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Introduction of fluorine atoms to vitamin D_3 side-chain and synthesis of 24, 24-difluoro-25-hydroxyvitamin D_3

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ABSTRACT

During our ongoing studies of vitamin D, we focused on the vitamin D_3 side-chain 24-position, which is the major metabolic site of human CYP24A1. In order to inhibit the metabolism of vitamin D_3, 24,24-difluorovitamin D_3analogues are important candidates. In this paper, we report the practical introduction of the difluoro-unit to the 24-position to synthesize 24,24-difluoro-CD ring (**1**) and 24,24-difluoro-25-hydroxyvitamin D_3 (**2**).

1. Introduction

Since the discovery of metabolic pathways of vitamin D_3 (VD_3), numerous metabolites of VD_3 and their biological roles have been reported [1,2]. Many analogues that are related to VD_3 metabolites have also been synthesized and their specific biological activities have been revealed [3–14]. By utilizing this knowledge, fluorinated VD_3 analogues with a longer half-life have been designed and synthesized as well [15–19]. Especially, fluorine atoms were actively introduced to the side-chain of VD_3, because it contains important metabolic sites of CYP24A1, which is the cytochrome P450 component of the 25-hydroxyvitamin D_3 [25(OH)D_3]-24-hydroxylase enzyme. It is well-known that C24 hydroxylation and subsequent 5-step oxidation of the 25(OH) D_3 side-chain by CYP24A1 leads to calcitroic acid (Scheme 1) [2].

In order to block this (24*R*)-oxidation metabolic pathway, the introduction of fluorine atoms to the C24 position may be an efficient strategy. That is why there has been considerable interest in 24,24-difluorovitamin D_3 analogues and some of these related analogues have been reported. For example the Kobayashi and Takayama groups independently reported a synthetic method to produce 24,24-difluorovitamin D_3 analogues from steroidal skeletons in 1979 [20,21]. After that, the Takayama group reported an improved method to introduce the 24,24-difluoro unit to the vitamin D_3 side-chain starting from androst-5-ene or vitamin D_2 in 1992 [22,23] and 1998 [24]. We have explored a more direct method to synthesize the 24,24-difluoro unit. This time, we focused on the 24,24-difluoro-CD ring (**1**), because it is an important precursor of 24,24-difluorovitamin D_3 analogues if coupled with varieties of A-ring parts. To our knowledge, only one study has been reported that synthesized the 24,24-difluoro-CD ring (**1**) with the Barton-McCombie reduction process to remove a OH group on a synthetic intermediate [25]. In this paper, we describe a new synthetic method to produce **1** and 24,24-difluoro-25-hydroxyvitamin D_3 (**2**) utilizing the Horner-Emmons reagent **3** (Fig. 1).

2. Results and discussion

A retrosynthetic plan for **1** and **2** is shown in Scheme 2. Inhoffen-Lythogoe diol (**4**) was used as the starting material. Introduction of the difluoro-unit was performed using *N*,*N*-diethylaminosulfur trifluoride (DAST) against α-ketoester [21,24,26]. The triene unit of **2** was constructed by applying the Wittig-Horner method that was reported previously (Scheme 2) [27].

The synthesis of Horner-Emmons reagent **3** is shown in Scheme 3 [28,29]. Dimethyl tartrate was used as a starting material. Cleavage of diol, followed by the nucleophilic addition of diethyl phosphite to aldehyde **13** afforded alcohol **14**. Protection of **14** with triethylsilyl chloride in the presence of imidazole successfully yielded **3** [29].

In Scheme 4, the synthesis of the 24,24-difluoro-CD ring (**1**) is

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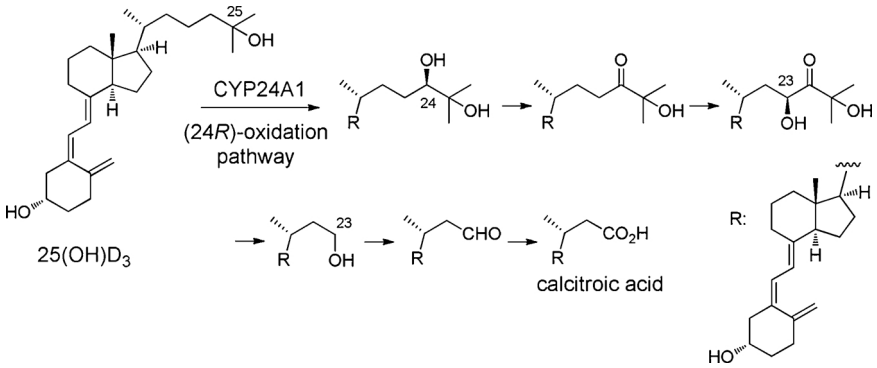


Scheme 1. One of the major metabolic pathways of 25-hydroxyvitamin D_3 by CYP24A1 includes (24*R*)-oxidation leading to calcitroic acid [2].

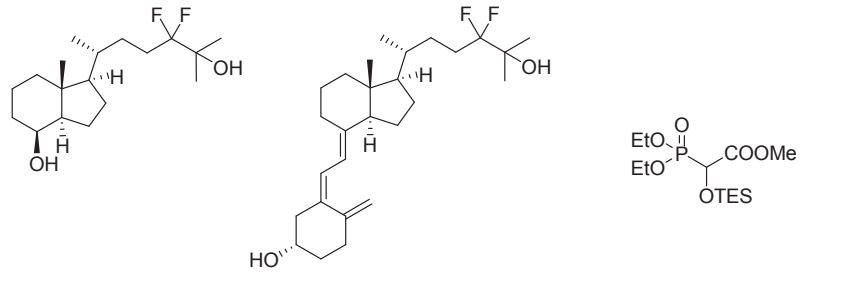
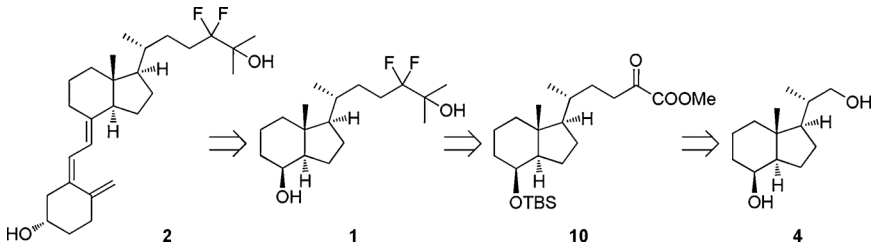
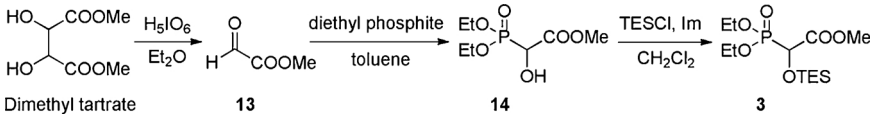


Fig. 1. Target compounds 24,24-difluoro-CD-ring (**1**) and 24,24-difluoro-25-hydroxyvitamin D_3 (**2**) as well as the Horner-Emmons reagent **3** for synthesizing **1.**



Scheme 2. Retrosynthetic analysis of 24,24-difluoro-CD ring (**1**) and 24,24-difluoro-25-hydroxyvitamin D_3 (**2**) via a key compound **10.**



Scheme 3. Preparation of Horner-Emmons reagent **3** [28,29].

shown. The synthetic route started from Inhoffen-Lythgoe diol (**4**). Selective iodination of the primary alcohol and nucleophilic displacement of the iodide by KCN allowed conversion to nitrile **6**. Silyl protection of **6**, followed by reduction of the nitrile group with DIBAL-H afforded aldehyde **8** [30]. Horner-Emmons reaction of **3** with aldehyde **8** afforded silyl enol ether **9**. Hydrolysis of the silyl enol was performed with tetrabutylammonium fluoride in the presence of acetic acid to yield α-ketoester **10** [24]. The key part of the 24,24-difluoro unit was constructed using DAST toward **10**, and the difluorination proceeded smoothly. Treatment of difluoromethylester **11** with an excess amount of methyl Grignard reagent followed by deprotection of the silyl protecting group afforded the desired CD-ring **1**.

Next, the 24,24-difluorovitamin D_3 precursor **15** was synthesized from 24,24-difluoro-CD-ring (**1**) (Scheme 5). The C8-OH group was oxidized by tetrapropylammonium perruthenate (TPAP) in the presence of 4-methylmorpholine *N*-oxide (NMO) followed by triethylsilylation of the C25-OH group furnished 8-ketone **15** [25,31].

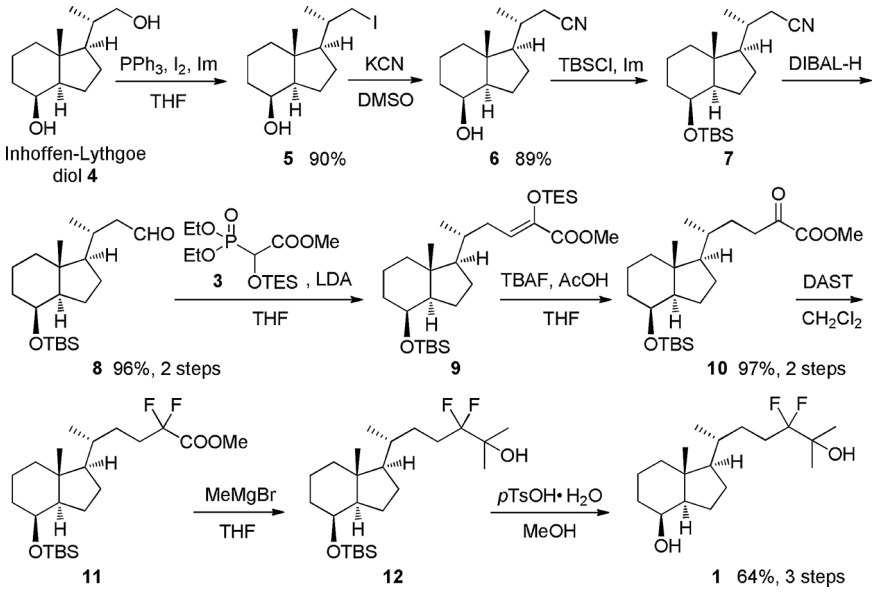
We synthesized 24,24-difluoro-25-hydroxyvitamin D_3 (**2**) using the CD-ring and the A-ring precursor phosphine oxide **18**. The coupling reaction was performed by the Wittig-Horner method. The resulting coupling product was treated with tetrabutylammonium fluoride to give the desired product **2** in 24% yield (2 steps) (Scheme 6).

3. Conclusion

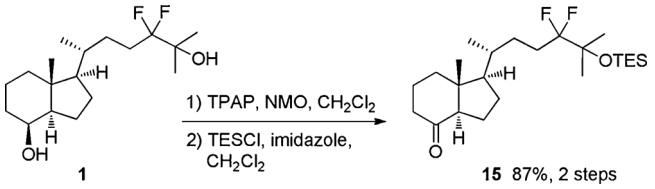
In conclusion, we developed a convenient method to synthesize 24,24-difluoro-CD ring **1**, which is an important precursor of 24,24-difluorovitamin D_3 analogues. Construction of the 24,24-difluoro unit was achieved by treatment of the α-ketoester **10** with *N*,*N*-diethylaminosulfur trifluoride (DAST). Using 8-keto-CD ring **15**, we were able to synthesize 24,24-difluoro-25-hydroxyvitamin D_3 (**2**) as well.

4. Experimental section

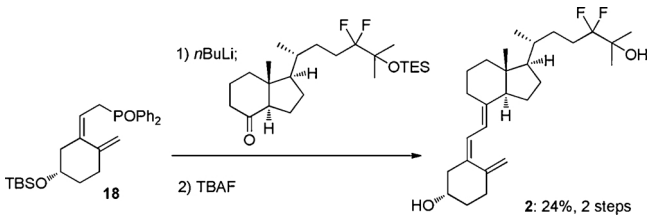
^{1}H and ^{13}C NMR spectra were recorded on JEOL AL-400 NMR (400 MHz) and ECP-600 NMR (600 MHz) spectrometers. ^{1}H NMR spectra were referenced with $(CH_3)_4Si$ (δ 0.00 ppm) as an internal standard. ^{13}C NMR spectra were referenced with deuterated solvent (δ



Scheme 4. Synthesis of 24,24-difluoro-CD ring (**1**).



Scheme 5. Synthesis of 8-keto-24,24-difluoro-CD ring **15.**



Scheme 6. Coupling reaction and deprotection steps for **2**.

77.0 ppm for $CDCl_3$ and 49.3 ppm for CD_3OD). IR spectra were recorded on a JASCO FT-IR-800 Fourier transform infrared spectrophotometer. High resolution mass spectra were obtained on a SHIMADZU LCMS-IT-TOF mass spectrometer with a positive electrospray ionization (ESI) method. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. Column chromatography was performed on silica gel 60 N (Kanto Chemical Co., Inc., 40–50 μm) or silica gel 60 (Merck, 0.040-0.063 mm). Preparative thin-layer chromatography was performed on silica gel 60 F_{254} (Merck, 0.5 mm). All experiments were performed under anhydrous conditions in an atmosphere of argon, unless otherwise stated.

4.1. Methyl 2-(diethoxyphosphoryl)-2-[(triethylsilyl)oxy]acetate (3)

This reagent was prepared according to the literature [29].

3: IR (neat) 1754, 1268, 1133, 1025, 969, 810, 750 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 0.64 (q, J = 7.8 Hz, 6 H), 0.96 (t, J = 7.8 Hz, 9 H), 1.33 (q, J = 6.6 Hz, 6 H), 3.79 (s, 3 H), 4.12–4.26 (m, 4 H), 4.16 (d, J = 17.4 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 4.4, 6.5, 16.4 (d, J = 5.7 Hz), 52.5, 63.6 (d, J = 7.2 Hz), 70.5 (t, J = 24.8 Hz), 169.1; HRMS (ESI^+) calcd for $C_{13}H_{30}O_6SiP$ $[M+H]^+$ 341.1544, found 341.1556.

4.2. Methyl 5-{4-[(tert-butyldimethylsilyl)oxy]-7a-methyloctahydro-1H-inden-1-yl}-2-oxohexanoate (10)

To the solution of Horner-Emmons reagent **3** (7.34 g, 21.6 mmol) in THF (20 mL) was added LDA (lithium diisopropylamide) (10.9 mL, 2 M THF/heptane/ethylbenzene solution, 21.8 mmol) at -40 °C, the mixture was stirred at the same temperature for 20 min, and a solution of **8** [30] (6.65 g, 19.6 mmol) in THF (15 mL) was added. The reaction mixture was stirred at 0 °C for 5 min. After the reaction had been quenched with H_2O and saturated aqueous NH_4Cl at 0 °C, the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The crude residue of **9** was used for the next reaction without further purification. To the crude residue of **9** in CH_2Cl_2 (40 mL) were added AcOH (6 mL) and tetrabutylammonium fluoride (27.4 mL, 1 M THF solution, 27.4 mmol) at 0 °C, and the mixture was stirred at room temperature for 30 min. After the reaction had been quenched with H_2O at room temperature, the mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 7 : 1) to obtain **10** (7.77 g, 97%) as a colorless oil [24].

4.3. 1-(5,5-Difluoro-6-hydroxy-6-methylheptan-2-yl)-7a-methyloctahydro-1H-inden-4-ol (1)

To the solution of **10** (8.08 g, 19.7 mmol) in CH_2Cl_2 (30 mL) was slowly added *N*,*N*-diethylaminosulfur trifluoride (DAST) (6.5 mL, 7.3 g, 49.2 mmol) at 0 °C, and the mixture was stirred at room temperature for 17 h. The mixture was cooled to −78 °C and MeOH and H_2O were slowly added. The mixture was extracted with CH_2Cl_2 three times, dried over Na_2SO_4, filtered, and concentrated. The residue was roughly purified by flash column chromatography on silica gel (hexane : EtOAc = 20 : 1) to obtain a crude residue of **11**. To the solution of the crude residue of **11** in THF (30 mL) was added MeMgCl (16.7 mL, 3.0 M THF solution, 50.0 mmol) at 0 °C, and the mixture was stirred for 15 min. After the reaction had been quenched with H_2O and HCl (1.0 M in H_2O), the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The crude residue of **12** was used for the next reaction without further purification. To the crude residue of **12** in MeOH (30 mL) was added *p*-toluenesulfonic acid monohydrate (6.12 g, 32.2 mmol), and the mixture was stirred at room temperature for 19 h under air. After the reaction had been quenched with H_2O and saturated aqueous $NaHCO_3$ at room temperature, the mixture was

extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 3 : 1) to obtain **1** (4.0 g, 64%, in 3 steps) as a white powder [25].

1: $[\alpha]_D^{27}$ +32.3 (c 0.98, $CHCl_3$); IR (neat) 3414, 1471, 1380, 1180, 1021, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 (d, J = 6.4 Hz, 3 H), 0.94 (s, 3 H), 1.06–2.07 (m, 25 H), 4.08 (brs, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 17.4, 18.3, 22.5, 23.6, 26.6, 27.0, 27.3 (t, J = 24.8 Hz), 33.5, 34.9, 40.3, 41.9, 52.6, 56.3, 69.4, 73.3 (t, J = 26.7 Hz), 125.5 (t, J = 246.0 Hz); HRMS (ESI^-) calcd for $C_{19}H_{33}O_4$ $[M + HCOO]^-$ 449.3058, found 449.3064.

4.4. 24,24-Difluoro-25-hydroxyvitamin D_3 (2)

*n*BuLi (45.1 μL, 1.6 M hexane solution, 0.073 mmol) was added to the solution of A-ring phosphine oxide **18** (29.9 mg, 0.066 mmol) in THF (0.5 mL) at −78 °C. After stirring for 30 min, the solution of ketone **15** (17.1 mg, 0.040 mmol) in THF (0.5 mL) was added to the reaction mixture, and the mixture was stirred at −78 °C for 1 h. After the reaction had been quenched with H_2O at room temperature, the mixture was extracted with EtOAc three times, washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 20 : 1) to obtain the crude coupling product (12.4 mg), and it was used for the next reaction without further purification. Tetrabutylammonium fluoride (300 μL, 1 M THF solution, 0.30 mmol) was added to the solution of the crude coupling product (12.4 mg) in THF (1 mL), and the mixture was stirred at room temperature for 5 h. After the reaction had been quenched with H_2O at room temperature, the mixture was extracted with EtOAc three times, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (hexane : EtOAc = 2 : 1 – EtOAc only) to obtain **2** (4.1 mg, 24%, in 2 steps) as a white powder.

2: $[\alpha]_D^{27}$ +97.8 (c 0.32, EtOH); IR (neat) 3395, 1468, 1380, 1176, 1049 cm^{-1}; ^1H NMR (600 MHz, CD_3OD) δ 0.61 (s, 3 H), 1.01 (d, J = 6.6 Hz, 3 H), 1.29–1.41 (m, 11 H), 1.48–1.63 (m, 5 H), 1.71–1.90 (m, 4 H), 1.94–2.25 (m, 7 H), 2.44 (dt, J = 4.8, 13.8 Hz, 1 H), 2.58 (dd, J = 3.9, 12.9 Hz, 1 H), 2.90–2.92 (m, 1 H), 3.80 (ddd, J = 3.3, 9.0, 12.6 Hz, 1 H), 4.79 (brs, 1 H), 5.08 (brs, 1 H), 6.08 (d, J = 11.4 Hz, 1 H), 6.26 (d, J = 11.4 Hz, 1 H); ^{13}C NMR (150 MHz, CD_3OD) δ 12.7, 19.5, 23.5, 24.2, 24.2, 24.8, 28.4, 28.7 (t, J = 24.5 Hz), 28.9, 30.2, 33,9, 36.9, 37.4, 42.2, 47.2, 47.3, 57.8, 57.9, 70.9, 74.0 (t, J = 27.3 Hz), 112.9, 119.3, 122.9, 127.1 (t, J = 246.3 Hz), 137.7, 142.7, 147.3; HRMS (ESI^-) calcd for $C_{28}H_{43}O_4F_2$ $[M + HCOO]^-$ 481.3135, found 481.3137.

Acknowledgements

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References

[1] G. Jones, S.A. Strugnell, H.F. DeLuca, Current understanding of the molecular actions of vitamin D, Physiol. Rev. 78 (4) (1998) 1193–1231.
[2] T. Sakaki, N. Sawada, K. Komai, S. Shiozawa, S. Yamada, K. Yamamoto, Y. Ohyama, K. Inouye, Dual metabolic pathway of 25-hydroxyvitamin D_3 catalyzed by human CYP24, Eur. J. Biochem. 267 (2000) 6158–6165.
[3] T. Eguchi, S. Takatsuto, M. Ishiguro, N. Ikekawa, Y. Tanaka, H.F. DeLuca, Synthesis and determination of configuration of natural 25-hydroxyvitamin D_3 26,23-lactone, Proc. Natl. Acad. Sci. U. S. A. 78 (11) (1981) 6579–6583.
[4] A. Nagata, Y. Akagi, S. Sedghi Masoud, M. Yamanaka, A. Kittaka, M. Uesugi, M. Odagi, K. Nagasawa, Stereoselective synthesis of four calcitriol lactone diastereomers at C23 and C25, J. Org. Chem. 84 (2019) 7630–7641.
[5] Y. Akagi, A. Nagata, M. Odagi, K. Nagasawa, Synthetic studies of (23*S*,25*R*)-1α,25-dihydroxyvitamin D_3 26,23-lactone (calcitriol lactone) and its derivatives, J. Steroid Biochem. Mol. Biol. 177 (2018) 240–246.
[6] N. Saito, A. Kittaka, Highly potent vitamin D receptor antagonists: design, synthesis, and biological evaluation, ChemBioChem 7 (2006) 1478–1490.
[7] F. Kawagoe, T. Sugiyama, K. Yasuda, M. Uesugi, T. Sakaki, A. Kittaka, Concise synthesis of 23-hydroxylated vitamin D_3 metabolites, J. Steroid Biochem. Mol. Biol. 186 (2019) 161–168.
[8] N.E. Lee, G. Satyanarayana Reddy, A.J. Brown, P.G. Williard, Synthesis, stereochemistry, and biological activity of 1α,23,25-trihydroxy-24-oxovitamin D_3, a major natural metabolite of 1α,25-dihydroxyvitamin D_3, Biochemistry 36 (1997) 9429–9437.
[9] R. Sigüeiro, P. González-Berdullas, J. Loureiro, A. Mouriño, M.A. Maestro, Stereoselective synthesis of 25*S*,26-dihydroxyvitamin D_3, J. Steroid Biochem. Mol. Biol. 177 (2018) 247–249.
[10] W. Stepanenko, J. Wicha, Enantioselective synthesis of 24,25-dihydroxy vitamin D_3 northern portion from (*S*)-3-hydroxy-2,2-dimethylcyclohexane-1-one. Remote asymmetric introduction in an acid-catalysed conjugated addition, Tetrahedron Lett. 39 (1998) 885–888.
[11] H.-Y. Lam, H.K. Schnoes, H.F. DeLuca, T.C. Chen, 24,25-Dihydroxyvitamin D_3. Synthesis and biological activity, Biochemistry 12 (1973) 4851–4855.
[12] D. Nicoletti, C. Gregorio, A. Mouriño, M. Maestro, A short practical approach to 24*R*,25-dihydroxyvitamin D_3, J. Steroid Biochem. Mol. Biol. 212 (2010) 43–45.
[13] C. Fernández, Z. Gándara, G. Gómez, B. Covelo, Y. Fall, D- and L-Serine, useful synthons for the synthesis of 24-hydroxyvitamin D_3 metabolites. A formal synthesis of 1α,24*R*,25-$(OH)_3$-D_3, 24*R*,25-$(OH)_2$-D_3 and 24*S*,25-$(OH)_2$-D_3, Tetrahedron Lett. 48 (2007) 2939–2942.
[14] I. Cornella, R.M. Suárez, A. Mouriño, J. Pérez Sestelo, L.A. Sarandeses, Stereoselective convergent synthesis of 24-substituted metabolites and analogues of vitamin D, J. Steroid Biochem. Mol. Biol. 89-90 (2004) 19–23.
[15] F. Kawagoe, T. Sugiyama, M. Uesugi, A. Kittaka, Recent developments for introducing a hexafluoroisopropanol unit into the vitamin D side chain, J. Steroid Biochem. Mol. Biol. 177 (2018) 250–254.
[16] F. Kawagoe, K. Yasuda, S. Mototani, T. Sugiyama, M. Uesugi, T. Sakaki, A. Kittaka, Synthesis and CYP24A1-dependent metabolism of 23-fluorinated vitamin D_3 analogues, ACS Omega 4 (2019) 11332–11337.
[17] T. Taguchi, S. Mitsuhashi, A. Yamanouchi, Y. Kobayashi, H. Sai, N. Ikekawa, Synthesis of 23,23-difluoro-25-hydroxyvitamin D_3, Tetrahedron Lett. 25 (43) (1984) 4933–4936.
[18] M. Ikeda, H. Matsumura, N. Sawada, K. Hashimoto, T. Tanaka, T. Noguchi, M. Hayashi, Synthesis and biological evaluations of C-23-modified 26,26,26,27,27,27-F_6-vitamin D_3 analogues, Bioorg. Med. Chem. 8 (2000) 1809–1817.
[19] S.-J. Shiuey, J.J. Partridge, M.R. Uskoković, Triply convergent synthesis of 1α,25-dihydroxy-24(*R*)-fluorocholecalciferol, J. Org. Chem. 53 (5) (1988) 1040–1046.
[20] Y. Kobayashi, T. Taguchi, T. Terada, J. Oshida, M. Morisaki, N. Ikekawa, Synthesis of 24,24-difluoro- and 24ξ-fluoro-25-hydroxyvitamin D_3, Tetrahedron Lett. 20 (22) (1979) 2023–2026.
[21] S. Yamada, M. Ohmori, H. Takayama, Synthesis of 24,24-difluoro-25-hydroxyvitamin D_3, Tetrahedron Lett. 20 (21) (1979) 1859–1862.
[22] K. Konno, K. Ojima, T. Hayashi, H. Takayama, An alternative and efficient synthesis of 24,24-difluoro-1α,25-dihydroxyvitamin D_3, Chem. Pharm. Bull. 40 (5) (1992) 1120–1124.
[23] K. Ando, F. Kondo, F. Koike, H. Takayama, An improved synthesis of 24,24-difluoro-1α,25-dihydroxyvitamin D_3 from vitamin D_2, Chem. Pharm. Bull. 40 (6) (1992) 1662–1664.
[24] H. Iwasaki, R. Hosotani, Y. Miyamoto, Y. Nakano, K. Yamamoto, S. Yamada, T. Shinki, T. Suda, K. Yamaguchi, K. Konno, H. Takayama, Stereoselective synthesis and structural establishment of (25*S*)-24,24-difluoro-1α,25,26-trihydroxyvitamin D_3, a major metabolite of 24,24-difluoro-1α,25-dihydroxyvitamin D_3, Tetrahedron 54 (49) (1998) 14705–14724.
[25] A. Flores, I. Massarelli, J.B. Thoden, L.A. Plum, H.F. DeLuca, A methylene group on C-2 of 24,24-difluoro-19-nor-1α,25-dihydroxyvitamin D_3 markedly increases bone calcium mobilization in vivo, J. Med. Chem. 58 (24) (2015) 9731–9741.
[26] A.H. Fauq, Diethylaminosulfurtrifluoride, e-EROS Encyclopedia of Reagents for Organic Synthesis, (2006), pp. 1–14.
[27] H.T. Toh, W.H. Okamura, Studies on a convergent route to side-chain analogues of vitamin D: 25-hydroxy-23-oxavitamin D_3, J. Org. Chem. 48 (1983) 1414–1417.
[28] E. Nakamura, New acyl anion equivalent. A short route to the enol lactam intermediate in cytochalasin synthesis, Tetrahedron Lett. 22 (1981) 663–666.
[29] C. Kuroda, T. Ueshino, S. Honda, H. Suzuki, Homo-cope-type five-carbon ring-expansion reaction via silyl enol ether, Synlett 17 (2006) 2830–2832.
[30] Y. Kato, Y. Hashimoto, K. Nagasawa, Novel heteroatom-containing vitamin D_3 analogs: efficient synthesis of 1α,25-dihydroxyvitamin D_3-26,23-lactam, Molecules 8 (2003) 488–499.
[31] K. Ono, A. Yoshida, N. Saito, T. Fujishima, S. Honzawa, Y. Suhara, S. Kishimoto, T. Sugiura, K. Waku, H. Takayama, A. Kittaka, Efficient synthesis of 2-modified 1α,25-dihydroxy-19-norvitamin D_3 with Julia olefination: high potency in induction of differentiation on HL-60 cells, J. Org. Chem. 68 (2003) 7407–7415.