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A NEW SYNTHETIC METHOD FOR THE FRAMEWORK OF ASPIDOSPERMA ALKALOIDS USING SINGLET OXYGEN CHEMISTRY

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Abstract—A singlet oxygen adduct of 1-benzyloxycarbonyl-1,2-dihydro-5-(2-methyl-1,3-dioxolan-2-yl)pyridine (**21**) was treated with indole in the presence of stannous chloride to yield directly the complex compound **22**, which will act as a suitable starting material for the synthesis of various kinds of indole alkaloids. Further transformation from **22**, including a new device for construction of the aspidosperma framework, was investigated and pentacyclic compounds (**25**) (Y = H and OH) were synthesized in moderate yields. The structure of **25** (Y = H) = **38** was confirmed by correlation with 1-acetyl-20-deethylaspidospermidine (**44**). Determination of the structure of a by-product (**39**) was carried out by single crystal X-ray analysis.

In 1979 we reported a novel type of reaction using singlet oxygen chemistry, in which a C—C bond was formed on the piperidine ring.[1] The reaction consists of two successive operations which are carried out in one pot (Chart 1). (i) The sensitized photo-oxygenation reaction is applied to dihydropyridine derivatives (**2**)[2,3] obtained from variously substituted pyridines (**1**). For convenience to the next step, dichloromethane† is used as a solvent and the oxygenation is performed by bubbling dry oxygen at *ca* −50° into a solution of **2** using a 500 W halogen lamp as a light source and methylene blue as a sensitizer.[4] The (4 + 2) adduct (**3**) of singlet oxygen is formed as a single product, as shown when the mixture is examined by TLC.‡ The stereochemistry of the endoperoxide bridge in **3** is determined to be *trans* with respect to the substituent R^2. This high selectivity is probably due to the exclusive approach from the opposite side of R^2 of the bulky dye-stuff on which the singlet oxygen is generated.

(ii) Without isolation of **3**, a nucleophile is added to the cooled solution, followed by the addition of a suspension of stannous chloride in ethyl acetate. The temperature of the reaction mixture is then gradually raised to *ca* −10°, resulting in the formation of a reaction product. Carbon nucleophiles, such as enol ethers, indole, furan and pyrrole derivatives can be caused to react with **3** to produce mostly 2,6-*cis* substituted derivatives (**4**), accompanied by occasional formation of 2,6-*trans* derivatives (**5**) as by-products. Predominant formation of **4** is postulated to originate from the S_N2 attack of a nucleophile on the activated centre at the C-6 position of the possible intermediate (**6**).

The important features of this reaction are: (i) introduction of the substituent R is achieved without the use of carbanions; (ii) variously substituted products can be obtained by selecting a combination of starting pyridines and R^2 which designates hydrogen, alkyl, alkenyl or alkynyl groups; (iii) stereochemically definite compounds can be prepared in good yields; and (iv) further structural elaboration is possible by modifying an allyl alcoholic function of **4**. Thus, using

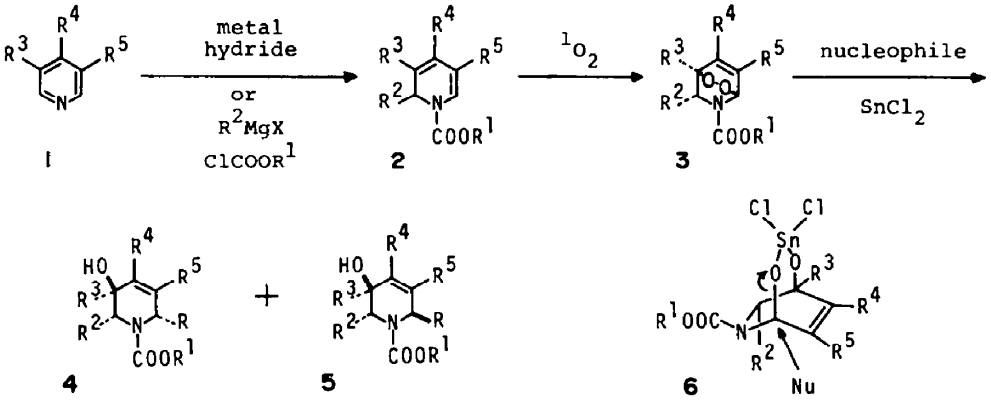


Chart 1.

† Commercial CH_2Cl_2 was washed with H_2O, dried over $CaCl_2$ and distilled in the presence of P_2O_5. Otherwise reaction with MeOH instead of a carbon nucleophile is inevitable.

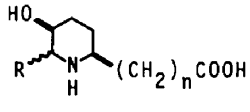
‡ ^{1}H-NMR spectral study of **3** (R^1 = Me, R^2 = R^3 = R^4 = R^5 = H) and **3** (R^2 = $PhCOOCH_2$, R^3 = R^4 = H, R^5 = CN, N—COPh) confirmed their structures. The latter is stable crystals.[4]

reaction products **4** and **5** as starting materials, we have accomplished total synthesis of a variety of natural products (Chart 2), such as carpamic acid (**7**),[5] azimic acid (**8**),[5] pseudocarpamic acid (**9**),[6] prosafrinine (**10**),[6] prosophyllin (**11**),[7] prosopinine (**12**),[8] isoprosopinine B (**13**),[8] nupharolutine (**14**),[9] sedacryptine (**15**),[10] 'deoxypalustrine' (**16**),[11]† 'palustrine' (**17**)[12]† cannabisativine (**18**),[13] and epiulein (**19**).[14] A preliminary study of the synthesis of an aspidosperma type of indole alkaloids [15,16] has also been reported.[17]

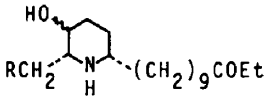
Table 1. Reduction of **20** with metal hydrides in the presence of $PhCH_2OCOCl$ at −70°

Reagent	Solvent	Ratio of 21:26+27[a]
$NaBH_4$	THF–MeOH	2:5
$LiAl(t\text{-}BuO)_3H$	THF	3:2
$NaAl(MeOCH_2CH_2O)_2H_2$	THF	4:1

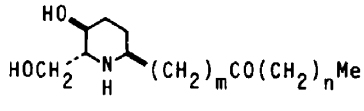
[a] Ratio was estimated from analysis of ^{1}H-NMR signals.



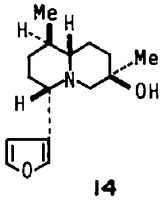
7 R=β-Me n=7
8 R=β-Me n=5
9 R=α-Me n=7



10 R=H α-OH
11 R=OH β-OH



12 m=9 n=1
13 m=7 n=3



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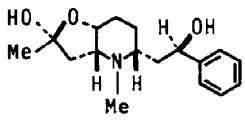

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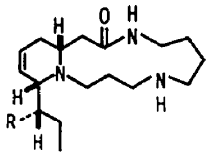
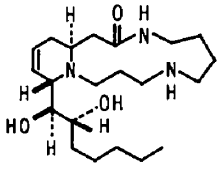


16 R=H
17 R=OH



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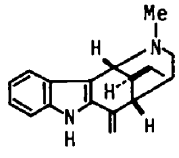

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Chart 2.

In order to develop an alternative, more effective procedure for the preparation of the framework of aspidosperma alkaloids, we envisaged a synthetic route, outlined in Chart 3, applying the above reaction as the key step. For the realization of this scheme, a crucial problem had to be solved beforehand: how in general to prepare 1-alkoxycarbonyl-5-alkyl-1,2-dihydropyridine derivatives, **2** ($R^1 = R^5$ = alkyl, $R^2 = R^3 = R^4$ = H), since the usual procedure[3a] furnished only 1-alkoxycarbonyl-3-alkyl derivatives, **2** ($R^1 = R^3$ = alkyl, $R^2 = R^4 = R^5$ = H).[18]‡ Fortunately, the C-2 position of our starting material (**20**) was sterically congested owing to the neighbouring 2'-methyl-1',3'-dioxolanyl group, so it was anticipated that the desired dihydropyridine derivative (**21**) could be obtained in competition with the formation of 1,4- and 1,2-dihydro derivatives (**26** and **27**) if the reduction was carried out using bulky reagent in the presence of benzyl chloroformate. As shown in Table 1, sodium bis(2-methoxyethoxy)aluminium hydride (Vitride) was found to be suitable and rapid separation over silica gel afforded unstable **21** in 58% yield, while a crude mixture of **26** and **27** was formed in 16% yield.

The sensitized photo-oxygenation reaction on **21** proceeded readily, as expected, and the subsequent treatment with indole in the presence of stannous chloride produced the requisite compound (**22**) in 57% yield, and a by-product (**28**) in 2% yield.

Our main objective in this synthesis is to convert **22** to **23** having an activated C-2 side chain at the N_b group, followed by a novel type of ring closure reaction (**23** → **24** → **25**) which consists of two successive C—C bond formations at the C-3 and C-2 positions in the indole ring during a single operation. This provides a new methodology for the construction of the aspidosperma alkaloids. In practice, our intention was realized as described below.

At first, removal of the OH group in **22** was attempted to simplify further steps (Chart 4). The ethylene ketal group in **22** was hydrolysed to **29** in 93% yield and its methanesulphonyl (mesyl) derivative (**30**) was hydrogenated over 10% Pd–C. Addition of a small amount of triethylamine was essential for the selective cleavage of the O-mesyl group located at the special position of a neighbour of the α,β-unsaturated ketone system. Both the double bond and the N-protecting group remained intact and **31** was obtained in 93.5% yield. Further hydrogenation was carried out by catalysis of PtO_2 to afford **32** and **33** in 56% and 17% yields, respectively. The former compound exhibiting H-2 and H-3 signals at δ 6.45 (d, J = 5.5 Hz) and δ 2.93 (ddd, J = 10.5, 5.5, 5.5 Hz) in its ^{1}H-NMR spectrum is

† We synthesized the compounds bearing proposed structures. Lack of identity required reinvestigation of the structure of natural products.

‡ Multi-step preparation of 1-acyl-5-ethyl-1,2-dihydropyridines was reported.[19]

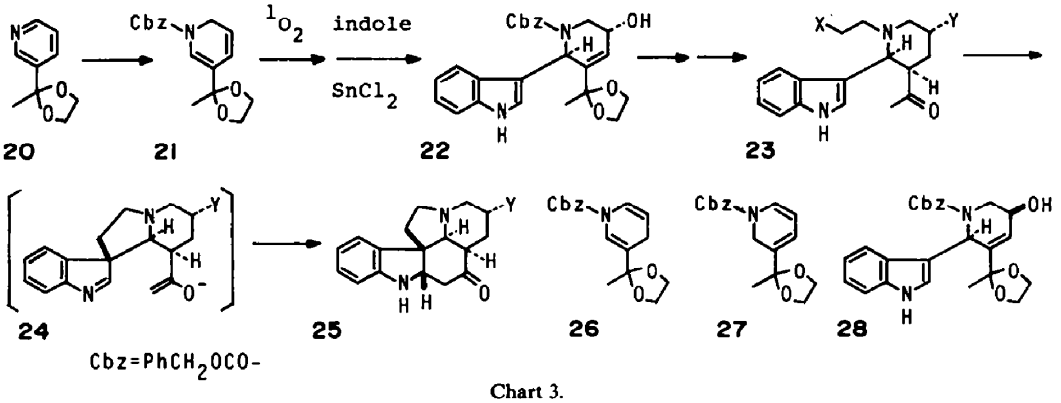

Chart 3.

assigned as a *cis* product, since the indolyl group at the α-position of the N-acylpiperidine system is determined to be axially oriented[20] and, hence, H-3 should be axially situated judging from the above coupling pattern. The benzyloxycarbonyl function of **32** and **33** was split off by 10% Pd–C catalysed hydrogenation to furnish **34** (70% yield) and **35** (57% yield) which were treated with ethylene oxide to give **36** and **37** in 44% and 75% yields, respectively.

As the key reaction of the present synthesis, the O-mesylate of the *cis*-**36** was prepared by treatment with methanesulphonyl chloride and potassium carbonate at room temperature. The desired cyclization reaction was effected only by reaction of potassium bis(trimethylsilyl)amide[21] with the crude mesylate in tetrahydrofuran initially at −70° and then at room temperature (*ca* 20°) to afford the two products, **38** and **39**, in 35% and 3% yields. The same operation applied to *trans*-**37** also produced the same derivatives, **38** and **39**, in 14% and 24% yields, respectively. Both these derivatives exhibit almost identical mass spectra with fragment ions *m/z* 268, 226 and 96, suggesting that the pentacyclic structure can be assigned to **38** and **39** on the basis of the report of Wenkert *et al.*[22]

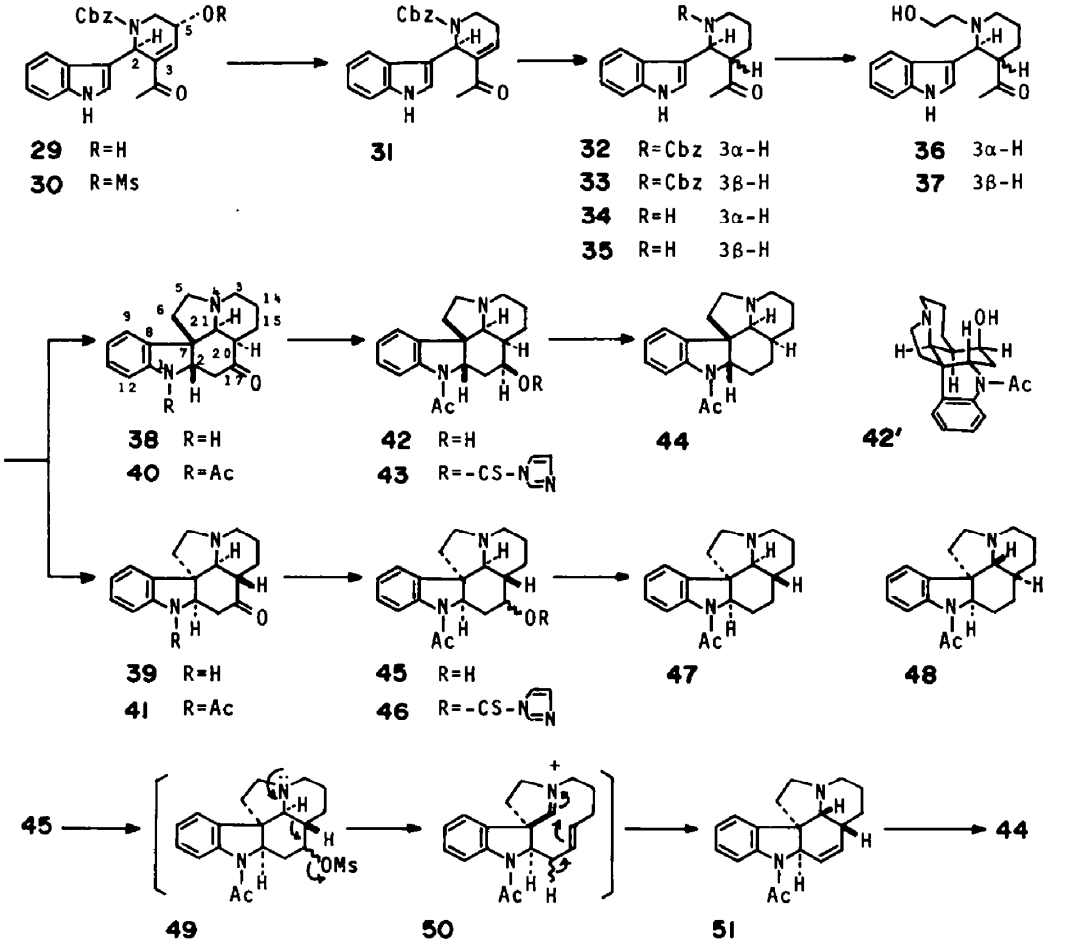

Chart 4.

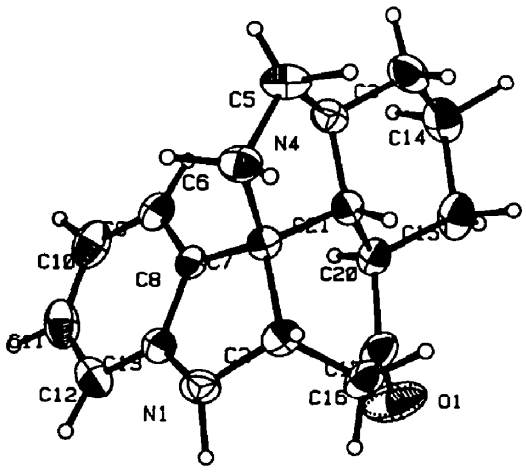

Fig. 1. The ORTEP drawing of **39**.

The structural determination of **38** was attained by correlation with 1-acetyl-20-deethylaspidospermidine (**44**),[23] obtained in our previous study.[17] N-Acetate (**40**), derived from **38** in 73% yield, was reduced with sodium borohydride to give a single compound, **42**, in 81% yield. In its ^{1}H-NMR spectrum, a H-17 signal appears at δ 3.96 as a broad singlet and this indicates the stereochemistry of the OH group as shown, assuming that **42** possesses a conformational structure **42'** analogous to that of (−)-17-O-methylaspidospermine

benzene solution of **45**-mesylate with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) for 12 hr. Successive hydrogenation of **51** took place readily with PtO_2 in 99% yield but, surprisingly, the product was found to be **44**. Therefore, a crystal of **39** was subjected to X-ray crystallographic analysis and the stereostructure (Fig. 1) confirmed the stereochemical arrangement of **39** as a hitherto unencountered pattern in the natural products. As the structure of **45** is definitely established, the above coincidence is now interpreted to occur due to bond cleavage between C-20 and C-21 (**49** → **50**), followed by closing the rings again to form the thermodynamically favourable **51**.

Next, the synthesis of pentacyclic cyclization products (**56**) bearing an OH function at the D ring was attempted starting from the catalytic hydrogenation of **29** with PtO_2 in dimethoxyethane to afford a single product, **52**, in 70% yield (Chart 5). This time, the Pt catalyst approaches the double bond exclusively from the opposite side of the indolyl group, probably due to coordination of the catalyst with the OH group. The OH function of **52** was protected by 1-ethoxy-1-ethyl, benzoyl, or methoxyethoxymethyl (MEM) groups and **53a**, **53b** and **53c** were each converted to **56** and **57**, as shown in Table 2. A benzoate (**55b**) directly afforded **56** (R^1 = H) in 41% yield, which was also obtained from **56a** in 78% yield by acid hydrolysis [1% HCl in MeOH–H_2O (10 : 1), room temp, 10 min] and from **56c** in 39% yield by treatment with titanium tetrachloride[26] in dichloromethane at 0° for 1 hr. Compound **57** (R^1 = H) was prepared from **57a** by hydrolysis with 1% HCl in a mixture of methanol and water (9 : 1).

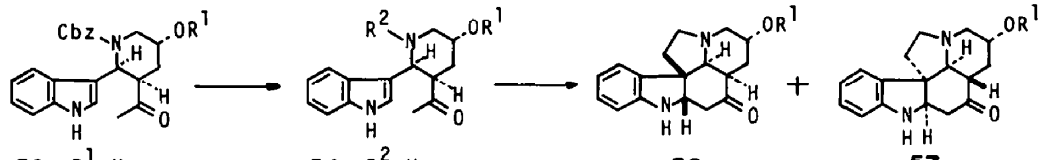

Chart 5.

hydrobromide, which was determined by X-ray analysis.[24] The OH function of **42** was removed by Barton's procedure.[25] Compound **42** was treated with 1,1'-thiocarbonyldiimidazole in hot dichloroethane to afford **43** in 62% yield and this was reduced with tri-n-butyltin hydride to produce, in 93% yield, the final compound, **44**, which was identical with the previous sample in all respects.

In order to get information about the structure of another cyclization product, **39**, the same transformation sequence as above was applied to it by way of **41** (87% yield), **45** with uncharacterized configuration of the OH group (70% yield) and **46** (65% yield), then converting into the corresponding N-acetyldeoxo derivative, **47** (71% yield from **46**). However, **47** was found to be different from the known **48**.[17] Removal of the OH group of **45** was tried by chance through a dehydration route. A compound (**51**) having a disubstituted double bond, evidenced by its ^{1}H-NMR signals, was obtained in 46% yield by gently refluxing a

In conclusion, the present work demonstrates further the utility of our reaction involving the singlet oxygen adducts of 1,2-dihydropyridines in the preparation of complex molecules and opens a way to total synthesis of the aspidosperma type of indole alkaloids of biological interest.

EXPERIMENTAL

All m.p.s were taken on Yanagimoto micro-melting point apparatus and are uncorrected. IR spectra were recorded on Hitachi 215 IR spectrophotometer. ^{1}H-NMR spectra were determined on Varian EM-390 (90 MHz) spectrometer with TMS as an internal standard. Chemical shifts (δ) are expressed in ppm. Coupling constants are reported in Hz and splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br (broad). Mass spectra were obtained on a Hitachi RMS-4 spectrometer with a direct inlet system operating at 70 eV. Merck silica gel PF_{254} was used for preparative TLC. Elemental analyses were performed by Shionogi Research Laboratories. For experiments requiring

Table 2. Reaction conditions and yields for synthesis of **56a–56c** and **57a**

	53	54	55	56	57
a	OEt, TsOH · Pyridine CH_2Cl_2, room temp, 16 hr, 89%	H_2, 10% Pd–C 95% EtOH, room temp, 14 hr, 67%	, MeOH room temp, 14 hr, 81%	(i) MsCl, K_2CO_3, CH_2Cl_2 room temp, 15 hr (ii) $(Me_3Si)_2NK$, THF, −60°, 15 min, 0°, 1.5 hr 28%	22%
b	PhCOCl, Pyridine, room temp, 14 hr, 89%	H_2, 10% Pd–C 95% EtOH, room temp, 14 hr, 73%	 , MeOH room temp, 14 hr, 88.5%	(i) MsCl, K_2CO_3, CH_2Cl_2, room temp, 18 hr (ii) $(Me_3Si)_2$ NK, THF, −60°, 20 min, room temp, 1 hr 41% (R^1 = H)	None
c	MEMCl, iso-Pr_2NEt CH_2Cl_2, room temp, 15 hr, 87%	H_2, 10% Pd–C 95% EtOH room temp, 2 hr, 75%	, MeOH room temp, 14 hr, 85%	(i) MsCl, K_2CO_3, CH_2Cl_2 room temp, 18 hr (ii) $(Me_3Si)_2NK$, THF, −70°, 30 min, room temp, 45 min 32.5%	None

dry solvents, CH_2Cl_2 and dichloroethane were distilled over P_2O_5. THF and Et_3N were distilled over LAH. Pyridine was distilled over CaH_2. Xylene was distilled over Na.

Reduction of **20**. To a stirred soln of **20** (204 mg, 1.27 mmol) in dry THF (10 ml) was added a 30–35% toluene soln of $PhCH_2OCOCl$ (0.8 ml, *ca* 1.6 mmol) at −70°. After 30 min, a soln of 70% NaAl $(MeOCH_2CH_2O)_2H_2$ in toluene (451 mg, 1.56 mmol) in THF (4 ml) was added dropwise at −70° with stirring. After 30 min, the mixture was poured into H_2O and extracted with Et_2O. The extract was dried over Na_2SO_4 and evaporated at reduced pressure at *ca* 30°. The residue was separated by preparative TLC (CH_2Cl_2). Elution of the upper layer gave a mixture of **26** and **27** (59 mg, 16%) as an unstable oil. ^{1}H-NMR ($CDCl_3$) δ 1.47 (s, Me), 2.70–2.87 (m, H-4 of **26**), 3.63–4.10 (m, OCH_2CH_2O), 4.32 (br s, H-2 of **27**), 6.73 (br d, J = 7.5 Hz, H-6 of **27**) and 6.85–7.10 (m, H-2 and H-6 of **26**). Elution of the lower layer gave **21** (214 mg, 58%) as an unstable oil. IR ν_{max}^{film} 1710, 1665 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.49 (3H, s, Me), 3.63–4.10 (4H, m, OCH_2CH_2O), 4.34 (2H, dd, J = 3.5, 2 Hz, H-6), 5.22 (2H, s, OCH_2Ph), 5.55 (1H, br d, J = 10.5 Hz, H-4), 5.94 (1H, ddd, J = 10.5, 3.5, 2 Hz, H-5), 6.92 (1H, br s, H-2), 7.36 (5H, s, Ph).

Sensitized photo-oxygenation of **21**. O_2 gas was bubbled into a soln of **21** (310 mg, 1.03 mmol) and methylene blue (41 mg) in purified CH_2Cl_2 (see footnote on page 2115) (100 ml) at −60° for 30 min, while the mixture was irradiated externally by an Iwasaki 500 W halogen lamp (JD 110 V 500 W-M5). After terminating the irradiation, a soln of indole (133 mg, 1.13 mmol) in purified CH_2Cl_2 (5 ml) and a soln of $SnCl_2$ (251 mg, 1.32 mmol) in dry EtOAc (100 ml) were successively added at −60° with stirring. The mixture was stirred at −60° for 10 min and the cooling bath was removed. After stirring at −60 to −5° for 2 hr, sat $NaHCO_3$ aq was added and the ppt was removed by filtration. The CH_2Cl_2 extract was washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo* to leave a crystalline solid, which was recrystallized from Et_2O–CH_2Cl_2 to afford **22** (224 mg) as colourless prisms, m.p. 192.5–193°. Separation of the mother liquor by preparative TLC (hexane–EtOAc, 1:1) gave a further yield of **22** (32 mg) and a by-product, **28** (9 mg, 2%) as colourless glass. The total yield of **22** was 256 mg (57%). Compound **22**: (Found: C, 69.04; H, 6.05; N, 6.51%. Calc for $C_{25}H_{26}N_2O_5$: C, 69.11; H, 6.03; N, 6.45%.) IR ν_{max}^{KBr} 3355, 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 70°) δ 1.28 (3H, s, Me), 3.31 (1H, dd, J = 15, 4 Hz, H-6), 3.53–3.97 (4H, m, OCH_2CH_2O), 5.23 (2H, s, OCH_2Ph), 6.30 (1H, d, J = 3 Hz, H-4), 6.33 (1H, s, H-2), 7.35 (s, Ph). MS *m/z* 434 $[M]^+$, 416, 345, 343, 299, 255, 237, 91 (base peak). Compound **28**: IR ν_{max}^{KBr} 3420, 1676 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 70°) δ 1.26 (3H, s, Me), 2.99 (1H, dd, J = 13.5, 9 Hz, H-6), 3.47–3.90 (4H, m, OCH_2CH_2O), 5.17 (2H, s, OCH_2Ph), 6.19 (2H, br s, H-2 and H-4), 7.32 (s, Ph). MS *m/z* 434 $[M]^+$, 416, 345, 343, 299, 255, 237, 91 (base peak).

Deketalization of **22**. A soln of **22** (50 mg, 0.12 mmol) in MeOH (10 ml) containing 10% HCl (2 ml) was stirred at room temp for 10 min. The mixture was neutralized with sat $NaHCO_3$ aq and extracted with CH_2Cl_2. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by preparative TLC (hexane–EtOAc, 1:1) to afford **29** (42 mg, 93%) as a colourless glass. IR ν_{max}^{KBr} 3420, 1678 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 2.21 (3H, s, Me), 3.10 (1H, dd, J = 15, 3 Hz, H-6), 4.15 (1H, br d, J = 15 Hz, H-6), 4.23 (1H, br s, H-5), 5.16 (2H, s, OCH_2Ph), 6.58 (1H, br s, H-2), 6.93 (d, J = 5 Hz, H-4), 7.33 (br s, Ph). MS *m/z* 390 $[M]^+$ (base peak), 372, 299, 255, 237, 195, 91.

Formation of **31**. To an ice-cooled soln of **29** (281 mg, 0.72 mmol) in CH_2Cl_2 (5 ml) containing Et_3N (0.5 ml), $MeSO_2Cl$ (0.1 ml, 1.3 mmol) was added with stirring. After 15 min, sat $NaHCO_3$ aq was added. The CH_2Cl_2 extract was washed with 10% HCl, sat $NaHCO_3$ aq and H_2O, and dried over Na_2SO_4. The solvent was evaporated to dryness *in vacuo* at *ca* 30°. A soln of the dried residue of **30** (354 mg) in MeOH (15 ml) containing Et_3N (1 ml) was hydrogenated over 10% Pd–C (71 mg) for 1.5 hr at atmospheric pressure. The catalyst was removed by filtration and the filtrate evaporated *in vacuo*. After the work-up described above, the residue was purified by preparative TLC (hexane–EtOAc, 1:1) to afford 252 mg (93.5%) of **31**. IR ν_{max}^{KBr} 3375, 1695–1664 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 70°) δ 2.17 (s, Me), 2.97 (1H, ddd, J = 13.5, 10.5, 5 Hz, H-6), 4.01 (1H, br dd, J = 13.5, 5 Hz, H-6), 5.13 (1H, d, J = 13.5 Hz) and 5.24 (1H, d, J = 13.5 Hz) (OCH_2Ph), 6.55 (1H, br s, H-2), 7.31 (br s, Ph). MS *m/z* 374 $[M]^+$, 283, 239 (base peak), 195, 168, 91.

Hydrogenation of **31**. A soln of **31** (1.583 g, 4.23 mmol) in MeOH (30 ml) was hydrogenated over PtO_2 (124 mg) for 2 hr at atmospheric pressure. The catalyst was removed by filtration and the filtrate was evaporated *in vacuo*. The residue was chromatographed over silica gel (50 g) with CH_2Cl_2. The first elution afforded the *cis* isomer, **32** (883 mg, 56%), as colourless prisms, m.p. 153.5–154.5°, from MeOH. (Found: C, 73.42; H, 6.26; N, 7.41%. Calc for $C_{23}H_{24}N_2O_3$: C, 73.38; H, 6.43; N, 7.44%.) IR ν_{max}^{KBr} 3410, 1678 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 70°) δ 2.04 (s, Me), 2.68 (1H, ddd, J = 13.5, 13.5, 3 Hz, H-6), 2.93 (1H, ddd, J = 10.5, 5.5, 5.5 Hz, H-3), 3.93 (1H, br d, J = 13.5 Hz, H-6), 5.27 (2H, s, OCH_2Ph), 6.45 (1H, d, J = 5.5 Hz, H-2), 7.36 (s, Ph). MS *m/z* 376 $[M]^+$, 285, 241 (base peak), 225, 199, 91. The second elution afforded **33** (268 mg, 17%) as colourless prisms (from MeOH), m.p. 132–134°. (Found: C, 73.52; H, 6.31; N, 7.37%. Calc for $C_{23}H_{24}N_2O_3$: C, 73.38; H, 6.43; N, 7.44%.) IR ν_{max}^{KBr} 3380, 1714, 1692 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 2.30 (3H, s, Me), 4.02 (1H, br d, J = 13.5 Hz, H-6), 5.20 (2H, s, OCH_2Ph), 6.32 (1H, br s, H-2), 7.32 (s, Ph). MS *m/z* 376 $[M]^+$, 285, 241 (base peak), 225, 199, 91.

Removal of the Cbz group from **32**. A soln of **32** (776 mg, 2.06 mmol) in MeOH (35 ml) containing 10% Pd–C (122 mg) was hydrogenated for 4 hr at atmospheric pressure. The catalyst was removed by filtration and the filtrate evaporated *in vacuo* to leave a crystalline solid, which was recrystallized from $CHCl_3$ to afford **34** (316 mg) as slightly yellow needles, m.p. 146–147°. The mother liquor was purified by preparative TLC (CH_2Cl_2–MeOH, 9:1) to give a further yield (36 mg) of **34**. Total yield was 352 mg (70%). (Found: C, 74.16; H, 7.51; N, 11.39%. Calc for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56%.) IR ν_{max}^{KBr} 3455, 1695 cm^{-1}. ^{1}H-NMR ($CDCl_3$–CD_3OD, 1:4) δ 1.77 (s, Me), 4.42 (1H, d, J = 3.5 Hz, H-2), 7.01 (s, H-2 of indole). MS *m/z* 242 $[M]^+$ (base peak), 223, 199, 171.

Removal of the Cbz group from **33**. A mixture of **33** (74 mg, 0.20 mmol) in 95% EtOH (20 ml) containing 10% HCl (0.8 ml) was hydrogenated over 10% Pd–C (51 mg) at atmospheric pressure. After 4 hr, the catalyst was filtered off and the filtrate neutralized with an ion-exchanger resin IRA-400 (OH^-). The solvent was removed *in vacuo* to leave an oil, which was purified by preparative TLC (CH_2Cl_2–MeOH, 9:1) to afford 27 mg (57%) of **35**. IR $\nu_{max}^{CHCl_3}$ 3500, 3340, 1705 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.71 (s, Me), 4.05 (1H, d, J = 10 Hz, H-2), 6.83–7.35 (4H, m, aromatic H), 7.63–7.84 (1H, m, aromatic H). MS *m/z* 242 $[M]^+$, 223, 199, 171 (base peak).

Treatment of **34** *with ethylene oxide*. A soln of **34** (84 mg, 0.35 mmol) and ethylene oxide (2 ml) in MeOH (15 ml) was stirred at room temp for 14 hr. After removal of the solvent, the residue was purified by preparative TLC (CH_2Cl_2–MeOH, 9:1) to afford **36** (44 mg, 44%) as slightly yellow prisms, m.p. 152.5–153.5° from MeOH. (Found: C, 71.44; H, 7.96; N, 9.79%. Calc for $C_{17}H_{22}N_2O_2$: C, 71.30; H, 7.74; N, 9.78%.) IR ν_{max}^{KBr} 3410, 3250, 1692 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.93 (s, Me), 2.93–3.37 (1H, m, H-3), 4.91 (1H, d, J = 5 Hz, H-2), 7.00–7.43 (4H, m, aromatic H), 7.54–7.78 (1H, m, aromatic H). MS *m/z* 286 $[M]^+$, 255 (base peak).

Treatment of **35** *with ethylene oxide*. A soln of **35** (26 mg, 0.11 mmol) and ethylene oxide (1 ml) in MeOH (10 ml) was stirred at room temp for 6 hr. After removal of the solvent, the residue was purified by preparative TLC (CH_2Cl_2–MeOH, 9:1) to afford 23 mg (75%) of **37** as a slightly yellow oil. IR ν_{max}^{KBr} 3400, 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.61 (s, Me), 2.63 (br s, OH), 3.65 (1H, d, J = 10.5 Hz, H-2), 6.87–7.39 (4H, m, aromatic H), 7.67–7.93 (1H, m, aromatic H). MS *m/z* 286 $[M]^+$, 255 (base peak).

Cyclization of **36**. To a mixture of **36** (100 mg, 0.35 mmol) and anhyd. K_2CO_3 (551 mg) in dry CH_2Cl_2 (25 ml), $MeSO_2Cl$ (63 mg, 0.55 mmol) was added at room temp with stirring. After 16

hr, H_2O was added and the mixture extracted with CH_2Cl_2. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness *in vacuo* at *ca* 30°. To a soln of this dried residue (106 mg) in dry THF (20 ml), $(Me_3Si)_2NK$[21] (241 mg, 1.21 mmol) was added with stirring at −70° under N_2. The mixture was stirred for 45 min at −70° and then for 1 hr at room temp. The mixture was diluted with brine, extracted with CH_2Cl_2–MeOH (9:1) and the extract dried over Na_2SO_4. After evaporation of solvent, the residue was separated by preparative TLC (hexane–EtOAc, 1:1) to afford **38** (33 mg, 35%) and **39** (3 mg, 3%) both as colourless prisms. Compound **38**: m.p. 136–137° (MeOH) (lit.[22] m.p. 113–115°). (Found: C, 75.95; H, 7.40; N, 10.36%. Calc for $C_{17}H_{20}N_2O$: C, 76.08; H, 7.51; N, 10.44%.) IR ν_{max}^{KBr} 3350, 1700 cm^{-1}. IR $\nu_{max}^{CHCl_3}$ 3410, 1712 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 2.12 (d, J = 3 Hz, H-21), 2.52 (dd, J = 17, 3 Hz, H-16), 3.08 (dd, J = 17, 3 Hz, H-16), 3.93 (1H, dd, J = 3, 3 Hz, H-2), 6.59 (1H, d, J = 7 Hz, aromatic H), 6.79 (1H, dd, J = 7, 7 Hz, aromatic H), 6.93–7.22 (2H, m, aromatic H). MS *m/z* 268 $[M]^+$, 226, 130, 96 (base peak). Compound **39**: m.p. 172–173.5° (MeOH–H_2O). (Found: C, 76.39; H, 7.70; N, 10.42%. Calc for $C_{17}H_{20}N_2O$: C, 76.08; H, 7.51; N, 10.44%.) IR ν_{max}^{KBr} 3365, 1695 cm^{-1}. IR $\nu_{max}^{CHCl_3}$ 3400, 1714 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 2.17 (dd, J = 16, 6 Hz, H-16), 2.72 (1H, dd, J = 16, 6 Hz, H-16), 3.88 (1H, dd, J = 6, 6 Hz, H-2), 6.54–6.87 (2H, m, aromatic H), 7.06 (1H, dd, J = 7.5, 7.5 Hz, aromatic H), 7.62 (1H, d, J = 7.5 Hz, aromatic H). MS *m/z* 268 $[M]^+$, 226, 130, 96 (base peak).

Cyclization of **37**. To a stirred mixture of **37** (124 mg, 0.434 mmol) and anhyd. K_2CO_3 (511 mg) in CH_2Cl_2 (20 ml), $MeSO_2Cl$ (0.1 ml, 0.8 mmol) was added at room temp. After stirring for 19 hr, the mixture was treated as above. To a soln of the dried residue (161 mg) in dry THF (25 ml), $(Me_3Si)_2NK$[21] (312 mg, 1.57 mmol) was added at −70° with stirring under N_2. After 20 min, the cooling bath was removed and then the mixture was stirred at room temp for 40 min. After work-up as above, the crude product was separated by preparative TLC (hexane–EtOAc, 3:2) to afford 16 mg (14%) of **38** and 28 mg (24%) of **39** both as colourless prisms.

Acetylation of **38**. A soln of **38** (32 mg, 0.12 mmol) and Ac_2O (0.7 ml) in pyridine (1 ml) was stirred at room temp for 3 hr. The mixture was neutralized with sat $NaHCO_3$ aq and extracted with CH_2Cl_2. The extract was washed with H_2O and dried over Na_2SO_4. Removal of the solvent gave an oil which was purified by preparative TLC (hexane–EtOAc, 1:1) to afford 27 mg (73%) of **40**. IR $\nu_{max}^{CHCl_3}$ 1720, 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 2.30 (s, Me), 2.36 (dd, J = 15, 9 Hz, H-16), 2.83 (dd, J = 15, 6 Hz, H-16), 4.54 (1H, dd, J = 9, 6 Hz, H-2), 6.97–7.42 (3H, m, aromatic H), 7.94 (1H, br d, J = 7.5 Hz, H-12). MS *m/z* 310 $[M]^+$, 268, 144, 130, 96 (base peak).

Acetylation of **39**. A soln of **39** (17 mg, 0.63 mmol) and Ac_2O (0.5 ml) in pyridine (0.8 ml) was stirred at room temp for 3 hr. After the usual work-up, the residue was purified by preparative TLC (hexane–EtOAc, 1:1) to give 17 mg (87%) of **41**. IR $\nu_{max}^{CHCl_3}$ 1716, 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 70°) δ 2.30 (s, Me), 2.92 (1H, dd, J = 17, 7.5 Hz, H-16), 4.18–5.03 (1H, br s, H-2), 6.87 7.36 (2H, m, aromatic H), 7.80 (1H, d, J = 7.5 Hz, aromatic H), 7.50–8.37 (1H, br s, aromatic H). MS *m/z* 310 $[M]^+$, 309, 291, 268, 267, 130, 96 (base peak).

Reduction of **40** *with* $NaBH_4$. To a soln of **40** (32 mg, 0.103 mmol) in MeOH (5 ml), $NaBH_4$ (14 mg, 0.37 mmol) was added at room temp with stirring. After 10 min, the mixture was diluted with H_2O, extracted with CH_2Cl_2 and the extract dried over Na_2SO_4. Evaporation of the solvent followed by preparative TLC (PhH–EtOAc, 1:1) gave 26 mg (81%) of **42** as colourless oil. IR $\nu_{max}^{CHCl_3}$ 3270, 1652 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 2.32 (s, Me), 2.78 (1H, br s, H-21), 3.96 (1H, br s, H-17), 4.35 (1H, dd, J = 11, 6 Hz, H-2), 6.90–7.33 (3H, m, aromatic H), 8.12 (1H, br d, J = 7.5 Hz, H-12). MS *m/z* 312 $[M]^+$, 311, 269, 241, 144, 130, 96 (base peak).

Formation of **43**. A mixture of **42** (25 mg, 0.081 mmol) and 1,1′-thiocarbonyldiimidazole (43 mg, 0.24 mmol) in 1,2-dichloroethane (3 ml) was gently refluxed for 3 hr and evaporated *in vacuo*. The residue was purified by preparative TLC (PhH–EtOAc, 2:3) to afford **43** (21 mg, 62%). IR ν_{max}^{KBr} 1664 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 70°) δ 2.20 (3H, s, Me), 3.87–4.55 (1H, br s, H-2), 5.79–5.96 (1H, br s, H-17), 6.90–7.38 (3H, m, aromatic H), 7.06 (1H, br s) and 7.84 (1H, d, J = 1 Hz) (H-4 and H-5 of imidazole), 8.53 (1H, br s, H-2 of imidazole).

Formation of **44**. To a refluxed soln of Bu_3SnH (71 mg, 0.24 mmol) in dry xylene (3 ml) was added dropwise a soln of **43** (20 mg, 0.047 mmol) in dry xylene (3 ml) under N_2. After 2 hr, the solvent was removed under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2–MeOH, 19:1) to afford 13 mg (93%) of **44**. Picrate: m.p. 206–209°. Identification with the authentic sample was confirmed by comparison of IR and NMR spectra and also by admixture of picrate.

Reduction of **41** *with* $NaBH_4$. A mixture of **41** (17 mg, 0.055 mmol) and $NaBH_4$ (10 mg, 0.26 mmol) in MeOH (3 ml) was stirred at room temp for 10 min. After the usual work-up, 12 mg (70%) of **45** was obtained by preparative TLC (PhH–EtOAc, 1:1). IR $\nu_{max}^{CHCl_3}$ 3400, 1646 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 70°) δ 1.51 (br s, OH), 2.28 (s, Me), 3.65–4.82 (1H, br s, H-2), 6.75–7.30 (2H, m, aromatic H), 7.78 (1H, br d, J = 7.5 Hz, H-9 or H-12), 7.83–8.29 (1H, br s, H-9 or H-12). MS *m/z* 312 $[M]^+$, 311, 293, 268, 225, 144, 130, 96 (base peak).

Formation of **46**. A mixture of **45** (25 mg, 0.081 mmol) and 1,1′-thiocarbonyldiimidazole (47 mg, 0.26 mmol) in dichloroethane (3 ml) was gently refluxed for 20 hr under N_2. Removal of the solvent and preparative TLC ($CHCl_3$) afforded 22 mg (65%) of **46**. IR $\nu_{max}^{CHCl_3}$: 1650 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 70°) δ 2.30 (3H, s, Me), 3.90–4.87 (1H, br s, H-2), 5.19–5.55 (1H, br s, H-17), 6.94 (1H, br s) and 7.44 (1H, br s) (H-4 and H-5 of imidazole), 7.84 (d, J = 7.5 Hz, aromatic H), 8.14 (1H, s, H-2 of imidazole).

Formation of **47**. A soln of **46** (20 mg, 0.047 mmol) in dry xylene (3 ml) was added dropwise to a refluxed soln of Bu_3SnH (73 mg, 0.25 mmol) in dry xylene (3 ml). After 2 hr, the solvent was removed *in vacuo*. The residue was purified twice by preparative TLC (PhH–EtOAc, 1:1 and then CH_2Cl_2–MeOH, 99:1) to give 10 mg (71%) of **47**. IR $\nu_{max}^{CHCl_3}$ 1645 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 70°) δ 2.26 (s, Me), 3.73–4.31 (1H, br s, H-2), 6.77–7.31 (2H, m, aromatic H), 7.77 (1H, br d, J = 7 Hz, H-9 or H-12), 7.90–8.30 (1H, br s, H-9 or H-12). MS *m/z* 296 $[M]^+$, 295, 281, 268, 253, 223, 144, 130, 96 (base peak).

Dehydration of **45**. A methanesulphonate was formed from **45** (16 mg, 0.051 mmol), Et_3N (0.3 ml) and $MeSO_2Cl$ (19 mg, 0.17 mmol) in CH_2Cl_2 (4 ml) as above. A soln of the sulphonate and DBU (1.5 ml) in benzene (1.5 ml) was gently refluxed for 12 hr with stirring under N_2. The cooled mixture was diluted with CH_2Cl_2 and washed successively with sat $CuSO_4$ aq, sat $NaHCO_3$ aq and H_2O. The CH_2Cl_2 layer was dried over Na_2SO_4 and evaporated to leave the residue, which was purified by preparative TLC (hexane–EtOAc, 1:1) to give 7 mg (46%) of **51**. IR $\nu_{max}^{CHCl_3}$ 1642 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 70°) δ 2.32 (3H, s, Me), 4.40–4.84 (1H, br s, H-2), 5.57 (2H, br s, olefinic protons), 6.79–7.28 (2H, m, aromatic H), 7.70 (1H, br d, J = 7 Hz, H-9 or H-12), 7.87–8.27 (1H, br s, H-9 or H-12). MS *m/z* 294 $[M]^+$ (base peak), 293, 279, 266, 251, 223, 180, 167.

Hydrogenation of **51**. A soln of **51** (6 mg) in MeOH (20 ml) was hydrogenated over PtO_2 (9 mg) for 11 hr at atmospheric pressure. After removal of the catalyst, the filtrate was evaporated to dryness. The residue was purified by preparative TLC (CH_2Cl_2–MeOH, 94:6) to afford **44** (6 mg, 99%).

Hydrogenation of **29**. A mixture of **29** (887 mg, 2.27 mmol) and PtO_2 (70 mg) in 1,2-dimethoxyethane (30 ml) was hydrogenated for 3 hr at atmospheric pressure. Filtration of the catalyst followed by concentration gave a crystalline solid, which was recrystallized from CH_2Cl_2 to afford 625 mg (70%) of **52** as colourless prisms, m.p. 205.5–207°. (Found: C, 69.79; H, 6.08; N, 7.10%. Calc for $C_{23}H_{24}N_2O_4$: C, 70.39; H, 6.16; N, 7.14%.) IR ν_{max}^{KBr}: 3410, 1700, 1662 cm^{-1}. ^{1}H-NMR (DMSO–d_6) δ 2.02 (s, Me), 2.72 (1H, br d, J = 15 Hz, H-6), 3.65–4.04 (2H, m, H-5 and H-6), 4.75 (1H, br d, J = 3 Hz, OH), 5.18 (2H, br s, OCH_2Ph), 6.35 (1H, br d, J = 6 Hz, H-2). MS *m/z* 392 $[M]^+$, 374, 301, 257 (base peak), 215, 187, 91.

Compound **53a**. Colourless oil, purified by preparative TLC (hexane–EtOAc, 1:1). IR ν_{max}^{KBr} 3375, 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.10 (3H, br t, J = 7 Hz, Me), 1.22 (3H, br d, J = 6 Hz,

Me), 2.10 (br s, COMe), 2.71 (1H, dd, J = 13.5, 7.5 Hz, H-6), 4.57–5.00 (1H, m, O—CHMe—O), 6.29–6.65 (1H, m, H-2), 7.37 (s, Ph), 7.73 (1H, br d, J = 7.5 Hz, aromatic H). MS *m/z* 464 $[M]^+$ (base peak), 419, 418, 391, 375, 347, 329, 257, 239, 91.

Compound **53b**. Colourless oil, purified by preparative TLC (hexane–EtOAc, 1:1). IR ν_{max}^{KBr}: 3395, 1720–1680 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 2.12 (3H, s, Me), 2.21–2.70 (2H, m, H-4), 2.88 (1H, br d, J = 15 Hz, H-6), 3.24–3.73 (1H, m, H-3), 4.80 (1H, d, J = 12 Hz), 5.16 (1H, d, J = 12 Hz, OCH_2Ph), 6.51 (d, J = 5 Hz), 6.65 (d, J = 6 Hz, H-2 of rotamers). MS *m/z* 496 $[M]^+$, 361, 105, 91 (base peak).

Compound **53c**. Colourless oil, purified by preparative TLC (hexane–EtOAc, 1:1). IR ν_{max}^{film}: 3340, 1715–1670 cm^{-1}. ^{1}H-NMR ($CDCl_3$, 70°) δ 2.10 (s, Me), 2.68 (1H, d, J = 15 Hz, H-6), 3.35 (s, OMe), 5.19 (1H, d, J = 13.5 Hz), 5.34 (1H, d, J = 13.5 Hz, OCH_2Ph), 6.50 (1H, br d, J = 4.5 Hz, H-2), 7.37 (br s, Ph). MS *m/z* 480 $[M]^+$, 405, 404, 391, 375, 345, 269, 241, 239, 91 (base peak).

Compound **54a**. Colourless oil, purified by preparative TLC (CH_2Cl_2–MeOH, 9:1). IR ν_{max}^{KBr} 3380, 1702 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.20 (3H, t, J = 7 Hz, Me), 1.33 (3H, d, J = 6 Hz, Me), 1.70 (3H, s, COMe), 3.88–4.27 (1H, m, H-5), 4.49 (1H, d, J = 4 Hz, H-2), 4.77 (1H, q, J = 6 Hz, O—CHMe—O), 6.93 (1H, br s, H-2 of indole). MS *m/z* 330 $[M]^+$, 301, 285, 257, 242, 241, 187 (base peak), 185.

Compound **54b**. Colourless needles, purified by preparative TLC (PhH–EtOAc, 1:1), followed by recrystallization from Et_2O–CH_2Cl_2, m.p. 168–169°. (Found: C, 72.52; H, 5.96; N, 7.73%. Calc for $C_{22}H_{22}N_2O_3$: C, 72.91; H, 6.12; N, 7.73%.) IR ν_{max}^{KBr}: 3430, 1715, 1703 (sh) cm^{-1}. ^{1}H-NMR ($CDCl_3$–D_2O) δ 1.82 (3H, s, Me), 2.13 (1H, ddd, J = 14, 9, 4.5 Hz, H-4), 2.47 (1H, ddd, J = 14, 4.5, 4.5 Hz, H-4), 2.90 (1H, dd, J = 13.5, 7.5 Hz, H-6), 3.35 (1H, dd, J = 13.5, 4.5 Hz, H-6), 3.54 (1H, ddd, J = 4.5, 4.5, 4 Hz, H-3), 4.68 (1H, d, J = 4 Hz, H-2), 5.43 (1H, dddd, J = 9, 7.5, 4.5, 4.5 Hz, H-5). MS *m/z* 362 $[M]^+$, 240, 222, 197, 187, 105 (base peak).

Compound **54c**. Colourless oil, purified by preparative TLC (CH_2Cl_2–MeOH, 9:1). IR ν_{max}^{film} 3340, 1705 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.72 (3H, s, Me), 1.89 (1H, ddd, J = 13.5, 8, 5 Hz, H-4), 2.25 (1H, ddd, J = 13.5, 4.5, 4.5 Hz, H-4), 2.67 (1H, dd, J = 13.5, 8 Hz, H-6), 3.22 (1H, dd, J = 13.5, 4 Hz, H-6), 3.39 (s, OMe), 4.04 (1H, dddd, J = 8, 8, 4.5, 4 Hz, H-5), 4.54 (1H, d, J = 4.5 Hz, H-2), 4.80 (2H, s, OCH_2O), 6.88 (1H, d, J = 2 Hz, H-2 of indole), 6.97–7.45 (3H, m, aromatic H), 7.45–7.80 (1H, m, aromatic H). MS *m/z* 346 $[M]^+$, 328, 294, 271, 269, 241, 223, 187 (base peak), 185.

Compound **55a**. Colourless oil, purified by preparative TLC (CH_2Cl_2–MeOH, 19:1). IR ν_{max}^{KBr}: 3380, 1707 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.22 (3H, t, J = 7 Hz, Me), 1.34 (d, J = 5 Hz), 1.35 (d, J = 5 Hz, 3H, O—CHMe—O), 1.91 (s, COMe), 3.02 (1H, br s, OH), 4.07 (1H, br s, H-5), 6.90–7.50 (4H, m, aromatic H), 7.50–7.77 (1H, m, aromatic H). MS *m/z* 374 $[M]^+$, 343 (base peak), 341, 329, 301, 286, 285, 271, 253.

Compound **55b**. Colourless needles, recrystallized from MeOH, m.p. 189–190°. (Found: C, 70.58; H, 6.35; N, 6.84%. Calc for $C_{24}H_{26}N_2O_4$: C, 70.91; H, 6.45; N, 6.89%.) IR ν_{max}^{KBr} 3405, 1712 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.80 (3H, s, Me), 2.63 (br s, OH), 5.05 (1H, d, J = 6 Hz, H-2), 5.37–5.57 (1H, m, H-5). MS *m/z* 375, 268, 253, 248, 222, 105 (base peak).

Compound **55c**. Colourless oil, purified by preparative TLC (CH_2Cl_2–MeOH, 19:1). IR ν_{max}^{film} 3350, 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.90 (3H, s, Me), 3.39 (s, OMe), 4.06 (1H, br s, H-5), 4.80 (2H, s, OCH_2O), 4.89 (1H, d, J = 5 Hz, H-2), 6.87–7.41 (4H, m, aromatic H), 7.49–7.76 (1H, m, aromatic H). MS *m/z* 390 $[M]^+$, 374, 359, 315, 285, 231, 188, 169, 130 (base peak).

Compound **56a**. Colourless oil, purified by preparative TLC (hexane–EtOAc, 1:1). IR $\nu_{max}^{CHCl_3}$ 1712 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.20 (t, J = 7 Hz, Me), 1.27 (d, J = 5 Hz, Me), 3.93 (1H, dd, J = 3, 3 Hz, H-2), 4.71 (1H, q, J = 5 Hz, O—CHMe—O), 6.61 (1H, d, J = 7 Hz, aromatic H), 6.80 (1H, dd, J = 7.5, 7 Hz, aromatic H), 6.96–7.22 (2H, m, aromatic H). MS *m/z* 356 $[M]^+$, 283, 267, 242, 184 (base peak), 130, 112.

Compound **57a**. Colourless oil, separated from **56a** by preparative TLC as above. IR ν_{max}^{KBr} 3365, 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.20 (t, J = 6 Hz), 1.23 (t, J = 6 Hz, OCH_2Me), 1.32 (d, J = 5 Hz, O—CHMe—O), 2.74 (1H, dd, J = 16, 7 Hz, H-16), 4.80 (1H, q, J = 5 Hz, O—CHMe—O), 6.47–6.91 (2H, m, aromatic H), 7.07 (1H, ddd, J = 7.5, 7.5, 1 Hz, aromatic H), 7.57 (1H, br d, J = 7.5 Hz, aromatic H). MS *m/z* 356 $[M]^+$, 327, 311, 283, 267, 242, 241, 184 (base peak), 130.

Compound **56** (R^1 = H). Colourless oil, purified by preparative TLC (PhH–EtOAc, 1:1). IR ν_{max}^{KBr} 3375, 1703 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.07 (1H, ddd, J = 13.5, 11.5, 6 Hz, H-15), 2.98 (dd, J = 13.5, 3 Hz, H-16), 3.67 (1H, dddd, J = 11.5, 10.5, 5.5, 5.5 Hz, H-14), 3.93 (1H, dd, J = 3, 3 Hz, H-2), 6.61 (1H, d, J = 7.5 Hz, H-9 or H-12), 6.81 (1H, dd, J = 7.5, 7.5 Hz, H-10 or H-11), 7.09 (1H, dd, J = 7.5, 7.5 Hz, H-10 or H-11), 7.13 (1H, d, J = 7.5 Hz, H-9 or H-12). MS *m/z* 284 $[M]^+$, 242, 154, 144, 130, 112 (base peak).

Compound **56c**. Colourless oil, purified by preparative TLC (hexane–EtOAc, 1:1). IR $\nu_{max}^{CHCl_3}$ 1715 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.11 (1H, ddd, J = 11, 11, 4 Hz, H-15), 2.52 (dd, J = 15, 3 Hz, H-16), 3.02 (1H, dd, J = 15, 3 Hz, H-16), 3.37 (s, OMe), 3.74 (1H, dd, J = 3, 3 Hz, H-2), 4.73 (2H, s, OCH_2O), 6.62 (1H, d, J = 7.5 Hz, H-9 or H-12), 6.80 (1H, br dd, J = 7.5, 7.5 Hz, H-10 or H-11), 7.10 (1H, br dd, J = 7.5, 7.5 Hz, H-10 or H-11), 7.14 (1H, br d, J = 7.5 Hz, H-9 or H-12). MS *m/z* 372 $[M]^+$, 341, 330, 313, 283, 268, 267, 242, 200 (base peak).

Hydrolysis of **57a**. A soln of **57a** (62 mg, 1.74 mmol) in MeOH (4.5 ml) containing 10% HCl (0.5 ml) was stirred at room temp for 5 min. The mixture was neutralized with sat $NaHCO_3$ aq and extracted with CH_2Cl_2. The extract was washed with H_2O, dried over Na_2SO_4 and evaporated to give the residue. Preparative TLC (hexane–EtOAc, 1:1) afforded 36 mg (73%) of **57** (R^1 = H). IR $\nu_{max}^{CHCl_3}$ 3400, 1712 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ 1.17 (1H, ddd, J = 12, 12, 12 Hz, H-15), 3.67–4.08 (2H, m, H-2 and H-14), 6.48–6.87 (2H, m, aromatic H), 7.03 (1H, ddd, J = 7.5, 7.5, 1 Hz, H-10 or H-11), 7.52 (1H, br d, J = 7.5 Hz, H-9 or H-12). MS *m/z* 284 $[M]^+$, 242, 223, 154, 144, 130, 112 (base peak).

Crystallographic data and structure analysis. Compound **39** was shown to have the following crystal data: triclinic, $P\bar{1}$, a = 11.129 (6), b = 14.624 (6), c = 10.465 (4) Å, α = 101.67 (4), β = 84.67 (4), γ = 59.73 (4)° and Z = 4. Lattice constants and intensity data were measured by using graphite-monochromated MoK_α radiation on a Rigaku AFC-5 diffractometer. A total of 4442 unique reflections with Fo > 4σ(Fo) were obtained using the $\omega - 2\theta$ scanning method at 2°/min in 2θ in the range up to 2θ = 55°. The structure was solved by the structure determination package RASA-11 system of Rigaku Corp. based on the direct method.[27] All the C, N, and O atoms were allocated and, at this stage of the work, the anisotropic temp factors were assumed for all the C, N, O atoms except C-8, C-13, C-8′ and C-13′; for these four carbons the isotropic temp factors were assumed. The subsequent structural work[28] was transferred to a Hitac M280H system computer at the Computer Center of Tokyo University, which enables us to refine all the C, N, and O atoms anisotropically and to find all the hydrogen atoms by the difference Fourier synthesis. The resulting structure was finally refined by two cycles of full-matrix least-squares calculation to the R value of 0.058.† The ORTEP drawing[29] of the fully deduced structure is shown in Fig. 1.

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