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STEREOSELECTIVE SYNTHESIS OF [11 β-^{3}H]PROSTAGLANDIN E_1

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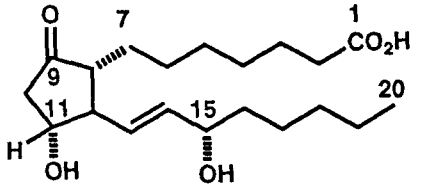
SUMMARY

This report describes an efficient stereoselective synthesis of [11β-^{3}H]prostaglandin E_1 ([11β-^{3}H]PGE_1). The key multiply protected 11-keto intermediate was prepared in only three steps from PGE_1. Reduction of the ketone function at C-11 with sodium borodeuteride and sodium borotritide, followed by sequential removal of protecting groups, afforded PGE_1 labeled with deuterium and tritium, respectively, at the 11-beta position. The reduction and deprotection were accomplished in one reaction flask without requiring purification of intermediates. Trace amounts of C_{11}-epimer formed in the reduction were readily separated by means of preparative reversed-phase HPLC. Using sodium borotritide of nominally 67 Ci/mmol, we obtained [11β-^{3}H]PGE_1 with specific activity of 15 Ci/mmol. A disposition study in the monkey with intravenous administration of this material indicated excellent *in vivo* metabolic stability of the 11β-tritium label.

Key Words: Prostaglandin E_1, tritium, stereoselective reduction, prostaglandin D_1 derivative, sodium borotritide.



PGE_1

INTRODUCTION

To provide high specific activity radioisotope labeled prostaglandin E_1 (PGE_1) in support of drug metabolism studies, we needed to develop a method for preparing tritium

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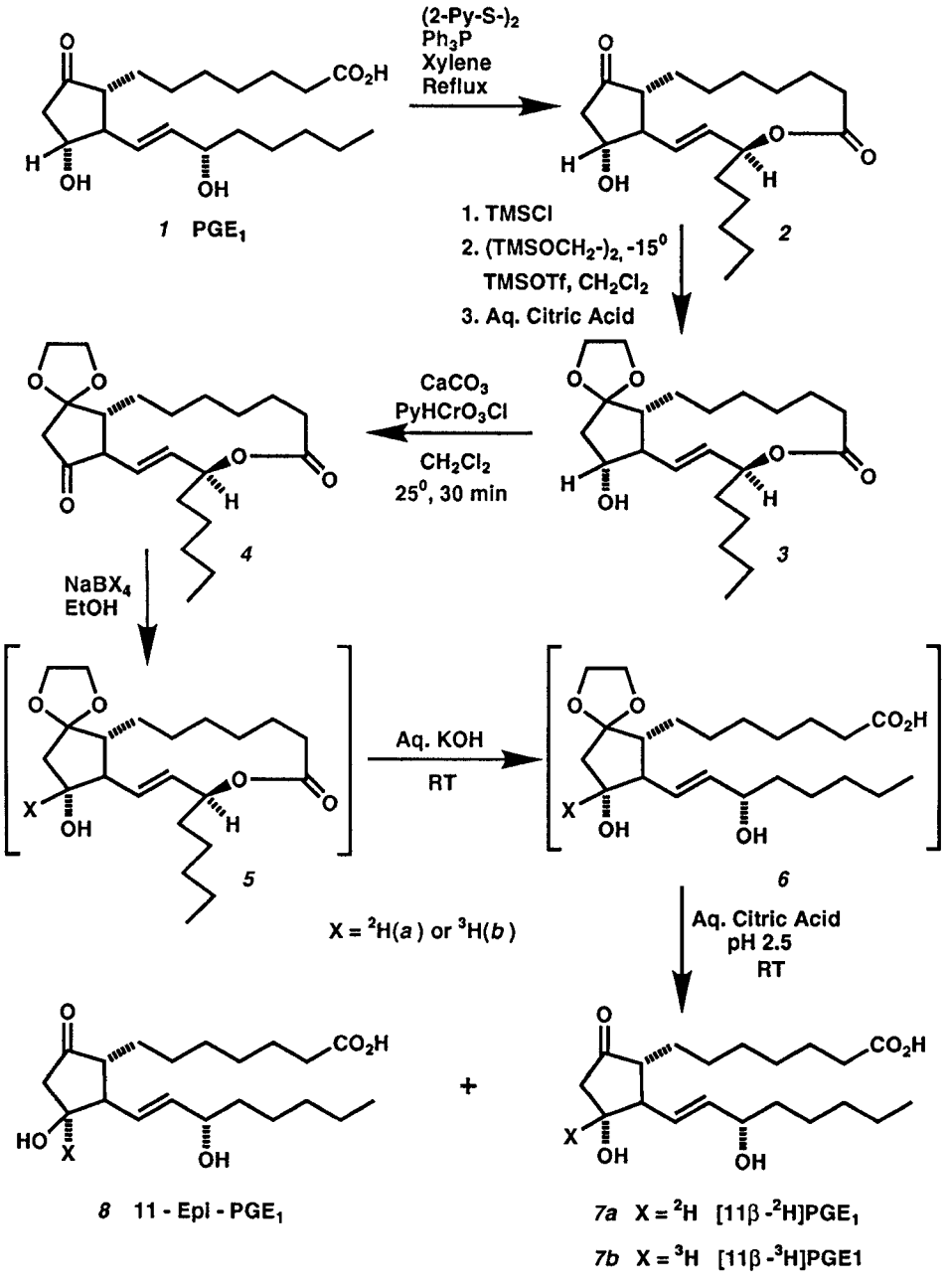
labeled PGE_1 with good metabolic stability for the label. The incorporation of tritium into the E-series of prostaglandins has been previously accomplished with several different approaches. Enzymatic biosynthesis utilizing di-tritiated (1) or multiply tritiated (2) unsaturated fatty acids led to products with uncertain label positions and/or distribution, and more problematically, the labels would be at least partly introduced into metabolically vulnerable positions. Tritium labels have also been introduced via catalytic reduction (3) with tritium gas of a carbon-carbon multiple bond pre-positioned in a side chain of a prostaglandin precursor. Although this approach allowed the preparation of a diverse group of labeled prostaglandins from a common intermediate, it required multi-step handling of labeled intermediates, which would be inefficient and undesirable for the synthesis of a single product with high specific activity. A third approach of sodium borotritide reduction of an appropriately protected 11-keto prostaglandin (4-7), i.e., PGD, appeared more amenable to solving the problem at hand. Thus our efforts became focused on the generation of the required 11-keto intermediate.

DISCUSSION AND RESULTS

The strategy of borotritide reduction of a PGD derivative was first reported by Tanouchi and Hayashi (4). Variations of this approach were employed in the synthesis of 15-methyl-[11β-^{3}H]PGE_2 (5), 16,16-dimethyl-[11β-^{3}H]PGE_2 (6), and [11β-^{3}H]PGI_2 (7). For our purposes, a properly masked PGD_1 was required as the starting material. It appeared that the most direct access to our desired 11-keto prostaglandin could be provided by PGE_1 (*1*) itself. To manipulate the 11-hydroxy function in PGE_1, it would be necessary to mask the ketone at C-9, the carboxylic acid at C-1, and the hydroxy function at C-15, so that oxidation and reduction could be carried out at C-11 without interference. This was done in a reaction sequence shown in Scheme 1. Lactonization between the C-1 acid and C-15 hydroxy function in 54% yield according to a previously published procedure (8) achieved protection at both of these positions in a single step. Simultaneously, this conversion to *2* conveniently distinguished the C-15 hydroxy from the C-11 hydroxy in *1*, since 1-11 lactonization was all but excluded under the reaction conditions (8). Thus, the C-11 hydroxy remained available

SCHEME 1 SYNTHESIS OF 11-BETA LABELED PGE_1



for oxidation later to produce the C-11 ketone. Acetal formation at C-9 to form the acetal-lactone ***3*** was carried out according to the mild conditions reported by Noyori, *et al.*, (9). *In situ* protection and deprotection of the C-11 hydroxy as its TMS derivative was incorporated

into the procedure to avoid potential dissipation of the TMSOTf reagent necessary for effecting the acetal formation between $(TMSOCH_2)_2$ and the C-9 ketone. The overall yield of the conversion from ***2*** to ***3*** was 35%. Oxidation at C-11 of ***3*** to afford the protected PGD_1 ***4*** was accomplished in 56% yield with buffered pyridinium chlorochromate (10).

The protocol for purifying ***4*** warrants a comment. The product in solution in ethyl acetate/hexane proved unstable to contact with silica gel during purification. The instability in solution apparently resulted from sensitivity of the doubly activated proton at C-12 toward acid, imparting a strong inclination for the double bond at C-13 to shift into conjugation with the ketone at C-11, which in turn tended to trigger carboxylate elimination at C-15 to give a 12, 14-dien-11-one. However, ***4*** exhibited good stability in the crystalline state. Thus, when the silica gel chromatography was carried out as a rapid filtration (5-6 minutes), which was adequate to remove reagent-related impurities, followed by crystallization, we obtained ***4*** which was stable to storage at -20°C for at least 4 months.

Reduction of ***4*** with excess sodium borohydride proceeded smoothly in methanol to give ***5***. After subsequent deprotection at C-1/C-15 and C-9, analysis of the product showed that the reduction had been highly stereoselective and resulted in the desired C-11 stereochemistry (α-OH) predominantly, with production of the C-11 epimer (β-OH) amounting to only ~5%. Also, although ***5*** was isolable, we found that the sequential base and acid hydrolyses, in that order, to open the lactone and remove the acetal, respectively, could be carried out in one single reaction flask without isolation of intermediates ***5*** and ***6***. This provided highly desirable economy of post-label manipulations. However, to render the procedure compatible with use of tritium, we needed to avoid using expensive reducing agent in excess, and to substitute ethanol for methanol. Methanol undergoes much more rapid reaction than ethanol with borohydride, with evolution of hydrogen (tritium in the case of borotritide) gas, and coincidental depletion of reagent available for reduction. It was found that the choice of solvent for reduction with sodium borodeuteride had no significant effect on the yield of [11β-^{2}H]PGE_1 (***7a***). Reversed-phase HPLC analysis of the product showed that the 11-epimer [11α-^{2}H]PGE_1 (***8a***), was produced in comparable amounts, 4.0% with ethanol and 6.5% with methanol as the solvent during reduction.

The protocol for the reduction of ketone ***4*** with sodium borotritide in ethanol was designed for minimization of isotopic dilution to achieve high product specific activity without compromising safe handling of radioactive material. Thus, 0.08 mmol of ***4*** was reduced with nominally 2 Ci of NaB^3H_4 (67 Ci/mmol, 0.03 mmol) in 2 mL of ethanol. The reaction continued with the addition of a large excess (1 mmol) of $NaBH_4$ to complete the reduction of any remaining ketone ***13***. Finally, the reaction was concluded with the addition of 0.5 mL of acetone to consume unreacted sodium borohydride and any remaining traces of sodium borotritide*. Acetone was added to consume the excess reducing agent to produce 2-[2-^{3}H]propanol instead of releasing tritium gas when the reaction was quenched with water in the workup. The crude reduction product ***5*** was subjected to sequential base and acid hydrolysis without purification, in one pot, to give crude [11β-^{3}H]PGE_1. Preparative HPLC purification of the latter removed the labeled 11-epimer to afford, after crystallization, 170 mCi of [11β-^{3}H]PGE_1 (***7b***) with specific activity of 42.2 mCi/mg, or 15 Ci/mmol. From NaB^3H_4 of 67 Ci/mmol, the maximum achievable sp. act. of [11β-^{3}H]PGE_1 would have been 16.8 Ci/mmol.

To evaluate the *in vivo* metabolic stability of the 11β-tritium label in ***7b***, a single intravenous (bolus) dose of 106 μCi of [11β-^{3}H]PGE_1 (2.0 μg/kg body weight) was administered to male monkeys (n=3). Most of the radioactivity was excreted in the urine (84.9±4.95%) and the feces (5.07±4.51%) within the first 72 hours. Analysis of all the urine samples for tritiated water by lyophilization indicated the presence of negligible quantities of tritiated water (0.191±0.0499% of the administered dose; see Table 1). These results clearly demonstrated the metabolic stability of the 11β-tritium label. [11β-^{3}H]PGE_1 should be well suited for use in drug disposition and metabolism studies.

EXPERIMENTAL

PGE_1, 9-ethylene acetal, 1,15-lactone

A. Silylation at C-11: A solution of 2.12 g (6.29 mmol) of PGE_1 1,15-lactone (**2**) (8) in 70 mL of dry tetrahydrofuran was treated with 15.7 mL of hexamethyldisilazane (HMDS) and

*In the event any NaB^3H_4 was not completely consumed in the original reduction, any unused borotritide would have been diluted with $NaBH_4$ and remained in the reaction mixture.

Table 1.

Tritiated Water Excreted in the Urine of Monkeys (N=3) Following Intravenous (bolus) Administration of [11β-^{3}H]PGE$_1$ (Dose=2.0 μg/kg, 106 μCi; 2.0 μg/kg/body wt).

^3H_2O As Percent Of Administered Dose

Time (hours)	Monkey #7197	Monkey #7201	Monkey #9193	Mean±S.D.
0-4	0.0242	0.0342	0.0479	0.0354 ± 0.0119
4-8	0.00395	0.0209	0.0130	0.0126 ± 0.00848
8-24	0.0279	0.0526	0.0554	0.0453 ± 0.0151
24-48	0.0319	0.0613	0.0286	0.0406 ± 0.0180
48-72	0.0505	0.0677	0.0536	0.0573 ± 0.00917
Total ^3H_2O	0.138	0.237	0.198	0.191 ± 0.0499

3.3 mL of chlorotrimethylsilane, and the resulting fine suspension was stirred under nitrogen at room temperature for 4 hr. Following removal of the solvents in vacuo (high vacuum at the end to remove the HMDS), the residue was dissolved in 60 mL of xylene, the solution filtered through Celite to remove the ammonium chloride, and concentrated. The crude product was chromatographed* on 185 g of 40-60 μ silica gel. The column was packed in and eluted rapidly (nitrogen pressure) with 10% ethyl acetate in hexane (18 mL fractions). Fractions 34-50 contained the pure 11-TMS derivative and were combined. Evaporation of the solvent and drying (40°, 8 h, 0.02 mm) yielded 1.91 g (74%) of the 11-TMS derivative of ***2*** as a white solid, which was used immediately. [TLC Silica Gel GF: Rf 0.71 (30% ethyl acetate in hexane; ***2*** exhibited Rf 0.29 on the same plate].

B. Acetal formation: A stirred solution of 1.17 g (2.87 mmol) of the 11-TMS derivative of ***2*** prepared in section A above in 2.3 mL of methylene chloride was treated with

*It is important that the 11-TMS ether of *2* be purified by chromatography before converting the ketone at C-9 to acetal.

1.17 mL of 1,2-bis-(trimethylsilyloxy)ethane and cooled to -73°. With good stirring, 240 μL of a solution of 100 mg of trimethylsilyl triflate in 900 μL of methylene chloride was added to the reaction mixture in a syringe over 30 sec. The colorless, homogenous solution was stirred for 10 min at -78°, by which time solids had appeared. The mixture was then allowed to warm to -10 to -15° (solids dissolved, mixture turned yellow) and was maintained at that temperature for 16 h, and finally at 25° for 3 h. The reaction mixture was then diluted with 100 mL of cold methylene chloride containing 4 drops of pyridine, and the resulting solution was poured into cold aqueous sodium bicarbonate and extracted with two 100 mL portions of methylene chloride. The extracts were washed with brine, dried over anhydrous sodium sulfate, and evaporated, thereby affording 1.25 g of the crude 9-acetal-11-TMS intermediate.

C. Desilylation: The part B product was dissolved in 30 mL of methanol and treated with 5 mL of 2% aqueous citric acid. The resulting clear solution was stirred at 25° for 30 min, and poured into a mixture of brine (150 mL), aqueous sodium bicarbonate (100 mL) and water (50 mL), and extracted with three 100 mL portions of ethyl acetate. The extracts were washed with brine, dried over sodium sulfate and evaporated, and the residue (1.05 g) was chromatographed on a column containing 160 g of 40-60 μ silica gel. The column was packed and eluted (15 mL fractions) with 40% ethyl acetate in methylene chloride. Fractions 33-44 were homogenous by TLC and were combined, thereby yielding 546 mg (50% oversteps B&C) of pure lactone-acetal ***3*** as a white solid. Recrystallization of a 30 mg portion of the product from ether/pentane afforded, after drying (2 hr, 25°, 0.05 mm), 21 mg of pure ***3*** with mp 102-103°C. Residue from the mother liquors, 9 mg, also solidified readily and was shown to be pure by TLC. (Generally, material from this step was used directly in the oxidation step which follows without recrystallization). Spectral and TLC analyses showed ***3*** had υ_{max} (Nujol mull) 3434, 1727, 1441, 1305, 1284, 1240, 1190, 1179, 1159, 1064, 1034, 1022, 1016, 966, 956, 915 cm^{-1}; ^{1}H-NMR ($CDCl_3$; TMS): δ 5.93-5.78 (m, 2H), 5.22-5.15 (m, 1H), 4.00-3.82 (m, 5H ketal and C-11), 2.42-2.33 (m, 1H), 0.88 (t, J=6.6 Hz, 3H); ^{13}C-NMR ($CDCl_3$; TMS): δ 173.25, 135.02, 131.09, 114.84, 73.75, 71.95, 64.60, 64.49, 56.36, 49.81, 44.65, 34.28, 33.55, 31.29, 26.45, 26.11, 25.95, 25.21, 24.31, 23.60, 22.28, and 13.78 ppm; mass spectrum (FAB): $(M+1)^+$ observed at m/z 381.2636; calc'd. for $C_{22}H_{36}O_5$+H=381.2641; other ions at m/z 363, 337, 151,

125, 115, 99, 87, 67, 55; TLC (silica gel GF)* Rf 0.27 (30% EtOAc in hexane). Anal. Calc'd for $C_{22}H_{36}O_5$: C, 69.44, H, 9.54; Found: C, 69.41; H, 9.68.

11-Keto-PGE$_1$, 9-ethylene acetal, 1,15-lactone (*4*)

A vigorously stirred solution of 380 mg (1 mmol) of *3* in 38 mL of anhydrous methylene chloride was treated with 475 mg of calcium carbonate, followed by 950 mg of powdered pyridinium chlorochromate, both added in one portion at room temperature. The resulting brown suspension was stirred for 30 min, and the whole reaction mixture was poured onto a column containing 18 g (36 mL) of silica gel in a 50 mL buret. The reaction solution was pushed onto the column under positive nitrogen pressure and elution was performed as rapidly as possible using 20% ethyl acetate in hexane (17 mL fractions). Fractions 6-9 were combined and concentrated to yield 236 mg (62%) of a white solid which crystallized readily. (Total silica contact time was limited to 5-6 min.) The product was recrystallized from methyl acetate/hexane and dried (18 h, 25°, 0.02 mm), thereby affording 212 mg of pure *4*, which exhibited mp 124-125°C. Spectral analyses of *4* showed it had υ_{max} (Nujol mull) 1748 (ketone), 1722 (lactone), 1666, 1290, 1251, 1201, 1175, 1115, 1091, 1031, 988 and 979 cm^{-1}; ^{1}H-NMR ($CDCl_3$; TMS): δ 5.89-5.70 (m, 2H), 5.23-5.17 (m, 1H), 4.06-3.94 (m, 4H), 2.86-2.80 (m, 1H, C-12), and 0.88-0.86 ppm (m, 3H); ^{13}C-NMR ($CDCl_3$; TMS): δ 211.89, 173.46, 134.18, 129.43, 117.97, 72.32, 65.49, 65.02, 58.72, 49.62, 48.93, 34.45, 33.42, 31.41, 26.73, 26.52, 26.26, 25.18, 24.35, 23.83, 22.41, 13.92 ppm; mass spectrum (FAB): $(M+1)^+$ observed at m/z 379.2481 calc'd. for $C_{22}H_{34}O_5$+H, 379.2484, other ions at m/z 337, 229, 207, 151, 113, 99, 81, 67, 55, 41. TLC (Silica Gel GF) analysis showed *4* had Rf 0.56 with 30% EtOAc in hexane; Anal. Calc'd. for $C_{22}H_{34}O_5$: C, 69.81, H, 9.05; Found: C, 69.66, H, 8.99. The extreme sensitivity of *4* towards silica gel is addressed in the Discussion section of this report.

*In a variety of solvent systems, ketone *2* and ketal *3* were inseparable by TLC. The best solvent combinations for analysis of reaction products were 40% EtOAc in methylene chloride, Rf 0.48 for *2*, 0.43 for *3*, and 55% EtOAc in hexane, Rf 0.45 for *2*, 0.41 for *3*.

[11β-^{2}H]PGE$_1$ (***7a***)

A mixture of 30 mg of ***4*** (0.08 mmol), 1.8 mg of NaB^2H_4 (0.043 mmol), and 2 mL of absolute ethanol was stirred under nitrogen at 0°C for 1 h. Then 40 mg of NaB^2H_4 was added and the reaction mixture stirred for another 20 min at 0°C. The excess NaB^2H_4 was quenched with 0.3 ml of acetone, and 1 mL of 1M KOH was added. The mixture was stirred for 18 h at room temperature to hydrolyze the lactone. Fifteen mL of 0.5 M citric acid in H_2O was added and the reaction mixture stirred for 24 h at room temperature to hydrolyze the ketal. The reaction mixture was partitioned with 50 mL of brine and 50 mL of ethyl acetate. The aqueous layer was extracted with 25 mL of ethyl acetate. The combined organic extracts were washed with 25 mL of brine, dried over Na_2SO_4 and concentrated. The crude residue was chromatographed in 3 equal portions on a Zorbax Rx C18 (21.2 mm ID x 250 mm) semi-prep column using 30:70 v/v ACCN:Buffer (50 mM H_3PO_4, pH=3.0) as mobile phase, which was pumped isocratically at 25 mL/min. The eluate was monitored by UV detection at 210 nm. The pooled collection of the peak at 15.5 min was concentrated to remove acetonitrile. The aqueous residue was partitioned with 60 mL of brine and 50 mL of ethyl acetate. The combined organic extracts were washed with 50 mL of brine, dried over Na_2SO_4 and concentrated to give 12.5 mg of crude ***7a***. Crystallization from 600 μL of ethyl acetate and 600 μL of hexane gave 10.5 mg of [11β-^{2}H]PGE$_1$ (***7a***) as white solids after drying under high vacuum at room temperature, >99% pure by HPLC (Zorbax Rx C-18 column of 4.6 mm ID x 250 mm, mobile phase as above, at 2 mL/min); NMR: ^{1}H (MeOH-d_4, TMS): δ 0.91 (t, 3H, ^{3}J=6.66 Hz, C-20), 1.2-1.7 (m, 18H, C-3, 4, 5, 6, 7, 16, 17, 18, 19), 2.05-2.14 (m, 2H, C-10), 2.26 (t, 2H, ^{3}J=7.37 Hz, C-2), 2.32-2.38 (m, 1H, C-8), 2.65 (d, 1H, ^{2}J=18.3 Hz, C-12), 4.00-4.03 (m, 1H, C-15), 4.91 (s, 3H, OH), 5.55-5.66 (m, 2H, C-13, 14); ^{13}C-NMR (MeOH-d_4, TMS): δ 14.44 (C-20), 23.79, 26.06, 26.39, 27.78, 28.70, 30.06, 30.60, 33.00, 34.94, 38.35 (C-3, 4, 5, 6, 7, 10, 16, 17, 18, 19), 47.16 (C-8), 49.02 (C-12), 55.34 (C-2), 73.00 (C-11), 73.76 (C-15), 132.66 (C-13 or 14), 137.58 (C-13 or 14), 178.00 (C-1 or 9), 217.61 (C-1 or 9).

[11β-^{3}H]PGE$_1$ ***7b***

The reaction was carried out in the P-2 container in which sodium borotritide was

shipped*. To the unsealed ampule containing nominally 2 Ci (67 Ci/mmol) of NaB^3H_4 was added 30 mg of ***4*** (0.08 mmol) and 2 mL of absolute ethanol. The reaction was stirred at 0° under N_2 for 1 h, after which 40 mg (1 mmol) of $NaBH_4$ was added and the mixture was stirred for another 20 min. The reduction was quenched with 0.5 mL of acetone. The reaction mixture was then transferred to a 35 mL round bottom flask with 1 mL of absolute ethanol rinse. One mL of 1 M KOH was added and the mixture was stirred at room temperature for 18 h. Fifteen mL of 0.5 M citric acid in water was added. The mixture, pH 2.5, was stirred for 24 h at room temperature, and partitioned with 50 mL of brine and 50 mL of ethyl acetate. The aqueous layer was extracted with 25 mL and 50 mL portions of ethyl acetate. The combined organic extracts were washed with 30 mL of brine, dried over Na_2SO_4 and concentrated. The crude residue was dissolved in 1.5 mL of mobile phase (see below) and chromatographed in 3 equal injections on a Zorbax Rx C18 (21.2 mm I.D. x 250 mm) semi-prep column with a mobile phase of 30:70 v/v AcCN:Buffer (50 mM H_3PO_4, pH=3) pumped isocratically at 25 mL/min. The eluate was monitored by UV detection at 210 nm. The pooled collection of the peaks at 15.5 minutes was concentrated to remove acetonitrile, and lyophilized for 4 h to remove most of the water. The remaining concentrated aqueous solution was partitioned between 25 mL of brine and 50 mL of ethyl acetate. The aqueous layer was extracted with 25 mL of ethyl acetate. The combined organic layers were washed with 25 mL of brine, dried over Na_2SO_4 and concentrated. The residue was crystallized from 400 µL of ethyl acetate and 600 µl of hexane. The white crystals were collected and dried to give 3.7 mg of ***7b***, sp. act. 42.2 mCi/mg, >99% radiochemically pure by HPLC and TLC (silica gel, 92:6:1:0.74 v/v $CHCl_3$:MeOH:HOAc:water). The remaining crystals and specific activity solutions (in 95% ethanol) were combined and diluted with 95% ethanol to give a solution specific activity of 445 µCi/mL. A second crop of 14.4 mCi of ***7b*** was obtained from the mother liquor, and dissolved in ethyl acetate at 580 µCi/ml, 99% radiochemically pure by HPLC.

*Sodium borotritide TRK. 838, Batch 41, nominally 2 Ci, 67 Ci/mmol, was supplied by Amersham Corp., Arlington Heights, IL.

Formulation of [11β,^{3}H]PGE_1 for Intravenous Administration

Bacteriostatic water for injection USP (1 mL) was added to a sealed vial containing 60 μg of PGE_1. This solution was mixed well with [11β,^{3}H]PGE_1 (890 μCi) which had been prepared as a dried residue. The specific activity of this formulated [11β,3H]PGE_1 was 707.5 μCi/mL or 9.22 μCi/μg.

Intravenous (bolus) Administration

After an overnight fasting, three male cynomolgus macaque monkeys (av. wt. = 5.77 kg) received a single bolus intravenous dose of [11β,^{3}H]PGE_1, (0.15 mL per monkey, containing 11.51 μg of PGE_1 and 106 μCi of [11β,^{3}H]PGE_1). The monkeys received water and food *ad libitum*. Urine samples were collected at 0-4, 4-8, 8-24, 24-48, and 48-72 h. Fecal collections were made at 0-24, 24-48 and 48-72 h. All samples were kept frozen at -17°C for analysis.

Sample Analysis

Radioactivity measurements were made with a Packard Model CA 1900 Tri Carb Liquid Scintillation Spectrometer. All urine samples were counted in duplicate (0.5 mL aliquots) with Ultima Gold® scintillant (10 mL, Packard Co.). Feces samples were homogenized with four to five times their weight of water. Duplicate aliquots (0.5 g by weight) were removed, dried, combusted in a Tri Carb Oxidizer Mode P 300, and analyzed for radioactivity. Two-mL aliquots of monkey urine samples were lyophilized with trapping of the vaporized water. Duplicate aliquots of the trapped water were analyzed for radioactivity.

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