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Improved Synthesis of Fluocinolone Acetonide and Process Research of 6α,9α-Fluorination

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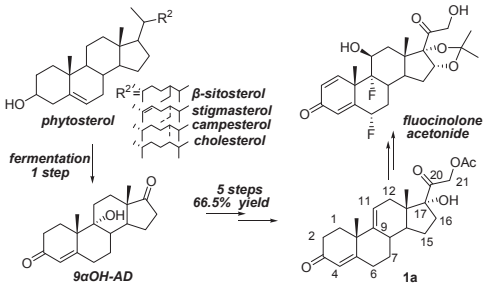
An efficient and improved synthetic route of fluocinolone acetonide with combination of bio-fermentation was developed from 21-acetyloxy-17α-hydroxy-4,9(11)-diene-3,20-dione (**1a**). Process of the 6α and 9α fluorination steps was studied, and it was observed that the stereoselectivity of 6α fluorination is highly substrate dependent. After an extensive screening on the fluorinating reagents and activation reagents, 6α-F was introduced in 85% yield with 98.9% stereoselectivity. Instead of HF gas, aqueous HF solution was applied in 9α fluorination step to provide the desired product in 89% yield. Starting from **1a**, fluocinolone acetonide was prepared in 9 steps with an overall 38.5% yield.

Keywords: Fluocinolone acetonide | Fluorination | Bio-fermentation

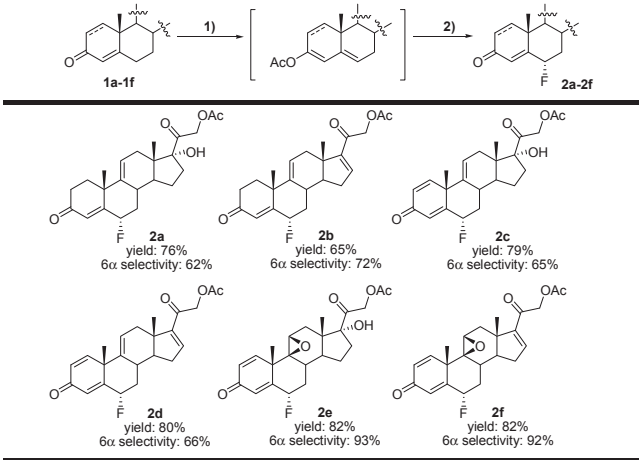
Fluocinolone acetonide (**8**), firstly reported in 1960,[1] is a potent glucocorticoid used typically as an anti-inflammatory agent for the treatment of skin disorders such as eczema and seborrhoeic dermatitis. It also has been used in the treatment of facial melasma, diabetic retinopathy, and non-infectious uveitis.[2] Due to its wide applications and recent discoveries, chemists were always searching for efficient ways to improve its synthesis.[3] Traditionally, most glucocorticoids, including fluocinolone acetonide, were semi-synthesized from natural steroid derivatives, such as diosgenin, tigogenin, and hecogenin.[4] These raw materials were firstly converted to intermediate 11α-hydrocortison (epicortisol) or 16,17α-epoxy-11-hydroxyprogesterone in several steps, and then fluocinolone acetonide was produced with a total yield of 5.2% or 2.8%, respectively, via each intermediate.[5] Although some steps in those established synthetic protocol were improved so far, they still face several problems: 1) low stereoselectivity of 6α-fluorination, 2) extra bioconversion to introduce 11-OH lead low efficiency,[6] 3) these raw materials, which themselves are extracted from a specific plant with low extraction efficiency, are getting obsolete because their production tends to suffer from pollution, expensive cost, and limited source.[7] Hence, efforts are directed toward the use of new starting materials and routes for their syntheses.

In this paper, we demonstrated a new and efficient synthesis of fluocinolone acetonide from **1a**, as an important intermediate for many glucocorticoids, compound **1a** could be readily prepared in 66.5% yield in 5 steps starting from 9α-hydroxyandrost-4-ene-3,17-dione (**9αOH-AD**),[8] which could be prepared via simple bio-fermentation of phytosterol on a large scale (Scheme 1).[9] Analysis on its structure, compound **1a**, is an ideal platform for the synthesis of fluocinolone acetonide: (a) direct bio-fermentation[10] or DDQ oxidation[11] could introduce $\Delta^{1(2)}$. (b) 6α-F could be introduced via electrophilic fluorination at activated C6.[12] (c) 9α-F and 11β-OH can be obtained from $\Delta^{9(11)}$.[13] (d) Vicinal hydroxy groups at 16, 17C could be



Scheme 1. The new raw materials of fluocinolone acetonide.

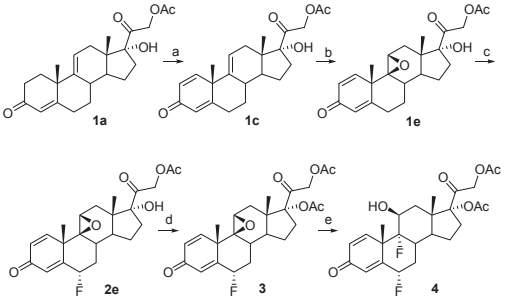
Table 1. 6α-Fluorination of different substrates via 3,5-dienol acetate[a]



[a]Reaction condition: 1) 0.01 mol of substrate, 32 mL of isopropenyl acetate, 0.12 g of *p*-Ts, 60 °C, 3 h; 2) 20 mL of CH_3CN, 3.6 g of Selectfluor™, −5–10 °C, 5–8 h.

prepared from 17α-OH via an olefin intermediate. Our study centered on the 6α and 9α fluorination steps. 6α-F can be introduced via the reaction of the corresponding 3,5-dienol esters with electrophilic fluorinating reagents.[14] However, due to low stereoselectivity of this transformation, a mixture of both stereoisomers is typically obtained and pure 6α-fluorosteroids have to be prepared by selective crystallization or another transformation step.[15] Our strategy to tackle this problem was based on the following assumptions: stereoselective 6α-fluorination of steroids may be substrate dependent.[16]

Consequently, we prepared six steroids with different groups at specific positions,[17] which were easily derivatized from **1a**, and subjected them to the fluorination reaction using Selectfluor™ as the fluorinating reagent. The results are summarized in Table 1; different stereoselectivities were obtained under the identical reaction conditions with various acetyl 3,5-dienol



Scheme 2. Synthesis of intermediate **4** for fluocinolone acetonide. Reaction condition: a) Nocardioides simplex/glucose/phosphate buffer, 86%; b) $HClO_4$/DBH, actone/H_2O, K_2CO_3, 96%; c) CH_3CN, Selectfluor^{TM}; d) isopropenyl acetate, *p*-Ts; e) HF, solvent.

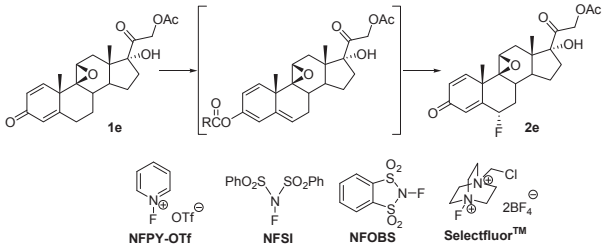
esters. With substrates **1a** and **1b**, once the 16, 17 double bond was formed, the stereoselectivity could be increased from 62% to 72%, even though the yield of fluorination reaction dropped from 76% to 65%. However, **1c** and **1d**, the same transformation did not have much effect on the yield as well as the stereoselectivity. These observations all highlighted that the fluorination step may be substrate dependent. Much to our delight, when $\Delta^{9(11)}$ was oxidized to epoxides (**1e** and **1f**), 6α-F selectivity was increased to >92%, indicating that the β-face is significantly hindered by 9(11)β-epoxide. We could also see from Table 1 that the substitutions on 16 and 17 positions of substrates **1e** and **1f** are of little importance to either the yield or the selectivity of the fluorination reaction. The best results of 82% yield and 93% 6α-F stereoselectivity were obtained with **2e**.

Based on the above results, we decided to use **1e** as the intermediate for the synthesis of fluocinolone acetonide and the following route was applied in the final preparation of the fluorinated intermediate (Scheme 2). Fermentation of **1a** provided **1c** in 86% isolated yield. Then, **1c** was treated with 1,3-dibromo-5,5-dimethylhydantoin (DBH) in acetone and water, followed by the treatment with K_2CO_2 carefully, through which the in situ generated bromo-alcohol was cyclized to produce the desired 9,11β-epoxide (**1e**) in 96% yield as an off-white solid.

We then systematically studied the fluorination reaction conditions to convert **1e** to **2e** (Table 2). Four different electrophilic fluorination reagents were employed, and almost all the fluorinating reagent tested on 3,5-dienol acetate esters provide **2e** in over 90% conversion and good stereoselectivities (Entry 1 to 4). However, Selectfluor^{TM} provided the highest conversion and better selectivity than those of the other three. We also tried to investigate the influence of ester on the reactivity and stereoselectivity of 6α-fluorination (Entry 4 to 11). Apart from 2,3,4,5,6-pentafluorobenzoate (Entry 9) and 3,5-dinitrobenzoate (Entry 10), which gave bad conversions, other substituted benzoate generally led to better conversions and stereoselectivities compared with those of 3,5-dienol acetate. It was found that the best result was obtained with 4-nitrobenzoate and 85% isolated yield was achieved with almost quantitative conversion and 98.9% selectivity (Entry 11). The reaction worked best at −5 °C; further lowing the reaction temperature would decrease the yield (Entries 12 and 13).

Next, 17-hydroxy of steroid **2e** was transformed into the corresponding acetate with isopropenyl acetate smoothly and we

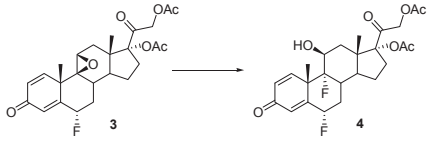
Table 2. Optimisation of 6α-fluorination[a]



Entry	R	Fluorinating reagent	Yield /%	Selectivity (α/β) /%
1	CH_3	NFPY-OTf	73	88.0/12.0
2	CH_3	NFSI	76	92.1/7.9
3	CH_3	NFOBS	69	91.1/8.9
4	CH_3	Selectfluor^{TM}	82	92.8/7.2
5	4-MeC_6H_4	Selectfluor^{TM}	80	93.0/7.0
6	Ph	Selectfluor^{TM}	83	95.4/4.6
7	4-ClC_6H_4	Selectfluor^{TM}	79	93.2/6.8
8	4-FC_6H_4	Selectfluor^{TM}	83	95.2/4.8
9[a]	C_6F_5	Selectfluor^{TM}	62	90.3/3.7
10[b]	3,5-$(NO_2)_2C_6H_3$	Selectfluor^{TM}	45	91.4/3.6
11	4-$NO_2C_6H_4$	Selectfluor^{TM}	85	98.9/1.1
12[c]	4-$NO_2C_6H_4$	Selectfluor^{TM}	83	98.1/1.8
13[d]	4-$NO_2C_6H_4$	Selectfluor^{TM}	72	98.5/1.5

[a]Reaction condition: 0.01 mol of anhydride or acyl chloride, 0.006 mol of **1e**, 20 mL of CH_3CN, 80 °C 3 h, 2 mL of MeOH; 0.007 mol of fluorine reagents, −5 °C, 8–12 h. [b]−5 °C, then rise to −10 °C. [c]−10 °C. [d]−15 °C.

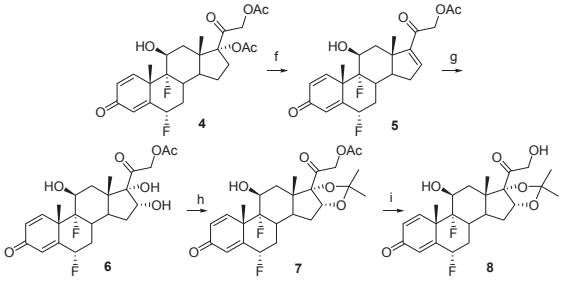
Table 3. Optimisation of 9α-fluorination[a]



Entry	Fluorinating reagent	Solvent	Conv. /%	Yield /%
1	HF(gas)	DMF	97	82
2	40%HF	DMF	53	22
3[b]	70%HF	DMF	97	74
4[c]	70%HF	DMF	98	85
5	70%HF/NaF	DMF	90	67
6	70%HF	MeOH	63	34
7	70%HF	acetone	96	83
8	70%HF	NMP	99	83
9	70%HF	1,4-dioxane	80	62
10	70%HF	DMA	99	89

[a]Reaction condition: 0.01 mol of **3**, 2.5 mL of solvent, 25 mL of aqueous HF, −25–15 °C. [b]0–5 °C. [c]−5–0 °C.

were faced with 9α-fluorination (Table 3). It had been reported that the stereoselective ring opening of epoxide could be performed using HF gas with a good yield.[18] However, this type of reaction is not recommended for industry application due to its safety concerns. On the other hand, aqueous HF solution is commercially available and much easier and safer to handle.



Scheme 3. Synthesis of fluocinolone acetonide from **4**. Reaction condition: f) DMF/AcOK, 85.7%; g) $KMnO_4$/HCOOH, acetone, −5–0 °C, 98.0%; h) $HClO_4$/acetone, 87.3%; i) DCM/MeOH/K_2CO_3, 99.0%.

Although the initial trial using 40% HF provided only moderate conversion and low isolated yield of compound **4** (Table 3, Entry 2), we were glad to find out that the application of 70% HF solution pushed the conversion to 97% and isolated yield was increased to 74% (Entry 3). It is worth to mention that steroid **3** could be dissolved in aqueous HF (70%), and we thought homogeneous reaction is the key to high conversion. Decreasing the reaction temperature from −5 to −20 °C further improved the yield to 85% (Entry 4). In contrast, using NaF (20%) as an additive did not help the reaction (Entry 5). Upon solvent screening, we have found that solvent has great effect on the transformation. Protonic solvent, such as methanol, is detrimental to the reaction (Entry 6). Among polar non-protonic solvents (Entries 7, 8, 9, and 10), DMA provided complete conversion and an 89% isolated yield of compound **4** was obtained.

With fluorinated compound **4** in hand, the following steps were effected by conventional chemistry without any difficulties (Scheme 3). Elimination of 17α-acetyloxy at 90–100 °C with AcOK/DMF gave **5** in 85.7% yield after decoloration and recrystallization. Treating **5** with $KMnO_4$/HCOOH in acetone at low temperatures (−5–0 °C) provided crude **6** in 98% yield. With a catalytic amount of perchloric acid in acetone, **6** was converted into 16α,17α-acetonide **7** in 87% yield and 99% purity after purification.

Finally, hydrolysis of acetate **7** was carried out quantitatively with DCM/MeOH/K_2CO_3, and fluocinolone acetonide (**8**) was obtained with 38.5% total yield, 9 steps from **1a**.

In summary, we have developed an efficient synthesis of fluocinolone acetonide from 21-acetyloxy steroid **1a**, which was readily available from bio-fermentation and chemical synthesis. Other notable features of our synthesis centered on the 6α and 9α fluorination steps. Research indicated that the stereoselectivity of 6α fluorination is highly substrate dependent. After optimizing fluorinating reagents and activation reagents to form 3,5-dienol esters, 6α-F was induced in 98.9% stereoselectivity. Instead of HF gas, aqueous HF solution was applied in 9α-fluorination step to provide the desired product in 89% yield. Starting from **1a**, we successfully prepared fluocinolone acetonide in 9 steps with 38.5% yield, which is highly practical in industry production.

Supporting Information is available on http://dx.doi.org/10.1246/cl.170923.

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