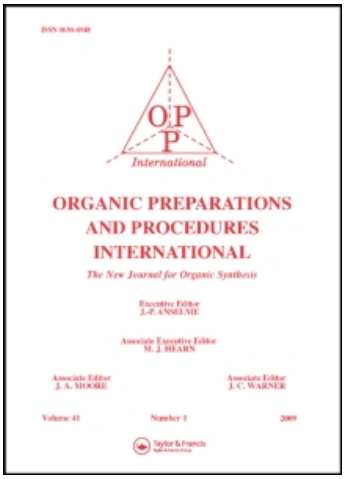

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SYNTHESIS OF SUBSTANCES RELATED TO FLUTICASONE PROPIONATE

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SYNTHESIS OF SUBSTANCES RELATED TO FLUTICASONE PROPIONATE

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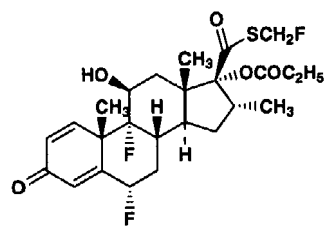
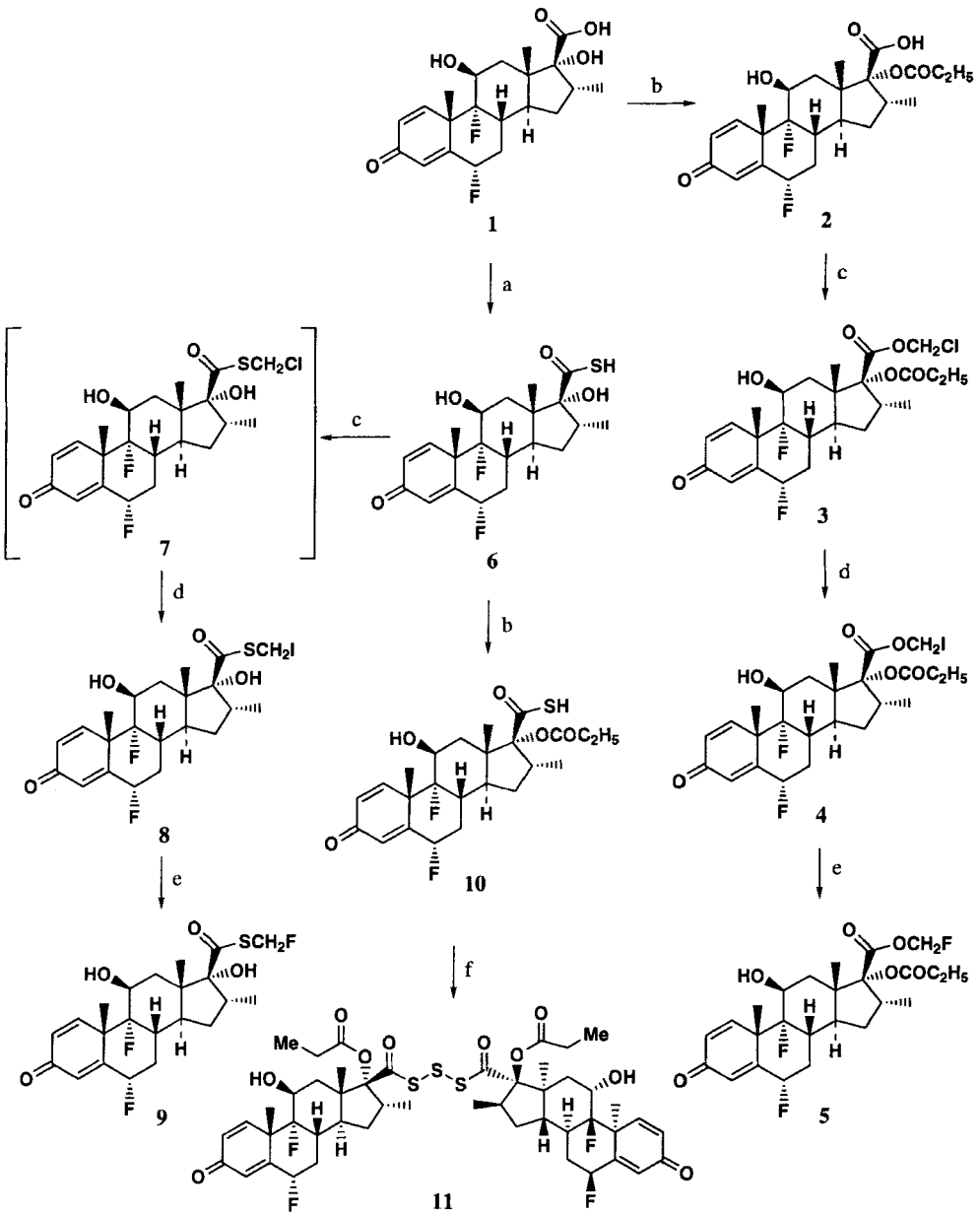
Related substances or impurities of active pharmaceutical ingredients (API) are important issues in process development, manufacturing and quality control of pharmaceutical compounds. In addition to drug efficacy, there is a strong emphasis on the purity of final drug substances and it is necessary to do full characterization and identification of any impurities to ensure the drug safety in clinical trials.[1] Fluticasone propionate is widely used for the treatment of allergy and inflammatory disorders,[2-4] and analysis and control of impurities are important to clinical safety. Gram-scale amounts of such impurities were required by quality control (QC) department as markers to locate the known related substances in fluticasone. The preparation of



Fluticasone Propionate

the impurities is also important to understand the possible mechanisms of their formation and thus helps to optimize the process and reduce their level in the API. We herein report the synthesis of three impurities **5**, **9**, **11** related to fluticasone propionate found in the course of our optimization of the preparation of fluticasone propionate (*Scheme 1*).



Reagents: a) i. CDI; ii. H_2S; b) i. C_2H_5COCl/Et_3N; ii. Et_2NH; c) $BrCH_2Cl$; d) NaI; e) AgF; f) $CH_3COS_3OCH_2CH_3$.

Scheme 1

Impurity **5** is a new compound isolated during our process optimization. Impurity **9** had been synthesized[6] in 22% yield from **1** as a biologically active compound used to treat allergy and immunoinflammatory disorder[3,7] and compound **11** has been suggested as another possible impurity.[5,11] However, as far as we know no synthetic details and spectral data of these three compounds related to fluticasone propionate (**5**, **9** and **11**)[8] have been described and now we report their synthesis (*Scheme 1*).

Regioselective acylation of **1** with propionyl chloride gave **2** (91%) which was alkylated with bromochloromethane in *N,N*-dimethylacetamide to afford **3** in 61% yield. Reaction of **3** with sodium iodide led to the iodomethyl derivative **4** (84%) which was then treated with silver fluoride to give the **5**. Similarly, compound **9** was easily obtained via an analogous procedure in a yield higher (36%) than that previously reported [6]. Compound **1** was converted to compound **6** by using H_2S in DMF with CDI in 92% yield. Regioselective acylation of **6** with propionyl chloride gave **10** (91%)[8].

EXPERIMENTAL SECTION

Melting points were determined on a WRR melting point apparatus and are uncorrected. Elemental analyses were performed on Elementar Vario EL. All reagents, solvents and compound **1** are commercially available and used as received. ^{1}H NMR spectra were obtained on a Bruker AMX-400/600 at 300 MHz using TMS as an internal standard. ^{13}C NMR spectra were obtained from a Gemini-300 spectrometer in deuterated solvents with TMS as an internal standard at room temperature. The mass spectra were recorded on a Finnigan MAT-95/711spectrometer.

6a,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxoandrosta-17α-(propionyloxy)androsta-1,4-diene-17β-carboxylic Acid (2). A solution of compound **1** (396 mg, 1.0 mmol) and Et_3N (353 µL, 2.5 mmol) in CH_2Cl_2 (10 mL) at -5°C was treated dropwise with stirring with propionyl chloride (219 µL, 2.5 mmol) in CH_2Cl_2 (0.5 mL). After 1 h, the reaction mixture was diluted with 10 mL CH_2Cl_2, washed with water, 10% hydrochloric acid, water, and brine, dried, and evaporated. The solid residue was stirred in acetone (10 mL), and treated with Et_2NH (363 µL, 3.5 mmol) for 1 h then the solution was poured into 10% hydrochloric acid (20 mL) and ice (20 mL). The precipitate was collected and dried to give compound **2** as a white solid (411 mg, 91%), mp. 219-220°C, *lit.*[10] mp. 217-218°C. The spectroscopic data correspond to those reported in literature.[10]

Chloromethyl-6a,9a-difluoro-11b-hydroxy-16a-methyl-3-oxoandrosta-17a-(propionyloxy)androsta-1,4-diene-17b-carboxylate (3). A solution of compound **2** (452 mg, 1.0 mmol) in DMA (2 mL) was stirred with $NaHCO_3$ (168 mg, 2.0 mmol) and bromochloromethane (325 µL, 5.0 mmol) for 40 h, diluted with EtOAc (10 mL), washed with 5% $NaHCO_3$ and water, dried, evaporated and crystallized to give compound **3** as a white solid (306 mg, 61%), mp. 239-241°C. ^{1}H-NMR (300 MHz, acetone-d_6): δ 7.28 (dd, J = 9.9, 1.5 Hz,

1H), 6.27 (dd, J = 9.9, 1.8 Hz, 1H), 6.21 (m, 1H), 5.93 (d, J = 6.1 Hz, 1H), 5.72 (d, J = 6.1 Hz, 1H), 5.62 (dddd, J = 49.5, 11.8, 6.8, 1.8 Hz, 1H), 4.39 (ddd, J = 9.5, 3.7, 2.3 Hz, 1H), 3.29 (m, 1H), 2.66 (m, 1H), 2.38 (q, J = 7.5 Hz, 2H), 2.34 (m, 1H), 2.22 (m, 2H), 1.89 (m, 2H), 1.62 (m, 1H), 1.61 (s, 3H), 1.31 (m, 1H), 1.12 (s, 3H), 1.07 (t, J = 7.5 Hz, 3H), 0.92 (d, J = 6.9 Hz, 3H). ^{13}C-NMR (100 MHz, acetone-d_6): δ 185.3, 173.5, 168.2, 162.8, 152.0, 129.8, 120.5, 101.1, 99.4, 86.4, 71.1, 70.0, 48.8, 43.7, 36.7, 36.2, 34.5, 34.3, 33.5, 33.0, 27.4, 23.2, 16.3, 16.2, 9.1.

HRMS(ESI) m/z Calcd for $C_{25}H_{31}ClF_2O_6$ [M+Na]$^+$ 523.1675. Found: 523.1669.

Anal. Calcd. for $C_{25}H_{31}ClF_2O_6$: C, 59.94; H, 6.24. Found: C, 60.07; H, 6.28

Iodomethyl-6α,9a-difluoro-11β-hydroxy-16α-methyl-3-oxoandrosta-17α-(propionyloxy)androsta-1,4-diene-17β-carboxylate (4). Compound **3** (501 mg, 1.0 mmol) and NaI (1.5 g, 10 mmol) were refluxed in acetone (10 mL) for 7 h, EtOAc (7.5 mL) was added, and the solution was washed with water, 10% sodium thiosulfate, 5% $NaHCO_3$, and water, dried, evaporated *in vacuo* and crystallized to give compound **4** as a white solid (497 mg, 84%), mp. 189-191°C. ^{1}H-NMR (300 MHz, acetone-d_6): δ 7.23 (dd, J = 10.2, 1.5 Hz, 1H), 6.27 (dd, J = 10.2, 2.0 Hz, 1H), 6.21 (m, 1H), 5.93 (d, J = 6.1 Hz, 1H), 5.72 (d, J = 6.1 Hz, 1H), 5.62 (dddd, J = 48.9, 11.5, 6.7, 1.7 Hz, 1H), 4.40 (ddd, J = 9.8, 3.6, 2.5 Hz, 1H), 3.27 (m, 1H), 2.65 (m, 1H), 2.38 (q, J = 7.5 Hz, 2H), 2.34 (m, 1H), 2.22 (m, 2H), 1.85 (m, 2H), 1.62 (m, 1H), 1.61 (s, 3H), 1.31 (m, 1H), 1.13 (s, 3H), 1.07 (t, J = 7.5 Hz, 3H), 0.92 (d, J = 7.5 Hz, 3H). ^{13}C-NMR (100 MHz, acetone-d_6): δ 185.2, 173.4, 168.3, 163.0, 151.9, 129.9, 120.5, 101.1, 99.3, 86.5, 71.4, 48.6, 43.8, 36.8, 36.2, 34.3, 33.8, 33.5, 33.1, 31.7, 27.5, 23.2, 16.3, 16.2, 9.1.

HRMS(ESI)m/z: Calcd for $C_{25}H_{31}F_2IO_6$ [M+Na]$^+$ 615.1031. Found: 615.1044

Anal. Calcd. for $C_{25}H_{31}F_2IO_6$: C, 50.69; H, 5.27. Found: C, 50.73; H, 5.32

Fluoromethyl-6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxoandrosta-17α-(propionyloxy)androsta-1,4-diene-17β-carboxylate (5). Compound **4** (592 mg, 1.0 mmol) and AgF (634mg, 5.0 mmol) were stirred in the dark at room temperature in CH_3CN (10 mL) for 3 h. The reaction mixture was diluted with EtOAc (100 mL) and filtered. The filtrate was washed with water, dried, evaporated *in vacuo* and crystallized to give **5** as a white solid (402 mg, 83%), mp. 233-235°C. ^{1}H-NMR (300 MHz, acetone-d_6): δ 7.28 (dd, J = 10.3, 1.6 Hz, 1H), 6.27 (dd, J = 10.3, 1.8 Hz, 1H), 6.21 (m, 1H), 5.88 (dd, J = 51.1, 2.2 Hz, 1H), 5.62 (dd, J = 50.9, 2.2 Hz, 1H), 5.61 (m, 1H), 4.40 (ddd, J = 9.8, 3.8, 2.4 Hz, 1H), 3.30 (m, 1H), 2.70 (m, 1H), 2.39 (q, J = 7.5 Hz, 2H), 2.34 (m, 1H), 2.24 (m, 2H), 1.89 (m, 2H), 1.62 (m, 1H), 1.61 (s, 3H), 1.32 (m, 1H), 1.10 (s, 3H), 1.07 (t, J = 7.5 Hz, 3H), 0.92 (d, J = 7.2 Hz, 3H). ^{13}C-NMR (100 MHz, acetone-d_6): δ 185.1, 173.4, 168.4, 162.8, 151.7, 130.0, 120.5, 101.0, 99.3, 93.7, 86.5, 71.3, 48.8, 48.6, 43.7, 36.7, 36.2, 34.5, 34.3, 33.6, 33.1, 23.2, 16.3, 16.2, 9.1.

HRMS(ESI) m/z: Calcd for $C_{25}H_{31}F_3O_6$ [M+Na]$^+$ 507.1970. Found: 507.1951.

Anal. Calcd for $C_{25}H_{31}F_3O_6$: C, 61.97; H, 6.45. Found: C, 61.93; H, 6.38

6α,9α-Difluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioic Acid (6). A solution of compound **1** (396 mg, 1.0 mmol) in DMF (10 mL) was treated with CDI

(324 mg, 2.0 mmol), and the mixture was stirred under nitrogen at room temperature for 4 h. Hydrogen sulfide was bubbled into the reaction mixture for 30 min. After 4 h the reaction mixture was poured into 2 mol/L HCl (10 mL) and ice (10 mL), the precipitate was collected and dried to give **6** as a white solid (380 mg, 92%) mp. 230-231°C, *lit.*[8] mp. 230-232°C. The spectroscopic data correspond to those reported in literature.[8]

***S*-Iodomethyl-6α,9a-difluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate (8).** A solution of compound **6** (412 mg, 1.0 mmol) in DMA (2 mL) was stirred with $NaHCO_3$ (168 mg, 2.0 mmol) and bromochloromethane (325 μL, 5.0 mmol) for 40 h, diluted with EtOAc (10 mL), washed with 5% $NaHCO_3$ and water, dried, evaporated *in vacuo* to give crude compound **7** as a white solid (EIMS m/z 460 [M^+]). The crude compound **7** and NaI (1.5 g, 10 mmol) were refluxed in acetone (10 mL) for 7 h, EtOAc (7.5 mL) was added, and the solution was washed with water, 10% sodium thiosulfate, 5% $NaHCO_3$, and water, dried, evaporated and crystallized to give compound **8** as a white solid (199 mg, 36%), mp. 218-220∞C. ^{1}H-NMR (300 MHz, acetone-d_6): δ 7.27 (dd, J = 10.2, 1.5 Hz, 1H), 6.25 (dd, J = 10.2, 2.0 Hz, 1H), 6.20 (m, 1H), 5.62 (dddd, J = 48.8, 11.4, 6.7, 1.9 Hz, 1H), 4.52 (s, 2H), 4.35 (ddd, J = 10.6, 3.9, 2.1 Hz, 1H), 3.09 (m, 1H), 2.64 (m, 1H), 2.31 (m, 3H), 1.86 (m, 1H), 1.63 (m, 2H), 1.61 (s, 3H), 1.29 (m, 1H), 1.12 (s, 3H), 0.96 (d, J = 7.4 Hz, 3H). ^{13}C-NMR (100 MHz, acetone-d_6): δ 201.3, 185.1, 163.0, 151.8, 129.9, 120.5, 92.4, 88.4, 86.6, 71.6, 49.6, 48.8, 44.4, 37.7, 36.1, 34.6, 34.4,33.5, 30.1, 23.3, 16.8, 14.8.

HRMS(ESI) m/z: Calcd for $C_{22}H_{27}F_2IO_4S$ [M+Na]$^+$ 575.0540. Found: 575.0555.

Anal. Calcd. for $C_{22}H_{27}F_2IO_4S$: C, 47.83; H, 4.93. Found: C, 48.08; H, 4.91

***S*-Fluoromethyl-6α,9α-difluoro-11β,17α-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β-carbothioate (9).** Compound **8** (552 mg, 1.0 mmol) and AgF (634mg, 5.0 mmol) were stirred in the dark at room temperature in CH_3CN (10 mL) for 3 h. The reaction mixture was diluted with EtOAc (10 mL) and filtered. The filtrate was washed with water, dried, evaporated and crystallized to give **9** as a white solid (364 mg, 82%), mp. 237-239°C. The spectroscopic data correspond to those reported in literature.[6]

6α,9α-Difluoro-11β-hydroxy-16α-methyl-3-oxoandrosta-17α-(propionyloxy)androsta-1,4-diene-17β-carbothioic Acid (10). A solution of compound **6** (412 mg, 1.0 mmol) and Et_3N (353 μL, 2.5 mmol) in CH_2Cl_2 (10 mL) at -5°C was treated dropwise with stirring with propionyl chloride (219 μL, 2.5 mmol) in CH_2Cl_2 (0.5 mL). After 1 h the reaction mixture was diluted with CH_2Cl_2, washed with water, 10% hydrochloric acid, water, and brine, dried, and evaporated. The residue was stirred in acetone (10 mL), and treated with Et_2NH (363 μL, 3.5 mmol) for 1 h then the solution was poured into 10% hydrochloric acid (20 mL) and ice (20 mL). The precipitate was collected and dried to give compound **10** as a white solid (427 mg, 91%), mp. 161-163°C, *lit.*[8] mp. 161-164°C. The spectroscopic data correspond to those reported in literature.[8]

17,17'-(Trisulfanediyldicarbonyl)*bis*(6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17α-yl) Dipropanoate (11)[5,11]. Compound **10** (469 mg, 1.0 mmol) and

acetylethoxytrisulfides (92 mg, 1.0 mmol) were refluxed in CCl_4 (3 mL) and CH_2Cl_2(3 mL) for 8 h. the solution was evaporated and the residue was chromatographed on silica gel using CH_2Cl_2-CH_3OH (100:2) to give **11** as a yellow solid (203mg, 42%), mp. 178-180°C. ^{1}H-NMR (300 MHz, acetone-d_6): δ 7.26 (dd, J = 10.3, 1.6 Hz, 2H), 6.26 (dd, J = 10.3, 2.0 Hz, 2H), 6.20 (m, 2H), 5.61 (dddd, J = 48.8, 11.5, 6.5, 1.7 Hz, 2H), 4.40 (m, 2H), 3.37 (m, 2H), 2.67 (m, 2H), 2.46 (q, J = 7.5 Hz, 4H), 2.34 (m, 2H), 2.22 (m, 4H), 1.97 (m, 4H), 1.62 (m, 2H), 1.61 (s, 6H), 1.39 (m, 2H), 1.12 (m, 12H), 0.99(d, J = 7.8 Hz, 6H). ^{13}C-NMR (100 MHz, DMSO-d_6): δ 192.1, 184.4, 172.5, 162.8, 151.8, 129.1, 119.4, 100.8, 96.1, 87.6, 69.6, 48.0, 47.8, 42.8, 36.6, 35.1, 33.5, 33.5, 30.7, 26.8, 22.7, 16.8, 16.1, 8.9.

HRMS (ESI) m/z Calcd for $C_{48}H_{58}F_4O_{10}S_3$ $[M+Na]^+$ 989.3026. Found: 989.3005.

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