1.82, $CHCl_3$), in 83% overall yield. Enone **12** was linked with aldehyde **7** by the similar procedure described above to afford **9**.[17] 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]

Acknowledgment. We are grateful to Prof. R. Noyori, Nagoya University, for providing helpful information and valuable discussion, and to Prof. P. J. Scheuer, University of Hawaii, for generously providing the authentic samples of natural PUGs. We kindly thank Y. Shida, Tokyo College of Pharmacy, for mass measurement, and also thank Dr. Y. Kobayashi, Tokyo Institute of Technology, for helpful discussion. This work was supported in part by a Grant-in-Aid (No. 60571004) for Scientific Research from Japanese Ministry of Education, Science and Culture.

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

(16) **12**: ^1H NMR (400 MHz, $CDCl_3$) 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 (7*E*)- and (7*Z*)-Punaglandin 4. Structural Revision[1]

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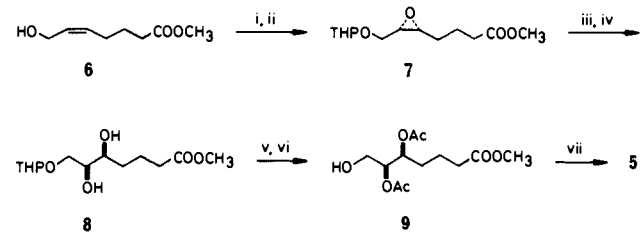
Received February 7, 1986

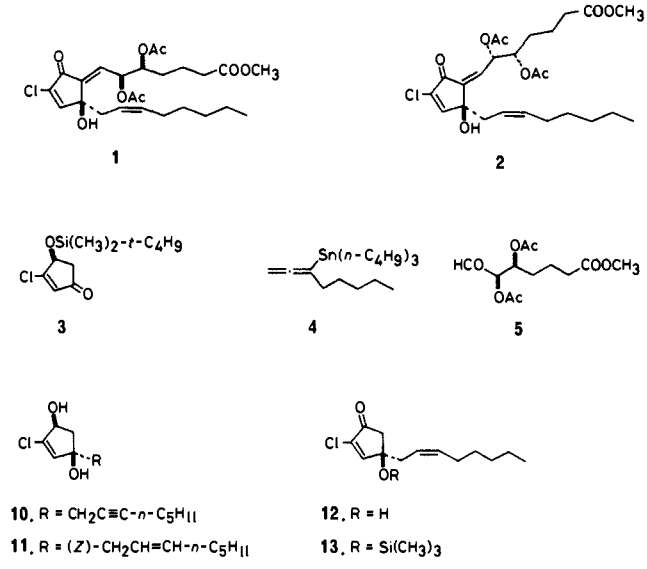
Punaglandins (PUGs) are halogenated eicosanoids isolated from a marine source, *Telestro riisei*.[2] In this family, PUG 3 and 4 have received particular attention because of the potent inhibitory effects on L1210 leukemia cell proliferation.[3] Although the structures have been postulated recently,[2] 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, clavulones[4] 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 (7*E*)- and (7*Z*)-PUG 4.

We planned to synthesize **1** (structure proposed for (7*E*)-PUG 4[2]) and the 7*Z* isomer **2**, having the same C-5 and C-6 configurations, by introducing two side chains to the (4*S*)-cyclopentenone **3**.[6] The requisite lower side chain precursor **4** was made by reacting of 3-chloro-1-(tributylstannyl)propyne and a tributylphosphine-complexed pentylcopper reagent[7] (−78 °C, THF). The upper side chain aldehyde **5**, $[\alpha]^{23}_D$ −22.4° (*c* 0.36, C_6H_6), was prepared according to Scheme I. The two chiral centers were created by Sharpless asymmetric epoxidation[8] of the *Z*-allylic alcohol **6**,[9] followed by the intramolecular carboxylate-participated ring opening[10] of the hydroxyl-masked[14] epoxide **7**. The stereo- and 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, $CDCl_3$)).[13]

Scheme I[a]



[a] (i) Ti(O-*i*-$C_3H_7)_4$, L-(+)-diethyl tartrate, *t*-C_4H_9OOH (2 equiv), CH_2Cl_2, −50 to −20 °C, 57%; (ii) dihydropyran, pyridinium *p*-toluenesulfonate (PPTS), 16 °C, 15 h, 94%; (iii) 0.5 N NaOH in 5:1 H_2O/*t*-C_4H_9OH, 60 °C, 40 min; (iv) CH_2N_2, ether, 82% overall in two steps; (v) $(CH_3CO)_2O$, 4-(dimethylamino)pyridine, 18 °C, 20 min, 96%; (vi) CH_3OH, PPTS, 50 °C, 55 min, 90%; (vii) DCC, Me_2SO, CF_3COOH, pyridine, 22 °C, 3 h, 75%.



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 tetrabutylammonium fluoride,[15] gave the crystalline acetylenic diol **10**, $[\alpha]^{11}_D$ −56.4° (*c* 0.14, $CHCl_3$) (42%), together with the un-

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

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(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.

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

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(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 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% ee[11] to 94% ee).

(11) The optical yield was assayed by 500-MHz ^1H NMR analysis of MTPA ester[12] of the epoxy alcohol ($[\alpha]^{14}_D$ −2.5° (*c* 1.74, $CHCl_3$)). The epoxy alcohol obtained from 2-deoxy-D-ribose showed $[\alpha]_D$ −2.3° (*c* 1.5, $CDCl_3$)).[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, Y. *ibid.* **1981**, *22*, 2763.

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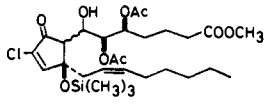
(15) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

0002-7863/86/1508-5021$01.50/0

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, $CHCl_3$), which in turn was oxidized by pyridinium dichromate in DMF to give the hydroxy enone **12**, $[\alpha]^{25}_D$ −57.6° (*c* 0.25, $CHCl_3$) (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 CH_2Cl_2 gave **13**, $[\alpha]^{23}_D$ −20.9° (*c* 0.31, $CHCl_3$) (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 5*S*,6*S*,12*S* configuration. However, the 500-MHz ^1H NMR spectra of these products were not identical with those of the naturally occurring (7*E*)- and (7*Z*)-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 (2*S*,3*R*)-diacetoxyaldehyde (enantiomer of **5**) showed consistent ^1H NMR[18] 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 (7*E*)-PUG 4 (CH_3OH), $\Delta\epsilon$ −5.0 at 250 nm; natural (7*Z*)-PUG 4 (CH_3OH), $\Delta\epsilon$ −4.8 at 268 nm. The natural (7*E*)- and (7*Z*)-PUG 4 (**15** and **16** respectively 2:5) were synthesized likewise from the enantiomer of **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**.



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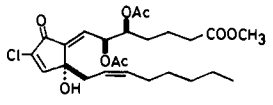
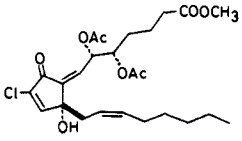


15, 7*E*-PUG 4



16, 7*Z*-PUG 4

We now can conclude that natural (7*E*)- and (7*Z*)-PUG 4 have the 5*S*,6*S*,12*R* configuration. The 17,18-dehydro derivatives, (7*E*)- and (7*Z*)-PUG 3, must have the same stereochemistry.[2] 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, clavulones[4] or claviridenones.[5] Recently isolated chlorovulones possess also 12*R* configuration.[21] The chlorine atom at C-10 seems to alter the biosynthetic pathway.[22,23]

Acknowledgment. We are grateful to Professor Y. Yamada, Tokyo College of Pharmacy, for providing valuable information prior to publication. Suggestions by Professor N. Harada, Tohoku University, on the CD measurements and valuable comments by Dr. Y. Kobayashi, Tokyo Institute of Technology, on the mechanism of the epoxide ring opening are also appreciated.

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.

(16) Enantiomer of **5**, $[\alpha]^{22}_D$ +21.8° (*c* 0.97, C_6H_6), was prepared by Scheme I by using D-(−)-diethyl tartrate as the chiral auxiliary in the Sharpless epoxidation. The (2*S*,3*S*)-diacetoxy aldehyde, $[\alpha]^{23}_D$ −0.97° (*c* 0.81, C_6H_6), was obtained from (5*S*,6*R*)-methyl 5,6,7-trihydroxyheptanoate[17] through a four-step sequence: (i) *t*-$C_4H_9(C_6H_5)_2SiCl$, imidazole, 17 °C, 0.5 h, 98%; (ii) $(CH_3CO)_2O$, 4-(dimethylamino)pyridine, 17 °C, 15 min, 91%; (iii) HF–pyridine, CH_3CN, 18 °C, 2.5 h, 94%; (iv) DCC, Me_2SO, CF_3COOH, pyridine, 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.

(18) ^1H 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 7*E* and 7*Z* stereoisomers determined in $CDCl_3$ at 500 MHz as follows: (5*R*,6*R*,12*S*)-7*E* isomer, δ 6.04 and 6.37; 4.4 and 9.2 Hz. (5*S*,6*S*,12*S*)-7*E* isomer **1**, δ 5.69 and 6.32; 4.3 and 10.4 Hz. (5*S*,6*R*,12*S*)-7*E* isomer, δ 6.24 and 6.53; 2.6 and 9.5 Hz. (5*S*,6*R*,12*R*)-7*E* isomer, δ 5.77 and 6.31; 4.9 and 10.3 Hz. (5*R*,6*R*,12*S*)-7*Z* isomer, δ 6.36 and 6.10; 3.7 and 7.8 Hz. (5*S*,6*S*,12*S*)-7*Z* isomer **2**, δ 6.62 and 6.07; 4.4 and 7.9 Hz. (5*S*,6*R*,12*S*)-7*Z* isomer, δ 6.48 and 6.18; 3.5 and 8.9 Hz. (5*S*,6*R*,12*R*)-7*Z* isomer, δ 6.68 and 6.23; 4.0 and 9.2 Hz.

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

(20) The aldol condensation of the enantiomer of **13** ($[\alpha]^{12}_D$ +23.7° (*c* 1.14, $CHCl_3$)) and **5** was effected in 58% yield (95% yield corrected for the 39% recovery of the starting enone).

(21) Nagaoka, H.; Iguchi, K.; Miyakoshi, T.; Yamada, N.; Yamada, Y. *Tetrahedron Lett.* **1986**, *27*, 223.

(22) Corey, E. J. *Experientia* **1983**, *39*, 1084.

(23) PUG 3 and 4 are derived from PUG 1 and 2, respectively, by elimination 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.

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

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Received April 14, 1986

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 A[1] and later as fawcettimine.[2] A collaborative effort of three research groups 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 serratinine[4] 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 CCl_4 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

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(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.

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