PREPARATION OF ALKYL-SUBSTITUTED INDOLES IN THE BENZENE PORTION. Part 1

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Abstract ——— Variously alkylated 4-(1-methoxycarbonyl-2-pyrrolyl)-2-butenals (11 and 12) were cyclized to 1-methoxycarbonylindoles (14) having alkyl substituents in the benzene portion, simply by refluxing in benzene solution with a catalytic amount of *p*-TsOH. A natural product, 7-(3-methyl-2-butenyl)indole (27) was synthesized by this technique, whereas the corresponding 6-isomer (28), also a natural product, was obtained by treatment of 32 with TMSOTf.

Previously we reported a novel preparative method of 4-alkylindoles,[1] based on our two reactions : (i) a $SnCl_2$-mediated ring-opening reaction of the endo-peroxide (2) of 1-methoxycarbonylpyrrole (1) in the presence of 1-trimethylsilyloxy-1,3-butadiene to afford the enal (3), and (ii) a $SnCl_4$-catalyzed indole-cyclization reaction of enones (4) derived from 3 to yield 5 (Chart 1). One of the products obtained here, 1-methoxycarbonyl-4-(3-oxo-1-butyl)indole (6) was an important starting material in synthesizing a variety of ergot alkaloids[2] and a mycotoxin, α-cyclopiazonic acid.[3] This knowledge was now extended to a general method for synthesizing mono- and polyalkylindole derivatives having alkyl substituents in the benzene portion of the indole nucleus. It was hoped that this could be applied in a total synthesis of teleocidins A (7)[4,5] and B (8).[6,7]

Variously substituted enals (9a – 9g) were converted to the corresponding trimethylsilyloxybutadiene (10) according to the procedure (refluxing in C_6H_6 with Me_3SiCl in the presence of Et_3N and $ZnCl_2$) described in the literature.[8] These were condensed with the endo-peroxide (2), as reported previously, to afford α-substituted pyrrole derivatives (11a – 11g) mostly bearing *E* enal side chain in 40-50% yields, calculated from 1-methoxycarbonylpyrrole (1) (Table 1). Occasional formation of Z-

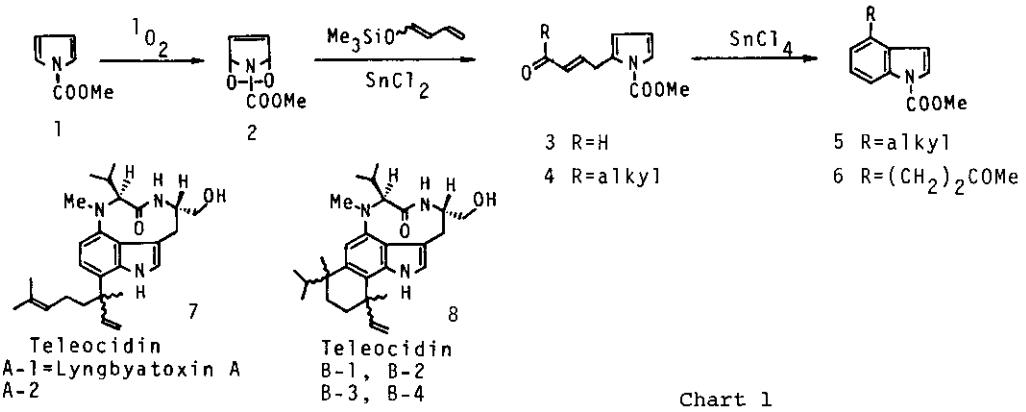
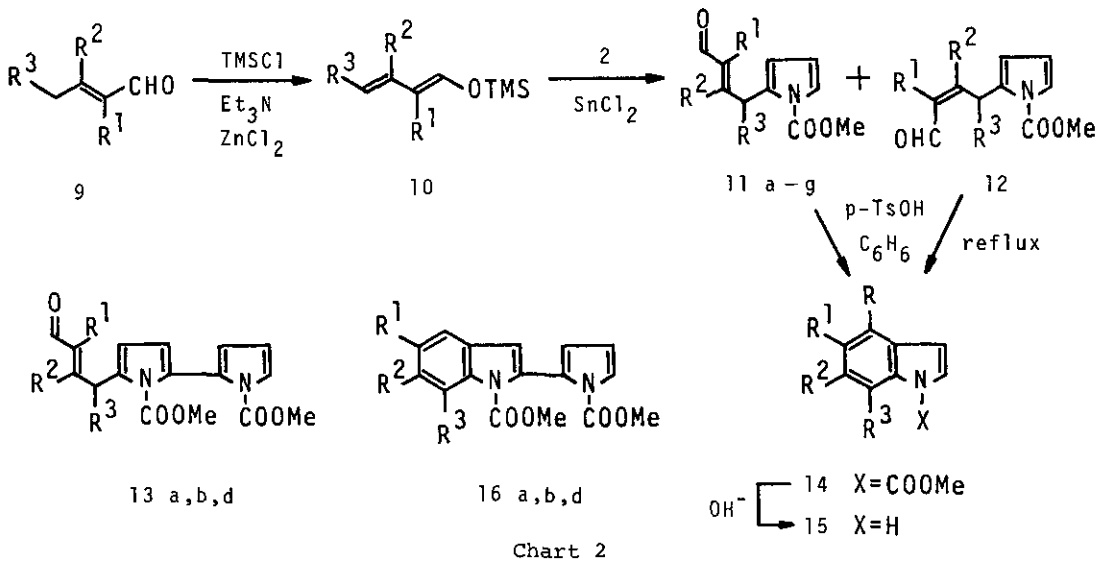


Chart 1

isomers (12) and by-products (13) was observed. Cyclization to the indole derivatives (14) was investigated using 11c as a model compound in the presence of various kinds of acids : $BF_3 \cdot Et_2O$, $SnCl_4$, $AlCl_3$, $ZnCl_2$, and F_3CCOOH. 7-Ethylindole derivative (14c) was obtained in 18%, 19%, 64%, 68%, and 90% yields respectively. Finally, simple refluxing of a C_6H_6 solution of 11c with a catalytic amount of *p*-TsOH for 15 min was found to be the best condition to produce 14c in 89% yield, judging from a high yield as well as cleanness of the reaction. Pyrrole derivatives (11a, 11b, 11d, 11e, 11f, and 11g) were cyclized under the same condition to produce the expected alkylindole derivatives in very good yields, although prolonged heating was required for 5-alkylindole derivatives (14a and 14d). The by-products (13a, 13b, and 13d) were also converted to 1-methoxycarbonyl-2-(1-methoxycarbonyl-2-pyrrolyl)indoles (16a, 16b, and 16d) in 81%, 87%, and 78% yields by refluxing for 1 h, 15 min, and 1.5 h respectively. In the case of 4-alkylindole derivatives, 4,6,7-trialkylindole derivative (14h) was obtained in high yield by the same TsOH treatment of 11h, prepared as shown in Table 1. However, for the preparation of 4-monoalkylindole derivative (14j) as well as 1-methoxycarbonylindole (14i) itself, cyclization with $SnCl_4$ gave a better result, supporting the previous finding.[1] The nitrogen protecting group was readily removed as usual by alkaline hydrolysis to yield 15. The indole derivatives (14f and 14g), which contain fused cyclopentene and cyclohexene moieties at the 6 and 7 positions served as model compounds for synthesizing trikentrins[9] and teleocidins B.[6]

The enal compound (11g) was oxidized to 17 with $NaClO_2$ in the presence of NaH_2PO_4 and 2-methyl-2-butene[10] in 88% yield, and 17 was condensed with methyl (±)-*N*-methylvalinate by applying the mixed anhydride method to give an amide-ester (18) in 78% yield. Bischler-Napieralski reaction of 18 was examined using trichloro-



9 10 11 a – g 12

13 a,b,d 16 a,b,d

Chart 2

Table 1. Formation of 11 and/or 12 by Reaction of 2 with 10, and Synthesis of Alkylindole Derivatives 14 and 15

	R^1	R^2	R^3	R	Yield % 11[a]	12[a]	13[a]	14	15
a	Et	H	H	H	44	0	11	80	92
b	H	Me	H	H	40	0	8.5	94	98
c	H	H	Et	H	40	0	0	89	99
d	Et	H	Et	H	42 (13:1)		7	74	97
e	H	Et	Me	H	45	5	0	85 from 11e 92 from 12e	—
f	H	-$(CH_2)_3$-		H	50	5	0	92 from 11f 87 from 12f	—
g	H	-$(CH_2)_4$-		H	47	0	0	86	96
h	H	Et	Me	Bu	b	—	—	96	—
i	H	H	H	H	ref.1	—	—	45 (69[c])	—
j	H	H	H	Bu	ref.1	—	—	28 (44[c])	—

a. Calculated from 1-methoxycarbonylpyrrole (1).
b. Prepared from 11e with BuMgBr (90%), followed by PCC oxidation (62%).
c. Yield using $SnCl_4$.

methyl chloroformate or $POCl_3$, and formation of the expected indole derivative (19) was found to occur in either 36% or 62% yield. The latter condition, however, afforded in addition a secondary amine derivative (20) in 11% yield by unknown reaction mechanism. The production of 20 was suppressed to 2% yield, when 18 was treated by a mixture of $POCl_3$ and PCl_3 (5:1) in refluxing CH_2Cl_2 to give 19 in 66%

yield.

With a simple model of teleocidin B intermediate secured, we next intended to prepare the compound (21) having two quaternary centers in the cyclohexane ring. 3,3,5,5-Tetramethylcyclohexanone (22)[11] derived from isophorone (3,5,5-trimethyl-2-cyclohexenone) was treated with vinylmagnesium bromide, followed by oxidation with PCC[12] to afford 23 in 53% yield. This was converted to its enol ether (24) and coupled with the endo-peroxide (2) as usual to produce 26 in 33% yield as an unstable syrup. The structure of 26 was easily deduced by its nmr spectral analysis, concluding that the steric hindrance of the geminal dimethyl group altered the reaction site of 24 and the compound (25) was an intermediate to afford the undesired 26.

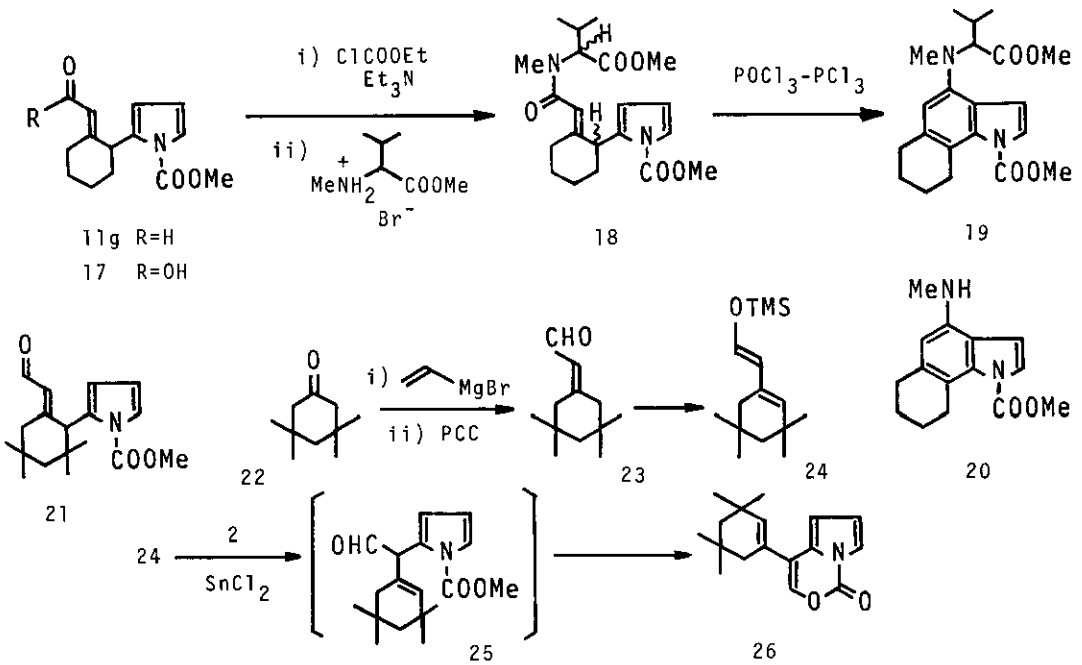
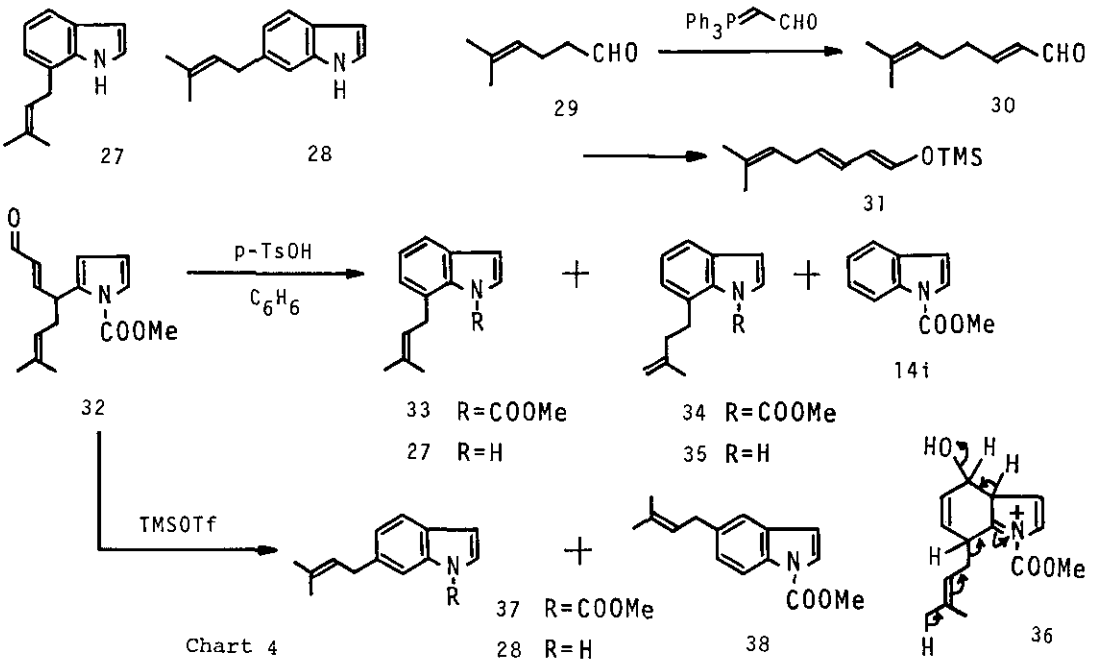


Chart 3

7- and 5-(3-Methyl-2-butenyl)indoles (27 and 28) are natural products isolated from *Riccardia sinuata* (Hook.) Trev,[13] and recently 27 has been reported to be a constituent of *Annonidium manni* Engl. and Diels.[14] Concerning to the synthesis of these indoles, Plieninger and Ishii reported their successful results of 28.[15,16] Here we describe our synthetic study on these natural products. 5-Methyl-4-hexenal (29)[17] was elongated with Ph_3P=CHCHO[18] to give 30 in 63% yield. This was coverted to its enol ether (31) as mentioned above and reacted with the endo-peroxide (2) to form the enal (32) in 28% yield, calculated from 1. Refluxing a C_6H_6 solution of

32 with *p*-TsOH for 10 min afforded an inseparable mixture of 33 and 34, accompanied by the formation of 1-methoxycarbonylindole (14i) in 26% yield. Separation of the mixture was achieved after alkaline hydrolysis of 33 and 34, forming the requisite product (27), mp 43.5-44.5°C (lit.[14]: mp 43-44°C) and a by-product (35) in 40% and 7% yields respectively, calculated from 32. Identity of 27 with the authentic material was confirmed by admixture and comparison of TLC [silica gel; cyclohexane, hexane-CH_2Cl_2 (2:1), hexane-EtOAc (9:1)], ms, ir (KBr, CCl_4), ^1H and ^{13}C nmr spectra. Formation of 14i was explained as shown in 36 by ready cleavage of the side chain due to the allylic character.

The enal (32) was treated with trimethylsilyl trifluoromethanesulfonate (TMSOTf) in CH_2Cl_2 at -77°C for 12 min. The compound (38) was a by-product obtained in 8% yield. The rest of the reaction mixture was purified after alkaline hydrolysis and a main product (28), colorless oil, was isolated in 35% yield. The structures of 38 and 28 were suggested by their ^1H nmr spectral analysis, and finally, 28 [trinitrobenzene complex, mp 108-109°C (lit.[15a]: mp 106°C; lit.[15b]: mp 111.5-113°C)] was identified as the authentic material by comparison of ir (CCl_4) and ^1H nmr spectra.



27 28 29 30 31 32 33 R=COOMe 27 R=H 34 R=COOMe 35 R=H 14i 37 R=COOMe 28 R=H 38 36

Chart 4

EXPERIMENTAL

Melting points were obtained on Yanagimoto micro-melting point apparatus and are not corrected. Mass spectra were taken on Hitachi RMS-4 spectrometer. Infrared

absorption spectra were determined on Hitachi 215 spectrophotometer. Proton magnetic resonance spectra were measured at Varian EM 390 spectrometer. Column chromatography was conducted on silica gel, Fuji Devison BW 200 and preparative thin-layer chromatography (PTLC) was carried out on glass plates (20×20 cm) coated with Merck silica gel 60 PF_{254} (1 mm thick). Usual work-up refers to washing the oraganic layers with water or brine, drying on anhydrous sodium sulfate and evaporating the solvents under reduced pressure.

General Procedure for Preparation of Pyrrole Derivatives 11 (12, 13) from 1

Preparation of 11a is shown as a representative. A solution of 1-methoxycarbonylpyrrole (1) (1.096 g) and methylene blue (30 mg) in CH_2Cl_2 (125 ml) was irradiated with halogen lamp (500W × 2, Iwasaki JD 110V 500W-MS], while O_2 gas was bubbled slowly at *ca.* -60°C for 3.5 h. To this was added a CH_2Cl_2 solution (8 ml) of a condensate (*ca.* 3.8 g) including 1-trimethylsilyl-2-ethyl-1,3-butadiene (10a), prepared[8] from 2-ethyl-2-butenal (9a) (1.300 g), TMSCl (6.0 ml), Et_3N (9.5 ml), and $ZnCl_2$ (80 mg) in C_6H_6 (40 ml), followed by drop-wise addition of an EtOAc solution (65 ml) of $SnCl_2$ (2.004 g) during 20 min. After being stirred at -75°C for 30 min and 0°C for 1 h, the mixture was quenched with sat. $NaHCO_3$-H_2O. It was filtered through a celite bed and treated as usual. The residue was purified by column chromatography [hexane-EtOAc (7:1)] to afford 11a (850 mg, 44%), colorless oil, and 13a(162 mg, 11%), colorless scales, mp 107.5-108.5°C (hexane-CH_2Cl_2). 11a: Ms *m/z*: 221 (M^+). Ir (film) cm^{-1}: 1750, 1693, 1643. Nmr ($CDCl_3$) δ: 0.97 (3H, t, J=7.5 Hz), 2.32 (2H, q, J=7.5 Hz) 3.90 (3H, s), 3.93 (2H, d, J=7 Hz), 5.94-6.04 (1H, m), 6.09 (1H, dd, J=3.5, 3.5 Hz), 6.57 (1H, t, J=7 Hz), 7.21 (1H, dd, J=3.5, 2 Hz), 9.38 (1H, s). 13a: Anal. Calcd for $C_{18}H_{20}N_2O_5$: C, 62.78; H, 5.85; N, 8.14. Found: C, 62.85; H, 5.79; N, 8.20. Ms *m/z*: 344 (M^+). Ir (KBr) cm^{-1}: 1742, 1694, 1641. Nmr ($CDCl_3$) δ: 1.01 (3H, t, J=7.5 Hz), 2.37 (2H, q, J=7.5 Hz), 3.17 (3H, s), 3.84 (3H, s), 3.98 (2H, d, J=7 Hz), 6.03 (1H, d, J=3.5 Hz), 6.16 (1H, d, J=3.5 Hz), 6.22 (2H, d, J=3 Hz), 6.61 (1H, t, J=7 Hz), 7.35 (1H, dd, J=3, 3 Hz), 9.46 (1H, s). 11b: Colorless prisms, mp 61.5-62.5°C (hexane-CH_2Cl_2). Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.74; H, 6.35; N, 6.90. Ms *m/z*: 207 (M^+). Ir (KBr) cm^{-1}: 1740, 1680, 1655. Nmr ($CDCl_3$) δ: 2.23 (3H, s), 3.76 (2H, s), 3.89 (3H, s), 5.61 (1H, d, J=8 Hz), 6.00-6.15 (1H, m), 6.15 (1H, dd, J=3.5, 3.5 Hz), 7.22 (1H, dd, J=3.5, 2 Hz), 10.00 (1H, d, J=8 Hz). 13b: Colorless prisms, mp 99-100°C (Et_2O). Anal. Calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.82; H, 5.40; N, 8.63. Ms *m/z*: 330 (M^+). Ir (KBr) cm^{-1}: 1726, 1680, 1660. Nmr ($CDCl_3$) δ: 2.25 (3H, s), 3.64 (3H, s), 3.80 (5H, s), 5.72 (1H, d, J=8 Hz), 6.05 (1H, d, 3.5 Hz), 6.15 (1H, d, J=3.5 Hz), 6.20 (2H, d, J=2.5 Hz), 7.35 (1H, dd, J=2.5, 2.5 Hz), 10.01 (1H, d, J=8 Hz).

11c: Colorless oil. Ms *m/z*: 221 (M^+). Ir (film) cm^{-1}: 1753, 1695, 1635. Nmr ($CDCl_3$) δ: 0.98 (3H, t, J=7.5 Hz), 1.57-2.03 (2H, m), 3.91 (3H, s), 4.35 (1H, ddd, J=7.5, 7.5, 7.5 Hz), 6.01 (1H, ddd, J=15, 7.5, 1.5 Hz), 6.03-6.28 (2H, m), 6.91 (1H, dd, J=15, 7.5 Hz), 7.23 (1H, dd, J=3, 2 Hz), 9.51 (1H, d, J=7.5 Hz).

11d+12d (13:1): Colorless oil. Ms *m/z*: 249 (M^+). Ir (film) cm^{-1}: 1747, 1691, 1640. Nmr ($CDCl_3$) δ: 0.91 (3H, dd, J=7.5, 7.5 Hz), 0.94 (3H, t, J=7.5 Hz), 2.33 (2H, q, J=7.5 Hz), 3.80 and 3.91 (3H, 1:13, s each), 4.62 (1H, ddd, J=10, 7.5, 6 Hz), 6.10 (2H, d, J=2.5 Hz), 6.42 (1H, d, J=10 Hz), 7.20 (1H, dd, J=2.5, 2.5 Hz), 9.39 and

9.56 (1H, 13:1, s each). 13d: Colorless syrup. Ms *m/z*: 372 (M^+). Ir (film) cm^{-1}: 1752, 1693, 1642. Nmr ($CDCl_3$) δ: 0.97 (6H, t, J=7.5 Hz), 1.45-2.14 (2H, m), 2.33 (2H, q, J=7.5 Hz), 3.65 (3H, s), 3.77 (3H, s), 4.58 (1H, ddd, J=10, 7.5, 6 Hz), 6.08 (1H, d, J=3.5 Hz), 6.13 (1H, d, J=3.5 Hz), 6.17 (2H, d, J=2.5 Hz), 6.43 (1H, d, J=10 Hz), 7.32 (1H, dd, J=2.5, 2.5 Hz), 9.40 (1H, s).
11e: Colorless oil. Ms *m/z*: 235 (M^+). Ir (film) cm^{-1}: 1752, 1671, 1630. Nmr ($CDCl_3$) δ: 1.16 (3H, t, J=7.5 Hz), 1.41 (3H, d, J=7 Hz), 2.34-2.96 (2H, m), 3.86 (3H, s), 4.36 (1H, q, J=7 Hz), 5.56 (1H, d, J=8 Hz), 6.12 (2H, d, J=2.5 Hz), 7.22 (1H, dd, J=2.5, 2.5 Hz), 9.99 (1H, d, J=8 Hz). 12e: Colorless oil. Ms *m/z*: 235 (M^+). Ir (film) cm^{-1}: 1753, 1677, 1628. Nmr ($CDCl_3$) δ: 0.87 (3H, t, J=7.5 Hz), 1.51 (3H, d, J=7 Hz), *ca.* 1.60-2.38 (2H, m), 3.84 (3H, s), 5.27 (1H, q, J=7 Hz), 5.84 (1H, d, J=8 Hz), 6.10-6.28 (2H, m), 7.18-7.32 (1H, m), 10.16 (1H, d, J=8 Hz).
11f: Colorless prisms, mp 78-79.5°C (Et_2O). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.94; H, 6.35; N, 6.28. Ms *m/z*: 233 (M^+). Ir (KBr) cm^{-1}: 1744, 1662. Nmr ($CDCl_3$) δ: 1.63-2.33 (4H, m), 2.84-3.13 (2H, m), 3.89 (3H, s), 4.37-4.66 (1H, m), 5.74 (1H, dddd, J=8, 2.5, 2.5, 2.5 Hz), 5.96-6.05 (1H, m), 6.10 (1H, dd, J=3.5, 3.5 Hz), 7.21 (1H, dd J=3.5, 2 Hz), 9.87 (1H, d, J=8 Hz).
12f: Colorless prisms, mp 85-86°C (Et_2O). Anal. Calcd for $C_{13}H_{15}NO_3$: C, 66.93; H, 6.48; N, 6.01. Found: C, 66.97; H, 6.51; N, 5.98. Ms *m/z*: 233 (M^+). Ir (KBr) cm^{-1}: 1747, 1679, 1635. Nmr ($CDCl_3$) δ: 1.53-2.87 (6H, m), 3.94 (3H, s), 4.91-5.13 (1H, m), 5.79-5.90 (1H, m), 5.94-6.14 (1H, m), 6.04 (1H, dd, J=3.5, 3.5 Hz), 7.20 (1H, dd, J=3.5, 2 Hz), 9.59 (1H, d, J=8.5 Hz).
11g: Colorless prisms, mp 113-115°C (hexane-CH_2Cl_2). Anal. Calcd for $C_{14}H_{17}NO_3$: C, 67.99; H, 6.93; N, 5.67. Found: C, 67.90; H, 6.74; N, 5.66. Ms *m/z*: 247 (M^+). Ir (KBr) cm^{-1}: 1745, 1663, 1628. Nmr ($CDCl_3$) δ: 1.24-2.49 (7H, m), 3.34-3.63 (1H, m), 3.86 (3H, s), 3.99-4.34 (1H, m), 5.17 (1H, d, J=8.5 Hz), 6.03-6.24 (2H, m), 7.25 (1H, dd, J=3.5, 2 Hz), 10.02 (1H, d, J=8.5 Hz).
11h from 11e —— A THF solution (4 ml) of 11e (139 mg) was treated with *ca.* 0.4 M Et_2O solution (2.40 ml) of BuMgBr at 0°C for 20 min to give colorless oil (156 mg, 90%). Ms *m/z*: 275 (M^+-H_2O). A CH_2Cl_2 solution (5 ml) of this (154 mg) was oxidized with pyridinium chlorochromate (450 mg) at 17°C for 30 min to afford 11h (95 mg, 62%), colorless oil. Ms *m/z*: 291 (M^+). Ir (film) cm^{-1}: 1754, 1690, 1613. Nmr ($CDCl_3$) δ: 0.74-0.96 (3H, m), 0.98 (3H, t, J=7.5 Hz), 1.11-1.71 (4H, m), 1.39 (3H, d, J=7 Hz), 2.20-2.82 (4H, m), 3.86 (3H, s), 4.28 (1H, q, J=7 Hz), 5.79 (1H, s), 6.11 (2H, d, J=2.5 Hz), 7.21 (1H, dd, J=2.5, 2.5 Hz).

Indole Cyclization from 11 to 14 with p-TsOH

Preparation of 14c is shown as a representative. A C_6H_6 solution (3 ml) of 11c (54 mg) and *p*-TsOH·H_2O (9 mg) was gently refluxed for 15 min. After cooling in an ice bath, sat. $NaHCO_3$-H_2O was added and the mixture was extracted with CH_2Cl_2. Usual work-up followed by purification by PTLC [hexane-EtOAc (7:1)] gave 14c (44 mg, 89%), colorless oil. Ms *m/z*: 203 (M^+). Ir (film) cm^{-1}: 1760. Nmr ($CDCl_3$) δ: 1.24 (3H, t, J=7.5 Hz), 3.10 (2H, q, J=7.5 Hz), 3.93 (3H, s), 6.53 (1H, d, J=4 Hz), 7.12-7.25 (2H, m), 7.25-7.48 (1H, m), 7.53 (1H, d, J=4 Hz).
14a: Colorless oil. Ms *m/z*: 203 (M^+). Ir (film) cm^{-1}: 1740. Nmr ($CDCl_3$) δ: 1.24 (3H, t, J=7.5 Hz), 2.70 (2H, q, J=7.5 Hz), 3.97 (3H, s), 6.49 (1H, d, J=4 Hz), 7.14 (1H, dd, J=8.5, 1.5 Hz), 7.34 (1H, s), 7.52 (1H, d, J=4 Hz), 8.05 (1H, d, J=8.5 Hz).

14b: Colorless prisms, mp 42.5-43.5°C (MeOH). Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.98; H, 5.93; N, 7.53. Ms *m/z*: 189 (M^+). Ir (KBr) cm^{-1}: 1735. Nmr ($CDCl_3$) δ: 2.47 (3H, s), 4.02 (3H, s), 6.52 (1H, d, J=4 Hz), 7.04 (1H, d, J=7.5 Hz), 7.41 (1H, d, J=7.5 Hz), 7.50 (1H, d, J=4 Hz), 8.01 (1H, s).
14d: Colorless oil. Ms *m/z*: 231 (M^+). Ir (film) cm^{-1}: 1759. Nmr ($CDCl_3$) δ: 1.23 (3H, t, J=7.5 Hz), 1.26 (3H, t, J=7.5 Hz), 2.69 (2H, q, J=7.5 Hz), 3.09 (2H, q, J=7.5 Hz), 3.94 (3H, s), 6.47 (1H, d, J=4 Hz), 7.00 (1H, s), 7.18 (1H, s), 7.52 (1H, d, J=4 Hz).
14e: Colorless oil. Ms *m/z*: 217 (M^+). Ir (film) cm^{-1}: 1754. Nmr ($CDCl_3$) δ: 1.20 (3H, t, J=7.5 Hz), 2.43 (3H, s), 2.73 (2H, q, J=7.5 Hz), 3.87 (3H, s), 6.43 (1H, d, J=4 Hz), 7.02 (1H, d, J=8 Hz), 7.28 (1H, d, J=8 Hz), 7.42 (1H, d, J=4 Hz).
14f: Colorless needles, mp 46-47°C (MeOH). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.74; H, 6.21; N, 6.71. Ms *m/z*: 215 (M^+). Ir (KBr) cm^{-1}: 1763. Nmr ($CDCl_3$) δ: 2.04 (2H, tt, J=7.5, 7.5 Hz), 2.97 (2H, t, J=7.5 Hz), 3.41 (2H, t, J=7.5 Hz), 3.92 (3H, s), 6.50 (1H, d, J=4 Hz), 7.11 (1H, d, J=8.5 Hz), 7.31 (1H, d, J=8.5 Hz), 7.48 (1H, d, J=4 Hz).
14g: Colorless oil. Ms m/z: 229 (M^+). Ir (film) cm^{-1}: 1759. Nmr ($CDCl_3$) δ: 1.56-2.02 (4H, m), 2.77-3.13 (4H, m), 3.94 (3H, s), 6.48 (1H, d, J=4 Hz), 7.00 (1H, d, J=8 Hz), 7.29 (1H, d, J=8 Hz), 7.45 (1H, d, J=4 Hz).
14h: Colorless oil. Ms *m/z*: 273 (M^+). Ir (film) cm^{-1}: 1752. Nmr ($CDCl_3$) δ: 0.93 (3H, t, J=6.5 Hz), *ca.* 1.13-1.84 (4H, m), 1.22 (3H, t, J=7.5 Hz), 2.42 (3H, s), 2.74 (2H, q, J=7.5 Hz), 2.79 (2H, t, J=7 Hz), 3.94 (3H, s), 6.54 (1H, d, J=4 Hz), 6.92 (1H, s), 7.45 (1H, d, J=4 Hz).
16a: Colorless glass. Ms *m/z*: 326 (M^+). Ir (KBr) cm^{-1}: 1742. Nmr ($CDCl_3$) δ: 1.25 (3H, t, J=7.5 Hz), 2.72 (2H, q, J=7.5 Hz), 3.74 (3H, s), 3.81 (3H, s), 6.23 (1H, dd, J=3.5, 3.5 Hz), 6.30 (1H, dd, J=3.5, 2 Hz), 6.56 (1H, s), 7.15 (1H, dd, J=8.5, 1.5 Hz), 7.33 (1H, s), 7.39 (1H, dd, J=3.5, 2 Hz), 8.03 (1H, d, J=8.5 Hz).
16b: Colorless prisms, mp 121-122°C (CH_2Cl_2-MeOH). Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.37; H, 5.16; N, 8.97. Found: C, 65.39; H, 5.06; N, 8.98. Ms *m/z*: 312 (M^+). Ir (KBr) cm^{-1}: 1758, 1730. Nmr ($CDCl_3$) δ: 2.48 (3H, s), 3.74 (3H, s), 3.82 (3H, s), 6.23 (1H, dd, J=3.5, 3.5 Hz), 6.31 (1H, dd, J=3.5, 2 Hz), 6.56 (1H, s), 7.05 (1H, d, J=8 Hz), 7.34-7.47 (1H, m), 7.41 (1H, d, J=8 Hz), 7.99 (1H, s).
16d: Colorless prisms, mp 109-110°C (MeOH). Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.91. Found: C, 67.65; H, 6.23; N, 8.05. Ms *m/z*: 354 (M^+). Ir (KBr) cm^{-1}: 1760, 1743. Nmr ($CDCl_3$) δ: 1.22 (3H, t, J=7.5 Hz), 1.26 (3H, t, J=7.5 Hz), 2.70 (2H, q, J=7.5 Hz), 2.89 (2H, q, J=7.5 Hz), 3.70 (3H, s), 3.74 (3H, s), 6.22 (1H, dd, J=3.5, 3.5 Hz), 6.30 (1H, dd, J=3.5, 2 Hz), 6.52 (1H, s), 7.00 (1H, s), 7.19 (1H, s), 7.41 (1H, dd, J=3.5, 2 Hz).

Alkaline Hydrolysis of 14 to 15

A solution of 14c (48 mg) in 2.5% KOH in MeOH-DME-H_2O (2:2:1) (2.5 ml) was stirred at 22°C for 1 h. Sat. NH_4Cl-H_2O was added and the mixture was extracted with CH_2Cl_2. Usual work-up and purification of the residue by PTLC [hexane-EtOAc (6:1)] furnished 15c (34 mg, 99%), colorless oil. Ms *m/z*: 145 (M^+). Nmr ($CDCl_3$) δ: 1.29 (3H, t, J=7.5 Hz), 2.75 (2H, q, J=7.5 Hz), 6.49 (1H, dd, J=3.5, 2 Hz), 6.88-7.10 (3H, m), 7.36-7.59 (1H, m), 7.83 (1H, s). Picrate: Orange needles, mp 151-152°C (C_6H_6-hexane). Anal. Calcd for $C_{10}H_{11}N \cdot C_6H_3N_3O_7$: C, 51.34; H, 3.77; N, 14.97.

Found: C, 51.11; H, 3.89; N, 14.92.
15a: Colorless oil. Ms *m/z*: 145 (M^+). Nmr ($CDCl_3$) δ: 1.26 (3H, t, J=7.5 Hz), 2.71 (2H, q, J=7.5 Hz), 6.40 (1H, ddd, J=3, 2, 1 Hz), 6.92 (1H, dd, J=3, 3 Hz), 6.98 (1H, d, J=8 Hz), 7.13 (1H, d, J=8 Hz), 7.40 (1H, s), 7.59 (1H, s). Picrate: Red needles, mp 128-130°C (C_6H_6-hexane). Anal. Calcd for $C_{10}H_{11}N \cdot C_6H_3N_3O_7$: C, 51.34; H, 3.77; N, 14.97. Found: C, 51.22; H, 3.89; N, 14.91.
15b: Colorless oil. Picrate, mp 155-156°C (C_6H_6) (lit.,[19] mp 152°C).
15d: Colorless prisms, mp 40-41°C (hexane, 0°C). Anal. Calcd for $C_{12}H_{15}N$: C, 83.18; H, 8.73; N, 8.09. Found: C, 83.34; H, 8.77; N, 8.07. *Ms m/z*: 173 (M^+). Nmr ($CDCl_3$) δ: 1.26 (6H, t, J=7.5 Hz), 2.65 (2H, q, J=7.5 Hz), 2.69 (2H, q, J=7.5 Hz), 6.38, (1H, dd, J=3.5, 2 Hz), 6.82 (1H, s), 6.86 (1H, dd, J=3.5, 3.5 Hz), 7.24 (1H, s), 7.56 (1H, s).
15g: Colorless prisms, mp 92.5-93.5°C (hexane-CH_2Cl_2) (lit.,[20] mp 88-89°C).

Oxidation of 11g to 17

Oxidation of 11g (122 mg) was carried out according to the literature.[10] Recrystallization of the resulting material (134 mg) from CH_2Cl_2-MeOH, followed by PTLC of the mother liquor (2% MeOH-CH_2Cl_2) afforded 17 (114 mg, 88%), colorless prisms, mp 191.5-192°C. Anal. Calcd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.69; H, 6.42; N, 5.49. Ms *m/z*: 263 (M^+). Ir (KBr) cm^{-1}: 1745, 1681, 1632. Nmr ($CDCl_3$) δ: 3.85 (3H, s), 4.92 (1H, s), 6.01-6.13 (1H, m), 6.14 (1H, dd, J=3.5, 3.5 Hz), 7.17-7.31 (1H, m), 9.29-11.37 (1H, exchangeable with D_2O).

Preparation of 18

To a solution of 17 (160 mg) and Et_3N (0.6 ml) in THF (8 ml), 5% ClCOOEt in THF (1.40 ml) was added at -20°C. After stirring for 5 min, methyl (±)-*N*-methylvalinate hydrobromide[21] (282 mg) was added and stirring was continued at -20°C for 15 min and at room temperature for 38 h. Sat. $NaHCO_3$-H_2O was added and the whole was shaken with CH_2Cl_2. The aqueous layer was acidified (pH 5) with 30% HOAc-H_2O and extracted with CH_2Cl_2. Usual work-up, followed by purification by PTLC [hexane-EtOAc (2:1) for 18 and then 2% MeOH-CH_2Cl_2 for the recovery of 17 (31 mg, 19%)] furnished 18 (184 mg, 78%), colorless syrup. Ms *m/z*: 390 (M^+). Ir ($CHCl_3$) cm^{-1}: 1746, 1621.

Indole Cyclization of 18 with $POCl_3$-PCl_3

A mixture of $POCl_3$ and PCl_3 (5:1) (0.5 ml) was heated at 50°C for 1 h. To this was added a solution of 18 (35 mg) in CH_2Cl_2 (2.5 ml) and the whole was refluxed for 3 h under N_2 atmosphere. After cooling at 0°C, the mixture was poured into sat. $NaHCO_3$-H_2O and stirred vigorously at room temperature for 15 min. Filtration, extraction with CH_2Cl_2 and usual work-up, followed by purification by PTLC [hexane-EtOAc (6:1)] afforded 19 (22 mg, 66%), colorless needles, mp 101-102°C (MeOH) and 20 (0.5 mg, 2%) along with the recovery of 18 (3 mg, 9%). 19: Anal. Calcd for $C_{21}H_{28}N_2O_4$: C, 67.72; H, 7.58; N, 7.52. Found: C, 67.75; H, 7.50; N, 7.54. Ms *m/z*: 372 (M^+). Ir (KBr) cm^{-1}: 1746, 1729. Nmr ($CDCl_3$) δ: 0.90 (3H, d, J=6.5 Hz), 1.04 (3H, d, J=6.5 Hz), 2.33 (1H, dqq, J=10.5, 6.5, 6.5 Hz), 2.95 (3H, s), 3.64 (3H, s), 3.78 (1H, d, J=10.5 Hz), 3.95 (3H, s), 6.57 (1H, s), 6.71 (1H, d, J=4 Hz), 7.39 (1H, d, J=4 Hz). 20: Ms *m/z*: 258 (M^+). Ir ($CHCl_3$) cm^{-1}: 1751. Nmr ($CDCl_3$) δ: *ca.* 2.37-2.91 (1H, exchangeable with D_2O), 2.91 (3H, s), 3.94 (3H, s), 6.23 (1H, s), 6.42 (1H, d, J=4 Hz), 7.35 (1H, d, J=4 Hz).

Preparation of 23

The compound 22 (7.40 g) was reacted with the Grignard reagent prepared from Mg (1.80 g) and 20% vinyl bromide in THF (29.0 ml) to give a crude product (9.1 g), which was oxidized with PCC (41.5 g) according to the literature.[12] Distillation of the reaction mixture afforded 23 (4.58 g, 53%), colorless oil, bp 89-94°C/5 mm Hg. Ir (neat) cm^{-1}: 1672, 1633. Nmr ($CDCl_3$) δ: 0.95 (6H, s), 0.99 (6H, s), 1.38 (2H, s), 2.05 (2H, s), 2.44 (2H, s), 5.93 (1H, d, J=8.5 Hz), 9.97 (1H, d, J=8.5 Hz).

Formation of 26

To a CH_2Cl_2 solution (90 ml) of 2, prepared from 1 (568 mg) and methylene blue (25 mg) was added at -70°C a CH_2Cl_2 solution (5 ml) of 24 (2.30 g), prepared from 23 (1.500 g), TMSCl (7.2 ml), Et_3N (12.0 ml), and $ZnCl_2$ (90 mg) in C_6H_6 (30 ml). A EtOAc solution (40 ml) of $SnCl_2$ (1.025 g) was added dropwise during 15 min, and the mixture was stirred at -70 – -74°C for 30 min; -20°C, 30 min; and room temperature, 1 h. Column chromatagraphy [hexane-EtOAc (49:1)] and PTLC [hexane-EtOAc (97:3)] afforded 26 (408 mg, 33%), unstable colorless oil. Ms *m/z*: 271 (M^+). Ir (film) cm^{-1}: 1765, 1688, 1620. Nmr ($CDCl_3$) δ: 1.02 (6H, s), 1.08 (6H, s), 1.40 (2H, s), 1.99 (2H, d, J=1.5 Hz), 5.72 (1H, t, J=1.5 Hz), 6.33 (1H, dd, J=3.5, 1.5 Hz), 6.52 (1H, dd, J=3.5, 3.5 Hz), 6.76 (1H, s), 7.44 (1H, dd, J=3.5, 1.5 Hz).

Preparation of 7-Methyl-2,6-octadienal (30)

The aldehyde (29) (860 mg) was reacted with Ph_3P=CHCHO (2.530 g) in C_6H_6 (25 ml), according to the literature.[18] Column chromatography (hexane) afforded 30 (664 mg, 63%), colorless oil. Ir (neat) cm^{-1}: 1693, 1640. Nmr ($CDCl_3$) δ: 1.61 (3H, s), 1.70 (3H, s), 5.07 (1H, t, J=6.5 Hz), 6.08 (1H, dd, J=16, 8 Hz), 6.80 (1H, dt, J=16, 6 Hz), 9.45 (1H, d, J=8 Hz).

Preparation of 32

A CH_2Cl_2 (5 ml) solution of a crude compound (31) (1.65 g), prepared from 30 (566 mg), TMSCl (2.5 ml), Et_3N (5.0 ml), and $ZnCl_2$ (43 mg) in C_6H_6 (15 ml), was added to a CH_2Cl_2 solution (80 ml) of 2, prepared from 1 (405 mg) and methylene blue (30 mg), dropwise at -80°C. An EtOAc solution (50 ml) of $SnCl_2$ (790 mg) was added dropwise during 10 min, and the mixture was further stirred at -80°C for 30 min; 0°C, 1.5 h; and room temperature, 1.5 h. Column chromatography [hexane-CH_2Cl_2 (1:1)] afforded 32 (234 mg, 28%), slightly yellow oil. Ms *m/z*: 261 (M^+). Ir (film) cm^{-1}: 1755, 1693, 1632. Nmr ($CDCl_3$) δ: 1.60 (3H, s), 1.67 (3H, s), 2.49 (2H, dd, J=7, 7 Hz), 3.88 (3H, s), 4.43 (1H, dt, J=7, 7 Hz), 5.10 (1H, t, J=7 Hz), 5.90 (1H, ddd, J=16, 7.5, 1 Hz), 6.02-6.17 (2H, m), 6.89 (1H, dd, J=16, 7 Hz), 7.20 (1H, dd, J=3, 2 Hz), 9.46 (1H, d, J=7.5 Hz).

Preparation of 7-(3-Methyl-2-butenyl)indole (27)

A solution of 32 (61 mg) and *p*-TsOH·H_2O (9 mg) in C_6H_6 (4 ml) was refluxed for 10 min. After cooling, sat. $NaHCO_3$-H_2O was added and the mixture was extracted with CH_2Cl_2. Usual work-up and PTLC [hexane-CH_2Cl_2 (2:1)] gave 1-methoxycarbonylindole (14i) (10.5 mg, 26%) and the mixture of 33 and 34 (*ca.* 6:1) (27 mg). The latter was hydrolyzed with 2% KOH in MeOH-DME-H_2O (2:2:1) (2 ml) by stirring at room temperature for 45 min. Addition of sat. NH_4Cl-H_2O, extraction with CH_2Cl_2, usual work-up and PTLC [hexane-CH_2Cl_2 (4:1), twice] furnished 27 (17.5 mg, 40%), colorless prisms, mp 43.5-44.5°C (hexane, -20°C), undepressed on admixture with the authentic scales,[14] and 35 (3 mg, 7%), colorless syrup. 27: Anal. Calcd for $C_{13}H_{15}$-

N: C, 84.28; H, 8.16; N, 7.56. Found: C, 83.91; H, 8.36; N, 7.45. Ms *m/z* (%): 185 (M^+, 93), 170 (100), 155 (25), 130 (76), 117 (31). Ir (KBr) cm^{-1}: 3400, 1606, 1588, 1573. Nmr ($CDCl_3$) δ: 1.76 (3H, s), 1.78 (3H, s), 3.54 (2H, d, J=7 Hz), 5.38 (1H, tqq, J=7, 1.5, 1.5 Hz), 6.51 (1H, dd, J=3.5, 2 Hz), 6.89-7.07 (2H, m), 7.12 (1H, dd, J=3.5, 2.5 Hz), 7.36-7.60 (1H, m), 8.07 (1H, s). ^{13}C Nmr (67.8 MHz, $CDCl_3$) δ: 17.9 (q), 25.7 (q), 30.8 (t), 102.9 (d), 118.7 (d), 120.0 (d), 121.5 (d), 122.2 (d), 123.8 (d), 123.9 (s), 127.8 (s), 133.3 (s), 135.1 (s). Trinitrobenzene adduct: Orange needles, mp 115-115.5°C (EtOH) (lit.[13], mp 110.5-111°C). Anal. Calcd for $C_{13}H_{15}N \cdot C_6H_3N_3O_6$: C, 57.28; H, 4.55; N, 14.07. Found: C, 57.34; H, 4.69; N, 13.66.

35: Ms *m/z*: 185 (M^+). Ir ($CHCl_3$) cm^{-1}: 3500, 1647. Nmr ($CDCl_3$) δ: 1.80 (3H, s), 2.31-2.57 (2H, m), 2.86-3.12 (2H, m), 4.79 (2H, s), 6.54 (1H, dd, J=3.5, 2 Hz), 6.96-7.10 (2H, m), 7.12 (1H, dd, J=3.5, 3.5 Hz), 7.37-7.60 (1H, m), 8.11 (1H, s).

Preparation of 6- and 5-(3-Methyl-2-butenyl)indoles (28 and 38)

A solution of 32 (32 mg) in CH_2Cl_2 (3 ml) was treated with TMSOTf (0.04 ml) at -77°C under N_2 atmosphere for 12 min. The reaction mixture was quenched with sat. $NaHCO_3$-H_2O and it was extracted with CH_2Cl_2. Usual work-up and PTLC [hexane-CH_2Cl_2 (6:1), three times] furnished a mixture containing 37 (17 mg) and 38 (2.5 mg, 8%), colorless syrup. Ms *m/z*: 243 (M^+). Ir ($CHCl_3$) cm^{-1}: 1737. Nmr (CCl_4) δ: 1.74 (6H, s), 3.36 (2H, d, J=7 Hz), 4.00 (3H, s), 5.31 (1H, t, J=7 Hz), 6.41 (1H, d, J=4 Hz), 7.02 (1H, d, J=9 Hz), 7.21 (1H, s), 7.46 (1H, d, J=4 Hz), 7.97 (1H, d, J=9 Hz). The mixture containing 37 was hydrolyzed with 2% KOH in MeOH-DME-H_2O (2:2:1) (2 ml) at room temperature for 40 min. Sat. NH_4Cl-H_2O was added and the mixture was extracted with CH_2Cl_2. Usual wor-up and PTLC [hexane-CH_2Cl_2 (4:1)] afforded 28 (8 mg, 35%), colorless oil. Ms *m/z* (%): 185 (M^+, 81), 170 (100), 155 (25), 130 (41), 117 (23). Ir (CCl_4) cm^{-1}: 3510, 1628, 1575. Nmr ($CDCl_3$) δ: 1.75 (6H, s), 3.44 (2H, d, J=7.5 Hz), 5.37 (1H, t, J=7.5 Hz), 6.47 (1H, ddd, J=3.5, 2, 1 Hz), 6.94 (1H, dd, J=8.5, 1.5 Hz), 7.08 (1H, dd, J=3.5, 2.5 Hz), 7.15 (1H, s), 7.52 (1H, d, J=8.5 Hz), 7.94 (1H, s). Trinitrobenzene adduct: Light orange needles, mp 108-109°C [EtOH-H_2O (7:3)] (lit.[15a], mp 106°C; lit.[15b], mp 111.5-113°C). Anal. Calcd for $C_{13}H_{15}N \cdot C_6H_3N_3O_6$: C, 57.28; H, 4.55; N, 14.07. Found: C, 57.11; H, 4.79; N, 13.95.

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