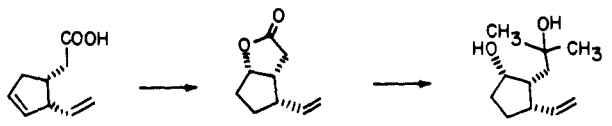
15 (Bu_3SnH, toluene, 80 °C) with 95% efficiency. Exposure of **15** to 3 equiv of methyllithium afforded diol **16** which was directly subjected to NMR examination ($CDCl_3$ solution).[23] In the presence of ~30 mol % of tris[(trifluoromethyl)hydroxymethylene-*d*-camphorato]europium(III), the diastereotopic 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 (±)-**7** with *endo*-bornylamine[24] afforded a diastereomeric crystalline salt, mp 107–108 °C, $[\alpha]^{22}_D$ +114° (*c* 2.72, C_2H_5OH), after several recrystallizations from acetone. Recovery of the free acid from this salt gave an oily



7 **15** **16**

product, $[\alpha]^{22}_D$ +151° (*c* 3.22, C_2H_5OH). The sequential conversion of this material into optically active **8**, $[\alpha]^{22}_D$ −21.5° (*c* 2.34, C_2H_5OH), and then into **16**, followed by $Eu(tfc)_3$ 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**, $[\alpha]^{23}_D$ +236° (*c* 1.06, $CHCl_3$). When allowance is made for optical purity, the extrapolated rotation for (+)-**13** becomes 241°, in excellent agreement with the $[\alpha]_D$ 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**.

Acknowledgment. The authors are indebted to the National Institutes of Health for partial financial support of this work (Grant AI-11490), to Robert Henderson of the Cities Service Co. for a generous quantity of *cis*[2]-1,5-cyclooctadiene, and to Professor E. J. Corey, Dr. Norman A. Nelson, and Dr. Edward D. Brown for ^1H NMR spectra, certain physical constants, and (in the last instance) an authentic sample of **14**.

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(25) We have been informed by Dr. N. A. Nelson (Upjohn) that authentic **13**, mp 74–75.5 °C, exhibits $[\alpha]^{25}_D$ +240° (*c* 21.0, $CHCl_3$).

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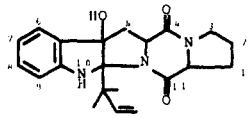
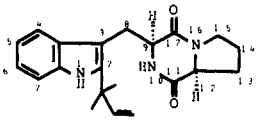
Asymmetric Total Synthesis of Brevianamide E

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]



1



2

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 aminomalonate[4] gave the amide **4** (Scheme I), mp 75.5–76 °C, $[\alpha]^{18}_D$ −43° (*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, $[\alpha]^{18}_D$ −54° (*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′,-

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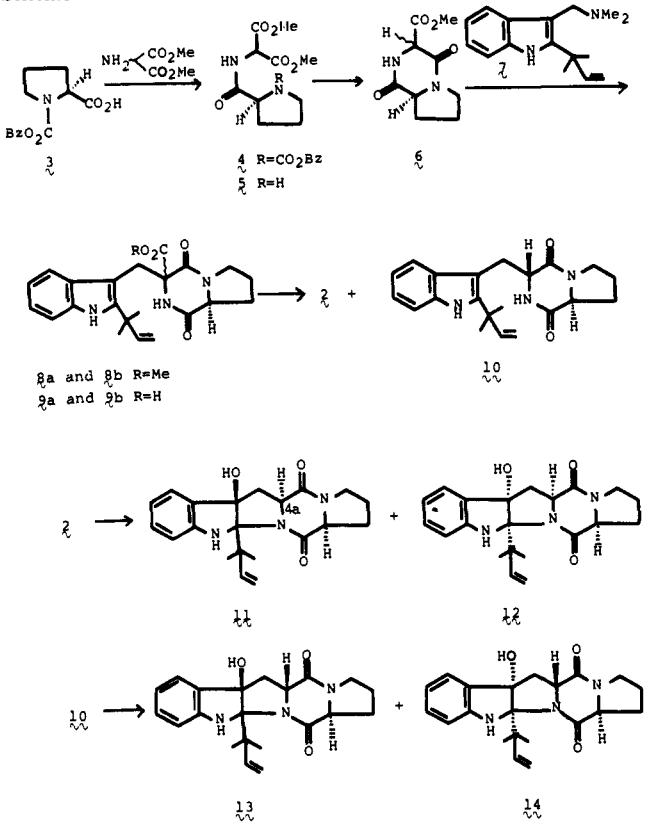
Scheme I



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° (*c* 0.15, MeOH), and **8b**[10] (51.7%), mp 197–202 °C, $[\alpha]^{20}_D$ −70.8° (*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° (*c* 0.132, $CHCl_3$), and its epimer **10**[12] (55%), $[\alpha]^{20}_D$ −13.3° (*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° (*c* 0.1, $CHCl_3$), and the isomer **10** (59.3%), $[\alpha]^{20}_D$ −61.3° (*c* 0.405, MeOH). The above results indicate that a small amount of epimerization occurred at the C_{12} position as well as at the C_9 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° (*c* 0.093, EtOH), and its isomer **12**[16] (20.9%), $[\alpha]^{20}_D$ + 38.3° (*c* 0.060, EtOH), which were separated by LC using Waters μ-Bondapak C_{18} and eluting with MeOH–H_2O containing 0.5% $(NH_4)_2CO_3$ (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 brevianamide 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.

Acknowledgment. We thank Dr. P. S. Steyn for his kind gift of the NMR spectrum of deoxybrevianamide E. We are also grateful to Professors T. Hino and M. Nakagawa for their useful information about the photooxygenation.

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(10) IR ($CHCl_3$) 3500, 3400 (NH), 1745, 1680, and 1660 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.53 (8 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–), 8.23 (1 H, dd, *J* = 10, 18 Hz, CH_2=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 ($CHCl_3$) 3500, 3480, 3400 (NH), 1890, and 1670 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.55 (8 H, s, 2 Me), 1.8–2.43 (4 H, m, 2 CH_2), 3.13 (1 H, dd, *J* = 3.4, 14.9 Hz, C_8 H), 3.72 (1 H, dd, *J* = 11.4, 14.9 Hz, C_8 H), 4.0 (1 H, t, *J* = 7.1 Hz, C_{12} H), 4.4 (1 H, dd, *J* = 3.4, 11.4 Hz, C_9 H), 5.12 (1 H, d, *J* = 17.7 Hz, CH_2=CH–), 5.14 (1 H, d, *J* = 9.1 Hz, CH_2=CH–), 6.1 (1 H, dd, *J* = 9.1, 17.7 Hz, CH_2=CH–), 7.0–7.5 (4 H, m, 4 ArH), 6.1 and 8.1 (each 1 H, each s, 2 NH); MS *m/e* 351 (M^+).
(12) IR ($CHCl_3$) 3520, 3490, 3440 (NH), 1685, and 1660 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.52 (8 H, s, 2 Me), 1.6–2.08 (4 H, m, 2 CH_2), 4.2 (1 H, m, C_9 H), 5.09 (1 H, d, *J* = 11.4 Hz, CH_2=CH–), 5.14 (1 H, d, *J* = 17.1 Hz, CH_2=CH–), 6.1 (1 H, dd, *J* = 11.4, 17.1 Hz, CH_2=CH–), 7.0–7.5 (4 H, m, 4 ArH), 5.98 and 8.12 (2 H, s, 2 NH); MS *m/e* 351 (M^+).
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(15) NMR ($CDCl_3$) δ 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, 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, CH_2=CH–), 5.07 (1 H, dd, *J* = 1.5, 17.7 Hz, CH_2=CH–), 6.3 (1 H, dd, *J* = 14.4, 17.7 Hz, CH_2=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° (EtOH).[1] We assume the natural compound was contaminated.
(16) NMR ($CDCl_3$) δ 1.38 (6 H, s, 2 Me), 1.9–2.3 (4 H, m, 2 CH_2), 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, CH_2=CH–), 5.16 (1 H, dd, *J* = 1.5, 11.4 Hz, CH_2=CH–), 6.38 (1 H, dd, *J* = 11.4, 17.1 Hz, CH_2=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 ($CDCl_3$) δ 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, 12 Hz, C_{4a} H), 5.10 (1 H, dd, *J* = 1, 10 Hz, CH_2=CH–), 5.20 (1 H, dd, *J* = 1, 20 Hz, CH_2=CH–), 6.35 (1 H, dd, *J* = 10, 20 Hz, CH_2=CH–), 6.4–7.45 (4 H, m, 4 Ar H); MS *m/e* 367 (M^+). **14**: NMR ($CDCl_3$) δ 1.57 (8 H, s, 2 Me), 1.8–2.3 (4 H, m, 2 CH_2), 5.17 (1 H, dd, *J* = 1, 12 Hz, CH_2=CH–), 5.23 (1 H, dd, *J* = 1, 18 Hz, CH_2=CH–), 6.47 (1 H, dd, *J* = 12, 18 Hz, CH_2=CH–), 7.2–7.7 (4 H, m, 4 Ar H); MS *m/e* 367 (M^+).

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