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Expedient synthesis of 17α,21-dihydroxy-9β,11β-epoxy-16α-methylpregna-1,4-diene-3,20-dione 21-acetate from prednisolone utilising a novel Mattox rearrangement

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ABSTRACT

A six step transformation of prednisolone to 17α,21-dihydroxy-9β,11β-epoxy-16α-amethylpregna-1,4-diene-3,20-dione 21-acetate has been achieved in 13% unoptimised yield. Novel conditions for effecting a Mattox rearrangement and double dehydration of prednisolone were identified. Enhanced knowledge on the oxidation of silyl $\Delta^{19,20}$-enol ethers and structural factors that impact the success of the oxidation are also presented.

1. Introduction

17α,21-Dihydroxy-9β,11β-epoxy-16α-methylpregna-1,4-diene-3,20-dione 21-acetate **1** is a key synthetic intermediate in the synthesis of a range of medicinal glucocorticoids, such as mometasone furoate **2** [1], dexamethasone **3** [2], flumethasone **4** and fluticasone propionate **5**, Fig. 1. These glucocorticoids see widespread use as therapeutic agents for the treatment of inflammatory skin disorders and respiratory diseases. As such, a robust and economical synthesis of this key intermediate is important for delivering a resilient and economically viable supply chain for these medicines. The vast majority of bulk steroids are synthesized from steroidal sapogenins in multi-step syntheses [3]. Quicker and cheaper routes to this key synthetic intermediate would offer a substantial business advantage.

As part of an assessment of improved routes to 17α,21-dihydroxy-9β,11β-epoxy-16α-methylpregna-1,4-diene-3,20-dione 21-acetate to support GlaxoSmithKline's steroid portfolio, a route from prednisolone (**6**) was considered. While prednisolone itself is typically derived from steroidal sapogenins [4], the routes to access it and the required biotransformations are very well developed resulting in its general availability from numerous suppliers [5]. Another advantage of utilizing prednisolone as the starting material for this approach is that the synthesis is likely to be considerably shorter compared to routes from sapogenins. This would result in the requirement for process optimization of relatively few synthetic steps and, potentially, quick introduction into the supply chain.

2. Experimental

2.1. General procedures

All reactions were carried out under a nitrogen atmosphere. Solvents and reagents were of analytical grade purchased from commercial sources and used without any purification or drying. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker spectrometer in $CDCl_3$ or DMSO-d_6 at frequencies of 400 and 100 MHz. Chemical shifts are given as δ ppm values relative to residual un-deuterated solvent. High-resolution mass spectra were recorded on a linear ion trap combined with a Fourier transform ion cyclotron resonance mass spectrometer using an electrospray ionisation source operated in positive ion mode. IR spectra were recorded as solids. HPLC chromatograms were recorded on either: a C18(2) column at 40 °C; eluent gradient: 100% 0.05% v/v TFA in water to 95% 0.05% v/v TFA in MeCN over 8 min; or a C18 column at 60 °C; eluent gradient: 100% 0.05% v/v TFA in water to 95% 0.05% v/v TFA in MeCN over 2.5 min.

2.2. Chemical syntheses

2.2.1. Mattox rearrangement product *9*

Prednisolone (2.0 g) was dissolved in tetrahydrofuran (20 mL) and cooled to 0 °C in an ice bath. Thionyl chloride (3 equiv.) was

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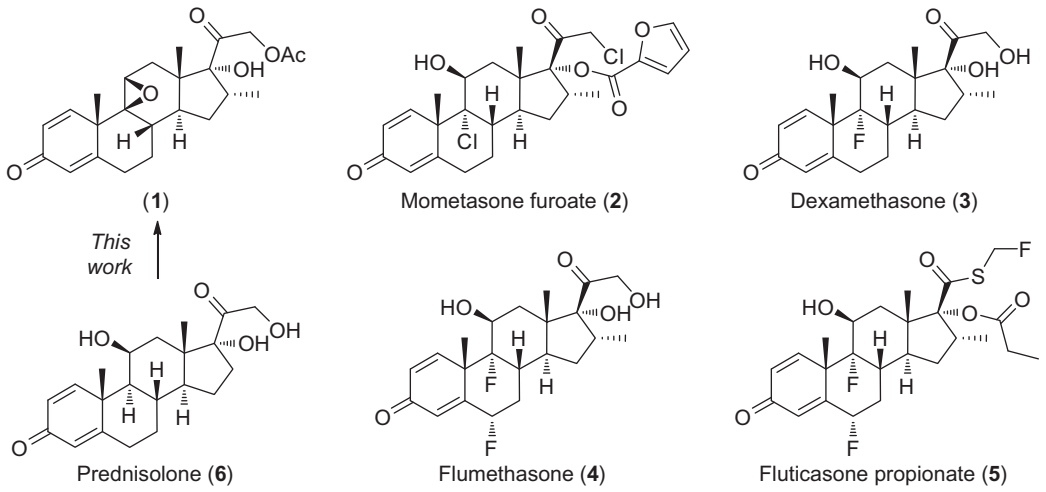


Fig. 1. Key medicines synthesized via 17α,21-dihydroxy-9β,11β-epoxy-16α-methylpregna-1,4-diene-3,20-dione 21-acetate 1.

added slowly over 10 min and the mixture was stirred for 30 min at 0 °C. Triethylamine (15.5 equiv.) was added drop wise maintaining the reaction below 5 °C and the reaction was stirred for an additional 15 min. The reaction was allowed to warm to ambient temperature for 1 h. Saturated aqueous sodium chloride (20 mL) was added followed by water (5 mL) to dissolve the precipitated solid and generate a biphasic mixture. The upper organic layer was concentrated to approximately 6 mL and water (20 mL) was added drop wise at ambient temperature and the resultant slurry was aged for 1 h at ambient temperature. The solid was collected by filtration, washed twice with water (5 mL) and dried under vacuum at 40 °C to yield **9** (1.14 g, 63%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.63 (s, 1H), 7.87 (s, 1H), 7.45 (d, J = 10.2 Hz, 1H, 1-H), 6.20 (dd, J = 10.1 and 1.9 Hz, 1H, 2-H), 6.04 (s, 1H, 4-H), 5.60 (d, J = 5.8 Hz, 1H, 11-H), 3.00 (dd, J = 18.2 and 8.4 Hz, 1H), 2.81–2.60 (m, 3H), 2.52–2.40 (m, 2H), 2.30–2.14 (m, 2H), 2.02–1.91 (m, 1H), 1.52–1.05 (m, 4H), 1.44 (s, 3H, 19-CH_3), 0.97 (s, 3H, 18-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.3, 185.1, 167.4, 155.5, 146.8, 143.2, 143.0, 126.4, 122.9, 120.6, 51.1, 45.7, 43.8, 37.7, 34.9, 34.5, 31.3, 26.3, 25.7, 25.6, 15.1; HRMS (ESI): m/z calcd for $C_{21}H_{25}O_3$ (M+H)+, 325.1804; found, 325.1793.

2.2.2. Tetraene 7

Mattox rearrangement product **9** (2.0 g) was slurried with *N*,*N*-dimethylaminopyridine (1.1 equiv.) in dichloromethane (10 mL) at ambient temperature. Acetic anhydride (1.1 equiv.) was added and the mixture was stirred at ambient temperature for 30 min to provide a solution of acetate **10**. The dichloromethane was removed under vacuum and the residue was dissolved in tetrahydrofuran (10 mL). 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU, five drops, catalytic) was added and the reaction mixture was heated to 60 °C for 3 h. The reaction mixture was cooled to ambient temperature, washed twice with saturated sodium chloride (20 mL) and concentrated to approximately 4 mL. Water (40 mL) was added over 30 min and the resultant slurry was aged at ambient temperature for 1 h then isolated by filtration and dried under vacuum to yield **7** (1.92 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (d, J = 10.3 Hz, 1H, 1-H), 6.75 (m, 1H, 16-H), 6.27 (dd, J = 10.3 and 1.7 Hz, 1H, 2-H), 6.06 (s, 1H, 4-H), 5.55 (m, 1H, 11-H), 5.03 (d, J = 16.1 Hz, 1H, 21-H), 4.88 (d, J = 15.9 Hz, 1H, 21-H′), 2.37–2.73 (m, 5H), 2.05–2.23 (m, 3H), 2.16 (s, 3H, 21-OAc), 1.47–1.57 (m, 1H), 1.42 (s, 3H, 19-CH_3), 1.15–1.29 (m, 1H), 0.91 (s, 3H, 18-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.3, 186.3, 170.4, 166.3, 154.5, 150.2, 143.4, 143.4, 127.3, 123.9, 121.1, 65.6, 52.3, 46.0, 45.2, 37.4, 34.4, 34.3, 33.4, 31.9, 26.7, 20.5, 15.4; HRMS (ESI): m/z calcd for $C_{23}H_{27}O_4$ (M+H)+, 367.1904; found, 367.1914.

2.2.3. Alkene 11

Copper(II) chloride (0.051 g, 0.382 mmol) was slurried in tetrahydrofuran (10 mL) and cooled to <3 °C. A tetrahydrofuran solution of methyl magnesium chloride (3 M, 0.332 mL, 0.996 mmol) was added to the chilled slurry over 1 min keeping the contents <3 °C. A solution of **7** (1.00 g, 2.73 mmol) in tetrahydrofuran (7.5 mL) was added over 2 min keeping the contents <3 °C. Trimethylchlorosilane (0.698 mL, 5.46 mmol) was added in one portion followed by more solution of methyl magnesium chloride in tetrahydrofuran (3 M, 1.137 mL, 3.41 mmol) which was added drop wise over 23 min keeping the contents <2.0 °C. After 12 min, the reaction was quenched with triethylamine (0.856 mL, 6.14 mmol) followed by saturated aqueous ammonium chloride (5 mL). This addition was highly exothermic (0–23 °C). Water (3 mL) was added to dissolve the solids and the quenched mixture was stirred vigorously for at least 30 min. The layers were separated and the blue aqueous layer was extracted with heptane (2 × 4 mL). The organic layers were dried through sodium sulfate and concentrated to dryness to give crude silyl enol ether (1.20 g). The crude silyl enol ether was dissolved in dichloromethane (10 mL) and cooled to <3 °C. A solution of peracetic acid in acetic acid (32%, 0.566 mL, 2.73 mmol) was added drop wise over 4 min keeping the contents <4 °C. After 19 h, the reaction was quenched with aqueous hydrochloric acid (2 N, 3 mL) and stirred vigorously. The organic layer was washed with aqueous potassium carbonate (25%, 4 mL) and concentrated to dryness to give a pale yellow foam. *tert*-Butylmethyl ether (10 mL) was added and the mixture was sonicated to cause crystallisation. The slurry was heated to reflux and stirred to break down any larger lumps. The material gummed out and so was concentrated to dryness to give crude product as a pale yellow foam (1.1079 g). The crude material was analysed by HPLC and LCMS. This analysis indicated a significant impurity isomeric to protonation at C-17 but not the same as for protonation of the silyl enol ether. Also present was a significant amount of di-oxygenated material, potentially a 9,11-epoxide. The sample was analysed by TLC and an aliquot of foam (~205 mg) was purified by prep-TLC (Macherey–Nagel SIL G-200 UV254 plates; 20 × 20 cm × 2 mm) eluted with 1:1 v/v ethyl acetate/heptane. Bands corresponding to Spots 1, 2, 3 and 4 were scraped off and put into a Bond Elut filter. The material was extracted with ethyl acetate (25 mL) followed by 1:1 v/v ethyl acetate/dichloro-

methane (25 mL). The filtrates were concentrated to dryness and the residues were dissolved in dichloromethane, filtered through cotton wool and re-concentrated to give:

Band 1 (5.2 mg): Analysis indicated only 79% purity with some contamination from Band 2 material. This material appears to be consistent with protonation of the silyl enol ether from the β-face, indicated by structure **14**. While no strong NoE correlations support this, the presence of two protonated species visible in the HPLC of the silyl enol ether indicate that diastereoisomeric protonations can occur in the presence of acid (i.e. **13** and **14**). This is the minor of those two species and so would be consistent with protonation from the most hindered position. Conceivably, the material could be consistent with addition of the methyl group to C-16 with a β-orientation.
Band 2 (24.2 mg): Analysis indicated a 61:32 mixture of **11** and **14**.
Band 3 (47.8 mg): This material was still somewhat crude but with one major component. Analysis indicated a $m/z = 415$ amu which indicated extra oxidation. The minor components were $m/z = 399$ and isomeric with main product. The NMR data indicated the extra oxygen to be present as a 9α,11α-epoxide. The corresponding 9β,11β-epoxide (**1**) is known and the NMR is not consistent with this. An NoE interaction with 7β-H indicated a β-orientation of 11-H and hence the α-orientation of the oxygen implying structure **12**.
Band 4 (11.5 mg): Analysis indicated a mixture of two compounds in a ratio of 29:64 with corresponding masses of 373/415 amu. The more massive (major component) is isomeric with **12** and so was tentatively assigned as the C-17 epimer, **15**. The minor component is concordant with and tentatively assigned as **16**.

*2.2.4. Alkene analogue **18***

Copper(II) chloride (0.246 g, 1.829 mmol) was slurried in tetrahydrofuran (40.0 mL) and cooled to <3 °C. A tetrahydrofuran solution of methyl magnesium chloride (3 M, 1.590 mL, 4.77 mmol) was added to the chilled slurry over 3 min keeping the contents <3 °C. The slurry was cooled to −5 °C. A slurry of **17** (4.03 g, 13.07 mmol) in tetrahydrofuran (30.0 mL) was added over 1 min keeping the contents <1 °C. Trimethylchlorosilane (3.34 mL, 26.1 mmol) was added in one portion. More tetrahydrofuran solution of methyl magnesium chloride (3 M, 5.44 mL, 16.33 mmol) was added drop wise over 28 min keeping the contents <2.5 °C. After 25 min, the reaction was quenched with triethylamine (4.10 mL, 29.4 mmol) followed by saturated aqueous ammonium chloride (20 mL). This addition was highly exothermic (0–23 °C). Water (10 mL) was added to dissolve the solids and the quenched mixture was stirred vigorously for at least 30 min. The layers were separated and the blue aqueous layer was extracted with heptane (2 × 12 mL). The organic layers were dried through sodium sulfate and concentrated to dryness to give intermediate silyl enol ether (5.55 g). ^{1}H NMR analysis indicated one major component that appeared to be consistent with the silyl enol ether. The crude silyl enol ether was dissolved in dichloromethane (40.0 mL) and cooled to <3 °C. A solution of peracetic acid in acetic acid (32%, 2.71 mL, 13.07 mmol) was added drop wise over 4 min keeping the contents <3.5 °C. After 50 min, more peracetic acid solution in acetic acid (32%, 0.678 mL, 3.27 mmol) was added in one portion and the mixture was allowed to warm to ambient temperature. After 105 min the reaction was quenched with hydrochloric acid (2 N, 12 mL) and stirred vigorously for 15 min. The organic layer was washed with 25% aqueous potassium carbonate solution (12 mL) and concentrated to dryness to give a pale yellow gum. The gum was triturated with acetone (8 mL) and stirred at ambient temperature. The solids were collected by filtration and washed with acetone (2 mL) and sucked dry to give **18** (1.982 g, 44%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (d, $J = 10.3$ Hz, 1H, 1-H), 6.24 (dd, $J = 10.3$ and 1.7 Hz, 1H, 2-H), 6.03 (s, 1H, 4-H), 5.50 (d, $J = 5.9$ Hz, 1H, 11-H), 2.95–3.13 (m, 1H), 2.87 (s, 1H), 2.64 (dd, $J = 13.7$ and 3.9 Hz, 1H), 2.52–2.61 (m, 1H), 2.04–2.43 (m, 3H), 2.23 (s, 3H, 21-H3), 1.86 (dd, $J = 19.8$ and 10.3 Hz, 1H), 1.35–1.78 (m, 3H), 1.38 (s, 3H, 19-CH_3), 1.18 (ddd, $J = 26.2$, 13.0 and 4.4 Hz, 1H), 0.90 (d, $J = 7.1$ Hz, 3H, 16-CH_3), 0.78 (s, 3H, 18-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.5, 186.3, 166.8, 154.6, 142.6, 127.2, 123.7, 120.6, 90.6, 48.0, 47.4, 45.9, 36.6, 36.4, 34.7, 33.5, 32.6, 32.2, 27.6, 26.7, 15.4, 14.5.

The liquors were analysed by TLC. Concentrated liquors (~580 mg) were purified by prep-TLC (Macherey–Nagel SIL G-200 UV254 plates; 20 × 20 cm × 2 mm) eluted with 1:1 v/v ethyl acetate/heptane. Bands corresponding to Spots 3, 4 and 6 were scraped off and put into a Bond Elut filter. For each band, the material was extracted with ethyl acetate (25 mL) followed by 1:1 v/v ethyl acetate/dichloromethane (25 mL). The filtrates were concentrated to dryness. The residues were dissolved in dichloromethane, filtered through cotton wool and re-concentrated to give **20** (79.1 mg) as a colourless foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.15 (d, $J = 10.3$ Hz, 1H, 1-H), 6.25 (dd, $J = 10.3$ and 1.7 Hz, 1H, 2-H), 6.05 (s, 1H, 4-H), 5.47 (m, 1H, 11-H), 2.57–2.69 (m, 1H), 2.37–2.45 (m, 1H), 2.10–2.37 (m, 4H), 2.21 (s, 3H, 21-H3), 1.96 (dd, $J = 19.8$ and 9.8 Hz, 1H), 1.69–1.88 (m, 3H), 1.52–1.63 (m, 2H), 1.41 (s, 3H, 19-CH_3), 1.12–1.25 (m, 1H), 0.99 (s, 3H, 18-CH_3), 0.95 (d, $J = 7.1$ Hz, 3H, 16-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 212.4, 186.2, 166.5, 154.4, 143.7, 127.3, 123.9, 120.4, 92.9, 46.8, 46.1, 45.9, 37.4, 34.5, 34.3, 33.0, 32.1, 30.3, 29.7, 26.7, 14.8, 14.2.

Also isolated was crude **19** (19.9 mg) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$, relevant peaks for identification only): δ 7.16 (d, $J = 10.3$ Hz, 1H, 1-H), 6.27 (m, 1H, 2-H), 6.05 (s, 1H, 4-H), 5.50 (d, $J = 5.6$ Hz, 1H, 11-H), 2.11 (s, 3H, 21-H3), 1.38 (s, 3H, 19-CH_3), 0.94 (d, $J = 6.8$ Hz, 3H, 16-CH_3), 0.64 (s, 3H, 18-CH_3).

*2.2.5. Epoxide analogue **22***

Copper(II) chloride (24.08 mg, 0.179 mmol) was slurried in tetrahydrofuran (4.5 mL) and cooled to <3 °C. A tetrahydrofuran solution of methyl magnesium chloride (3 M, 0.156 mL, 0.467 mmol) was added to the chilled slurry over 3 min keeping the contents <3 °C. A slurry of **21** (415.1 mg, 1.279 mmol) in tetrahydrofuran (3.38 mL) was added over 1 min keeping the contents <3.5 °C. Trimethylchlorosilane (0.327 mL, 2.56 mmol) was added in one portion. More tetrahydrofuran solution of methyl magnesium chloride (3 M, 0.533 mL, 1.599 mmol) was added drop wise over 24 min keeping the contents <3.5 °C. After a further 21 min the reaction was quenched with triethylamine (0.401 mL, 2.88 mmol) followed by saturated aqueous ammonium chloride (2 mL). Water (1 mL) was added to dissolve the solids and the quenched mixture was stirred vigorously for at least 30 min. The layers were separated and the blue aqueous layer was extracted with heptanes (2 × 3 mL). The organic layers were dried through sodium sulfate and concentrated to dryness to give intermediate silyl enol ether (513.3 mg). ^{1}H NMR analysis indicated one major component that appeared to be consistent with the silyl enol ether. The crude silyl enol ether was dissolved in dichloromethane (4.50 mL) and cooled to <3 °C. A solution of peracetic acid in acetic acid (32%, 0.269 mL, 1.279 mmol) was added drop wise over 10 min keeping the contents <3.5 °C. After 1 h, more peracetic acid solution in acetic acid (32%, 0.054 mL, 0.813 mmol) was added in one portion and the mixture was allowed to warm to ambient temperature. After 20 min the reaction was quenched with aqueous hydrochloric acid (2 N, 7 mL) and stirred vigorously for 20 min. The organic layer was washed with aqueous potassium carbonate solution (25%, 10 mL) and concentrated to dryness to give a pale yellow solid. The solid was slurried in acetone (2 mL) and heated to reflux. The resultant

slurry was allowed to cool to ambient temperature and the solids were collected by filtration, washed with acetone (0.5 mL) and sucked dry to give **22** (262.3 mg, 57%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.58 (d, J = 10.0 Hz, 1H, 1-H), 6.17 (dd, J = 10.0 and 1.7 Hz, 1H, 2-H), 6.13 (s, 1H, 4-H), 3.19 (s, 1H, 11-H), 2.95–3.18 (m, 1H), 2.90 (s, 1H), 2.60–2.71 (m, 1H), 2.17–2.54 (m, 4H), 2.22 (s, 3H, 21-H3), 1.76–1.88 (m, 1H), 1.28–1.70 (m, 4H), 1.43 (s, 3H, 19-CH_3), 1.00 (s, 3H, 18-CH_3), 0.86 (d, J = 7.1 Hz, 3H, 16-CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 211.1, 185.9, 164.8, 152.0, 128.0, 125.1, 90.3, 66.2, 62.9, 48.0, 47.9, 44.1, 35.3, 34.1, 33.6, 30.5, 29.7, 29.1, 27.7, 23.7, 18.3, 14.6.

*2.2.6. Bromoformate **23***

Tetraene **7** (5.08 g, 13.86 mmol) was slurried in *N,N*-dimethylformamide (17.5 mL). Perchloric acid (70%, 0.536 mL, 6.24 mmol) was added and an exotherm from ca 20 to 27 °C was noted. The mixture was allowed to cool to ambient temperature again. 1,3-Dibromo-5,5-dimethylhydantoin (DBH, 3.37 g, 11.78 mmol) was added in one portion. After an initiation period of ca 30 s, an exotherm to 35 °C occurred with dissolution of the solids. After stirring overnight, additional 1,3-dibromo-5,5-dimethylhydantoin (0.24 g, 0.839 mmol) was added in one portion. After stirring for an additional 6 h, water (50 mL) was added drop wise over 26 min and the generated slurry was aged overnight. The solids were collected by filtration, washed twice with water (50 mL) and dried under vacuum overnight to give **23** (6.72 g, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (s, 1H), 6.78 (d, J = 10.0 Hz, 1H, 1-H), 6.73 (m, 1H, 16-H), 6.31 (dd, J = 10.0 and 1.7 Hz, 1H, 2-H), 6.07 (s, 1H, 4-H), 5.87 (s, 1H, 11-H), 5.03 (d, J = 16.1 Hz, 1H, 21-H), 4.83 (d, J = 16.1 Hz, 1H, 21-H′), 2.20–2.70 (8H, m), 2.15 (s, 3H, 21-OAc), 1.68–1.95 (m, 2H), 1.60 (s, 3H, 19-CH_3), 1.16 (s, 3H, 18-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.0, 185.6, 170.3, 164.2, 158.8, 152.2, 150.5, 143.0, 129.8, 125.4, 83.3, 75.0, 65.4, 49.7, 49.5, 46.1, 36.8, 35.1, 32.1, 30.4, 28.3, 24.7, 20.4, 18.5; HRMS (ESI): m/z calcd for $C_{24}H_{27}BrO_6$ (M+H)+, 491.1064; found, 491.1056.

*2.2.7. Epoxide **24***

Bromoformate **23** (1.50 g, 3.05 mmol) was slurried in acetone (22.5 mL) and the mixture was heated to 46 °C. Aqueous potassium carbonate (25%, 6.75 mL, 12.21 mmol) was added and a small endotherm to 40 °C occurred. The stirrer was stopped and the two layers were allowed to settle. The lower aqueous layer was removed by pipette and then the organic layer was allowed to cool to ambient temperature with stirring. When the contents had reached ambient temperature a fine precipitate had formed. The slurry was concentrated at ambient temperature under reduced pressure to a volume of about 5 mL. The solids were collected by filtration, washed with acetone (3 mL) and sucked dry to give **24** (0.62 g, 53% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.66 (d, J = 1.5 Hz, 1H, 16-H), 6.60 (d, J = 10.0 Hz, 1H, 1-H), 6.17 (dd, J = 10.0 and 1.7 Hz, 1H, 2-H), 6.13 (s, 1H, 4-H), 4.95 (d, J = 16.1 Hz, 1H, 21-H), 4.86 (d, J = 16.0 Hz, 1H, 21-H′), 3.12 (s, 1H, 11-H), 2.60–2.80 (m, 2H), 2.30–2.55 (m, 4H), 2.15 (s, 3H, 21-OAc), 2.01–2.14 (m, 1H), 1.33–1.70 (m, 3H), 1.46 (s, 3H, 19-CH_3), 1.09 (s, 3H, 18-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.0, 186.1, 170.4, 164.7, 152.3, 152.0, 141.9, 127.9, 125.2, 77.4, 66.9, 65.5, 61.7, 45.0, 44.2, 35.3, 33.3, 32.4, 29.3, 28.8, 23.8, 20.5, 18.6; HRMS (ESI): m/z calcd for $C_{23}H_{27}O_5$ (M+H)+, 383.1853; found, 383.1849.

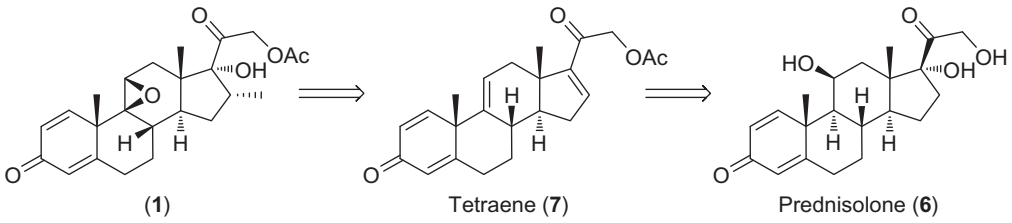
*2.2.8. 17α,21-Dihydroxy-9β,11β-epoxy-16α-methylpregna-1,4-diene-3,20-dione 21-acetate **1***

Copper(II) chloride (0.025 g, 0.183 mmol) was slurried in tetrahydrofuran (5.0 mL) and cooled to <3 °C. A tetrahydrofuran solution of methyl magnesium chloride (3 M, 0.159 mL, 0.477 mmol) was added to the chilled slurry over 1 min keeping the contents <3 °C. A solution of epoxide **24** (0.4996 g, 1.306 mmol) in tetrahydrofuran (3.75 mL) was added to the resulting mixture over 2 min keeping the contents <3 °C. Trimethylchlorosilane (0.334 mL, 2.61 mmol) was added in one portion followed by more tetrahydrofuran solution of methyl magnesium chloride (3 M, 0.544 mL, 1.633 mmol), which was added drop wise over 30 min keeping the contents <2.5 °C. After 75 min, the reaction was quenched with triethylamine (0.41 mL, 2.94 mmol) followed by saturated ammonium chloride (2.5 mL). This addition was highly exothermic (0–23 °C). Water (1.5 mL) was added to dissolve the colourless solids and the quenched mixture was stirred vigorously for at least 30 min. The layers were separated and the blue aqueous layer was extracted with heptane (2 × 2 mL). The organic layers were dried over sodium sulfate and concentrated to dryness to give intermediate crude silyl enol ether (0.6768 g). ^{1}H NMR analysis indicated one major component that was consistent with the silyl enol ether. The crude silyl enol ether was dissolved in dichloromethane (5 mL) and cooled to <3 °C. A solution of peracetic acid in acetic acid (32%, 0.271 mL, 1.306 mmol) was added drop wise over 7 min keeping the contents <4 °C and the mixture was allowed to warm to ambient temperature. After stirring for 18 h the reaction was quenched with aqueous hydrochloric acid (2 N, 1.5 mL) and stirred vigorously for 15 min. Stirring was stopped and the layers were separated. The organic layer was washed with aqueous potassium carbonate (25%, 2.0 mL) and concentrated to dryness to give a yellow foam. *tert*-Butylmethyl ether (3 mL) was added and the mixture was sonicated to cause crystallisation. The slurry was aged at ambient temperature for 1 h. The solids were collected by filtration and washed with *tert*-butylmethyl ether (1 mL) and sucked dry to give **1** (254.5 mg, 47% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.59 (d, J = 10.0 Hz, 1H, 1-H), 6.19 (dd, J = 10.0 and 1.7 Hz, 1H, 2-H), 6.14 (s, 1H, 4-H), 5.02 (d, J = 17.1 Hz, 1H, 21-H), 4.83 (d, J = 17.1 Hz, 1H, 21-H′), 3.21 (s, 1H), 2.88–3.10 (m, 1H), 2.60–2.71 (m, 1H), 2.43–2.53 m, 1H), 2.28–2.39 (m, 2H), 2.18–2.27 (m, 1H), 2.15 (s, 3H, 21-OAc), 1.76–1.88 (m, 2H), 1.25–1.67 (m, 4H), 1.43 (s, 3H, 19-CH_3), 0.93 (s, 3H, 18-CH_3), 0.88 (d, J = 7.3 Hz, 3H, 16-CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.5, 186.0, 170.6, 164.8, 152.1, 128.0, 125.1, 90.5, 67.4, 66.0, 62.7, 48.1, 47.6, 44.1, 35.3, 34.2, 33.2, 30.4, 29.9, 29.1, 23.7, 20.4, 17.3, 14.4; HRMS (ESI): m/z calcd for $C_{24}H_{31}O_6$ (M+H)+, 415.2115; found, 415.2110.

3. Results and discussion

We envisaged a retrosynthesis of **1** *via* key tetraene **7** back to prednisolone **6**, Scheme 1. In a forward sense, the conversion of **6** to **7** requires simple dehydration of the two alcohol groups at C-11 and C-17 to generate alkenes. Although this conversion appears trivial, we have found no reports of the direct double dehydration of **6**, or a C-21 protected analogue, to give a $\Delta^{1,4,9(11),16}$-tetraene steroid. The forward conversion of **7** to **1** requires formation of a $\Delta^{9,11}$-epoxide and conjugate addition of a methyl group followed by oxidation at C-17. This sequence could conceivably be performed in two different orders.

Dehydration of steroidal alcohols is typically achieved by a direct dehydration step or a two-step sequence of activation followed by elimination. The former can be achieved by treatment with thionyl chloride or phosphorus oxychloride in combination with pyridine [6] or *N,N*′-sulfinyl diimidazole [7]. The second approach is usually initiated by activation with methanesulfonyl chloride or *p*-tolunesulfonyl chloride followed by base induced elimination [8]. Additionally, acetates of steroidal alcohols at C-17 can be treated with potassium acetate in DMF at high temperatures to provide the required $\Delta^{16,17}$-alkene [9]. Of critical importance for our synthesis of **1** was the necessity for the alcohol



Scheme 1. Retrosynthesis of 17α,21-dihydroxy-9β,11β-epoxy-16α-methylpregna-1,4-diene-3,20-dione 21-acetate **1** to Prednisolone **6**.

functionality at C-21 to be retained throughout the sequence. It was anticipated that this would require suitable use of a protecting group during the synthetic sequence.

We found that activation of the C-11 hydroxyl and elimination of the activated group was very facile but that activation of the C-17α-hydroxyl was more problematic. Placement of a mesyl group on the hydroxyl was not achievable using forcing conditions. We were able to repeat the work of Salce and co-workers [9] through preparation of prednisolone triacetate and elimination of the 17α-acetate to provide a $\Delta^{16,17}$-alkene. No elimination of the 11β-acetate was observed so this method was not suitable for rapid formation of **7**. It is likely that the 11β-acetate is unable to achieve the correct orientation to enable a *syn*-elimination.

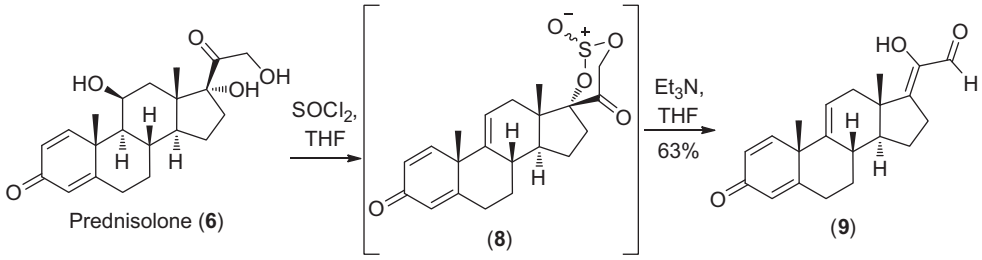
We found that treatment of six with three equivalents of thionyl chloride led to formation of two disatereoisomers of a cyclic sulfite 8, as judged by LCMS. It was not clear whether the 11β-hydroxyl group had been eliminated under the reaction conditions or under the conditions of the LCMS analysis. Upon treatment with 15.5 equivalents of triethylamine, these rapidly provided the Mattox rearrangement product 9 in a moderate, but unoptimised yield, Scheme 2. The Mattox rearrangement is typically carried out under acidic conditions upon the parent dihydroxyacetone structure of the corticosteroid [10]. The same rearrangement product has also been produced from 17,21-diesters of corticosteroids under basic conditions [11]. While providing a versatile method of functionalizing the D-ring of steroids and the side chain attached to C-17, the Mattox rearrangement has not been extensively used in synthesis.

The proposed mechanisms for the classical Mattox rearrangement of dihydroxyacetone structures and the base-mediated rearrangement of di-esters of these structures differ subtly. Mattox proposed a number of possible mechanisms all relying on enolisations and eliminations of water although he was unable to determine the precise order of events [10]. Li and co-workers showed that both esters were required in their work and proposed an enolisation-hydrolysis-elimination pathway for the rearrangement in basic conditions [11]. The thionyl chloride-triethylamine rearrangement described above offers an additional potential mechanism, Scheme 3, whereby the cyclic sulfite undergoes a pericyclic rearrangement with extrusion of sulfur dioxide. This potential mechanism is precluded from the other reported rearrangements.

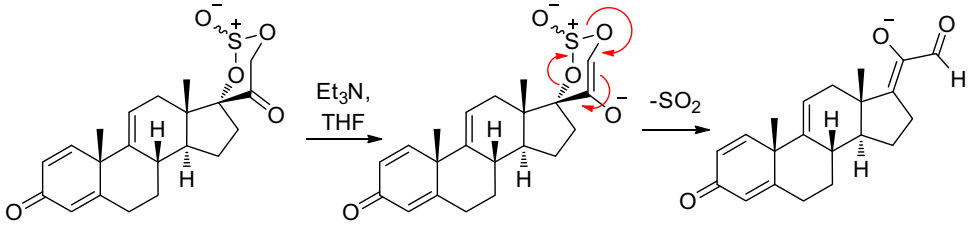
With Mattox rearrangement product **9** in hand we were able to convert this rapidly to the desired tetraene **7**, Scheme 4. Acylation of **9** provided the enolacetate **10** which was immediately rearranged under nucleophilic catalysis to **7** in 85% yield.

At this junction, progression of **7** to **1** requires three fundamental changes: epoxidation of the $\Delta^{9,11}$-olefin, conjugate addition of a methyl group to C-16 and oxidation of C-17. The latter two of these are commonly combined into a single reaction sequence. The precise ordering of the transformations was something that offered flexibility to the synthesis although the optimum way forward was not clear at the outset. As a consequence, we elected to study both approaches to **1** to identify the most efficient pathway.

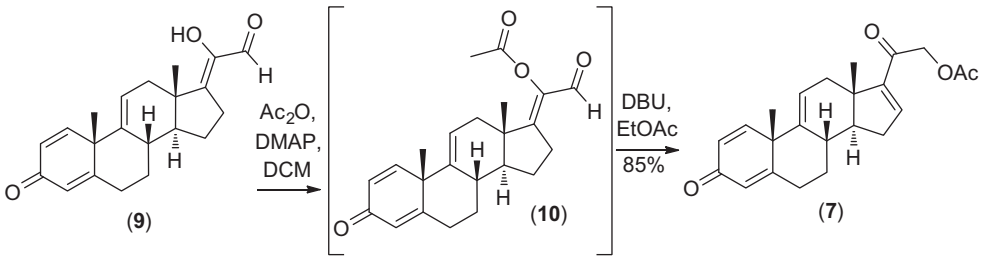
We initially chose to examine the copper-catalysed addition of a methyl Grignard reagent to **7**, followed by trapping of the resultant enolate as the trimethylsilylenol ether. Unfortunately, peracetic acid mediated oxidation of the silylenol ether derived from **7** gave an intractable mixture of compounds containing only small amounts of **11**. Attempted purification of the mixture failed to generate any single purified compound, yet tentative structural assignments could be made which indicated significant over oxidation to compounds containing a 9α,11α-epoxide, **12** and **16**. An additional



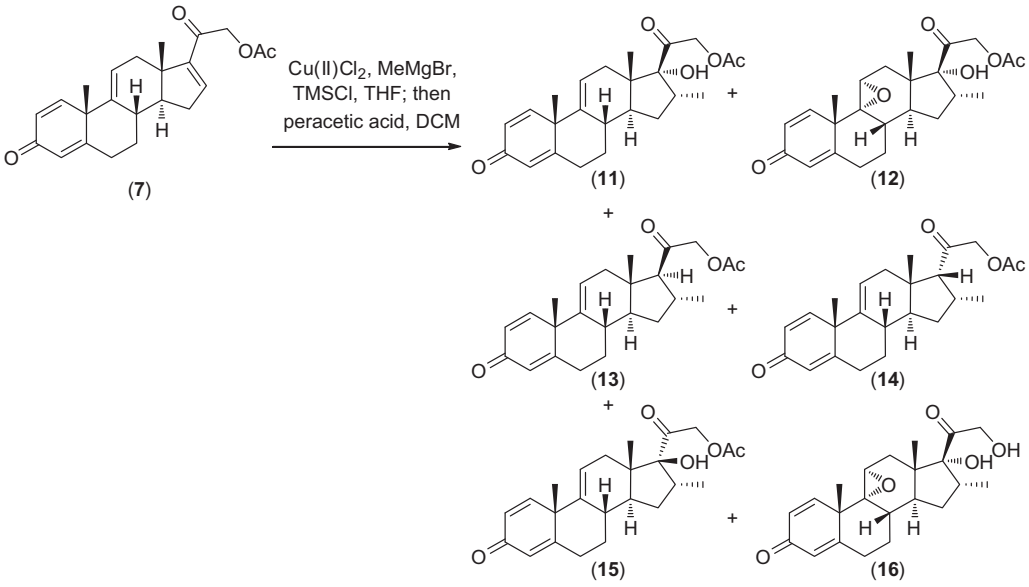
Scheme 2. One pot Mattox rearrangement and elimination.



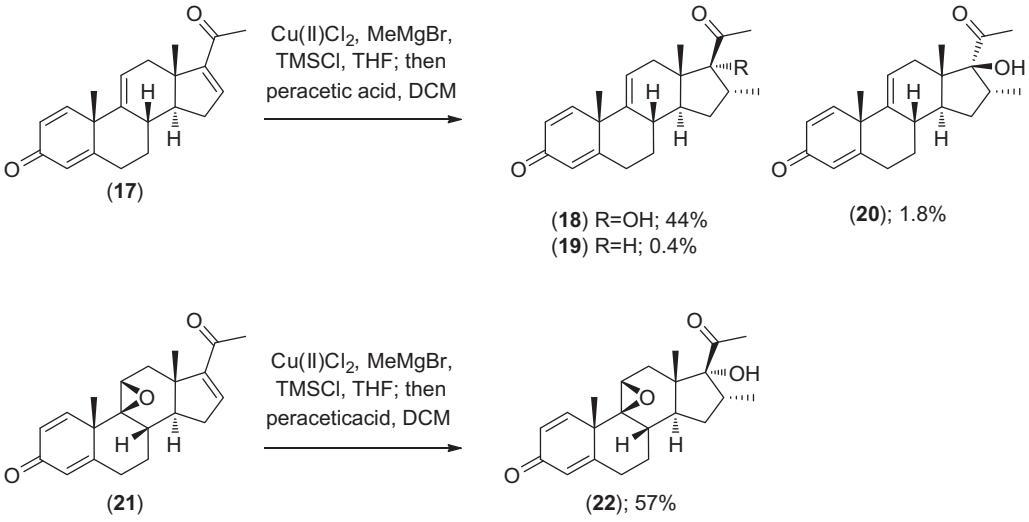
Scheme 3. Potential pericyclic mechanism for Mattox rearrangement of cyclic sulfites.



Scheme 4. Rearrangement of Mattox product **9** to tetraene **7**.



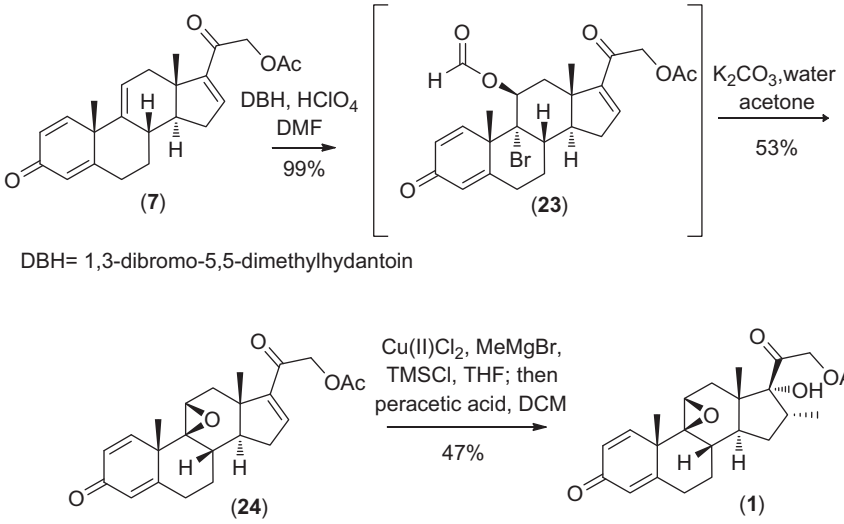
Scheme 5. Unsuccessful conversion of **7** to alkene **11**.



Scheme 6. Conjugate addition–oxidation of simpler analogues **17** and **21**.

C-17-epimer of this product **15** was also detectable and products that were protonated at C-17 rather than oxidized, both on the α- and β-faces could be detected, **13** and **14**, Scheme 5.

This unexpected difficulty prompted study of a simpler model system using 9,11-alkene analogue **17**, which underwent clean methyl Grignard addition to C-16 and trapping of the corresponding trimethylsilyl enol ether as a single diastereomer. For this analogous silyl enol ether the rate of oxidation with peracetic acid was more rapid, compared to **7**, due to the lack of steric crowding of the silyl enol ether moiety by the C-21 acetoxy group. Again, though, clean oxidation was not observed resulting in a number of products, including the expected product **18** along with



Scheme 7. Completion of the synthesis of **1**.

small quantities of the C-17 protonated compound **19**, the 17,21-dihydroxylated product [12] and, surprisingly, the C-17 β -hydroxylated product **20**, Scheme 6.

At this point, we turned our attention to the functionalisation of steroids bearing a 9,11-epoxide. Initially we looked at the reaction of **21**. This 9,11-epoxide analogue underwent clean methyl Grignard addition to C-16 and trapping of the corresponding trimethylsilyl enol ether followed by clean Rubottom oxidation to provide **22**, Scheme 6. This pleasing result was in stark contrast to the results seen with **7** and **17**.

Finally we looked at application to the system that would prepare **1**. Formation of epoxide **24** was achieved *via* the intermediacy of bromoformate **23**, which was isolated as a damp filter cake, Scheme 7. Copper-catalysed Grignard addition was followed by trapping of the resultant enolate as the trimethylsilylenol ether, which underwent clean oxidation with peracetic acid providing **1** without other impurities and allowing isolation by crystallisation in modest yield, Scheme 7.

This striking difference in reactivity between the 9,11-alkene substrates **7** and **17** and 9,11-epoxide substrates **21** and **24** was unexpected at the start of this endeavour. Molecular models do not provide much insight into the divergent reactivity seen upon silyl enol ether oxidation for the $\Delta^{9,11}$-alkenes and 9β,11β-epoxides. The introduction of the additional ring of the epoxides would be anticipated to introduce additional strain as a complicating factor. Despite the ambiguity of the origin of the divergent behavior, it is readily apparent that addition of substituents to C-16 and oxidation of C-17 is more favourable for the epoxide substrates. The copper catalysed Grignard addition-C-17 oxidation sequence has been described in the patent literature previously for a range of substrates [13], although in these instances the oxidizing agent was 3-chloroperbenzoic acid.

In conclusion, we have demonstrated a rapid synthesis of **1** from prednisolone in six steps and 13% yield without process optimisation. Highlights include the development of novel conditions for effecting a Mattox rearrangement of prednisolone and extensive knowledge generation on substituent effects on C-17 oxidation of silyl enol ethers. The Mattox rearrangement conditions constitute the first example of double dehydration of prednisolone.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.steroids.2013.09.008.

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