9 mmol) and the reaction mixture was stirred for 17 h under argon. The solvent was evaporated off to give a residue, which was purified by column chromatography (CH_2Cl_2 : AcOEt = 10 : 1) to give **6** (1.05 g, 71%), mp 164-165°C (*n*-hexane-CH_2Cl_2). IR (nujol) 1692, 1527 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.86 (3H, s, OCH_3), 4.08 (1H, d, *J* = 24 Hz, C*H*PPh_3), 5.50 (2H, s, C*H*$_2$Ph), 7.00-7.70 (23H, m, aromatic protons), 8.22 (1H, dt, *J* = 8, 1 Hz, H-4). *Anal.* Calcd for $C_{37}H_{30}NO_3P$: C, 78.29; H, 5.33; N, 2.47. Found: C, 78.15; H, 5.47; N, 2.60.

Reaction of 6 with Aldehydes: Synthesis of α,β-Unsaturated Ketones (7) (General Procedure)

A solution of the ylide (**6**) (0.1 mmol) and benzaldehyde (0.1 mmol) in mesitylene (2 mL) was refluxed under argon. The solvent was evaporated off to afford a residue, which was purified by column chromatography (*n*-hexane or CH_2Cl_2 : AcOEt = 5 : 1) to give **7**.

(*E*)-1-(1-Benzyl-3-methoxycarbonylindol-2-yl)-3-phenyl-2-propen-1-one (7a)

7a; mp 140-143°C (MeOH). IR (nujol) 1692, 1655 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.83 (3H, s, OCH_3), 5.39 (2H, s, C*H*$_2$Ph), 7.03 (1H, d, *J* = 16 Hz, COC*H*=CHPh), 7.08-7.44 (14H, m, COCH=C*H*Ph and

aromatic protons), 8.24-8.27 (1H, m, H-4). *Anal.* Calcd for $C_{26}H_{21}NO_3$: C, 78.97; H, 5.35; N, 3.54. Found: C, 79.05; H, 5.45; N,3.51.

(*E*)-1-(1-Benzyl-3-methoxycarbonylindol-2-yl)-3-(4-nitrophenyl)-2-propen-1-one (7b)

7b; mp 187-188°C (AcOMe). IR (nujol) 1680, 1665, 1514, 1347 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.86 (3H, s, OCH_3), 5.42 (2H, s, C*H*$_2$Ph), 7.04-7.58 (12H, m, COC*H*=C*H*Ph and aromatic protons), 8.16-8.28 (3H, m, aromatic protons). *Anal.* Calcd for $C_{26}H_{20}N_2O_5$: C, 70.90; H, 4.58; N, 6.36. Found: C, 70.75; H, 4.68; N, 6.27.

(*E*)-1-(1-Benzyl-3-methoxycarbonylindol-2-yl)-3-(4-methoxyphenyl)-2-propen-1-one (7c)

7c; mp 185-186°C (AcOMe-MeOH). IR (nujol) 1688, 1647 cm^{-1}; ^{1}H -NMR ($CDCl_3$) δ: 3.82 (6H, s, OCH_3x2), 5.37 (2H, s, C*H*$_2$Ph), 6.80-6.90 (2H, m, aromatic protons), 6.93 (1H, d, *J* = 16 Hz, COC*H*=CHPh), 7.08-7.42 (11H, m, COCH=C*H*Ph and aromatic protons), 8.22-8.28 (1H, m, aromatic protons). *Anal.* Calcd for $C_{27}H_{23}NO_4$: C, 76.22; H, 5.45; N, 3.29. Found: C, 76.02; H, 5.56; N, 3.25.

(*E*)-1-(1-Benzyl-3-methoxycarbonylindol-2-yl)-2-buten-1-one (7d)

A solution of the ylide (**6**) (397 mg, 0.7 mmol) in acetaldehyde (8 mL) was stirred for 16 h under argon. The reaction mixture was evaporated off to afford a residue, which was purified by column chromatography (*n*-hexane : AcOEt = 5 : 1) to give **7d** (73 mg, 31%), mp 106-109 °C (MeOH). IR (nujol) 1699, 1656 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.75 (3H, dd, *J* = 7, 1 Hz, CH_3), 3.86 (3H, s, OCH_3), 5.32 (2H, s, C*H*$_2$Ph), 6.41 (1H, dq, *J* = 16, 1 Hz, COC*H*=CHCH$_3$), 6.56 (1H, dq, *J* = 16, 7 Hz, COCH=C*H*CH$_3$), 7.03-7.37 (8H, m, aromatic protons), 8.14-8.25 (1H, m, aromatic protons). *Anal.* Calcd for $C_{21}H_{19}NO_3$: C, 75.66; H, 5.74; N, 4.20. Found: C, 75.60; H, 5.88; N, 4.23.

[2-(1-Benzylindol-2-yl)-2-oxoethylidene]triphenylphosphorane (8)

1) from The Ylide (4)

A suspension of the ylide (**4**) (3.32 g, 6 mmol) in 20% hydrochloric acid (120 mL) was refluxed for 2 h. The reaction mixture was made alkaline by 10% sodium hydroxide solution, and extracted with CH_2Cl_2. The organic extracts were washed with water, dried over Na_2SO_4, and concentrated to give a residue, which was purified by column chromatography (CH_2Cl_2 : MeOH = 50 : 1) to yield **8** (2.25 g, 74%), mp 234-235 °C (*n*-hexane-CH_2Cl_2) as a pale yellow solid. IR (nujol) 1529 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 4.39 (1H, d, *J* = 24 Hz, C*H*PPh$_3$), 5.98 (2H, s, C*H*$_2$Ph), 7.00-7.70 (25H, m, aromatic protons). HRMS *m/z* (M^+) calcd for $C_{35}H_{28}NOP$: 509.1908. Found: 509.1927.

2) from The Ylide (11)

Using a procedure similar to that described for the preparation of **8** from the ylide (**4**), **8** (89%) was obtained from **11**.

(*E*)-1-(1-Benzylindol-2-yl)-3-phenyl-2-propen-1-one (9a)

A solution of the ylide (**8**) (51 mg, 0.1 mmol) and benzaldehyde (12 μL, 0.12 mmol) in benzene (1 mL) was refluxed for 2 h under argon. The solvent was evaporated off and the residue was purified by column

chromatography (*n*-hexane : AcOEt = 10 : 1) to give **9a** (33 mg, 97%), mp 94-96°C (*n*-hexane). IR (nujol) 1654 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 5.95 (2H, s, C*H*$_2$Ph), 7.06-7.45 (11H, m, aromatic protons), 7.53 (1H, s, H-3), 7.58 (1H, d, *J* = 16 Hz, COCH=C*H*Ph), 7.60-7.79 (3H, m, aromatic protons), 7.79 (1H, d, *J* = 16 Hz, COC*H*=CHPh). *Anal.* Calcd for $C_{24}H_{19}NO$: C, 85.43; H, 5.68; N, 4.15. Found: C, 85.39; H, 5.80; N, 4.23.

1-(1-Benzylindol-2-yl)-2-buten-1-one (9b)

A suspension of the ylide (**8**) (509 mg, 1.0 mmol) in acetaldehyde (10 mL) was stirred for 1 h at 0°C under argon. The reaction mixture was evaporated off and the residue was purified by column chromatography (*n*-hexane : AcOEt = 20 : 1) to give **9b** (241 mg, 88%), mp 69-70°C (*n*-hexane). IR (nujol) 1661 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.98 (3H, dd, *J* = 6, 1 Hz, CH_3), 5.90 (2H, s, C*H*$_2$Ph), 6.91-7.40 (11H, m, aromatic protons), 7.72 (1H, dt, *J* = 8, 1 Hz, H-4). *Anal.* Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.86; H, 6.38; N, 5.06.

4-Benzyl-1-phenyl-3-oxo-1,2,3,4-tetrahydrocyclopenta[*b*]indole (10a)

A mixture of the ketone (**9a**) (135 mg, 0.4 mmol) and boron trifluoride etherate (49 μL, 0.4 mmol) in CH_2Cl_2 (12 mL) was refluxed for 2 h under argon. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The extracts were washed with water, dried over Na_2SO_4, and evaporated off. The residue was purified by column chromatography on silica gel (*n*-hexane : AcOEt = 10 : 1) to give **10a** (133 mg, 96%), mp 182-183°C (AcOEt). IR (nujol) 1678 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 2.91 (1H, dd, *J* = 18, 2 Hz), 3.54 (1H, dd, *J* = 18, 7 Hz), 4.67 (1H, dd, *J* = 7, 2 Hz), 5.58 (1H, d, *J* = 18 Hz, one of C*H*$_2$Ph), 5.62 (1H, d, *J* = 18 Hz, one of C*H*$_2$Ph), 7.00-7.40 (14H, m, aromatic protons). *Anal.* Calcd for $C_{24}H_{19}NO$: C, 85.43; H, 5.68; N, 4.15. Found: C, 85.40; H, 5.84; N, 4.10.

4-Benzyl-1-methyl-3-oxo-1,2,3,4-tetrahydrocyclopenta[*b*]indole (10b)

Using a procedure similar to that described for the preparation of **10a**, **10b** (98%) was obtained from **9b**, mp 83-84°C (*n*-hexane). IR (nujol) 1681 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.50 (3H, d, *J* = 7 Hz, CH_3), 2.57 (1H, dd, *J* = 18, 2 Hz, one of CH_2), 3.25 (1H, dd, *J* = 18, 7 Hz, one of CH_2), 3.56 (1H, double of quintet, *J* = 7, 2 Hz), 5.49 (1H, d, *J* = 18 Hz, one of C*H*$_2$Ph), 5.56 (1H, d, *J* = 18 Hz, one of C*H*$_2$Ph), 7.12-7.37 (8H, m, aromatic protons), 7.73 (1H, dt, *J* = 8, 1 Hz, H-4). *Anal.* Calcd for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 83.01; H, 6.29; N, 4.85.

[2-(1-Benzyl-3-carboxyindol-2-yl)-1-ethoxycarbonyl-2-oxoethylidene]triphenylphosphorane (11)

A solution of **1** (277 mg, 1 mmol) and carbethoxymethylenetriphenylphosphorane (348 mg, 1 mmol) in benzene (10 mL) was refluxed for 2 h under argon. The reaction mixture was concentrated *in vacuo* and the residue was purified by column chromatography (CH_2Cl_2 : MeOH = 20 : 1) to give **11** (518 mg, 83%), mp 205-206°C (*n*-hexane-$CHCl_3$). IR (nujol) 1680, 1656, 1542, 1519 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 0.48 (3H, t, *J* = 7 Hz, CH_2CH_3), 3.62 (2H, q, *J* = 7 Hz, C*H*$_2$CH$_3$), 5.28 (1H, d, *J* = 17 Hz, one of C*H*$_2$Ph),

5.56 (1H, d, J = 17 Hz, one of CH_2Ph), 7.11-7.83 (25H, m, aromatic protons), 8.29 (1H, d, J = 8 Hz, H-4). HRMS m/z (M^+) calcd for $C_{39}H_{33}NO_5P$: 626.2097. Found: 626.2104.

Ethyl 2-(4-Benzyl-1,3-dihydro-1-oxo-*4H*-furo[3,4-*b*]indol-3-ylidene)propionate (13) and Ethyl (*E*)-2-(4-Benzyl-1,3-dihydro-3-oxo-4*H*-furo[3,4-*b*]indol-1-ylidene)propionate (14)

A solution of **1** (277 mg, 1.0 mmol) and carbethoxyethylidenetriphenylphosphorane (398 mg, 1.1 mmol) in benzene (10 mL) was stirred for 2 days under argon. The reaction mixture was evaporated off and the residue was purified by column chromatography (*n*-hexane : CH_2Cl_2 = 5 : 1) to afford **13** (218 mg, 60%) and **14** (114 mg, 32%).

13; mp 121-122°C (*n*-hexane-AcOEt). IR (nujol) 1773, 1700, 1647 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.14 (3H, t, J = 7 Hz, CH_2CH_3), 2.21 (3H, s, CH_3), 4.00 (2H, q, J = 7 Hz, CH_2CH_3), 5.57 (2H, s, CH_2Ph), 6.86-7.38 (8H, m, aromatic protons), 7.92-7.99 (1H, m, H-4). *Anal.* Calcd for $C_{22}H_{19}NO_4$: C, 73.12; H, 5.30; N, 3.88. Found: C, 73.09; H, 5.40; N, 3.89.

14; mp 142-143°C (*n*-hexane-AcOEt). IR (nujol) 1765, 1719, 1632 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.40 (3H, t, J = 7 Hz, CH_2CH_3), 2.25 (3H, s, CH_3), 4.41 (2H, q, J = 7 Hz, CH_2CH_3), 5.57 (2H, s, CH_2Ph), 7.20-7.42 (8H, m, aromatic protons), 8.24 (1H, dt, J = 8, 1 Hz, H-4). *Anal.* Calcd for $C_{22}H_{19}NO_4$: C, 73.12; H, 5.30; N, 3.88. Found: C, 73.08; H, 5.40; N, 3.93.

Ethyl 2-(4-Benzyl-1,3-dihydro-1-oxo-4*H*-furo[3,4-*b*]indol-3-yl)propionate (15)

A suspension of **13** (144 mg, 0.4 mmol) and 5% palladium on activated carbon (14 mg) in AcOEt (8 mL) was stirred for 1 day under hydrogen. The catalyst was removed by filtration through Celite and the filtrate was evaporated off. The residue was purified by column chromatography (CH_2Cl_2 : AcOEt = 30 : 1) to yield **15** (135 mg, 93%), mp 157-158°C (*n*-hexane-AcOEt). IR (nujol) 1748 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, t, J = 7 Hz, $CHCH_3$), 1.19 (3H, d, J = 7 Hz, $CHCH_3$), 3.10-3.20 (1H, m, $CHCH_3$), 3.79-4.01 (2H, m, CH_2CH_3), 5.30 (1H, d, J = 17 Hz, one of CH_2Ph), 5.53 (1H, d, J = 17 Hz, one of CH_2Ph), 5.56 (1H, d, J = 3 Hz, $CHCHCH_3$), 7.04-7.40 (8H, m, aromatic protons), 7.88-7.96 (1H, m, H-4). *Anal.* Calcd for $C_{22}H_{21}NO_4$: C, 72.21; H, 5.82; N, 3.85. Found: C, 72.50; H, 5.82; N, 3.72.

Ethyl 2-(4-Benzyl-1,3-dihydro-3-oxo-4*H*-furo[3,4-*b*]indol-1-yl)propionate (16)

Using a procedure similar to that described for the preparation of **15**, **16** (90%) was obtained as an oil from **14** by using 10% palladium on activated carbon and eluent solvent (*n*-hexane : AcOEt = 5 : 1). IR (neat) 1758 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, d, J = 7 Hz, $CHCH_3$), 1.29 (3H, t, J = 7 Hz, $CHCH_3$), 3.12 (1H, dq, J = 7, 6 Hz, $CHCH_3$), 4.27 (2H, q, J = 7 Hz, CH_2CH_3), 5.55 (2H, s, CH_2Ph), 5.97 (1H, d, J = 6 Hz, $CHCHCH_3$), 7.16-7.45 (8H, m, aromatic protons), 7.66 (1H, dt, J = 8, 1 Hz, H-4). HRMS m/z (M^+) calcd for $C_{22}H_{21}NO_4$: 363.1471. Found: 363.1449

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