SYNTHESES OF DI-TRITIATED 9(*O*)-METHANO-$\Delta^{6(9\alpha)}$-PROSTAGLANDIN I_1 METHYL ESTERS[1]

Kenji Manabe, Toshio Tanaka,* Seizi Kurozumi, and Yoshinori Kato

Teijin Institute for Bio-Medical Research I, Teijin Ltd.,
4-3-2 Asahigaoka, Hino, Tokyo 191, JAPAN

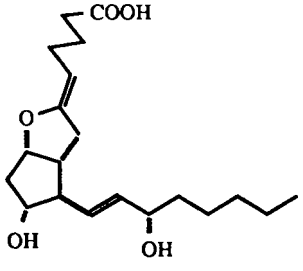
SUMMARY

Two di-tritiated isocarbacyclin [9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1] methyl esters **5**, **10** were synthesized from (*Z*)-olefinic precursors **23**, **31** at ω-side chain by catalytic hydrogenation with tritium gas, respectively. These substances **5**, **10** having high specific activities can be used for the pharmacokinetics and metabolism studies of 9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 methyl ester **2** and its (17*S*)-17,20-dimethyl derivatives **7**.

KEYWORDS: isocarbacyclin-[$^3H_2$], 9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1-[$^3H_2$], (17*S*)-17,20-dimethylisocarbacyclin-[$^3H_2$].

INTRODUCTION

Prostacyclin (**1**) is a useful therapeutic agent in cardio-vascular field because of its potent vasoactive properties.[2] Isocarbacyclin[3] [9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1] (**3**) is one of stable prostacyclin analogues which is a promising therapeutic agent for cardio-vascular diseases because of its high chemical stability and potent biological activity.[4] We have chosen two isocarbacyclin derivatives **2** and **7** as therapeutic candidates. Previously, we synthesized two mono-tritiated isocarbacyclins, **4** and **9**, where each 11β-hydrogen was substituted by tritium atom.[5] In the course of our

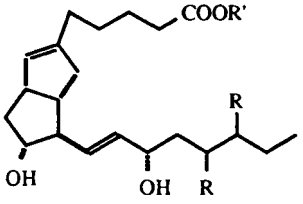


1
Prostacyclin
(Prostaglandin I_2)

0362–4803/91/101107–13$06.50

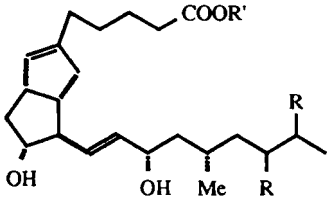
Received 3 June, 1991

development of its derivatives, **2** and **7**, tritium-labeled materials with high specific activities were required for use in pre-clinical studies as well as for use in RIA analysis. We now describe the syntheses of di-tritiated isocarbacyclin methyl esters, **5** and **10**, *via* catalytic hydrogenation of (Z)-Δ^{17} olefin for the compound **5** and (Z)-Δ^{19} olefin for **10** with tritium gas as a key step, respectively.



2; R = H, R' = Me, R" = H
3; R = H, R' = H, R" = H
(Isocarbacyclin)
4; R = H, R' = Me, R" = T

5; R = T, R' = Me, R" = H
6; R = T, R' = H, R" = H



7; R = H, R' = Me, R" = H
8; R = H, R' = H, R" = H

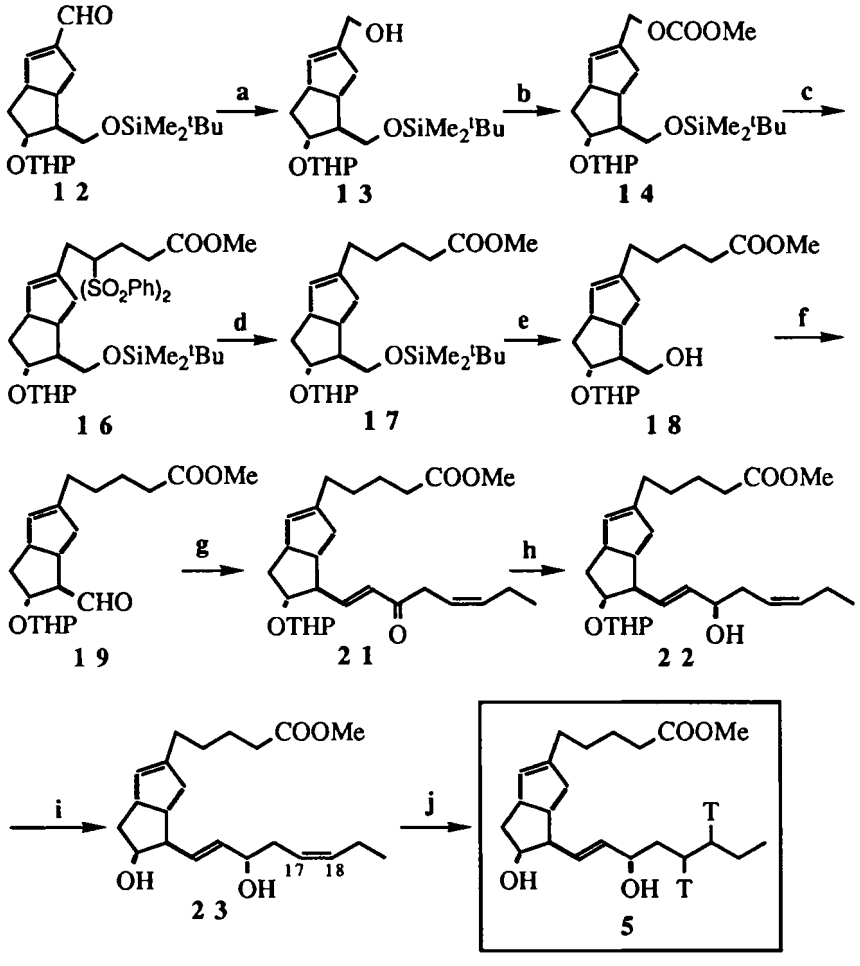
9; R = H, R' = Me, R" = T

10; R = T, R' = Me, R" = H
11; R = T, R' = H, R" = H

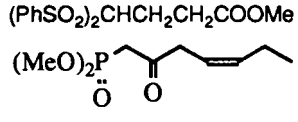
SYNTHESIS

The first target substance of the di-tritiated isocarbacyclin is [17,18-$^{3}H_2$] derivative **5**, where two hydrogens on ω-side chain of the isocarbacyclin structure **2** are substituted by tritium atoms. The tritiated **5** was synthesized from the (Z)-Δ^{17} precursor **23** by a catalytic hydrogenation with tritium gas, which was prepared starting from commercially available bicyclic synthon **12** in nine steps (Scheme 1).

Reduction of the bicyclic synthon **12** with sodium borohydride afforded the reduced product **13** (89%), which was esterified with methyl chloroformate in the presence of pyridine to provide the allyl carbonate **14** (98%). Reaction[6] of **14** with methyl 4,4-bis(phenylsulfonyl)butanoate **15** in the presence of palladium(0) bis[ethylenebis(diphenylphosphine)] yielded the regiospecifically γ-alkylated **16** (95%), which was allowed to react with magnesium[7] in methanol to furnish the desulfonylated **17** in 82% yield. Desilylation of **17** with tetrabutylammonium fluoride.



a) $NaBH_4$; **b)** ClCOOMe, pyridine; **c)** **15**, $Pd_2(dba)_3CHCl_3$-$Ph_2PCH_2CH_2PPh_2$; **d)** Mg, MeOH; **e)** $^nBu_4N^+F^-$; **f)** SO_3-pyridine, dimethyl sulfoxide; **g)** **20**, NaH; **h)** (*S*)-(-)-binaphthol-$LiAlH_4$-EtOH; **i)** CH_3COOH-THF-H_2O; **j)** T_2, Pd/C, cyclododecene,



15

20

[THP; tetrahydrofuran
dba; dibenzylideneacetone]

Scheme 1

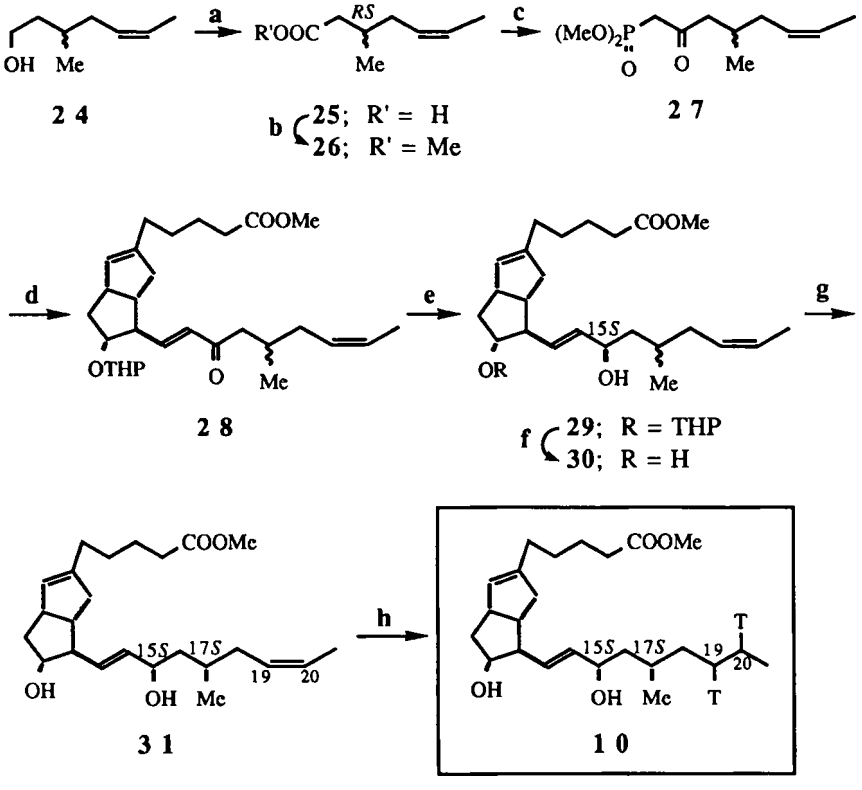
gave the alcohol **18** (77%), which was oxidized by a combination of triethylamine, sulfur trioxide pyridine complex, and dimethyl sulfoxide to yield the aldehyde **19** (83%). Reaction of the aldehyde **19** with a mixture of sodium hydride and dimethyl (Z)-2-oxo-4-

heptenylphosphonate **20**, prepared from *cis*-3-hexenyl *cis*-3-hexenoate, gave the coupling enone **21** (58%). Asymmetric reduction of **21** with (*S*)-BINAL-H[8] afforded the chiral allyl alcohol **22** (54%), which was deprotected by aqueous acetic acid to furnish the (*Z*)-Δ^{17}-isocarbacyclin methyl ester **23** as the precursor to be tritiated in 87% yield. Catalytic reduction of **23** with hydrogen gave the (*Z*)-olefin-reduced product **2** (40%) after HPLC purification, which was identical with the authentic sample[6,9] of **2**. A similar reduction of **23** with tritium gas using rhodium catalyst furnished the final di-tritiated product **5** after HPLC purification, whose specific activity was found to be 36.7 Ci / mmol. Hydrolysis of the di-tritiated methyl ester **5** with lithium hydroxide provided the di-tritiated carboxylic acid **6**.

The second target compound of the di-tritiated isocarbacyclin is [19,20-$^3H_2$] derivative **10**, where two hydrogens on ω-side chain of the isocarbacyclin structure **7** are substituted by tritium atoms. The desired product **10** was synthesized from the (*Z*)-Δ^{19} precursor **31** also by a catalytic hydrogenation with tritium gas. The precursor was prepared by coupling of the above-mentioned bicyclic aldehyde **19** with the phosphonate **27** in three steps (Scheme 2).

Oxidation of the olefinic alcohol **24**, prepared by the cited procedure,[10] with Jones' reagent provided the carboxylic acid **25** (62%), which was esterified with diazomethane to afford the olefinic ester **26** (95%). Reaction of **26** with the lithium salt of dimethyl methylphosphonate obtained by treatment with *n*-butyllithium yielded the 2-oxophosphonate **27** (67%). Horner-Emmons reaction of the above aldehyde **19** with the phosphonate **27** in the presence of sodium hydride gave the coupling enone **28** (98%). In a similar manner to the preparation of **22**, asymmetric reduction of the product **28** with (*S*)-BINAL-H[8] afforded the 15*S*-alcohol **29** (90%), which was deprotected by treatment with aqueous acetic acid to furnish the (*Z*)-Δ^{19}-isocarbacyclin derivative **30** as a diastereomeric mixture of 17*S* and 17*R* isomers in 86% yield. Separation of the diastereomeric mixture **30** by preparative HPLC yielded the desired (*Z*)-Δ^{19} precursor **31** (43%) accompanied by the 17*R* diastereomer of **31** (41%). In the cold run, catalytic reduction of the obtained **31** under a hydrogen atmosphere gave the hydrogenated product **7** (30%) after preparative HPLC purification, which was coincided with the authentic sample[9,11] of **7**. A similar reduction of **31** with tritium gas using rhodium

catalyst furnished the final di-tritiated product **10** after HPLC purification, whose specific activity was found to be 50 Ci / mmol. Hydrolysis of the di-tritiated methyl ester **5** with lithium hydroxide provided the di-tritiated carboxylic acid **11**.



a) Jones' oxidation; b) CH_2N_2; c) ^{n}BuLi, $(MeO)_2P(=O)CH_3$; d) NaH, **19** ; e) (*S*)-(-)-binaphthol-$LiAlH_4$-EtOH; f) CH_3COOH-THF-H_2O; g) HPLC separation; h) T_2, cyclododecene, Pd/C

Scheme 2

EXPERIMENTAL

IR spectra were recorded on a JASCO A 102 spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were obtained on a HITACHI R-90H (90 MHz) and a JEOL JNM-GX 400 (400 MHz) spectrometer in $CDCl_3$, respectively. Chemical shifts and coupling constants (J) are given in δ (ppm) relative to internal tetramethylsilane and Hz, respectively. The following abbreviation are used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), b (broad). Mass spectra (MS) were taken at 70 eV on a LKB-9000 mass

spectrometer. For high-performance liquid chromatography (HPLC) analysis, a Shimadzu Model LC-6A equipped with a Shimadzu SPD-6A UV detector (210 nm) and a Shimadzu C-R3A chromatopac was employed. Preparative HPLC was conducted on a Shimadzu Model LC-6A equipped with a YMC-PACK SH-043 SIL using 3% ethanol-hexane. Thin-layer chromatography (TLC) was performed using Merck silica gel (Kiesel gel 60 F_{254}) analytical plate. The plates were sprayed with a solution of 2% *p*-anisaldehyde in 5% ethanolic sulfuric acid and then heated until the spots became clearly visible. Column chromatography was carried out on Daiso gel IR-60 silica gel. All reactions were performed under argon or nitrogen. Solvents for reactions were purified if necessary before use by distillation from suitable drying agents. Solvents for extraction and chromatography were GR grades.

Synthesis of [17,18-$^3H_2$]-9(*O*)-Methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 Methyl Ester (5)

(1*S*,5*S*,6*R*,7*R*)-6-*t*-Butyldimethylsilyloxymethyl-3-hydroxymethyl-7-(2-tetrahydropyranyl)bicyclo[3.3.0]-2-octene (13)

Sodium borohydride (31 mg, 0.816 mmol) was added at 0°C to a stirred solution of (1*S*,5*S*,6*R*,7*R*)-6-*t*-butyldimethylsilyloxymethyl-3-formyl-7-(2-tetrahydropyranyl)-bicyclo[3.3.0]-2-octene (600 mg, 1.63 mmol) in methanol (10 ml), and the reaction mixture was stirred at 0°C for 30 min. Saturated aqueous (aq.) ammonium chloride (5 ml) solution was poured into the reaction mixture, and the mixture was extracted twice with ethyl acetate (50 ml). The combined organic extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residual oil (629 mg) was subjected to silica gel (50 g) column chromatography using a 5 : 1 mixture of hexane and ethyl acetate as an eluant to give the reduced product **13** (538 mg, 1.45 mmol, 89%); IR (neat): 3400, 2950, 2850, 1470, 1460, 1440, 1380, 1350, 1250 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 0.03 (s, 6H), 0.90 (s, 9H), 1.1-2.8 (m, 12H), 2.8-3.15 (m, 1H), 3.4-4.1 (m, 6H), 4.15 (bs, 2H), 4.77 (m, 1H), 5.56 (bs, 1H); EI-MS (m/z): 382 (M^+), 364, 325, 307, 298, 223, 159, 131, 105; High-resolution MS for $C_{21}H_{38}O_4Si$: Calcd m/z: 382.2539; Found 382.2636.

(1*S*,5*S*,6*R*,7*R*)-6-*t*-Butyldimethylsilyloxymethyl-3-methoxycarbonyloxymethyl-7-(2-tetrahydropyranyl)bicyclo[3.3.0]-2-octene (14)

Pyridine (4.6 ml, 4.5 g, 57 mmol) and then methyl chloroformate (2.24 ml, 2.74 g, 29.0 mmol) were added at 0°C to a stirred solution of the allyl alcohol **13** (2.10 g, 5.68 mmol) in dichloromethane (15 ml), and the reaction mixture was stirred at 0°C for 40 min. Saturated aq. ammonium chloride (10 ml) solution was added to the reaction mixture, and the mixture was extracted twice with ethyl acetate (50 ml). The combined organic extracts were washed with aq. potassium bisulfate solution, aq. sodium bicarbonate solution, and then brine. The separated organic layer was dried over magnesium sulfate, filtered, and evaporated to give the almost pure carbonate **14** (2.44 g, 5.55 mmol, 98%); IR (neat): 2950, 2990, 2850, 1750, 1730, 1460, 1440, 1260 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 0.03 (s, 6H), 0.88 (s, 9H), 1.0-2.7 (m, 12H), 2.8-3.15 (m, 1H), 3.5-4.15 (m, 5H), 3.85 (s, 3H), 4.63 (bs, 3H), 5.63 (bs, 1H); EI-MS (m/z): 440 (M^+), 422, 383, 364, 356, 307, 263, 223, 201, 181, 149, 129, 103; High-resolution MS for $C_{23}H_{40}O_6Si$: Calcd m/z: 440.2595; Found 440.2668.

(1*S*,5*S*,6*R*,7*R*)-6-*t*-Butyldimethylsilyloxymethyl-3-[4-methoxycarbonyl-2,2-bis(phenylsulfonyl)butyl]-7-(2-tetrahydropyranyl)bicyclo[3.3.0]-2-octene (16)

A mixture of the carbonate **14** (700 mg, 1.59 mmol) and methyl 4,4-bis(phenylsulfonyl)butanoate[6a] (**15**; 790 mg, 2.07 mmol) in dry tetrahydrofuran (THF; 16 ml) was added at room temperature (r. t.) to a stirred solution of tris(dibenzylideneacetone)-dipalladium(0)-chloroform (218 mg, 0.238 mmol) and ethylenebis(phenylphosphine) (190 mg, 0.476 mmol) in THF (24 ml). The resulting mixture was heated to reflux for 20 h. Aq. ammonium chloride solution was added and the mixture was extracted with ethyl acetate (3 x 50 ml). The combined extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to leave a crude product (2.1 g), which was purified on silica gel (80 g) column chromatography with a 6 : 1 and then 4 : 1 mixture of hexane and ethyl acetate as eluants, yielding the alkylated **16** (1.13 g, 1.51

mmol, 95%); IR (neat): 2950, 2900, 2850, 1740, 1440, 1330, 1310, 1140 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 0.03 (s, 6H), 0.90 (s, 9H), 1.1-3.1 (m, 20H), 3.3-4.2 (m, 5H), 3.71 (s, 3H), 4.5-4.75 (m, 1H), 5.6 (bs, 1H), 7.4-7.85 (m, 6H), 7.9-8.2 (m, 4H); EI-MS (m/z): 715 (M^+-31), 689, 662, 645, 631, 613, 605, 431, 379, 339, 289, 229, 159, 115, 75.

(1*S*,5*S*,6*R*,7*R*)-6-*t*-Butyldimethylsilyloxymethyl-3-(4-methoxycarbonylbutyl)-7-(2-tetrahydropyranyl)bicyclo[3.3.0]-2-octene (17)

Magnesium ((900 mg) was added at 0°C to a solution of the bis(phenylsulfone) **16** (1.13 g, 1.51 mmol) in methanol (25 ml), and the mixture was stirred at 35°C for 1 h. The reaction mixture was poured into aq. ammonium chloride solution (50 ml), and the mixture was extracted twice with ethyl acetate (100 ml). The separated organic layers were combined, washed with brine, dried over magnesium sulfate, and filtered. The filtrate was evaporated to leave a crude residue (712 mg), which was chromatographed on silica gel (50 g) with hexane-ethyl acetate (9 : 1) to provide the desulfonylated **17** (534 mg, 1.23 mmol, 82%); IR (neat): 2950, 2900, 2850, 1740, 1730, 1450, 1430, 1250 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 0.03 (s, 6H), 0.90 (s, 9H), 1.1-2.6 (m, 20H), 2.7-3.15 (m, 1H), 3.3-4.2 (m, 5H), 3.68 (s, 3H), 4.69 (bs, 1H), 5.29 (bs, 1H); EI-MS (m/z): 466 (M^+), 448, 435, 409, 391, 382, 362, 351, 333, 325, 233, 201, 159, 131, 85; High-resolution MS for $C_{26}H_{46}O_5Si$: Calcd m/z: 466.3115; Found 466.3159.

(1*S*,5*S*,6*S*7*R*)-6-Hydroxymethyl-3-(4-methoxycarbonylbutyl)-7-(2-tetrahydropyranyl)bicyclo[3.3.0]-2-octene (18)

A 1.0 M THF solution of tetrabutylammonium fluoride (3.70 ml, 3.70 mmol) was added at r. t. to a stirred solution of **17** (534 mg, 1.23 mmol) in THF (10 ml), and the mixture was stirred at r. t. for 18 h. Aq. ammonium chloride solution (30 ml) was added and the mixture was extracted with ethyl acetate (3 x 50 ml). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and evaporated under reduced pressure. The residual oil was purified by column chromatography on silica gel (80 g) using hexane-ethyl acetate (1 : 2) to yield the desilylated product **18** (301 mg, 0.94 mmol, 77%); IR (neat): 3450, 2950, 2860, 1740, 1720, 1430, 1350 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 1.1-2.7 (m, 21H), 2.7-3.2 (m, 1H), 3.3-4.1 (m, 6H), 3.67 (s, 3H), 4.5-4.8 (m, 1H), 5.30 (bs, 1H); EI-MS (m/z): 352 (M^+), 334, 316, 303, 268, 250, 232, 219, 179, 159, 131, 105, 85; High-resolution MS for $C_{20}H_{32}O_5$: Calcd m/z: 352.2249; Found 352.2346.

(1*S*,5*S*,6*R*,7*R*)-6-Formyl-3-(4-methoxycarbonylbutyl)-7-(2-tetrahydropyranyl)bicyclo[3.3.0]-2-octene (19)

Triethylamine (951 mg, 9.40 mmol) and then sulfur trioxide pyridine complex (705 mg, 4.70 mmol) were added at r. t. to a stirred solution of the alcohol **18** (301 mg, 0.94 mmol) in dimethyl sulfoxide (DMSO; 11 ml), and the mixture was stirred at r. t. for 3 h. The mixture was poured into ice-water and the mixture was extracted twice with ether (50 ml). The combined organic layers were washed with water, and then brine, dried over magnesium sulfate, filtered, and evaporated. The residual crude product (223 mg) was chromatographed on silica gel (60 g) with a 5 : 1 and then 4 : 1 mixture of hexane and ethyl acetate as eluants to obtain the aldehyde **19** (248 mg, 0.780 mmol, 83%); IR (neat): 2950, 2870, 2850, 1740, 1720, 1430, 1350 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 1.1-3.2 (m, 21H), 3.67 (s, 3H), 3.2-4.5 (m, 3H), 4.63 (m, 1H), 5.3 (bs, 1H), 9.72 (d, 1H, J = 2 Hz); EI-MS (m/z): 350 (M^+), 332, 319, 306, 301, 266, 248, 216, 188, 147, 128, 105, 85; High-resolution MS for $C_{20}H_{30}O_5$: Calcd m/z: 350.2093; Found 350.2141.

Dimethyl (*Z*)-2-oxo-4-heptenylphosphonate (20)

A 1.57 M hexane solution of *n*-butyllithium (31.3 ml, 49.2 mmol) was added at -78°C to a stirred solution of dimethyl methylphosphonate (6.45 g, 52.0 mmol) in THF (60 ml), and the mixture was stirred at -78°C for 1 h. To this mixture was added a solution of *cis*-3-hexenyl *cis*-3-hexenoate (4.64 g, 23.6 mmol) in THF (60 ml), and the resulting mixture was stirred at -78°C for 1 h, then warmed up to 0°C. Aq. ammonium chloride solution was added. The organic layer was taken up in ethyl acetate (300 ml). The separated organic solution was washed with water and then brine, dried over magnesium sulfate, filtered, and evaporated. The residual material was chromatographed on silica gel (500 g) with a 1 : 4 mixture of hexane and ethyl acetate to yield the phosphonate **20** (530 mg, 2.4 mmol, 10%) accompanied by the recoverd *cis*-3-hexenyl *cis*-3-hexenoate (3.49 g, 17.8 mmol, 75%); IR (neat): 3415, 3255, 3020, 2960, 2935, 2875, 2855, 1715, 1460, 1260, 1185,

1030, 840, 810 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.97 (t, 3H, J = 7 Hz), 1.6-2.4 (m, 2H), 3.12 (d, 2H, J = 22 Hz), 3.37 (d, 2H, J = 5 Hz), 3.73 & 3.86 (s x 2, 6H), 5.3-5.8 (m, 2H); EI-MS (m/z): 220 (M^+), 191, 179, 151, 124, 109, 94, 79, 67, 55, 41.

(1*S*,5*S*,6*R*,7*R*)-3-(4-Methoxycarbonylbutyl)-6-[(1*E*,5*Z*)-3-oxo-1,5-octadienyl]-7-(2-tetrahydropyranyl)bicyclo[3.3.0]-2-octene (21)

To a suspension of sodium hydride (60% content; 81 mg, 2.03 mmol) in THF (25 ml) was added at r. t. a solution of the phosphonate **20** (466 mg, 2.12 mmol) in THF (20 ml), and the mixture was stirred at r. t. for 30 min. To the mixture was added at r. t. a solution of the aldehyde **19** (430 mg, 1.23 mmol) in THF (20 ml), and the resulting mixture was stirred at r. t. for 4 h. Aq. ammonium chloride solution was added and the mixture was extracted with ether (200 ml). The separated organic layer was washed with brine, dried over magnesium sulfate, filtered, and evaporated to give a crude product, which was subjected to silica gel (100 g) column chromatography (hexane : ethyl acetate = 9 : 1) to yield the product **21** (315 mg, 0.713 mmol, 58%); IR (neat): 3060, 2935, 2875, 1735, 1695, 1670, 1620, 1600, 1515, 1465, 1435, 1340, 1275, 1210, 1175, 1140, 1075, 1035, 1025, 980, 815, 750 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.99 (t, 3H, J = 7 Hz), 1.1-2.7 (m, 22H), 2.85-3.15 (m, 1H), 3.2-4.3 (m, 5H), 3.67 (s, 3H), 4.45-4.75 (m, 1H), 5.28 (bs, 1H), 5.45-5.8 (m, 2H), 6.25 (d, 1H, J = 16 Hz), 6.7-7.1 (m, 1H); EI-MS (m/z): 426 (M^+-H_2O), 342, 248, 216, 199, 187, 174, 161, 147, 133, 117, 105; High-resolution MS for $C_{27}H_{38}O_4$ (M^+-H_2O): Calcd m/z: 426.2768; Found 426.2821.

(1*S*,5*S*,6*R*,7*R*)-6-[(3*S*,1*E*,5*Z*)-3-Hydroxy-1,5-octadienyl]-3-(4-methoxycarbonylbutyl)-7-(2-tetrahydro-pyranyl)bicyclo[3.3.0]-2-octene (22)

A solution of **21** (315 mg, 0.710 mmol) in THF (35 ml) was treated at -100°C for 2 h with a solution of (*S*)-BINAL-H[8] in THF prepared by mixing lithium aluminium hydride (404 mg, 10.6 mmol), ethanol (586 μl, 461 mg, 10.6 mmol), and (*S*)-(-)-binaphthol (2.99 g, 10.4 mmol) in THF (100 ml). After methanol (9 ml) was added at -78°C to decompose the excess reducing agent, saturated aq. sodium sulfate solution (17 ml) and then ethyl acetate (100 ml) was added at r. t.. The resulting mixture was treated with magnesium sulfate (25 g) and filtered. The filtrate was evaporated and diluted with hexane to precipitate binaphthol as crystals. After filtration, the resulting organic solution was evaporated to give a crude product (350 mg), which was purified by column chromatography on silica gel (70 g) using a 4 : 1 mixture of hexane and ethyl acetate to afford the reduced product **22** (171 mg, 0.383 mmol, 54%); IR (neat): 3460, 3040, 2980, 2950, 2900, 1700, 1440, 1200, 1140, 1120, 1080, 1035, 1020, 975 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.96 (t, 3H, J = 7 Hz), 1.1-2.6 (m, 24H), 2.75-3.15 (m, 1H), 3.67 (s, 3H), 3.2-4.25 (m, 4H), 4.66 (bs, 1H), 5.3-5.75 (m, 4H).

(1*S*,5*S*,6*R*,7*R*)-7-Hydroxy-6-[(3*S*,1*E*,5*Z*)-3-hydroxy-1,5-octadienyl]-3-(4-methoxy-carbonylbutyl)-bicyclo[3.3.0]-2-octene [(*E*)-Δ^{17}-9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 methyl ester] (23)

A solution of **22** (170 mg, 0.381 mmol) in THF (4 ml), acetic acid (6 ml), and water (2 ml) was stirred at 40°C for 20 h. Aq. sodium bisulfate solution was added, and the resulting mixture was extracted twice with ethyl acetate (100 ml). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residual oily product was subjected to column chromatography on silica gel (100 g) with a 1 : 1 and then 1 : 3 mixture of hexane and ethyl acetate as eluants to yield the deprotected **23** (120 mg, 0.331 mmol, 87%); IR (neat): 3375, 3010, 2930, 2875, 1740, 1455, 1435, 1205, 1175, 1090, 995, 970, 870 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.97 (t, 3H, J = 7 Hz), 1.1-2.7 (m, 20H), 2.8-3.2 (m, 1H), 3.67 (s, 3H), 3.6-4.3 (m, 2H), 5.27 (bs, 1H), 5.35-5.75 (m, 4H); EI-MS (m/z): 344 (M^+-H_2O), 326, 313, 300, 293, 275, 257, 243, 225, 199, 179, 161, 147, 129, 117, 105, 91, 79, 67, 55; High-resolution MS for $C_{22}H_{32}O_3$ (M^+-H_2O): Calcd m/z: 344.2350; Found 344.2363.

9(*O*)-Methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 methyl ester (2)---cold synthesis---

Palladium on activated carbon (5%; 1.3 mg) and cyclododecene (25 μl) were added to a solution of the (Z)-Δ^{17} olefin **23** (10 mg, 0.028 mmol) in a 1 : 1 mixture (1 ml) of benzene and cyclohexane. The mixture was stirred at 0°C for 1.5 h under a hydrogen

atmosphere. The catalyst was filtered off through Celite and the separated catalyst was washed with ethyl acetate. The filtrate and washings were evaporated under vacuum to give a crude residue, which contained the desired partially reduced product **2** coinciding (TLC and HPLC) with the authentic sample of **2**.[6,9] The obtained crude product including **2** was separated by preparative HPLC (Inertsil ODS column; 25 cm x 4.6 mm I.D.) eluting with a 7 : 3 mixture of acetonitrile and water (flow rate; 1.1 ml / min, UV detection 210 nm) to furnish the desired product **2** (4 mg, 0.011 mmol, 40%), which was identical (TLC HPLC, IR, NMR, and MS) with the authentic sample of **2**.[7]

[17,18-$^3H_2$]-9(*O*)-Methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 methyl ester (5)---hot synthesis---

Tris(triphenylphosphine)rhodium(I) chloride (10 mg) was added to a solution of the (*Z*)-Δ^{17} precursor **23** (9 mg, 0.025 mmol) in a 1 : 1 mixture of benzene and cyclohexane. The resulting mixture was stirred with tritium gas (5 Ci) at ambient temperature for 2.5 h. After removal of the solvents, the residual material (1.1 Ci) was applied to preparative silica-gel plates (4 x 0.5 mm), eluted with a 2 : 1 mixture of dichloromethane and acetone. The plates were dried, autoradiographed, and the major radioactive band was extracted with methanol to yield the radioactive extract (642 mCi). The obtained crude radioactive product was purified by preparative HPLC (Inertsil ODS column; 25 cm x 20 mm I.D.) eluting with a 1 : 1 mixture of acetonitrile and water to furnish the pure di-tritiated final product **5** (435 mCi). The radiochemical purity of the final product **5** was determined to be 99.2% by analytical HPLC (Inertsil ODS column; 25 cm x 6.0 mm I.D.) eluting with a 65 : 35 mixture of acetonitrile and water. The specific activity of the product **5** was determined using fast atom bombardment (FAB) mass spectrometry with the sample entrained in a dithiothreitol / dithioerithritol matrix. The calculation was based on the MNa^+ ion bundle, which although relatively weak, was free from the interferring losses of H_2O observed in other ion bundles to be 36.7 Ci / mmol.

[17,18-$^3H_2$]-9(*O*)-Methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 (6)

To a solution of the di-tritiated methyl ester **5** (1.34 mCi) in methanol (200 µl) was added at r. t. a aq. 5.0 N solution of sodium hydroxide (40 µl), and the mixture was stirred at 37 °C. for 1 h. To the reaction mixture were added a 2.0 N hydrochloric acid (100 µl) and then sodium acetate buffer solution (1 ml). The resulting mixture was loaded into a Sep-Pak C18 cartridge treated with the same sodium acetate buffer solution. The cartridge was eluted with ethanol to give a radioactive eluate, which was subjected to HPLC purification (Shimadzu Model LC-3A; Lichrosorb RP-18 column, 25 cm x 4.6 mm I.D.) eluting with a 40 : 60 mixture of acetonitrile and water containing 0.01% acetic acid (flow rate; 1.0 ml / min, UV detection 210 nm) to provide the carboxylic acid **6** (1.14 mCi, 85%). The product **6** was identical (HPLC) with the cold authentic sample[6,9] of **6**, and the radiochemical purity of the acid **6** was found to be 96.8% by HPLC analysis under the same condition using Lichrosorb column.

Synthesis of (17*S*)-[19,20-$^3H_2$]-17,20-Dimethyl-9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 Methyl Ester (10)

(±)-(*Z*)-3-Methyl-5-heptenoic acid (25)

A solution of Jones' reagent (46 ml, 122.8 mmol) was added to a cooled solution of the alcohol **24** (3.93 g, 30.7 mmol) in acetone (250 ml) at 0°C. After being stirred at 0°C for 2 h, the reaction mixture was quenched with isopropyl alcohol. Ether was added and the insoluble material was removed by filtration through Celite. The filtrate was washed with water and the separated aqueous layer was extracted with ether. The combined organic layers were dried over magnesium sulfate and evaporated under reduced pressure to leave a crude product (8.23 g). Purification of the crude product by column chromatography (silica gel, 200 g, hexane : ethyl acetate = 6 : 1) gave the carboxylic acid **25** (2.72 g, 19.2 mmol, 62%); IR (neat): 3050, 3020, 2960, 2820, 2660, 1705, 1405, 1305, 1225, 1175, 935, 675 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 0.98 (d, 3H, J = 3 Hz), 1.60 (d, 3H, J = 6 Hz), 1.8-2.8 (m, 5H), 5.2-5.8 (m, 2H), 9.5 (bs, 1H).

Methyl (±)-(Z)-3-methyl-5-heptenoate (26)

To a stirred solution of the carboxylic acid **25** (2.70 g, 19.0 mmol) in ether (50 ml) was added at 0°C an ethereal solution of diazomethane prepared from 1-methyl-3-nitro-1-nitrosoguanidine. Acetic acid was added to the pale yellow reaction mixture and then, toluene (250 ml) was added. Removal of solvents gave a crude ester (2.21 g), which was chromatographed on silica gel (150 g) with hexane-ethyl acetate (9 : 1) to afford the ester **26** (2.82 g, 18.0 mmol, 95%); IR (neat): 3020, 2950, 2930, 1740, 1430, 1360, 1300, 1250, 1205, 1160, 1005 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.94 (d, 3H, J = 6 Hz), 1.58 (d, 3H, J = 6 Hz), 1.8-2.6 (m, 5H), 3.76 (s, 3H), 5.2-5.8 (m, 3H).

Dimethyl (±)-(Z)-4-methyl-2-oxo-6-octenylphosphonate (27)

A 1.62 M hexane solution of *n*-butyllithium (12.5 ml, 20.2 mmol) was added at -78°C to a stirred solution of dimethyl methylphosphonate (2.65 g, 21.3 mmol) in THF (80 ml), and the mixture was stirred at -78°C for 1 h. To this mixture was added a solution of the ester **26** (1.51 g, 9.7 mmol) in THF (80 ml), and the resulting mixture was stirred at -78°C for 1 h, then warmed up to 0°C during 30 min. Aq. ammonium chloride solution was added. The organic layer was taken up in ethyl acetate (200 ml). The separated organic solution was washed with water and then brine, dried over magnesium sulfate, filtered, and evaporated. The residual material (2.50 g) was chromatographed on silica gel (100 g) with a 3 : 1 mixture of hexane and ethyl acetate to yield the phosphonate **27** (1.53 g, 6.54 mmol, 67%); IR (neat): 3460, 3020, 2950, 2920, 2850, 1705, 1450, 1255, 1175, 1020, 820, 800 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.93 (d, 3H, J = 6 Hz), 1.59 (d, 3H, J = 6 Hz), 1.7-2.7 (m, 5H), 3.06 (d, 2H, J = 24 Hz), 3.73 & 3.84 (s × 2, 6H), 5.1-5.8 (m, 2H).

(1*S*,5*S*,6*R*,7*R*)-3-(4-Methoxycarbonylbutyl)-6-[(*RS*)-(1*E*,7*Z*)-5-methyl-3-oxo-1,7-nonadienyl]-7-(2-tetrahydropyranyl)bicyclo[3.3.0]-2-octene (28)

In a similar procedure to the preparation of the above enone **21** from the aldehyde **19** and the phosphonate **20**, a solution of the phosphonate **27** (600 mg, 2.54 mmol) in THF (30 ml) was added at r. t. to a suspension of sodium hydride (60% content; 97 mg, 2.43 mmol) in THF (35 ml) , and the mixture was stirred at r. t. for 40 min. To the mixture was added at r. t. a solution of the aldehyde **19** (566 mg, 1.62 mmol) in THF (30 ml), and the resulting mixture was stirred at r. t. for 4 h. Aq. ammonium chloride solution was added and the mixture was extracted with ether (2 × 100 ml). The separated organic layers were washed with brine, dried over magnesium sulfate, filtered, and evaporated to give a crude product, which was subjected to silica gel (100 g) column chromatography (hexane : ethyl acetate = 4 : 1) to yield the product **28** (749 mg, 1.59 mmol, 98%); IR (neat): 3040, 2960, 2900, 1740, 1695, 1665, 1625, 1440, 1200, 1135, 1120, 1080, 1035, 1020, 975 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.94 (d, 3H, J = 6 Hz), 1.2-2.7 (m, 28H), 2.8-3.2 (bs, 1H), 3.3-4.2 (m, 3H), 3.70 (s, 3H), 4.5-4.75 (m, 1H), 5.31 (bs, 1H), 5.3-5.7 (m, 2H), 6.23 (d, 1H, J = 16 Hz), 6.4-6.9 (m, 1H); EI-MS (m/z): 472 (M^+), 454, 441, 428, 370, 344, 315, 273, 245, 192, 145, 117, 85, 55; High-resolution MS for $C_{29}H_{42}O_4$ (M^+-H_2O): Calcd m/z: 454.3083; Found 454.3077.

(1*S*,5*S*,6*R*,7*R*)-3-(4-Methoxycarbonylbutyl)-6-[(*S*)-(1*E*,7*Z*)-3-hydroxy-5-methyl-1,7-nonadienyl]-7-(2-tetrahydropyranyl)bicyclo[3.3.0]-2-octene (29)

In a similar manner to the preparation of the chiral allyl alcohol **22** from the enone **21**, a solution of **28** (1.27 g, 2.69 mmol) in THF (40 ml) was treated at -100°C for 2 h with a solution of (*S*)-BINAL-H[8] in THF prepared by mixing lithium aluminium hydride (1.53 g, 40.3 mmol), ethanol (2.22 ml, 30.7 mmol), and (*S*)-(-)-binaphthol (11.31 g, 39.5 mmol) in THF (80 ml). After methanol (30 ml) was added at -78°C to decompose the excess reducing agent, saturated aq. sodium sulfate solution and then ethyl acetate (200 ml) was added at r. t.. The resulting mixture was treated with magnesium sulfate (50 g) and filtered. The filtrate was evaporated and diluted with hexane to precipitate binaphthol as crystals. After filtration, the resulting organic solution was evaporated to give a crude product, which was purified by column chromatography on silica gel (150 g) using a 4 : 1 mixture of hexane and ethyl acetate to afford the reduced product **22** (1.15 g, 2.43 mmol, 90%); IR (neat): 3460, 3040, 2980, 2950, 2900, 1700, 1440, 1200, 1140, 1120, 1080, 1035, 1020, 975 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.95 (d, 3H, J = 6 Hz), 1.1-2.6 (m, 29H), 2.8-3.1 (m, 1H), 3.3-4.3 (m, 4H), 3.69 (bs, 1H), 4.66 (bs, 1H), 5.27 (bs, 1H), 5.4-5.7 (m, 4H);

EI-MS (m/z): 456 (M^+-H_2O), 438, 425, 412, 388, 372, 328, 299, 246, 180, 117, 85, 55; High-resolution MS for $C_{29}H_{44}O_4$ (M^+-H_2O): Calcd m/z: 456.3239; Found 456.3217.

(1*S*,5*S*,6*R*,7*R*)-7-Hydroxy-3-(4-methoxycarbonylbutyl)-6-[(*S*)-(1*E*,7*Z*)-3-hydroxy-5-methyl-1,7-nonadienyl]bicyclo[3.3.0]-2-octene (30)

In an analogous procedure to the preparation of the (*Z*)-Δ^{17} precursor **23** from the chiral allyl alcohol **22**, a solution of **29** (550 mg, 1.16 mmol) in THF (8 ml), acetic acid (6 ml), and water (3 ml) was stirred at 40°C for 20 h. Aq. sodium bisulfate solution was added, and the resulting mixture was extracted twice with ethyl acetate (100 ml). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residual oily product was subjected to column chromatography on silica gel (30 g) with a 2 : 1 and then 1 : 1 mixture of hexane and ethyl acetate as eluants to yield the deprotected **30** (390 mg, 1.00 mmol, 86%) as a diastereomeric mixture of 17*S* and 17*R* epimers; IR (neat): 3400, 3040, 2970, 2950, 2900, 1740, 1440, 1200, 1170, 1090, 1060, 1000, 965 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 0.93 (d, 3H, J = 6 Hz), 1.1-2.6 (m, 24H), 2.8-3.2 (m, 1H), 3.6-4.0 (m, 1H), 3.69 (s, 3H), 4.0-4.3 (m, 1H), 5.31 (s, 1H), 5.3-5.9 (m, 4H); EI-MS (m/z): 354, 328, 299, 273, 246, 219, 179, 145, 119, 91, 55.

(17*S*,*Z*)-Δ^{19}-17,20-Dimethyl-9(*O*)-Methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 methyl ester (31)

The obtained diastereomeric mixture (390 mg) of 17*S* and 17*R* epimers was subjected to preparative HPLC (Zorbax SIL column; 25 cm x 2.2 cm I.D.) eluting with 3.5% ethanolic hexane (15 ml / min) to give the desired 17*S*-product **31** (169 mg, 43%) as a fraction with a longer retention time and the 17*R*-isomer of **31** (160 mg, 41%) with a shorter retention time. The longer Rt product **31** was reduced under the catalytic hydrogenation condition (*vide infra*) to produce the desired product **7**. **31**; IR (neat): 3400, 3040, 2970, 2950, 2900, 1740, 1440, 1200, 1170, 1090, 1060, 1000, 965 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 0.93 (d, 3H, J = 6 Hz), 1.1-2.6 (m, 24H), 2.8-3.2 (m, 1H), 3.6-4.0 (m, 1H), 3.69 (s, 3H), 4.0-4.3 (m, 1H), 5.31 (s, 1H), 5.3-5.9 (m, 4H); EI-MS (m/z): 372 (M^+-H_2O), 354, 328, 299, 273, 246, 219, 179, 145, 119, 91, 55; High-resolution MS for $C_{24}H_{36}O_3$ (M^+-H_2O): Calcd m/z: 372.2662; Found 372.2680. 17(*R*) epimer of **31**; IR (neat): 3400, 3040, 2970, 2950, 2900, 1740, 1440, 1200, 1170, 1090, 1060, 1000, 965 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 0.93 (d, 3H, J = 6 Hz), 1.1-2.6 (m, 24H), 2.8-3.2 (m, 1H), 3.6-4.0 (m, 1H), 3.69 (s, 3H), 4.0-4.3 (m, 1H), 5.31 (s, 1H), 5.3-5.9 (m, 4H); EI-MS (m/z): 354, 328, 299, 273, 246, 219, 179, 145, 119, 91, 55; High-resolution MS for $C_{24}H_{36}O_3$ (M^+-H_2O): Calcd m/z: 372.2662; Found 372.2658.

(17*S*)-17,20-Dimethyl-9(*O*)-Methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 methyl ester (7)---cold synthesis---

In a similar manner to the cold synthesis of the compound **2** from the (*Z*)-Δ^{17} precursor **23**, palladium on activated carbon (5%; 1.4 mg) and cyclododecene (30 μl) were added to a solution of the (*Z*)-Δ^{19} precursor **31** (12 mg, 0.031 mmol) in a 1 : 1 mixture (1.5 ml) of benzene and cyclohexane. The mixture was stirred at 0°C for 1.5 h under a hydrogen atmosphere. The catalyst was filtered off through Celite and the separated catalyst was washed with ethyl acetate. The filtrate and washings were evaporated under vacuum to give a crude residue, which contained the desired partially reduced product **7** coinciding (TLC and HPLC) with the authentic sample of **7**.[6,9] The obtained crude product including **7** was separated by preparative HPLC (Inertsil ODS column; 25 cm x 4.6 mm I.D.) eluting with a 7 : 3 mixture of acetonitrile and water (flow rate; 1.1 ml / min, UV detection 210 nm) to furnish the desired product **7** (3.6 mg, 0.0093 mmol, 30%), which was identical (TLC HPLC, IR, NMR, and MS) with the authentic sample of **7**.

(17*S*)-[19,20-$^3H_2$]-17,20-Dimethyl-9(*O*)-Methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 methyl ester (10)---hot synthesis---

In a similar procedure to the hot synthesis of the above [17,18-$^3H_2$] ester **5** from the (*Z*)-Δ^{17} precursor **23**, the (*Z*)-Δ^{19} precursor **31** (29.4 mg, 0.075 mmol) was added to a solution of tris(triphenylphosphine)rhodium(I) chloride (14.5 mg) in a 1 : 1 mixture of benzene and cyclohexane. The resulting mixture was stirred under 10 Ci of tritium gas

at ambient temperature for 3.5 h. After removal of the solvents, the residual material (4.72 Ci) was applied to preparative silica-gel plates (2 x 1.0 mm), eluted with a 2 : 1 mixture of dichloromethane and acetone. The plates were dried, autoradiographed, and the major radioactive band was extracted with a 9 : 1 mixture of toluene and methanol to yield the radioactive extract (2.32 Ci). The obtained crude radioactive product was repeatedly purified by preparative HPLC (μ Bondapak ODS, acetonitrile : water containing 0.1% acetic acid = 2 : 1; Macro Dynamax ODS, acetonitrile : water containing 0.1% acetic acid = 3 : 1; Merck Supersphere 3μ C18, gradient elution from acetonitrile : water containing 0.01% acetic acid = 2 : 3 to acetonitrile; Macro Dynamax ODS, gradient elution from water containing 0.1% acetic acid to acetonitrile) to furnish the pure di-tritiated final product **10** (175 mCi). The radiochemical purity of the final product **10** was determined to be 99% by analytical HPLC (5μ Lichrosorb C18; 12.5 cm x 4.0 mm I.D.) eluting with a 3 : 1 mixture of acetonitrile and water containing 0.01% acetic acid. The specific activity of the product **10** was determined using chemical ionization (CI) mass spectrometry with ammonia as carrier gas. The calculation was based on the relative abundance the mean of twelve scans) of the MNH_4^+ cluster to be 50 Ci / mmol.

(17*S*)-[19,20-$^3H_2$]-17,20-Dimethyl-9(*O*)-Methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 (11)

In an analogous manner to the hot synthesis of the above [17,18-$^3H_2$] acid **6** from the tritiated ester **5**, A solution of the di-tritiated methyl ester **10** (200 mCi) in methanol (1 ml) and 5.0 N solution of sodium hydroxide (40 μl, 0.2 mmol) was stirred at 37 °C. for 1 h. To the reaction mixture were added a 11.3 N hydrochloric acid (20 μl, 0.226 mmol) The resulting mixture was evaporated at 20°C to dryness and methanol (3 x 1 ml) successively removed by rotary evaporation. The obtained residue was purified by preparative HPLC (Macro Dynamax ODS; 35 cm x 22 mm I.D., gradient elution using water containing 0.1% acetic acid and acetonitrile to provide the carboxylic acid **11** (45 mCi). The product **11** was identical (HPLC and TLC) with the cold authentic sample[6,9] of **8**, and the radiochemical purity of the acid **11** was found to be 97% by HPLC analysis (3μ Superspere C18, 25 cm x 4 6 mm I.D., acetonitrile : water containing 0.01% acetic acid = 1 : 1). The specific activity of the product **11** was also determined using chemical ionization (CI) mass spectrometry with ammonia as carrier gas. The calculation was based on the relative abundance (the mean of ten scans) of the MNH_4^+ cluster to be 44.9 Ci / mmol.

ACKNOWLEDGMENT

We are indebted to Amersham International plc. for the tritiation experiments to prepare the compounds **5**, **10** and **11**.

REFERENCES

1. Prostaglandin Chemistry Part XXXIX. For Part XXXX: Sugiura S., Tanaka T., Bannai K., Kurozumi S.—*J. Labelled compds.Radiopharm.*, in press
2. (a) *Prostacyclin*, ed. by Vane J. R.and Bergstrom S., Raven Press, New York, 1979; (b) Vane J. R—*Angew. Chem. Int. Ed. Engl.*, **22**: 741 (1983); (c) "Prostaglandin; Clinical Trials" ed. by Gryglewski R. J., Szczeklik A., and McGiff J. C., Raven Press, New York (1985)
3. Shibasaki M., Torisawa Y., and Ikegami S.—*Tetrahedron Lett.* **24**: 3493 (1983)
4. (a) Mizushima Y., Igarashi R., Hoshi K., Sim A. K., Cleland M. E., Hayashi H., and Goto—*Prostaglandins*, **33**: 161 (1987); (b) Hoshi K. and Mizushima Y—*Prostaglandins* **40**: 155 (1990); (c) Iseki K. and Shibasaki M—"Kohza Prostaglandin, 7. Iyakuhin,"

ed. by Yamamoto S., Murota S., Tokyo Kagaku Dohjin, Tokyo (1988), Chap. 3, pp 115-128, and references cited therein.

5. Sugiura S., Bannai., Tanaka T., Kurozumi S. and Ikegami S—*J. Labelled Compds. Radiopharm.*, in press
6. (a) Hazato A., Tanaka T., Okamura N., Bannai K., Sugiura S., Manabe K., Tomimori K., Kurozumi S., and Noyori R.–*7th IUPAC Conference on Organic Synthesis*, Nancy, **1988**, Abstr., No. 4-A10; (b) Tanaka T., Bannai K., Hazato A., Manabe K., and Kurozumi S—*J. Labelled Compds. Radiopharm.*, in press
7. Brown A. C. and Carpino L. A.—*J. Org. Chem.* **50**: 1749 (1985)
8. Noyori R., Tomino I., Tanimoto Y., and Nishizawa M.—*J. Amer. Chem. Soc.* **106**: 6709 (1984)
9. (a) Bannai K., Tanaka T., Hazato A., Sugiura S., Manabe K., Kato Y., Kurozumi S., and Noyori R.—*Tetrahedron*, **46**: 6689 (1990), (b) Tanaka T., Bannai K., Hazato A., Koga M., Kurozumi S., and Kato Y—*Tetrahedron*, **47**: 1861 (1991)
10. Tanaka T., Bannai K., Manabe K., and Kurozumi S—*J. Labelled Compds. Radiopharm.*, **29**:667 (1991)
11. Tanaka T., Okamura N., Bannai K., Hazato A., Sugiura S., Manabe K., Kamimoto, and Kurozumi S—*Chem. Pharm. Bull.* **33**: 2359 (1985)