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

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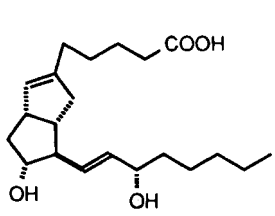
SUMMARY

Two types of poly-deuterated isocarbacyclin [9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1] methyl ester have been synthesized for the use of GC-MS quantitative analysis as internal standards and for the use of metabolic study as substrates. The 5,13,14-$^2H_3$ derivative **2** was prepared *via* H-D exchange, deuteroboration, and sodium borodeuteride reduction. The 2,2,3,3,4,4-$^2H_6$ derivatives **3**, **4** were prepared starting from tetrahydrofuran-d_8.

KEYWORDS: Isocarbacyclin-[^{2}H], 9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1-[^{2}H],

INTRODUCTION

Isocarbacyclin[2] [9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1] methyl ester (**1**) is a stable prostaglandin I_2 analog which is a promising therapeutic agent for cardiovascular diseases because of its high chemical stability and potent biological activity.[3] Consequently, it has become necessary for pre-clinical evaluations to assess the bioavailability of this agent **1** and to estimate its metabolic fate. In this paper, we describe the three types of syntheses for poly-deuterated isocarbacyclin derivatives **2**, **3**, and **4**.



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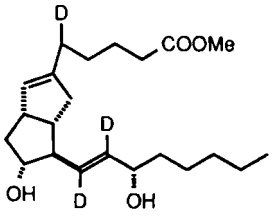

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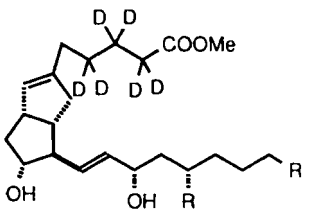

3: R = H, **4**: R = Me

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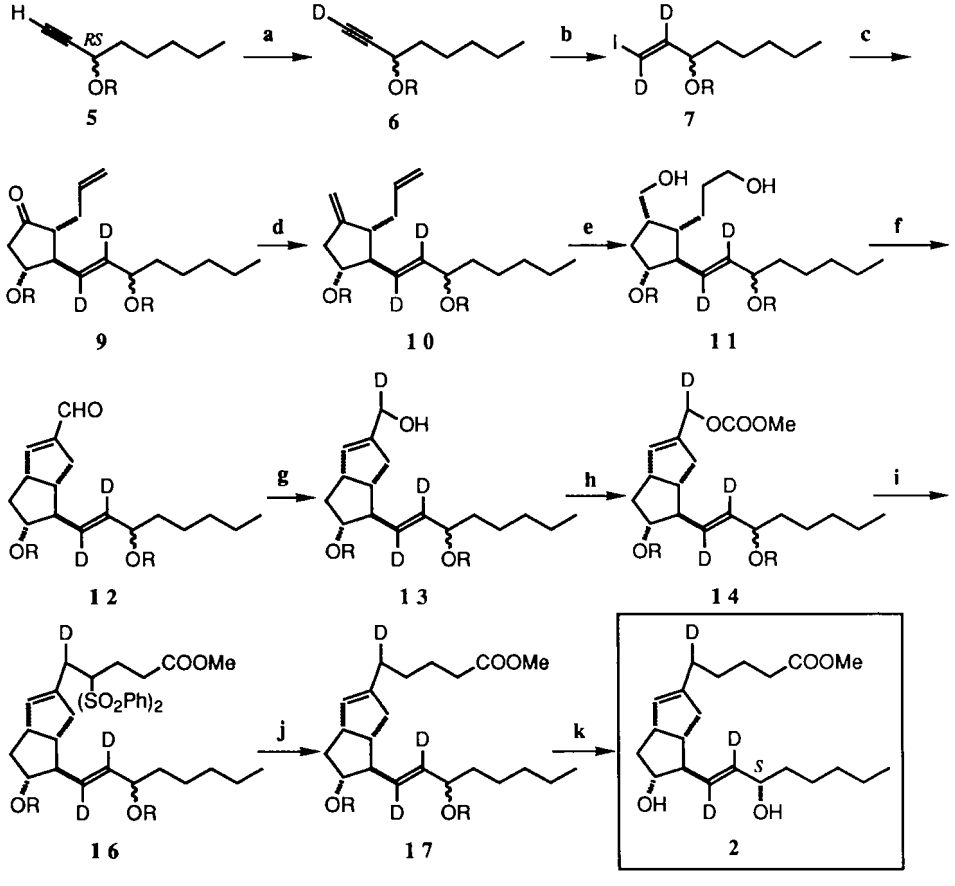
SYNTHESIS

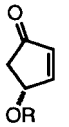
The first target compound of the deuterated isocarbacyclin is 5,13,14-$^2H_3$ derivative **2**, where three hydrogens resistant to the possible metabolism of **1** are substituted by deuterium atoms. The compound **2** was prepared starting from racemic 3-*t*-butyldimethylsilyloxy-1-octyne (**5**) *via* H-D exchange, deuteroboration, and sodium borodeuteride reduction in eleven steps (Scheme 1).

The hydrogen-deuterium exchange reaction of the acetylene **5** provided the deuterated acetylene **6** in 96% yield by treatment with *n*-butyllithium (^{n}BuLi) followed by deuterium oxide. Hydroboration[4] of the product **6** with deuteroborane and subsequent treatment with iodine in the presence of sodium hydroxide gave the di-deuterated vinyl iodide **7** (78%), which was confirmed by mass spectrometry. An organocopper reagent prepared from the di-deuterated vinyl iodide **7** was coupled with the chiral 2-cyclopentenone **8** to form the enolate which was then trapped *in situ* with allyl iodide furnishing the three-component coupling product **9** in 86% yield.[5] The resulting 2-allylcyclopentanone **9** was easily converted into the bicyclic enal **12** according to Shibasaki's procedure:[6] (1) Methylenation of the compound **9** with a dibromomethane-zinc-titanium tetrachloride reagent afforded a methylenecyclo-pentane **10** (89%); (2) Hydroboration of the product **10** with 9-borabicyclo[3.3.1]-nonane, followed by oxidation with hydrogen peroxide gave the diol **11** in 93% yield; (3) Oxidation of the diol **11** with dimethyl sulfoxide and subsequent cyclization with dibenzylammonium trifluoroacetate yielded **12** (88%). Reduction of **12** with sodium borodeuteride gave the tri-deuterated allyl alcohol **13** (83%), which was confirmed by mass spectroscopic measurement. The compound **13** was then converted into the allyl carbonate **14** (94%) by treatment with methyl chloroformate and triethylamine. Reaction of **14** with methyl 4,4-bis(phenylsulfonyl)butanoate **15** in the presence of palladium(0) bis[ethylenebis(diphenylphosphine)] afforded the regiospecifically alkylated adduct **16** (91%), which was allowed to react with magnesium in methanol to give the desulfonylated product **17** in 81% yield.[7] Desilylation of **17** with tetrabutylammonium fluoride in tetrahydrofuran completed the synthesis of [5,13,14-$^2H_3$]-isocarbacyclin methyl ester **2** in 48% yield together with its 15*R* epimer (**15R-2**, 43%) after chromatographic separation. The product **2** was estimated to have a deuterium

distribution of 1% d_1, 12% d_2, and 87% d_3 by mass spectroscopic measurement, and showed triplet signals at the ^{13}C-NMR chemical shifts corresponding to 5, 13, and 14 carbons (prostaglandin numbering).



a, ^{n}BuLi, D_2O; **b**, 2-methyl-2-butene—B_2D_6, Me_3N—O, I_2 (NaOH); **c**, ^{t}BuLi, ^{n}Pr C≡CCu—$(Me_2N)_3P$, **8**, then Ph_3SnCl, allyl iodide; **d**, CH_2Br_2—Zn—$TiCl_4$, **e**, 9-BBN, H_2O_2 (NaOH); **f**, $(COCl)_2$—DMSO, Et_3N, $(PhCH_2)_2NH_2^+$ $^-$OCOCF$_3$; **g**, $NaBD_4$; **h**, ClCOOMe (pyridine); **i**, $Pd_2(dba)_3CHCl_3$—$Ph_2PCH_2CH_2PPh_2$, **15**; **j**, Mg (MeOH); **k**, ^{n}Bu$_4$N$^+$F$^-$, then separation



8

$(PhSO_2)_2CHCH_2CH_2COOMe$

15

[9-BBN; 9-borabicyclo[3.3.1]nonane
dba; dibenzylideneacetone
R = SiMe$_2$^{t}Bu]

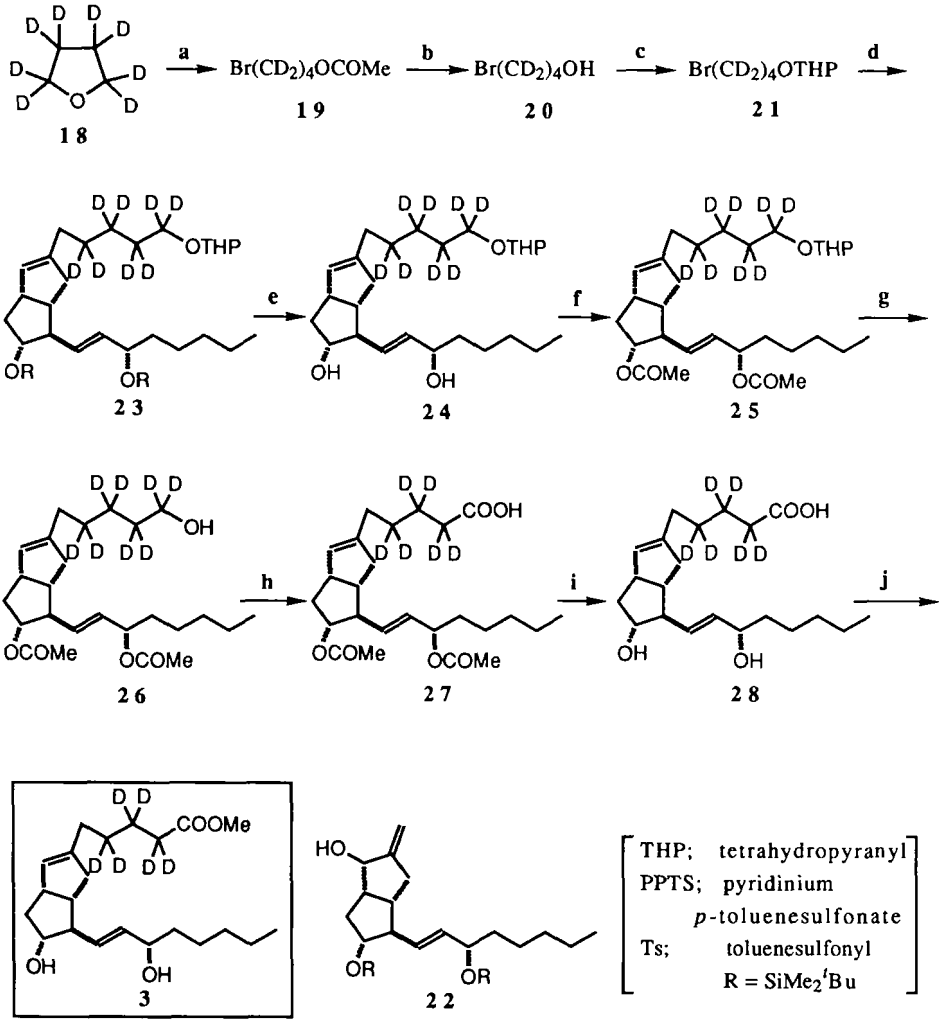
Scheme 1

The second target compound is 2,2,3,3,4,4-$^2H_6$ derivative **3**, where the six hydrogens at the position of 2, 3, and 4 are substituted by deuterium atoms. The desired product **3** was prepared from the combination of a perdeuterated bromobutanol **21** and a bicyclic allyl alcohol **22** in seven steps (Scheme 2).

The starting material **21** was obtained from tetrahydrofuran-d_8 **18** in three steps as follows: (1) Treatment of **18** with acetyl bromide in the presence of zinc chloride gave the bromobutyl acetate **19** in 98% yield;[8] (2) Reaction of **19** with lithium aluminum hydride afforded the deuterated bromobutanol **20** (91%); (3) Protection of **20** by dihydropyrane furnished **21** in 83% yield. The other partner **22** was synthesized from the chiral cyclopentenone **8** *via* vicinal carbacondensation reaction according to the cited procedure.[9] Copper-catalyzed coupling reaction of **22** with the lithiated derivative of **21** in the presence of a phosphonium salt gave the product **23** in 78% yield.[9,10] There was obtained the acetate **25** by desilylation (90%) of **23** with tetrabutylammonium fluoride followed by re-protection (94%) of the resultant **24** with acetic anhydride and pyridine. Deprotection of the tetrahydropyranyl ether **25** with *p*-toluenesulfonic acid provided the acetylated alcohol **26** (91%) which was oxidized with Jones' reagent to furnish the protected hexa-deuterated isocarbacyclin **27** in 73% yield. Deprotection of **27** with aqueous sodium hydroxide gave the hexa-deuterated isocarbacyclin **28** (91%) whose esterification with methyl iodide in the presence of ethyldiisopropylamine completed the synthesis of [2,2,3,3,4,4-$^2H_6$]isocarbacyclin methyl ester **3** in 81% yield. The product **3** was found to have a deuterium distribution of 1% d_4, 4% d_5, and 95% d_6 by mass spectroscopic measurement, and showed three missing ^{13}C-NMR signals at the chemical shifts corresponding to 2, 3, and 4 carbons. The deuterated products of **2** and **3** were used as internal standards for GC-MS quantitative analysis and in a metabolic study of isocarbacyclin methyl ester **1**.

The other target compound of the deuterated isocarbacyclin was 2,2,3,3,4,4-$^2H_6$ 17(*S*),20-dimethyl derivative **4**. The compound **4** was prepared by the coupling reaction of methyl hexa-deuterated 4-iodobutanoate **31** and a bicyclic allylic alcohol **32** in two steps (Scheme 3).[11] The deuterated component **31** was obtained from the above-mentioned bromo alcohol **20** in 45 % yield as follows: (1) Oxidation of **20** by Jones' reagent gave the perdeuterated 4-bromobutanoic acid **29**; (2) Esterification of **29**

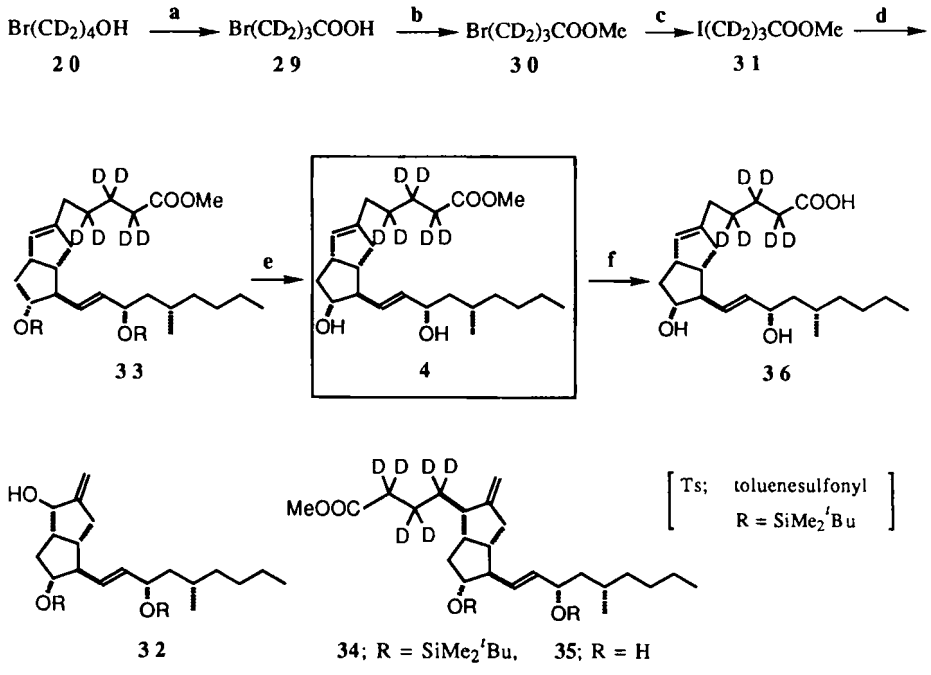
provided the bromo ester **30**; (3) Iodination of the bromide **30** with sodium iodide furnished the iodide **31**. The other component **32** was also obtained from the chiral 2-cyclopentenone **7** *via* three-component coupling process.[9] Copper-catalyzed alkylation



a, MeCOBr ($ZnCl_2$); **b**, $LiAlH_4$; **c**, dihydropyran (PPTS);
d, ^{t}BuLi, **21**—^{n}BuLi, CuI, $^n Bu_3P^+NMePhI^-$; **e**, $^n Bu_4N^+F^-$; **f**, $(MeCO)_2O$ (pyridine);
g, *p*-TsOH; **h**, Jones' reagent; **i**, NaOH; **j**, MeI ($^i Pr_2EtN$)

Scheme 2

reaction[12] of the *in situ* generated tosylate intermediate of **32** with the organozinc compound, prepared from **31** and an activated zinc metal, gave the coupling adduct **33** accompanied by an α-alkylated by-product **34** (**33**:**34** = 80:20) in 73% yield. Desilylation of crude product **33** with tetrabutylammonium fluoride yielded the deprotected diol ester **4** (49%) after purification by preparative HPLC to separate **35**. Hydrolysis of **4** with lithium hydroxide provided the corresponding carboxylic acid **36** in 97% yield. The products of **4** and **36** were found to show a similar deuterium distribution (1% d_4, 4% d_5, and 95% d_6) to the hexa-deuterated **3** and **28**. They also served as internal standards for GC-MS quantitative analysis of **1**.



a, Jones' reagent; b, MeOH, H_2SO_4; c, NaI; d, Zn, CuCN—LiCl, then **32**—^{n}BuLi, TsCl; e, $^n Bu_4N^+F^-$; f, LiOH

Scheme 3

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.

Deuterium oxide (99.95 atom% D) was provided from Merck Sharp and Dohme (Montreal, Quebec, Canada). Sodium borodeuteride (98 atom% D) and tetrahydrofuran-d_8 (99.5 atom% D) were obtained from Aldrich Chemical Co. (Milwaukee, Wisconsin, U.S.A.).

Synthesis of [5,13,14-$^2H_3$]-9(*O*)-Methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 Methyl Ester (2)

(±)-3-*t*-Butyldimethylsilyloxy[1-^{2}H]-1-octyne (6)

A 1.53 M hexane solution of *n*-butyllithium (^{n}BuLi) (25 ml, 37.5 mmol) was added at -78°C to a stirred solution of (±)-3-*t*-butyldimethylsilyloxy-1-octyne (5; 6.0 g, 25 mmol) in tetrahydrofuran (THF) (100 ml). After the mixture was stirred at -78°C for 2 h, deuterium oxide (99.95 atom% D; 1 ml, 50 mmol) was added at 0°C, and the mixture was stirred at 0°C for 10 min. Aqueous (aq.) NH_4Cl (30 ml) was added and the resulting mixture was extracted with ethyl acetate (EtOAc) (3 × 50 ml). The separated organic layers were washed with brine, dried over magnesium sulfate ($MgSO_4$), and concentrated *in vacuo* to afford a deuterated product **6** (5.79 g, 24 mmol, 96%); IR(neat): 2610, 1980, 1460, 1255, 1120, 1090, 1040, 835, 775 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.11 (s, 3H), 0.13 (s, 3H), 0.93 (s + t, 12H), 1.1-1.9 (m, 8H), 4.33 (t, 1H, J = 6 Hz).

(±)-(*E*)-3-*t*-Butyldimethylsilyloxy-1-iodo[1,2-$^2H_2$]-1-octene (7)

A slurry of sodium borodeuteride (98 atom% D; 3.78 g, 90 mmol) in bis(2-methoxyethyl) ether (90 ml) was added dropwise at room temperature (r. t.) during 1 h to a stirred solution of boron trifluoride etherate (25.5 g, 180 mmol) in bis(2-methoxyethyl) ether (20 ml). The generated gaseous deuteroborane (B_2D_6) was continuously bubbled *via* a double-tipped needle into the THF (150 ml). 2-Methyl-2-butene (16.8 g, 240 mmol) was added at 0°C to the resulting THF solution of B_2D_6. After being stirred for 10 min, a solution of the above deuterated alkyne **6** (5.79 g, 24 mmol) in THF (100 ml) was added at 0 °C, and then the mixture was stirred at r. t. for 1 h. Anhydrous trimethylamine oxide (18 g, 240 mmol) was added, and the mixture was stirred at r. t. for 40 min. The resulting mixture was poured into a cooled 4.0 N sodium hydroxide (NaOH) solution (500 ml) at 0°C. Then, a solution of iodine (30 g, 120 mmol) in THF (90 ml) was added to the mixture, and the whole mixture was stirred at r. t. for 30 min. The organic layer was taken up to hexane (500 ml), and the separated aqueous layer was extracted with hexane (2 × 500 ml). The combined organic layer was washed with aq. sodium thiosulfate solution, then brine, and dried ($MgSO_4$). Evaporation of the solvent left a crude product, which was separated by column chromatography on silica gel (200 g) with hexane to yield a deuterated vinyl iodide **7** (6.98 g, 18.9 mmol, 78%); IR(neat): 2300, 1575, 1460, 1260, 1125, 1095, 890, 840, 775 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.03 (s, 3H), 0.04 (s, 3H), 0.90 (s + t, 12H), 1.1-1.6 (m, 8H), 4.10 (t, 1H, J = 6 Hz); EI-MS (m/z): 370 (1, M^+), 355 (18), 313 (63), 299 (11), 243 (13), 239 (24), 215 (11), 111 (100).

(2*R*,3*S*,4*R*)-2-Allyl-4-*t*-butyldimethylsilyloxy-3-[(*E*)-(*RS*)-3-*t*-butyldimethylsilyloxy[1,2-$^2H_2$]-1-octenyl]cyclopentanone (9)

A solution of **7** (5.77 g, 15.6 mmol) in ether (15 ml) was added at -78°C to a stirred 1.52 M pentane solution of *t*-butyllithium (^{t}BuLi) (20.5 ml, 31.2 mmol) in ether (15 ml), and the mixture was stirred at -78°C for 2 h. A solution of 1-pentynylcopper(I) (2.04 g, 15.6 mmol) and hexamethylphosphorous triamide (5.09 g, 31.2 mmol) in ether (15 ml)

was added at -78°C, and the resulting mixture was stirred at -78°C for 1 h. Then, a solution of (*R*)-4-*t*-butyldimethylsilyloxy-2-cyclopentenone (**8**; 2.76 g, 13.0 mmol) in THF (75 ml) was added at -78°C during 2 h, and the mixture was stirred at -50°C for 30 min. To the mixture was added at -78°C hexamethylphosphoric triamide (11.6 g, 65 mmol), and a solution of triphenyltin chloride (6.01 g, 15.6 mmol) in THF (30 ml) after 30 min. Then, allyl iodide (10.92 g, 65 mmol) was added at -50°C, and the whole mixture was stirred at -50°C for 10 min, at -20°C for 2 h, and stood at -20°C for 18 h. Acetic acid (AcOH) (10 ml) was added and the resulting mixture was poured into an aq. 4.0 M acetate buffer solution (300 ml). The organic layer was taken up to hexane (500 ml), and the separated aqueous layer was extracted with hexane (2 × 500 ml). The combined organic layer was washed with aq. NH_4Cl, aq. NH_3-NH_4Cl, aq. NH_4Cl, and brine, and then dried over $MgSO_4$. Removal of the solvent *in vacuo* afforded 13.35 g of a crude product, which was chromatographed on silica gel (400 g) with hexane-EtOAc (49:1) to give the enolate-trapping product **9** (5.55 g, 11.21 mmol, 86%); IR (neat): 3180, 2220, 1745, 1640, 1255, 1115, 835, 775 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.05 (s, 12H), 0.75-1.0 (s × 2 + t, 21H), 1.1-1.6 (m, 8H), 1.8-2.8 (m. 6H), 3.9-4.2 (m, 2H), 4.9-5.2 (m, 2H), 5.5-6.0 (m, 1H).

(1*R*,2*S*,3*R*)-1-Allyl-3-*t*-butyldimethylsilyloxy-2-[(*E*)-(*RS*)-3-*t*-butyldimethylsilyloxy[1,2-$^2H_2$]-1-octenyl]-5-methylenecyclopentane (10)

To a stirred solution of **9** (3.56 g, 7.18 mmol) in dichloromethane (CH_2Cl_2) (100 ml) was added at 0°C a slurry of the methylenation reagent, which was prepared by treatment of dibromomethane (12 g, 69 mmol), zinc (13.7 g, 210 mmol), and titanium tetrachloride (9.5 g, 50 mmol) in THF (100 ml) at -40°C for 2 h. After the starting material **9** disappeared on monitoring by TLC, the resulting precipitate was washed three times with CH_2Cl_2 by decantation, and washings were filtered through Celite. Hexane (300 ml) was added to the filtrate, and the resulting mixture was washed with aq. 10% tartaric acid, aq. sodium bicarbonate ($NaHCO_3$), and brine. The separated organic layer was dried ($MgSO_4$), and concentrated *in vacuo* to leave 3.86 g of an oily residue. The residue was chromato-graphed on silica gel (200 g) with hexane-EtOAc (99:1) to provide the methylenated **10** (3.17 g, 6.42 mmol, 89%); IR (neat): 3190, 2220, 1660, 1640, 1260, 1115, 835, 775 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.03 (s, 12H), 0.80-1.0 (s × 2 + t, 21H), 1.1-1.6 (m, 8H), 2.1-2.9 (m, 6H), 3.7-4.2 (m, 2H), 4.8-5.3 (m, 4H), 5.7-6.1 (m, 1H).

(1*R*,2*S*,3*S*,4*S*)-1-*t*-Butyldimethylsilyloxy-2-[(*E*)-(*RS*)-3-*t*-butyldimethylsilyloxy[1,2-$^2H_2$]-1-octenyl]-4-hydroxymethyl-3-(3-hydroxypropyl)-cyclopentane (11)

A solution of 9-borabicyclo[3.3.1]nonane (6.3 g, 25.68 mmol) in THF (80 ml) was added at 0°C to a stirred solution of **10** (3.17 g, 6.42 mmol) in THF (50 ml), and the mixture was stirred at 0°C for 1 h. Aq. 5.0 N NaOH (30 ml), and then aq. 38% hydrogen peroxide (20 ml) were added at 0°C to the resulting mixture, and the whole mixture was stirred at 0°C for 10 min, and at 60°C for 30 min. The reaction mixture was poured into brine (200 ml), and extracted with EtOAc (3 × 300 ml). The separated organic layers were combined, dried over $MgSO_4$, and evaporated. The crude residue (7.77 g) was purified by column chromatography (silica gel, 200 g) using hexane-EtOAc (3:2) for elution to give **11** (3.16 g, 5.96 mmol, 93%); IR (neat): 3360, 2200, 1255, 1060, 835, 775 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.05 (s, 12H), 0.8-1.0 (s × 2 + t, 21H), 1.1-2.6 (m, 17H), 2.6-3.3 (m, 2H), 3.4-4.2 (m, 6H).

(1*S*,5*S*,6*S*,7*R*)-7-*t*-Butyldimethylsilyloxy-6-[(*E*)-(*RS*)-3-*t*-butyldimethylsilyloxy[1,2-$^2H_2$]-1-octenyl]-3-formylbicyclo[3.3.0]-2-octene (12)

A solution of dimethyl sulfoxide (DMSO) (3.81 g, 48.8 mmol) in CH_2Cl_2 (6 ml) was added at -60°C to a stirred solution of oxalyl chloride (2.86 g) in CH_2Cl_2 (30 ml), and the mixture was stirred at -60°C for 10 min. To the reaction mixture was added at -60°C a solution of **12** (3.15 g, 5.94 mmol) in CH_2Cl_2 (15 ml), and the mixture was stirred at -60°C for 30 min. Triethylamine (Et_3N) (11.4 g, 113 mmol) was added at -60°C, and the resulting mixture was stirred at r. t. for 50 min. Dibenzylammonium trifluoroacetate (2.34 g, 7.5 mmol) was added to the reaction mixture. After CH_2Cl_2 was evaporated under reduced pressure, benzene (60 ml) was added, and the whole mixture was refluxed with stirring for 2 h. The mixture was diluted with hexane (300 ml), the separated aqueous layer was extracted twice with hexane (300 ml). The combined organic layer was

washed with aq. pottasium bisulfate ($KHSO_4$), aq. $NaHCO_3$, and brine, dried ($MgSO_4$), and evaporated to give a crude product (4.35 g), which was chromatographed on silica gel (200 g) with hexane-EtOAc (20:1) to furnish the cyclized enal **12** (2.65 g, 5.21 mmol, 88%); IR (neat): 2720, 2220, 1685, 1660, 1620, 1120, 1080, 835, 775 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 0.03 (s, 12H), 0.75-1.0 (s × 2 + t, 21H), 1.1-1.6 (m, 8H), 1.8-2.9 (m, 6H), 3.0-3.5 (m, 1H), 3.6-4.0 (m, 1H), 3.9-4.2 (m, 1H), 6.75 (m, 1H), 9.81 (s, 1H).

(1*S*,5*S*,6*S*,7*R*)-7-*t*-Butyldimethylsilyloxy-6-[(*E*)-(*RS*)-3-*t*-butyldimethylsilyloxy[1,2-$^2H_2$]-1-octenyl]-3-hydroxy[^2H]methylbicyclo[3.3.0]-2-octene (13)

Sodium borodeuteride (98 atom% D; 84 mg, 2.0 mmol) was added at 0°C to a stirred solution of **12** (1.10 g, 2.17 mmol) in methanol (MeOH) (10 ml), and the mixture was stirred at 0°C for 30 min. Aq. NH_4Cl was added and the resulting mixture extracted with EtOAc (3 × 50 ml). The separated organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford a crude product (1.12 g). Purification of the crude product by silica gel (50 g) column chromatography (hexane:EtOAc = 9:1) gave the trideuterated alcohol **13** (924 mg, 1.81 mmol, 83%); IR (neat): 3360, 2220, 2150, 1260, 1120, 900, 840, 775 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 0.03 (s, 12H), 0.8-1.0 (s × 2 + t, 21H), 1.1-1.8 (m, 8H), 1.8-2.8 (m, 7H), 2.8-3.3 (m, 1H), 3.6-4.0 (m, 1H), 4.0-4.3 (m, 2H), 5.67 (m, 1H); EI-MS (m/z): 551 (2, M^+), 494 (30), 454 (98), 440 (20), 380 (58), 362 (56), 322 (17), 308 (13), 248 (22), 230 (68), 215 (25), 173 (35), 133 (69), 75 (80), 73 (100), 57 (40).

(1*S*,5*S*,6*S*,7*R*)-7-*t*-Butyldimethylsilyloxy-6-[(*E*)-(*RS*)-3-*t*-butyldimethylsilyloxy[1,2-$^2H_2$]-1-octenyl]-3-methoxycarbonyloxy[^2H]methylbicyclo-[3.3.0]-2-octene (14)

Methyl chloroformate (1.42 g, 15.0 mmol), pyridine (2.37 g, 30.0 mmol) was added at 0°C to a stirred solution of **13** (1.50 g, 2.95 mmol) in CH_2Cl_2 (30 ml). After being stirred at 0°C for 10 min, aq. NH_4Cl was added, and the resulting mixture was extracted with CH_2Cl_2 (3 × 100 ml). The combined extracts were washed with aq. $KHSO_4$, aq. $NaHCO_3$, and brine, and then dried ($MgSO_4$). Evaporation of the solvent gave a crude product (1.70 g), which was purified by column chromatography (silica gel, 150 g) using hexane-EtOAc (19:1) to afford the methoxycarbonylated **14** (1.57 g, 2.76 mmol, 94%); IR (neat): 2210, 1760, 1660, 1440, 1265, 1115, 850, 835, 775 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 0.03 (s, 12H), 0.75-1.0 (s × 2 + t, 21H), 1.1-1.6 (m, 9H), 1.8-2.8 (m, 5H), 2.8-3.3 (m, 1H), 3.5-3.9 (m, 1H), 3.8 (s, 3H), 3.9-4.2 (m, 1H), 4.5-4.7 (m, 1H), 5.66 (m, 1H).

(15*RS*)-11,15-*O*-bis(*t*-Butyldimethylsilyloxy)-4,4-bis(phenylsulfonyl)-[5,13,14-$^2H_3$]-9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 methyl ester (16)

A mixture of **14** (1.50 g, 2.64 mmol) and methyl 4,4-bis(phenylsulfonyl)butanoate (**15**; 1.51 g, 3.96 mmol) in THF (20 ml) was added to a stirred solution of tris(dibenzylideneacetone)dipalladium(0)-chloroform (104 mg, 0.10 mmol) and ethylenebis(diphenylphosphine) (105 mg, 0.264 mmol) in THF (20 ml), and the resulting mixture was refluxed for 15 h. Aq. NH_4Cl was added and the mixture was extracted with EtOAc (3 × 150 ml). The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford a crude product (3.68 g), which was purified on silica gel (200 g) column chromatography with hexane-EtOAc (9:1 up to 6:1) to yield the alkylated **16** (2.10 g, 2.39 mmol, 91%); IR (neat): 3180, 2220, 1740, 1640, 1585, 1445, 1330, 1310, 1255, 1150, 1080, 1005, 900, 840, 780, 720, 690 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 0.03 (s, 12H), 0.75-1.0 (s × 2 + t, 21H), 1.0-1.7 (m, 11H), 1.7-2.5 (m, 3H), 2.5-3.1 (m, 6H), 3.5-3.9 (m, 1H), 3.71 (s, 3H), 3.9-4.2 (m, 1H), 5.6 (m, 1H), 7.4-7.9 and 7.9-8.3 (m, 10H).

(15*RS*)-11,15-*O*-bis(*t*-Butyldimethylsilyloxy)[5,13,14-$^2H_3$]-9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 methyl ester (17)

A mixture of the bis(phenylsulfone) **16** (2.05 g, 2.34 mmol) and magnesium (1.14 g, 46.8 mmol) in MeOH (35 ml) was stirred at 35°C for 2 h. Aq. NH_4Cl was added to the reaction mixture, and the resulting mixture was extracted with EtOAc (3 × 150 ml). The separated organic layers were combined, washed with brine, and dried over $MgSO_4$. Removal of the solvent left a crude residue (1.30 g), which was chromatographed on

silica gel (150 g) with hexane-EtOAc (40:1) to provide the desulfonylated **17** (1.13 g, 1.90 mmol, 81%); IR (neat): 2220, 2140, 1745, 1260, 1115, 1080, 1005, 900, 835, 775 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 0.03 (s, 12H), 0.75-1.0 (s × 2 + t, 21H), 1.0-1.7 (m, 13H), 1.8-2.6 (m, 8H), 2.6-3.2 (m, 1H), 3.5-4.0 (m, 1H), 3.69 (s, 3H), 3.9-4.2 (m, 1H), 5.27 (m, 1H).

(15*S*)-[5,13,14-$^2H_3$]-9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 methyl ester (2) and its 15*R* isomer (15R-2)

A 1.0 M THF solution of tetrabutylammonium fluoride (15 ml, 15 mmol) was added at r. t. to a stirred solution of **17** (1.12 g, 1.88 mmol) in THF (15 ml), and the mixture was stirred at r. t. for 5 h. Aq. NH_4Cl was added and the reaction mixture was extracted with EtOAc (3 × 150 ml). The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated under reduced pressure to give a crude product. The crude product was separated by column chromatography on silica gel (150 g) using hexane-EtOAc (1:2) to the desired **2** (336 mg, 0.92 mmol, 48%) and its 15*R* epimer of **2** (**15R-2**, 295 mg, 0.80 mmol, 43%). A pure sample of **2** for analysis was further purified by preparative HPLC. **2**; IR (neat): 3390, 3040, 2210, 2120, 1740, 1640, 1440, 1250, 1200, 1170, 1090, 1060, 1020, 1000, 720 cm^{-1}; ^1H-NMR ($CDCl_3$), δ 0.90 (t, 3H, J = 6 Hz), 1.1-1.7 (m, 8H), 1.8-2.1 (m, 3H), 2.2-2.7 (m, 5H), 2.8-3.2 (m, 1H), 3.70 (s, 3H), 3.7-3.8 (q, 1H, J = 6 Hz), 4.0-4.2 (t, 1H, J = 6 Hz), 5.30 (bs, 1H); EI-MS (m/z): 349 (32), 348 (4), 331 (26), 305 (100), 278 (14), 234 (34), 202 (17), 181 (38), 133 (29), 99 (42), 71 (31); 1% d_1, 12% d_2, 87% d_3; ^{13}C-NMR ($CDCl_3$): δ 14.02, 22.64, 24.67, 25.21, 27.12, 30.18 (t), 31.77, 33.94, 37.23, 39.59, 39.70, 44.33, 45.65, 51.47, 58.04, 73.08, 77.17, 128.39, 132.84 (t), 135.06 (t), 141.32, 174.23. **15R-2**: IR (neat): 3400, 3050, 2220, 2130, 1745, 1640, 1440, 1250, 1200, 1170, 1085, 1000, 720 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 0.90 (t, 3H, J = 6 Hz), 1.1-1.8 (m, 8H), 1.8-2.2 (m, 3H), 2.2-2.7 (m, 5H), 2.8-3.2 (m, 1H), 3.70 (m, 1H), 3.6-4.0 (m, 1H), 4.0-4.2 (m, 1H), 5.32 (bs, 1H).

Synthesis of [2,2,3,3,4,4-$^2H_6$]-9(*O*)-Methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 Methyl Ester (3)

4-Bromo[1,1,2,2,3,3,4,4-$^2H_8$]butyl acetate (19)

Acetyl bromide (3.32 g, 27 mmol) was added at 0°C to a stirred suspension of tetrahydrofuran-d_8 (99.5 atom% D; 1.80 g, 22.5 mmol) and zinc chloride (14 mg, 0.1 mmol). The mixture was stirred at r. t. for 30 min and then quenched with MeOH (2 ml). The mixture was extracted with EtOAc (3 × 50 ml). The combined extract was washed with aq. $NaHCO_3$, and brine, dried ($MgSO_4$), and evaporated under reduced pressure to give **19** (4.49 g, 22.1 mmol, 98%), which was homogeneous by TLC without further purification; IR (neat): 2220, 2120, 1740, 1375, 1270, 1240, 1170, 1080, 1035, 990 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 2.05 (s, 3H).

4-Bromo[1,1,2,2,3,3,4,4-$^2H_8$]butanol (20)

A solution of **19** (4.49 g, 22.1 mmol) in ether (50 ml) was added at 0°C to a stirred suspension of $LiAlH_4$ (1.03 g, 27 mmol) in ether (30 ml), and the reaction mixture was stirred at r. t. for 30 min. Saturated aq. Na_2SO_4 solution was added dropwise to the mixture until complete formation of the alum cake. The resulting cake was separated from the organic layer and washed several times with ether. The combined organic layers were dried and concentrated *in vacuo* to afford the bromo alcohol **20** (3.24 g, 20.1 mmol, 91%); IR (neat): 3340, 2210, 2110, 1160, 1135, 1110, 990, 970, 920 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 3.47 (s, 1H).

4-Bromo-1-(2-tetrahydropyranyloxy)[1,1,2,2,3,3,4,4-$^2H_8$]butane (21)

To a stirred solution of **20** (3.24 g, 20.1 mmol) in CH_2Cl_2 (20 ml) was added at 0°C 3,4-dihydro-2H-pyran (1.89 g, 22.5 mmol) and then a catalytic amount of pyridinium *p*-toluenesulfonate. Then mixture was stirred at r. t. for 2 h, and was diluted with CH_2Cl_2 (100 ml). The resulting mixture was washed with aq. $KHSO_4$, aq. $NaHCO_3$, and brine. The separated organic layer was dried over $MgSO_4$, evaporated *in vacuo* to give 4.82 g of a crude material. The residual product was subjected to column chromatography on silica gel (100 mg) using hexane-EtOAc (9:1) as an eluant to yield the protected **21** (4.06 g, 16.6 mmol, 83%) as a colorless oil; IR (neat): 2750, 2680, 2220, 2100, 1170, 1140, 1080, 1025, 990,

900, 870, 815 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.3-2.1 (m, 6H), 3.3-3.7 (m, 1H), 3.7-4.1 (m, 1H), 4.57 (m, 1H).

(1*S*,5*S*,6*R*,7*R*)-7-*t*-Butyldimethylsilyloxy-6-[(*E*)-(*S*)-3-*t*-butyldimethylsilyloxy-1-octenyl]-3-[5-(2-tetrahydropyranyloxy)[1,1,2,2,3,3,4,4-$^2H_8$]-pentyl]bicyclo[3.3.0]-2-octene (23)

A 1.5 M hexane solution of ^{n}BuLi (1.73 ml, 2.59 mmol) was added at 0°C to a solution of (1*S*,2*R*,3*R*,5*S*,6*RS*)-3-*t*-butyldimethylsilyloxy-2-[(*E*)-(*S*)-3-*t*-butyldimethylsilyloxy-1-octenyl]-6-hydroxy-7-methylenebicyclo[3.3.0]octane (**22**; 1.096 g, 2.16 mmol) in THF (20 ml), and the mixture was stirred at r. t. for 30 min. This solution was added at r. t. to a stirred suspension of cuprous iodide (535 mg, 2.8 mmol) in THF (10 ml). After being stirred at r. t. for 30 min, the resulting solution was cooled to -78°C. To the mixture was added at -78°C the lithiated perdeuterobutane solution, prepared by treatment of **21** (1.06 g, 4.32 mmol) with a 1.5 M pentane solution of ^{t}BuLi (4.32 ml, 6.48 mmol) in ether (30 ml) at -78°C for 2 h. After being stirred at -78°C for 30 min, a solution of (methylphenylamino)tributylphosphonium iodide (1.22 g, 2.81 mmol) in dimethylformamide (5 ml) was added, and the reaction mixture was stirred at -78°C for 10 min, and then at r. t. for 2 h. The reaction was quenched with aq. NH_4Cl (80 ml). The organic layer was separated and the remainder was extracted with EtOAc (2 × 200 ml). The extracts were combined, dried ($MgSO_4$), and concentrated *in vacuo* to leave a crude residue (2.66 g). Column chromatographic separation (hexane:EtOAc = 15:1) of the product furnished the coupling product **23** (1.105 g, 1.68 mmol, 78%); IR (neat): 3040, 2210, 2100, 1260, 1120, 1030, 860, 840, 775 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.03 (s, 12H), 0.8-1.0 (s × 2 + t, 21H), 1.0-2.7 (m, 22H), 2.7-3.2 (m, 1H), 3.3-4.2 (m, 4H), 4.60 (bs, 1H).

(1*S*,5*S*,6*R*,7*R*)-7-Hydroxy-6-[(*E*)-(*S*)-3-hydroxy-1-octenyl]-3-[5-(2-tetrahydropyranyloxy)[1,1,2,2,3,3,4,4-$^2H_8$]pentyl]bicyclo[3.3.0]-2-octene (24)

A 1.0 M THF solution of tetrabutylammonium fluoride (13 ml, 13 mmol) was added at r. t. to a solution of **23** (1.031 g, 1.57 mmol) in THF (10 ml), and the mixture was stirred at r. t. for 12 h. Aq. NH_4Cl was added and the resulting mixture was extracted with EtOAc (2 × 100 ml). The separated organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to afford a crude product (1.15 g). Column chromatographic separation of the product on silica gel (150 g) using hexane-EtOAc (1:4) as an eluant gave the desilylated **24** (602 mg, 1.41 mmol, 90%); IR (neat): 3400, 3040, 2210, 2110, 1130, 1080, 1030, 970, 735 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.88 (t, 3H, J = 6 Hz), 1.1-2.6 (m, 24H), 2.8-3.2 (m, 1H), 3.3-4.3 (m, 5H), 4.57 (m, 1H), 5.3 (bs, 1H), 5.5-5.7 (m, 2H).

(1*S*,5*S*,6*R*,7*R*)-7-Acetoxy-6-[(*E*)-(*S*)-3-acetoxy-1-octenyl]-3-[5-(2-tetrahydropyranyloxy)[1,1,2,2,3,3,4,4-$^2H_8$]pentyl]bicyclo[3.3.0]-2-octene (25)

A mixed solution of **24** (582 mg, 1.36 mmol) and acetic anhydride (1.5 ml) in pyridine (2.0 ml) was stirred at r. t. for 5 h. Ethanol (5 ml) was added at 0°C and the mixture was stirred at r. t. for 10 min. Toluene (50 ml) was added to the mixture, and the resulting mixture was azeotropically evaporated *in vacuo* to leave the almost pure acetate **25** (679 mg, 1.33 mmol, 94%); IR (neat): 3040, 2210, 2110, 1740, 1370, 1240, 1080, 1025, 970 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ0.89 (t, 3H, J = 6 Hz), 1.0-2.6 (m, 22H), 2.00 (s, 3H), 2.05 (s, 3H), 2.8-3.2 (m, 1H), 3.4-3.7 (m, 1H), 3.7-4.0 (m, 1H), 4.60 (m, 1H), 4.6-5.0 (m, 1H), 5.1-5.4 (m, 2H), 5.4-5.65 (m, 2H).

(1*S*,5*S*,6*R*,7*R*)-7-Acetoxy-6-[(*E*)-(*S*)-3-acetoxy-1-octenyl]-3-(5-hydroxy)-[1,1,2,2,3,3,4,4-$^2H_8$]pentyl]bicyclo[3.3.0]-2-octene (26)

The tetrahydropyranyl ether **25** (660 mg, 1.29 mmol) was dissolved in a mixture of AcOH (9 ml), water (3 ml), and THF (3 ml). The mixture was heated at 50°C for 8 h and toluene (100 ml) was added. The reaction mixture was azeotropically concentrated *in vacuo* to give the crude product (598 mg). Chromatographic purification of the crude product on silica gel (50 g) with hexane-EtOAc (2:1) gave the acetyl alcohol **26** (500 mg, 1.17 mmol, 91%); IR (neat): 3460, 3040, 2210, 2110, 1740, 1370, 1240, 1170, 1145, 1115, 970 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 0.87 (t, 3H, J = 6 Hz), 1.0-1.8 (m, 9H), 1.9-2.7 (m, 8H), 2.00 (s, 3H), 2.05 (s, 3H), 2.8-3.2 (m, 1H), 4.6-5.1 (m, 1H), 5.1-5.4 (m, 2H), 5.4-5.65 (m, 2H).

11,15-*O*-bis(Acetyl)[2,2,3,3,4,4-$^2H_6$]-9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 (27)

A solution of Jones' reagent (5.0 ml, 13.4 mmol) was added to a cooled solution of **26** (400 mg, 0.93 mmol) in acetone (10 ml) at 0°C. After being stirred at 0°C for 30 min, 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 ($MgSO_4$) and evaporated under reduced pressure to give a crude product (384 mg). Purification of the crude product by column chromatography (silica gel, 50 g, hexane:EtOAc = 1:1) gave the caroxylic acid **27** (300 mg, 0.68 mmol, 73%); IR (neat): 3200, 3040, 2220, 2110, 1740, 1720, 1370, 1245, 1045, 1020, 970, 755 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 0.88 (t, 3H, J = 6 Hz), 1.1-1.8 (m, 9H), 1.8-2.7 (m, 7H), 2.00 (s, 3H), 2.06 (s, 3H), 2.8-3.3 (m, 1H), 4.6-5.1 (m, 1H), 5.1-5.4 (m, 2H), 5.4-5.7 (m, 2H); EI-MS (m/z): 380 (2), 338 (6), 320 (46), 308 (20), 263 (3), 249 (7), 150 (10), 99 (10), 93 (12), 91 (10), 81 (12), 79 (13), 67 (10), 43 (100).

[2,2,3,3,4,4-$^2H_6$]-9(*O*)-Methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 (28)

Aqueous 5.0 N NaOH (0.6 ml, 3.0 mmol) was added at r. t. to a solution of **27** (220 mg, 0.50 mmol) in MeOH (3.0 ml), and the mixture was stirred at r. t. for 1.5 h. The reaction mixture was acidified with aq. $KHSO_4$, and extracted with EtOAc (3 × 50 ml). The separated organic layers were washed twice with brine and evaporated to yield a crude product (188 mg). The crude product was chromatographed on silica gel (30 g) with hexane-EtOAc (1:4) containing 0.2% AcOH to provide **28** (168 mg, 0.46 mmol, 91%); IR (neat): 3350, 3040, 2650, 2220, 2120, 1710, 1290, 1270, 1080, 970, 830 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 0.89 (t, 3H, J = 6 Hz), 1.2-1.7 (m, 9H), 1.8-2.6 (m, 7H), 2.9-3.1 (m, 1H), 3.65-3.8 (m, 1H), 3.95-4.1 (m, 1H), 5.3 (s, 1H), 5.4-5.6 (m, 2H); EI-MS (m/z): 338 (18), 320 (26), 294 (44), 267 (17), 224 (23), 172 (46), 131 (31), 99 (39), 79 (63), 43 (100); ^{13}C-NMR ($CDCl_3$): δ 14.01, 22.62, 25.21, 29.98, 31.69, 36.90, 39.07, 39.42, 44.32, 45.51, 57.91, 73.36, 77.16, 128.96, 133.30, 135.58, 141.10, 177.67.

[2,2,3,3,4,4-$^2H_6$]-9(*O*)-Methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 methyl ester (3)

Methyl iodide (0.346 ml, 5.55 mmol) and then ethyldiisopropylamine (0.967 ml, 5.55 mmol) were added at r. t. to a stirred solution of **28** (130 mg, 0.37 mmol) in acetonitrile (13 ml). After being stirred for 18 h, the reaction mixture was concentrated *in vacuo* and water was added. The resulting mixture was extracted with EtOAc (3 × 50 ml). The separated organic layers were combined, washed with brine, and dried ($MgSO_4$). Removal of the solvent under reduced pressure left a crude ester, which was chromatographed on silica gel (30 g) with hexane-EtOAc (2:3) to furnish **3** (111 mg, 0.30 mmol, 81%). An analytical sample of **3** was further purified by preparative HPLC; IR (neat): 3380, 3040, 2220, 2110, 1740, 1435, 1270, 1210, 1125, 1080, 970, 830 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 0.89 (t, 3H, J = 6 Hz), 1.2-1.6 (m, 9H), 1.85-2.05 (m, 4H), 2.25-2.45 (m, 3H), 2.9-3.1 (m, 1H), 3.67 (s, 3H), 3.7-3.8 (m, 1H), 4.0-4.1 (m, 1H), 5.28 (s, 1H), 5.45-5.6 (m, 2H); EI-MS (m/z): 352 (22), 334 (23), 308 (60), 281 (14), 238 (17), 186 (37), 154 (24), 131 (32), 109 (46), 91 (59), 67 (67), 43 (100); 1% d_4, 4% d_5 95% d_6; ^{13}C-NMR ($CDCl_3$): δ 14.02, 22.62, 25.20, 30.31, 31.72, 37.26, 39.65, 39.72, 44.35, 44.66, 51.47, 58.12, 73.03, 77.17, 128.31, 132.88, 135.41, 141.42, 174.29.

Synthesis of [2,2,3,3,4,4-$^2H_6$]-17(*S*),20-Dimethyl-9(*O*)-Methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 Methyl Ester (4)

Methyl 4-iodo[2,2,3,3,4,4-$^2H_6$]butanoate (31)

A solution of Jones' reagent (100 ml, 267 mmol) was added to a cooled solution of the perdeuterated bromo alcohol **20** (8.0 g, 49.7 mmol) in acetone (200 ml) at 0°C. The mixture was stirred at r. t. for 1 h and the reaction mixture was quenched by addition of 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 layer was dried ($MgSO_4$) and evaporated under reduced pressure to give a crude carboxylic acid **29** (6.34 g). The crude acid **29** (6.34 g) was dissolved in MeOH (500 ml) and a drop of H_2SO_4 was added. After the

resulting mixture was refluxed for 5 h, MeOH was evaporated under reduced pressure. Ethyl acetate (200 ml) was added to the obtained residue and the organic layer was washed with aq. $NaHCO_3$ and brine, and then dried over $MgSO_4$. Removal of the solvent left an oily crude bromo ester **30** (5.73 g). To a solution of the crude ester **30** (5.73 g) in methyl ethyl ketone (35 ml) was added NaI (9 g, 60 mmol) and the mixture was refluxed for 10 h. After removal of the solvent, ether (150 ml) was added and the organic mixture was washed with aq. $Na_2S_2O_3$ solution and brine. The separated organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give a crude iodo ester **31** (6.34 g). Distillation of the crude ester **31** under reduced pressure provided the pure product **31** (5.29 g, 22.6 mmol, 45% in 3 steps); bp: 45°C/2 mmHg; IR (neat): 2220, 2150, 2110, 1740, 1435, 1280, 1200, 1125, 1175, 1040, 970 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 3.67 (s, 3H); EI-MS (m/z): 191 (8), 145 (36), 121 (20), 107 (100), 82 (25).

(17*S*)-*O*-bis(*t*-butyldimethylsilyloxy)[2,2,3,3,4,4-$^2H_6$]-17,20-dimethyl-9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 methyl ester (33)

In a 25 ml flask were placed zinc powder (392 mg, 6.0 mmol) and THF (3 ml). To the mixture was added 1,2-dibromoethane (30 μl) and the mixture was heated at 65°C for 1 min. The mixture was cooled to r. t., and stirred at the same temperature for 30 min. Then, chlorotrimethylsilane (40 μl) was added and the mixture was stirred at r. t. for 30 min. To the reaction mixture was added perdeuterated iodo ester **31** (1.17 g, 5.0 mmol) in THF (5 ml), and the resulting mixture was heated at 40°C for 18 h. In another 50 ml flask were placed cuprous cyanide (448 mg, 5.0 mmol), anhydrous LiCl (425 mg, 10 mmol), and THF (10 ml). To the cooled suspension at 0°C was added the above organozinc supernatant solution by using a syringe, and the mixture was stirred at 0°C for 30 min.

A 1.50 M hexane solution of ^{n}BuLi (740 μl, 1.1 mmol) was added at -78°C to a stirred solution of a (1*S*,2*R*,3*R*,5*S*,6*RS*)-3-*t*-butyldimethylsilyloxy-2-[(*E*)-(3*S*,5*S*)-3-*t*-butyldimethylsilyloxy-5-methyl-1-nonenyl]-6-hydroxy-7-methylenebicyclo[3.3.0]octane (**32**; 571 mg, 1.06 mmol) in THF (5 ml), and the mixture was stirred at -78°C for 10 min. To the mixture was added tosyl chloride (286 mg, 1.5 mmol) at 0°C and the resulting mixture was stirred at r. t. for 2 h. To the resulting reaction mixture was added the above obtained zinc-copper reagent (5.0 mmol) at 0°C, and the whole mixture was stirred at 0°C for 2 h. The reaction mixture was poured into saturated aqueous NH_4Cl solution and EtOAc (100 ml) was added for extraction. The separated aqueous layer was extracted twice with EtOAc (2 × 100 ml). The combined organic extracts were washed with aq. $KHSO_4$ solution, aq. $NaHCO_3$, and brine, and then dried over $MgSO_4$. Removal of the solvent left an oily residue, which was subjected to silica gel column chromatography (200 g) eluting with a 19:1 mixture of hexane and EtOAc to give the desired product **33** (485 mg, 0.775 mmol, 73%) together with an undesired (1*S*,2*R*,3*R*,5*S*,6*R*)-3-*t*-butyldimethylsilyloxy-2-[(*E*)-(3*S*,5*S*)-3-*t*-butyldimethylsilyloxy-5-methyl-1-nonenyl]-6-(3-methoxycarbonyl[1,1,2,2,3,3-$^2H_6$]propyl)-7-methylenebicyclo[3.3.0]octane (**34**). The by-product **34** was identical with an authentic sample **34** by HPLC analysis. The product ratio of **33**:**34** was estimated to be 80:20 by ^1H-NMR observation calculated by their olefinic protons. **33**: IR (neat): 3050, 2220, 2110, 1745, 1260, 1120, 1080, 1005, 970, 835, 775 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 0.03 (s, 12H), 0.8-1.0 (s × 2 + t, 24H), 1.0-2.8 (m, 17H), 2.8-3.2 (m, 1H), 3.6-3.9 (m, 1H), 3.68 (s, 3H), 4.0-4.3 (m, 1H), 5.23 (bs, 1H), 5.35-5.55 (m, 2H).

(17*S*)-[2,2,3,3,4,4-$^2H_6$]-17,20-dimethyl-9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 methyl ester (4)

A 1.0 M THF solution of tetrabutylammonium fluoride (5 ml, 5 mmol) was added at r. t. to a solution of the above mixture (**33**:**34** = 80:20, 485 mg, 0.775 mmol) in THF (10 ml), and the mixture was stirred at r. t. for 10 h. Aqueous $KHSO_4$ solution was added and the resulting mixture was extracted with EtOAc (3 × 100 ml). The separated organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to afford a crude product (371 mg). Column chromatographic separation of the product on silica gel (40 g) using hexane-EtOAc (1:2 up to 1:4) as an eluant gave the desilylated product **4** (273 mg, 0.686 mmol, 89%) accompanied by **35** as a minor product, which was constituted of 79:21 of a product ratio judged by a HPLC examination as compared with authentic perhydro samples **4** and **35**. Preparative HPLC separation of the product mixture furnished the pure ester **4** (118 mg, 0.296 mmol, 55%); IR (neat): 3400, 3050,

2220, 2120, 1745, 1440, 1380, 1275, 1205, 1090, 1000, 970, 830 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 0.8-1.0 (m, 6H), 1.0-2.6 (m, 17H), 2.8-3.4 (m, 3H), 3.6-3.9 (m, 1H), 3.66 (s, 3H), 3.9-4.3 (m, 1H), 5.27 (bs, 1H), 5.35-5.6 (m, 2H); EI-MS (m/z): 380 (3, M^+-18), 374 (6), 330 (18), 275 (4), 245 (4), 131 (14), 117 (17), 105 (18), 91 (27), 79 (26), 57 (68), 43 (100); 1% d_4, 4% d_5, 95% d_6; ^{13}C-NMR ($CDCl_3$): δ 14.20, 20.04, 22.98, 29.15, 29.43, 30.34, 36.90, 39.43, 39.57, 44.21, 44.41, 45.53, 51.46, 58.16, 71.59, 76.90, 128.21, 133.66, 135.67, 141.05, 174.10.

(17*S*)-[2,2,3,3,4,4-$^2H_6$]-17,20-dimethyl-9(*O*)-methano-$\Delta^{6(9\alpha)}$-prostaglandin I_1 (36)

To a stirred solution of **4** (88 mg, 0.22 mmol) in MeOH (5 ml) and water (1 ml) a 4.0 M LiOH solution (0.55 ml, 2.2 mmol) was added and the resulting mixture was stirred at r. t. for 4 h. Aqueous $KHSO_4$ solution was added and the mixture was extracted with EtOAc (3 × 100 ml). The separated extracts were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to leave an oily residue (87 mg), which was chromatographed on silica gel (30 g) using a 1:4 mixture of hexane-EtOAc as an eluant to give the corresponding carboxylic acid **36** (82 mg, 0.21 mmol, 97%); IR (neat): 3350, 3050, 2220, 2120, 1720, 1300, 1090, 970, 830 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 0.8-1.0 (m, 6H), 1.0-2.7 (m, 17H), 2.8-3.2 (m, 1H), 3.6-4.0 (m, 1H), 2.27 (bs, 1H), 5.35-5.7 (m, 5H); EI-MS (m/z): 366 (8, M^+-18), 348 (8), 322 (22), 263 (7), 249 (4), 224 (18), 172 (20), 93 (22), 81 (27), 57 (80), 43 (100).

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