

Improved Synthesis of Fluticasone Propionate

Jiadi Zhou, Can Jin, and Weike Su*

Key Laboratory for Green Pharmaceutical Technologies and Related Equipment of Ministry of Education, Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals, College of Pharmaceutical Sciences, Zhejiang University of Technology, Hangzhou 310014, P. R. China

Supporting Information

ABSTRACT: A novel process for the preparation of fluticasone propionate (**1**), a corticosteroid, is reported. In this paper, compound **2** was used as starting material to prepare **6** by using NaClO or NaBrO which was much cheaper than H₅IO₆ as an oxidizing agent. Furthermore, toxic, expensive, and pollutive BrCH₂F was replaced by AgNO₃ and Selectfluor in decarboxylative fluorination.

INTRODUCTION

Steroidal glucocorticoid agonists such as fluticasone propionate (**1**) are anti-inflammatory agents used widely against a broad spectrum of inflammatory diseases. Fluticasone propionate (**1**), synthesized by Glaxo Wellcome and launched in 1993, is a trifluorinated glucocorticosteroid. It shows good topical anti-inflammatory activity and is commonly used as a safe and effective inhaled treatment for asthma and allergic rhinitis.¹ The previous route for the synthesis of **6** from **2** was in the commercial scale. Compound **6** was synthesized from commercial grade flumethasone (**5**) by H₅IO₆ oxidation with a yield of 95.0%.^{2a} Flumethasone (**5**) can be prepared from **2** in three steps with a unclear yield (Scheme 1).³ According to the literature,^{2a,3} we obtained **6** from **2** in a total yield of 45%.

The compound **7** was synthesized from **6** by propionyl chloride or propionic anhydride acylation. Compound **7** reacted with *N,N*-dimethylthiocarbamoyl chloride⁴ in the presence of an iodide catalyst and Et₃N to produce **8**, followed by hydrolyzation with K₂CO₃,^{2a} Et₂NH,^{2b} or NaSH^{4a} to obtain **9**. Alternatively, the combination of 1,1'-carbonyldiimidazole (CDI) with NaSH^{2b} can also be used to prepare **9** from **7**. Fluticasone propionate (**1**) can be synthesized from **9** by using BrCH₂F,^{2a} ClCH₂F,^{5a} or *S*-(monofluoromethyl) diarylsulfonium tetrafluoroborate^{5f,g} directly. Using BrCH₂F can get an ideal yield; however, BrCH₂F is costly and will destroy the ozone layer. In addition, **9** reacted with BrCH₂Cl or Br₂CH₂ and then by an anion exchange with AgF,^{2c,5c} KF, or tetrabutylammonium fluoride^{5b} to afford **1** in a low yield. Fluticasone propionate (**1**) could be obtained from **10**, in the presence of fluorodecarboxylating reagents such as XeF₂ and BrF₃.^{5d} Unfortunately, XeF₂ is extremely expensive, and BrF₃ which should be stored in Teflon containers is a strong corrosive toxic liquid, which tends to react very exothermically with water and release poisonous vapours. Furthermore, the high toxicities and instabilities of XeF₂ and BrF₃ prevented practical applications of this method. According to the literature,^{5c} Deoxo-Fluor or DAST can also be used as monofluoromethylation reagent to acquire **1** from **11** at -60 °C (Scheme 2). Considering the different literature sources, the highest overall yield for the previous synthesis of fluticasone propionate (**1**) from **2** was close to 30%.

The disadvantages of the above processes include safety issues, high expenses, and environmental problems, such as the use of costly H₅IO₆ as an oxidant and BrCH₂F, XeF₂, BrF₃, or Deoxo-Fluor as monofluoromethylation reagents. Considering these drawbacks, we have subjected this synthetic route to further researches and intended to develop an efficient, eco-friendly, and commercially feasible process for fluticasone propionate (**1**). In this article, we describe an improved process with an overall yield of 42.3% in method A and 54.5% in method B (Scheme 3).

RESULTS AND DISCUSSION

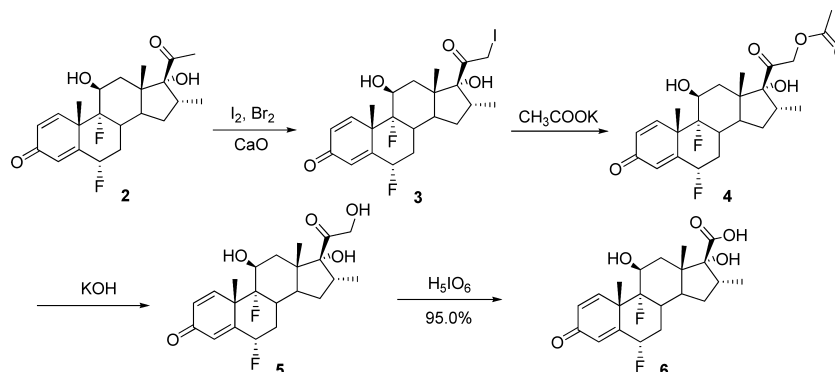
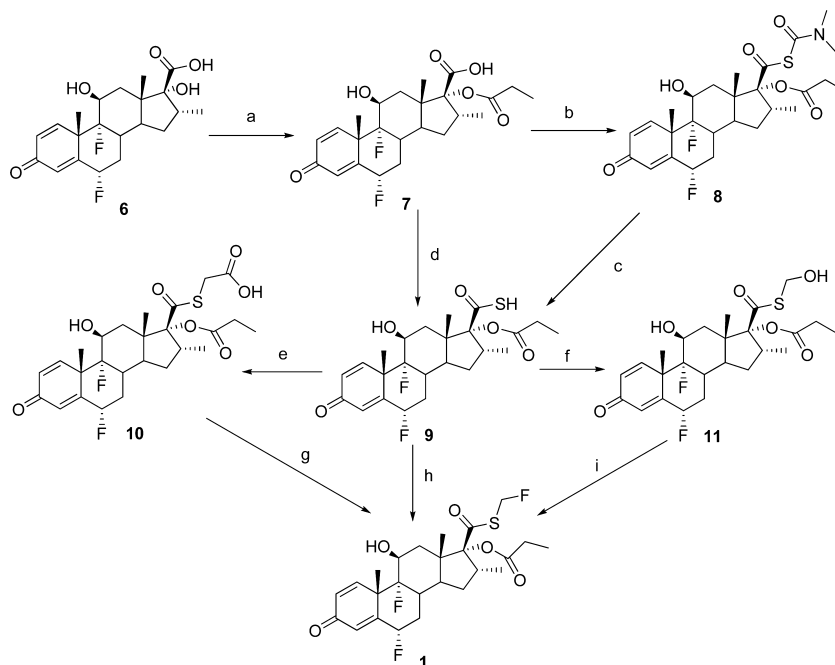
Preparation of 6 α ,9 α -Difluoro-11 β ,17 α -dihydroxy-16 α -methyl-3-oxoandrosta-1,4-diene-17 β -carboxylic Acid (6**).** As one of the oldest known organic reactions, the haloform reaction can be used to convert a terminal methyl ketone into appropriate carboxylic acid.⁶ Applying this reaction to the synthesis of compound **6** from **2** could shorten reaction routes,⁷ reduce the cost,⁸ and improve the total yield compared with the traditional method in four steps. Luckily, we found that using NaClO in the presence of NaOH could successfully obtain compound **6** in room temperature with a yield of 63.7%,⁹ and 11 β ,17 α -dihydroxy and 1,4-diene were tolerated. A series of solvents such as dioxane/H₂O, THF/H₂O, dimethoxyethane/H₂O, and EtOH/H₂O, were screened in order to find an optimal solvent. The results showed that all of those mixed solvents did not work well to afford the desired product **6** except THF/H₂O/EtOH, which provided a homogeneous reaction system.

By contrast, the usage of NaBrO which has a stronger activity than NaClO could get a higher yield of 84.5% in a lower temperature (Scheme 3). To this reaction, dioxane/H₂O was proved to be the best solvent.¹⁰ Other solvents such as THF/H₂O, dimethoxyethane/H₂O, EtOH/H₂O, and THF/H₂O/EtOH did not work well, and the reaction did not proceed in biphasic systems. When the reaction was finished, the remaining oxidizing agent (NaClO or NaBrO) was destroyed by the addition of excess sodium sulfite solution, and the

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Scheme 1. Previous route for the synthesis of 6

Scheme 2. Previous method for the synthesis of fluticasone propionate (1)^a

^aReactions and conditions: (a) (i) propionic anhydride or propionyl fluoride/Et₃N; (ii) Et₂NH; (b) *N,N*-dimethylthiocarbonyl chloride/Et₃N/NaI or tetrabutylammonium iodide; (c) K₂CO₃ or Et₂NH or NaSH; (d) CDI/NaSH; (e) BrCH₂COOH/Et₃N; (f) formaldehyde; (g) XeF₂/BrF₃; (h) BrCH₂F or ClCH₂F or *S*-(monofluoromethyl) diarylsulfonium tetrafluoroborate or BrCH₂Cl/AgF or BrCH₂Cl/KI/KF; (i) Deoxo-Fluor or DAST.

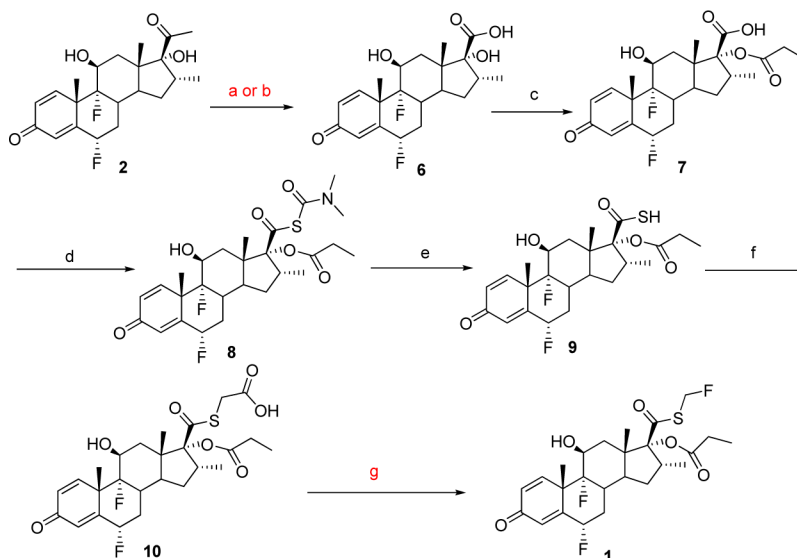
solvent THF/EtOH or dioxane was removed under reduced pressure. After extraction with ethyl acetate, the aqueous phase was acidified with hydrochloric acid to furnish a white precipitate of **6**, which was collected by filtration, washed with water, and dried.

Preparation of 6 α ,9 α -Difluoro-11 β -hydroxy-16 α -methyl-17 α -propionyloxy-3-oxoandrosta-1,4-diene-17 β -carbothioate (10). According to the literature,^{2a,5d} the compound **10** can be synthesized from **6** in four steps including esterification, acylation, alcoholysis, and alkylation (Scheme 3). In the original methods,^{5d} the product **10** was acquired from **9** by BrCH₂COOH alkylation under the condition of using DCM as the solvent. In our improved process, lower toxic solvent acetone was used to replace DCM. When the reaction was finished, the compound **10** could be obtained by filtration conveniently after acidification with 1 mol/L HCl.

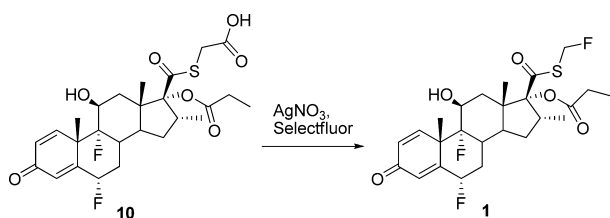
Preparation of *S*-Fluoromethyl-6 α ,9 α -difluoro-11 β -hydroxy-16 α -methyl-17 α -propionyloxy-3-oxoandrosta-1,4-diene-17 β -carbothioate (1). Recently reported *N*-F

reagents, such as Selectfluor and NFSI, are commercially available, easy to use, and stable electrophilic fluorinating reagents that can be used to conduct decarboxylative fluorination.¹¹ In our improved process, fluticasone propionate (**1**) was prepared from **10** with AgNO₃/Selectfluor (Scheme 4).¹² According to the literature,^{11a} the combination of AgNO₃ (20 mol %) with Selectfluor (2.5 equiv) shows a considerable decarboxylative fluorination ability (Table 1, entry 1). Other Ag(I) salts, such as AgOAc and AgOTf, exhibited a weaker catalytic activity (Table 1, entries 2 and 3), while no reaction occurred without the presence of a Ag(I) salt (Table 1, entry 4). Switching the electrophilic fluorinating reagent from Selectfluor to NFSI caused no reaction (Table 1, entry 5). In addition to Ag(I) ions, water also was turned out to be essential (Table 1, entry 6). Much of the experimental results was similar to the optimization done by the Li group.^{11a}

The Ag(II)- or Ag(III)-mediated decarboxylation of carboxylic acids is well-documented.¹³ According to the literature,^{11a} a tentative mechanism of the decarboxylative

Scheme 3. Improved process for the synthesis of fluticasone propionate (**1**)^a

^aReactions and conditions: (a) NaClO/NaOH, THF/EtOH/H₂O, 25 °C, 63.7%; (b) NaBrO/NaOH, dioxane/H₂O, 0–5 °C, 84.5%; (c) (i) propionic anhydride/Et₃N, acetone, 15–25 °C; (ii) Et₂NH, 15–25 °C, 97.3%; (d) *N,N*-dimethylthiocarbamoyl chloride/Et₃N/NaI, acetone/H₂O, 30 °C, 96.0%; (e) K₂CO₃, CH₃OH, 25 °C, 95.0%; (f) BrCH₂COOH/Et₃N, acetone, 15–25 °C, 97.1%; (g) AgNO₃/Selectfluor, acetone/H₂O, 45 °C, 92.7%.

Scheme 4. Decarboxylative fluorination for the synthesis of **1**Table 1. Screening of Ag(I) catalyst and N–F reagent of decarboxylative fluorination of **10**^a

entry	catalyst (equiv)	N–F reagent (equiv)	solvent	time (h)	yield ^b (%)	purity ^c (%)
1	AgNO ₃	Selectfluor	acetone/H ₂ O	3	92.7	92.6
2	AgOAc	Selectfluor	acetone/H ₂ O	8	64.2	74.2
3	AgOTf	Selectfluor	acetone/H ₂ O	8	48.8	79.5
4		Selectfluor	acetone/H ₂ O	8	0	
5	AgNO ₃	NFSI	acetone/H ₂ O	8	0	
6	AgNO ₃	Selectfluor	acetone	8	trace	

^aReagents and conditions: 1.0 equiv **10**, 0.2 equiv catalyst, 2.5 equiv N–F reagent, 45 °C, under nitrogen. ^bThe isolated yield was calculated with **10**. ^cThe purity was monitored by HPLC.

fluorination with AgNO₃/Selectfluor was proposed. The oxidation of Ag(I) by Selectfluor generates an Ag(III)–F intermediate, which initiated the decarboxylative fluorination of carboxylic acids (Figure 1).

Further optimization of the decarboxylative fluorination was carried out by screening of a range of temperatures, and of reagent stoichiometries, using AgNO₃ and Selectfluor (Table 2). As shown in (Table 2, entry 1), **10** was treated with AgNO₃ (20 mol %) and Selectfluor (2.5 equiv) at 30 °C for 8 h under a nitrogen atmosphere giving **1** in 80.1% yield, when raising the temperature to 45 °C improved the yield of **1** to 92.7% (Table 2, entry 2). However, more impurities were generated when the

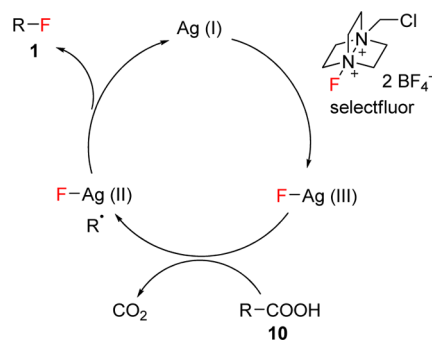


Figure 1. Proposed mechanism of silver-catalyzed decarboxylative fluorination.

reaction was performed at 55 °C (Table 2, entry 3). Unfortunately, using AgNO₃ (10 mol %)/Selectfluor (2.5 equiv) or AgNO₃ (20 mol %)/Selectfluor (2.0 equiv) as fluorodecarboxylating reagents provided **1** in only 75.2% and 70.3% yields, respectively (Table 2, entries 4 and 5).

The activity of decarboxylative fluorination was proved to be solvent-dependent, the mixed solvent of acetone/H₂O (2:1, v:v) exhibited the best activity (Table 2, entry 2). By contrast, a higher reaction temperature was needed in CH₃CN/H₂O (2:1, v:v) solution that led to more impurity **12** (Table 2, entry 6). No fluorodecarboxylation occurred in THF/H₂O (2:1, v:v) solution (Table 2, entry 7) or other biphasic systems.

The optimized reaction conditions (Table 2, entry 2), **10** was treated with AgNO₃ (20 mol %) and Selectfluor (2.5 equiv) in acetone/H₂O (2:1, v:v) solution at 45 °C for 3 h under a nitrogen atmosphere giving the expected product fluticasone propionate **1**. Dilution with water upon completion of the reaction and collection of the product by filtration followed by washing with water gave **1** in 92.7% isolated yield.

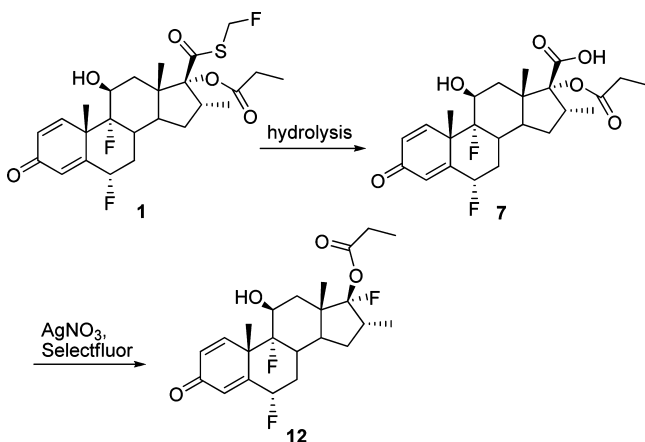
The major impurity **12** was obtained by preparative HPLC, the process of impurity formation was studied (Scheme 5). We suspected that fluticasone propionate (**1**) could be hydrolyzed

Table 2. Optimisation of decarboxylative fluorination of 10

entry	AgNO ₃ (equiv)	Selectfluor (equiv)	solvent	temp (°C)	time (h)	yield ^a (%)	purity ^b (%)
1	0.2	2.5	acetone/H ₂ O	30	8	80.1	85.0
2	0.2	2.5	acetone/H ₂ O	45	3	92.7	92.6
3	0.2	2.5	acetone/H ₂ O	55	3	92.0	79.7
4	0.1	2.5	acetone/H ₂ O	45	8	75.2	80.2
5	0.2	2.0	acetone/H ₂ O	45	8	70.3	83.1
6	0.2	2.5	MeCN/H ₂ O	55	8	80.5	67.0
7	0.2	2.5	THF/H ₂ O	55	8	0	

^aThe isolated yield was calculated with 10. ^bThe purity was monitored by HPLC.

Scheme 5. Process of impurity 12 generated



to 7 which might generate 12 through decarboxylative fluorination rapidly. The C-17 stereochemistry of compound 12 was established by X-ray crystallography. In order to confirm the speculation, we successfully using 7 as material to obtain 12 with AgNO₃/Selectfluor in acetone/H₂O solution at 45 °C.

CONCLUSION

In conclusion, an efficient, eco-friendly, and commercially viable process for the synthesis of fluticasone propionate (1) has been developed. In this method, compound 2 was used as the starting material, which was transformed to 1 in six steps including oxidation, esterification, acylation, alcoholysis, alkylation, and fluorodecarboxylation. Especially, compared to traditional flumethasone oxidation with H₅IO₆, application of haloform reaction to the synthesis of compound 6 for the first time could shorten reaction routes, reduce the cost, and improve the total yield dramatically. Furthermore, the usage of toxic, extremely costly, and pollutive BrCH₂F was replaced by an efficient method with AgNO₃ and Selectfluor in a good yield.

EXPERIMENTAL SECTION

Compound 2 was provided by Zhejiang Xianju Junye Pharmaceutical Co., Ltd., and all other chemicals were purchased from commercial sources and were used without further purification. HPLC analysis for fluticasone propionate (1) was carried out on an Agilent HPLC system (series 1200, Agilent Technologies, Germany) equipped with Agilent ZORBAX SB-C18 reversed-phase column (250 mm × 4.6 mm, 5 μm). A mobile phase of methanol, acetonitrile, and buffer with 1.2 g/L of monobasic ammonium phosphate, a pH of 3.5 adjusted with phosphoric acid, (50:15:35) was used at a flow rate of 1.5 mL/min and a column temperature of 40 °C.

The UV detector was set at 239 nm to analyze the column effluent. ¹H (400 MHz) NMR, ¹³C (101 MHz) NMR, and ¹⁹F (376 MHz) NMR spectra were recorded on a Varian spectrometer in CDCl₃ or DMSO-*d*₆ using tetramethylsilane (TMS) as internal standards.

6α,9α-Difluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carboxylic Acid (6). *Method A.* NaOH (25.0 g, 0.625 mol) was dissolved in H₂O (0.040 L), the mixture was diluted with 0.500 L of THF and 0.500 L of EtOH. Into the solution, 2 (50.0 g, 0.126 mol) was added, then 10% NaClO (0.500 L) was added gradually at 25 °C. The reaction was kept at 25–30 °C for 6 h. When the reaction was finished, the remaining oxidizing agent (NaClO) was destroyed by the addition of excess 10% Na₂SO₃ solution. The solvent THF/EtOH was removed under reduced pressure. Ethyl acetate (0.500 L) was added to the solution; the layers were separated, and then acidification of the aqueous phase to pH = 1.0–2.0 by 3 mol/L HCl furnished a white precipitate of 6 (32.0 g), which was collected by filtration, washed with water, and dried. Yield: 63.7%; HPLC purity 96.0%.

Method B. Br₂ (140.0 g, 0.875 mol) was added slowly to a vigorously stirred solution of 130.0 g of NaOH in 1.170 L of H₂O while cooling in an ice-salt-bath. When all of the Br₂ had dissolved, the mixture was diluted with 0.600 L of cold dioxane, and the ice-cold NaBrO was added slowly to a stirred solution of 100.0 g of 2 in 1.400 L of dioxane which was maintained at a temperature below 8 °C throughout the oxidation. After 5 h, the remaining oxidizing agent (NaBrO) was destroyed by the addition of excess 10% Na₂SO₃ solution. The solvent dioxane was removed under reduced pressure. Ethyl acetate (1.000 L) was added to the solution; the layers were separated, then acidification of the aqueous phase to pH = 1.0–2.0 by 3 mol/L HCl furnished a white precipitate of 6 (85.0 g), which was collected by filtration, washed with water, and dried. Yield: 84.5%; HPLC purity 95.6%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.45 (s, 1H), 7.24 (d, *J* = 10.3 Hz, 1H), 6.27 (dd, *J*₁ = 10.2 Hz, *J*₂ = 1.6 Hz, 1H), 6.08 (s, 1H), 5.70–5.54 (2m, 1H), 5.32 (s, 1H), 4.69 (s, 1H), 4.12 (d, *J* = 11.7 Hz, 1H), 2.88–2.80 (m, 1H), 2.50–2.35 (m, 2H), 2.25–1.96 (m, 3H), 1.70–1.50 (m, 2H), 1.49 (s, 3H), 1.12–1.05 (m, 1H), 0.99 (s, 3H), 0.86 (d, *J* = 7.0 Hz, 3H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 184.14 (s), 174.35 (s), 162.86 (d, *J* = 13.7 Hz), 151.86 (s), 128.85 (s), 119.23 (d, *J* = 12.9 Hz), 100.13 (d, *J* = 176.0 Hz), 86.83 (d, *J* = 178.0 Hz), 85.34 (s), 70.61 (d, *J* = 36.0 Hz), 48.14 (d, *J* = 19.5 Hz), 47.31 (s), 42.23 (s), 35.42 (s), 35.19 (s), 33.91 (d, *J* = 18.8 Hz), 32.30 (m), 31.99 (s), 22.86 (s), 16.93 (s), 15.45 (s); MS(ESI-) *m/z* 395.2 [M – H]⁺.

6α,9α-Difluoro-11β-hydroxy-16α-methyl-17α-propionyloxy-3-oxoandrosta-1,4-diene-17β-carboxylic Acid (7). To a suspension of 6 (85.0 g, 0.215 mol) in acetone (0.425 L) at 10–15 °C was added sequentially Et₃N (65.1 g,

0.645 mol) and propionic anhydride (83.8 g, 0.645 mol). After stirring for 4 h at 25 °C, Et₃NH (31.4 g, 0.430 mol) was added dropwise at 10–15 °C and then stirred at 25 °C for 1 h. Thereafter, the reaction mixture was acidified to pH 1.0–1.5 with 1 mol/L HCl at 0 °C. The precipitated product **7** (93.3 g) was obtained by filtered, washed with water, and dried. Yield 96.0%; HPLC purity 97.0%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.24 (d, *J* = 10.3 Hz, 1H), 6.27 (dd, *J* = 10.1, 1.9 Hz, 1H), 6.09 (s, 1H), 5.70–5.54 (2m, 1H), 5.46 (s, 1H), 4.16 (m, 1H), 3.14 (m, 1H), 2.50 (m, 1H), 2.30 (q, *J* = 7.2 Hz, 2H), 2.23 (m, 1H), 2.05 (m, 2H), 1.82–1.68 (m, 2H), 1.49 (m, 4H), 1.18 (m, 1H), 1.01 (t, *J* = 7.2 Hz, 3H), 1.00 (s, 3H), 0.84 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 184.03 (s), 171.96 (s), 169.79 (s), 162.59 (d, *J* = 13.5 Hz), 151.64 (s), 128.88 (s), 119.24 (d, *J* = 12.1 Hz), 99.96 (d, *J* = 175.9 Hz), 91.13 (s), 86.69 (d, *J* = 180.8 Hz), 70.23 (d, *J* = 36.1 Hz), 47.96 (d, *J* = 22.2 Hz), 47.64 (s), 42.63 (s), 35.41 (s), 35.30 (s), 33.86 (d, *J* = 18.9 Hz), 33.08 (s), 32.19 (m), 27.02 (s), 22.77 (s), 16.44 (s), 16.43 (s), 9.26 (s); MS(ESI+) *m/z* 475.4 [M + Na]⁺.

6α,9α-Difluoro-11β-hydroxy-16α-methyl-17α-propionyloxy-3-oxoandrosta-1,4-diene-17β-carbothioic Acid (9). A solution of **7** (93.3 g, 0.206 mol) and *N,N*-dimethylthiocarbonyl chloride (50.8 g, 0.449 mol) in acetone (1.866 L) at room temperature was cooled to 10–15 °C. It was sequentially treated with Et₃N (41.3 g, 0.413 mol), NaI (15.0 g, 0.080 mol), and water (9.330 mL, 10% w/w with **7**) at 10–15 °C. The solution was stirred for 6 h at 30 °C, then added DMF (0.466 L) and water (3.000 L). The resultant was cooled to 0 °C and stirred for 1 h. The precipitated product **8** (106.6 g) was obtained by filtration, washed with water, and dried. Yield 96.0%; HPLC purity 96.5%.

A suspension of **8** (106.6 g, 0.196 mol) and K₂CO₃ (54.1 g, 0.392 mol) in methanol (0.530 L) was stirred at 25 °C for 5 h under a blanket of nitrogen. Thereafter, water (0.530 L) was added to the reaction mixture, and the resultant clear solution was washed twice with toluene (0.212 L). The aqueous layer was acidified with 1 mol/L HCl until pH is 1.5 to 2.0. The precipitated product was filtered, washed with water, and dried to obtain **9** (87.1 g). Yield 95.0%; HPLC purity 96.0%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.25 (d, *J* = 11.2 Hz, 1H), 6.30 (dd, *J* = 10.1, 1.8 Hz, 1H), 6.11 (s, 1H), 5.80 (d, *J* = 5.0 Hz, 1H), 5.72–5.55 (2m, 1H), 4.27 (m, 1H), 3.30 (m, 1H), 2.64–2.54 (m, 1H), 2.40 (q, *J* = 7.5 Hz, 2H), 2.30–2.09 (m, 4H), 1.92–1.88 (m, 1H), 1.51 (m, 4H), 1.26 (m, 1H), 1.13 (s, 3H), 1.03 (t, *J* = 7.5 Hz, 3H), 0.87 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 189.76 (s), 184.00 (s), 172.36 (s), 162.45 (d, *J* = 13.5 Hz), 151.38 (d, *J* = 10.9 Hz), 128.92 (s), 119.27 (d, *J* = 12.5 Hz), 99.73 (d, *J* = 176.4 Hz), 96.90 (s), 86.63 (d, *J* = 174.0 Hz), 69.85 (d, *J* = 36.1 Hz), 48.34 (s), 47.87 (d, *J* = 24.4 Hz), 42.90 (s), 36.63 (s), 35.44 (s), 33.76 (d, *J* = 18.8 Hz), 33.51 (s), 32.01 (m), 27.07 (s), 22.84 (s), 17.08 (s), 15.51 (s), 9.05 (s); MS(ESI-) *m/z* 467.1 [M - H]⁺.

6α,9α-Difluoro-11β-hydroxy-16α-methyl-17α-propionyloxy-3-oxoandrosta-1,4-diene-17β-carbothioate (10). A solution of **9** (87.1 g, 0.186 mol), Et₃N (28.2 g, 0.279 mol), and BrCH₂COOH (28.2 g, 0.205 mol) in acetone (0.871 L) was stirred at 25 °C for 5 h. Thereafter, water (0.871 L) was added, and the reaction mixture was acidified to pH 1.0–1.5 with 1 mol/L HCl at 0 °C. The precipitated product **10** (95.0 g) was obtained by filtered, washed with water, and dried. Yield 97.1%; HPLC purity 97.0%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.24 (d, *J* = 10.6 Hz, 1H), 6.28 (dd, *J* = 10.0, 1.6 Hz, 1H), 6.10 (s, 1H), 5.60 (d, *J* = 4.4 Hz, 1H), 5.70–5.53 (2m, 1H), 4.19

(m, 1H), 3.67 (s, 2H), 3.25 (m, 1H), 2.56–2.45 (m, 1H), 2.33 (q, *J* = 7.4 Hz, 2H), 2.24 (m, 1H), 2.08 (m, 2H), 1.91–1.86 (m, 2H), 1.48 (m, 4H), 1.24 (m, 1H), 1.02 (s, 3H), 1.00 (t, *J* = 7.6 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 194.93 (s), 184.01 (s), 171.81 (s), 169.19 (s), 162.49 (d, *J* = 13.4 Hz), 151.46 (d, *J* = 8.1 Hz), 128.90 (s), 119.25 (d, *J* = 12.8 Hz), 99.84 (d, *J* = 176.4 Hz), 95.63 (s), 86.68 (d, *J* = 180.7 Hz), 70.00 (d, *J* = 35.0 Hz), 48.65 (s), 47.90 (d, *J* = 19.9 Hz), 42.71 (s), 35.75 (s), 35.07 (s), 33.78 (d, *J* = 19.3 Hz), 33.40 (s), 31.98 (m), 31.47 (s), 27.09 (s), 22.77 (s), 17.03 (s), 15.83 (s), 9.10 (s); MS(ESI-) *m/z* 525.0 [M - H]⁺.

S-Fluoromethyl-6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-propionyloxy-3-oxoandrosta-1,4-diene-17β-carbothioate (1). A solution of **10** (95.0 g, 0.180 mol), Selectfluor (159.3 g, 0.450 mol), and AgNO₃ (6.1 g, 0.036 mol) in acetone (1.900 L) and water (0.950 L) was stirred at 45 °C for 3 h under a blanket of nitrogen. Then water (1.900 L) was added to the solution; the resultant was cooled to 0 °C and stirred for 1 h. The precipitated product **1** (83.5 g) was collected by filtered, washed with water, and dried. Yield 92.7%; HPLC purity 92.6%.

Purification. The crude product **1** (83.5 g) was dissolved in ethyl acetate (0.835 L) and ethanol (3.340 L). The suspension was refluxed for 30 min, gradually cooled to 0 °C, and stirred for 1 h, and the solid was collected by filtration and dried at 40 °C under vacuum to provide 69.5 g (83%) of product **1**. HPLC purity 99.2%; residual silver content 0.04633 (μg/g).¹⁴

¹H NMR (400 MHz, DMSO-*d*₆) δ 7.23 (d, *J* = 10.0 Hz, 1H), 6.28 (dd, *J* = 10.1, 1.6 Hz, 1H), 6.10 (s, 1H), 5.92 (*J* = 50.0 Hz, 2H), 5.70–5.54 (2m, 1H), 5.58 (d, *J* = 3.2 Hz, 1H), 4.20 (m, 1H), 3.28 (m, 1H), 2.36 (q, *J* = 7.2 Hz, 2H), 2.23 (m, 1H), 2.09 (m, 2H), 1.86 (m, 2H), 1.53 (m, 1H), 1.48 (s, 3H), 1.26 (m, 1H), 1.05 (m, 1H), 1.01 (t, *J* = 7.2 Hz, 3H), 0.99 (s, 3H), 0.89 (d, *J* = 7.1 Hz, 3H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 192.87 (s), 183.98 (s), 172.07 (s), 162.43 (d, *J* = 13.5 Hz), 151.54 (s), 128.91 (s), 119.25 (d, *J* = 12.1 Hz), 99.72 (d, *J* = 176.3 Hz), 95.94 (s), 86.62 (d, *J* = 178.0 Hz), 80.92 (d, *J* = 211.8 Hz), 69.97 (d, *J* = 37.2 Hz), 48.40 (s), 47.84 (d, *J* = 22.4 Hz), 42.84 (s), 35.74 (s), 35.10 (s), 33.73 (d, *J* = 19.4 Hz), 33.37 (s), 31.93 (m), 26.94 (s), 22.73 (s), 16.95 (s), 16.08 (s), 9.05 (s); ¹⁹F NMR (376 MHz, CDCl₃) δ -165.35 (dd, *J* = 27.5, 8.5 Hz), -187.00 (dd, *J* = 48.3, 13.8 Hz), -191.35 (t, *J* = 49.6 Hz); MS(ESI+) *m/z* 501.0 [M + H]⁺.

6α,9α,17α-Trifluoro-11β-hydroxy-16α-methyl-17β-propionyloxy-3-oxoandrosta-1,4-diene (12). ¹H NMR (400 MHz, CDCl₃) δ 7.11 (d, *J* = 10.1 Hz, 1H), 6.41 (s, 1H), 6.35 (dd, *J* = 10.1, 1.2 Hz, 1H), 5.45–5.29 (2m, 1H), 4.35 (m, 1H), 2.58–2.46 (m, 1H), 2.35 (q, *J* = 7.6 Hz, 2H), 2.28–2.23 (m, 1H), 2.05–1.68 (m, 6H), 1.52 (s, 3H), 1.35–1.28 (m, 1H), 1.18–1.07 (m, 9H); ¹³C NMR (101 MHz, CDCl₃) δ 185.20 (s), 171.28 (s), 160.94 (d, *J* = 13.8 Hz), 150.23 (s), 130.10 (s), 121.93 (d, *J* = 250 Hz), 121.08 (d, *J* = 9.7 Hz), 98.53 (d, *J* = 177.4 Hz), 86.47 (d, *J* = 181.1 Hz), 71.76 (d, *J* = 35.1 Hz), 48.05 (d, *J* = 22.6 Hz), 47.08 (d, *J* = 20.6 Hz), 42.09 (s), 39.58 (s), 39.36 (s), 37.79 (s), 33.21 (m), 32.08 (s), 28.13 (s), 23.25 (s), 16.44 (s), 15.32 (d, *J* = 13.1 Hz), 9.04 (s); ¹⁹F NMR (376 MHz, CDCl₃) δ -129.60 (d, *J* = 17.3 Hz), -165.39 (dd, *J* = 27.5, 8.3 Hz), -187.05 (dd, *J* = 48.3, 13.7 Hz); HRMS(ESI+): C₂₃H₃₀F₃O₄ [M + H]⁺; calculated: 427.2091, found: 427.2089.

■ ASSOCIATED CONTENT

Supporting Information

Safety assessment for the NaClO oxidation and fluorodecarboxylation, ^1H and ^{13}C NMR copies for compounds **6**, **7**, **9**, **10**, **1**, and **12**, ^{19}F NMR copies for compounds **1** and **12**, and X-ray crystallographic data for compound **12**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*Telephone/fax: (+86)57188320899. E-mail: pharmlab@zjut.edu.cn.

Notes

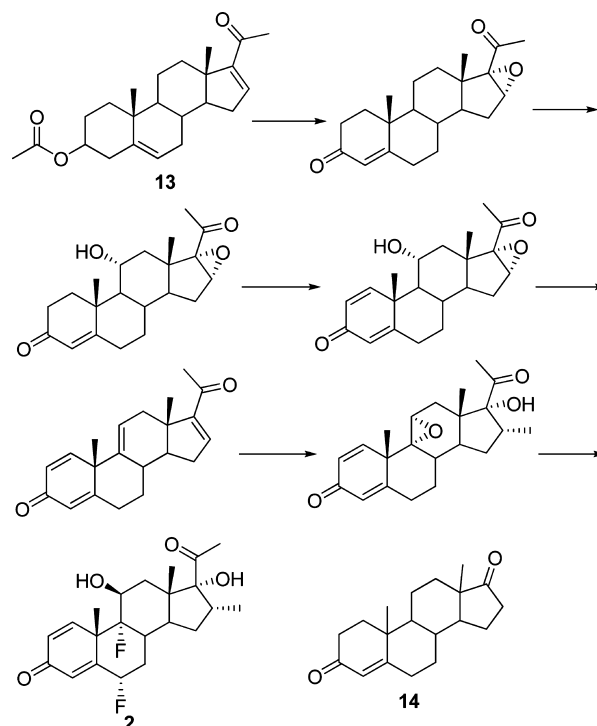
The authors declare no competing financial interest.

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- (7) Compound **13**, acquired by chemical degradation of Saponin, is a basic raw material for the synthesis of steroidal glucocorticoid drugs. Compound **14** (17-keto), acquired by biological selective degradation of phytosterol side chain, is a basic raw material for the synthesis of sex hormones. It is difficult to synthesize 21-desoxy from 17-keto. Compound **2** could be prepared from **13** in several steps, and flumethasone (**5**) was prepared from **2**. In our improved process, applying haloform reaction to the synthesis of compound **6** from **2** could shorten reaction routes, reduce the cost, and improve the total yield (see scheme below).



(8) We have checked the prices for NaClO, Br₂, and H₂IO₆ on a tonne scale. 10% NaClO (96 \$ per ton), Br₂ (288 \$ per ton), and NaBrO could be prepared by Br₂ on the spot. H₂IO₆ needs 136085 \$ per ton, and it was not friendly to the environment.

(9) The yield of NaClO oxidation (63.7%) was higher than previous synthesis in four steps (45%), even if it was lower than NaBrO oxidation (84.5%). Furthermore, the NaClO oxidation system was more environmentally friendly and suitable for industrialization.

(10) Dioxane could be recycled under reduced pressure, and the water in the recycled dioxane has no significant influence for the next halogen reaction.

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(12) In the previous routes, BrCH₂F is used as the major electrophilic monofluoromethylation reagent. However, BrCH₂F is costly (2500 \$ per kg) and toxic and will destroy the ozone layer. The cost of Selectfluor (170 \$ per kg)/AgNO₃ (500 \$ per kg) is lower than BrCH₂F. Furthermore, Selectfluor/AgNO₃ is more environmentally friendly than BrCH₂F.

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(14) According to the ICH Q3D, we calculated the USP Inhalation Limit of Silver was close to 0.69 (μg/g). The residual silver content of compound **1** was 0.04633 (μg/g) by ICP-MS detection. In addition, the silver salts in the aqueous waste stream could be recycled. Silver salts reacted with HCl or NaCl could generate the AgCl precipitation which could be collected by filtration.