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A Novel Ring Transformation of 3,5-Bis(methoxycarbonyl)-4-phenyl-2-isoxazoline-2-oxides into 2-Methoxycarbonyl-1-oxido-3*H*-indole-3-acetates[1)]

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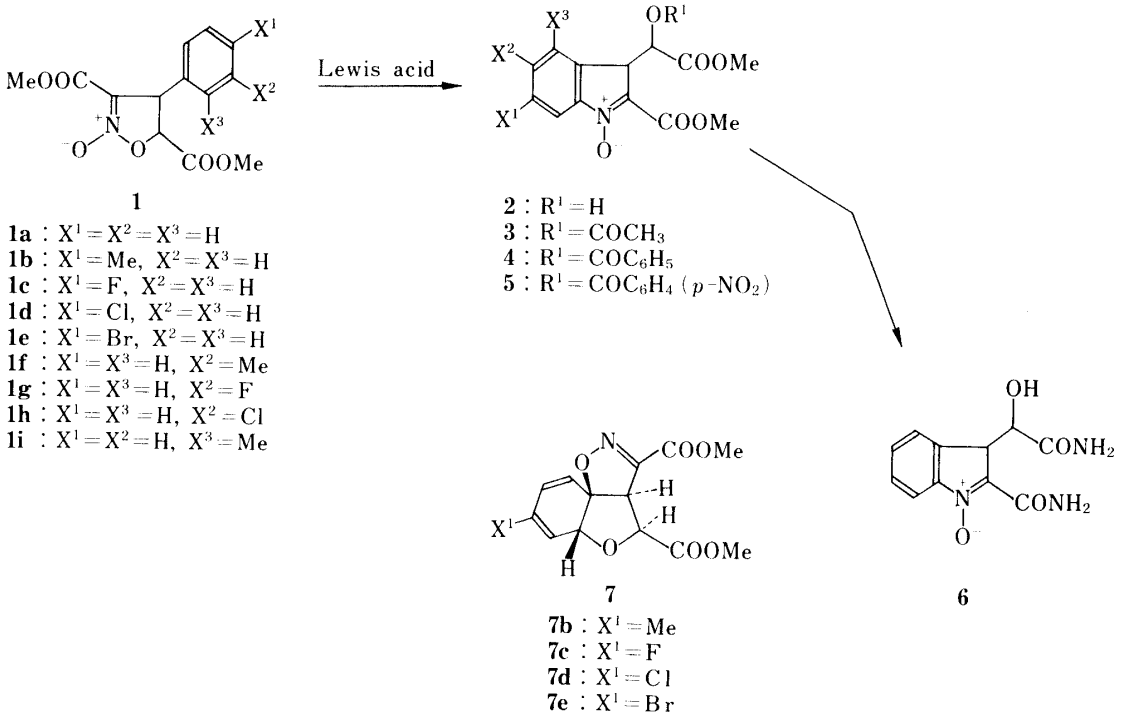
3,5-Bis(methoxycarbonyl)-4-phenyl-2-isoxazoline-2-oxides (**1**) were readily transformed into 2-methoxycarbonyl-1-oxido-3*H*-indole-3-acetates (**2**) in the presence of Lewis acids such as titanium tetrachloride in dichloromethane. The reaction may occur *via* initial N–O bond fission to form an ionic intermediate (**B**), which cyclizes to 3*H*-indole-1-oxide (**2**) through an intramolecular aromatic substitution, on the basis of deuterium incorporation experiments as well as stereochemical considerations. With regard to the substituent effect, the reaction of *meta*-substituted phenylisoxazolines (**1f—h**) having an *o,p*-orientating group such as halogen was facilitated to provide 5-substituted 3*H*-indole-1-oxides (**2f—h**) in good yield. In contrast, the reaction of *para*-substituted compounds (**1b—e**) having the same substituents gave benzofuro-[3,3a-*d*]isoxazoles (**7b—e**) preferentially, rather than 6-substituted 3*H*-indole-1-oxides (**2b—e**).

Keywords—— 2-isoxazoline-2-oxide; 1-oxido-3*H*-indole-3-acetate; titanium tetrachloride; ring transformation; intramolecular aromatic substitution

Ring transformation of simple heterocycles may, in certain cases, provide a novel and facile access to relatively complex, fused heterocyclic systems which could not be obtained so conveniently by stepwise synthesis.[2)] In this respect, 3,5-bis(methoxycarbonyl)-4-phenyl-2-isoxazoline-2-oxides (**1**) seem to be useful candidates for ring transformation, inasmuch as they are readily available, multi-functionalized, and highly reactive, being cyclic nitronic esters.[3)] Conversion of 2-isoxazoline-2-oxides into isoxazoles or γ-amino alcohols is well known,[4)] but little is known of the ring transformation of these compounds. In this article we wish to report a novel ring transformation of **1** into 1-oxido-3*H*-indole-3-acetates (**2**) in the presence of Lewis acids such as titanium tetrachloride, boron trifluoride etherate, *etc.* The mechanism of the transformation is discussed.

3,5-Bis(methoxycarbonyl)-4-phenyl-2-isoxazoline-2-oxides (**1**),[6)] which are readily available by the reaction of benzaldehydes with a two-fold molar excess of methyl nitroacetate, were treated under various reaction conditions with Lewis acids. The use of boron trifluoride etherate in benzene solution gave rise to a molecular rearrangement of **1a** to provide 2-methoxycarbonyl-1-oxido-3*H*-indole-3-acetate (**2a**) in 48% yield, as already reported in a preliminary communication.[5)] Spectral and combustion analyses of **2a** suggested the 3*H*-indole-1-oxide structure, which was corroborated by a conversion of **2a** into an indole-3-acetate derivative.[7)]

In an attempt to optimize the yield of **2a**, several kinds of Lewis acids and solvents were examined; a four-fold molar excess of titanium tetrachloride, stannic chloride, ferric chloride, or aluminum chloride in dichloromethane resulted in 85, 82, 70, or 54% yield of **2a**, respectively. Thus, titanium tetrachloride in dichloromethane was applied to the other isoxazoline-2-oxides (**2b—i**), which possess a methyl or halogen substituent on the 4-phenyl group of **1** at the *ortho*-, *meta*-, or *para*-position. It should be noted that *m*-substituents (**1f—h**) facilitate this ring transformation to afford **2f—h** in good yields, while *p*-substituents (**1b—e**) suppress the formation of **2b—e** (8—15% yield), but result preferentially in an alternative



1

1a : $X^1=X^2=X^3=H$
1b : $X^1=Me$, $X^2=X^3=H$
1c : $X^1=F$, $X^2=X^3=H$
1d : $X^1=Cl$, $X^2=X^3=H$
1e : $X^1=Br$, $X^2=X^3=H$
1f : $X^1=X^3=H$, $X^2=Me$
1g : $X^1=X^3=H$, $X^2=F$
1h : $X^1=X^3=H$, $X^2=Cl$
1i : $X^1=X^2=H$, $X^3=Me$

2 : $R^1=H$
3 : $R^1=COCH_3$
4 : $R^1=COC_6H_5$
5 : $R^1=COC_6H_4$ (p-NO_2)

7

7b : $X^1=Me$
7c : $X^1=F$
7d : $X^1=Cl$
7e : $X^1=Br$

6

Chart 1

TABLE I. Substituent Effect on the Ring Transformation of **1** into **2** and **7**

	1			**2**		**7**	
	X^1	X^2	X^3	Yield (%)	mp (°C)	Yield (%)	mp (°C)
a	H	H	H	85	84—85	—	—
b	Me	H	H	15	114.5—115.5[a]	44	106—107
c	F	H	H	12	Syrup	77	97.5—98.5
d	Cl	H	H	8	68—70[b]	81	107—108.5
e	Br	H	H	11	Syrup	73	101.5—102
f	H	Me	H	69	125—127[b]	—	—
g	H	F	H	76	Syrup	—	—
h	H	Cl	H	69	76—79[b]	—	—
i	H	H	Me	18	149—150[b]	—	—

a) *O*-Acetyl derivative (**3**). *b*) *O*-*p*-Nitrobenzoyl derivative (**5**).

rearrangement to yield benzofuro[3,3a-*d*]isoxazole derivatives (**7b—e**) in 44—81% yields. Structural assignment by nuclear magnetic resonance (NMR) and X-ray analyses of **7**, as well as the reaction mechanism, was described in the previous communications.[8,9] The results of substituent effect are summarized in Table I.

Compounds **2**, being obtained mostly in a syrupy state, were also characterized as *O*-acetyl (**3**), *O*-benzoyl (**4**), or *O*-*p*-nitrobenzoyl (**5**) derivatives after crystallization. The diamide (**6**) was obtained from **2a** by treatment with aqueous ammonia-ammonium chloride.

Ring transformation of **1** into **2** is specified from 2-isoxazoline-2-oxide, because the same treatment of the corresponding 2-isoxazoline (**14**), prepared from **1a** by deoxygenation with triethyl phosphite, led to the quantitative recovery of **14**. A plausible reaction mechanism for this molecular rearrangement is illustrated in Chart 3. The initial electrophilic attack of the

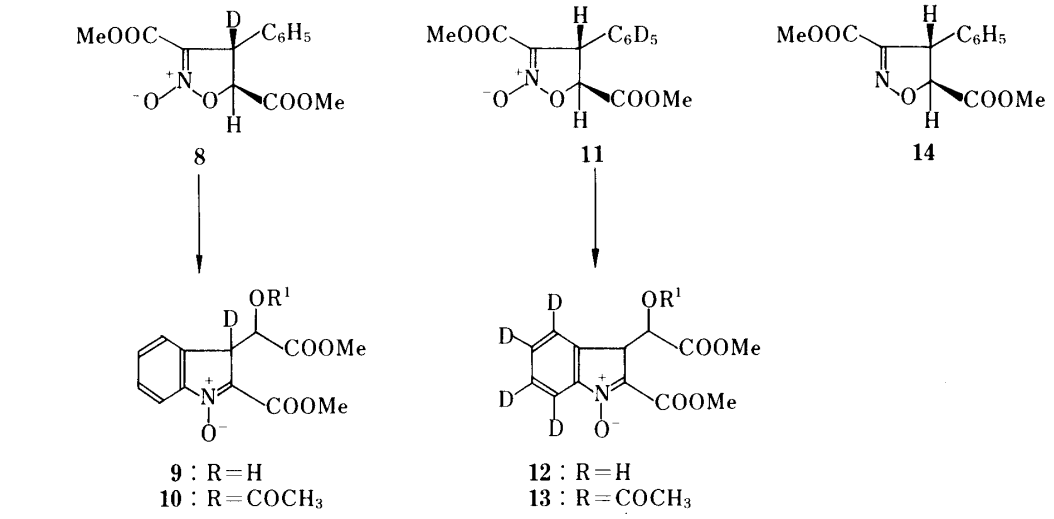


Chart 2

Lewis acid on **1** causes N–O bond cleavage to give an ionic intermediate (B), which cyclizes through intramolecular aromatic substitution at the *ortho* site by the nitrosonium species in a rotamer (C) to form 1-oxido-3*H*-indole-3-acetate (**2**). An alternative mechanism for **2** *via* the azirine→indole route[10] was excluded by deuterium incorporation experiments. 3,5-Bis-(methoxycarbonyl)-4-phenyl-2-isoxazoline-2-oxide-4-d[11] (**8**) was treated with boron trifluoride etherate to furnish **9** exclusively; this product, as well as its *O*-acetate (**10**), was characterized on the basis of the proton nuclear magnetic resonance (^{1}H-NMR) and mass spectra. Furthermore, the formation of **12** from **11** (prepared from benzaldehyde-d_5 and methyl nitroacetate) suggests that the reaction may involve non-concerted proton rearrangement. With regard to the stereochemistry of the ring transformation, the relative configuration of 4,5-substituents of **1** should be retained through the rearrangement. Hence, *trans*-isoxazoline-2-oxide (**1**) provides the intermediate (B) with *erythro*-configuration, and subsequently yields the final product (**2**) uniformly as the 3,α-*erythro*-compound as depicted in Chart 3. This is in good agreement with the experimental results; no other isomer of **2** was

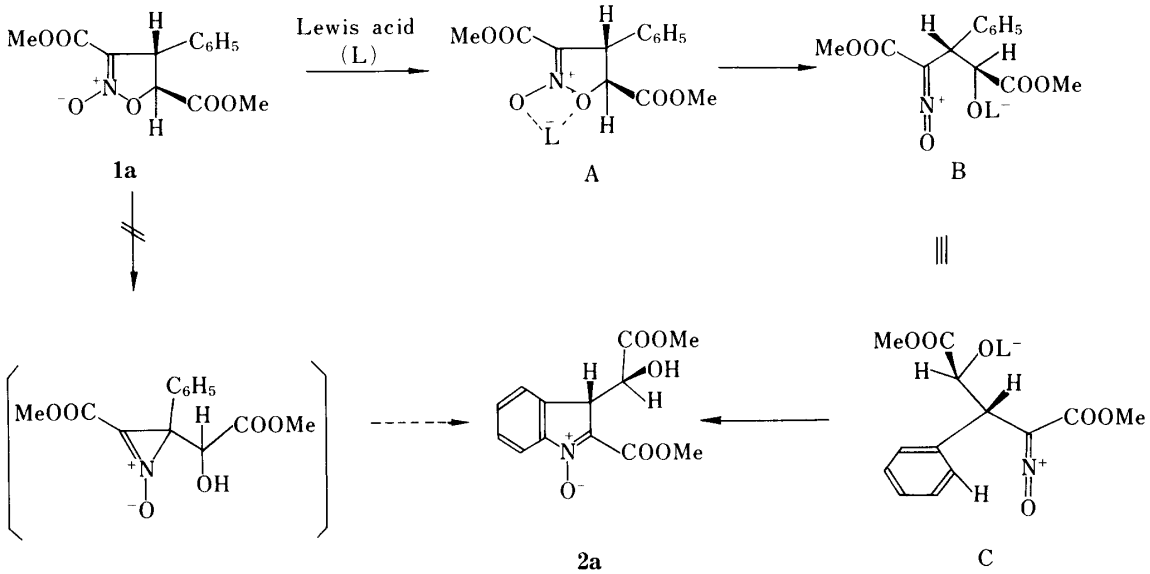


Chart 3

detected in the reaction mixture. The substituent effect on this reaction is consistent with the proposed mechanism, *i.e.* *m*-substituted **1** with an *o,p*-directing group activates an *ortho* position of the phenyl ring to provide 3*H*-indole-1-oxide (**2**), whilst the *p*-substituted compound with the same group activates the *ipso*-position mainly to give benzofuro[3,3a-*d*]isoxazoles (**7**).[8,9] Under the same reaction conditions, a *meta*-directing, electron-attracting group such as nitro, either *meta*- or *para*-substituted on the phenyl ring, resulted in complete recovery of the starting material.

It should be noted that this novel ring transformation appears to be a facile and efficient entry to 5-substituted 1-oxido-3*H*-indole-3-acetates, which may be widely applicable to syntheses of biologically active indole derivatives.

Experimental

Melting points were measured with a Yamato MP-1 apparatus and are uncorrected. Spectral data were recorded on the following instruments: Jasco IRA-1 (infrared (IR)), Hitachi 340 (ultraviolet (UV)), JMS D-100 (mass spectrum (MS)), Varian EM-390 (^{1}H-NMR), and JEOL PS-100 (carbon-13 nuclear magnetic resonance (^{13}C-NMR)). Tetramethylsilane was used as an internal standard for NMR measurement in chloroform-*d*. Thin-layer chromatography (TLC) was carried out on Kieselgel 60 (Merck). Developers were the same as those for column chromatography described in the same experimental section, spots being detected with iodine vapor or by charring with 10% aq. sulfuric acid. Column chromatography was done on a silica-gel (Kanto Kagaku Co.; up to 100 mesh) column.

Methyl α-Hydroxy-2-methoxycarbonyl-1-oxido-3*H*-indole-3-acetate (2a)——Titanium tetrachloride (0.45 ml, 4 mmol) was added to a solution of 3,5-bis(methoxycarbonyl)-4-phenyl-2-isoxazoline-2-oxide[11] (**1a**; 279 mg, 1 mmol) in dichloromethane (20 ml), and the mixture was stirred at 0 °C for 0.5 h. After further stirring at room temperature for 0.5 h, the mixture was quenched with 10% Na_2CO_3 aq. and extracted with dichloromethane (3 × 20 ml). The extract was washed with water (3 × 30 ml), dried over anhydr. Na_2SO_4, and evaporated to dryness *in vacuo*. The residual syrup was applied to a silica-gel column and eluted with $CHCl_3$–AcOEt (4 : 1, v/v) to give **2a** (236 mg, 85% yield) as yellowish crystals. Recrystallization from AcOEt–hexane provided colorless prisms, mp 84—85 °C. IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1720 (ester C=O), 1620 (C=N). UV λ_{max}^{MeOH} nm (log ε): 282 (3.62). ^{1}H-NMR ($CDCl_3$) δ: 3.05 (1H, br m, OH), 3.71 and 3.96 (each 3H, s, ester Me), 4.31—4.44 (2H, m, H-3, α), 7.0—7.4 (4H, m, H-4, 5, 6, 7). ^{13}C-NMR δ: 37.7 (d, C-3), 53.0 and 53.3 (q, ester Me), 73.2 (d, C-α), 115.2 (s, C-2), 147.9 (s, C-3a), 152.3 (s, C-7a), 163.1 and 172.3 (s, ester C=O), 114.2, 125.4, 128.2, and 129.2 (d, C-4, 5, 6, 7). MS *m/z*: 279 (M^+). *Anal.* Calcd for $C_{13}H_{13}NO_6$: C, 55.91; H, 4.70; N, 5.02. Found: C, 55.84; H, 4.66; N, 5.03.

Methyl α-Hydroxy-2-methoxycarbonyl-6-methyl-1-oxido-3*H*-indole-3-acetate (2b) and Dimethyl 7-Methyl-3a,4-dihydro-5a*H*-benzofuro[3,3*a*-*d*]isoxazole-3,4-dicarboxylate (7b)——**1b**[6] (293 mg, 1 mmol) was processed as described for **2a**; TLC (silica gel, benzene–AcOEt (8 : 1, v/v)) showed two products, which were separated by silica-gel column chromatography with the same solvent system as that used for TLC. The major, faster-eluting fraction was concentrated and the residue, after purification by preparative TLC (Merck Kieselgel 60 G, $CHCl_3$–AcOEt (4 : 1, v/v)), was crystallized from Et_2O–hexane to afford **7b** (80 mg, 44% yield) as yellow prisms, mp 106—107 °C. IR ν_{max}^{KBr} cm^{-1}: 1755 and 1730 (ester C=O), 1590 (C=N). ^{1}H-NMR ($CDCl_3$) δ: 1.85 (3H, s, 7-Me), 3.70 and 3.85 (each 3H, s, ester Me), 4.13 (1H, d, J=7.5 Hz, H-3a), 4.66 (1H, d, J=7.5 Hz, H-4), 5.17 (1H, m, H-5a), 5.59 (1H, m, H-6), 5.81 (1H, d, J=10 Hz, H-9), 5.94 (1H, d, J=10 Hz, H-8). MS *m/z*: 293 (M^+), 276 (M^+-17), 216 (M^+-77). *Anal.* Calcd for $C_{14}H_{15}NO_6$: C, 57.34; H, 5.16; N, 4.78. Found: C, 57.52; H, 5.19; N, 4.83.

The second, minor fraction was treated as above to give **2b** (45 mg, 15% yield) as a brownish syrup. IR $\nu_{max}^{liq.\,film}$ cm^{-1}: 3400 (OH), 1740 and 1730 (ester C=O), 1630 (C=N). ^{1}H-NMR ($CDCl_3$) δ: 2.39 (3H, s, C_6-Me), 3.16 (1H, br m, OH), 3.76 and 3.97 (each 3H, s, ester Me), 4.42 (2H, m, H-3, α), 6.9—7.1 (3H, m, H-4, 5, 7). MS *m/z*: 293 (M^+).

Methyl 6-Fluoro-α-hydroxy-2-methoxycarbonyl-1-oxido-3*H*-indole-3-acetate (2c) and Dimethyl 7-Fluoro-3a,4-dihydro-5a*H*-benzofuro[3,3*a*-*d*]isoxazole-3,4-dicarboxylate (7c)——**1c**[6] (297 mg, 1 mmol) was treated with titanium tetrachloride and worked up as described for **2a**. TLC (silica gel, $CHCl_3$–AcOEt (4 : 1, v/v)) showed two products, which were separated by silica-gel column chromatography with the same solvent system as used for TLC. The major, faster-eluting fraction was concentrated, and the residue crystallized from Et_2O to give **7c** (229 mg, 77% yield) as pale yellow crystals, mp 97.5—98.5 °C. IR ν_{max}^{KBr} cm^{-1}: 1750 and 1710 (ester C=O), 1590 (C=N). ^{1}H-NMR ($CDCl_3$) δ: 3.79 and 3.93 (each 3H, s, ester Me), 4.27 (1H, d, J=7.0 Hz, H-3a), 4.76 (1H, d, J=7.0 Hz, H-4), 5.37 (1H, s, H-5a), 5.50, 6.02, and 6.10 (each 1H, s with fine splittings, H-6, 8, 9). MS *m/z*: 297 (M^+). *Anal.* Calcd for $C_{13}H_{12}FNO_6$: C, 52.33; H, 4.07; N, 4.71. Found: C, 52.11; H, 3.94; N, 4.49.

The second fraction was concentrated to give **2c** (35 mg, 12% yield) as a yellow syrup. IR $\nu_{max}^{liq.\,film}$ cm^{-1}: 3440 (OH), 1755 and 1730 (ester C=O), 1590 (C=N). ^{1}H-NMR ($CDCl_3$) δ: 3.13 (1H, br m, OH), 3.70 and 3.94 (each 3H,

s, ester Me), 4.43 and 4.84 (each 1H, m, H-3, α), 6.22 (1H, s, H-7), 6.75—7.2 (2H, m, H-4, 5). MS *m/z*: 297 (M^+).

Methyl 6-Chloro-α-hydroxy-2-methoxycarbonyl-1-oxido-3*H*-indole-3-acetate (2d) and Dimethyl 7-Chloro-3a,4-dihydro-5a*H*-benzofuro[3,3*a*-*d*]isoxazole-3,4-dicarboxylate (7d)——**1d**[6] (313 mg, 1 mmol) was processed as described for **2c** and **7c** to provide **2d** (26 mg, 8% yield) and **7d** (257 mg, 81% yield). **2d**: A yellow syrup. IR $\nu_{max}^{liq.film}$ cm^{-1}: 3400 (OH), 1740 and 1725 (ester C=O), 1580 (C=N). ^{1}H-NMR ($CDCl_3$) δ: 3.11 (1H, br m, OH), 3.77 and 3.96 (each 3H, s, ester Me), 4.42 (2H, m, H-3, α), 7.1—7.4 (3H, m, H-4, 5, 7). MS *m/z*: 313 and 315 (M^+). **7d**: Yellowish crystals, mp 107—108.5 °C (Et_2O). IR ν_{max}^{KBr} cm^{-1}: 1750 and 1710 (ester C=O), 1590 (C=N). ^{1}H-NMR ($CDCl_3$) δ: 3.71 and 3.85 (each 3H, s, ester Me), 4.21 (1H, d, J=7.0 Hz, H-3a), 4.68 (1H, d, J=7.0 Hz, H-4), 5.29 (1H, m, H-5a), 5.98 (3H, m, H-6, 8, 9). MS *m/z*: 313 and 315 (M^+). *Anal.* Calcd for $C_{13}H_{12}ClNO_6$: C, 49.77; H, 3.86; Cl, 11.30; N, 4.46. Found: C, 49.67; H, 3.82; Cl, 11.54; N, 4.38.

Methyl 6-Bromo-α-hydroxy-2-methoxycarbonyl-1-oxido-3*H*-indole-3-acetate (2e) and Dimethyl 7-Bromo-3a,4-dihydro-5a*H*-benzofuro[3,3*a*-*d*]isoxazole-3,4-dicarboxylate (7e)——**1e**[6] (358 mg, 1 mmol) was processed as above to give **2e** (39 mg, 11% yield) and **7e** (261 mg, 73% yield). **2e**: A yellow syrup. IR $\nu_{max}^{liq.film}$ cm^{-1}: 3460 (OH), 1750 and 1730 (ester C=O), 1585 (C=N). ^{1}H-NMR ($CDCl_3$) δ: 3.11 (1H, br m, OH), 3.77 and 3.96 (each 3H, s, ester Me), 4.41 (2H, m, H-3, α), 7.1—7.4 (3H, m, H-4, 5, 7). MS *m/z*: 357 and 359 (M^+). *Anal.* Calcd for $C_{13}H_{12}BrNO_6$: C, 43.60; H, 3.38; Br, 22.31; N, 3.91. Found: C, 43.60; H, 3.55; Br, 22.60; N, 3.63. **7e**: Colorless crystals, mp 101.5—102 °C (Et_2O). IR ν_{max}^{KBr} cm^{-1}: 1755 and 1720 (ester C=O), 1600 (C=N). ^{1}H-NMR ($CDCl_3$) δ: 3.79 and 3.92 (each 3H, s, ester Me), 4.27 (1H, d, J=7.0 Hz, H-3a), 4.76 (1H, d, J=7.0 Hz, H-4), 5.26 (1H, d, J=4.0 Hz, H-5a), 5.8—6.3 (3H, m, H-6, 8, 9). MS *m/z*: 357 and 359 (M^+). *Anal.* Calcd for $C_{13}H_{12}BrNO_6$: C, 43.60; H, 3.38; Br, 22.31; N, 3.91. Found: C, 43.59; H, 3.25; Br, 22.15; N, 3.67.

Methyl α-Hydroxy-2-methoxycarbonyl-5-methyl-1-oxido-3*H*-indole-3-acetate (2f)——**1f**[6] (293 mg, 1 mmol) was processed as described for **2a** to give **2f** (202 mg, 69% yield) as a yellow syrup. IR $\nu_{max}^{liq.film}$ cm^{-1}: 3480 (OH), 1735 (ester C=O), 1595 (C=N). ^{1}H-NMR ($CDCl_3$) δ: 2.30 (3H, s, C_5-Me), 3.02 (1H, m, OH), 3.71 and 3.92 (each 3H, s, ester Me), 4.34 (2H, m, H-3, α), 7.0—7.2 (3H, m, H-4, 6, 7). MS *m/z*: 293 (M^+).

Methyl 5-Fluoro-α-hydroxy-2-methoxycarbonyl-1-oxido-3*H*-indole-3-acetate (2g)——**1g**[6] (297 mg, 1 mmol) was processed as described for **2a** to give **2g** (227 mg, 76% yield) as an orange-yellow syrup. IR $\nu_{max}^{liq.film}$ cm^{-1}: 3460 (OH), 1740 and 1730 (ester C=O), 1610—1590 (C=N). ^{1}H-NMR ($CDCl_3$) δ: 3.14 (1H, m, OH), 3.79 and 3.98 (each 3H, s, ester Me), 4.44 (2H, m, H-3, α), 6.9—7.1 (3H, m, H-4, 6, 7). MS *m/z*: 297 (M^+).

Methyl 5-Chloro-α-hydroxy-2-methoxycarbonyl-1-oxido-3*H*-indole-3-acetate (2h)——**1h**[6] (313.5 mg, 1 mmol) was processed as described for **2a** to give **2h** (217 mg, 69% yield) as an orange-yellow syrup. IR $\nu_{max}^{liq.film}$ cm^{-1}: 3440 (OH), 1725 (ester C=O). ^{1}H-NMR ($CDCl_3$) δ: 3.13 (1H, m, OH), 3.78 and 3.96 (each 3H, s, ester Me), 4.41 (2H, m, H-3, α), 7.0—7.4 (3H, m, H-4, 6, 7). MS *m/z*: 313 (M^+, weak).

Methyl α-Hydroxy-2-methoxycarbonyl-4-methyl-1-oxido-3*H*-indole-3-acetate (2i)——**1i**[6] (293 mg, 1 mmol) was processed as described for **2a** to give **2i** (54 mg, 18% yield) as a yellow syrup. IR $\nu_{max}^{liq.film}$ cm^{-1}: 3460 (OH), 1730 (ester C=O), 1590 (C=N). ^{1}H-NMR ($CDCl_3$) δ: 2.41 (3H, s, C_4-Me), 2.99 (1H, m, OH), 3.85 and 3.93 (each 3H, s, ester Me), 4.61 (2H, m, H-3, α), 6.9—7.2 (3H, m, H-5, 6, 7). MS *m/z*: 293 (M^+).

Methyl α-Acetoxy-2-methoxycarbonyl-1-oxido-3*H*-indole-3-acetate (3a)——A solution of **2a** (550 mg, 1.96 mmol) in acetic anhydride (5 ml) and pyridine (5 ml) was stirred at room temperature for 1.5 h, then the mixture was partitioned between Et_2O (20 ml) and H_2O (20 ml). The ether extract was washed with H_2O (3×20 ml), dried over anhydr. Na_2SO_4, and evaporated to dryness *in vacuo* to give a residue, which was applied to a silica-gel column and eluted with benzene–AcOEt (4:1, v/v). The major fraction was concentrated to furnish colorless crystals. Recrystallization from AcOEt–hexane gave **3a** (545 mg, 86% yield) as colorless prisms, mp 111.5—112.5 °C. IR ν_{max}^{KBr} cm^{-1}: 1765 (acetyl C=O), 1755 and 1730 (ester C=O), 1590 (C=N). ^{1}H-NMR ($CDCl_3$) δ: 2.06 (3H, s, acetyl Me), 3.72 and 3.94 (each 3H, s, ester Me), 4.61 (1H, d, J=3.0 Hz, H-3), 5.08 (1H, d, J=3.0 Hz, H-α), 7.0—7.4 (4H, m, H-4, 5, 6, 7). MS *m/z*: 321 (M^+). *Anal.* Calcd for $C_{15}H_{15}NO_7$: C, 56.07; H, 4.71; N, 4.36. Found: C, 55.95; H, 4.73; N, 4.34.

Methyl α-Acetoxy-2-methoxycarbonyl-6-methyl-1-oxido-3*H*-indole-3-acetate (3b)——**2b** (100 mg, 0.34 mmol) was processed as described for **3a**, except that column chromatography was carried out with $CHCl_3$–AcOEt (4:1, v/v) as the eluant. Recrystallization from MeOH–H_2O provided **3b** (45 mg, 40% yield) as yellowish crystals, mp 114.5—115.5 °C. IR ν_{max}^{KBr} cm^{-1}: 1745, 1730, and 1710 (acetyl and ester C=O), ^{1}H-NMR ($CDCl_3$) δ: 2.09 (3H, s, acetyl Me), 2.38 (3H, s, C_6-Me), 3.73 and 3.96 (each 3H, s, ester Me), 4.57 (1H, d, J=3.0 Hz, H-3), 5.08 (1H, d, J=3.0 Hz, H-α), 6.9—7.1 (3H, m, H-4, 5, 7). MS *m/z*: 335 (M^+). *Anal.* Calcd for $C_{16}H_{17}NO_7$: C, 57.31; H, 5.11; N, 4.18. Found: C, 57.01; H, 5.08; N, 4.12.

Methyl α-Acetoxy-6-chloro-2-methoxycarbonyl-1-oxido-3*H*-indole-3-acetate (3d)——**2d** (110 mg, 0.35 mmol) was processed as described for **3b** to give **3d** (103 mg, 82% yield) as a yellowish syrup. IR $\nu_{max}^{liq.film}$ cm^{-1}: 1760 (acetyl C=O), 1740 and 1725 (ester C=O), 1580 (C=N). ^{1}H-NMR ($CDCl_3$) δ: 2.07 (3H, s, acetyl Me), 3.72 and 3.96 (each 3H, s, ester Me), 4.56 (1H, d, J=3.0 Hz, H-3), 5.07 (1H, d, J=3.0 Hz, H-α), 7.0—7.3 (3H, m, H-4, 5, 7). MS *m/z*: 355 and 357 (M^+).

Methyl α-Acetoxy-6-bromo-2-methoxycarbonyl-1-oxido-3*H*-indole-3-acetate (3e)——**2e** (100 mg, 0.28 mmol) was processed as described for **3b** to give **3e** (80 mg, 71% yield) as an orange-yellow syrup. IR $\nu_{max}^{liq.film}$ cm^{-1}: 1760 (acetyl

C=O), 1735 (ester C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.05 (3H, s, acetyl Me), 3.76 and 3.88 (each 3H, s, ester Me), 4.62 (1H, d, J=3.0 Hz, H-3), 5.09 (1H, d, J=3.0 Hz, H-α), 7.0—7.3 (3H, m, H-4, 5, 7). MS m/z: 399 and 401 (M^+).

Methyl α-Acetoxy-2-methoxycarbonyl-5-methyl-1-oxido-3*H*-indole-3-acetate (3f)——**2f** (50 mg, 0.17 mmol) was processed as described for **3b** to give **3f** (47 mg, 83% yield) as a yellow syrup. IR $\nu_{max}^{liq.film}$ cm^{-1}: 1755 (acetyl C=O), 1730 (ester C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.03 (3H, s, acetyl Me), 2.32 (3H, s, C_5-Me), 3.79 and 3.90 (each 3H, s, ester Me), 4.51 (1H, m, H-3), 5.02 (1H, d, J=3.0 Hz, H-α), 7.0—7.2 (3H, m, H-4, 6, 7). MS m/z: 335 (M^+).

Methyl α-Acetoxy-5-fluoro-2-methoxycarbonyl-1-oxido-3*H*-indole-3-acetate (3g)——**2g** (100 mg, 0.34 mmol) was processed as described for **3b** to give **3g** (94 mg, 82% yield) as a yellow syrup. IR $\nu_{max}^{liq.film}$ cm^{-1}: 1755 (acetyl C=O), 1730 (ester C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.16 (3H, s, acetyl Me), 3.87 and 4.00 (each 3H, s, ester Me), 4.63 (1H, d, J=4.0 Hz, H-3), 5.16 (1H, d, J=4.0 Hz, H-α), 6.9—7.2 (3H, m, H-4, 6, 7). MS m/z: 339 (M^+).

Methyl α-Acetoxy-5-chloro-2-methoxycarbonyl-1-oxido-3*H*-indole-3-acetate (3h)——**2h** (50 mg, 0.16 mmol) was processed as described for **3b** to give **3h** (38 mg, 67% yield) as a yellow syrup. IR $\nu_{max}^{liq.film}$ cm^{-1}: 1760—1735 (acetyl and ester C=O). ^{1}H-NMR ($CDCl_3$) δ: 2.04 (3H, s, acetyl Me), 3.70 and 3.91 (each 3H, s, ester Me), 4.55 (1H, d, J=3.0 Hz, H-3), 5.05 (1H, d, J=3.0 Hz, H-α), 7.1—7.3 (3H, m, H-4, 6, 7). MS m/z: 355 and 357 (M^+).

Methyl α-Benzoyloxy-2-methoxycarbonyl-1-oxido-3*H*-indole-3-acetate (4a)——Benzoyl chloride (84 mg, 0.6 mmol) was added to a solution of **2a** (140 mg, 0.5 mmol) in pyridine (2 ml) and the mixture was stirred at room temperature for 1 h, followed by partition between Et_2O (10 ml) and H_2O (10 ml). The ether layer was washed with H_2O (3 × 20 ml), dried over anhydr. Na_2SO_4, and evaporated to dryness *in vacuo* to yield a residue, which was applied to a silica-gel column and eluted with $CHCl_3$–AcOEt (4:1, v/v). The major fraction was concentrated and recrystallized from MeOH to provide **4a** (106 mg, 55% yield) as colorless needles, mp 120—122 °C. IR ν_{max}^{KBr} cm^{-1}: 1755 and 1730 (ester C=O). ^{1}H-NMR ($CDCl_3$) δ: 3.70 and 3.86 (each 3H, s, ester Me), 4.78 (1H, d, J=3.0 Hz, H-3), 5.19 (1H, d, J=3.0 Hz, H-α), 7.1—7.6 (5H, m, H-4, 5, 6, 7 and benzoyl H-4), 7.41 and 7.91 (each 2H, dd, J=2.0 Hz and 9.0 Hz, other benzoyl H). MS m/z: 383 (M^+). *Anal.* Calcd for $C_{20}H_{17}NO_7$: C, 62.66; H, 4.44; N, 3.65. Found: C, 62.36; H, 4.42; N, 3.79.

Methyl 2-Methoxycarbonyl-α-(*p*-nitrobenzoyloxy)-1-oxido-3*H*-indole-3-acetate (5a)——*p*-Nitrobenzoyl chloride (111 mg, 0.6 mmol) was added to a solution of **2a** (140 mg, 0.5 mmol) in pyridine (2 ml) and the mixture was stirred at room temperature for 2 h, then partitioned between Et_2O (10 ml) and H_2O (10 ml). The ether layer was washed with H_2O (3 × 20 ml), and dried over anhydr. $MgSO_4$. After removal of the solvent, the residue was applied to a silica-gel column and eluted with $CHCl_3$–AcOEt (4:1, v/v). The product was recrystallized from MeOH to furnish **5a** (190 mg, 89% yield) as colorless needles, mp 122—124 °C. IR ν_{max}^{KBr} cm^{-1}: 1760 and 1720 (ester C=O), 1530 and 1350 (NO_2). ^{1}H-NMR ($CDCl_3$) δ: 3.76 and 3.90 (each 3H, s, ester Me), 4.78 (1H, d, J=3.0 Hz, H-3), 5.21 (1H, d, J=3.0 Hz, H-α), 7.0—7.3 (4H, m, H-4, 5, 6, 7), 8.06 and 8.21 (each 2H, d, J=9.0 Hz, benzoyl H). MS m/z: 428 (M^+). *Anal.* Calcd for $C_{20}H_{16}N_2O_9$: C, 56.08; H, 3.76; N, 6.54. Found: C, 55.87; H, 3.72; N, 6.48.

Methyl 6-Chloro-2-methoxycarbonyl-α-(*p*-nitrobenzoyloxy)-1-oxido-3*H*-indole-3-acetate (5d)——**2d** (157 mg, 0.5 mmol) was processed as described for **5a** to give **5d** (76 mg, 33% yield) as pale yellow crystals, mp 68—70 °C (Et_2O–petr. ether). IR ν_{max}^{KBr} cm^{-1}: 1760 and 1735 (ester C=O), 1610 (C=N), 1535 and 1350 (NO_2). ^{1}H-NMR ($CDCl_3$) δ: 3.77 and 3.90 (each 3H, s, ester Me), 4.73 (1H, d, J=3.0 Hz, H-3), 5.19 (1H, d, J=3.0 Hz, H-α), 7.1—7.3 (3H, m, H-4, 5, 7), 8.06 and 8.24 (each 2H, d, J=9.0 Hz, benzoyl H). MS m/z: 462 and 464 (M^+). *Anal.* Calcd for $C_{20}H_{15}ClN_2O_9$: C, 51.91; H, 3.27; Cl, 7.66; N, 6.05. Found: C, 52.21; H, 3.53; Cl, 8.01; N, 5.73.

Methyl 2-Methoxycarbonyl-5-methyl-α-(*p*-nitrobenzoyloxy)-1-oxido-3*H*-indole-3-acetate (5f)——**2f** (100 mg, 0.34 mmol) was processed as described for **5a** to give **5f** (77 mg, 51% yield) as colorless crystals, mp 125—127 °C (MeOH). IR ν_{max}^{KBr} cm^{-1}: 1760 and 1730 (ester C=O), 1535 and 1350 (NO_2). ^{1}H-NMR ($CDCl_3$) δ: 2.35 (3H, s, C_5-Me), 3.80 and 3.93 (each 3H, s, ester Me), 4.76 (1H, m, H-3), 5.25 (1H, d, J=3.0 Hz, H-α), 7.0—7.2 (3H, m, H-4, 6, 7), 8.09 and 8.21 (each 2H, d with fine splittings, J=9.0 Hz, benzoyl H). MS m/z: 442 (M^+). *Anal.* Calcd for $C_{21}H_{18}N_2O_9$: C, 57.02; H, 4.10; N, 6.33. Found: C, 56.92; H, 4.13; N, 6.32.

Methyl 5-Chloro-2-methoxycarbonyl-α-(*p*-nitrobenzoyloxy)-1-oxido-3*H*-indole-3-acetate (5h)——**2h** (80 mg, 0.26 mmol) was processed as described for **5a** to give **5h** (48 mg, 40% yield) as yellowish crystals, mp 76—79 °C (dec.) (Et_2O–hexane). IR ν_{max}^{KBr} cm^{-1}: 1765, 1735, and 1725 (ester C=O), 1610 (C=N), 1530 and 1350 (NO_2). ^{1}H-NMR ($CDCl_3$) δ: 3.78 and 3.92 (each 3H, s, ester Me), 4.74 (1H, d, J=3.0 Hz, H-3), 5.22 (1H, d, J=3.0 Hz, H-α), 7.0—7.3 (3H, m, H-4, 6, 7), 8.09 and 8.26 (each 2H, d, J=9.0 Hz, benzoyl H). MS m/z: 462 and 464 (M^+).

Methyl 2-Methoxycarbonyl-4-methyl-α-(*p*-nitrobenzoyloxy)-1-oxido-3*H*-indole-3-acetate (5i)——**2i** (100 mg, 0.34 mmol) was processed as described for **5a** to give **5i** (33 mg, 22% yield) as colorless needles, mp 149—150 °C (MeOH). IR ν_{max}^{KBr} cm^{-1}: 1760 and 1730 (ester C=O), 1535 and 1350 (NO_2). ^{1}H-NMR ($CDCl_3$) δ: 2.49 (3H, s, C_4-Me), 3.81 and 3.90 (each 3H, s, ester Me), 4.89 (1H, d, J=3.0 Hz, H-3), 5.11 (1H, d, J=3.0 Hz, H-α), 6.9—7.3 (3H, m, H-5, 6, 7), 8.08 and 8.21 (each 2H, d with fine splittings, J=9.0 Hz, benzoyl H). MS m/z: 442 (M^+). *Anal.* Calcd for $C_{21}H_{18}N_2O_9$: C, 57.02; H, 4.10; N, 6.33. Found: C, 57.29; H, 4.16; N, 6.36.

2-Carbamoyl-α-hydroxy-1-oxido-3*H*-indole-3-acetamide (6)——A mixture of **2a** (100 mg, 0.36 mmol), ammonium chloride (18 mg), and conc. aq. ammonia (1.8 ml) was stirred at room temperature overnight. The precipitates were collected, washed with H_2O, and dried over P_2O_5 to give **6** (36 mg, 40% yield) as colorless powdery crystals insoluble in most solvents, mp 174—175 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 3320 and 3140 (NH), 1690 and

1660 (amide C=O), 1580 (C=N). MS *m/z*: 249 (M^+). *Anal.* Calcd for $C_{11}H_{11}N_3O_4$: C, 53.01; H, 4.45; N, 16.86. Found: C, 52.85; H, 4.35; N, 17.10.

Methyl 3-Deuterio-α-hydroxy-2-methoxycarbonyl-1-oxido-3*H*-indole-3-acetate (9)——Boron trifluoride etherate (4 ml) was added to a solution of *trans*-3,5-bis(methoxycarbonyl)-4-phenyl-2-isoxazoline-2-oxide-4-*d*[11] (**8**; 500 mg, 1.8 mmol) in dry benzene (30 ml), and the mixture was stirred at 0 °C for 0.5 h. After further stirring at room temperature for 0.5 h, the resulting dark-red solution was quenched with 10% Na_2CO_3 aq., washed with H_2O (3 × 30 ml), dried over anhydr. Na_2SO_4, and evaporated to dryness *in vacuo* to give a residue, which was applied to a silica-gel column and eluted with benzene–AcOEt (4 : 1, v/v). The major fraction was concentrated to afford **9** (161 mg, 32% yield) as yellowish crystals. Recrystallization from AcOEt–hexane gave colorless prisms, mp 85.5—86.5 °C. IR $\nu_{max}^{liq.film}$ cm^{-1}: 3450 (OH), 1730—1710 (ester C=O), 1620 (C=N). UV λ_{max}^{MeOH} nm (log ε): 283 (3.59). ^{1}H-NMR ($CDCl_3$) δ: 3.08 (1H, d, *J*=7.0 Hz, OH), 3.72 and 3.93 (each 3H, s, ester Me), 4.37 (1H, d, *J*=7.0 Hz, H-α), 7.0—7.4 (4H, m, H-4, 5, 6, 7), no H-3 signal was observed. MS *m/z*: 280 (M^+). *Anal.* Calcd for $C_{13}H_{12}DNO_6$: C, 55.71; N, 5.00. Found: C, 55.67; N, 5.04.

Methyl α-Acetoxy-3-deuterio-2-methoxycarbonyl-1-oxido-3*H*-indole-3-acetate (10)——Acetic anhydride (1 ml) was added to an ice-cooled, stirred solution of **9** (96 mg, 0.34 mmol) in pyridine (1 ml), and the mixture was stirred at room temperature for 1.5 h, then partitioned between Et_2O (10 ml) and H_2O (10 ml). The ether layer was washed with H_2O (3 × 10 ml), dried over anhydr. Na_2SO_4, and evaporated to dryness *in vacuo* to give a yellowish solid, which was applied to a silica-gel column and eluted with benzene–AcOEt (5 : 1, v/v). The major fraction was concentrated and the residue was recrystallized from AcOEt–hexane to afford **10** (86 mg, 78% yield) as colorless prisms, mp 110.5—111.5 °C. IR ν_{max}^{KBr} cm^{-1}: 1755 (acetyl C=O), 1740—1720 (ester C=O), 1615 (C=N). UV λ_{max}^{MeOH} nm (log ε): 282 (3.63). ^{1}H-NMR ($CDCl_3$) δ: 2.07 (3H, s, acetyl Me), 3.73 and 3.95 (each 3H, s, ester Me), 5.09 (1H, s, H-α), 7.0—7.4 (4H, m, H-4, 5, 6, 7), no H-3 signal was observed. MS *m/z*: 322 (M^+). *Anal.* Calcd for $C_{15}H_{14}DNO_7$: C, 55.90; H(D), 5.00; N, 4.35. Found: C, 55.79; H(D), 4.82; N, 4.20.

***trans*-3,5-Bis-(methoxycarbonyl)-4-pentadeuteriophenyl-2-isoxazoline-2-oxide (11)**——Diethylamine (1.03 ml, 10 mmol) was added to a stirred solution of methyl nitroacetate[12] (2.38 g, 20 mmol) and benzaldehyde-d_5[13] (1.11 g, 10 mmol) in *N*, *N*-dimethylacetamide (30 ml), and the mixture was stirred at room temperature overnight (16 h). The resulting yellow solution was partitioned between ice-water (120 ml) and benzene (60 ml), and the aqueous layer was extracted with benzene (2 × 60 ml). The combined extracts were washed with H_2O (3 × 60 ml), dried over anhydr. Na_2SO_4, and concentrated under reduced pressure to furnish a yellow syrup, which crystallized on standing at room temperature overnight. Recrystallization from AcOEt–hexane provided **11** (1.6 g, 56% yield) as colorless needles, mp 92.5—93.5 °C. IR ν_{max}^{KBr} cm^{-1}: 1735 (ester C=O), 1605 (C=N). UV λ_{max}^{MeOH} nm (log ε): 266 (4.03). ^{1}H-NMR ($CDCl_3$) δ: 3.77 and 3.90 (each 3H, s, ester Me), 4.85 (1H, d, *J*=2.0 Hz, H-4), 4.95 (1H, d, *J*=2.0 Hz, H-5), no signal due to aromatic protons was observed. MS *m/z*: 284 (M^+). *Anal.* Calcd for $C_{13}H_8D_5NO_6$: C, 54.93; N, 4.93. Found: C, 55.04; N, 4.97.

Methyl 4,5,6,7-Tetradeuterio-α-hydroxy-2-methoxycarbonyl-1-oxido-3*H*-indole-3-acetate (12)——Isoxazoline-2-oxide (**11**) was processed as described for **9** to afford **12** (264 mg) as a yellow syrup, which crystallized from AcOEt–hexane to yield pale yellow crystals (224 mg, 45% yield), mp 86—87 °C. IR ν_{max}^{KBr} cm^{-1}: 3430 (OH), 1745 and 1725 (ester C=O), 1610 (C=N). UV λ_{max}^{MeOH} nm (log ε): 282 (3.60). ^{1}H-NMR ($CDCl_3$) δ: 3.02 (1H, m, OH), 3.70 and 3.92 (each 3H, s, ester Me), 4.25—4.43 (2H, m, H-3, α), no signal due to aromatic protons was observed. MS *m/z*: 283 (M^+). *Anal.* Calcd for $C_{13}H_9D_4NO_6$: C, 55.12; N, 4.94. Found: C, 55.18; N, 4.96.

Methyl α-Acetoxy-4,5,6,7-tetradeuterio-2-methoxycarbonyl-1-oxido-3*H*-indole-3-acetate (13)——**12** (100 mg, 0.35 mmol) was processed as described for **10**; column chromatography was unnecessary. The product was directly recrystallized from AcOEt–hexane to give **13** (103 mg, 90% yield) as colorless prisms, mp 111.5—112.5 °C. IR ν_{max}^{KBr} cm^{-1}: 1760 (acetyl C=O), 1750 and 1730 (ester C=O), 1610 (C=N). UV λ_{max}^{MeOH} nm (log ε): 282 (3.64). ^{1}H-NMR ($CDCl_3$) δ: 2.05 (3H, s, acetyl Me), 3.70 and 3.93 (each 3H, s, ester Me), 4.61 (1H, d, *J*=3.5 Hz, H-3), 5.08 (1H, d, *J*=3.5 Hz, H-α), no signal due to aromatic protons was observed. MS *m/z*: 325 (M^+). *Anal.* Calcd for $C_{15}H_{11}D_4NO_7$: C, 55.38; N, 4.31. Found: C, 55.43; N, 4.26.

***trans*-3,5-Bis(methoxycarbonyl)-4-phenyl-2-isoxazoline (14)**——A mixture of **1a**[11] (500 mg, 1.8 mmol), triethyl phosphite (300 mg, 1.8 mmol), and dry toluene (4 ml) was refluxed for 5 h under a nitrogen atmosphere. The solvent was removed under reduced pressure, and the residue was applied to a silica-gel column and eluted with AcOEt–hexane (1 : 2, v/v). The major fraction was concentrated and the residual solid was recrystallized from Et_2O–hexane to give **14** (256 mg, 54% yield) as colorless needles, mp 80.5—81.5 °C. IR ν_{max}^{KBr} cm^{-1}: 1755 and 1725 (ester C=O), 1590 (C=N). UV λ_{max}^{MeOH} nm (log ε): 236 (3.79). ^{1}H-NMR ($CDCl_3$) δ: 3.82 and 3.88 (each 3H, s, ester Me), 4.89 (1H, d, *J*=5.0 Hz, H-4), 5.12 (1H, d, *J*=5.0 Hz, H-5), 7.2—7.5 (5H, m, aromatic H). MS *m/z*: 263 (M^+). *Anal.* Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.36; H, 5.00; N, 5.32.

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