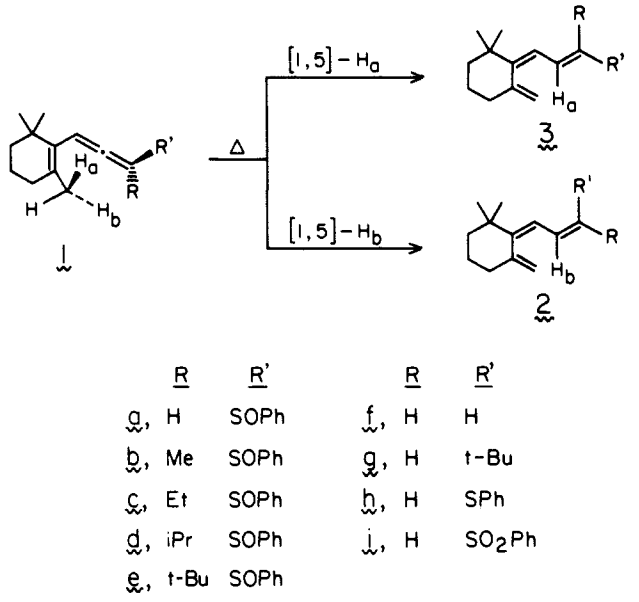
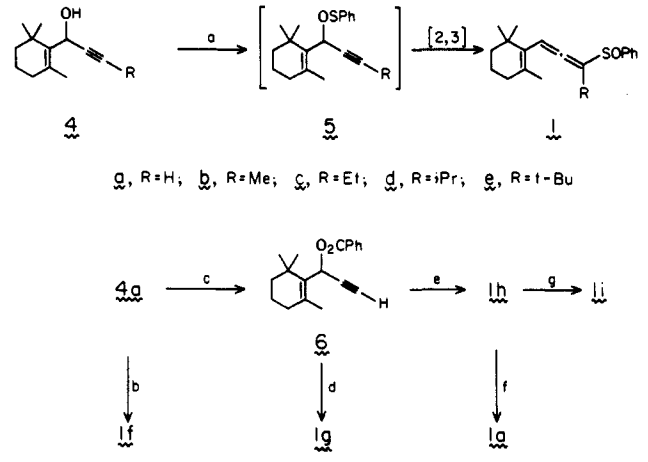
Scheme I



	R	R'		R	R'
a,	H	SOPh	f,	H	H
b,	Me	SOPh	g,	H	t-Bu
c,	Et	SOPh	h,	H	SPh
d,	iPr	SOPh	i,	H	SO_2Ph
e,	t-Bu	SOPh			

Scheme II[a]



[a] Reaction conditions: (a) $PhSCl$, Et_3N, THF, -78 °C to room temperature; (b) 3:1 of $LiAlH_4$:$AlCl_3$, ether; (c) *n*-BuLi, PhCOCl, ether, -4 °C; (d) $(t\text{-Bu})_2Cu(CN)Li_2$, ether, -78 °C to room temperature; (e) $PhSCu{\cdot}P(OMe)_3$, LiBr, THF; (f) 1 equiv of *m*-CPBA, CH_2Cl_2, -20 °C; (g) 2 equiv of *m*-CPBA, CH_2Cl_2, -20 °C.

Note particularly that neither the sulfide **1h** nor the sulfone **1i** exerts significant geometric selectivity and that for the sulfoxides, both diastereomers afford similar results. (b) For the sulfoxides, the geometric selectivity increases as the size of R increases (4:1 to >98:2) but reactivity is not affected. (c) Sulfur substituents accelerate the [1,5]-hydrogen shift relative to hydrocarbon substituent and the reactivity order parallels the electron-withdrawing ability of the substituents (sulfone > sulfoxide > sulfide >> H, *t*-Bu). (d) The polarity of the solvent (benzene, pyridine, acetonitrile) has little effect on the rate and selectivity of the reaction, which is characteristic of other [1,5]-sigmatropic shifts.[6]

In summary, we have discovered that the sulfoxide group is a useful substituent which not only exerts an acceleration of the [1,5]-shift but also can effect control of π-facial stereoselection in these triene syntheses.[7] Although the origin of this effect is as of yet uncertain, the results should further enhance the utility of vinylallenes in stereoselective syntheses of sensitive polyenes bearing useful functional groups.

Table I. Half-Lives, Relative Rates, and Product Ratios for the Thermal Rearrangement of Vinylallenes

	$\tau_{1/2}$, min[a,b]	k_{rel}	2/3[c]
1a'[d]	38.5 ± 1.8	131	75/25
1a[e]	48.3 ± 0.7	104	82/18
1b[e]	34.2 ± 1.7	147	92/8
1c[e]	44.8 ± 1.2	112	92/8
1d[e]	46.2 ± 0.4	110	93/7
1e[e]	36.4 ± 0.1	138	>98/2[f]
1f	5010 ± 80	1	
1g	6780 ± 180	0.74	39/61
1h	123 ± 3	41	50/50
1i	7.0 ± 0.1	717	53/47
1a[e,g]	37.8 ± 0.8	133	81/19
1a[e,h]	50.2 ± 0.6	100	79/21

[a] These were determined at 40.0 ± 0.1 °C in benzene-d_6 (dielectric constant, ϵ 2.3) unless otherwise noted. Details are provided as Supplementary Material. [b] The uncertainties are absolute deviations. [c] Measured by ^1H NMR and confirmed by HPLC. The product ratios remained constant (±1%) during the kinetic runs and individual product isomers were stable to the reaction conditions. Assignments of geometric configuration were based on NMR and other data. [d] Less polar diastereomer, minor isomer. [e] More polar diastereomer, major isomer. [f] No isomer 3 detected by ^1H NMR. [g] In pyridine-d_5 (ϵ 12.3). [h] In acetonitrile-d_3 (ϵ 37.5).

Acknowledgment. This study was supported by NIH Grants AM-16595 and EY-02452. Giin-Yuan Shen acknowledges receipt of a Phi Beta Kappa Scholarship and a Chancellor's Patent Fund grant from UC Riverside for partial support. Ricardo Tapia also acknowledges the support provided by the Pontifica Universidad Catolica de Chile (Santiago). The β-cyclocitral utilized in this investigation was generously provided by Badische-Anilin und Soda Fabrik (Ludwigshafen). Finally, we acknowledge helpful discussions with Professor W. J. Hehre and Dr. S. D. Kahn.

Supplementary Material Available: Spectral and analytical data and details of kinetic studies including a table of rate constants and *Z*/*E* ratios. (36 pages). Ordering information is given on any current masthead page.

(6) ter Borg, A. P.; Kloosterziel, H. *Recl. Trav. Chim. Pays-Bays* **1963**, *82*, 741. However, a moderate solvent effect has been recently observed for [1,5] shifts of alkyl groups in cyclopentadienes. See: Replogle, K. S.; Carpenter, B. K. *J. Am. Chem. Soc.* **1984**, *106*, 5751.

(7) For a recent discussion of π-facial stereoselectivity on [1,5] shifts, see: Washburn, W. N.; Hillson, R. A. *J. Am. Chem. Soc.* **1984**, *106*, 4575.

Synthesis of Punaglandin 3 and 4. Revision of the Structures

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The structures of a series of chlorinated prostanoids punaglandins[1] (PUGs) isolated from the Hawaiian octocoral *Telesto riisei* have been reported by Scheuer and his colleagues. To PUG 3 and 4, which have higher antitumor activity[1,2] than the related marine prostanoids clavulones[3] (claviridenones[4]) (isolated from the Japanese octocoral *Clavularia viridis*), formula **1** and **2**

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

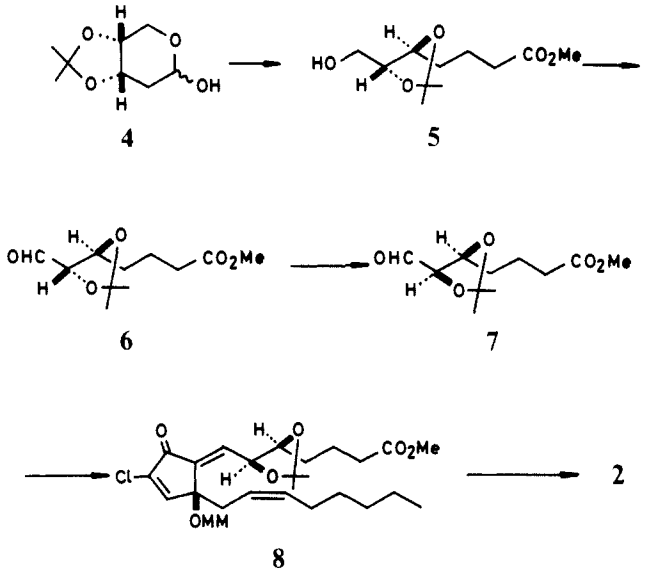
(2) Fukushima, M.; Kato, T. *Kyoto Conference on Prostaglandins, Abstracts*; 1984, S6-8; p 56.

(3) Kikuchi, H.; Tsukitani, Y.; Iguchi, K.; Yamada, Y. *Tetrahedron Lett.* **1982**, *23*, 5171. Kikuchi, H.; Tsukitani, Y.; Iguchi, K.; Yamada, Y. *Tetrahedron Lett.* **1983**, *24*, 1549.

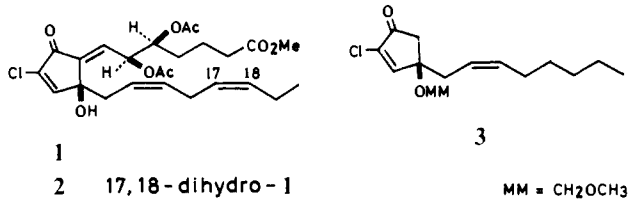
(4) Kobayashi, M.; Yasuzawa, T.; Yoshihara, M.; Akutsu, H.; Kyogoku, Y.; Kitagawa, I. *Tetrahedron Lett.* **1982**, *23*, 5331. Kobayashi, M.; Yasuzawa, T.; Yoshihara, M.; Son, B. W.; Kyogoku, Y.; Kitagawa, I. *Chem. Pharm. Bull.* **1983**, *31*, 1440.

0002-7863/86/1508-5019$01.50/0

Scheme I



(17,18-dihydro-**1**), respectively, were assigned without definite evidence for the stereochemistry.

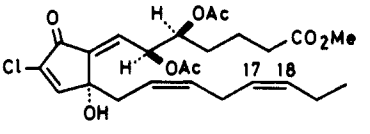


Our recent studies on chlorovulones,[5] newly discovered chlorinated prostanoids from *C. viridis* with antitumor activity comparable to that of PUG 3 and 4, showed the chlorovulones to possess the *R* configuration at C-12. This is opposite to the *S* configuration assigned to clavulones which coexist in the same marine animal. These facts led us to reconsider the proposed C-12 *S* assignment and to pursue the enantioselective syntheses of PUGs. This paper describes the total synthesis of PUG 3 and 4 and presents revision of their structures.

PUGs were synthesized in a straightforward way by applying the synthetic methodology described for the synthesis of clavulones[6] and (−)-chlorovulone II.[5b] The synthesis of **2** (proposed structure for PUG 4[1]) involved linking of a chiral α side chain **7**, easily derived from 2-deoxy-D-ribose, to the chiral cyclopentenone **3**[5b] with an ω side chain (Scheme I).

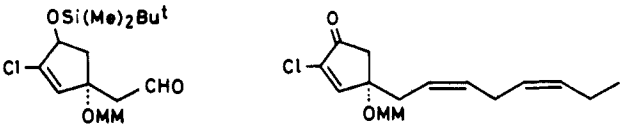
Hydroxy ester **5**, $[\alpha]_D$ +21.0° (*c* 1.84, $CHCl_3$, >99% ee[7]), prepared from 2-deoxy-D-ribose through acetonide **4** according to the method[10] of Corey, was oxidized[11] (2 equiv of dimethyl sulfoxide, 1.5 equiv of oxalyl chloride, methylene chloride, −78 °C, 10 min, and then 5 equiv of triethylamine, −78 to 0 °C over 20 min) to give aldehyde **6**, $[\alpha]_D$ −12.7° (*c* 2.08, $CHCl_3$), in 89% yield. Aldehyde **6** was isomerized[12] with a catalytic amount of potassium carbonate in methanol at 23 °C to aldehyde **7**, $[\alpha]_D$ +6.3° (*c* 0.64, $CHCl_3$), in 95% yield. The lithium enolate of **3**, prepared from enone **3** and 1.2 equiv of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C for 10 min, was treated with 2 equiv of aldehyde **7** in THF at −78 °C for 10 min to give a diastereomeric mixture of aldols in 79% yield based on the consumed **3** (41% yield uncorrected). The aldol mixture was treated with acetic anhydride and 4-(dimethylamino)pyridine in pyridine at 60 °C for 40 min to give **8** and its 7*Z* isomer (2:3 ratio) in 92% yield. After separation of these isomers by silica gel column chromatography, **8** was converted into **2** in 43% overall yield by three sequential reactions: (1) removal of the isopropylidene group (4:1 acetic acid–water, 60 °C, 1 h); (2) acetylation (acetic anhydride, pyridine, 70 °C, 40 min); (3) demethoxymethylation (1:50 36% hydrochloric acid–acetic acid, 40 °C, 15 min). However, the ^1H NMR spectrum of synthetic **2**[13] (5*S*,6*S*,12*S*) was not identical with that of PUG 4, indicating the stereostructure of PUG 4 is different from the proposed one.

The above result prompted the synthesis of all possible diastereomers resulting from relative configuration changes at C-5, -6, and - 2. Analogous linking of two segments, enone **3** and aldehyde **6**, gave the 5*S*,6*R*,12*S* isomer.[13] On the other hand, condensation of aldehyde **6** and **7** with the enantiomer[14] of **3** afforded the 5*S*,6*R*,12*R* isomer[13] and 5*S*,6*S*,12*R* isomer **10**,[13] respectively. The spectral data (^1H NMR, IR, UV, CD), optical rotation, and HPTLC behavior of **10** were found to be identical with those of the natural authentic specimen of PUG 4.[1] These results lead to the conclusion that the structure of PUG 4 is as depicted in **10**.



9 PUG 3

10 17,18-dihydro-9 PUG 4



11 **12**

The results also suggest that PUG 3 is of the structure **9** and not **1**. The synthesis of **9** was conducted as follows. A Wittig reaction of aldehyde **11**[14] with the ylide, prepared from (*Z*)-(3-hexenyl)triphenylphosphonium bromide and *n*-butyllithium, in THF containing 1.5 equiv of hexamethylphosphoramide (−42 °C, 10 min) and subsequent desilylation with 1.2 equiv of tetra-*n*-butylammonium fluoride (THF, 25 °C, 30 min) followed by Jones oxidation (acetone, 0 °C) afforded enone **12**,[16] $[\alpha]_D$ +43.7° (*c*

(5) (a) Iguchi, K.; Kaneta, S.; Mori, K.; Yamada, Y.; Honda, A.; Mori, Y.; *Tetrahedron Lett.* **1985**, *26*, 5787. (b) Nagaoka, H.; Iguchi, K.; Miyakoshi, T.; Yamada, N.; Yamada, Y. *Tetrahedron Lett.* **1986**, *27*, 223. (c) Nagaoka, H.; Miyakoshi, T.; Iguchi, K.; Kasuga, J.; Yamada, Y. *Symp. Pap.-Chem. Nat. Prod., 27th* **1985**, 405.

(6) Nagaoka, H.; Miyakoshi, T.; Yamada, Y. *Tetrahedron Lett.* **1984**, *25*, 3621.

(7) The optical yield was determined by 400-MHz ^1H NMR analysis[8] of the MTPA ester[9] of **5**.

(8) Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1373.

(9) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(10) Corey, E. J.; Marfat, A.; Goto, G.; Brion, F. *J. Am. Chem. Soc.* **1980**, *102*, 7984.

(11) Mancuso, A.; Juang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.

(12) Aldehyde **6** was not detected in the reaction mixture by 400-MHz ^1H NMR.

(13) $[\alpha]_D$ and ^1H NMR data (400 MHz, $CDCl_3$) of C-6, -7, and -11 protons of these compounds. For **2** (5*S*,6*S*,12*S*): $[\alpha]_D$ −148.6° (*c* 0.11, $CHCl_3$); ^1H NMR δ 5.70 (dd, *J* = 10.4, 4.3 Hz, 1 H, H-6), 6.31 (dd, *J* = 10.4, 0.6 Hz, 1 H, H-7), 7.31 (d, *J* = 0.6 Hz, 1 H, H-11). For the 5*S*,6*R*,12*S* isomer: $[\alpha]_D$ −75.8° (*c* 0.24, $CHCl_3$); ^1H NMR δ 6.24 (dd, *J* = 9.6, 2.6 Hz, 1 H, H-6), 6.53 (dd, *J* = 9.6, 0.7 Hz, 1 H, H-7), 7.29 (d, *J* = 0.7 Hz, 1 H, H-11). For the 5*S*,6*R*,12*R* isomer: $[\alpha]_D$ +42.5° (*c* 0.18, $CHCl_3$); ^1H NMR δ 5.77 (dd, *J* = 10.3, 4.8 Hz, 1 H, H-6), 6.31 (d, *J* = 10.3 Hz, 1 H, H-7), 7.35 (s, 1 H, H-11). For **10** (5*S*,6*S*,12*R*): $[\alpha]_D$ +72.3° (*c* 0.39, $CHCl_3$); ^1H NMR δ 6.04 (dd, *J* = 9.1, 4.3 Hz, 1 H, H-6), 6.37 (dd, *J* = 9.1, 0.5 Hz, 1 H, H-7), 7.28 (d, *J* = 0.5 Hz, 1 H, H-11).

(14) The enantiomer of **3** was prepared from (*R*)-4-hydroxy-2-cyclopentenone,[15] $[\alpha]_D$ +78.5° (*c* 2.5, $CHCl_3$) [lit.[15] $[\alpha]_D$ +68.6° (*c* 2.48, $CHCl_3$)], through aldehyde **11** by the method developed for the synthesis of (−)-chlorovulone II.[5b]

(15) (*R*)-4-Hydroxy-2-cyclopentenone was prepared from D-(−)-diethyl tartrate according to the method of: Ogura, K.; Yamashita, M.; Tsuchihashi, G. *Tetrahedron Lett.* **1976**, 759. See also: Suzuki, M.; Kawaguchi, T.; Suzuki, T.; Noyori, R. *Tetrahedron Lett.* **1982**, *23*, 4057.

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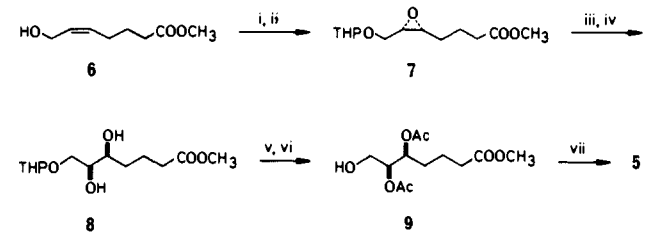
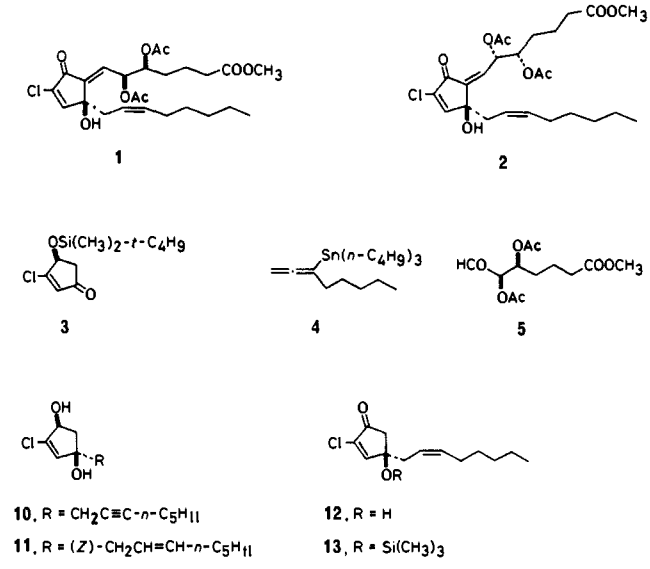
Punaglandins (PUGs) are halogenated eicosanoids isolated from a marine source, *Telestro riisei*.[2] In this family, PUG 3 and 4 have received particular attention because of the potent inhibitory effects on L1210 leukemia cell proliferation.[3] Although the structures have been postulated recently,[2]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

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

(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.

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

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

(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 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.

(14) Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, 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