1.82, CHCl₃), in 83% overall yield. Enone 12 was linked with aldehyde 7 by the similar procedure described above to afford 9.1^{7} The spectral data (¹H NMR, IR, UV, CD), optical rotation, and HPTLC behavior of 9 were in good agreement with those of natural PUG 3.1

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Supplementary Material Available: Spectroscopic data are given for compounds 2, 5S,6R,12S and 5S,6R,12R isomers of 2, 3, enantiomer of 3, 5-10, 12, the MTPA ester of 5, and the 7Z isomer of 8 (7 pages). Ordering information is given on any current masthead page.

(16) 12: ¹H NMR (400 MHz, CDCl₃) δ 0.93 (t, J = 7.6 Hz, 3 H), 3.32 (s, 3 H), 5.25–5.50 (m, 3 H), 5.54 (m, 1 H), 7.36 (s, 1 H). (17) The condensation of 12 and 7 gave aldols in 78% yield, corrected for

the 48% recovery of enone 12, and further transformation of the aldols into 9 was effected in 16% overall yield.

Synthesis of (7E)- and (7Z)-Punaglandin 4. Structural Revision¹

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Punaglandins (PUGs) are halogenated eicosanoids isolated from a marine source, Telestro riisei.² In this family, PUG 3 and 4 have received particular attention because of the potent inhibitory effects on L1210 leukemia cell proliferation.³ Although the structures have been postulated recently,² the grounds afforded by the spectroscopic data and assumed mechanism of the chemical transformation are not sufficiently firm. In addition, the absolute configuration has been suggested on the basis of the biosynthetic pathway of the related marine products, clavulones⁴ or claviridenones.⁵ Therefore an unambiguous structural elucidation should be made by authentic chemical synthesis using stereodefined building blocks. We report herein a convergent synthesis of naturally occurring (7E)- and (7Z)-PUG 4.

We planned to synthesize 1 (structure proposed for (7E)-PUG 4^2) and the 7Z isomer 2, having the same C-5 and C-6 configurations, by introducing two side chains to the (4S)-cyclopentenone $3.^6$ The requisite lower side chain precursor 4 was made by reacting of 3-chloro-1-(tributylstannyl)propyne and a tributyl-

(3) Fukushima, M.; Kato, T. Kyoto Conference on Prostaglandins, Abstracts; 1984, S6-8; p 56; Icosanoids and Cancer; Raven Press: New York, 1984; p 277. The presence of chlorine atom at C-10 is important for the

potency. See ref 1 and: Nagaoka, H.; Miyakoshi, T.; Kasuga, J.; Yamada, Y. Tetrahedron Lett. 1985, 26, 5053.
(4) Kikuchi, H.; Tsukitani, Y.; Iguchi, K.; Yamada, Y. Tetrahedron Lett. 1982, 23, 5171

(6) Gill, M.; Rickards, R. W. J. Chem. Soc., Chem. Commun. 1979, 121.

Scheme I^a



^a (i) Ti(O-i-C₃H₇)₄, L-(+)-diethyl tartrate, t-C₄H₉OOH (2 equiv), CH₂Cl₂, -50 to -20 °C, 57%; (ii) dihydropyran, pyridinium *p*-toluene-sulfonate (PPTS), 16 °C, 15 h, 94%; (iii) 0.5 N NaOH in 5:1 H₂O/t-C₄H₉OH, 60 °C, 40 min; (iv) CH₂N₂, ether, 82% overall in two steps; (v) (CH₃CO)₂O, 4-(dimethylamino)pyridine, 18 °C, 20 min, 96%; (vi) CH₃OH, PPTS, 50 °C, 55 min, 90%; (vii) DCC, Me₂SO, CF₃COOH, pyridine, 22 °C, 3 h, 75%.

phosphine-complexed pentylcopper reagent⁷ (-78 °C, THF). The upper side chain aldehyde 5, $[\alpha]^{23}_{D}$ -22.4° (c 0.36, C₆H₆), was prepared according to Scheme I. The two chiral centers were created by Sharpless asymmetric epoxidation⁸ of the Z-allylic alcohol 6,9 followed by the intramolecular carboxylate-participated ring opening¹⁰ of the hydroxyl-masked¹⁴ epoxide 7. The stereoand regiocontrolled sequence led to 5 in 94% ee.¹² The absolute configuration was proved by comparison of the triol ($[\alpha]^{20}_{D}$ -10.7° $(c 2.56, CDCl_3))$ obtained by acid hydrolysis of 8 with the antipode derived from 2-deoxy-D-ribose ($[\alpha]_D$ +11.9° (c 2.7, CDCl₃)).¹³



Reaction of cyclopentenone 3, $[\alpha]^{19}_{365}$ +850° (c 0.083, hexane, 100% ee),⁶ and the allenyltin 4 (1 equiv) with the aid of butyllithium (THF, -78 °C), followed by desilylation with tetra-butylammonium fluoride,¹⁵ gave the crystalline acetylenic diol 10, $[\alpha]^{11}_{D}$ -56.4° (c 0.14, CHCl₃) (42%), together with the un-

(7) Suzuki, M.; Suzuki, T.; Kawagishi, T.; Morita, Y.; Noyori, R. Isr. J. Chem. 1984, 24, 118.
(8) Katsuki, T.; Sharpless, K. B. J. Am. Chem. Soc. 1980, 102, 5974.
Rossiter, B. E.; Katsuki, T.; Sharpless, K. B. Ibid. 1981, 103, 464.
(9) Martel, J. Japanese Patent 46-28153; Japan Kokai 46-5625.
(10) Possibility of direct nucleophilic displacement by hydroxide ion at C-3 of the encourd not be excluded but such a mechanism is

of the epoxy THP ether could not be excluded, but such a mechanism is unlikely in view of the high degree of retention of optical purity during the 7 to 8 transformation (95% ee¹¹ to 94% ee).

7 to 8 transformation (95% ee'1 to 94% ee). (11) The optical yield was assayed by 500-MHz ¹H NMR analysis of MTPA ester¹² of the epoxy alcohol ($[\alpha]^{14}_D - 2.5^\circ$ (c 1.74, CHCl₃)). The epoxy alcohol obtained from 2-deoxy-D-ribose showed $[\alpha]_D - 2.3^\circ$ (c 1.5, CDCl₃).¹³ (12) Assayed by 500-MHz ¹H NMR analysis of MTPA ester of 9 (Dale, J. A.; Dull, D. L.; Mosher, H. S. J. Org. Chem. 1969, 34, 2543). (13) Rokach, J.; Zamboni, R.; Lau, C.-K.; Guindon, Y. Tetrahedron Lett. 1981, 22, 2759. See also: Rokach, J.; Lau, C.-K.; Zamboni, R.; Guindon, V. ikid 1961, 22, 2762

Y. ibid. 1981, 22, 2763.

(14) Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpiess, K. B.; Tuddenham, D.; Walker, F. J. J. Org. Chem. 1982, 47, 1373. (15) Corey, E. J.; Venkateswarlu, A. J. Am. Chem. Soc. 1972, 94, 6190.

0002-7863/86/1508-5021\$01.50/0 © 1986 American Chemical Society

⁽¹⁾ Prostaglandin Synthesis. 12. Part 11: Sugiura, S.; Hazato, A.; Ta-naka, T.; Okamura, N.; Bannai, K.; Manabe, K.; Kurozumi, S.; Suzuki, M.; Noyori, R. Chem. Pharm. Bull. 1985, 33, 4120.

⁽²⁾ Baker, B. J.; Okuda, R. K.; Yu, P. T. K.; Scheuer, P. J. J. Am. Chem. Soc. 1985, 107, 2976

⁽⁵⁾ Kobayashi, M.; Yasuzawa, T.; Yoshihara, M.; Akutsu, H.; Kyogoku, Y.; Kitagawa, I. Tetrahedron Lett. 1982, 23, 5331.

desired allenic condensation product (22%). The stereochemistry of 10 was definitely established by X-ray crystallographic analysis. Hydrogenation of 10 over Lindlar catalyst in methanol afforded the Z-olefinic product 11 (98%), $[\alpha]^{21}_{D}$ -23.0° (c 0.13, CHCl₃), which in turn was oxidized by pyridinium dichromate in DMF to give the hydroxy enone 12, $[\alpha]^{25}_{D}$ -57.6° (c 0.25, CHCl₃) (91%). Thus in going from 3 to 12, chirality of the hydroxylated carbon was transferred cleanly in a 1,3 manner. Silylation of 12 with trimethylsilyl triflate and diisopropylethylamine in CH₂Cl₂ gave 13, $[\alpha]^{23}_{D}$ -20.9° (c 0.31, CHCl₃) (86%). Aldol condensation of the enone 13 and the aldehyde 5 (1:3 ratio) was then effected with LDA in THF at -78 °C, leading to 14 in 44% yield (75% yield corrected for recovery of 13). Dehydration of the aldol product with acetic anhydride and 4-(dimethylamino)pyridine in CH_2Cl_2 and subsequent desilylation in a 6:3:1 mixture of acetic acid, water, and THF gave the desired 1 and 2 (1:4 ratio) (41%) having 5S,6S,12S configuration. However, the 500-MHz ¹H NMR spectra of these products were not identical with those of the naturally occurring (7E)- and (7Z)-PUG 4, thus dictating revision of the originally postulated structures.²

We then prepared all possible diastereomers with respect to C-5, C-6, and C-12 relative configurations similarly from the appropriate chiral cyclopentenones and side-chain units.¹⁶ Of these, only product obtained from 3 and the (2S,3R)-diacetoxyaldehyde (enantiomer of 5) showed consistent ¹H NMR¹⁸ and HPLC behavior (Yamamura Chemical Co., YMC A-003-3 + A-002-3, 1:1 hexane-ether as eluant). However, the CD curves indicated that the synthetic samples were the antipodes of those of the natural specimen: natural (7E)-PUG 4 (CH₃OH), $\Delta \epsilon$ -5.0 at 250 nm; natural (7Z)-PUG 4 (CH₃OH), Δε -4.8 at 268 nm. The natural (7E)- and (7Z)-PUG 4 (15 and 16 respectively 2:5) were synthesized likewise from the enantiomer of $\hat{\mathbf{3}}$,¹⁹ allenyltin 4, and aldehyde 5.²⁰ Irradiation of pure 15 or 16 in benzene (Pyrex, 25-W fluorescent lamp, 25 °C) led to a 7:3 photoequilibrated mixture of 15 and 16.



We now can conclude that natural (7E)- and (7Z)-PUG 4 have the 5S,6S,12R configuration. The 17,18-dehydro derivatives, (7*E*)- and (7*Z*)-PUG 3, must have the same stereochemistry.²

(19) Gill, M.; Rickards, R. W. Tetrahedron Lett. 1979, 1539.

Most significantly, the R configuration at C-12 in PUG 3 and 4 is the opposite of the S stereochemistry (*ent*-prostanoid structure) of the closely related marine eicosanoids, clavulones⁴ or claviridenones.⁵ Recently isolated chlorovulones possess also 12R configuration.²¹ The chlorine atom at C-10 seems to alter the biosynthetic pathway.^{22,23}

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Supplementary Material Available: Analytical and spectral data for 1, 2, 5, and 7-16, as well as the C-5, C-6, and C-12 diastereomers (12 pages). Ordering information is given on any current masthead page.

(21) Nagaoka, H.; Iguchi, K.; Miyakoshi, T.; Yamada, N.; Yamada, Y. Tetrahedron Lett. 1986, 27, 223. (22) Corey, E. J. Experientia 1983, 39, 1084.

Total Synthesis of (\pm) -Fawcettimine (Burnell's Base A)

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In 1959, from extracts of alkaloids of Lycopodium fawcetti collected in the Blue Mountain Range of Jamaica, Burnell isolated a compound initially referred to as base A¹ and later as faw-A collaborative effort of three research groups cettimine.² eventually suggested that fawcettimine has the keto carbinolamine structure 1, and that this structure is in equilibrium with a negligible amount of its ring-chain tautomer 3, which gives rise to N-acetyl, N-nitroso, and methiodide derivatives having the nine-membered ring structure.3

The gross structure of fawcettimine has been confirmed by chemical correlation of the alkaloid with serratinine⁴ and with lycothunine,⁵ both of which have been characterized by X-ray crystallography. However, reasonable doubt about the stereostructure of the native alkaloid at C-4 still exists, and there is some confusion about the nature of the keto amine/carbinolamine tautomerization. For example, whereas the infrared spectrum of a CCl₄ solution of fawcettimine has one carbonyl stretch (1730 cm⁻¹), the spectra of the methiodide^{2a} and N-acetyl^{2b} derivatives each contain two ketonic carbonyl bands (1692, 1730 cm⁻¹ and 1710, 1735 cm^{-1} , respectively). On the other hand, Burnell has reported that the hydrochloride and perchlorate salts of fawcettimine both have 1690 cm⁻¹ carbonyl absorptions, suggesting that these compounds are salts of the tautomeric form $5.^2$ However, it is impossible to construct a molecular model of 5, although such a model can easily be constructed for the C-4 epimer 6. The

⁽¹⁶⁾ Enantiomer of 5, $[\alpha]^{22}_{D}$ +21.8° (c 0.97, C₆H₆), was prepared by (16) Enantomer of 5, $[\alpha]^{12}{}_{\rm D}$ +21.8° (c 0.97, C₆H₆), was prepared by Scheme I by using D-(-)-diethyl tartrate as the chiral auxiliary in the Sharpless epoxidation. The (2S,3S)-diacetoxy aldehyde, $[\alpha]^{23}{}_{\rm D}$ -0.97° (c 0.81, C₆H₆), was obtained from (5S,6R)-methyl 5,6,7-trihydroxyheptanoate¹⁷ through a four-step sequence: (i) t-C₄H₉(C₆H₅)₂SiCl, imidazole, 17 °C, 0.5 h, 98%; (ii) (CH₃CO)₂O, 4-(dimethylamino)pyridine, 17 °C, 15 min, 91%; (iii) HF-pyridine, CH₃CN, 18 °C, 2.5 h, 94%; (iv) DCC, Me₂SO, CF₃COOH, pyri-dine, 17 °C, 3 h, 75%. (17) Corey, E. J.; Marfat, A.; Munroe, J.; Kim, K. S.; Hopkins, P. B.; Brion, F. *Tetrahedron Lett.* **1981**, 22, 1077.

Tetrahedron Lett. 1981, 22, 1077. Brion, F

^{(18) &}lt;sup>1</sup>H NMR chemical shifts of the C-6 and C-7 protons and the H-H coupling constants, $J_{5,6}$ and $J_{6,7}$, of the 7E and 7Z stereoisomers determined in CDCl₃ at 500 MHz as follows: (5R,6R,12S)-7E isomer, δ 6.04 and 6.37; 4.4 and 9.2 Hz. (5S,6S,12S)-7E isomer 1, δ 5.69 and 6.32; 4.3 and 10.4 Hz. (5S, 6R, 12S)-7E isomer, δ 6.24 and 6.53; 2.6 and 9.5 Hz. (5S, 6R, 12R)-7E isomer, 8 5.77 and 6.31; 4.9 and 10.3 Hz. (5R,6R,12S)-7Z isomer, 8 6.36 and 6.10; 3.7 and 7.8 Hz. (5S,6S,12S)-7Z isomer 2, δ 6.62 and 6.07; 4.4 and 7.9 Hz. (5S,6R,12S)-7Z isomer, δ 6.48 and 6.18; 3.5 and 8.9 Hz. (5S,6R,12R)-7Z isomer, δ 6.68 and 6.23; 4.0 and 9.2 Hz.

⁽²⁰⁾ The aldol condensation of the enantiomer of 13 ($[\alpha]^{12}_{D} + 23.7^{\circ}$ (c 1.14, CHCl₃)) and 5 was effected in 58% yield (95% yield corrected for the 39% recovery of the starting enone).

⁽²³⁾ PUG 3 and 4 are derived from PUG 1 and 2, respectively, by elim-ination of acetic acid.² The trans relationship of the two side chains in PUG 1 and 2^2 dictates the R configuration at C-8. At present, however, we should refrain from postulating the remaining C-7 configuration by simple NMR analysis.

⁽¹⁾ Burnell, R. H. J. Chem. Soc. 1959, 3091.

^{(2) (}a) Burnell, R. H.; Mootoo, B. S. Can. J. Chem. 1961, 39, 1090. (b)
Burnell, R. H.; Chin, C. G.; Mootoo, B. S.; Taylor, D. R. Ibid. 1963, 41, 3091.
(3) Inubushi, Y.; Ishii, H.; Harayama, T.; Burnell, R. H.; Ayer, W. A.;

⁽⁴⁾ Nishio, K.; Fujiwara, T.; Tomita, K.; Ishii, H.; Inubushi, Y.; Harayama, T. *Tetrahedron Lett.* 1969, 861.
(5) Inubushi, Y.; Harayama, T. *Chem. Pharm. Bull.* 1981, 29, 3418.