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TOTAL SYNTHESIS OF PUNAGLANDIN 4

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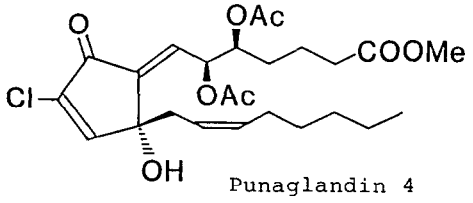
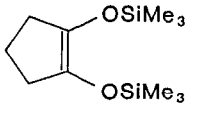
Abstract: A marine prostanoid, punaglandin 4 has been synthesized from 1,2-bis-trimethylsilyloxycyclopentene (**1**) via rearrangement of the allylic methanesulfonate **9** as a key step.

C-10 Chlorinated prostanoids, punaglandins were isolated from Hawaiian octocoral *telesto riisei*,[1] and their potent antitumor activity[2] has attracted the attention of many synthetic chemists. The very recent papers concerning total syntheses of punaglandins with revision of the structures of punaglandins 3[3] and 4[3,4] prompt us to report a synthesis of punaglandin 4 via the novel synthetic route.



Punaglandin 4

Our synthesis of punaglandin 4 commenced with (±)-2-hydroxy-2-((Z)-2-octenyl)cyclopentanone (**2**), easily obtainable from 1,2-bis-trimethylsilyloxycyclopentene (**1**) in two steps (66% yield). The cyclopentanone derivative **2** has been already shown to be an excellent synthetic intermediate for other marine prostanoids, clavulones.[5] Chlorination of **2** with NCS and NaOAc in dioxane at room temperature afforded the dichloro-cyclopentanone derivative **3**[6] in 72% yield, while the olefin moiety of ω-chain remained unchanged. Dehydrochlorination of **3** using LiCl in DMF at 120 °C gave the α-chlorinated enone **4**[6] in 93% yield. At this stage it was considered that the protection of the hydroxyl group would be necessary for the following allylic rearrangement step. Accordingly the hydroxyl group of **4** was first protected (TMSOTf, Et_3N) to give **5**, but attempts at reducing the enone **5** in a 1,2-fashion gave **6** only in an unsatisfactory yield (<40%). In contrast to this result, reduction of **4** with $NaBH_4$-$CeCl_3$[7] gave the diol **7** in 87% yield as a mixture at C-11.[8] From the diol **7** the requisite allylic alcohol **6** could be obtained by treatment with TMSOTf-Et_3N followed by preferential hydrolysis of the secondary trimethylsilyl ether of **8** using AcOH in aq. EtOH (53% yield, and 38% of **7** was recovered). However, careful studies on the allylic rearrangement of the methanesulfonates **9** and **10** revealed that the protection of the tertiary alcohol was not necessary. That is, selective mesylation (1.3 eq. Ms_2O- 0.2eq. DMAP in pyridine-CH_2Cl_2, 0 °C, 50 min) of **7** and successive solvolysis in 80% aqueous Me_2SO afforded **11** (1:1 mixture at C-9[8]) in *ca.* 70% yield. When the allylic methanesulfonate **9** was treated with basic reagents such as AcONa, CsOAc and



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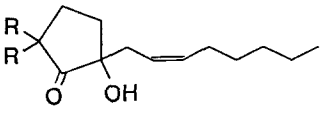
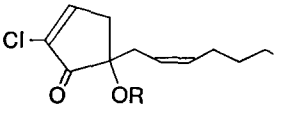
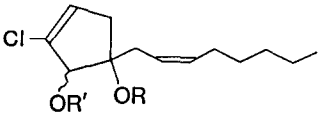


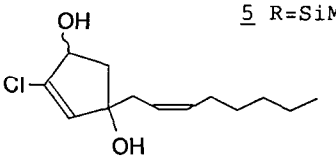
2 R=H
3 R=Cl



4 R=H
5 R=$SiMe_3$



6 R=$SiMe_3$ R'=H 7 R=R'=H
8 R=R'=$SiMe_3$ 9 R=H R'=Ms
10 R=$SiMe_3$ R'=Ms



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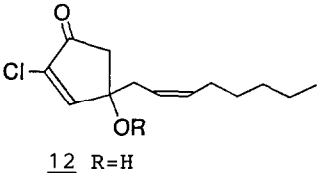
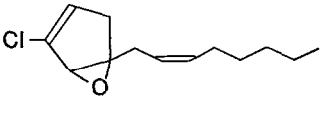


12 R=H
13 R=MOM



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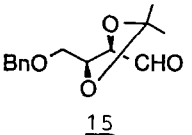

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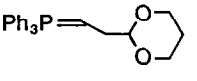

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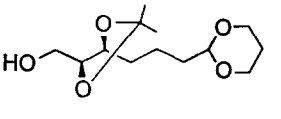

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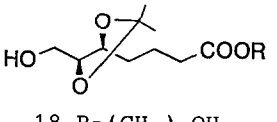
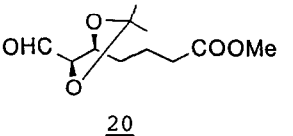


18 R=$(CH_2)_3OH$
19 R=Me



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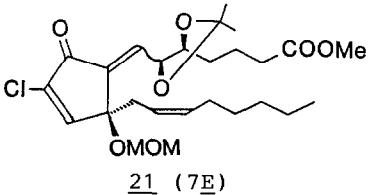
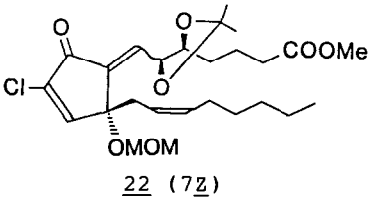
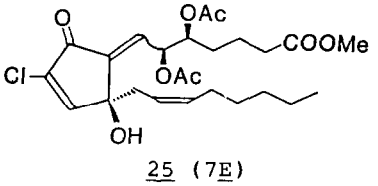


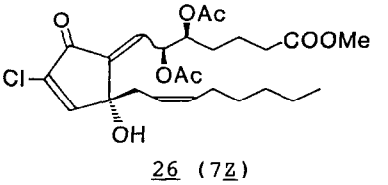
21 (7E)
24 (7Z)



22 (7Z)
23 (7E)



25 (7E)
28 (7Z)



26 (7Z)
27 (7E)

KO_2 gave the epoxide **14**, which was not further rearranged under the above conditions. Without purification, oxidation of **11** using PDC in DMF gave the cyclopentenone derivative **12**[4,6] in 51% yield from **7**, and the hydroxyl group of **12** was protected as methoxymethyl ether ($MeOCH_2Cl$-$^iPr_2NEt/ClCH_2CH_2Cl$, 60 °C) to give **13**[3,6] in 87% yield.

The synthon of the α-chain was synthesized from 4-O-benzyl-2,3-O-isopropylidene-L-threose (**15**), which was readily prepared from L-(+)-diethyl tartrate according to Mukaiyama's method.[9] Wittig reaction of the aldehyde **15** with the phosphorane **16** derived from commercially available [2-(1,3-dioxan-2-yl)ethyl]triphenylphosphonium bromide[10] (n-BuLi/THF, -20 °C) followed by catalytic hydrogenation (H_2, Pd-black) gave the alcohol **17** in 63% yield. Ozonolysis[11] of **17** afforded the ester **18**, which was converted into the methyl ester **19**[6] (0.5*N* MeONa/MeOH, 0 °C, 2 hr) in 72% yield. Swern oxidation ($(CO)_2Cl_2$-Me_2SO, -78 °C, 15min then Et_3N) gave the aldehyde **20**[3,6] in 94% yield.

Treatment of **13** with LDA (-78 °C, 15 min) followed by addition of **20** (-78 °C, 15 min then -20 to 0 °C, 3 hr) gave a mixture of the four diastereomers **21**,[6] **22**,[6] **23**,[6] and **24**[6] in a ratio of *ca.* 1:1:1:1 in 53% yield (conversion yield was 72%), which was separated chromatographically.[12] Absolute configurations of these products were determined by comparison of the ^1H-NMR spectra and optical rotations with the synthetic intermediates prepared by Yamada.

Selective hydrolysis (80% aq. AcOH, 80 °C)[13] of the isopropylidene group of each condensation product[14] followed by acetylation (Ac_2O-Py/CH_2Cl_2) and hydrolysis (80% aq. AcOH, 100 °C) afforded **25**,[6] **26**, **27**,[6] and **28** respectively (30-40% yield). The spectral properties of **27** was indistinguishable from an authentic sample, synthesized by Yamada and/or Noyori.

In summary we have completed a total synthesis of punaglandin 4 in naturally occurring form starting with (±)-2-hydroxy-2-((Z)-2-octenyl)cyclopentanone (**2**). The synthesis of optically active **2** is currently under study.

Acknowledgment: The authors thank Prof. Y. Yamada, Tokyo College of Pharmacy and Prof. R. Noyori, Nagoya University for providing helpful information and spectra of synthetic punaglandin 4.

References and Notes

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4. Suzuki, M.; Morita, Y.; Yanagisawa, A.; Noyori, R.; Baker, B.J.; Scheuer, P.J., *J. Am. Chem. Soc.*, **1986**, 108, 5021.
5. Shibasaki, M.; Ogawa, Y., *Tetrahedron Lett.*,**1985**, 26, 3841.
6. Selected physical and spectral data are as follows.
   3: ^1H-NMR (90 MHz, $CDCl_3$) δ 0.89 (t, 3H, J=5Hz), 1.1-1.5 (m, 6H), 2.05(dt, 2H, J=1Hz, J=3Hz), 2.16 (d, 2H, J=6Hz), 2.49 (d, 2H, J=7Hz),

5.19-5.83 (m, 2H). IR(neat) 3400(OH), 1780cm^{-1}(C=O). **4**: ^{1}H-NMR (90 MHz, $CDCl_3$) δ 0.88 (t, 3H, J=5Hz), 1.27 (bs, 6H), 2.42 (d, 2H, J=7Hz), 2.72 (d, 2H, J=3Hz), 5.05-5.80 (m, 2H), 7.51 (t, 1H, J=3Hz). IR(neat) 3400 (OH), 1730(C=O), 1600cm^{-1}(C=C). **12**: ^{1}H-NMR (90 MHz, $CDCl_3$) δ 0.90 (t, 3H, J=5Hz), 1.30 (m, 6H), 5.21-5.93 (m, 2H), 7.38 (s, 1H). IR(neat) 3350(OH), 1730(C=O), 1600cm^{-1}(C=C). **13**: ^{1}H-NMR (90 MHz, $CDCl_3$) δ 0.90 (t, 3H, J=6Hz), 1.29 (m, 6H), 3.40 (s, 3H), 5.2-5.9 (m, 2H), 7.43 (s, 1H). **19**: $[\alpha]_D^{20}$ -18.7° (c 1.1, $CHCl_3$). **20**: $[\alpha]_D^{20}$ +5.8° (c 7.0, $CHCl_3$), ^{1}H-NMR (90 MHz, $CDCl_3$) δ 1.43 and 1.48 (2s, 3H and 3H), 1.77 (m, 4H), 2.40 (m, 2H), 3.70 (s,3H), 4.00 (m, 2H), 9.76 (d,1H, J=1.5Hz). **21**: $[\alpha]_D^{20}$ -8.23° (c 1.09, $CHCl_3$), ^{1}H-NMR (90 MHz, $CDCl_3$) δ 0.90 (t, 3H, J=5Hz), 1.42 and 1.53 (2s, 3H and 3H), 3.41 (s, 3H), 3.67 (s, 3H), 5.10-5.85 (m, 2H), 6.61 (d, 1H, J=11Hz), 7.34 (s, 1H). **22**: $[\alpha]_D^{20}$ +4.66° (c 0.69, $CHCl_3$), ^{1}H-NMR (90 MHz, $CDCl_3$) δ 0.90 (t, 3H, J=6Hz), 1.43 and 1.53 (2s,3H and 3H), 3.39 (s, 3H), 3.67 (s,3H), 4.56 (s, 2H), 5.10-5.80 (m, 2H), 6.22 (d,2H, J=8.5 Hz), 7.32 (s,1H). **23**: $[\alpha]_D^{20}$ -27.25° (c 0.49, $CHCl_3$), ^{1}H-NMR (90 MHz, $CDCl_3$) δ 0.89 (t, 3H, J=5Hz), 3.40 (s, 3H), 3.67 (s, 3H), 5.05-5.80 (m, 2H), 6.62 (d, 2H, J=11Hz), 7.40 (s, 1H). **24** $[\alpha]_D^{20}$ +17.3° (c 0.48, $CHCl_3$), ^{1}H-NMR (90 MHz, $CDCl_3$) δ 0.89 (t, 3H, J=6Hz), 1.45 (s, 6H), 3.35(s, 3H), 3.66 (s, 3H), 5.15-5.8 (m, 2H), 6.27 (d, 1H, J=8.5Hz), 7.26 (s, 1H). **25**: $[\alpha]_D^{20}$ +53.0° (c 0.1, $CHCl_3$), ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.89 (t, 3H, J=6.8Hz), 1.97 (q, 2H, J=6.3Hz), 2.11 (s, 6H), 2.35 (t, 2H, 6.9Hz), 2.48 (dd, 1H, J=6.6 and 14.1Hz), 2.76 (dd, 1H, J=8.7 and 14.1Hz), 3.68 (s, 3H), 5.53-5.61 (m, 1H), 5.69 (dd, 1H, J=4.2 and 10.3 Hz), 6.31 (d, 1H, J=10.3Hz) 7.31 (d, 1H, J=0.5Hz). **27**: ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.89 (t, 3H, J=7.1Hz), 2.05 (s, 3H), 2.14 (s, 3H), 2.67 (dd, 1H, J=7.0 and 14.3Hz), 3.01 (dd, 1H, J=8.4 and 14.3Hz), 3.50 (s, 1H), 3.66 (s, 3H), 5.21-5.33 (m, 2H), 5.52-5.62 (m, 1H), 6.04 (dd, 1H, J=4.4 and 9.0Hz), 6.38 (dd, 1H, J=8.9 and 0.6Hz) 7.28 (d, 1H, J=0.6Hz).

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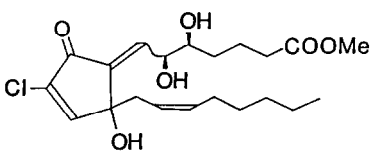
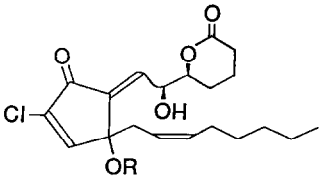
8. The numbering was accorded with that for punaglandin.
9. Mukaiyama, T.; Suzuki, K.; Yamada, T., *Chem. Lett.*, **1982**, 929.
10. Stowell, J.C.; Keith, D.R., *Synthesis*, **1979**, 132.
11. a) Deslongchamps, P.; Atlani, P.; Frehel, D.; Malaval, A.; Moreau, C., *Can. J. Chem.*, **1974**, 52, 3651. b) Cohen, N.; Banner, B.L.; Lopresti, P.J., *Tetrahedron Lett.*, **1980**, 21, 4163.
12. Elution by hexane-ethyl ether 4:1 gave two fractions and the each fraction was chromatographed by toluene-ethyl acetate 20:1.
13. Attempt to remove all protective groups at the same time using 80% aq. AcOH at 100 °C or Me_2BBr at -78 °C gave an unsatisfactory yield of the triol **A** with the undesired lactone **B** or **C**.
14. The lactone **B** was also obtained as a by-product.



[A]



[B] R=MOM

[C] R=H

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