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Kilogram-Scale Synthesis of an Inhaled Corticosteroid†

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Supporting Information

ABSTRACT: The development and implementation of a safe and scalable process for the manufacture of corticosteroid PF-4714224 (**1**) is described. Initial routes used to synthesise analogues from this series directly from fluocinolone acetonide (**2**) were unsuitable for large-scale use. Key aspects of the route are the efficient and simple method for the preparation of the steroid tetraol (**6**), acetal formation by reaction of the tetraol with a bisulphite adduct (**12**), and isolation of the product by sequential recrystallisations.

INTRODUCTION

Inhaled corticosteroids, such as fluticasone propionate, are widely used as treatments for asthma.[1] As part of a project to identify agents with an improved therapeutic index, a series of acetals of fluocinolone were investigated of which PF-4714224 (**1**)[2] was selected for preclinical development requiring a kilogram-scale supply of material.

The medicinal chemistry route to early analogues proceeded directly from commercially available fluocinolone acetonide (**2**) by transacetalisation, catalysed by perchloric acid[3] (Scheme 1). Whilst suitable for rapid analogue provision on small scale, this method was unsuitable for larger-scale use for a number of reasons; the addition of sand was required to prevent the products from forming intractable gums under reaction conditions, the use of perchloric acid, a powerful oxidizing agent, represented an unacceptable safety hazard on scale, and the isolated yield was low. In addition, considerable difficulties were presented in purifying a poorly soluble, crude reaction product containing both epimers of the product and the acetonide starting material **2**.

DISCUSSION

Reaction of aldehydes with the steroid tetraol fluocinolone (**6**) was found to proceed smoothly and to give a cleaner reaction profile (Scheme 2) than reaction with the acetonide **2**, giving the product as a mixture of α- and β-epimers. The epimers could be separated by chromatography, and any residual tetraol was more readily separated by chromatography than the acetonide.

The reported route to the tetraol **6** uses formic acid to solvolyse the acetonide **2** to a mixture of formate esters which are then cleaved by methanolic potassium hydroxide[4] (Scheme 3). However, the need for strict exclusion of oxygen from the second step (to avoid oxidative cleavage of the hydroxyl-ketone moiety to a carboxylate), led the process team to explore alternatives to this method. Hydrolysis using dilute hydrochloric acid (7:3 ration of cHCl:H_2O, at ambient temperature) gave the tetraol in good yield (82%) but progress was hampered by the apparent instability of the tetraol to acidic reaction conditions and the need to very closely monitor the reaction progress in order to avoid degradation of the product. Simple acidic conditions were investigated to directly hydrolyse the acetonide **2** to the tetraol **6**. A range of aqueous acids (including H_2SO_4, HCl, and HBF_4) and the use of *n*-butanol, 2-methyltetrahydrofuran and isopropyl alcohol as cosolvents were investigated in an effort to achieve a homogeneous reaction mixture with the potential for a direct-drop isolation. The apparent instability to acidic reaction conditions was observed during most of the hydrolysis reactions screened; for example, the highest conversion to product observed during the screening process was only 55% when using conc. H_2SO_4 (10 equiv) in 50% aqueous isopropyl alcohol.

Efficient conversion to product was achieved by heterogeneous acetonide hydrolysis in 48% aqueous HBF_4;[5] under these conditions both starting material and product were poorly soluble, but conversion proceeded smoothly, and the desired tetraol was provided without the need for exclusion of oxygen. Dilution with water upon completion of the reaction and collection of the product by filtration followed by washing with ethyl acetate gave clean tetraol **6** in good yield (Scheme 3). Further optimisation of this step allowed reaction volumes to be driven down to 5 mL per gram of feed acetal. In contrast to the hydrochloric acid conditions previously employed, this method gave a very stable reaction mixture with no significant degradation even when workup was delayed for several days.

Optimisation of the acetal-forming reaction between fluocinolone tetraol **6** and aldehyde **3** (used as a representative example of this series) identified the use of 3 or more equivalents of trifluoromethanesulphonic (triflic) acid, in the presence of dried magnesium sulphate, in dioxane, as improved conditions for this step (Scheme 4).[6] Weaker acids such as trifluoroacetic or sulphuric acid failed to give product under any conditions investigated; conversion to product was only observed when using very strong acids. Additionally, the presence of a drying agent such as dried sodium sulphate or magnesium sulphate was found to be essential; the use of triflic acid in the absence of drying agent gave very low conversion and a very messy reaction profile. Whilst dioxane is not the ideal solvent for large-scale chemistry, due to safety concerns, these reaction conditions were workable for multigram-scale preparation of **1** and analogues of **1**. The use of sodium or magnesium sulphate as a solid drying agent additionally served to maintain a mobile reaction mixture, replacing sand and

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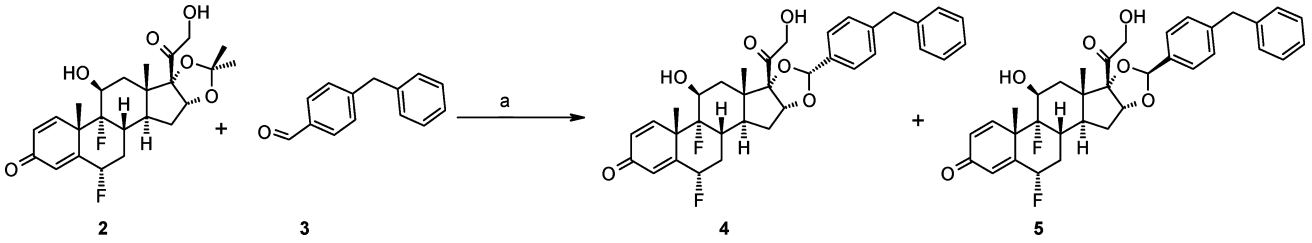
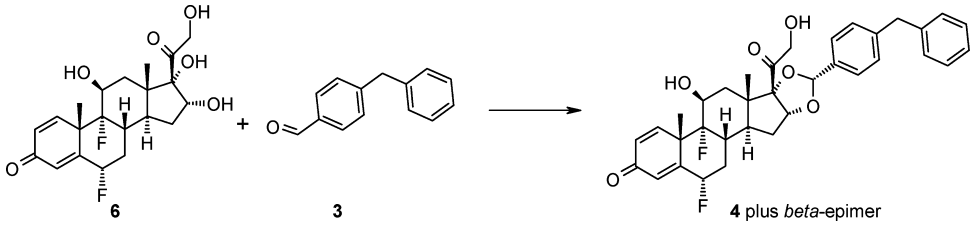
Scheme 1. Transacetalisation route to 4[a]



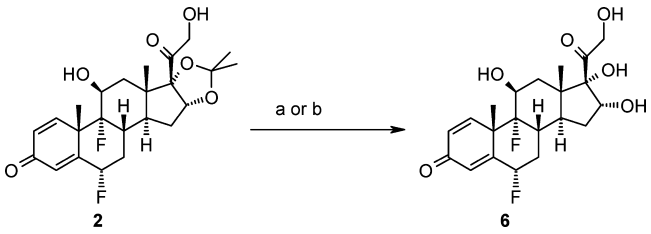
[a]**Reagents and conditions:** $HClO_4$, PhMe, sand, ambient temperature, 18 h, 44%.

Scheme 2. Preparation of 4 by reaction of aldehyde and tetraol[a]



[a]**Reagents and conditions:** $HClO_4$, DCM, ambient temperature, 36%.

Scheme 3. Routes to steroid tetraol 6[a]



[a]**Reagents and conditions:** (a) (i) 60% $HCO_2H_{(aq)}$, reflux; (ii) KOH, MeOH, ambient temperature, 63% (over two steps); (b) 48% $HBF_{4\ (aq)}$, ambient temperature, 94%.

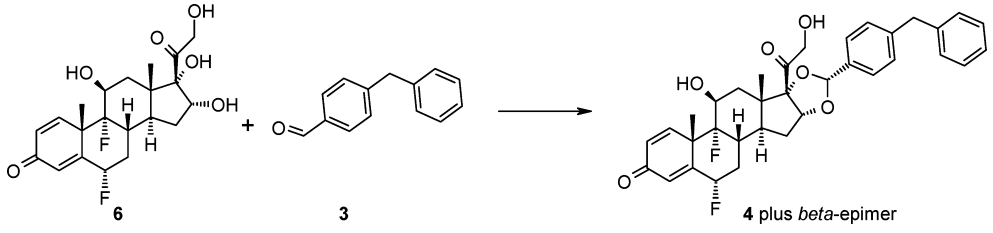
avoiding the scouring action on laboratory glassware observed when sand was used. With the use of these reaction conditions, a number of analogues of **1** were prepared;[2] in each case the crude reaction mixture contained both epimers with α-epimer predominating.

Efforts were made to move towards chemical routes suitable for large-scale use prior to candidate nomination arising from close collaboration between the medicinal chemistry and research-API (process chemistry) groups. In light of the need to progress the project rapidly to clinical assessment, work was carried out, prior to the identification of the candidate molecule, to identify features of the route likely to cause difficulties and safety concerns upon scale-up.

PF-4714224 (**1**) was identified as the project lead and subsequently as a development candidate. The aldehyde fragment (**10**) required for the preparation of **1** was initially prepared by the homogeneous reaction of commercially available 4-fluorobenzaldehyde with the known 3-methylthiothiophenol (**8**),[7] itself prepared by the reported alkylation of 1,3-benzenedithiol (**7**) with dimethyl sulphate (Scheme 5). Acetal formation to give **1** by reaction of **6** and aldehyde **10** using the project conditions and reaction in dioxane in the presence of triflic acid and magnesium sulphate gave the product in 18% yield following an unoptimised isolation procedure (Scheme 6).

Further optimisation of the acetal formation was carried out by automated screening[8] of a range of solvents and of reagent stoichiometries, using the aldehyde **10** and tetraol **6** (Table 1). Acetonitrile was identified as a suitable reaction solvent, being less hazardous than dioxane and giving equivalent results. Substituting dimethoxyethane for acetonitrile gave similar results but a range of other solvents screened (including tetrahydrofuran, 2-methyltetrahydrofuran, propionitrile, *N*-methylpyrrolidinone and dimethylsulphoxide) gave either poorer conversion or a more complicated reaction profile. A small excess of aldehyde was found to be required for full conversion of the tetraol to product, no improvement in

Scheme 4. Improved conditions for preparation of 4 by reaction of aldehyde and tetraol[a]



[a]**Reagents and conditions:** CF_3SO_3H, dioxane, $MgSO_4$, ambient temperature, 46%.

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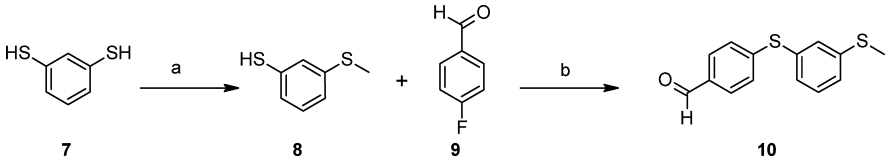
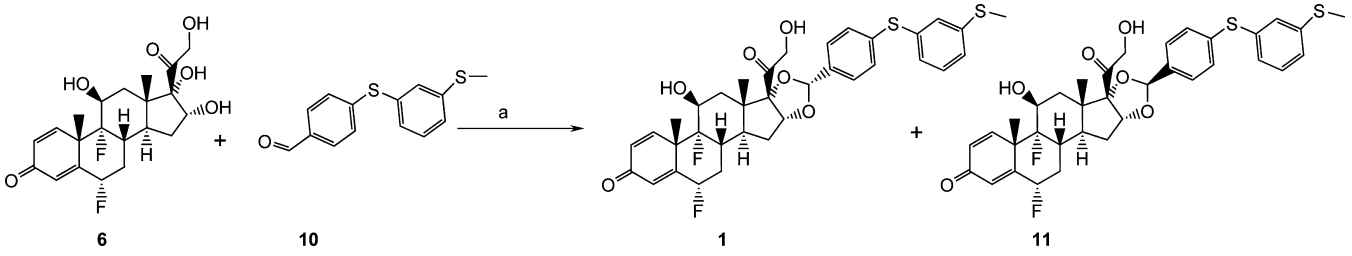
Scheme 5. Preparation of aldehyde 10, medicinal chemistry route[a]



[a]**Reagents and conditions:** (a) Me_2SO_4, H_2O, 0 °C (used without isolation); (b) K_2CO_3, MeCN, ambient temperature, 86%.

Scheme 6. Preparation of 1 by medicinal chemistry route[a]



[a]**Reagents and conditions:** CF_3SO_3H, dioxane, $MgSO_4$, ambient temperature, **1** isolated in 18% yield (note, crude reaction product was a mixture of 1:11 in ration of approximately 87:13).

Table 1. Optimisation of acetal formation (reaction of aldehyde 10 with tetraol 6)

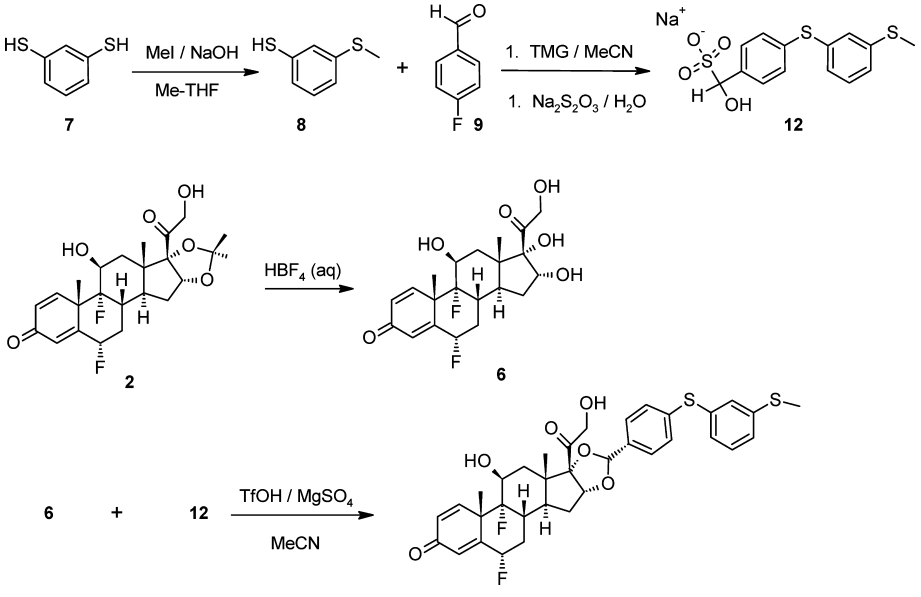
aldehyde (equiv)	solvent	$MgSO_4$ (equiv)	TfOH (equiv)	temp (°C)	conversion (%)[a]
1.0	MeCN	3	5	20	98
1.2	MeCN	3	5	20	100
1.5	MeCN	3	5	20	99
1.2	MeCN	5	1	20	28
1.2	MeCN	5	2	20	52
1.2	MeCN	5	3	20	66
1.2	MeCN	5	4	20	95
1.2	MeCN	5	5	60	58
1.2	MeCN	5	5	20	100

[a]Reactions were sampled after 2 h. Reaction screening was carried out on 20-mg scale and monitored by HPLC.

reaction rate or profile was observed when increasing this beyond 1.3 equiv. The quantity of triflic acid used was varied between 1 and 5 equiv. When using less than 3 equiv of acid the reaction slowed significantly, taking 4−5 h to reach maximum conversion, but the quantity of product produced did not match that generated when a larger excess was used. The quantity of magnesium sulphate used was found to be less critical with 3 or 5 equiv performing equally well. Given the low cost and hazards associated with this reagent and the ease of its removal during workup, no further variation of this quantity was explored. When applied on gram-scale, the optimized reaction conditions employing 3 equiv of trifilic acid, 5 equiv of magnesium sulphate, and 1.3 equiv of aldehyde **10** relative to tetraol **2**, in acetonitrile at ambient temperature, yielded the product **1** in 32% yield after 1 h reaction time.

Throughout this project, the acetal formations, using a range of aldehydes, proceeded to give the product as a mixture of

Scheme 7. Final route to 1



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epimers, with the desired α-epimer predominating. The optimised conditions for the preparation of **1** gave a crude 87:13 mixture of isomers (α:β),[9] a ratio which was not improved upon despite considerable variation of reaction conditions. The use of dimethoxyethane or dioxane in place of acetonitrile gave almost identical ratios of epimeric products when compared by HPLC analysis of the crude reaction mixtures.

Extending the reaction time beyond 70 min led to degradation of the product under reaction conditions. Thus prompt analysis of the reaction mixture and response to the results were crucial to success upon scale-up. Rapid degradation of the reaction mixture was also observed when the reaction was heated; thus, it was vital to maintain the reaction vessel temperature below 25 °C during the addition of triflic acid. Attempts to equilibrate the isolated β-epimer (**11**) to a mixture of α- and β-epimers by resubmitting crude β-epimer to the reaction conditions gave significant degradation and very little observed conversion to the desired product.

Telescoping the alkylation and arylation steps gave the aldehyde **10** as a crude solution in ethyl acetate. A simple, homogeneous procedure was employed, using potassium hydroxide and dimethyl sulphate to alkylate benzene-1,3-thiol **7**, followed by extraction into *tert*-butylmethylether. During the development of this process it was found that too slow a rate of addition of base led to greater levels of bis-methylation; thus, it is important to keep the addition time to a minimum. Following solvent swap into acetonitrile, arylation was effected by reaction with fluorobenzaldehyde in the presence of tetramethyl guanidine. Sparging of the reaction solution with nitrogen prior to the arylation step was found to be vital to avoid formation of the symmetrical disulphide impurity which was readily formed by the thiol under basic conditions. The aldehyde **9** had initially been isolated as an oil; however, this was found to be vulnerable to oxidation upon storage. To circumvent this and to allow the isolation of a convenient, solid intermediate, the bisulphite adduct (**12**) was prepared directly from the crude solution of aldehyde. Following aqueous workup and solvent exchange into acetonitrile, treatment with aqueous sodium metabisulphite gave the solid bisulphite adduct which was collected by filtration and washed with water and acetonitrile (Scheme 7).

Fortuitously, the bisulphite adduct **12** was found to react cleanly with fluocinolone tetraol **6** without any need to convert to the aldehyde.[10] The optimal reaction profile was achieved by premixing the tetraol with magnesium sulphate for several hours prior to the addition of bisulphite adduct and trifluoromethyl sulphonic acid. This was believed to be due to the slow dissolution of the tetraol under reaction conditions; premixing the reactants allowed the very granular tetraol to be broken down into smaller particles, allowing rapid dissolution as the reaction progressed. Attempts to improve the ratio of isomers by carrying out the acetal formation at lower temperature gave a more complex mixture of products, possibly due to the low solubility of the tetraol. Applying the previously optimized reaction conditions (3 equiv of triflic acid, 5 equiv of magnesium sulphate, and 1.3 equiv of bisulphite adduct, in acetonitrile at ambient temperature) gave product **1** in 37% yield, with a ratio of epimers in the crude reaction mixture identical to that observed when employing the aldehyde (α:β, 87:13).

Isolation of product from the acetal formation by aqueous workup using ethyl acetate, followed by chromatography and crystallisation from ethyl acetate yielded material sufficient for early, medicinal chemistry, requirements. The solvent volumes required for workup (~40 mL per gram), however, made this impractical for use on large scale. Initial attempts to extract the product, following water quench of the acetonitrile reaction mixture and using methyl-THF, were hampered by the formation of emulsions and the requirement for large extraction volumes to give phase separations. Measurement of solubility in a range of organic solvents showed an unexpected trend towards higher solubility in the heavier ester solvents (Table 2).

Table 2. Solubility[a] of 1 in a range of solvents

solvent	solubility (g/L)	solvent	solubility (g/L)
Me-THF	49.4	MeOAc	3.1
MeCN	5.4	EtOAc	2.4
2-butanone	5.4	*i*-PrOAc	6.7
toluene	14.1	*n*-BuOAc	>100

[a]Solubility measured by HPLC at ambient temperature.

The use of *n*-butyl acetate to extract the crude product from an aqueous workup allowed the use of moderate total volumes and gave clean phase splits. Thus, following complete reaction as determined by HPLC, the reaction mixture was diluted with *n*-butyl acetate and washed with water, sodium bicarbonate solution, and finally water before filtration and partial concentration.

Early batches of **1** recrystallised from ethyl acetate or isopropyl alcohol were found to be stable solvates resistant to vacuum drying but recrystallisation from aqueous ethanol gave nonsolvated material; this was found to be a mixture of polymorphs but, nevertheless, was suitable for precandidate studies. Material recrystallised from acetonitrile could be dried in vacuo or at elevated temperature (>125 °C) to give a homogeneous form with a melting point of 190 °C. This form was subsequently found to be a desolvated solvate but was considered suitable for development purposes, possessing suitable physical properties for inhaled dosing following micronisiation by jet milling. Harsh conditions (jet mill at 7.5 bar pressure) were required to reduce the particle size to that required for inhalation use, but the resulting API was stable at 70 °C and 75% relative humidity without any observed increase in particle size from agglomeration or recrystallisation.

Following the identification of PF4714224 **1** as a development candidate, an isolation process was developed, avoiding chromatography and making use of the inherently high crystallinity of the steroid product. The crude *n*-butyl acetate solution of product was partially concentrated and triturated with 2-butanone to give crude product, purging it of residual tetraol and unreacted aldehyde. The removal of *n*-butyl acetate by codistillation with 2-butanone was found to be rather inefficient, giving an azeotrope of 8:1 2-butanone:*n*-butyl acetate. Hence, the concentration of the crude *n*-butyl acetate extract by distillation was crucial to the successful isolation of the product. Recrystallisation of the crude solid from ethanol was found to remove the undesired β-epimer (reducing levels of β-epimer to <2%), affording a granular solid, which could be subsequently recrystallised from acetontrile to give the product in the desired crystalline form. Recrystallisation of the crude product resulting from 2-butanone trituration using acetonitrile failed to purge the β-epimer. The precipitation of the crude product following the addition of MEK was found to occur

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reliably without seeding, as were the intermediate and final recrystallisations.

SAFETY CONSIDERATIONS

The very high potency of the product **1** and, consequently, the very low predicted dose size (<100 μg) led to concerns about worker safety in handling these products; glucocorticosteroid agonists are, as a class, known to be potential teratogens and to display dose-limiting systemic side effects when administered by inhalation or orally. Early assessment of the potential hazards presented by **1** led to the assignment of an occupational exposure limit of <1 $\mu g/m^3$. As a consequence, special precautions were taken to minimise exposure to the API; the use of over sleeves and disposable lab coats, worn over regular lab coats and gloves, coupled with a rigorous approach to occupational hygiene was deemed sufficient to ensure worker safety during gram-scale work. When planning the 100-g and kilogram-scale campaigns, it was considered necessary to also minimise the operational complexity of the isolation procedure and to handle intermediate solids as solvent-damp filter cakes to reduce exposure to airborne powders. Both the ethanol and acetonitrile recrystallization steps were found to be tolerant of a significant degree of solvent carry-over from the previous isolations. Deliberate spiking of each of these recrystallisations with 5% v/v of 2-butanone or ethanol, respectively, gave no significant loss of yield, purity, or crystalline form.

A batch of 2.56 kg of PF4714224 **1** was prepared in 43.5% yield and 97.9% purity by the method outlined in Scheme 7.

CONCLUSION

A concise synthesis of PF-4714224 **1** was achieved in four linear steps from commercially available starting materials (Scheme 7). Fluocinolone tetraol **6** was prepared by an operationally simple HBF_4 hydrolysis of fluocinolone acetonide **2**, in a significant improvement over the method reported in the literature. The aldehyde **10** was prepared by monomethylation of benzene-1,3-dithiol and subsequent reaction with fluorobenzaldehyde. The bisulphite adduct **12** was found to be a convenient, solid surrogate for the aldehyde **10** in this route. The inherent crystallinity of **1** was used to isolate the product from the undesired β-epimer **11**, which was inevitably formed as a byproduct of the acetal formation. The potential hazards represented by this exquisitely potent steroid were managed by careful design of the purification and isolation procedure to minimise exposure to dry solids by deliberately handling intermediate filter cakes whilst solvent-damp.

EXPERIMENTAL SECTION

^{1}H NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer. HPLC analyses were performed using a reverse phase technique. LC/MS analysis was performed using the following system; Hewlett-Packard 1100 with SB C18 3.0 mm ×50 mm, 1.8 μm particles; mobile phase consisting of solvent A, 0.05% TFA in water, solvent B, 0.05% TFA in acetonitrile; 0 min = 5% solvent B; 3.5 min = 100% solvent B; 4.5 min = 100% solvent B; 4.6 min = 5% solvent B; run time 5 min; column temperature 50 °C; 225 nm; with Waters Micromass ZQ 2000/4000 mass detector. Combustion analyses were performed by Warwick Analytical Service, University of Warwick Science Park, The Venture Centre, Sir William Lyons Road, Coventry CV4 7EZ, U.K. Experimental data are provided for the largest batch produced.

(6α,11β,16α)-6,9-Difluoro-11,16,17,21-tetrahydroxypregna-1,4-diene-3,20-dione (Fluocinolone Tetraol) (2). A suspension of fluocinolone acetonide (5.39 kg; 11.91 mol) in tetrafluoroboric acid (48% aq, 37.2 kg) was stirred at 22 °C for 2 h. The suspension was then diluted with water (27 kg) and stirred at 22 °C for 1 h before the solid was collected by filtration, washing with water (15 kg then 30 kg) and ethyl acetate (24.3 kg) to give the product as white solid (4.64 kg, 94.5%) after drying under vacuum at 45 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 0. 82 (s, 3H), 1.46 (s, 3H), 1.31−1.51 (m, 3H), 1.77−1.87 (m, 1H), 2.08−2.33 (m, 3H), 2.37−2.46 (m, 1H), 4.08 (dd, J = 12 and 2 Hz, 1H), 4.09−4.16 (m, 1H),4.48 (dd, J = 12 and 3 Hz, 1H), 4.63 (br, 1H), 4.75 (dd, J = Hz, J = Hz, 1H), 5.35 (d, J = 5 Hz, 1H), 5.51−5.69 (m, 1H), 6.08 (s, 1H), 6.26 (dd, J = 10 and 2 Hz, 1H), 7.24 (d, J = 10 Hz, 1H). ^{19}F NMR (400 MHz, DMSO-d_6) δ: −164.55 (dd J = 9 and 32 Hz), −186.39 (dd, J = 49 and 16 Hz). LRMS (ESI): m/z 411 $[M - H]^-$.

3-(Methylthio)benzenethiol (8). A solution of benzene-1,3-dithiol (1.6 kg; 11 mol) in 2-methyltetrahydrofuran (10.1 kg) was treated with dimethylsulphate (1.42 kg; 11.3 mol), followed by a line wash of 2-methyltetrahydrofuran (0.5 kg) and cooling to 2 °C. The mixture was treated with a solution of 2 M sodium hydroxide (1.35 kg 40% in 5.8 kg water), over 25 min (addition time should not exceed 40 min), whilst maintaining the vessel temperature below 15 °C. A line wash of 2-methyltetrahydrofuran (0.6 kg) was added, and the mixture was heated to 50 °C for 3 h before cooling to 20 °C. The mixture was diluted with *tert*-butylmethylether (11.8 kg) and stirred for 20 min, and the layers were separated. The organic layer was treated with 2 M sodium hydroxide solution (7.15 kg) and stirred for 10 min; the layers were separated, and the organic phase was treated as waste. The combined aqueous layers were treated with 6 M HCl (17.6 kg), whilst maintaining the temperature below 25 °C, and extracted with *tert*-butylmethylether (two portions of 5.9 kg). The two *tert*-butylmethylether extracts were combined and washed with water (16 kg) to give a solution of the product (1.33 kg, 11% solution in *tert*-butylmethylether; 75%). The product was found by HPLC to be identical to material prepared by the method of Rumpf.[5] ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.47 (s, 3H), 3.45 (s, H), 7.03 (m, 2H), 7.12−7.16 (m, 2H).

Sodium Hydroxyl(4-{[3-(methylthio)phenyl]thio}-phenyl)methanesulphonate (12). A solution of 3-(methylthio)-benzenethiol 7 (1.33 kg; 8.51 mol) in TBME (11.80 kg) was charged and distilled to a volume of 9 L, maintaining the temperature below 90 °C to remove TBME, and acetonitrile (10.5 kg) was added. The solution was distilled at atmospheric pressure to give a volume of 9 L, and acetonitrile (10.5 kg) was added. The solution was distilled a third time to give a final volume of 13.5 L; this solution was cooled to 10 °C and sparged with nitrogen for 1 h. This solution was treated with 4-fluorobenzaldehyde (1.06 kg; 8.55 mol) followed by a line wash of acetonitrile (0.79 kg). 1,1′,3′3′-Tetramethyl guanidine was added slowly (1.08 kg; 9.3 mol) with stirring, followed by a line wash of acetonitrile (0.79 kg). The reaction mixture was heated to 50 °C for 16 h, then cooled to 20 °C and treated with ethyl acetate (12 kg) followed by 2 M HCl (6.68 kg) and a line wash of ethyl acetate (0.6 kg). The mixture was stirred for 20 min, and then the layers were separated. The organic phase was washed successively with 1 M sodium bicarbonate solution (14.42 kg) and brine (1.73 kg NaCl in 6.7 kg water). The organic solution was treated with acetonitrile (3.9 kg) and

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distilled at atmospheric pressure to 10-L volume, diluted with acetonitrile (11.8 kg), and concentrated by distillation at atmospheric pressure to a volume of 10 L. The resulting solution was diluted with acetonitrile (11.8 kg) and concentrated by distillation at atmospheric pressure to a volume of 15 L before cooling to 22 °C (solvent composition found to be approximately 0.95% ethyl acetate). The solution was treated with sodium metabisulphite (1.88 kg) in water (15 kg) and stirred at 22 °C for 48 h before the solid was isolated by filtration. The crude solid was washed with water (two portions of 12.8 kg) and acetonitrile (two portions of 10.1 kg) to give the product bisulphite adduct as a white solid (2.18 kg; 70%) after drying under vacuum at 50 °C.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.41 (s, 3H), 4.97 (d, J = 6 Hz, 1H), 5.90 (d, J = 6 Hz, 1H), 6.98 (m, 1H), 7.12 (m, 2H), 7.26 (m, 3H), 7.46 (d, J = 10 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 15.25, 85.19, 124.98, 126.65, 126.91, 129.71, 130.47, 131.17, 132.16, 137.59, 140.35, 140.54. HRMS (ESI) m/z 283.0226 ($C_{14}H_{12}NaOS_2$, theoretical 283.022726, −1.60), 261.0407 ($C_{14}H_{13}OS_2$, theoretical 261.040781, −1.80).

(4a*S*,4b*R*,5*S*,6a*S*,6b*S*,8R,9a*R*,10a*S*,10b*S*,12*S*)-4b,12-Difluoro-6b-glycoloyl-5-hydroxy-4a,6adimethyl-8-(4-{[3-(methylthio)phenyl]thio}phenyl)-4a,4b,5,6,6a,6b,9a,10,10a,10b,11,12-dodecahydro-2H-naphtho-[2′,1′:4,5]indeno[1,2-*d*][1,3]dioxol-2-one (1). A suspension of magnesium sulphate (3.7 kg; 30.8 mol) and fluocinolone tetraol **6** (3.5 kg; 8.5 mol) in acetonitrile (26.7 kg) was stirred at 18 °C for 12 h. Bisulphite adduct **12** (3.63 kg; 9.96 mol) was charged to the vessel followed by trifluoromethanesulphonic acid (6.37 kg; 42.4 mol) whilst maintaining the vessel temperature below 25 °C (**critical process parameter**), and the mixture was stirred for 70 min at 22 °C. *n*-Butyl acetate (20.8 kg) followed by water (35 kg) was added, and the mixture was stirred for 40 min. The aqueous phase was removed, and the organic phase was washed with water (35 kg) followed by sodium bicarbonate solution (two portions of 1.57 kg in 17.5 kg water) and water (17.5 kg) before being passed through an inline ceramic filter which was subsequently washed with *n*-butyl acetate (6.2 kg). The combined organic solution was concentrated by distillation at reduced pressure (−0.940 barg, pot temperature of 29.5 °C) to a volume of approximately 10 L, cooled to 20 °C, treated with 2-butanone (24.7 kg), and aged for 11 h. The crude solid was collected by filtration (**visual inspection to check for presence of solid precipitate 2 h prior to filtration stage is a critical process parameter**) and washed with 2-butanone (two portions of 8.45 kg); whilst still damp the solid was transferred to a reaction vessel which had been charged with ethanol (55.2 kg); the resulting suspension was heated to reflux until a clear solution had formed. The solution was cooled to 20 °C over 20 min and stirred at this temperature for 2 h before collection of the resulting solid by filtration. The solid was then washed with ethanol (two portions of 13.8 kg) and acetonitrile (5.3 kg). The solid was transferred, whilst still damp, to a reaction vessel which had been charged with acetonitrile (24.8 kg) and the resulting solution concentrated by distillation at reduced pressure (−0.925 g, pot temperature 30 °C) to a volume of approximately 11 L. The solution was treated with acetonitrile (8.5 kg) and heated to reflux, and two further portions of acetonitrile (two portions of 1.73 kg) were added whilst maintaining the mixture at reflux, until a clear solution was obtained (**the visual observation of a clear solution at this stage is a critical process parameter**). The resulting solution was cooled to 20 °C over 6 h and the resulting solid collected by filtration. The solid was then washed with acetonitrile (two portions of 5.5 kg) and dried in vacuum at 50 °C to give pure acetal **1** as a white solid (2.56 kg; 46%). Mp 189.9 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 0.85 (s, 3H), 1.43−1.53 (m, 1H), 1.48 (s, 3H), 1.65−1.71 (m, 3H), 1.97−2.06 (m, 1H), 2. 14−2.31 (m, 2H), 2.41 (s, 3H), 2.55−2.67 (m, 1H), 4.16−4.22 (m, 2H), 4.52 (dd, J = 6 and 19 Hz, 1H), 4. 95 (d, J = 5 Hz, 1H), 5.06 (t, J = 6 Hz, 1H), 5.48 (s, 1H), 5.50−5.51(m, 1H), 5.54−5.79 (m, 1H), 6.10 (s, 1H), 6.27 (dd, J = 10 and 2 Hz, 1H), 7.06 (dt, J = 8 and 2 Hz, 1H), 7.18−7.20 (m, 2H), 7.23−7.26 (m, 1H), 7.27−7.29 (m, 1H), 7.32 (d, J = 8 Hz, 2H), 7.42 (d, J = 8 Hz, 2H). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.18, 16.19, 22.25, 30.90, 32.12, 33.57, 35.58, 42.69, 45.17, 47.91, 65.77, 70.09, 81.04, 86.50, 97.44, 99.50, 102.09, 119.24, 124.90, 127.36, 127.57, 127.65, 128.72, 129.79, 129.88, 134.81, 134.92, 136.93, 140.03, 151.39, 162.60, 184.54, 208.66. LRMS (ESI): m/z 655 $[M + H]^+$. ^{19}F NMR (400 MHz, DMSO-d_6) δ: −164.88 (dd, J = 49 and 15 Hz), −186.50 (dd, J = 28 and 9 Hz). HRMS ESI positive; m/z 655.2002 ($C_{25}H_{37}F_2O_6S_2$, theoretical 655.199962, −1.20), 677.1809 ($C_{35}H_{36}F_2NO_6S_2$, theoretical 677.181906, 0.70). Anal. Calcd For $C_{35}H_{36}F_2S_2O_6$: C, 64.2%; H, 5.53%; N, 0.00%. Found: C, 64.15%: H, 5.53%; N, 0.04%.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Proton and carbon NMR data and assignments of **1** and epimer **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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