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Improved Synthesis of Fluticasone Propionate

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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 H_5IO_6 as an oxidizing agent. Furthermore, toxic, expensive, and pollutive $BrCH_2F$ was replaced by $AgNO_3$ 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 H_5IO_6 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 chloride[4] in the presence of an iodide catalyst and Et_3N to produce **8**, followed by hydrolyzation with K_2CO_3,[2a] Et_2NH,[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 $BrCH_2F$,[2a] $ClCH_2F$,[5a] or *S*-(monofluoromethyl) diarylsulfonium tetrafluoroborate[5f,g] directly. Using $BrCH_2F$ can get an ideal yield; however, $BrCH_2F$ is costly and will destroy to the ozone layer. In addition, **9** reacted with $BrCH_2Cl$ or Br_2CH_2 and then by an anion exchange with AgF,[2c,5e] 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 XeF_2 and BrF_3.[5d] Unfortunately, XeF_2 is extremely expensive, and BrF_3 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 XeF_2 and BrF_3 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 H_5IO_6 as an oxidant and $BrCH_2F$, XeF_2, BrF_3, 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).

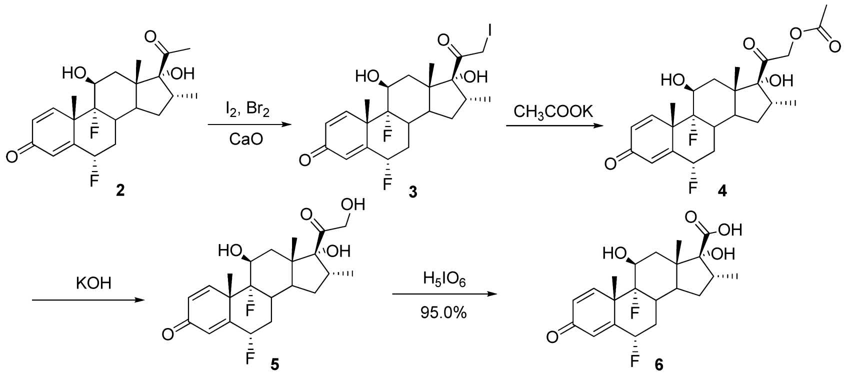
RESULTS AND DISCUSSION

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/H_2O, THF/H_2O, dimethoxyethane/H_2O, and EtOH/H_2O, 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/H_2O/EtOH, which provided a homogeneous reaction system.

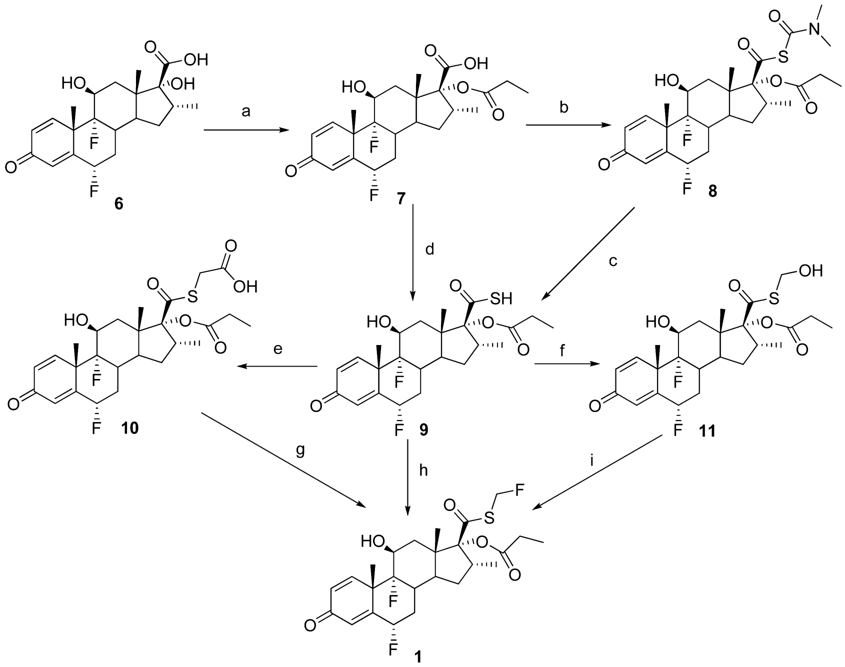
By contrast, the usage of NaBrO which has a stronger activity than NaClO could get a higher yield of 84.5% in a lower temperature (Scheme 3). To this reaction, dioxane/H_2O was proved to be the best solvent.[10] Other solvents such as THF/H_2O, dimethoxyethane/H_2O, EtOH/H_2O, and THF/H_2O/EtOH did not 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

Received: April 14, 2014

Scheme 1. Previous route for the synthesis of 6



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



[a] Reactions and conditions: (a) (i) propionic anhydride or propionyl fluoride/Et_3N; (ii) Et_2NH; (b) *N,N*-dimethylthiocarbamoyl chloride/Et_3N/NaI or tetrabutylammonium iodide; (c) K_2CO_3 or Et_2NH or NaSH; (d) CDI/NaSH; (e) $BrCH_2COOH$/Et_3N; (f) formaldehyde; (g) XeF_2/BrF_3; (h) $BrCH_2F$ or $ClCH_2F$ or *S*-(monofluoromethyl) diarylsulfonium tetrafluoroborate or $BrCH_2Cl$/AgF or $BrCH_2Cl$/KI/KF; (i) Deoxo-Fluor or DAST.

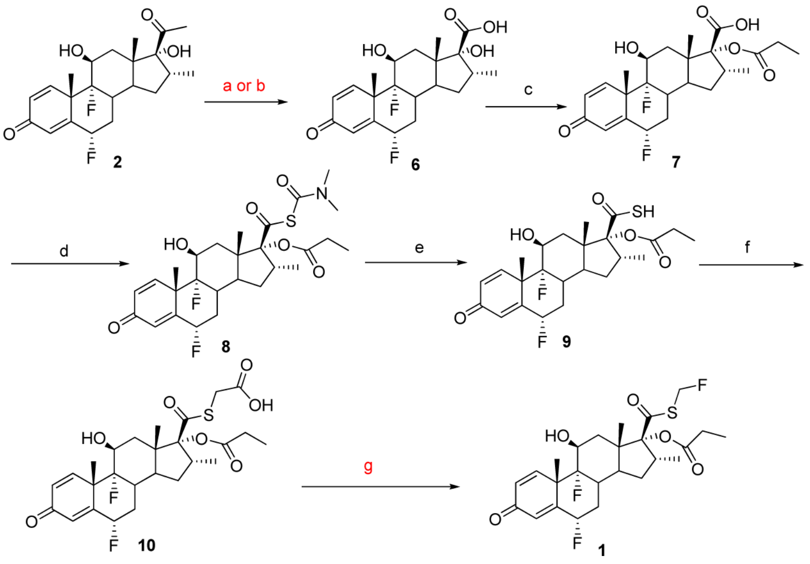
solvent THF/EtOH or dioxane was removed under reduced pressure. After extraction with ethyl acetate, the aqueous phase was acidified with hydrochloric acid to furnish a white precipitate of **6**, which was collected by filtration, washed with water, and dried.

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 $BrCH_2COOH$ 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 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 $AgNO_3$/Selectfluor (Scheme 4).[12] According to the literature,[11a] the combination of $AgNO_3$ (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]



[a]Reactions and conditions: (a) NaClO/NaOH, THF/EtOH/H_2O, 25 °C, 63.7%; (b) NaBrO/NaOH, dioxane/H_2O, 0−5 °C, 84.5%; (c) (i) propionic anhydride/Et_3N, acetone, 15−25 °C; (ii) Et_2NH, 15−25 °C, 97.3%; (d) *N*,*N*-dimethylthiocarbamoyl chloride/Et_3N/NaI, acetone/H_2O, 30 °C, 96.0%; (e) K_2CO_3, CH_3OH, 25 °C, 95.0%; (f) $BrCH_2COOH$/Et_3N, acetone, 15−25 °C, 97.1%; (g) $AgNO_3$/Selectfluor, acetone/H_2O, 45 °C, 92.7%.

Scheme 4. Decarboxylative fluorination for the synthesis of 1

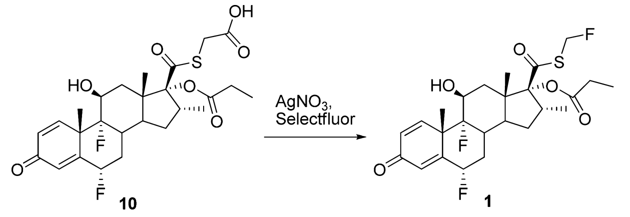


Table 1. Screening of Ag(I) catalyst and N−F reagent of decarboxylative fluorination of 10[a]

entry	catalyst (equiv)	N−F reagent (equiv)	solvent	time (h)	yield[b] (%)	purity[c] (%)
1	$AgNO_3$	Selectfluor	acetone/H_2O	3	92.7	92.6
2	AgOAc	Selectfluor	acetone/H_2O	8	64.2	74.2
3	AgOTf	Selectfluor	acetone/H_2O	8	48.8	79.5
4		Selectfluor	acetone/H_2O	8	0	
5	$AgNO_3$	NFSI	acetone/H_2O	8	0	
6	$AgNO_3$	Selectfluor	acetone	8	trace	

[a]Reagents and conditions: 1.0 equiv **10**, 0.2 equiv catalyst, 2.5 equiv N−F reagent, 45 °C, under nitrogen. [b]The isolated yield was calculated with **10**. [c]The purity was monitored by HPLC.

fluorination with $AgNO_3$/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 $AgNO_3$ and Selectfluor (Table 2). As shown in (Table 2, entry 1), **10** was treated with $AgNO_3$ (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 reaction was performed at 55 °C (Table 2, entry 3). Unfortunately, using $AgNO_3$ (10 mol %)/Selectfluor (2.5 equiv) or $AgNO_3$ (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).

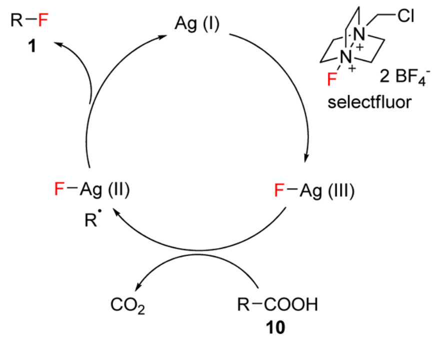


Figure 1. Proposed mechanism of silver-catalyzed decarboxylative fluorination.

The activity of decarboxylative fluorination was proved to be solvent-dependent, the mixed solvent of acetone/H_2O (2:1, v:v) exhibited the best activity (Table 2, entry 2). By contrast, a higher reaction temperature was needed in CH_3CN/H_2O (2:1, v:v) solution that led to more impurity **12** (Table 2, entry 6). No fluorodecarboxylation occurred in THF/H_2O (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 $AgNO_3$ (20 mol %) and Selectfluor (2.5 equiv) in acetone/H_2O (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.

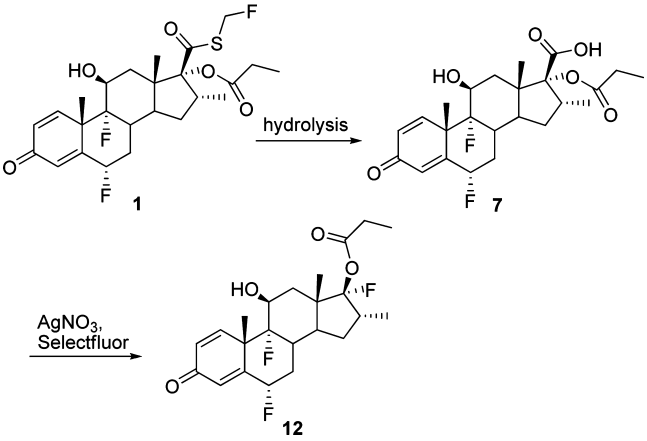
The major impurity **12** was obtained by preparative HPLC, the process of impurity formation was studied (Scheme 5). We suspected that fluticasone propionate (**1**) could be hydrolyzed

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_2O	30	8	80.1	85.0
2	0.2	2.5	acetone/H_2O	45	3	92.7	92.6
3	0.2	2.5	acetone/H_2O	55	3	92.0	79.7
4	0.1	2.5	acetone/H_2O	45	8	75.2	80.2
5	0.2	2.0	acetone/H_2O	45	8	70.3	83.1
6	0.2	2.5	MeCN/H_2O	55	8	80.5	67.0
7	0.2	2.5	THF/H_2O	55	8	0	

[a] The isolated yield was calculated with **10**. [b] The 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 $AgNO_3$/Selectfluor in acetone/H_2O 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 H_5IO_6, 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 $BrCH_2F$ was replaced by an efficient method with $AgNO_3$ 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, ^{13}C (101 MHz) NMR, and ^{19}F (376 MHz) NMR spectra were recorded on a Varian spectrometer in $CDCl_3$ or DMSO-d_6 using tetramethylsilane (TMS) as internal standards.

6*α*,9*α*-Difluoro-11*β*,17*α*-dihydroxy-16*α*-methyl-3-oxoandrosta-1,4-diene-17*β*-carboxylic Acid (6). *Method A.* NaOH (25.0 g, 0.625 mol) was dissolved in H_2O (0.040 L), the mixture was diluted with 0.500 L of THF and 0.500L 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% Na_2SO_3 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. Br_2 (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 H_2O while cooling in an ice-salt-bath. When all of the Br_2 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% Na_2SO_3 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); ^{13}C 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 $[M - H]^+$.

6*α*,9*α*-Difluoro-11*β*-hydroxy-16*α*-methyl-17*α*-propionyloxy-3-oxoandrosta-1,4-diene-17*β*-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 Et_3N (65.1 g, 0.645 mol) and propionic anhydride (83.8 g, 0.645 mol). After stirring for 4 h at 25 °C, Et_2NH (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%; ^{1}H 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); ^{13}C 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]$^+$.

6*α*,9*α*-Difluoro-11*β*-hydroxy-16*α*-methyl-17*α*-propionyloxy-3-oxoandrosta-1,4-diene-17*β*-carbothioic Acid (9). A solution of **7** (93.3 g, 0.206 mol) and *N*,*N*-dimethylthiocarbamoyl 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 Et_3N (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 K_2CO_3 (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%; ^{1}H 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); ^{13}C 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]$^+$.

6*α*,9*α*-Difluoro-11*β*-hydroxy-16*α*-methyl-17*α*-propionyloxy-3-oxoandrosta-1,4-diene-17*β*-carbothioate (10). A solution of **9** (87.1 g, 0.186 mol), Et_3N (28.2 g, 0.279 mol), and $BrCH_2COOH$ (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%; ^{1}H 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); ^{13}C 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-6*α*,9*α*-difluoro-11*β*-hydroxy-16*α*-methyl-17*α*-propionyloxy-3-oxoandrosta-1,4-diene-17*β*-carbothioate (1).** A solution of **10** (95.0 g, 0.180 mol), Selectfluor (159.3 g, 0.450 mol), and $AgNO_3$ (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 soild 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]

^{1}H 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); ^{13}C 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); ^{19}F NMR (376 MHz, $CDCl_3$) 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]$^+$.

6*α*,9*α*,17*α*-Trifluoro-11*β*-hydroxy-16*α*-methyl-17*β*-propionyloxy-3-oxoandrosta-1,4-diene (12). ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (101 MHz, $CDCl_3$) 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); ^{19}F NMR (376 MHz, $CDCl_3$) 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+): $C_{23}H_{30}F_3O_4$ [M + H]$^+$; calculated: 427.2091, found: 427.2089.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Safety assessment for the NaClO oxidation and fluorodecarboxylation, ^{1}H 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.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge financial support from National Natural Science Foundation of China (No. 21176222) and Collaborative Innovation Center of Yangtze River Delta Region Green Pharmaceuticals.

■ REFERENCES

(1) (a) Barnes, P. J. *Pharmaceuticals* **2010**, *3*, 514–540. (b) Rhen, T.; Cidlowski, J. A. *New Engl. J. Med.* **2005**, *353*, 1711–1723.

(2) (a) Jadav, K. J.; Kambhampati, S.; Chitturi, T. R.; Thennati, R. World Patent WO 2004/001369, 2004. (b) Phillipps, G. H.; Bailey, E. J.; Borella, R. A.; Buckton, J. B.; Clark, J. C.; Doherty, A. E.; English, A. F.; Fazakerley, H.; Laing, S. B.; Lane-Allman, E.; Robinson, J. D.; Sandford, P. E.; Sharratt, P. J.; Steeples, I. P.; Stonehouse, R. D.; Williamson, C. *J. Med. Chem.* **1994**, *37*, 3717–3729. (c) Myhren, F.; Sandvold, M. L.; Eriksen, O. H.; Hagen, S. World Patent WO 2008/115069 A2, 2008.

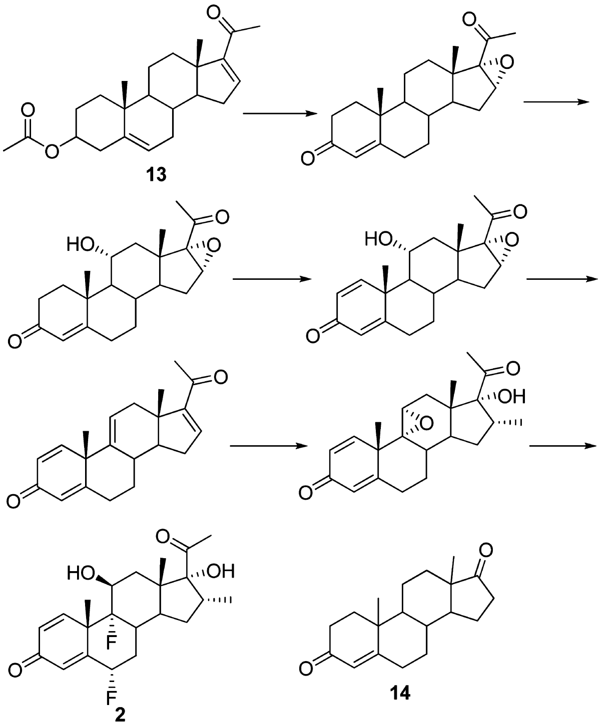
(3) Wu, M. Z. China Patent CN 101838301 A, 2010.

(4) (a) Barkalow, J.; Chamberlin, S. A.; Cooper, A. J. World Patent WO 01/62722 A2, 2001. (b) Qin, G. R. China Patent CN 100497367C, 2009.

(5) (a) Partridge, J. J.; Walker, D. S. World Patent WO 03/013427 A2, 2003. (b) Shen, Y. L.; Liu, X. L.; Xie, L. B.; He, H. X. China Patent CN 100549022C, 2009. (c) Cainelli, G.; Umani, R. A.; Sandri, S.; Contento, M.; Fortunato, G. World Patent WO 2004/052912 A1, 2004. (d) Leitao, E. P. T.; Heggie, W. World Patent WO 2011/151625 A1, 2011. (e) Zhu, D. J.; Zhang, D. F. China Patent CN 100560598C 2009. (f) Surya Prakash, G. K.; Ledneczki, I.; Chacko, S.; Olah, G. A. *Org. Lett.* **2008**, *10*, 557–560. (g) Leitao, E. P. T.; Turner, C. R. World Patent WO 2011/151624 A1, 2011.

(6) Djerassi, C.; Staunton, J. *J. Am. Chem. Soc.* **1961**, *83*, 736–743.

(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 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, Br_2, and H_5IO_6 on a tonne scale. 10% NaClO (96 $ per ton), Br_2 (288 $ per ton), and NaBrO could be prepared by Br_2 on the spot. H_5IO_6 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.

(11) (a) Yin, F.; Wang, Z. T.; Li, Z. D.; Li, C. Z. *J. Am. Chem. Soc.* **2012**, *134*, 10401–10404. (b) Ruedabecerril, M.; Sazepin, C. C.; Leung, J. C. T.; Okbinoglu, T.; Kennepohl, P.; Paquin, J. F.; Sammis, G. M. *J. Am. Chem. Soc.* **2012**, *134*, 4026–4029. (c) Leung, J. C.; Chatalova-Sazepin, C.; West, J. G.; Rueda-Becerril, M.; Paquin, J. F.; Sammis, G. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 10804–10807. (d) Mizuta, S.; Stenhagen, I. S. R.; O'Duill, M.; Wolstenhulme, J.; Kirjavainen, A. K.; Forsback, S. J.; Tredwell, M.; Sandford, G.; Moore, P. R.; Huiban, M.; Luthra, S. K.; Passchier, J.; Solin, O.; Gouverneur, V. *Org. Lett.* **2013**, *15*, 2648–2651. (e) Rueda-Becerril, M.; Mahé, O.; Drouin, M.; Majewski, M. B.; West, J. G.; Wolf, M. O.; Sammis, G. M.; Paquin, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 2637–2642.

(12) In the previous routes, $BrCH_2F$ is used as the major electrophilic monofluoromethylation reagent. However, $BrCH_2F$ is costly (2500 $ per kg) and toxic and will destroy the ozone layer. The cost of Selectfluor (170 $ per kg)/$AgNO_3$ (500 $ per kg) is lower than $BrCH_2F$. Furthermore, Selectfluor/$AgNO_3$ is more environmentally friendly than $BrCH_2F$.

(13) (a) Anderson, J. M.; Kochi, J. K. *J. Am. Chem. Soc.* **1970**, *92*, 1651–1659. (b) Anderson, J. M.; Kochi, J. K. *J. Org. Chem.* **1970**, *35*, 986–989. (c) Kouadio, I.; Kirschenbaum, L. J.; Mehrotra, R. N.; Sun, Y. *J. Chem. Soc., Perkin Trans. 2* **1990**, *12*, 2123–2127.

(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.