SYNTHESIS OF 7α-CHLORO-16α-METHYLPREDNISOLONE 17α,21-DIPROPIONATE-4-^{14}C (ALCLOMETASONE DIPROPIONATE-4-^{14}C)

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SUMMARY

Grignard reaction of the enol-lactone 8 with ^{14}C-methylmagnesium iodide afforded an adduct 9 which on subsequent treatment with lithium 2,6-di-t-butylphenoxide gave the enone 10. Conversion of 10 to the trienone 12 was performed by two-step dehydrogenation using chloranil and then DDQ. The protecting groups were removed on treatment whith 2N-hydrochloric acid-trifluoroacetic acid to give the triol 13. The 17α,21-bisesterification of 13 was carried out according to the orthoester procedure. Finally, addition of dry hydrogen chloride to the resulting diester 16 led to the title compound 17.

Key words : antiinflammatory agent; alclometasone dipropionate-4-^{14}C; tris(triphenylphosphine)chlororhodium; lithium 2,6-di-t-butylphenoxide; triethylorthopropionate.

INTRODUCTION

7α-Chloro-16α-methylprednisolone 17α,21-dipropionate (alclometasone dipropionate) has recently been developed as a novel topical antiinflammatory agent [1,2]. In a variety of animal tests, the non-fluorinated corticosteroid was found to possess a high topical antiinflammatory potency and exhibit favorable ratios of local to systemic effects compared to other corticoids [3].

In order to study the bioavailability, metabolism and protein-binding effects of the new corticoid, it was required to obtain the biochemically stable ^{14}C-labelled substrate. In the present publication we describe an efficient synthesis of the title compound.

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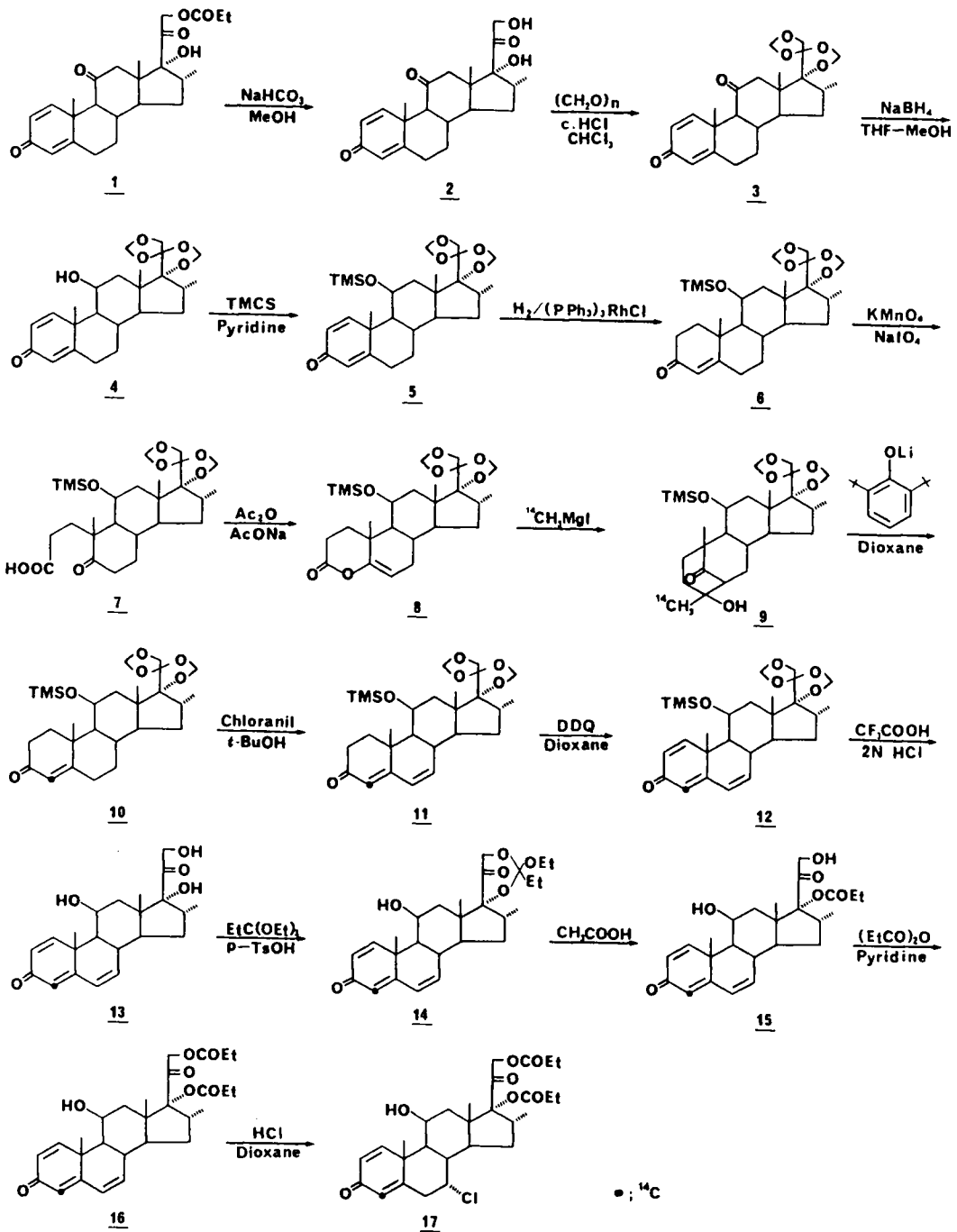
RESULTS AND DISCUSSION

Recently, Rao et al. has reported the synthesis of dexamethasone-4-^{14}C [4]. This methodology can be readily applied to the synthesis of the title compound. However, the target compound which has a 7α-chloro group instead of a 9α-fluoro group, is very sensitive to undergo facile elimination of hydrogen chloride. The chloro group, therefore, must favorably be introduced at the final stage of the synthetic sequence.

Our present synthesis started with 16α-methylprednisone (2) which was available from its 21-propionate 1 on alkaline hydrolysis. The dihydroxyacetone side chain of 2 was first protected as the bismethylenedioxy derivative 3, whcih was then reduced with sodium borohydride at -30°C to give predominantly the 11β-ol 4. The 11β-hydroxy group in 4 was silylated with trimethylchlorosilane and trimethylsilylimidazole in pyridine to give the trimethylsilyloxy derivative 5. The Δ^1-double bond of 5 was selectively hydrogenated over tris(triphenylphosphine)chlororhodium to result in the formation of Δ^4-3-oxo compound 6. Potassium permanganate-sodium metaperiodate oxidation of 6 effected cleavage of the A-ring to afford the seco-acid 7. On treatment with refluxing acetic anhydride containing sodium acetate, 7 was led to the desired enol-lactone 8, which was thus obtained in 21.8% overall yield from 16α-methylprednisone (2).

Here, incorporation of the ^{14}C-label at the 4-position of the steroid nucleus was carried out. Grignard reaction of 8 with ^{14}C-methylmagnesium iodide prepared from ^{14}C-methyl iodide (200mCi, 55.0mCi/mmole) yielded the ^{14}C-adduct 9. Treatment of 9 with lithium 2,6-di-t-butylphenoxide in boiling dioxane furnished the enone 10, which was identified with the corresponding unlabelled compound 6 by spectral (IR, NMR) and other (mp, TLC) data. Conversion of 10 to the trienone 12 was achieved via the dienone

Scheme 1


OCOEt
O
OH
NaHCO3
MeOH
(CH2O)n
c.HCl
CHCl3
NaBH4
THF–MeOH
HO
TMCS
Pyridine
TMSO
H2/(PPh3)3RhCl
KMnO4
NaIO4
HOOC
Ac2O
AcONa
14CH3MgI
14CH3
OLi
Dioxane
Chloranil
t-BuOH
DDQ
CF3COOH
2N HCl
EtC(OEt)3
p-TsOH
CH3COOH
(EtCO)2O
Pyridine
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1
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• ; 14C

11 by two-step dehydrogenation with chloranil in t-butanol under reflux followed by DDQ in boiling dioxane. The silyl ether and bismethylenedioxy groups were smoothly deprotected by treating 12 with 2N-hydrochloric acid and trifluoroacetic acid at room temperature to give the triol 13. The 17α,21-bisesterification of 13 was carried out according to the orthoester procedure of Ercoli et al. [5]. Reaction of 13 with triethylorthopropionate by means of p-toluenesulfonic acid in dimethyl sulfoxide yieded the orthoester 14 which was converted to the expected 17α-propionate 15 on partial hydrolysis with acetic acid. Further acylation of the latter compound with propionic anhydride in pyridine afforded the 17α,21-dipropionate 16. Finally, treatment of 16 with dry hydrogen chloride in dioxane furnished the desired target compound 17, having a specific activity of 32.7mCi/mmole, in 5.7% overall yield from ^{14}C-methyl iodide. This material proved to be identical with the unlabelled alclometasone dipropionate by comparison of spectral and other data (IR, NMR, mp, TLC).

EXPERIMENTAL

Melting points were uncorrected. IR spectra were obtained in a potassium bromide disk using a Hitachi 295 infrared spectrophotometer. NMR spectra were measured with a Hitachi R24-B spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. Silica gel 60 (grain size 0.063~0.2mm, Merck) was used for column chromatography. Radioactivity was measured by the scintillation technique using an Aloka Model 670 spectrometer. Radiochemical purity was determined on thin-layer chromatograms with an Aloka Model FC-25 radiochromatogram scanner system.

16α-Methylprednisone (2)

To a solution of 16α-methylprednisone 21-propionate (1, 4.28g,

10mmole) in methanol (225ml) was added saturated aqueous sodium bicarbonate solution (25ml). The mixture was stirred at 80°C for 2hr. After the solvent was removed under reduced pressure, the residue was extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate, and evaporated. The residue was crystallized from ethyl acetate-ether to give 2 (3.3g, 88.6%) ; mp 106-109°C ; νmax 3400, 1710, 1660, 1610cm^{-1} ; δ 0.73 (3H, s), 0.96 (3H, d, J=7.5Hz), 1.42 (3H, s), 4.16 (1H, d, J=20Hz), 4.54 (1H, d, J=20Hz), 6.05 (1H, s), 6.15 (1H, dd, J=9.5, 1.5Hz), 7.67 (1H, d, J=9.5Hz).

17α,20;20,21-Bismethylenedioxy-16α-methyl-1,4-pregnadiene-3, 11-dione (3)

A mixture of paraformaldehyde (40g), conc. hydrochloric acid (200ml), and water (120ml) was stirred at room temperature for 2hr. To it was added a solution of 2 (3.3g, 8.86mmole) in chloroform (200ml). After vigorous stirring was continued at the same temperature for 16hr, the organic layer separated was washed with saturated sodium bicarbonate solution and saturated sodium chloride solution, dried over sodium sulfate, and evaporated. The residue was crystallized from dichloromethane-methanol to give 3 (3.14g, 85.6%) ; mp 260-262°C ; νmax 1705, 1665, 1620, 1098, 1072cm^{-1} ; δ 0.88 (3H, s), 1.00 (3H, d, J=7Hz), 1.42 (3H, s), 3.94 (2H, s), 4.98 (2H, dd, J=9.5, 1.2Hz), 5.07 (2H, d, J=12Hz), 6.05 (1H, s), 6.15 (1H, dd, J=10, 1.5Hz), 7.64 (1H, d, J=10Hz).

17α,20;20,21-Bismethylenedioxy-11β-hydroxy-16α-methyl-1, 4-pregnadien-3-one (4)

To a solution of 3 (6.2g, 14.96mmole) in tetrahydrofuran (210ml) and methanol (70ml) was added sodium borohydride (1.68g, 44.4mmole) under an atmosphere of nitrogen at -30°C. After

stirring for 2hr, the mixture was quenched by adding cold 2N-hydrochloric acid, concentrated under reduced pressure, and then extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated. The residue was crystallized from dichloromethane-methanol to give 4 (5.27g, 84.6%) ; mp 262-265°C ; νmax 3340, 1660, 1605, 1095cm^{-1} ; δ 0.92 (3H, d, J=7Hz), 1.17 (3H, s), 1.45 (3H, s), 3.93 (2H, s), 4.37 (1H, m), 4.93 (2H, dd, J=8.5, 1.2Hz), 5.07 (2H, d, J=9.5Hz), 5.95 (1H, bs), 6.18 (1H, dd, J=9.5, 1.5Hz), 7.20 (1H, d, J=9.5Hz).

17α,20;20,21-Bismethylenedioxy-11β-trimethylsilyloxy-16α-methyl-1,4-pregnadien-3-one (5)

To a solution of 4 (10.5g, 25.21mmole) in pyridine (100ml) were added trimethylchlorosilane (15ml) and trimethylsilylimidazole (5ml). The mixture was stirred at room temperature for 16hr, then diluted with water, and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated. The residue was purified by column chromatography on silica gel with benzene-ethyl acetate (6:1 v/v) and crystallized from ether-pet. ether to give 5 (10.5g, 85.2%) ; mp 182-184°C, νmax 1665, 1625, 1600, 1100, 1075, 940, 840cm^{-1} ; δ 0.20 (9H, s), 0.91 (3H, d, J=7Hz), 1.13 (3H, s), 1.36 (3H, s), 3.94 (2H, s), 4.41 (1H, m), 4.95 (2H, dd, J=8.5, 1.2Hz), 5.08 (2H, d, J=8Hz), 5.96 (1H, bs), 6.20 (1H, dd, J=10, 1.5Hz), 7.05 (1H, d, J=10Hz).

17α,20;20,21-Bismethylenedioxy-11β-trimethylsilyloxy-16α-methyl-4-pregnen-3-one (6)

A solution of 5 (10.5g, 21.49mmole) in benzene (100ml) and ethanol (25ml) was hydrogenated over tris(triphenylphosphine)-chlororhodium (2.0g, 2.16mmole) at room temperature under atmospheric pressure for 16hr. The catalyst was filtered off and

the solvent was evaporated. The residue was purified by column chromatography on silica gel with benzene-ethyl acetate (6:1 v/v) and crystallized from ether-pet. ether to give 6 (7.5g, 71.1%) ; mp 186-188°C ; νmax 1677, 1617, 1098, 1077, 940, 840cm^{-1} ; δ 0.13 (9H, s), 0.93 (3H, d, J=7Hz), 1.12 (3H, s), 1.34 (3H, s), 3.95 (2H, s), 4.37 (1H, m), 4.97 (2H, dd, J=8.5, 1.2Hz), 5.09 (2H, d, J=7.5Hz), 5.63 (1H, bs).

17α,20;20,21-Bismethylenedioxy-11β-trimethylsilyloxy-16α-methyl-3,5-seco-4-norpregnan-5-one-3-carboxylic acid (7)

Solutions of sodium metaperiodate (25g) in water (175ml) and potassium permanganate in water (0.8%) were prepared prior to the reaction. To a solution of 6 (7.5g, 15.28mmole) in dichloromethane (50ml) were added t-butanol (175ml) and a solution of potassium carbonate (4.5g) in water (45ml).

A portion of the sodium metaperiodate solution (20ml) was added to the reaction mixture with stirring, followed by the addition of sufficient quantity of the potassium permanganate solution to maintain a constant purple color. The remaining periodate solution (155ml) was added over the next 30min, with addition of the permanganate solution when needed to maintain the color. After vigorous stirring at room temperature for 16hr, the reaction mixture was diluted to twice its volume with water, cooled to 0°C in an ice bath, and adjusted to pH 4 with sulfuric acid (50%). The mixture was extracted with chloroform, dried over sodium sulfate, and evaporated. The residue was crystallized from ether-pet. ether to give 7 (5.5g, 70.5%) ; mp 158-160°C ; νmax 3400, 1708, 1080, 940, 840cm^{-1} ; δ 0.14 (9H, s), 0.92 (3H, d, J=7Hz), 1.15 (3H, s), 1.27 (3H, s), 3.96 (2H, s), 4.30 (1H, m), 4.99 (2H, dd, J=8, 1.2Hz), 5.10 (2H, d, J=8Hz).

17α,20;20,21-Bismethylenedioxy-11β-trimethylsilyloxy-16α-methyl-3,5-seco-4-nor-5-pregnen-3-oic acid 3,5-lactone (8)

A mixture of 7 (5.5g, 10.77mmole), sodium acetate (10g, 121.9mmole) and acetic anhydride (200ml) was heated to reflux under nitrogen stream. Five min after initiation of reflux, triethylamine (20ml) was added. The mixture was then stirred at reflux for 2hr. After cooling, the mixture was filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel with benzene-ethyl acetate (6:1 v/v) and crystallized from ether-pet. ether to give 8 (3.75g, 70.7%) ; mp 158-160°C ; νmax 1763, 1695, 1100, 1080, 940, 840cm^{-1} ; δ 0.13 (9H, s), 0.94 (3H, d, J=7Hz), 1.12 (3H, s), 1.29 (3H, s), 3.95 (2H, s) 4.37 (1H, m), 4.94 (2H, dd, J=8.5, 1.2Hz), 5.08 (2H, d, J=8Hz).

17α,20;20,21-Bismethylenedioxy-11β-trimethylsilyloxy-16α-methyl-3-hydroxy-3-methyl-3(5→6βH)abeo-A-norpregnan-5-one-4-^{14}C (9)

To the Grignard reagent, prepared from the methyl-^{14}C iodide (516mg, 3.63mmole, 200.0mCi) and magnesium turnings (97.2mg, 4mmole) in anhydrous ether (5ml), was added with stirring a solution of 8 (1.85g, 3.74mmole) in anhydrous dichloromethane (5ml). After 3hr-stirring at room temperature, the reaction mixture was decomposed with saturated aqueous ammonium chloride solution and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to give 9 (1.46g, 79.1%, 158.1mCi) ; mp 128-132°C ; νmax 3450, 1720, 1090, 940, 840cm^{-1} ; δ 0.13 (9H, s), 0.94 (3H, d, J=7Hz), 1.06 (3H, s), 1.16 (3H, s), 1.26 (3H, s), 3.96 (2H, s), 4.21 (1H, m), 5.03 (2H, dd, J=8.5, 1.2Hz), 5.11 (2H, d, J=7Hz).

17α,20;20,21-Bismethylenedioxy-11β-trimethylsilyloxy-16α-methyl-4-pregnen-3-one-4-^{14}C (10)

To a stirred solution of 2,6-di-t-butylphenol (1.03g, 5mmole) in dry dioxane (17ml) was added dropwise a solution of n-butyl-

lithium in hexane (5mmole/3ml) under an atmosphere of nitrogen. The mixture was stirred at room temperature for 1hr. To a solution of 9 (1.46g, 2.87mmole, 158.1mCi) in dry dioxane (10ml) was added a portion (16ml) of the resulting lithium 2,6-di-t-butylphenoxide suspension under nitrogen. After refluxing for 3hr, the mixture was cooled, poured into an ice-cold phosphate buffer (pH 7), and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated. The residue was purified by column chromatography on silica gel with benzene-ethyl acetate (6:1 v/v) and crystallized from ether-pet. ether to give 10 (1.09g, 77.5%, 122.5mCi). This material was identical (IR, NMR, mp, TLC) with the unlabelled material 6.

17α,20;20,21-Bismethylenedioxy-11β-trimethylsilyloxy-16α-methyl-4,6-pregnadien-3-one-4-^{14}C (11)

A mixture of 10 (1.09g, 2.23mmole, 122.5mCi), chloranil (1.5g, 6.1mmole) in t-butanol (70ml) was heated at reflux for 4hr under a stream of nitrogen. The excess chloranil was filtered and the filtrate was evaporated. The residue was taken up in chloroform and the solution was washed with water (twice), 5% sodium hydroxide solution (twice) and water, dried over sodium sulfate, and evaporated. The residue was purified by column chromatography on silica gel with benzene-ethyl acetate (6:1 v/v) and crystallized from ether-hexane to give 11 (0.71g, 65.3%, 80.0mCi) ; mp 193-196 °C ; νmax 1660, 1612, 1540, 1090, 1075, 942, 837cm^{-1} ; δ 0.15 (9H, s), 0.97 (3H, d, J=6.5Hz), 1.20 (3H, s), 1.31 (3H, s), 4.06 (2H, s), 4.45 (1H, m), 5.09 (2H, dd, J=8.5, 1.2Hz), 5.22 (2H, dd, J=7.5, 1.6Hz), 5.68 (1H, bs), 6.19 (2H, s).

17α,20;20,21-Bismethylenedioxy-11β-trimethylsilyloxy-16α-methyl-1,4,6-pregnatrien-3-one-4-^{14}C (12)

A mixture of 11 (0.71g, 1.45mmole, 80.0mCi), DDQ (1g, 4.4

mmole) in dioxane (15ml) was refluxed for 4hr under a stream of nitrogen. The excess DDQ was filtered and the filtrate was evaporated. The residue was taken up in chloroform and the solution was washed with water (twice), 5% sodium hydroxide solution (twice), and water, dried over sodium sulfate, and evaporated. The residue was purified by column chromatography on silica gel with benzene-ethyl acetate (6:1 v/v) and crystallized from ether-hexane to give 12 (0.49g, 68.9%, 55.1mCi) ; mp 195-199°C ; νmax 1653, 1605, 1545, 1100, 1080, 940, 840cm^{-1}, δ 0.21 (9H, s), 0.95 (3H, d, J=7Hz), 1.20 (3H, s), 1.38 (3H, s), 4.01 (2H, s), 4.48 (1H, m), 5.01 (2H, dd, J=8.8, 1.2Hz), 5.16 (2H, d, J=8.5Hz), 5.97 (1H, bs), 6.17 (2H, bd), 6.30 (1H, dd, J=10.5, 1.5Hz), 7.15 (1H, d, J=10.5Hz).

11β,17α,21-Trihydroxy-16α-methyl-1,4,6-pregnatriene-3,20-dione-4-^{14}C (13)

A mixture of 12 (0.49g, 1.0mmole, 55.1mCi), trifluoroacetic acid (8ml), and 2N-hydrochloric acid (8ml) was stirred at room temperature for 9hr. The reaction mixture diluted with ethyl acetate was washed with water and dried over sodium sulfate. The solvent was removed and the residue was purified by column chromatography on silica gel with chloroform-ethanol (9:1 v/v), then crystallized from acetone-ether to give 13 (0.25g, 68.2%, 37.6mCi) ; mp 230-234°C ; νmax 3420, 1715, 1645, 1595cm^{-1} ; δ 0.88 (3H, d, J=7Hz), 1.04 (3H, s), 1.44 (3H, s), 4.74 (1H, m), 5.07 (2H, s), 6.24 (1H, bs), 6.53 (2H, bs), 6.55 (1H, dd, J=10, 2Hz), 7.72 (1H, d, J=10Hz).

11β,17α,21-Trihydroxy-16α-methyl-1,4,6-pregnatriene-3,20-dione 17α,21-ethylorthopropionate-4-^{14}C (14)

A mixture of 13 (0.25g, 0.68mmole, 37.6mCi), triethylorthopropionate (0.54ml, 2.68mmole), and p-toluenesulfonic acid mono-

hydrate (20mg) in dimethyl sulfoxide (1.5ml) was stirred at room temperature for 2.5hr. The mixture was poured into cold sodium bicarbonate solution and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated to give 14 (0.31g, 36.9mCi). The crude product was used for the next reaction without any purification.

11β,17α,21-Trihydroxy-16α-methyl-1,4,6-pregnatriene-3,20-dione 17α-propionate-4-^{14}C (15)

The crude 14 (0.31g, 0.67mmole, 36.9mCi) was dissolved in acetic acid (2.3ml) containing water (0.04ml) and the solution stirred at room temperature for 1.5hr. The reaction mixture was poured into water and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated. The residue was crystallized from ether-hexane to give 15 (0.25g, 83.8% from 13, 31.5mCi) ; mp 219-223°C ; νmax 3330, 1740, 1715, 1640, 1590cm^{-1} ; δ 0.98 (3H, d, J=7Hz), 1.07 (3H, s), 1.10 (3H, t, J=7Hz), 1.43 (3H, s), 4.26 (2H, s), 4.51 (1H, m), 5.92 (1H, bs), 6.15 (2H, bd), 6.23 (1H, dd, J=10, 2Hz), 7.27 (1H, d, J=10Hz).

11β,17α,21-Trihydroxy-16α-methyl-1,4,6-pregnatriene-3,20-dione 17α,21-dipropionate-4-^{14}C (16)

A mixture of 15 (0.25g, 0.57mmole, 31.5mCi) and propionic anhydride (0.6ml, 4.68mmole) in pyridine (3ml) was stirred at room temperature for 16hr. The reaction mixture was poured into water and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and evaporated. The residue was purified by column chromatography on silica gel with chloroform-acetone (9:1 v/v) to afford 16 (0.26g, 93.7%, 29.5mCi) ; mp 107-110°C ; νmax 3460, 1740, 1655, 1595, 1180cm^{-1} ; δ 0.97 (3H, d, J=7Hz), 1.11 (3H, t, J=7Hz), 1.16 (3H, t, J=7Hz), 1.16 (3H, s), 1.42 (3H, s), 4.52 (1H, m), 4.80 (2H, s) 5.92 (1H,

bs), 6.12 (2H, bd), 6.25 (1H, dd, J=10, 1.5Hz), 7.26 (1H, d, J=10Hz).

7α-Chloro-16α-methylprednisolone 17α,21-dipropionate-4-^{14}C (alclometasone dipropionate-4-^{14}C) (17)

Compound 16 (0.26g, 0.53mmole, 29.0mCi) was added to dioxane (3ml) saturated with dry hydrogen chloride. After stirring was continued for 3hr at room temperature, the reaction mixture was poured into ice-cold water and extracted with ethyl acetate. The extract was washed with water, dried over sodium sulfate, and evaporated. The residue was purified by preparative TLC (Silica gel F_{254}, E. Merck, 20cm×20cm×0.5mm, cyclohexane-dimethoxyethane 2:1 with triple development) to give 17 (0.12g, 12.7mCi). The crude material was diluted with unlabelled material and recrystallized from acetone-methanol-isopropyl ether to give pure 17 (178.6mg, 38.6%, 11.2mCi) ; specific activity 32.7 mCi/mmole (62.8μCi/mg) ; mp 210-213°C ; νmax 3500, 1740, 1660, 1615, 1200cm^{-1} ; δ 1.00 (3H, d, J=7Hz), 1.16 (3H, s), 1.16 (3H, t, J=7Hz), 1.20 (3H, t, J=7Hz), 1.51 (3H, s), 4.55 (1H, m), 4.86 (2H, s), 6.15 (1H, bs), 6.33 (1H, dd, J=10, 1.5Hz), 7.30 (1H, d, J=10Hz).

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