Studies on the Syntheses of Heterocyclic Compounds. Part 876.[1] The Chiral Total Synthesis of Brevianamide E and Deoxybrevianamide E

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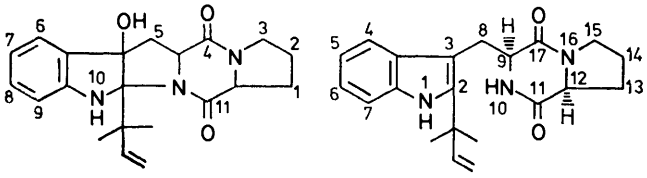
The chiral total synthesis of brevianamide E (1) and deoxybrevianamide E (2) starting from L-proline is described. Condensation of 2-(1,1-dimethylallyl)-3-dimethylaminomethylindole (3) and (−)-methyl 1,4-dioxoperhydropyrrolo[1,2-*a*]pyrazine-3-carboxylate (7) derived from L-proline followed by demethoxycarbonylation gave (−)-deoxybrevianamide E (2) and its epimer (10). Photo-oxygenations of (2) and (10) formed (−)-brevianamide E (14) and its three stereoisomers (15), (16), and (17). The absolute stereochemistry of brevianamide E (14) was determined as 4a*S*,5a*R*,10a*S*,11a*S* by this synthesis.

FROM the culture medium of *Penicillium brevicompactum*, Birch and Wright isolated brevianamide E along with some other fungal metabolites and proposed the structure (1) on the basis of spectroscopic evidence



(1) (2)

SCHEME 1

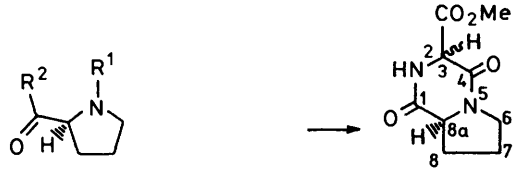
and plausible biogenetic arguments.[2] More recently a degradation product of brevianamide E, deoxybrevianamide E (2), has been found in a toxigenic fungi, *Aspergillus ustus* by Steyn [3] and has been synthesised by Ritchie and Saxton.[4] The absolute configuration of deoxybrevianamide E was assigned as 9*S*,12*S* by the above studies, but the stereochemistry of brevianamide E remained obscure. We here report chiral syntheses of brevianamide E and doxybrevianamide E starting from L-proline, which determine the relative stereochemistry and the absolute configuration of brevianamide E.[5]

2-(1,1-Dimethylallyl)-3-dimethylaminomethylindole (3) was prepared by a modification of the known method, namely the reaction of indole with succinimide–2-(3,3-dimethylallyl)ethylsulphonium chloride [6] followed by reductive desulphurisation with zinc–acetic acid [6] and a Mannich reaction.[7]

The diketopiperazine part of (2) was synthesised from L-proline as follows. Schotten–Baumann reaction of the acid chloride of *N*-benzyloxycarbonyl-L-proline (4) with dimethyl aminomalonate [8] gave the amide (5) in 69% yield. After debenzylation of (5) using 20% palladium–charcoal under a medium pressure of hydrogen in methanol, the resulting amine (6) was heated at 120 °C for 1 h to afford the dioxopiperazine (7) in 40% yield. Furthermore, this cyclisation was found to be effectively catalysed by 2-hydroxypyridine.[9] Thus the desired dioxopiperazine (7) was obtained as a single stereoisomer in 93% yield from the urethane (5), by heating (6) at 70 °C for 1 h in the presence of a catalytic amount of 2-hydroxypyridine.

Condensation of (7) with the gramine derivative (3) was carried out in the presence of 1 molar equivalent of sodium hydride in dimethylformamide at 55—60 °C to give two epimers, (8a) in 22% yield as a syrup and (8b) in 51.7% yield as crystals which were easily separated by chromatography on silica gel.

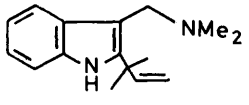
Demethoxycarbonylation of the esters (8a and b) was examined by the following two methods. First, hydrolysis of (8a) with sodium hydroxide in methanol at room temperature for 4.5 h, followed by heating of the resulting carboxylic acid (9a) in dioxan at 60—65 °C for 1.5 h, afforded deoxybrevianamide E (2) and its epimer (10) in 26.5 and 55% yield respectively. The n.m.r. spectrum of the synthetic deoxybrevianamide E was in good agreement with that (donated by Dr.



(4) $R^1 = CO_2CH_2Ph$, $R^2 = OH$ (7)

(5) $R^1 = CO_2CH_2Ph$, $R^2 = NHCH(CO_2Me)_2$

(6) $R^1 = H$, $R^2 = NHCH(CO_2Me)_2$

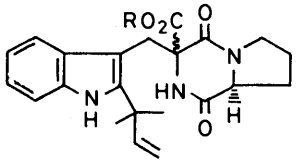


(3)

Steyn) of the natural product. By the same reaction procedure (8b) was converted *via* (9b) into deoxybrevianamide E (2) and its isomer (10) in 26.5 and 59.3% yield respectively. As shown from the above results, the ratio of the formation of the two products (2) and (10) from (8a) and (8b) was not changed by the above process although there were some differences between the optical rotations of the products derived from (8a) and (8b). It was assumed from a kinetic consideration that the major product (8b) obtained by the condensation

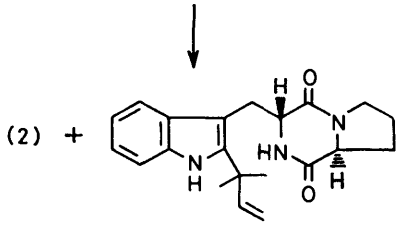
between the gramine (3) and the dioxopiperazine (7) has a β-oriented ester group at C-3 because (8b) should be formed by the approach of the indole molecule from the less-hindered α-side. Therefore some amount of epimerisation seems to occur at C-8a as well as at C-3 during the decarboxylation leading to racemisation. However the racemisation would be small in the case of the conversion of (8a) into deoxybrevianamide E (2) and (8b) into its epimer (10) and this was confirmed by n.m.r. spectroscopy using a chiral shift reagent.

Secondly the demethoxycarbonylation was tried in direct manner. Heating in dimethyl sulphoxide in the presence of sodium chloride [10] gave an unsatisfactory



(8a and b) R = Me

(9a and b) R = H



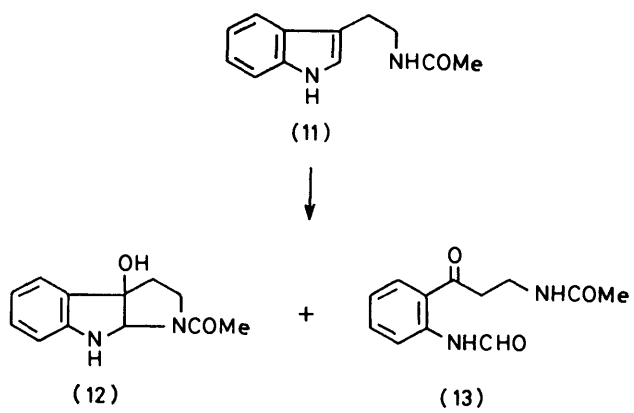
(10)

result. However the use of magnesium chloride [11] instead of sodium chloride produced quantitatively the demethoxycarboxylated product in which deoxybrevianamide E (2) predominated over the isomer (10) (*ca.* 1.5 : 1), although more racemisation was observed than in the first method.

Thus deoxybrevianamide E (2) was gained in 58.8% yield from (8a), by heating at 130—140 °C in the presence of magnesium chloride in dimethyl sulphoxide, along with the epimer (10) in 38.5% yield after chromatography on silica gel.

As a preliminary experiment, photo-oxygenation of N^{ω}-acetyltryptamine (11) was investigated. On irradiation in the presence of Rose Bengal in methanol,[12,13] the pyrrolo[2,3-*b*]indole (12) was formed together with the formylkynuramine (13) in the presence or the absence of pyridine. The yield of (12) was increased when the reaction was carried out at a lower temperature.

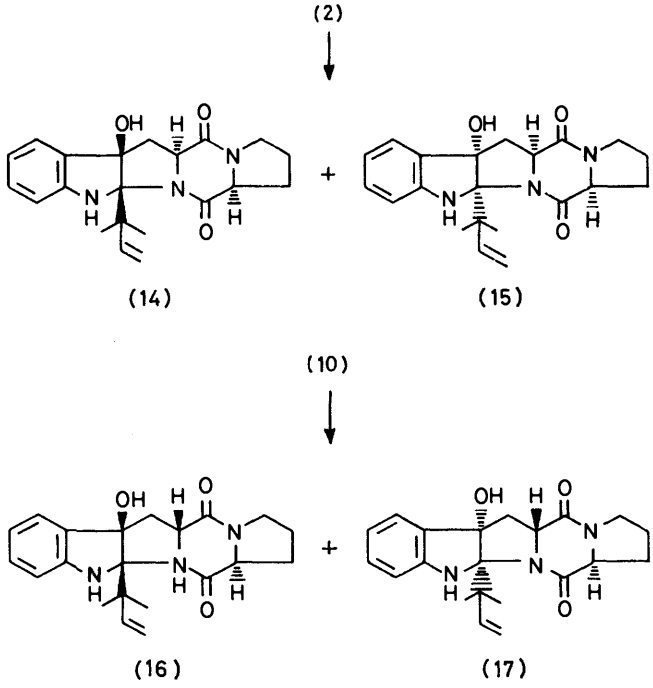
It was predicted from Dreiding models that oxidative cyclisation of the unnatural isomer (10) would be more difficult and produce more strained products than would cyclisation of the natural one. This was found to be the case: irradiation of deoxybrevianamide E (2), synthesised from (8a), in methanol containing Rose Bengal with a 200 W halogen lamp at −8 to −10 °C for 3 h with



SCHEME 2

oxygen bubbling, followed by treatment with dimethyl sulphide, afforded brevianamide E (14) and its isomer (15) in 42 and 20.9% yield, respectively, after separation using h.p.l.c. The spectral data of this synthetic brevianamide E were consistent with those of natural product.[2] The optical rotation of brevianamide E has been reported as $[\alpha]_D^{20}$ −30° (ethanol)[2] compared with our value of −157°. We assume this discrepancy between the reported data and the observed one for the synthetic product due to contamination of the natural product.

The angular hydrogen at the C-4a position of (14) is expected to resonate at higher field than that of (15), because this hydrogen in (15) should be shielded by the ring current, while the hydrogen in (14) should be deshielded by the presence of the *syn* hydroxy-group. Since this proton in brevianamide E was observed at δ 3.66 whereas that in the isomer appeared at δ 4.28, the



SCHEME 3

structures of these compounds were assigned as (14) and (15), respectively.

On the other hand, the dye-sensitised photo-oxygenation of (10) for 7 h, followed by treatment with dimethyl sulphide, yielded a rather unstable mixture of (16) and (17) in the ratio 1 : 2. The stereochemistries of the both compounds were also determined by the chemical shift due to the angular proton [δ 4.61 in (16) and below δ 4.0 in (17)]. The above assignments are further supported from a mechanistic consideration because the approach of singlet oxygen from the less hindered side would form (14) and (17) rather than (15) and (16).

This chiral synthesis determines that brevianamide E is derived from L-tryptamine and L-proline, and the absolute configuration is 4a*S*,5a*R*,10a*S*,11a*S*.

EXPERIMENTAL

I.r. spectra were obtained with a Hitachi 215 spectrometer, n.m.r. spectra with a JEOL-PMX-60 spectrometer (tetramethylsilane as an internal reference), and mass spectra with Hitachi M-52G and JEOL-JMS-01SG-2 spectrometers. Melting points were determined with a Yanaco micro-melting-point apparatus. Optical rotations were determined with a JASCO-DIP-4 automatic polarimeter. High-pressure liquid chromatography was carried out using a Hitachi 635 instrument monitored by u.v. absorption and refractive index measurements.

Dimethyl N-Benzyloxycarbonyl-L-prolylaminomalonate (5).—To a stirred solution of *N*-benzyloxycarbonyl-L-proline (4) (1.198 g, 4.8 mmol) in anhydrous benzene (10 ml) was added dropwise thionyl chloride (1 g) and the mixture was then refluxed for 2 h under nitrogen. Evaporation of the solvent and the excess of thionyl chloride gave an acid chloride as a yellow oil [$\nu_{max.}$ ($CHCl_3$) 1 780 cm^{-1} (COCl)]. To a stirred solution of the above acid chloride in dry ether (4 ml) was added dimethyl aminomalonate [8] (0.73 g, 5 mmol) in dry ether (8 ml) under cooling with ice and the resulting mixture was stirred for 1.5 h below 15 °C. A solution of sodium carbonate (0.42 g) in water (4.2 ml) was then added at a rate such that the reaction temperature was maintained at 15 °C. After stirring for 1 h under ice-cooling, chloroform was added to the reaction mixture and the organic layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent gave *dimethyl N-benzyloxycarbonyl-L-prolylaminomalonate* (5) (1.255 g, 69%) as a yellow solid, which was recrystallised from ethyl acetate–hexane, m.p. 75.5—76 °C, $[\alpha]_D^{18}$ −43° (*c*, 0.1 in EtOH) (Found: C, 57.0; H, 6.0; N, 7.15. $C_{18}H_{25}N_2O_2$ requires C, 57.15; H, 5.85; N, 7.4%); $\nu_{max.}$ ($CHCl_3$) 3 450 (NH), and 1 760, 1 740, and 1 680 (C=O); δ($CDCl_3$) 1.8—2.5 (4 H, m, 2 × CH_2), 3.5—3.7 (2 H, m, >NCH_2), 3.8 (6 H, s, 2 × OMe), 4.4 (1 H, m, 2-H), 5.08 (2 H, s, $ArCH_2$), and 7.3 (5 H, s, 5 × ArH); *m/e* 378 (M^+).

Methyl 1,4-Dioxoperhydropyrrolo[1,2-a]*pyrazine-3-carboxylate* (7).—A solution of the above urethane (5) (1 g, 2.6 mmol) in methanol (150 ml) was shaken for 1 h at 70 °C under 2 atm of hydrogen in the presence of 20% palladium–charcoal (300 mg). After removal of the catalyst by filtration, the filtrate was evaporated and the residue was neutralised with saturated sodium hydrogencarbonate solution and then extracted with chloroform. The organic layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent afforded the amine (6) as a yellow oil, which was stirred for 1 h at 70 °C with a catalytic amount of 2-hydroxypyridine under nitrogen. The reaction mixture was chromatographed on silica gel (30 g) using benzene–ethyl acetate (7 : 3 v/v) to give a yellow oil (1.52 g, 93%), which was crystallised from ethyl acetate–hexane to give the *dioxopiperazine* (7) as needles, m.p. 64—65 °C, $[\alpha]_D^{18}$ −54° (*c*, 0.111 in MeOH) (Found: C, 46.85; H, 6.0; N, 12.4. $C_9H_{12}N_2O_4 \cdot H_2O$ requires C, 46.95; H, 6.15; N, 12.15%); $\nu_{max.}$ ($CHCl_3$) 3 450 (NH), and 1 750, 1 685, and 1 675 (C=O); δ($CDCl_3$) 1.8—2.5 (4 H, m, 2 × CH_2), 3.5—3.7 (2 H, m, >NCH_2), 3.9 (3 H, s, OMe), 4.1—4.4 (1 H, m, 8a-H), 4.8—4.9 (1 H, m, 3-H), and 8.1—8.2 (1 H, m, NH); *m/e* 212 (M^+).

Condensation of the Dioxopiperazine (7) *and* 2-(1,1-*Dimethyallyl*)-3-*dimethylaminomethyl indole* (3).—To a stirred solution of the dioxopiperazine (7) (511 mg, 2.4 mmol) in anhydrous dimethylformamide (20 ml) was added 50% sodium hydride (244 mg, 2.6 mmol) followed by a solution of the gramine (3) [7] (643 mg, 2.4 mmol) in dimethylformamide (5 ml). The mixture was stirred for 1 h at room temperature and then heated for 6 h at 55—60 °C under nitrogen. After addition of an excess of crystalline ammonium chloride under ice cooling followed by evaporation of the solvent, the residue was partitioned between water and chloroform. The organic layer was separated and dried (Na_2SO_4). Evaporation of the solvent afforded an orange oil, which was chromatographed on silica gel (20 g) using dichloromethane–methanol (100 : 1 v/v) to give *methyl* 3-[2-(1,1-*dimethylallyl*)*indol*-3-*ylmethyl*]-1,4-*dioxoperhydropyrrolo*[1,2-a]*pyrazine*-3-*carboxylate* (8a) (218 mg, 22%) as a syrup, $[\alpha]_D^{20}$ −4.7° (*c*, 0.15 in MeOH) (Found: N, 10.15. $C_{23}H_{27}N_3O_4$ requires N, 10.25%); $\nu_{max.}$ ($CHCl_3$) 3 500 and 3 380 (NH), and 1 740, 1 685, and 1 675 (C=O); δ($CDCl_3$) 1.47 (6 H, s, 2 × Me), 1.8—2.6 (4 H, m, 2 × CH_2), 3.83 (3 H, s, OMe), 5.06 (1 H, d, *J* 10 Hz, CH_2=CH), 5.13 (1 H, d, *J* 18 Hz, CH_2=CH), 6.13 (1 H, dd, *J* 10 and 18 Hz, CH_2=C*H*), 5.9 and 8.56 (each 1 H, each s, 2 × NH), and 6.8—7.7 (4 H, m, 4 × ArH) (Found: M^+, 409.199 9. $C_{23}H_{27}N_3O_4$ requires *M*, 409.200 0).

Further elution with dichloromethane–methanol (50 : 1 v/v) gave a syrup (509.8 mg, 51.7%), which was crystallised from ethyl acetate–hexane to give the 3-epi-*monoester* (8b) as needles, m.p. 197—202 °C, $[\alpha]_D^{20}$ −70.8° (*c*, 0.274 in MeOH) (Found: C, 67.55; H, 6.75; N, 10.0. $C_{23}H_{27}N_3O_4$ requires C, 67.45; H, 6.65; H, 10.25%); $\nu_{max.}$ ($CHCl_3$) 3 500 and 3 400 (NH), and 1 745, 1 680, and 1 660 (C=O); δ($CDCl_3$) 1.53 (6 H, s, 2 × Me), 1.5—2.4 (4 H, m, 2 × CH_2), 3.9 (3 H, s, OMe), 5.17 (1 H, d, *J* 10 Hz, CH_2=CH), 5.23 (1 H, d, *J* 18 Hz, CH_2=CH), 6.23 (1 H, dd, *J* 10 and 18 Hz, CH_2=C*H*), 6.36 and 8.16 (each 1 H, each s, 2 × NH), and 7.0—7.8 (4 H, m, 4 × ArH); *m/e* 409 (M^+).

Deoxybrevianamide E (2) *and its Epimer* (10).—(*a*) To a solution of the monoester (8a) (190 mg, 0.5 mmol) in methanol (3 ml) was added a solution of sodium hydroxide (22 mg, 0.55 mmol) in water (0.1 ml) and the mixture was stirred for 4.5 h at room temperature. After evaporation of the solvent below 30 °C, the residue was acidified with 10% acetic acid and extracted with chloroform. The organic layer was washed with water and dried (Na_2SO_4). Evaporation of the solvent afforded the carboxylic acid (9a) as a solid, which was dissolved in dioxan (9 ml). The mixture was stirred for 1.5 h at 60—65 °C. After evaporation of the solvent, the residue was chromatographed on silica gel (15 g) using dichloromethane–methanol (100 : 1 v/v) to give *deoxybrevianamide E* (2) as a solid (47.4 mg,

29%), $[\alpha]_D^{20}$ −43.2° (*c*, 0.132 in $CHCl_3$) (Found: C, 69.95; H, 7.25; N, 11.65. $C_{21}H_{25}N_3O_2 \cdot 0.5H_2O$ requires C, 70.4; H, 7.1; N, 11.5%); $\nu_{max.}$ ($CHCl_3$) 3 500, 3 480, and 3 400 (NH), and 1 690 and 1 670 (C=O); δ($CDCl_3$) 1.55 (6 H, s, 2 × Me), 1.8—2.43 (4 H, m, 2 × CH_2), 3.13 (1 H, dd, *J* 3.4 and 14.9 Hz, 8-H), 3.72 (1 H, dd, *J* 3.4 and 11.4 Hz, 9-H), 5.12 (1 H, d, *J* 17.7 Hz, C*H*$_2$=CH), 5.14 (1 H, d, *J* 9.1 Hz, C*H*$_2$=CH), 6.1 (1 H, dd, *J* 9.1 and 17.7 Hz, CH_2=C*H*), 7.0—7.5 (4 H, m, 4 × ArH), and 6.1 and 8.1 (each 1 H, each s, 2 × NH) (Found: M^+, 351.193 6. $C_{21}H_{25}N_3O_2$ requires *M*, 351.194 7).

Further elution with dichloromethane–methanol (50 : 1 v/v) gave epi-*deoxybrevianamide E* (10) (90 mg, 55%) as a solid, $[\alpha]_D^{20}$ −13.3° (*c*, 0.105 in MeOH) (Found: C, 69.95; H, 7.25; N, 11.65. $C_{21}H_{25}N_3O_2 \cdot 0.5H_2O$ requires C, 71.1; H, 6.85; N, 11.2%); $\nu_{max.}$ ($CHCl_3$) 3 520, 3 490, and 3 440 (NH), and 1 685 and 1 660 (C=O); δ($CDCl_3$) 1.52 (6 H, s, 2 × Me), 1.6—2.08 (4 H, m, 2 × CH_2), 4.2 (1 H, m, 9-H), 5.09 (1 H, d, *J* 11.4 Hz, C*H*$_2$=CH), 5.14 (1 H, d, *J* 17.1 Hz, C*H*$_2$=CH), 6.1 (1 H, dd, *J* 11.4 and 17.1 Hz, CH_2=C*H*), 7.0—7.5 (4 H, m, 4 × ArH), and 5.98 and 8.12 (each 1 H, each s, 2 × NH) (Found: M^+, 351.196 9. $C_{21}H_{25}N_3O_2$ requires *M*, 351.194 7).

(*b*) To a solution of the monoester (9b) (250 mg, 0.6 mmol) in methanol (3 ml) was added a solution of sodium hydroxide (26.4 mg, 0.66 mmol) in water (0.1 ml) and the mixture was stirred for 6.5 h at room temperature. After the same work-up as described above, the resulting carboxylic acid (9b) was dissolved in dioxan (9 ml) and stirred for 1.5 h at 75—80 °C. Evaporation of the solvent gave a syrup, which was chromatographed on silica gel (20 g) using dichloromethane–methanol (100 : 1 v/v) to give *deoxybrevianamide E* (2) (57 mg, 26.5%) as a solid (Found: C, 69.95; H, 7.25; N, 11.65. $C_{21}H_{25}N_3O_2 \cdot 0.5H_2O$ requires C, 70.0; H, 6.8; N, 11.15%) (Found: M^+, 351.196 4. $C_{21}H_{25}N_3O_2$ requires *M*, 351.194 7); $[\alpha]_D^{20}$ −30° (*c*, 0.1 in $CHCl_3$), identical (i.r., n.m.r., and mass spectra) with the sample prepared by method (*a*).

Further elution with dichloromethane–methanol (50 : 1 v/v) gave *epi*-deoxybrevianamide E (10) (127.5 mg, 59.3%) as a solid (Found: M^+, 351.197 8. $C_{21}H_{25}N_3O_2$ requires *M*, 251.194 7), $[\alpha]_D^{20}$ −61.3° (*c*, 0.405 in MeOH), identical (i.r., n.m.r., and mass spectra) with the sample prepared by method (*a*).

(*c*) A mixture of the monoester (8a) (386 mg, 1.1 mmol) and magnesium chloride hexahydrate (0.191 7 g, 1.1 mmol) in dimethyl sulphoxide (1.33 ml) was stirred for 2.5 h at 130—140 °C under nitrogen. The resulting mixture was poured into water and extracted with chloroform. The extract was evaporated to afford a syrup, which was chromatographed on silica gel (10 g) using dichloromethane–methanol (100 : 1 v/v) to give deoxybrevianamide E (2) (194.9 mg, 58.8%) as a solid, $[\alpha]_D^{20}$ −24.7° (*c*, 1.037 in MeOH), identical (spectral data) with the samples prepared by methods (*a*) and (*b*).

Further elution with dichloromethane–methanol (50 : 1 v/v) gave *epi*-deoxybrevianamide E (10) (127.6 mg, 38.5%) as a solid, identical (spectral data) with the samples prepared by methods (*a*) and (*b*).

Photosensitised Oxygenation of N^{ω}-*Acetyltryptamine* (11).—To a solution of N^{ω}-acetyltryptamine (11) (0.3 g, 1.5 mmol) in methanol–pyridine (95 : 5 v/v) (180 ml) was added Rose Bengal (148.5 mg) and the mixture was irradiated with a 200 W halogen lamp for 5 h at 8—10 °C (inner temperature), while a stream of oxygen was bubbled through the reaction vessel. After evaporation of the solvent, the residue was subjected to column chromatography on neutral alumina (grade III) (20 g) using dichloromethane–methanol (100 : 1 v/v). The residue obtained was further chromatographed on silica gel (7 g) using benzene–acetone (9 : 1 v/v) to give *3-acetylamino-2′-formylaminopropiophenone* (13) (38.5 mg, 14.2%) (Found: C, 60.8; H, 6.5; N, 11.3. $C_{12}H_{14}N_2O_3 \cdot 0.25H_2O$ requires C, 60.35; H, 6.1; N, 11.75%), $\nu_{max.}$ ($CHCl_3$) 3 625 and 3 480 (NH), and 1 690 and 1 650 (C=O); δ($CDCl_3$) 2.0 (3 H, s, Me), 3.25—3.86 (4 H, m, 2 × CH_2), 6.4 (1 H, s, NH·CO·Me), 7.06—8.0 (3 H, m, 3 × ArH), 8.53—8.80 (2 H, CHO and ArH), and 11.6 (1 H, s, NHCHO); *m/e* 234 (M^+).

Further elution with benzene–acetone (85 : 15 v/v) gave 1-acetyl-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-*b*]indol-3a-ol (12) (64.7 mg, 28.4%), $\nu_{max.}$ ($CHCl_3$) 3 610 (NH), 3 450 (OH), and 1 640 (C=O); δ($CDCl_3$) 1.9 (3 H, s, Me), 1.9—2.6 (2 H, m, CH_2), 3.05—3.9 (2 H, m, CH_2), 5.30 (1 H, s, NCHN), and 6.53—7.4 (4 H, m, 4 × ArH); *m/e* 218 (M^+) (Found: M^+, 218.108 1. $C_{12}H_{14}N_2O_2$ requires *M*, 218.105 5).

Photosensitised Oxygenation of Deoxybrevianamide E (2).—To a solution of deoxybrevianamide E (2) (40 mg, 0.1 mmol), prepared by method (*a*), in methanol (180 ml) was added Rose Bengal (80 mg) and the mixture was irradiated with a 200 W halogen lamp for 3 h at −8 to −10 °C (inner temperature), while a stream of oxygen was bubbled through the reaction vessel. After addition of dimethyl sulphide (2 ml), the resulting solution was stirred overnight at −10 °C. Evaporation of the solvent below 30 °C gave a reddish oil, which was chromatographed on neutral alumina (grade III) (10 g) using dichloromethane to give a mixture of two compounds as a yellow syrup (26.3 mg, 62.9%), which was separated by h.p.l.c. using Waters μ-Bondapak C_{18} [elution with methanol–water containing 0.5% $(NH_4)_2CO_3$ (2 : 3 v/v) and flow rate 1 ml min^{-1}]. The first eluate (R_t 17.6 min) gave the isomer of brevianamide E (15), $[\alpha]_D^{20}$ +38.3° (*c* 0.060 in EtOH); δ($CDCl_3$) 1.38 (6 H, s, 2 × Me), 1.9—2.3 (4 H, m, 2 × CH_2), 4.0 (1 H, t, 11a-H), 4.28 (1 H, dd, *J* 2.9 and 10 Hz, 4a-H), 5.07 (1 H, dd, *J* 1.5 and 11.4 Hz, C*H*$_2$=CH), 5.16 (1 H, dd, *J* 1.5 and 17.1 Hz, C*H*$_2$=CH), 6.38 (1 H, dd, *J* 11.4 and 17.1 Hz, CH_2=C*H*), 6.35 (1 H, s, NH), and 6.56—7.32 (4 H, m, 4 × ArH) (Found: M^+, 367.190 0. $C_{21}H_{25}N_3O_3$ requires *M*, 367.189 6).

The second eluate (R_t 20 min) afforded brevianamide E (14), $[\alpha]_D^{20}$ −157° (*c* 0.093 in EtOH); δ($CDCl_3$) 1.27 (6 H, s, 2 × Me), 1.8—2.4 (4 H, m, 2 × CH_2), 3.66 (1 H, dd, *J* 2.9 and 11.4 Hz, 4a-H), 3.9 (1 H, t, *J* 7.1 Hz, 11a-H), 5.03 (1 H, dd, *J* 1.5 and 14.4 Hz, C*H*$_2$=CH), 5.07 (1 H, dd, *J* 1.5 and 17.7 Hz, C*H*$_2$=CH), 6.3 (1 H, dd, *J* 14.4 and 17.7 Hz, CH_2=C*H*), 6.31 (1 H, s, NH), and 6.68—7.3 (4 H, m, 4 × ArH) (Found: M^+, 367.187 7. $C_{21}H_{25}N_3O_3$ requires *M*, 367.189 6).

Photosensitised Oxygenation of epi-*Deoxybrevianamide E* (10).—A mixture of *epi*-deoxybrevianamide E (10) (100 mg, 0.3 mmol) and Rose Bengal (150 mg) in methanol–pyridine (19 : 1 v/v, 180 ml) was irradiated with a 200 W halogen lamp for 7 h at 8—15 °C (inner temperature), while a stream of oxygen was bubbled through the reaction vessel. To the reaction solution was added dimethyl sulphide (2 ml) and the mixture was stirred overnight at −10 °C. After evaporation of the solvents below 30 °C, the crude product was chromatographed on neutral alumina (grade III) (15 g) using dichloromethane–methanol (100 : 1 v/v) to give a mixture of two diastereoisomeric compounds in a 2 : 1 ratio

as a yellow oil. Separation of the minor product (16) and the major product (17) was achieved by preparative t.l.c. [Kieselgel $60F_{254}$, benzene–acetone (3 : 2 v/v)]. The zone of R_F *ca.* 0.5 gave an isomer of brevianamide E (17), δ($CDCl_3$) 1.57 (6 H, s, 2 × Me), 1.8—2.3 (4 H, m, 2 × CH_2), 5.17 (1 H, dd, *J* 1 and 12 Hz, CH_2=CH), 5.23 (1 H, dd, *J* 1 and 18 Hz, CH_2=CH), 6.47 (1 H, dd, *J* 12 and 18 Hz, CH_2=C*H*), and 7.2—7.7 (4 H, m, 4 × ArH) (Found: M^+ 367.190 8. $C_{21}H_{25}N_3O_3$ requires *M*, 367.189 6).

The zone of R_F *ca.* 0.44 provided the diastereoisomer of brevianamide E (16), δ($CDCl_3$) 1.30 (3 H, s, Me), 1.42 (3 H, s, Me), 1.75—2.3 (4 H, m, 2 × CH_2), 4.61 (1 H, dd, *J* 6 and 12 Hz, 4a-H), 5.10 (1 H, dd, *J* 1 and 10 Hz, CH_2=CH), 5.20 (1 H, dd, *J* 1 and 20 Hz, CH_2=CH), 6.35 (1 H, dd, *J* 10 and 20 Hz, CH_2=C*H*), and 6.4—7.45 (4 H, m, 4 × ArH); *m/e* 367 (M^+) (Found: M^+, 367.191 9. $C_{21}H_{25}N_3O_3$ requires *M*, 367.189 6).

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