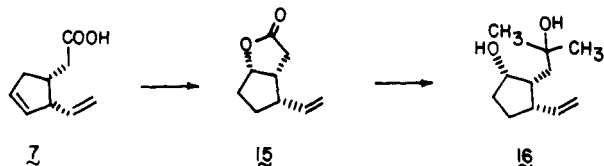


15 (Bu_3SnH , toluene, 80°C) with 95% efficiency. Exposure of **15** to 3 equiv of methyl lithium afforded diol **16** which was directly subjected to NMR examination (CDCl_3 solution).²³ In the presence of ~ 30 mol % of tris[(trifluoromethyl)hydroxymethylene-*d*-camphorato]europium(III), the diastereotopic methyl groups appear as two equally intense sets of twinned singlets at δ 4.0, 3.8, 2.7, and 2.5, sufficiently separated for accurate integration. Evidently, coordination to the lanthanide ion is adequate to cause restricted rotation about the tertiary hydroxyl bearing carbon.

The resolution of ($\pm$)-**7** with *endo*-bornylamine²⁴ afforded a diastereomeric crystalline salt, mp 107 – 108°C , $[\alpha]^{22}_{\text{D}} +114^\circ$ (*c* 2.72, $\text{C}_2\text{H}_5\text{OH}$), after several recrystallizations from acetone. Recovery of the free acid from this salt gave an oily



product, $[\alpha]^{22}_{\text{D}} +151^\circ$ (*c* 3.22, $\text{C}_2\text{H}_5\text{OH}$). The sequential conversion of this material into optically active **8**, $[\alpha]^{22}_{\text{D}} -21.5^\circ$ (*c* 2.34, $\text{C}_2\text{H}_5\text{OH}$), and then into **16**, followed by $\text{Eu}(\text{tfc})_3$ analysis, revealed that enantiomeric enrichment had progressed to a level of $>98\%$ ee. That the desired antipode had been obtained was established by conversion of the acid into (+)-**13**, $[\alpha]^{23}_{\text{D}} +236^\circ$ (*c* 1.06, CHCl_3). When allowance is made for optical purity, the extrapolated rotation for (+)-**13** becomes 241° , in excellent agreement with the $[\alpha]_{\text{D}}$ of an authentic pure sample.²⁵

Thus, a preparatively useful route to a wide selection of prostaglandin hormones from the simplest of achiral conjugated dienes has become available. A noteworthy feature of this synthesis, apart from its simplicity, is the unambiguous placement of four contiguous chiral centers about a cyclopentane ring without the benefit of a stereodirecting group in either **1** or **2**.

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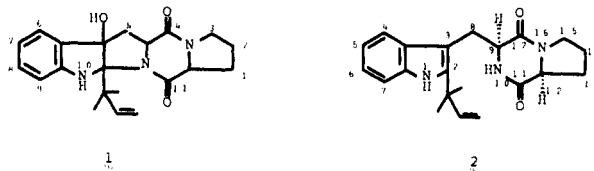
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Asymmetric Total Synthesis of Brevianamide E

Sir:

The structure of brevianamide E, isolated from the culture medium of *Penicillium brevicompactum*, was assigned as **1** mainly on the basis of spectroscopic evidence and plausible biogenetic argument.¹ More recently a degradation product of brevianamide E, deoxybrevianamide E [L-prolyl-2-(1',1'-dimethylallyl)tryptophyldiketopiperazine (**2**)], was found in a toxigenic fungi, *Aspergillus ustus*,² and synthesized.³

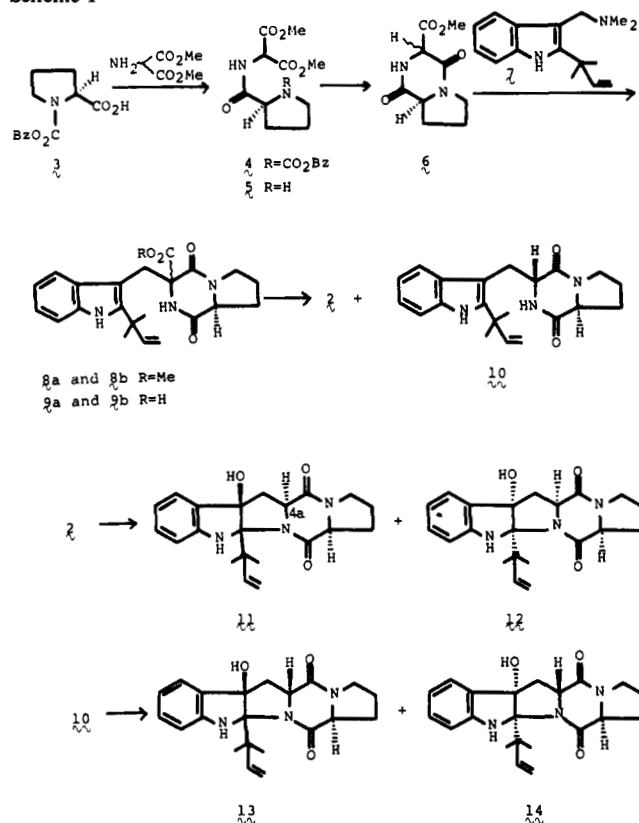


However the stereochemistry of brevianamide E remained obscure. We here report the first total synthesis of optically active brevianamide E, which determines the relative stereochemistry and the absolute configuration.

Schotten-Baumann reaction of the acid chloride of *N*-benzyloxycarbonyl-L-proline (**3**) with dimethyl aminomalonate⁴ gave the amide **4** (Scheme 1), mp 75.5 – 76°C , $[\alpha]^{18}_{\text{D}} -43^\circ$ (*c* 0.1, EtOH), in 69% yield. After debenzyloxycarbonylation of **4**, using 20% palladium/charcoal under 2 atm of hydrogen in methanol, the resulting amine **5** was heated at 120°C for 1 h to afford the diketopiperazine **6** in 40% yield. Furthermore this cyclization was found to be effectively catalyzed by 2-hydroxypyridine.⁵ Thus **6** was obtained as a single stereoisomer, mp 64 – 65°C , $[\alpha]^{18}_{\text{D}} -54^\circ$ (*c* 0.111, MeOH), in 93% yield from **4**, by heating **5** at 70°C for 1 h in the presence of a catalytic amount of 2-hydroxypyridine.

Condensation of **6** with 3-dimethylaminomethyl-2-(1',-

Scheme I



1'-dimethylallyl)indole (7)^{6,7} was carried out by heating the mixture with sodium hydride in dimethylformamide solution at 55–60 °C for 6 h, to give the two stereoisomers, **8a**⁹ (22%), a syrup, $[\alpha]^{20}_D -4.7^\circ$ (*c* 0.15, MeOH), and **8b**¹⁰ (51.7%), mp 197–202 °C, $[\alpha]^{20}_D -70.8^\circ$ (*c* 0.27, MeOH), separated by silica gel chromatography. 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 dioxane at 60–65 °C for 1.5 h, afforded deoxybrevianamide E (**2**,¹¹ 29%), $[\alpha]^{20}_D -43.2^\circ$ (*c* 0.132, CHCl₃), and its epimer **10**¹² (55%), $[\alpha]^{20}_D -13.3^\circ$ (*c* 0.105, MeOH). The NMR spectrum of our synthetic deoxybrevianamide E was in agreement with that (donated by Dr. Steyn) of the natural product. By the same reaction procedure as just described, **8b** was converted via **9b** into deoxybrevianamide E (**2**, 26.5%), $[\alpha]^{20}_D -30^\circ$ (*c* 0.1, CHCl₃), and the isomer **10** (59.3%), $[\alpha]^{20}_D -61.3^\circ$ (*c* 0.405, MeOH). The above results indicate that a small amount of epimerization occurred at the C₁₂ position as well as at the C₉ position during the decarboxylation step.

It was predicted from the examination of Dreiding models that oxidative cyclization of the unnatural (DL) isomer **10** would be more difficult and produce more strained products than would cyclization of the natural (LL) one. This was found to be the case. Namely, irradiation^{13,14} of deoxybrevianamide E (**2**), synthesized from **8a**, in methanol containing Rose Bengal with a 200-W halogen lamp at –8 to ca. –10 °C for 3 h with oxygen bubbling, followed by treatment with dimethyl sulfide, produced brevianamide E (**11**,¹⁵ 42%), $[\alpha]^{20}_D -157^\circ$ (*c* 0.093, EtOH), and its isomer **12**¹⁶ (20.9%), $[\alpha]^{20}_D +38.3^\circ$ (*c* 0.060, EtOH), which were separated by LC using Waters μ -Bondapak C₁₈ and eluting with MeOH–H₂O containing 0.5% (NH₄)₂CO₃ (2:3 v/v). The spectral data of this synthetic brevianamide E were consistent with those of the natural product.¹ The angular hydrogen at the C_{4a} position of **11** is expected to resonate at higher field than that of **12**, because this hydrogen in **11** should be shielded by the ring current, while the same hydrogen in **12** should be deshielded by the presence of the *syn*-hydroxyl group. Since this proton in bre-

vianamide E was observed at 3.66 ppm whereas that in the isomer appeared at 4.28 ppm, the stereostructures of these two compounds were assigned as **11** and **12**, respectively.

On the other hand, the dye-sensitized photooxygenation of **10** under the same condition as above for 7 h, followed by treatment with dimethyl sulfide, gave a rather unstable mixture of **13** and **14** in the ratio of 1:2.¹⁷ The stereochemistries of the both compounds were also determined by the chemical shift due to the angular proton: 4.61 ppm in **13** and <4.0 ppm in **14**. The above assignments are further supported from a mechanistic consideration since the approach of singlet oxygen from the less hindered side would form **11** and **14** rather than **12** and **13**.

This asymmetric synthesis suggests that brevianamide E (**11**) is derived from L-tryptophan and L-proline.

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- (10) IR (CHCl₃) 3500, 3400 (NH), 1745, 1680, and 1660 cm^{–1} (C=O); NMR (CDCl₃) δ 1.53 (6 H, s, 2 Me), 1.5–2.4 (4 H, m, 2 CH₂), 3.9 (3 H, s, OMe), 5.17 (1 H, d, *J* = 10 Hz, CH₂=CH–), 5.23 (1 H, d, *J* = 18 Hz, CH₂=CH–), 6.23 (1 H, dd, *J* = 10, 18 Hz, CH₂=CH–), 6.36 and 8.16 (2 H, s, 2 NH), 7.0–7.8 (4 H, m, Ar H); MS *m/e* 409 (M⁺).
- (11) IR (CHCl₃) 3500, 3480, 3400 (NH), 1690, and 1670 cm^{–1} (C=O); NMR (CDCl₃) δ 1.55 (6 H, s, 2 Me), 1.8–2.43 (4 H, m, 2 CH₂), 3.13 (1 H, dd, *J* = 3.4, 14.9 Hz, C₈ H), 3.72 (1 H, dd, *J* = 11.4, 14.9 Hz, C₈ H), 4.0 (1 H, t, *J* = 7.1 Hz, C₁₂ H), 4.4 (1 H, dd, *J* = 3.4, 11.4 Hz, C₉ H), 5.12 (1 H, d, *J* = 17.7 Hz, CH₂=CH–), 5.14 (1 H, d, *J* = 9.1 Hz, CH₂=CH–), 6.1 (1 H, dd, *J* = 9.1, 17.7 Hz, CH₂=CH–), 7.0–7.5 (4 H, m, 4 Ar H), 6.1 and 8.1 (each 1 H, each s, 2 NH); MS *m/e* 351 (M⁺).
- (12) IR (CHCl₃) 3520, 3490, 3440 (NH), 1685, and 1660 cm^{–1} (C=O); NMR (CDCl₃) δ 1.52 (6 H, s, 2 Me), 1.6–2.08 (4 H, m, 2 CH₂), 4.2 (1 H, m, C₉ H), 5.09 (1 H, d, *J* = 11.4 Hz, CH₂=CH–), 5.14 (1 H, d, *J* = 17.1 Hz, CH₂=CH–), 6.1 (1 H, dd, *J* = 11.4, 17.1 Hz, CH₂=CH–), 7.0–7.5 (4 H, m, 4 Ar H), 5.98 and 8.12 (2 H, s, 2 NH); MS *m/e* 351 (M⁺).
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- (15) NMR (CDCl₃) δ 1.27 (6 H, s, 2 Me), 1.8–2.4 (4 H, m, 2 CH₂), 3.66 (1 H, dd, *J* = 2.9, 11.4 Hz, C_{4a} H), 3.9 (1 H, t, *J* = 7.1 Hz, C_{11a} H), 5.03 (1 H, dd, *J* = 1.5, 14.4 Hz, CH₂=CH–), 5.07 (1 H, dd, *J* = 1.5, 17.7 Hz, CH₂=CH–), 6.3 (1 H, dd, *J* = 14.4, 17.7 Hz, CH₂=CH–), 6.31 (1 H, s, NH), 6.68–7.3 (4 H, m, 4 Ar H); MS *m/e* 367 (M⁺). The optical rotation of brevianamide E was reported as $[\alpha]^{20}_D -30^\circ$ (EtOH).¹ We assume the natural compound was contaminated.
- (16) NMR (CDCl₃) δ 1.38 (6 H, s, 2 Me), 1.9–2.3 (4 H, m, 2 CH₂), 4.0 (1 H, t, C_{11a} H), 4.28 (1 H, dd, *J* = 2.9, 10 Hz, C_{4a} H), 5.07 (1 H, dd, *J* = 1.5, 11.4 Hz, CH₂=CH–), 5.16 (1 H, dd, *J* = 1.5, 11.4 Hz, CH₂=CH–), 6.38 (1 H, dd, *J* = 11.4, 17.1 Hz, CH₂=CH–), 6.35 (1 H, s, NH), 6.56–7.32 (4 H, m, 4 Ar H); MS *m/e* 367 (M⁺).
- (17) Separation of **13** and **14** was achieved by preparative TLC on silica gel. **13**: NMR (CDCl₃) δ 1.30 (3 H, s, Me), 1.42 (3 H, s, Me), 1.75–2.3 (4 H, m, 2 CH₂), 4.61 (1 H, dd, *J* = 6, 12 Hz, C_{4a} H), 5.10 (1 H, dd, *J* = 1, 10 Hz, CH₂=CH–), 5.20 (1 H, dd, *J* = 1, 20 Hz, CH₂=CH–), 6.35 (1 H, dd, *J* = 10, 20 Hz, CH₂=CH–), 6.4–7.45 (4 H, m, 4 Ar H); MS *m/e* 367 (M⁺). **14**: NMR (CDCl₃) δ 1.57 (6 H, s, 2 Me), 1.8–2.3 (4 H, m, 2 CH₂), 5.17 (1 H, dd, *J* = 1, 12 Hz, CH₂=CH–), 5.23 (1 H, dd, *J* = 1, 18 Hz, CH₂=CH–), 6.47 (1 H, dd, *J* = 12, 18 Hz, CH₂=CH–), 7.2–7.7 (4 H, m, 4 Ar H); MS *m/e* 367 (M⁺).

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