Synthesis and CYP24A1-Dependent Metabolism of 23-Fluorinated Vitamin D₃ Analogues

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Supporting Information

ABSTRACT: Two novel 23-fluorinated 25-hydroxyvitamin D₃ analogues were synthesized using Inhoffen–Lythgoe diol as a precursor of the CD-ring, efficiently. Introduction of the C23 fluoro group was achieved by the deoxy-fluorination reaction using N,N-diethylaminosulfur trifluoride or 2-pyridinesulfonyl fluoride (PyFluor). Kinetic studies on the CYP24A1-dependent metabolism of these two analogues revealed that (23S)-23-fluoro-25-hydroxyvitamin D₃ was more resistant to CYP24A1-dependent metabolism than its 23R isomer.

INTRODUCTION

It is well known that human CYP24A1 plays an important role in the specific metabolism of 25-hydroxylated vitamin D₃ [25(OH)D₃] consisting of the 23-position and 24-position hydroxylation pathways that degrade the side chain (Scheme 1). The 3-step oxidation after the C23 hydroxylation of 25(OH)D₃ leads to the production of 25(OH)D₂6,23-lactone. On the other hand, the 24-hydroxylation pathway of 25(OH)D₃ produces calcitroic acid.

To increase the chemical or metabolic stability against CYP24A1, fluorine-substituted vitamin D₃ analogues have been actively synthesized. For example, falecalcitriol (1) has longer duration of action in vivo, and it was approved for the treatment of secondary hyperparathyroidism and hypoparathyroidism in Japan. Therefore, we focused on the importance of the fluorinated vitamin D₃ analogues and demonstrated an efficient synthetic methodology to introduce fluorine atoms to the side chain of vitamin D₃ On the 25(OH)D₃ side chain, the C23 position is one of the important catalytic sites of CYP24A1. However, to the best of our knowledge, only a few C23-fluorinated vitamin D₃ analogues have been synthesized thus far. The first report on C23-fluorinated vitamin D₃ analogues was the synthesis of 23,23-difluoro-25-hydroxyvitamin D₃ [23,23-F₂,25(OH)D₃ (2)] published by Kobayashi’s group in 1984. After that, Ikeda and colleagues reported (23R)-23,26,26,26,27,27,27-heptfluoro-1α,25-dihydroxyvitamin D₃ [(23R)-23,26,26,26,27,27,27-F₇,1α,25(OH)D₃] (3) and its 23S isomer [(23S)-23,26,26,26,27,27,27-F₇,1α,25-(OH)D₃] (4) in 2000. We have developed a novel practical approach to (23R)-23-fluoro-25-hydroxyvitamin D₃ [(23R)-23-F-25(OH)D₃] (5) and its 23S isomer [(23S)-23-F-25(OH)D₃] (6) (Figure 1), and clarified their biological activity, especially CYP24A1 metabolic resistance.

RESULTS AND DISCUSSION

The synthetic plan for analogues (5,6) is described in Scheme 2. Stereoselective introduction of the fluorine atom would be performed by deoxy-fluorination using N,N-diethylaminosulfur trifluoride (DAST) or 2-pyridinesulfonyl fluoride (PyFluor). Triene structures would be constructed by the Wittig–Horner coupling reaction between the CD-ring precursors (7,8) and the lithium salt of the A-ring anion from phosphine oxide 9.

The synthesis of CD-ring precursors 7 and 8 using PyFluor is shown in Scheme 3 (method A). The aldehyde 10 was synthesized in 4 steps by the established method from Inhoffen–Lythgoe diol. Introduction of the hydroxy group to C23 was accomplished by the aldol reaction with ethyl acetate, and the 25-hydroxy group was consequently constructed by Grignard reaction to provide diols 11 and 12. These two alcohols were separated by silica-gel column chromatography. Stereoselective deoxy-fluorination to the secondary hydroxy group (23-OH) of 11 and 12 was successfully performed by PyFluor to give 13 (from 12) and 14 (from 11) in moderate yields, without interfering with the
tertiary hydroxy group (25-OH). Deprotection of the TES group gave alcohols 15 and 16. Tetrapropylammonium perruthenate (TPAP) oxidation followed by trimethylsilylation of the 25-OH group gave ketones 7 and 8, respectively.

Next, we tried to improve the yield of the deoxy-fluorination step in Scheme 4 (method B). As we mentioned above, the yield of stereoselective deoxy-fluorination using PyFluor was relatively low, especially in the case of 23,23-diol (12). As shown in Scheme 4, another synthetic route to improve the yield of the CD-ring precursor (15) was developed. The synthetic intermediate in Scheme 3, aldehyde 10, was reacted with 2-methylallylmagnesium chloride to give a diastereomeric mixture of homoallylic alcohols 17 and 18.1 Diastereomers 17 and 18 were separated by silica gel column chromatography, and 17 was treated with mCPBA to give epoxide 19. Then, 19 was applied to stereoselective deoxy-fluorination using DAST. The reaction time became shorter and the yield of the desired fluorinated epoxide 20 was improved. Reductive opening of the epoxide progressed using LiAlH4, and subsequent desilylation provided 15.

The coupling reactions of 7 and 8 with carbanion of the A-ring precursor 9 and subsequent deprotection of the silyl ether group resulted in (23R)-23-F-25(OH)D3 (5) and (23S)-23-F-25(OH)D3 (6) in 68 and 43% yields, respectively (Scheme 5).

Metabolic studies of 5 and 6 were performed using a reconstituted system containing recombinant human CYP24A1. The metabolites of each analogue were analyzed by reversed-phase HPLC, and their kinetic parameters were estimated (Table 1).

The kcat/Km value of CYP24A1 for (23R)-23-F-25(OH)D3 (5) was similar to that for 25(OH)D3, whereas that for (23S)-23-F-25(OH)D3 (6) was approximately 4 times lower than that for 25(OH)D3. These results suggested that (23S)-23-F-25(OH)D3 (6) is more resistant to CYP24A1-dependent metabolism than both 25(OH)D3 and (23R)-23-F-25(OH)D3 (5).

Scheme 2. Retrosynthetic Analysis of 23-Fluoro-25-hydroxyvitamin D3 (5 and 6)

CONCLUSIONS

A new method to synthesize 23-fluorinated vitamin D3 analogues was developed. Introduction of a fluorine atom to the C23-position was accomplished by deoxy-fluorination using PyFluor or DAST in a stereoselective manner. We presented two synthetic routes to construct CD-ring precursors (7 and 8), and the subsequent Wittig–Horner reaction with A-ring (9) produced the target compounds (5 and 6). The CD-ring precursors (7 and 8) may aid in the metabolic studies of 5 and 6 using a reconstituted system containing recombinant human CYP24A1.
preparation of new 23-fluorinated vitamin D₃ analogues. Kinetic studies on the metabolism of 5 and 6 revealed that the stereochemistry at the C23-F position significantly affects the resistance to human CYP24A1. These results suggest that 5 may have more potent biological effects than 25(OH)D₃.

**Experimental Section.** General Information. ¹H NMR (internal tetramethylsilane (TMS) as reference): 400 MHz (CDCl₃ or CD3OD) with JEOL AL-400 NMR and 600 MHz (CDCl₃) with JEOL ECP-600. ¹³C NMR (deuterated solvent, δ 77.0 ppm for CDCl₃ or 49.3 ppm for CD3OD, as reference): 100 MHz (CDCl₃ or CD3OD) with JEOL AL-400 NMR and 150 MHz (CDCl₃) with JEOL ECP-600. IR: JASCO FT-IR-800 Fourier transform infrared spectrophotometer. HRMS: SHIMADZU LCMS-lT-TOF mass spectrometer with a positive electrospray ionization (ESI) method. Optical rotations: JASCO DIP-370 digital polarimeter. Flash column chromatography: silica gel 60N (Kanto Chemical Co., lnc., 40−50 μm) or silica gel 60 (Merck, 0.040−0.063 mm). Experiments were performed under argon, unless otherwise stated.

(4R,6R)-4-Fluoro-2-methyl-6-{(1R,3aR,4S,7aR)-7a-methyl-4-(triethylsilyloxy)octahydro-1H-inden-1-yl}heptan-2-ol (13). To the toluene solution (166 μL) of 12 (34.3 mg, 0.083 mmol) and DBU (25.3 mg, 25 μL, 0.17 mmol), PyFluor (16.1 mg, 0.10 mmol) was added, and the reaction mixture was stirred at room temperature (rt) for 90 h. To quench the reaction, water was added to the mixture at rt, and the mixture was extracted with ethyl acetate three times. The organic layer was dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography (hexane/ethyl acetate = 6:1) gave 13 (7.6 mg, 22%) as a colorless oil.

13: [α]D²⁷ +45.4 (c 0.81, CHCl₃); IR (neat) 3401, 1458, 1377, 1165, 1084, 1035, 738 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.55 (q, J = 8.3 Hz, 6H), 0.93−1.34 (m, 30H), 1.49−1.99 (m, 8H), 2.3 (dd, J = 2.3, 4.9 Hz, 1H), 4.86−5.04 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 4.9, 6.9, 13.5, 17.7, 18.7, 23.0, 27.3, 29.7, 29.9, 31.6 (d, J = 5.7 Hz), 34.6, 40.8, 42.3, 42.7 (d, J = 21.0 Hz), 48.7 (d, J = 18.2 Hz), 53.1, 57.1, 69.4, 70.2, 90.2 (d, J = 163.1 Hz); HRMS (ESI+) caleled for C₂₄H₄₇FO₂Si [M + Na]⁺ 437.3227, found 437.3211.

(4S,6R)-4-Fluoro-2-methyl-6-{(1R,3aR,4S,7aR)-7a-methyl-4-(triethylsilyloxy)octa-2,3-diene-1-yl}heptan-2-ol (14). PyFluor (946.3 mg, 5.87 mmol) was added to the solution of 11 (1.84 g, 4.46 mmol) and DBU (1.36 g, 1.33 mmol) in toluene (166 μL) and stirred at room temperature (rt) for 90 h. To quench the reaction, water was added to the mixture at rt, and the mixture was extracted with ethyl acetate three times. The organic layer was dried over Na₂SO₄, filtered, and concentrated in vacuo. Purification of the residue by flash column chromatography (hexane/ethyl acetate = 6:1) gave 14 (7.6 mg, 22%) as a colorless oil.

Scheme 4. Alternative Synthetic Route for (23R)-23-Fluorinated CD-ring Precursor 15 (Method B)

Table 1. Kinetic Parameters of Human CYP24A1 for 25(OH)D₃ and Its Two Analogues

| substrate       | kcat (min⁻¹) | Km (μM)  | kcat/Km |
|-----------------|-------------|----------|---------|
| 25(OH)D₃       | 15.3 ± 4.5  | 0.76 ± 0.21 | 20.1    |
| (23R)-23-F-25(OH)D₃ | 7.8 ± 2.1 | 0.39 ± 0.13 | 20.0    |
| (23S)-23-F-25(OH)D₃ | 2.1 ± 0.5 | 0.38 ± 0.13 | 5.5     |

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mL, 8.92 mmol) in toluene (10.4 mL), and the mixture was stirred at rt for 1 day. To quench the reaction, water was added to the mixture at rt, and the mixture was extracted with ethyl acetate three times. The organic layer was dried over Na₂SO₄, filtered, and concentrated in vacuo. The residual oil was purified by flash column chromatography (hexane/Et₂O = 2:1), followed by repurification by flash column chromatography (hexane/Et₂O = 3:1) to obtain 14 (1.02 g, 55%) as a colorless oil.

14: [α]°D +41.2 (c 1.05, CHCl₃); IR (neat) 3410, 1459, 1376, 1166, 1085, 1025, 739 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 0.55 (q, J = 7.2 Hz, 6H), 0.91 (s, 3H), 0.93–0.97 (m, 12H), 1.07–1.17 (m, 19H), 1.78–1.85 (m, 30H), 1.94 (dt, J(α) = 3.6 Hz, J(β) = 12.6 Hz, 1H), 4.03 (dd, J = 3.0, 4.5 Hz, 1H), 4.86–4.99 (m, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 4.9, 6.9, 13.5, 17.7, 19.2, 23.0, 27.6, 29.5, 30.0, 33.5 (d, J = 5.7 Hz), 33.6, 40.8, 42.1 (d, J = 18.6 Hz), 42.2, 47.9 (d, J = 18.8 Hz), 53.0, 57.1, 69.3, 70.2, 92.5 (d, J = 160.8 Hz); HRMS (ESI⁺) calc'd for C₁₅H₂₄O₂Si [M + Na]⁺ 347.2327, found 347.2324. 

(1R,3aR,4S,7aR)-1-[(2R,4S)-4-Fluoro-6-hydroxy-6-methyl-heptan-2-yl]-7a-methyloctahydro-1H-inden-4-ol (15). Method A. To the MeOH solution (5 mL) of 13, p-toluenesulfonic acid monohydrate (90.2 mg, 0.5 mmol) was added, and the mixture was stirred at rt for 15 min. To quench the reaction, water and sat. NaHCO₃ aq. were added to the mixture at rt, and it was extracted with ethyl acetate three times, washed with sat. NaCl, dried over Na₂SO₄, filtered, and concentrated in vacuo. The residual oil was purified by flash column chromatography (hexane/ethyl acetate = 2:1) to yield 15 (39.2 mg, 81%) as a colorless oil.

15: [α]°D +38.2 (c 0.69, CHCl₃); IR (neat) 3405, 1470, 1379, 1163, 992, 942 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 0.93 (s, 3H), 0.97 (d, J = 6.6 Hz, 3H), 1.11–1.69 (m, 20H), 1.79–1.91 (m, 4H), 1.98–2.00 (m, 1H), 4.06–4.07 (m, 1H), 4.86–4.98 (m, 1H); ¹³C NMR (150 MHz, CDCl₃) δ 13.4, 17.4, 19.1, 22.5, 27.4, 29.6, 29.9, 33.5 (d, J = 5.7 Hz), 33.5, 40.3, 41.9, 42.0 (d, J = 18.6 Hz), 47.9 (d, J = 20.1 Hz), 52.5, 56.9, 69.3, 70.2, 92.3 (d, J = 162.3 Hz); HRMS (ESI⁺) calc'd for C₁₃H₂₁O₂F [M + Na]⁺ 323.2357, found 323.2361. 

(1R,3aR,7aR)-1-[(2R,4S)-4-Fluoro-6-hydroxy-6-methyl-heptan-2-yl]-7a-methyloctahydro-1H-inden-4-one (16). To the MeOH solution (10 mL) of 14, p-toluenesulfonic acid monohydrate (190.2 mg, 1.0 mmol) was added, and the mixture was stirred at rt for 1 h. The additional same acid (190.2 mg, 1.0 mmol) was added to the mixture, and it was stirred for 1 h. After dilution with excess Et₂O, MeOH solution (10 mL) of 15, ¹H NMR (600 MHz, CDCl₃) δ 0.96 (s, 3H), 0.98 (d, J = 6.0 Hz, 3H), 0.99–1.11 (m, 2H), 1.14–1.20 (m, 1H), 1.25–1.36 (m, 2H), 1.28 (s, 3H), 1.31 (s, 3H), 1.42–1.73 (m, 8H), 1.80–1.95 (m, 5H), 2.01–2.03 (m, 1H), 4.07–4.08 (m, 1H), 4.89–5.02 (m, 1H);

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ACS Omega
mixture, and it was stirred for 10 min. To quench the reaction, 1H), 5.08 (brs, 1H), 6.08 (d, 6H), 1.43 (9H), 0.65 (s, 3H), 1.03 (d, 4H), 2.19 (t, 6H), 2.58 (dd, J = 13.8 Hz, 1H), 2.58 (dd, J = 6.0 Hz, 3H), 1.26–1.34 (m, 7H), 1.43–1.77 (m, 9H), 1.85–2.03 (m, 3H), 2.11–2.13 (m, 1H), 2.19–2.29 (m, 2H), 2.45 (dd, J = 7.8, 12.0 Hz, 3H), 4.79–4.91 (m, 1H); 13C NMR (150 MHz, CDCl3) δ 2.5, 13.4, 17.4, 19.1, 22.5, 27.4, 29.6, 29.9, 33.9 (d, J = 5.7 Hz, 33.5, 40.3, 41.9, 42.0 (d, J = 18.6 Hz), 47.9 (d, J = 20.1 Hz), 57.0, 62.0, 73.0, 89.1 ppm; IR (neat) 1715, 1461, 1382, 1265, 1159, 1052, 740 cm⁻¹.

8: [α]D₂⁰ +10.3 (c 2.21, CHCl₃); IR (neat) 1715, 1461, 1382, 1265, 1159, 1052, 740 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 161.3, 122.6, 58.5, 70.9, 90.2 (d, J = 165.0 Hz), 112.9, 119.4, 122.9, 137.7, 142.7, 137.7, 142.7, 147.3; HRMS (ESI⁺) calced for C₂₇H₄₃O₂F [M + Na]+ 441.3139, found 441.3134.

(23R)-23-Fluoro-25-hydroxyvitamin D₃ (5). To the THF solution (2 mL) of 9 (72.3 mg, 0.16 mmol), Bu₄NF (97 μL, 0.56 M hexane solution, 0.15 mmol) was added at −78 °C. After 30 min of stirring, the THF solution (2 mL) of ketone 8 (28.7 mg, 0.077 mmol) was added to the above reaction mixture. The mixture was stirred at −78 °C for 15 min and at 0 °C for 15 min, and then it was allowed to be warmed to rt for 10 min. To quench the reaction, water was added at rt, and the mixture was extracted with ethyl acetate three times, washed with sat. NaCl, dried over Na₂SO₄, and concentrated in vacuo. Purification of the residual oil by flash column chromatography (hexane/ethyl acetate = 5:1) gave 6 (28.7 mg, 74%, 2 steps) as a colorless oil.

6: [α]D₂⁰ +55.6 (c 0.54, EtOH); UV (EtOH) λmax 212.6, 264.6 nm; IR (neat) 3377, 1440, 1379, 1265, 1159, 1052, 740 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.09 (d, J = 6.0 Hz, 3H), 3.77–3.83 (m, 1H), 4.79 (d, J = 1.8 Hz, 1H), 4.83–5.02 (m, 1H), 5.08 (brs, 1H), 6.08 (d, J = 11.5 Hz, 1H), 6.26 (d, J = 11.5 Hz, 1H); ¹³C NMR (100 MHz, CD₂OD) δ 12.7, 19.6, 23.58, 24.8, 29.0, 30.2, 31.3, 33.9, 34.1, 36.9, 42.2, 44.5 (d, J = 21.0 Hz), 47.3 (d, J = 3.8 Hz), 50.6 (d, J = 19.1 Hz), 57.8, 58.5, 70.9, 90.2 (d, J = 165.0 Hz); 112.9, 119.4, 122.9, 137.7, 142.7, 137.7, 142.7, 147.3; HRMS (ESI⁺) calced for C₂₇H₄₃O₂F [M + Na]+ 441.3139, found 441.3141.

Metabolism of 25(OH)D₃ and Its Analogues by Human CYP24A1. The metabolism of 25(OH)D₃ and its analogues 5 and 6 by CYP24A1 were analyzed using the membrane fraction prepared from recombinant Escherichia coli cells expressing human CYP24A1 as described in our previous study. Briefly, the reaction mixture containing 0.02 μM human CYP24A1, 2.0 μM adrenodoxin (ADX), 0.2 μM NADPH—adrenodoxin reductase (ADR), 0.2–6.0 μM each substrate, 1.0 mM NADPH, 100 mM Tris—HCl (pH 7.4), and 1 mM EDTA was incubated at 37 °C for 1–10 min. The metabolites were extracted with 4 volumes of CHCl₃—CH₃OH (3:1) and analyzed by reversed-phase HPLC under the following conditions: column, CAPCELL PAK C18 C18 (34.6 mg, 0.12 mmol), 4-methylmorpholine N-oxide (23.6 mg, 0.20 mmol) was added, and the mixture was cooled to 0 °C. To the solution, TPAP (23.9 mg, 0.068 mmol) was added, and the reaction mixture was cooled to 0 °C without further purification. TMSCl (31.3 mg, 0.36 μL, 0.29 mmol) was added to the solution of crude ketone and imidazole (32.8 mg, 0.48 mmol) in CH₂Cl₂ (4 mL) at 0 °C. After 30 min with stirring, the THF solution (2 mL) of ketone 7 (34.6 mg, 0.29 mmol) was added to the above reaction mixture. The mixture was stirred at rt for 4 h and then it was allowed to be warmed to 37 °C for 15 min. To quench the reaction, water was added at rt, and the mixture was extracted with ethyl acetate three times, washed with sat. NaCl, dried over Na₂SO₄, and concentrated in vacuo. Purification of the residual oil by flash column chromatography (hexane/ethyl acetate = 5:1) afforded 5 (27.1 mg, 68%, in 2 steps) as a white powder.
ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.9b01500.

NMR spectra of all new compounds (PDF)

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Notes
The authors declare no competing financial interest.

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