THE PREPARATION OF [^{14}C]-LABELLED 16-ARYLOXY PROSTAGLANDIN F2α ANALOGUES [I.C.I. 81,008 AND I.C.I. 80,996]

D. F. White
Imperial Chemical Industries Limited, Pharmaceuticals Division,
Alderley Park, Macclesfield, Cheshire, SK10 4TG, England.

Received May 10, 1976

SUMMARY

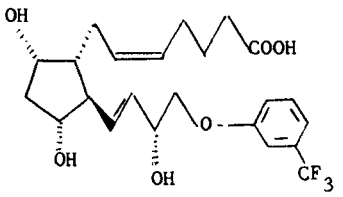
The preparations of [^{14}C]-labelled racemic (9S,11R,15R)-9,11,15-trihydroxy-16-(3-trifluoromethylphenoxy)-17,18,19,20-tetranor-5-cis,13-trans-prostadienoic acid [I.C.I. 81,008] from chloro[1-^{14}C]acetic acid and potassium[^{14}C]cyanide, and [^{14}C]-labelled racemic (9S,11R,15R)-16-(3-chlorophenoxy)-9,11,15-trihydroxy-17,18,19,20-tetranor-5-cis,13-trans-prostadienoic acid [I.C.I. 80,996] from chloro[1-^{14}C]acetic acid and potassium[^{14}C] cyanide are described.

The free names "fluprostenol" and "cloprostenol" designate specifically the sodium salts of I.C.I. 81,008 and I.C.I. 80,996 respectively, and not the free carboxylic acids.

The overall radiochemical yields were 3.4% at a specific activity of 128.5 μCi/mg and 4.1% at a specific activity of 18.2 μCi/mg for I.C.I. 81,008, and 5.4% at a specific activity of 125.8 μCi/mg and 8.6% at a specific activity of 120.9 μCi/mg for I.C.I. 80,996.

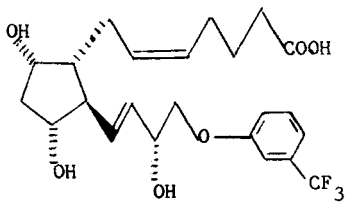
INTRODUCTION

Racemic (9S,11R,15R)-9,11,15-trihydroxy-16-(3-trifluoromethylphenoxy)-17,18,19,20-tetranor-5-cis,13-trans-prostadienoic acid [I.C.I. 81,008] and racemic (9S,11R,15R)-16--(3-chlorophenoxy)-9,11,15-trihydroxy-17,18,19,20-tetranor-5-cis,13-trans-prostadienoic acid [I.C.I. 80,996] are two of a series of novel compounds developed in these laboratories[1] in an attempt to extrapolate the luteolytic activity in animal species[2] of potent prostaglandin analogues related to prostaglandin F2α[PGF2α]. I.C.I. 80,996 has been shown to be an effective luteolytic agent in cattle and ewes in a single intramuscular dose and the most important single application of this property has been shown to be the synchronisation of oestrus.[3] I.C.I. 81,008 has been shown to be effective in the treatment of various infertility states associated with abnormal persistence of luteal function in mares.[4] The abortifacient efficacy of these two PGF2α analogues has also been examined in various other animal species.[5] The requirements for the study of the disposition and metabolism of these compounds in animals necessitated the preparation of I.C.I. 81,008 and I.C.I. 80,996 labelled in two positions.



(I)

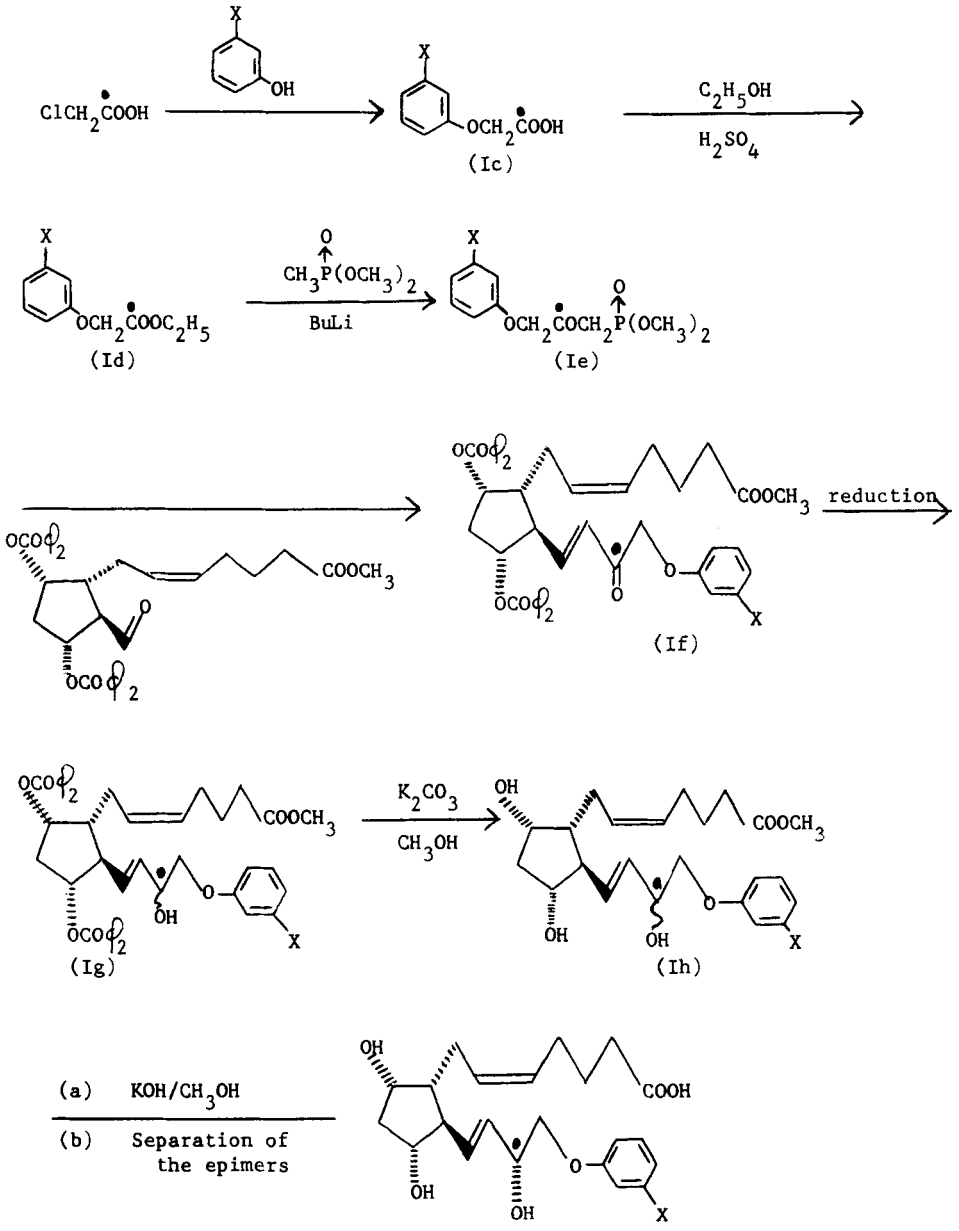
[I.C.I. 81,008]



(II)

[I.C.I. 80,996]

The [^{14}C] materials were prepared by the routes indicates in the schemes below:



X = CF_3 [I.C.I. 81,008] (Ia)

X = Cl [I.C.I. 80,996] (Ib)

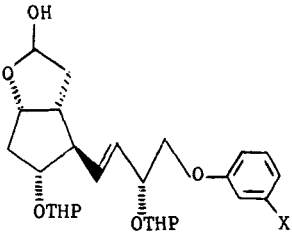
SCHEME I

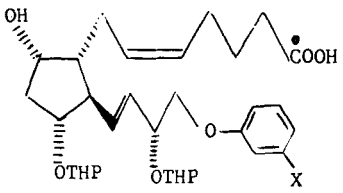
(A) $Br(CH_2)_4Br \xrightarrow[CH_3OH]{KCN} Br(CH_2)_4CN \xrightarrow[CH_3COOH]{HBr} Br(CH_2)_4COOH$

(IIc) (IId)

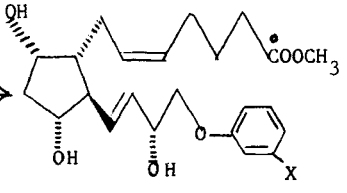
$\xrightarrow{Ph_3P}$ $[(C_6H_5)_3P^{\oplus}(CH_2)_4COOH]\,Br^{\ominus}$

(IIe)

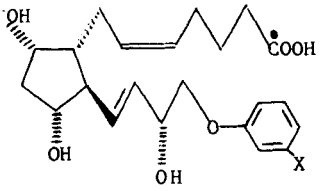
(B) $[(C_6H_5)_3P^{\oplus}(CH_2)_4COOH]\,Br^{\ominus}$ + 



(IIf)

$\xrightarrow[CH_3OH]{p\text{-}T.S.A.}$ 

(IIg)

$\xrightarrow[CH_3OH]{KOH}$ 

X = CF_3 [I.C.I. 81,008] (IIa)

X = Cl [I.C.I. 80,996] (IIb)

SCHEME II

MATERIALS

Sulphur-free toluene (May and Baker Ltd.) and dimethyl sulphoxide (B.D.H. Ltd.) were redistilled and stored over Molecular Sieve Type 4A (B.D.H. Ltd.) before use. Methanol (Hopkin and Williams Ltd.) was dried over magnesium and tetrahydrofuran was distilled from lithium aluminium hydride as required. The ether used was anhydrous di-ethyl ether. All other solvents used were either redistilled or of analytical reagent quality. Mallinckrodt CC4 Silica was obtained from Camlab Ltd. and Silica Gel MFC, 100 - 200 mesh, from Hopkin and Williams Ltd. The plates used for chromatography were Merck Precoated Silica Gel 60 F254, 0.25 mm thickness for thin-layer chromatography (t.l.c.), and 2.0 mm thickness for preparative t.l.c.

Potassium [^{14}C] cyanide was purchased from the Radiochemical Centre, Amersham, and chloro [1 - ^{14}C] acetic acid from Imperial Chemical Industries Limited, Physics and Radioisotope Services, Petrochemicals Division, P.O. Box 2, Billingham, Cleveland, TS23 1JB.

All samples were counted on a Packard Tri Carb Liquid Scintillation Spectrometer Model 3320 in standard 20 ml glass screw cap vials of low potassium content (Packard Instruments Ltd., Wembley). The photographic film used for autoradiography was Kodak "Kodirex" X-ray film.

The solvent systems used for chromatography were as follows:

(A)	toluene - ethyl acetate	(50 : 50)
(B)	ethyl acetate	
(C)	ether - light petroleum (b.p. 40 - 60)	(75 : 25)
(D)	ethyl acetate - acetic acid	(97 : 3)
(E)	cyclohexane - acetone	(70 : 30)
(F)	ethyl acetate - 98% formic acid	(90 : 10)
(G)	methylene dichloride - methanol	(95 : 5)
(H)	cyclohexane - acetone	(80 : 20)
(J)	toluene - dioxan - acetic acid	(60 : 60 : 3)

EXPERIMENTAL

Scheme I ($X = CF_3$)

2-(3-Trifluoromethylphenoxy) [1 - ^{14}C] acetic acid (Ic)

Chloro[1 - ^{14}C] acetic acid (141.75 mg) with a specific activity of 60 mCi/mM, m-trifluoromethylphenol (227.25 mg), and 2N sodium hydroxide solution (1.8 ml) were heated under reflux for 16 hr. The solution was cooled, acidified with concentrated hydrochloric acid solution, and extracted with ethyl acetate (5 X 10 ml). The extracts were washed with water, dried, and evaporated to dryness to give a cream coloured solid.

The product was examined by thin-layer chromatography (t.l.c.) in solvent system (A), visualised under UV 254 nm, and autoradiographed for 16 hr. Comparison of the UV and autoradiographic patterns showed that the product contained two impurities, one labelled and one unlabelled.

The crude material was purified by preparative scale t.l.c. on four 20 X 40 cm plates in solvent system (A) as eluant. The band on each plate corresponding in Rf to a reference sample was removed and the product extracted from the silica by stirring with ethanol (120 ml) for 16 hr. The suspension was filtered and the silica washed with ethanol (4 X 20 ml). The extracts and washings were combined and evaporated to dryness under reduced pressure. Traces of silica were removed by centrifugation of acetone extracts. Removal of the solvent under reduced pressure gave (Ic) (260 mg; 78.8%) as a white solid.

Ethyl 2-(3-trifluoromethylphenoxy) [1 - ^{14}C] acetate (Id)

2-(3-Trifluoromethylphenoxy)-[1 - ^{14}C] acetic acid (260 mg), ethanol (2 ml), and concentrated sulphuric acid solution (sg 1.84) (0.05 ml)

were heated under reflux for 16 hr. The solution was cooled, poured into water (5 ml), and extracted with ether (5 X 5 ml). The combined ether extracts were washed with water, dried, and evaporated to dryness to give a white solid (192 mg; 65.5%). Mass spectrometry and nuclear magnetic resonance spectroscopy showed the product to be the required ethyl 2-(3-trifluoromethylphenoxy)-[1 - ^{14}C] acetate.

Dimethyl 2-oxo-3-(3-trifluoromethylphenoxy)-[2 - ^{14}C] propylphosphonate (Ie)

A solution of dimethyl methylphosphonate (212 µl) in dry tetrahydrofuran was stirred under an atmosphere of argon, cooled to -78°C and treated with 2.29 M butyl lithium in hexane (810 µl) keeping the temperature below -65°C. The mixture was stirred at -78°C for 30 min and then a solution of ethyl 2-(3-trifluoromethylphenoxy)-[1 - ^{14}C] acetate (192 mg) in dry tetrahydrofuran (1.0 ml) was added slowly keeping the temperature below -65°C. The reaction mixture was stirred at -78°C for 2 hr, the cooling bath was then removed, and the mixture allowed to rise to room temperature overnight. The resulting clear solution was added to 1 M hydrochloric acid solution (2.2 ml) and extracted with ether (5 X 10 ml). The ether extracts were washed with water, dried, and evaporated to dryness under reduced pressure to give a pale yellow oil (215 mg).

The product was examined by t.l.c. in solvent system (B), visualised under UV 254 nm, and autoradiographed for 16 hr. Comparison of the UV and autoradiographic patterns showed that the product was mainly the required compound (Ie). No further purification was carried out at this stage.

Racemic methyl (9S,11R)-15-oxo-9,11-di-(4-phenylbenzoyloxy)-16-(3-trifluoromethylphenoxy)-17,18,19,20-tetranor-5-cis,13-trans-[15-^{14}C] prostadienoate (If)

Racemic methyl 7-[2β-formyl-3α,5α-di-(4-phenylbenzoyloxy)cyclopent-

1α-yl]hept-5-cis-enoate [6] (381 mg) and dimethyl 2-oxo-3-(3-trifluoromethylphenoxy)-[2-^{14}C]propylphosphonate (215 mg) were stirred at room temperature in toluene (7.7 ml) under an atmosphere of argon. 1 M sodium hydroxide solution (0.67 ml) was added and the two-phase system was vigorously stirred at room temperature for 16 hr. The mixture was neutralised with 2 N acetic acid solution, added to saturated brine solution (10 ml), and extracted with ethyl acetate (5 X 10 ml). The ethyl acetate extracts were washed with saturated brine solution and with water, dried, and evaporated to dryness under reduced pressure to give a pale yellow oil (476 mg; 87%).

Examination of the oil by t.l.c. in solvent system (A) followed by autoradiography for 16 hr showed it to be mainly the required product plus several more polar impurities. No further purification was carried out at this stage.

Racemic methyl (9S,11R)-15-hydroxy-9,11-di-(4-phenylbenzoyloxy)-16-(3-trifluoromethylphenoxy)-17,18,19,20-tetranor-5-cis,13-trans-[15-^{14}C] prostadienoate (Ig)

The enone (If) (476 mg) was stirred in dry toluene (12 ml) under argon at room temperature, and treated with a 0.36 M solution of di-isobornyloxyaluminium isopropoxide in toluene (4.2 ml). After 16 hr a saturated solution of sodium hydrogen tartrate (4.4 ml) was added. The mixture was stirred for 10 min, poured into an equal volume of saturated brine solution and extracted with ethyl acetate (5 X 20 ml). The ethyl acetate extracts were washed with saturated brine solution, dried, and evaporated to dryness under reduced pressure to a pale brown oil (492 mg).

Chromatographic and autoradiographic examination of the oil in solvent system (C) showed it to be the required enol (Ig) plus several minor impurities. No further purification was carried out at this stage.

Racemic methyl (9S,11R,15R)-9,11,15-trihydroxy-16-(3-trifluoromethylphenoxy)-17,18,19,20-tetranor-5-cis,13-trans-[15-^{14}C] prostadienoate (Ih)

The enol (Ig) was stirred at room temperature under argon in dry methanol (11 ml) with anhydrous potassium carbonate (260 mg) for 16 hr. The suspension was acidified to pH5 with 2N hydrochloric acid solution and extracted with ethyl acetate (5 X 20 ml). The ethyl acetate extracts were washed with saturated brine solution (2 X 10 ml), dried, and evaporated to dryness under reduced pressure to leave a residue consisting of methyl 4-phenylbenzoate and a mixture of the C-15 epimers of racemic methyl (9S,11R)-9,11,15-trihydroxy-16-(3-trifluoromethylphenoxy)-17,18,19,20-tetranor-5-cis, 13-trans- [15-^{14}C]prostadienoate.

To separate the epimers from the methyl 4-phenylbenzoate, the residue was run on a dry column containing deactivated silica (100 g) packed into 1 inch diameter nylon tubing. The eluting agent was solvent system (D) and the column was run until 30 ml of eluant had been collected. The column was sampled every 2 cm commencing at the bottom and the samples examined chromatographically on a Silica GF plate developed with solvent system (D) followed by autoradiography of the plate for 16 hr. The appropriate fractions containing only the mixture of epimers were removed from the column, extracted by stirring with ethyl acetate (120 ml) for 16 hr and filtered, and the solvent was evaporated under reduced pressure to leave a gum consisting of a mixture of the C-15 epimers. The epimers were separated by preparative-scale thin-layer chromatography on eight 20 X 40 cm Silica GF plates in solvent system (D). The plates were dried, run a second time in the same solvent system (D), and autoradiographed for 1 hr. The autoradiographs were used to "map" the plates and the band on each plate corresponding in Rf to a reference sample of the R-epimer was removed and the product extracted from the silica by slurrying with water and extracting the slurry with ethyl acetate (5 X 50 ml). The ethyl acetate extracts were evaporated under reduced pressure and the

residue was azeotroped with toluene (3 X 15 ml) and then re-dissolved in a small volume of ethyl acetate. The solution was centrifuged from a small amount of insoluble material, the mother liquors and washings combined and the solvent evaporated under a stream of argon. The residue was dried at room temperature under vacuum for 16 hr to give racemic methyl (9S,11R,15R)-9,11,15-trihydroxy-16-(3-trifluoromethylphenoxy)-17,18,19,20-tetranor-5-cis,13-trans-[15-^{14}C]-prostadienoate (58 mg) as a colourless gum.

Racemic (9S,11R,15R)-9,11,15-trihydroxy-16-(3-trifluoromethylphenoxy)-17,18,19,20-tetranor-5-cis,13-trans-[15-^{14}C]prostadienoic acid [I.C.I. 81,008] (Ia)

The methyl ester (Ih) (58 mg) was stirred at room temperature under argon in methanol (2 ml) and water added until precipitation had just commenced. Dimethoxyethane was added slowly until the precipitate redissolved. A 1 M solution of potassium hydroxide in methanol (2 ml) was added and the mixture was stirred at room temperature under argon for 16 hr, neutralised with 2N acetic acid solution, washed out with methanol and evaporated to dryness under reduced pressure. The residue was stirred with water (5 ml), acidified to pH3 with 2N oxalic acid solution and extracted with ethyl acetate (5 X 10 ml). The combined ethyl acetate extracts were washed with water (2 X 10 ml), dried, filtered, and evaporated to dryness to leave a yellow oil (32 mg).

A column (1.0 cm diameter) containing Mallinckrodt CC4 silica (15 g) was prepared and eluted with solvent system (E). The yellow oil was dissolved in the mobile phase (2 ml) and applied to the column; 200 X 2.0 ml fractions were collected and 5 µl aliquots of alternate fractions were spotted on a Silica GF plate and developed with solvent system (D). The plate was run for 10 cm, dried, examined under UV 254 nm and autoradiographed for 16 hr. The appropriate fractions containing one spot material with identical Rf to that of pure reference compound were combined and evaporated to dryness under reduced pressure. Traces of silica were removed by centrifugation of ethyl

acetate extracts. Removal of the solvent gave I.C.I. 81,008 as a colourless gum (24 mg; 42.6%) (Found: C, 60.2; H, 6.3. $C_{23}H_{29}O_6F_3$ requires C, 60.3; H, 6.3), representing an overall chemical yield of 3.5%.

The product was examined by t.l.c. in solvent systems (D) and (F) and the plates were autoradiographed for 16 hr. The autoradiographs were used to "map" the plates which were then segmented. Liquid scintillation counting of the segmented plates in a toluene-Butyl-PBD (6%) phosphor indicated a minimum radiochemical purity of 99.8%. Mass spectrometry and nuclear magnetic resonance spectroscopy showed no detectable impurities. The specific activity was 128.5 μCi/mg (58.85 mCi/m mole) which represented an overall radiochemical yield of 3.43%.

Scheme I (X = Cl)

In the same manner racemic (9S,11R,15R)-16-(3-chlorophenoxy)-9,11,15-trihydroxy-17,18,19,20-tetranor-5-cis,13-trans-[15-^{14}C]prostadienoic acid [I.C.I. 80,996] (Ib) was prepared from chloro[1-^{14}C]acetic acid (144 mg) (with a specific activity of 60 mCi/mM) and m-chlorophenol (225.4 mg) as a colourless gum (38 mg), (Found: C, 62.2; H, 6.7. $C_{22}H_{29}O_6Cl$ requires C, 62.2; H, 6.8), representing an overall chemical yield of 5.9%.

Examination of the product by t.l.c. in solvent systems (D), (F), and (J) was followed by autoradiography of the plates for 16 hr. The plates were "mapped" with the autoradiographs and segmented. Liquid scintillation counting of the segmented plates in a toluene-Butyl-PBD (6%) phosphor indicated a minimum radiochemical purity of 99.8%. Mass spectrometry and nuclear magnetic resonance spectroscopy showed no detectable impurities. The specific activity was 125.8 μCi/mg (53.40 mCi/m mole) which represented an overal radiochemical yield of 5.3%.

Scheme II(A)

5-Bromovalero-[^{14}C]nitrile (IIc)

Potassium [^{14}C] cyanide (248 mg) with a specific activity of 59.3 mCi/mM, 1,4-dibromobutane (3.8 g), and methanol (11 ml) were heated under reflux for 10 hr. The mixture was cooled, washed out with water (25 ml), and extracted with ether (5 X 15 ml). The extracts were washed with water (4 X 8 ml), dried, and evaporated to dryness.

Examination of the product by gas chromatography-mass spectrometry showed the presence of the required 5-bromovalero [^{14}C] nitrile plus 1,4-dibromobutane. No further purification was carried out at this stage.

5-Bromo-[1-^{14}C] valeric acid (IId)

The crude 5-bromovalero [^{14}C] nitrile, 48% aqueous hydrogen bromide solution (2.6 ml), and glacial acetic acid (0.36 ml) were heated under reflux for 6 hr. The solution was cooled, added to water (20 ml), and extracted with ether (5 X 15 ml). The combined ether layers were washed with water (4 X 8 ml) and extracted with 5% aqueous sodium hydroxide solution (5 X 10 ml). The combined alkaline extracts were washed with ether (4 X 5 ml), acidified with concentrated hydrochloric acid solution and extracted with ether (5 X 15 ml). The ether extracts were washed with water, dried and evaporated to dryness to give (IId) (348 mg) as a white solid.

(4-[^{14}C] Carboxybutyl) triphenyl phosphonium bromide (IIe)

5-Bromo[1-^{14}C] valeric acid (348 mg), triphenylphosphine (564 mg), and toluene (2 ml) were heated under reflux for 24 hr. The mixture was cooled and sodium dried ether (7 ml) was added. The product was centrifuged, washed with sodium dried ether (5 X 7 ml) and dried under vacuum at 40°C for 16 hr to

give (IIe) (691 mg; 81%) as a white crystalline solid.

Scheme II (B) (X = Cl)

Racemic (9S,11R,15R)-9-hydroxy-16-(3-chlorophenoxy)-11,15-bis (tetrahydropyran-2-yloxy)-17,18,19,20-tetranor-5-cis,13-trans-[1-^{14}C] prostadienoic acid (IIf)

Finely powdered (4-[^{14}C] carboxybutyl) triphenyl phosphonium bromide (691 mg) was heated to 100°C under vacuum for 1 hr. The evacuated reaction flask was filled with an atmosphere of dry nitrogen, the solid was dissolved in dimethylsulphoxide (3.5 ml) and the solution was cooled to room temperature. To this solution was added dropwise, a 2 M solution of methane sulphinylmethyl sodium in dimethyl sulphoxide (1.47 ml) followed by a solution of racemic 2,3, 3aβ,6aβ-tetrahydro-2-hydroxy-4β-[4-(3-chlorophenoxy)-3α-(tetrahydropyran-2-yloxy)-1-trans-butenyl]-5α-(tetrahydropyran-2-yloxy)cyclopenteno[b]furan[1] (302 mg) in dimethyl sulphoxide (3.5 ml). The solution was stirred for 1 hr and the solvent was removed by evaporation under reduced pressure at a temperature below 50°C. The residue was shaken with water (10 ml) and ethyl acetate (10 ml), the aqueous phase was separated, extracted with ethyl acetate (2 X 10 ml) and the extracts discarded. The aqueous solution was acidified to pH 3 - 4 with 2N aqueous oxalic acid, and extracted with a mixture of equal parts of ether and light petroleum (b.p. 40 - 60°C) (5 X 10 ml). The organic phase was separated, washed with saturated brine solution and dried. Evaporation of the solvents gave a pale yellow oil (364 mg).

Examination of the oil by t.l.c. in solvent system (G) followed by autoradiography for 16 hr showed it to be mainly the required product together with one major, non-polar impurity and several minor polar impurities.

A column (1.0 cm diameter) containing Silica Gel MFC (10 g) was prepared and eluted with solvent system (H). The oil was dissolved in the

mobile phase (2 ml) and applied to the column; 90 X 2.0 ml fractions were collected and 5 µl aliquots of alternate fractions were spotted on a Silica GF plate and developed with solvent system (G). The plate was run for 10 cm, dried, examined under UV 254 nm and autoradiographed for 16 hr. The appropriate fractions containing one spot material with identical Rf to that of pure reference compound were combined and evaporated to dryness under reduced pressure. Traces of silica were removed by centrifugation of ether extracts. The solvent was evaporated under reduced pressure and the residue dried under vacuum at room temperature to give (IIf) (297 mg; 32.8%) as a colourless oil.

Racemic methyl (9S,11R,15R)-16-(3-chlorophenoxy)-9,11,15-trihydroxy-17,18,19,20-tetranor-5-cis,13 trans-[1-^{14}C]-prostadienoate (IIg)

The ester (IIf) (297 mg) was dissolved in dry methanol (8.6 ml) and the solution stirred under argon at room temperature. A solution of 1% p-toluene sulphonic acid in dry tetrahydrofuran (1.1 ml) was added and the mixture stirred at room temperature for 16 hr. Pyridine (0.05 ml) was added and the mixture evaporated to dryness under reduced pressure. The residue was azeotroped with toluene (3 X 10 ml) and then dissolved in ether (20 ml). The ether solution was washed with 10% sodium bicarbonate solution (3 X 10 ml) and water (3 X 10 ml), dried, and evaporated to dryness under reduced pressure to give a pale yellow oil (221 mg; 99.7%).

The oil was examined by t.l.c. in solvent system (G). Autoradiography of the plate for 16 hr showed that the oil was the required ester (IIg) together with several minor less polar impurities. No further purification was carried out at this stage.

Racemic (9S,11R,15R)-16-(3-chlorophenoxy)-9,11,15-trihydroxy-17,18,19,20-tetranor-5-cis,13-trans-[1-^{14}C]prostadienoic acid [I.C.I. 80,996] (IIb)

The methyl ester (IIg) (221 mg) was stirred at room temperature under

argon in methanol (26 ml). Water (5.3 ml) and a 1 M solution of potassium hydroxide in methanol (5.7 ml) were added and the mixture was stirred at room temperature under argon for 16 hr, neutralised with 2N acetic acid solution, washed out with methanol, and the methanol removed under reduced pressure. The aqueous residue was stirred with water (5 ml), acidified to pH 3 with 2N oxalic acid solution, and extracted with ethyl acetate (5 X 10 ml). The extracts were washed with water (2 X 10 ml) and evaporated to dryness under reduced pressure. The residue was dissolved in saturated sodium hydrogen carbonate solution (10 ml), the solution washed with ether (3 X 10 ml), acidified to pH 3 with 2N aqueous oxalic acid solution and extracted with ethyl acetate (7 X 10 ml). The ethyl acetate extracts were washed with water (3 X 10 ml), dried, filtered and evaporated to dryness to leave a yellow oil.

A column (1.0 cm diameter) containing Mallenckrodt CC4 Silica (5.5 g) was prepared and eluted with solvent system (E). The oil was dissolved in the mobile phase (2 ml) and applied to the column; 90 X 2.0 ml fractions were collected and 5 µl aliquots of alternate fractions were spotted on a Silica GF plate and developed with solvent system (D). The plate was run for 10 cm, dried, examined under UV 254 nm and autoradiographed for 16 hr. The appropriate fractions containing one spot material with identical Rf to that of pure reference compound were combined and evaporated to dryness under reduced pressure. The residue was extracted with ethyl acetate (5 X 2 ml) and the extracts centrifuged to remove traces of silcia. Removal of the solvent by evaporation under a stream of argon, followed by drying under vacuum at room temperature gave (IIb) [I.C.I. 80,996] as a colourless gum (142 mg; 66.4%) (Found: C, 62.2; H, 6.9. $C_{22}H_{29}O_6Cl$ requires C, 62.2; H, 6.8), representing an overall chemical yield of 8.8%.

The product was examined by t.l.c. in solvent systems (D), (F), and (J) and the plates autoradiographed for 16 hr. The autoradiographs were used to "map" the plates which were then segmented. Liquid scintillation counting of the segmented plates in a toluene-Butyl-PBD (6%) phosphor indicated a mini-

mum radiochemical purity of 99.8%. Mass spectrometry and nuclear magnetic resonance spectroscopy showed no detectable impurities. The specific activity was 120.9 μCi/mg (51.32 mCi/m mole) which represented an overall radiochemical yield of 8.6%.

Scheme II (B) ($X = CF_3$)

In an analogous manner racemic (9S,11R,15R)-9,11,15-trihydroxy-16-(3-trifluoromethylphenoxy)-17,18,19,20-tetranor-5-cis,13-trans-[1-^{14}C]prostadienoic acid [I.C.I. 81,008] (IIa) was prepared from (4-[^{14}C]carboxybutyl)triphenyl phosphonium bromide (330 mg), made as previously indicated from potassium[^{14}C]cyanide (152 mg) with a specific activity of 8.5 mCi/m mole, as a colourless gum (45 mg) (Found: C, 60.3; H, 6.2. $C_{23}H_{29}O_6F_3$ requires C, 60.3; H, 6.3), representing an overall chemical yield of 4.2%.

Examination of the product by t.l.c. in solvent systems (D), (F), and (J) was followed by autoradiography of the plates for 16 hr. The plates were "mapped" with the autoradiographs and segmented. Liquid scintillation counting of the segmented plates in a toluene-Butyl-PBD (6%) phosphor indicated a minimum radiochemical purity of 99.6%. Mass spectrometry and nuclear magnetic resonance spectroscopy showed no detectable impurities. The specific activity was 18.2 μCi/mg (8.34 mCi/m mole) which represented an overall radiochemical yield of 4.1%.

ACKNOWLEDGMENTS

The author would like to thank Dr. E. R. H. Walker and Mrs. J. Bowler for their valuable discussions; Mr. D. Greatbanks for n.m.r. measurements and Mr. P. J. Phillips for mass spectrometric measurements.

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