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SYNTHESIS OF PUNAGLANDIN 4 BY MEANS OF ENZYMATIC RESOLUTION OF THE KEY CHLOROCYCLOPENTENE DERIVATIVE†

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Abstract -- Punaglandin 4, a chlorinated marine prostanoid, was synthesized starting from two chiral building blocks, (+)-tartaric acid and (1S,4R)-(-)-4-t-butyldimethylsilyloxy-3-chloro-2-cyclopenten-1-ol, which was prepared by asymmetric hydrolysis of the corresponding (±)-acetate with pig pancreatic lipase.

Punaglandin 4 (PUG 4, **1a**) is one of the chlorinated marine prostanoids isolated from the Hawaiian octocoral Telesto riisei by Scheuer and his co-workers.[1] Its remarkable antitumor activity together with its unique structure attracted attention of chemists, and two independent syntheses by Yamada et al.[2] and by Noyori et al.[3] appeared soon after Scheuer's structural proposal. Their works established the correct stereostructure of PUG 4 as depicted in **1a**. Another synthesis was reported recently by Sasai and Shibasaki.[4] We became interested in synthesizing **1a** so as to test the utility of enzymatic process in prostanoid area. Enzymatic preparation of (1S,4R)-(+)-4-acetoxy-2-cyclopenten-1-ol by employing pig pancreatic lipase (PPL)[5] was so successful that we planned to extend the scope of this enzyme reaction to the asymmetric hydrolysis of the chlorinated cyclopentene acetate to be used in the synthesis of punaglandins.

In Fig.1 is shown the outline of our synthesis of PUG 4. Like in all the other syntheses of PUG 4,[2-4] the final C-C bond formation step was the non-stereoselective aldol reaction between **A** and **B**. The cyclopentenone **A** was prepared, unlike other groups, by alkylating **C** with **D**. The alkyne **C** was the product of nucleophilic addition of the dianion derived from propyne **F** to the chiral cyclopentenone **E**, which was prepared by enzymatic method. For the peparation of **B**, we used a radical process to connect **G** with **H**. The iodide **G** was prepared from L-(+)-tartaric acid **I**, an abundant natural product. The details of our synthesis are described below.

Enzymatic preparation of the optically active chlorocyclopentene derivative.

The first stage of our work was the preparation of (R)-4-t-butyldimethylsilyloxy-3-chloro-2-cyclopentenone (**7**). The S-enantiomer of this ketone **7** had previous been prepared by Gill and Richards.[6] Our alternative synthesis of (R)-**7** is shown in Fig.2. The key-step of our route was to resolve stereoisomeric mixture **5** to give (1S,4R)-**6a** by means of an enzyme.

†Preparative Bioorganic Chemistry -- 9. Part 8, T. Sugai and K. Mori, Synthesis in the press.

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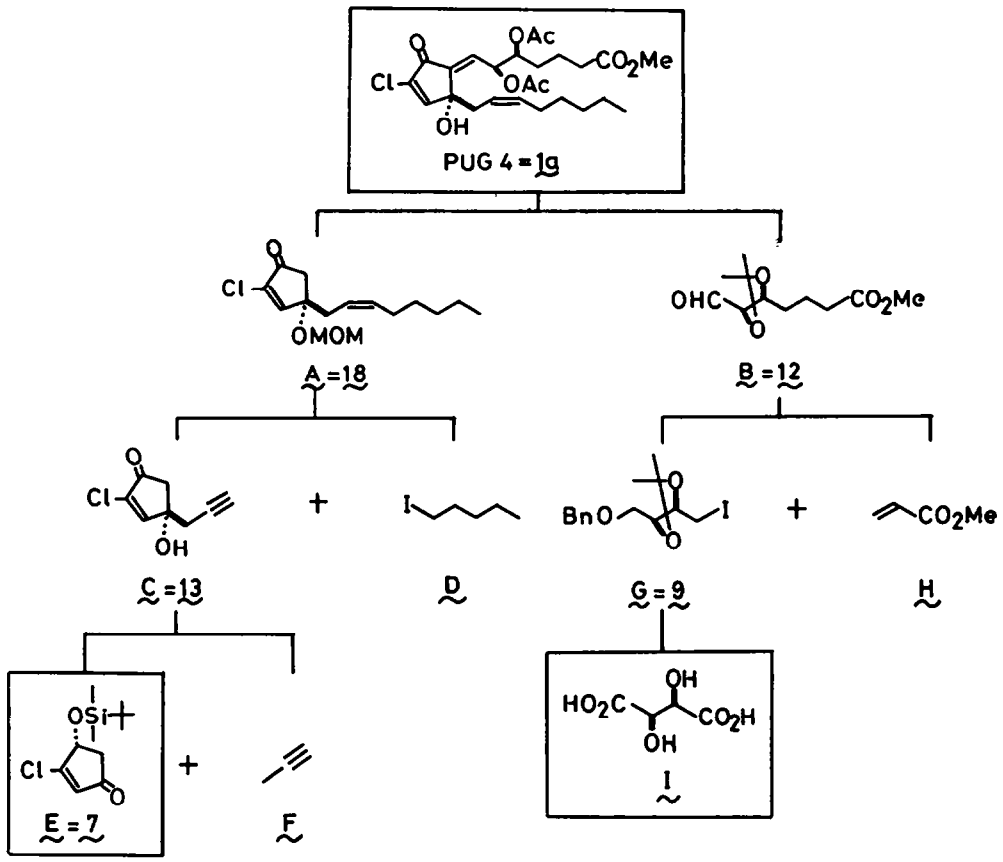
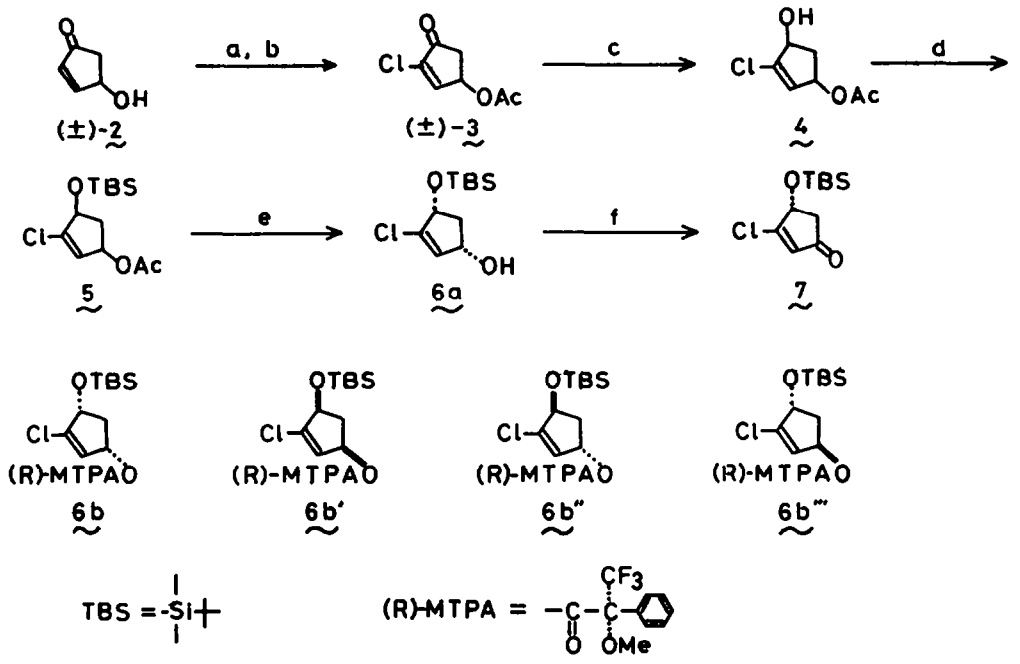


Fig. 1. Outline of the synthesis of punaglandin 4 (1a).

The starting (±)-2 was prepared efficiently (~50% yield) from 2-methylfuran by the method of Tanaka.[7] Introduction of Cl to (±)-2 was carried out as described by Yamada and his co-workers.[8,9] Namely, acetylation of (±)-2 with Ac_2O and NaOAc was followed by adittion of Cl_2. The resulting α,β-dichloroketone was treated with Et_3N to give crystalline (±)-acetoxy chloroketone 3 in 50% yield. This was reduced with $NaBH_4$ in the presence of $CeCl_3$[10] to give 4 as a mixture of (±)-cis-4 and (±)-trans-4. Although pure (±)-cis-4 could be obtained by recrystallization of the mixture,† we proceeded to the next step of silylation without separation of the isomers to give a stereoisomeric mixture of 5 in 71% yield from 3 by treatment with t-$BuMe_2SiCl$ and imidazole. Our previous experience convinced us that only the desired (1S,4R)-silyloxy alcohol **6a** would be genarated by treatment of the mixture 5 with PPL, because treatment of a mixture of cis- and trans-1,4-diacetoxy-2-cyclopentene with PPL directly yielded enantiomerically pure (1S,4R)-4-acetoxy-2-cyclopenten-1-ol.[5]

When the acetate 5 in MeOH and phosphate buffer (pH 7) was treated with PPL at 15°C for 12 h, a levorotatory oily alcohol was obtained in 25% yield after chromatographic purification. Its (R)-α-methoxy-α-trifluoromethylphenylacetate (MTPA ester) was prepared in the conventional manner,[11] and analyzed by HPLC to give a single peak. A mixture of all of the four possible (R)-MTPA esters **6b**, **6b'**, **6b"** and **6b"'** was prepared by treating 5

†Assignment of cis-stereochemistry to the crystalline isomer was made possible by comparing the ^1H NMR spectrum of (±)-cis-4 with that of the mixture. Both the CHOH and CHOAc protons of the cis-isomer resonated at higher field than those of the trans-isomer owing to the lack of the shielding effect caused by O atoms.[cf.5]



a) Ac_2O, NaOAc, THF, 35°C, 15 h; b) Cl_2, ether, Et_3N; c) $NaBH_4$, $CeCl_3$, MeOH; d) t-$BuMe_2SiCl$, imidazole, DMF; e) PPL (Sigma L-3126), 0.1M phosphate buffer (pH 7), MeOH; f) PDC, DMF, 5°C

Fig. 2. Preparation of the chiral building block E (7).

recovered unchanged after PPL hydrolysis† with lipase P (Amano Pharmaceutical Co.) for a week at room temp, and acylating the resulting mixture of alcohols with (S)-MTPA Cl. This mixture of the four MTPA esters **6b**, **6b'**, **6b''** and **6b'''** showed only two peaks upon HPLC analysis. Racemic cis-**4** was also converted to a mixture of (R)-MTPA esters **6b** and **6b'** by the following sequence: (i) silylation of (±)-cis-**4** with t-$BuMe_2SiCl$ followed by (ii) removal of Ac by treatment with lipase P, and (iii) acylation with (S)-MTPA Cl. The resulting mixture of **6b** and **6b'** were inseparable when analyzed by HPLC, showing a single peak whose Rt coincided with that of the (R)-MTPA ester derived from the resolved optically active alcohol. The optically active alcohol must therefore be **6a** or its antipode or their mixture. Because **6b** and **6b'** were not separable, HPLC could not be used for the determination of the enantiomeric purity of the resolved alcohol.

To estimate the enantiomeric purity of the resolved alcohol, its (R)-MTPA ester and the mixture of **6b** and **6b'** derived from (±)-cis-**4** were analyzed by ^1H NMR at 400 MHz. In the spectrum of the mixture, the signals due to t-Bu were observed as two singlets at δ 0.879 and δ 0.898, and those due to C=CH appeared as two separate signals at δ 5.878 and δ 5.965. In the spectrum of the (R)-MTPA ester of the resolved alcohol, the signal due to t-Bu appeared as a singlet at δ 0.898, and that due to C=CH was observed at δ 5.878 without any trace of the signals due to the diastereomer. The resolved alcohol was therefore enantiomerically pure.

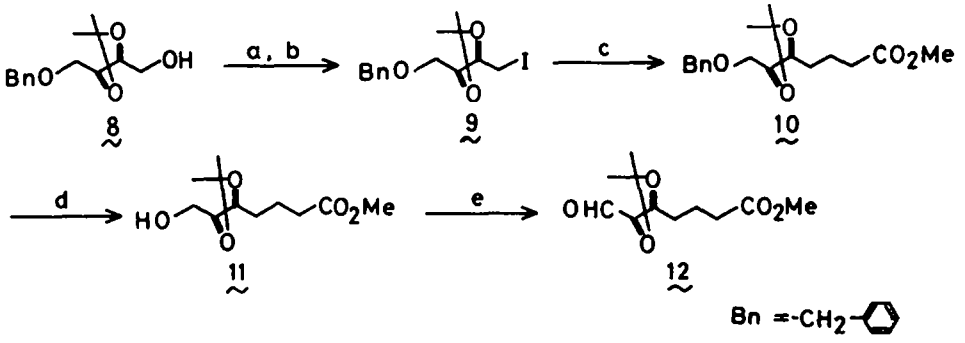
The absolute configuration of the resolved alcohol was assumed to be 1S,4R as depicted in **6a** on the basis of the known enantioselectivity of the hydrolytic reaction with PPL.[5] This assumption was found to be true when the resolved alcohol was oxidized

†The recovered **5** contained more (±)-trans-**5** than the original **5**.

with pyridinium dichromate (PDC) in DMF[12] to give the desired (R)-3-chloro-4-silyloxy-2-cyclopentenone 7, $[\alpha]_D^{25}$+16.2°(n-hexane); $[\theta]_{333}^{24}$ -6940 (n-hexane) <lit.[6] for (S)-7 : $[\theta]_{333}^{25}$ +6700 (hexane)>, in 91% yield. The overall yield of (R)-7 from (±)-2 was 8.2% without optimization or recycle of the unwanted isomers. All of the intermediates (2~6a) were stable, and our method might be a useful alternative in a large-scale preparation. This concluded the preparation of one of the key chiral building blocks by enzymatic method.

Preparation of the aliphatic chiral building block 12.

We then turned our attention to the synthesis of the aliphatic chiral building block B(=12), which in itself[2,4] or as its equivalent[3] was the common intermediate in the existing syntheses of PUG 4. In Yamada's synthesis this building block B was prepared from 2-deoxy-D-ribose,[2] while Noyori employed the Sharpless asymmetric epoxidation to prepare his equivalent of B.[3] Like Sasai and Shibasaki,[4] we started from L-(+)-tartaric



a) MsCl, Et_3N, CH_2Cl_2; b) NaI, $NaHCO_3$, DMF, 70°C, 96 h; c) (n-Bu)$_3$SnCl, $NaBH_4$, CH_2=$CHCO_2Me$, hν, MeOH, 5°C; d) H_2, Pd-black, MeOH; e) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2

Fig. 3. Preparation of the aliphatic chiral building block B (=12).

acid I, but constructed 12 in a different manner as shown in Fig.3. The known alcohol 8 was prepared from L-(+)-tartaric acid in 50.4% yield according to Hungerbühler and Seebach.[13] To prepare 12 from 8, it was necessary to execute efficiently the 3C elongation of the C-chain. Sasai and Shibasaki achieved it in several steps by employing a Wittig reaction.[4] Our strategy was to use a radical reaction for the chain-elongation.[14]

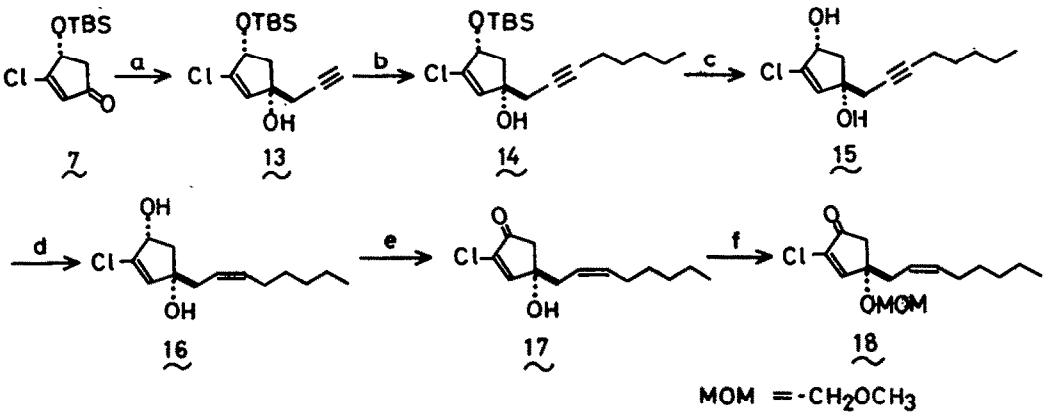
The appropriate substrate for the radical reaction was iodide 9, which was prepared from 8 in a conventional manner in 92% yield via the corresponding mesylate. The radical generated from 9 was added to methyl acrylate, an electron-defficient alkene, to give 10 in 51% yield.[cf.15] This photo-induced radical reaction was a clean one, and the unreacted 9 could be recovered from the reaction mixture. The yield of 10 on the basis of the consumed 9 amounted to 70%. Hydrogenolysis of 10 over Pd-black removed the benzyl protective group to give 11. Oxidation of 11 under the Swern condition with DMSO and $(COCl)_2$[16] gave the desired building block 12, $[\alpha]_D^{25}$ +42.2° ($CHCl_3$),† in 40% overall yield from 8 or in 20% overall yield from L-(+)-tartaric acid.

Attachment of (Z)-2-octenyl side-chain to 7 to give 18.

The third phase of our work was the attachment of (Z)-2-octenyl side-chain to the cyclopentene part 7 to give A (=18). We did this stepwise to furnish pure 18 in accepta-

†The same compound 12 as prepared by other groups showed far smaller $[\alpha]_D$ values (+6.3° as reported by Yamada,[2] and +5.8° as reported by Shibasaki.[4] We repeated the preparation of 12 several times, and observed the same $[\alpha]_D$ values (+42°) for different batches of 12. The reason for this discrepancy is unclear at present.

ble overall yield. Addition of the dianion derived from propyne ($LiCH_2C{\equiv}CLi$)[17] to **7** gave **13** stereoselectively. As direct quenching of the dianion of **13** in the reaction mixture by alkylation with n-$C_5H_{11}I$ was not so reproducible, **13** was first isolated in 84% yield, and then converted again to the dianion with n-BuLi in Et_2O-HMPA. This was alkylated with n-$C_5H_{11}I$ to give **14** in 55% yield with 46% recovery of **13**. Accordingly, the yield of **14** on the basis of the consumed **13** was as high as 93%. Removal of the silyl protective group of



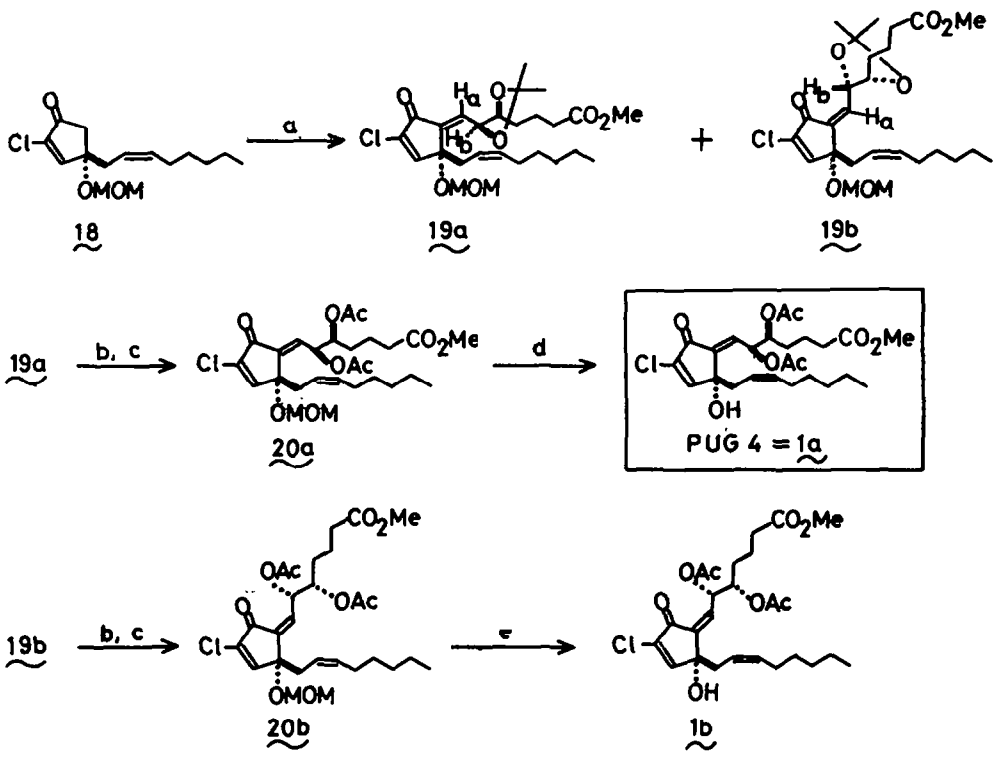
a) MeC≡CH, n-BuLi, THF; b) n-BuLi, n-$C_5H_{11}I$, Et_2O, HMPA; c) $(n\text{-}Bu)_4NF$, THF; d) H_2, Lindlar Pd-$CaCO_3$-$Pb(OAc)_2$, MeOH; e) PDC, DMF; f) $ClCH_2OMe$, $(i\text{-}Pr)_2NEt$, $ClCH_2CH_2Cl$

Fig. 4. Attachment of (Z)-2-octenyl side-chain to 7 to give A (=18).

14 with $(n\text{-}Bu)_4NF$ gave diol **15** in 70% yield after chromatographic purification and recrystallization, m.p. 91-92°C, $[\alpha]_D^{24}$+86.7° ($CHCl_3$) <lit.[3] its antipode: $[\alpha]_D^{11}$-56.4°($CHCl_3$)>. Semi-hydrogenation of **15** over Lindlar-Pd[18] in MeOH gave **16**, $[\alpha]_D^{24}$+36.5°($CHCl_3$), <lit.[3] its antipode: $[\alpha]_D^{21}$-23.0°($CHCl_3$)>. PDC oxidation of **16** gave **17**, whose t-OH group was protected as MOM group to give the chiral building block **A** (=**18**), $[\alpha]_D^{22}$+49.5°($CHCl_3$), <lit.[9] its antipode: $[\alpha]_D$-40.2°($CHCl_3$)>. We were thus able to prepare the partner **A** for the aldol reaction with **B** in 23% overall yield from **7**.

Aldol reaction between 12 and 18 and the completion of the synthesis.

With the two building blocks **A** (=**12**) and **B** (=**18**) in hand, we came to the final stage of combining these two by the aldol reaction as reported by others.[2-4] Thus the aldol reaction between **12** and **18** employing lithium diisopropylamide (LDA) in THF gave, after chromatographic separation, the desired (E)-isomer **19a** (25% yield) as the more polar one, while the earlier eluted fraction gave the less polar (Z)-isomer **19b** (37% yield). In their ^1H NMR spectra, the signal due to H_a of **19a** appeared at δ 6.58 (dd, J=0.7 and 10.3 Hz), while that of **19b** appeared at δ 6.18 (d, J=9.3 Hz). The signal due to H_b of **19a** was observed at δ 4.70 (dd, J=7.9 and 10.3 Hz), while that of **19b** appeared at δ ~5.4. The above observation was the basis on which we assigned the E-and Z-geometries to the respective isomers, considering the shielding effect caused by the CO group. Treatment of **19a** with hot 80% AcOH aq removed the isopropylidene protective group to give a diol, whose acetylation yielded **20a**. Finally, the MOM group of **20a** was removed by hydrolysis with aq HCl-AcOH to give PUG 4 (**1a**), $[\alpha]_D^{24}$+72.3°($CHCl_3$), <lit.[2,19] $[\alpha]_D^{25}$+72.3°($CHCl_3$); Prof.



a) LDA, 12, THF; b) 80% AcOH-H_2O, 60°C; c) Ac_2O, C_5H_5N, CH_2Cl_2; d) AcOH-H_2O-conc.HCl (16:4:1), 60°C, 15 min; e) 80% AcOH-H_2O, 100°C, 1.5 h

Fig. 5. Synthesis of PUG 4 (1a) and its (Z)-isomer 1b.

Scheuer's authentic PUG 4[19]: $[\alpha]_D^{25}$+65.6°($CHCl_3$)›, in 6.0% yield from **18**. The 400 MHz ^1H NMR spectrum of our synthetic PUG 4 **1a** was completely identical to the authentic spectrum of PUG 4 provided by Prof. Y. Yamada. In the same manner , **19b** was converted to the (Z)-isomer **1b** of PUG 4, $[\alpha]_D^{24}$+102.3°($CHCl_3$), in 13.7% yield from **18**.

In conclusion, (+)-punaglandin 4 (**1a**) was synthesized in 1.4% overall yield from the chiral chlorocyclopentene derivative **7**, which was prepared by enzymatic method. The overall yield of the (Z)-isomer of punaglandin 4 was 3.1% from **7**.

EXPERIMENTAL

All b.ps and m.ps were uncorrected. IR spectra were measured as films for oils or as KBr discs for solids on a Jasco IRA-102 spectrometer. ^1H NMR spectra were recorded with TMS as an internal standard as $CDCl_3$ soln at 60 MHz on a Hitachi R-24A spectrometer or at 100 MHz on a JEOL JNM FX-100 spectrometer or at 400 MHz on a JEOL JNM GX-400 spectrometer. Optical rotations were measured on a Jasco DIP 140 polarimeter. CD spectra were measured on a Jasco J-20C spectropolarimeter. Mass spectra were recorded on a JEOL JMS HX-110 spectrometer. Merck Kiesel-gel 60 (particle size 0.063-0.200 mm) or Fuji-Davison BW-820 MH were used for SiO_2 column chromatography.

4-Acetoxy-2-chloro-2-cyclopentenone **3**. To a soln of 4-hydroxycyclopent-2-enone **2** (30.2 g, 0.308 mol) in THF (150 ml) was added NaOAc (50.5 g, 0.616 mol) and Ac_2O (47.2 g, 0.462 mol) at room temp and the mixture was stirred for 15 h at 35°C. Then the mixture was diluted with water and extracted with EtOAc. The EtOAc soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in ether (540 ml), and Cl_2 gas was slowly bubbled into the stirred soln for 1.5 h at 26-29°C. The soln was then swept with N_2 to remove residual Cl_2 and cooled at 5°C. Et_3N (100 ml, 0.72 mol) was slowly added to the vigorously stirred mixture at 5-15°C. Then the mixture was poured into 10% NH_4Cl aq and extracted with ether. The ether soln was washed with brine, 2N-HCl and brine, dried ($MgSO_4$) and concentrated in vacuo. The oily residue was left to stand for solidification and it was recrystallized from ether-n-hexane to give 27.0 g (50%) of pure **3** as white crystals, m.p. 55°; νmax 1740 (s), 1610 (m), 1240 (s), 1036 (m), 957 (m) cm^{-1}; δ (60 MHz) 2.08 (3H, S), 2.44 (1H, dd, J=2.0, 18 Hz), 2.87 (1H, dd, J=6.3, 18 Hz), 5.75 (1H, m), 7.50 (1H, d, J=3.0 Hz); (Found: C, 48.14; H, 4.06. Calc for $C_7H_7O_3Cl$: C, 48.16; H, 4.04%).

3-Acetoxy-2-chloro-2-cyclopenten-1-ol **4**. To a stirred mixture of **3** (27.0 g, 0.155 mol) and $CeCl_3\ 7H_2O$ (63.7 g, 0.171 mol) in MeOH (750 ml) was added $NaBH_4$ (6.4 g, 0.169 mol) portionwise at 22-25°C. After stirring for 20 min, the mixture was poured into sat NH_4Cl aq and concentrated in vacuo to remove MeOH. The residue was diluted with 0.5 N-HCl, and the mixture was extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give 22.4 g of **4** as a crude solid. This was employed in the next step without further purification. A small amount of this was recrystallized from n-hexane-ether to give pure cis-(±)-**4**, m.p. 63°C; νmax 3370 (s), 3100 (w), 1730 (s), 1635 (m), 1250 (s) cm^{-1}; δ (100MHz) 1.87 (1H, ddd, J=4.4, 4.4, 15 Hz), 2.08 (3H, s), 2.37 (1H, d, J=6.5 Hz), 2.88 (1H, ddd, J=7.9, 8.1, 15 Hz), 4.35-4.57 (1H, m), 5.35-5.68 (1H, m), 5.92-6.04 (1H, m). (Found: C, 47.50; H, 5.06. Calc for $C_7H_9O_3Cl$: C, 47.61; H, 5.14%).

3-Acetoxy-5-tert-butyldimethylsilyloxy-1-chlorocyclopentene **5**. To a stirred soln of crude **4** (22.2 g) in DMF (220 ml) was added t-$BuMe_2SiCl$ (24.0 g, 0.159 mol) and imidazole (13.0 g, 0.191 mol) at room temp, and the mixture was stirred for 5 h at room temp. It was then poured into water and extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (470 g). Elution with n-hexane-EtOAc (15:1) gave 32.3 g (71% from **3**) of **5** as a colorless oil, n_D^{24} 1.4604; νmax 1750 (s), 1635 (m), 1240 (s) cm^{-1}; δ (60 MHz) 0.11 (6H, s), 0.91 (9H, s), 2.01 and 2.03 (each s, total 3H), 4.50 and 4.82 (1H, m), 5.17-5.77 (1H, m), 5.87 (1H, m). (Found: C, 53.44; H, 7.98. Calc for $C_{13}H_{23}O_3ClSi$: C, 53.68; H, 7.97%).

(1S,4R)-4-tert-Butyldimethylsilyloxy-3-chloro-2-cyclopenten-1-ol **6a**. To a soln of **5** (30.0 g, 0.103 mol) in MeOH (600 ml) was added 0.1M phosphate buffer (pH 7, 1800 ml) and PPL (15.0 g, SIGMA L-3126). The mixture was stirred for 12 h at 15°C. Then the mixture was extracted with ether. The ether soln was dried ($MgSO_4$), and concentrated in vacuo. The residue was chromatographed over SiO_2 (450 g). Elution with n-hexane-EtOAc (15:1) gave 21.2 g of acetates which consist of trans-**5** and cis-(3R,5S)-**5**. Further elution with n-hexane-EtOAc (3:1) gave 6.4 g (25%) of **6a** as a colorless oil, n_D^{25} 1.4711; $[\alpha]_D^{25}$ -31.7° (c=0.75, MeOH); νmax 3370 (s), 1630 (m) cm^{-1}; δ (100 MHz) 0.13 (3H, s), 0.15 (3H, s), 0.93 (9H, s), 1.68 (1H, ddd, J=4.4, 4.4, 14 Hz), 1.88 (1H, bs), 2.80 (1H, ddd, J=7.0, 7.0, 14Hz), 4.48 (1H, dd, J=4.4, 7.0 Hz), 4.38-4.73 (1H, m), 5.94 (1H, d, J= 2.6Hz). (Found: C, 52.61; H, 8.46. Calc for $C_{11}H_{21}O_2ClSi$: C, 53.10; H, 8.51%). A small amount of **6a** was converted to the corresponding (R)-MTPA ester in the conventional manner, which was submitted to the HPLC analysis and 400 MHz ^1H NMR measurement. HPLC (column, Senshu pack silica 1251N, 25 cm x 4.6 mm; solvent, n-hexane-THF (30:1), 1.0 ml/min; Detected at 254 nm) Rt of cis-**6** MTPA ester was 7.3 min and trans-**6** MTPA ester (Rt 6.1 min) was not detected. In 400 MHz ^1H NMR spectra, the signal due to the enantiomer was not detectable. Therefore our **6a** was of ca 100% e.e. **6b**, δ (400 MHz) 0.105 (3H, s), 0.130 (3H, s), 0.898 (9H, s), 1.881 (1H, ddd, J=4.4, 4.4, 14 Hz), 2.954 (1H, ddd, J=6.9, 6.9, 14 Hz), 5.878 (1H, dd, J=4.0, 9.2 Hz); **6b**, δ (400 MHz) 0.083 (3H, s), 0.118 (3H, s), 0.879 (9H, s), 1.803 (1H, ddd, J=4.4, 4.4, 14 Hz), 2.887 (1H, ddd, J=6.9, 6.9, 14 Hz), 5.965 (1H, dd, J=4.0, 9.2 Hz).

(R)-4-tert-Butyldimethylsilyloxy-3-chloro-2-cyclopentenone **7**. To a soln of **6a** (5.10 g, 20.5 mmol) in dry DMF (100 ml) was added PDC (27.0 g, 71.8 mmol) at 5°C and the mixture was stirred for 3 h at 5°C. It was then poured into water, and extracted with n-hexane. The extract was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (45 g). Elution with n-hexane-EtOAc (10:1) gave 4.61 g (91%) of **7** as a colorless oil, n_D^{24} 1.4734; $[\alpha]_D^{25}$ +16.2° (c=1.1, n-hexane); $[\Theta]_{333}^{24}$ -6940 (c=0.48, n-hexane), νmax 1730 (s), 1597 (m), 1260 (s), 1110 (s), 940 (m), 839 (s), 780 (m) cm^{-1}; δ (60 MHz) 0.16 (3H, s), 0.18 (3H, s), 0.93 (9H, s), 2.37 (1H, dd, J=2.2, 17.6 Hz), 2.83 (1H, dd, J=5.8, 17.6 Hz), 4.78 (1H, deformed dd, J=2.2, 5.8 Hz), 6.19 (1H, d, J=1.4 Hz). (Found: C, 53.33; H, 7.79. Calc for $C_{11}H_{19}O_2ClSi$: C, 53.53; H, 7.76%).

(4S,5R)-4-Benzyloxymethyl-5-iodomethyl-2,2-dimethyl-1,3-dioxolane **9**. MsCl (8.71 g, 76 mmol) was slowly added to a stirred soln of **8** (17.4 g, 69 mmol) and Et_3N (10.5 g, 0.104 mol) in CH_2Cl_2 (100 ml) at -20°C. The mixture was stirred for 2 h at -20°C. It was then poured into water and extracted with CH_2Cl_2. The CH_2Cl_2 soln was washed with sat $NaHCO_3$ aq, water, dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in DMF (450 ml). To this soln were added NaI (155.0 g, 1.03 mol) and $NaHCO_3$ (29.2 g, 0.35 mol) and the mixture was stirred vigorously for 96 h at 70°C. After cooling, the mixture was poured into water and extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (250 g). Elution with n-hexane-EtOAc (8:1) gave 23.2 g (92%) of **9** as a colorless oil, n_D^{23} 1.5355; $[\alpha]_D^{23}$ -10.1° (c=2.1, $CHCl_3$); νmax 1500 (m), 1240 (s), 1215 (s), 1095 (s), 1080 (s) cm^{-1}; δ (100 MHz) 1.43 (3H, d, J=0.5 Hz), 1.48 (3H, s), 3.29 (1H, dd, J=5.2, 10.4 Hz), 3.33 (1H, dd, J=4.7, 10.4 Hz), 3.53-3.71 (2H, m), 3.71-4.20 (2H, m), 4.61 (2H, s), 7.35 (5H, s). (Found: C, 46.09; H, 5.27. Calc for $C_{14}H_{19}O_3I$: C, 46.42; H, 5.29%).

Methyl (5S,6S)-7-benzyloxy-5,6-isopropylidenedioxyheptanoate **10**. A soln of **9** (7.24 g, 0.02 mol), methyl methacrylate (17.22 g, 0.20 mol) and $(n\text{-}Bu)_3SnCl$ (1.30 g, 4 mmol) in dry MeOH (250 ml) was irradiated (Quartz reaction vessel) with a high-pressure Hg lamp (450 W) at 5°C, and $NaBH_4$ (18.9 g, 0.5 mol) was added portionwise over 3 h. After irradiation for 1

h, the mixture was treated with a sat KF aq (6 ml) for 12 h at room temp. The mixture was filtered over Celite and the filtrate was concentrated in vacuo. The residue was chromatographed over SiO_2 (900 g). Elution with n-hexane-EtOAc (10:1) first afford 2.18 g of **9** and further elution gave 3.16 g (51%) of **10** as a colorless oil, n_D^{23} 1.4826; $[\alpha]_D^{23}$ -11.2° (c=3.4, $CHCl_3$); νmax 3100 (w), 3080 (w), 3050 (w), 1740 (s), 1500 (w), 1245 (s), 1215 (s), 1170 (s), 1090 (s) cm^{-1}; δ (100 MHz) 1.41 (6H, s), 1.44-2.05 (4H, m), 2.36 (2H, deformed t, J= 7.2Hz), 3.20-3.61 (2H, m), 3.67 (3H, s), 3.70-3.97 (2H, m), 4.59 (2H, s), 7.34 (5H, s). (Found: C, 66.79; H, 8.10. Calc for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13%).

Methyl (5S,6S)-7-hydroxy-5,6-isopropylidenedioxyheptanoate **11**. A soln of **10** (3.08 g, 9.55 mmol) in MeOH (60 ml) was hydrogenated (1 atm) over Pd-black (0.6 g) for 48 h at room temp. The Pd-black was filterd off, and the filtrate was concentrated in vacuo. The residue was chromatographed over SiO_2 (30 g). Elution with $CHCl_3$-MeOH (40:1) gave 2.18 g (98%) of **11** as a colorless oil, n_D^{24} 1.4466; $[\alpha]_D^{24}$ -23.9° (c=0.59, $CHCl_3$); νmax 3500 (s), 1740 (s), 1250 (s), 1220 (s), 1170 (s), 1090 (s), 1050 (s) cm^{-1}; δ (100 MHz) 1.43 (6H, s), 1.45-2.10 (5H, m), 2.38 (2H, deformed dd, J=7.0, 7.0 Hz), 3.40-4.10 (4H, m), 3.69 (3H, s). (Found: C, 56.58; H, 8.59. Calc for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68%).

Methyl (5S,6R)-5,6-isopropylidenedioxy-7-oxo-heptanoate **12**. A soln of $(COCl)_2$ (1.86 ml, 20.4 mmol) in CH_2Cl_2 (70 ml) was cooled at -60°C. DMSO (2.08 ml, 26.8 mmol) was added to the stirred soln at -60°C. Then a soln of **11** (2.13 g, 9.2 mmol) in CH_2Cl_2 (10 ml) was added to the stirred mixture at -70°C. After stirring for 15 min, Et_3N (9.5 ml, 67.6 mmol) was added to the stirring mixture at -78°C. The mixture was stirred for 30 min at -78°C, then water was added and the mixture was extracted with CH_2Cl_2. The CH_2Cl_2 soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (50 g). Elution with n-hexane-EtOAc (3:1) gave 1.84 g (87%) of **12** as a colorless oil, n_D^{25} 1.4385; $[\alpha]_D^{25}$ +42.2° (c=1.0, $CHCl_3$); νmax 1740 (s), 1215 (s), 1168 (s), 1083 (s) cm^{-1}; δ (100 MHz) 1.43 (3H, s), 1.49 (3H, s), 1.52-2.08 (4H, m), 2.20-2.50 (2H, m), 3.69 (3H, s), 3.97 (1H, dd, J=1.9, 7.0 Hz), 3.85-4.30 (1H, m), 9.73 (1H, d, J=1.9 Hz). (Found: C, 57.88; H, 7.92. Calc for $C_{11}H_{18}O_5$: C, 57.38; H, 7.88%).

(1S,4R)-4-tert-Butyldimethylsilyloxy-3-chloro-1-(2-propynyl)-2-cyclopenten-1-ol **13**. A soln of n-BuLi in n-hexane (1.6 M, 180 ml) was added to dry THF at -50°C under Ar. The mixture was immediately cooled to -30°C and liquid propyne (4.61 g, 0.115 mol) was added over 30 min, while keeping the temp below -20°C. Then the mixture was warmed gradually to 25°C and stirred for 2h at 25-30°C. After cooling to -78°C, a soln of **7** (4.61 g, 19mmol) in dry THF (30 ml) was added to the stirred mixture over 40 min. The stirring was continued for 30 min at -78°C. The mixture was quenched by the addition of a soln of AcOH (17 ml) in MeOH (20 ml). It was then poured into brine and extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (400 g). Elution with n-hexane-EtOAc (8:1) gave 4.53 g (84%) of **13** as a colorless oil, n_D^{25} 1.4776; $[\alpha]_D^{25}$ +49.2° (c=0.38, $CHCl_3$); νmax 3430 (s), 3350 (m), 1635 (m), 1260 (m), 1095 (s), 870 (s), 840 (s) cm^{-1}; δ (100 MHz) 0.13 (3H, s), 0.15 (3H, s), 0.93 (9H, s), 1.92 (1H, dd, J=4.1, 13.9 Hz), 2.06 (1H, d, J=2.6 Hz), 2.33 (1H, s), 2.52 (2H, d, J=2.6 Hz), 2.66 (1H, dd, J=7.2, 13.9 Hz), 4.57 (1H, ddd, J=0.8, 4.1, 7.2 Hz), 5.89 (1H, d, J=0.8 Hz). (Found: C, 58.43; H, 8.15. Calc for $C_{14}H_{23}O_2ClSi$: C, 58.62; H, 8.08%).

(1S,4R)-4-tert-Butyldimethylsilyloxy-3-chloro-1-(2-octynyl)-2-cyclopenten-1-ol **14**. To a stirred soln of **13** (4.3 g, 15 mmol) in dry HMPA (20 ml) and dry ether (80 ml) was added n-BuLi in hexane (1.6 M, 29 ml) at -40°C under Ar. After stirring for 1 h, n-$C_5H_{11}I$ (10.11 g, 51 mmol) was added to the stirred mixture at -40°C. The stirring was continued for 14 h at -45--20°C. 10% NH_4Cl aq (100 ml) was then added and the mixture was extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (600 g). Elution with n-hexane-EtOAc (12:1) gave 2.71 g (50%) of **14**, n_D^{25} 1.4747; $[\alpha]_D^{25}$ +43.3° (c=0.18, $CHCl_3$); νmax 3410 (s), 1635 (m), 1095 (s), 865 (s), 840 (s), 780 (m) cm^{-1}; δ (100 MHz) 0.13 (3H, s), 0.15 (3H, s), 0.93 (9H, s), 1.00-1.70 (6H, m), 1.89 (1H, dd, J=4.1, 13.9 Hz), 2.02-2.26 (2H, m), 2.30 (1H, s), 2.48 (2H, t, J=2.6 Hz), 2.64 (1H, dd, J=7.2, 13.9 Hz), 4.55 (1H, ddd, J=0.8, 4.1, 7.2 Hz), 5.87 (1H, d, J=0.8 Hz). (Found: C, 63.61; H, 9.36. Calc for $C_{19}H_{33}O_2ClSi$: C, 63.92; H, 9.32%). Further elution with the same solvent gave 1.97 g of **13**.

(1S,4R)-3-Chloro-1-(2-octynyl)-2-cyclopentene-1,4-diol **15**. A soln of $(n\text{-}Bu)_4NF$ in THF (1.0 M, 42 ml) was added to the stirred **14** (4.4 g, 12.3 mmol). The soln was stirred for 7 h at 10°C. It was then poured into brine and extraced with EtOAc. The EtOAc soln was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (130 g). Elution with n-hexane-EtOAc (2:1) gave crystalline solid, which was recrystallized from $CHCl_3$-n-hexane to give 2.10 g (70%) of **15**, m.p. 91-92°C; $[\alpha]_D^{24}$ +86.7° (c=0.18, $CHCl_3$); νmax 3280 (s), 1628 (m), 1332 (m), 1086 (m), 1020 (s) cm^{-1}; δ (100 MHz) 0.76-1.06 (3H, m), 1.14-1.63 (6H, m), 1.98 (1H, dd, J=3.8, 13.9 Hz), 2.07-2.40 (4H, m), 2.52 (2H, t, J=2.9 Hz), 2.67 (1H, dd, J=6.7, 13.9 Hz), 4.56 (1H, ddd, J=3.8, 6.7, 6.7 Hz), 5.96 (1H, s). (Found: C, 64.17; H, 7.90. Calc for $C_{13}H_{19}O_2Cl$: C, 64.32; H, 7.89%).

(1S,4R)-3-Chloro-1-[(Z)-2-octenyl]-2-cyclopentene-1,4-diol **16**. A soln of **15** (2.07 g, 8.53 mmol) in MeOH (42 ml) was hydrogenated (1 atm) over the Lindlar catalyst (0.21 g) for 5h at room temp. The catalyst was filtered off, and the filtrate was concentrated in vacuo. The residue was chromatographed over SiO_2 (50 g). Elution with n-hexane-EtOAc (2:1) gave 2.02 g (96%) of **16** as a waxy solid, $[\alpha]_D^{24}$ +36.5° (c=0.20, $CHCl_3$); νmax 3300 (s), 3040 (m), 1630 (m), 1330 (s), 1055 (s), 1015 (s) cm^{-1}; δ (100 MHz) 0.92 (3H, m), 1.30 (6H, m), 1.75-2.25 (3H, m), 2.25-2.85 (5H, m), 4.50 (1H, m), 5.15-5.80 (2H, m), 5.90 (1H, s). (Found: C, 63.73; H, 8.55. Calc for $C_{13}H_{21}O_2Cl$: C, 63.79; H, 8.65%).

(S)-2-Chloro-4-hydroxy-4-[(Z)-2-octenyl]-2-cyclopentenone **17**. A soln of **16** (1.92 g, 7.84 mmol) in DMF (10 ml) was added to a stirred soln of PDC (17.75 g, 47.18 mmol) in DMF (90 ml). The soln was stirred for 4 h at 5°C. Then the mixture was poured into water and extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give 1.91 g of crude **17**. νmax 3450 (s), 3080 (w), 3030 (w), 1730 (s), 1600 (m), 1060 (m), 960 (m) cm^{-1}; δ (100 MHz) 0.91 (3H, m), 1.29 (6H, m), 1.70-2.30 (3H, m), 2.30-2.90 (4H, m), 5.15-5.90 (2H, m), 7.37 (1H, s). This was employed in the

next step without further purification.

(S)-2-Chloro-4-methoxymethyloxy-4-[(Z)-2-octenyl]-2-cyclopentenone **18**. MOM chloride (3.0 ml, 39.5 mmol) was added dropwise to a stirred soln of crude **17** (1.89 g, 7.78 mmol) and i-Pr_2NEt (6.0 ml, 34.4 mmol) in 1,2-dichloroethane (50 ml) at 60°C. After stirring for 2 h, the mixture was poured into water and the aq layer was extracted with CH_2Cl_2. The CH_2Cl_2 soln was washed with dil-HCl, water, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (45 g). Elution with n-hexane-EtOAc (9:1) gave 1.62 g (82%) of **18** as a colorless oil, n_D^{22} 1.4859; $[\alpha]_D^{22}$ +49.5° (c=0.47, $CHCl_3$); νmax 3090 (w), 3030 (m), 1735 (s), 1600 (m), 1150(s), 1090 (s), 1025 (s), 955 (s) cm^{-1}; δ (100 MHz) 0.88 (3H, m), 1.28 (6H, m), 1.97 (2H, m), 2.35-2.95 (4H, m), 3.38 (3H, s), 4.63 (1H, d, J=8.2 Hz), 4.70 (1H, d, J=8.2 Hz), 5.13-5.77 (2H, m), 7.40 (1H, s). (Found: C, 62.63; H, 8.05. Calc for $C_{15}H_{23}O_3Cl$: C, 62.82; H, 8.08%).

Methyl (5S,6S)-5,6-isopropylidenedioxy-(7E)-7-[(2R)-4-chloro-2-methoxymethyloxy-2-[(Z)-2-octenyl]-5-oxo-3-cyclopentenylidene]heptanoate **19a**. and Methyl (5S,6S)-5,6-isopropylidenedioxy-(7Z)-7-[(2R)-4-chloro-2-methoxymethyloxy-2-[(Z)-2-octenyl]-5-oxo-3-cyclopentenylidene]heptanoate **19b**. A soln of LDA was prepared by the addition of a soln of n-BuLi in n-hexane (1.53 M, 1.5 ml) to a stirred and cooled soln of $(i\text{-}Pr)_2NH$ (0.32 ml) in dry THF (8 ml) at -50°C under Ar. After stirring for 1 h, a soln of **18** (0.65 g, 2.27 mmol) in dry THF (3 ml) was slowly added to the stirred soln at -78°C. After stirring for 45 min, a soln of **12** (2.12 g, 9.21 mmol) in dry THF (4 ml) was added rapidly at -78°C. The cooling bath was then removed and the stirring was continued for 3 h at -10°C. The reaction was quenched by the addition of sat NH_4Cl aq. The mixture was extracted with ether. The ether soln was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (200 g). Elution with n-hexane-EtOAc (9:1) gave 70 mg of **18**. Further elution with the same solvent gave 0.42 g (37%) of **19b**, n_D^{19} 1.4926; $[\alpha]_D^{19}$ +11.8° (c=0.63, $CHCl_3$); νmax 3100 (w), 3000 (m), 1740 (s), 1720 (s), 1670 (m), 1595 (m), 1160 (s), 1095 (s), 1030 (s) cm^{-1}; δ (100 MHz) 0.89 (3H, m), 1.27 (6H, m), 1.44 (6H, s), 1.47-2.12 (6H, m), 2.15-2.68 (4H, m), 3.38 (3H, s), 3.66 (3H, s), 3.73 (1H, m), 4.52 (2H, s), 5.05-5.73 (3H, m), 6.18 (1H, d, J=9.3 Hz), 7.28 (1H, s). (Found: C, 62.41; H, 7.89. Calc for $C_{26}H_{39}O_7Cl$: C, 62.58 ; H, 7.88%). Further elution gave 0.28 g (25%) of **19a**, n_D^{19} 1.4942; $[\alpha]_D^{19}$ -26.9° (c=0.63, $CHCl_3$); νmax 3100 (w), 3000 (m), 1740 (s), 1725 (s), 1675 (m), 1595 (m), 1160 (s), 1095 (s), 1025 (s) cm^{-1}; δ (100 MHz) 0.89 (3H, m), 1.28 (6H, m), 1.45 (6H, s), 1.48-2.16 (6H, m), 2.35 (2H, deformed t, J=7.3 Hz), 2.68 (1H, dd, J=7.9, 14.7 Hz), 2.86 (1H, dd, J=6.7, 14.7 Hz), 3.39 (3H, s), 3.67 (3H, s), 3.72-4.00 (1H, m), 4.48 (2H, s), 4.70 (1H, dd, J=7.9, 10.3 Hz), 5.13-5.74 (2H, m), 6.58 (1H, dd, J=0.7, 10.3 Hz), 7.37 (1H, d, J=0.7 Hz). (Found: C, 62.41; H, 7.99. Calc for $C_{26}H_{39}O_7Cl$: C, 62.58; H, 7.88%).

Methyl (5S,6S)-5,6-diacetoxy-(7E)-7-[(2R)-4-chloro-2-methoxymethyloxy-2-[(Z)-2-octenyl]-5-oxo-3-cyclopentenylidene]heptanoate **20a**. A soln of **19a** (0.19 g, 0.38 mmol) in AcOH (40 ml) and H_2O (10 ml) was stirred and heated at 60°C for 2 h. Then the soln was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (10 ml). To this was added C_5H_5N (7 ml) and Ac_2O (3 ml) at room temp and the mixture was stirred for 10 h at 45°C. After cooling, the mixture was poured into dil-HCl and extracted with CH_2Cl_2. The CH_2Cl_2 soln was washed with water, dried ($MgSO_4$) and concentrated in vacuo to give 0.19 g of crude **20a**. This was employed in the next step without further purification.

Methyl (5S,6S)-5,6-diacetoxy-(7Z)-7-[(2R)-4-chloro-2-methoxymethyloxy-2-[(Z)-2-octenyl]-5-oxo-3-cyclopentenylidene]heptanoate **20b**. A soln of **19b** (0.20 g, 0.4 mmol) in AcOH (40 ml) and H_2O (10 ml) was stirred and heated at 60°C for 1.5 h. Then the soln was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (10 ml). To this was added C_5H_5N (7 ml) and Ac_2O (3 ml) at room temp and the mixture was stirred for 10 h at 45°C. After cooling, the mixture was poured into dil HCl and extracted with CH_2Cl_2. The CH_2Cl_2 soln was washed with water , dried ($MgSO_4$) and concentrated in vacuo to give 0.21 g of crude **20b**. This was employed in the next step without further purification.

Methyl (5S,6S,7E)-7-[(2R)-4-chloro-2-hydroxy-2-[(Z)-octenyl]-5-oxo-3-cyclopentenylidene]-5,6-diacetoxyheptanoate [(+)-punaglandin 4] **1a**. A soln of crude **20a** (0.19 g) in AcOH (16 ml), H_2O (4 ml) and conc.HCl (1 ml) was stirred and heated at 60°C for 15 min. It was then poured into water and extracted with $CHCl_3$. The $CHCl_3$ soln was washed with water, dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over SiO_2 (25 g). Elution with n-hexane-EtOAc (3:1) gave 45 mg (24%) of **1a** as an oil, n_D^{24} 1.4967; $[\alpha]_D^{24}$ +72.3° (c=0.52, $CHCl_3$) <lit.[2,18] $[\alpha]_D^{25}$ +72.3° (c=0.39, $CHCl_3$); Prof. Scheuer's authentic PUG 4[18]: $[\alpha]_D^{25}$ +65.6° (c=0.19, $CHCl_3$)> ; $[\theta]_{358}^{24}$ +9300; $[\theta]_{249}^{24}$ -38000 (c=0.1, $CHCl_3$); νmax 3480 (m), 3080 (w), 3030 (w), 2975 (m), 2950 (m), 2870 (m), 1745 (s), 1725 (s), 1680 (m), 1595 (m), 1460 (sh), 1455 (sh), 1440 (m), 1375 (m), 1225 (s), 1170 (m), 1060 (sh), 1040 (m), 1025 (m), 960 (m), 880 (m), 820 (m), 765 (m), 730 (w) cm^{-1}; δ (400 MHz) 0.89 (3H, t, J=7.0 Hz), 1.20-1.38 (6H, m), 1.54-1.75 (4H, m), 2.00 (2H, ddd, J=7.0, 7.0, 7.0 Hz), 2.05 (3H, s), 2.13 (3H, s), 2.26-2.38 (2H, m), 2.68 (1H, dd, J=7.2, 14.5 Hz), 3.01 (1H, dd, J=8.5, 14.5 Hz), 3.56 (1H, bs), 3.66 (3H, s), 5.20-5.33 (2H, m), 5.52-5.61 (1H, m), 6.04 (1H, dd, J=4.4, 9.0 Hz), 6.38 (1H, dd, J=0.8, 9.0 Hz), 7.28 (1H, d, J=0.8 Hz); FD-MS:m/z 499 (M^++1, 14.92), 482 (30.90), 465 (1.96), 439 (5.54), 387 (base peak). (Found: C, 60.03; H, 7.02. Calc for $C_{25}H_{35}O_8Cl$: C, 60.18; H, 7.07%).

Methyl (5S,6S,7Z)-7-[(2R)-4-chloro-2-hydroxy-2-[(Z)-2-octenyl]-5-oxo-3-cyclopentenylidene]-5,6-diacetoxyheptanoate **1b**. A soln of crude **20b** (0.21 g) in AcOH (16 ml) and H_2O (4 ml) was stirred and heated at 100°C for 1.5 h and then concentrated in vacuo. The residue was chromatographed over SiO_2 (20 g). Elution with n-hexane-EtOAc (3:1) gave 74 mg (37%) of **1b** as an oil, n_D^{24} 1.4931; $[\alpha]_D^{24}$ +102.3° (c=0.52, $CHCl_3$); $[\theta]_{367}^{24}$ +13000; $[\theta]_{282}^{24}$ -35000 (c=0.18, $CHCl_3$); νmax 3450 (m), 3070 (w), 3030 (w), 2970 (m), 2940 (m), 2860 (m), 1750 (sh), 1745 (s), 1720 (sh), 1715 (s), 1665 (m), 1590 (m), 1460 (sh), 1450 (sh), 1435 (m), 1370 (m), 1220 (s), 1165 (m), 1060 (m), 1030 (m), 955 (m), 910 (w), 880 (m), 785 (w), 730 (w) cm^{-1}; δ (400 MHz) 0.89 (3H, t, J=7.0 Hz), 1.20-1.39 (6H, m), 1.60-1.78 (4H, m), 1.99 (2H, dddd, J=1.0, 7.4, 7.4, 7.4 Hz), 2.05 (3H, s), 2.13 (3H, s), 2.35 (2H, m), 2.45 (1H, ddd, J=1.0, 7.2, 14.5 Hz), 2.57 (1H, ddd, J=1.0, 7.8, 14.5 Hz), 2.64 (1H, bs), 3.66 (3H, s), 5.18-5.30 (2H, m), 5.55-5.64 (1H, m), 6.09 (1H, d, J=7.6 Hz), 6.34 (1H, dd, J=3.8, 7.6 Hz), 7.21 (1H,s); FD-MS:m/z 499 (M^++1, 7.92), 481 (4.18), 464 (2.11), 439 (3.75), 387 (base peak). (Found: C, 59.82; H, 7.05. Calc for $C_{25}H_{35}ClO_8$: C, 60.18; H, 7.07%).

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