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Process Development of Tacalcitol

Seung Jong Lee, Hyung Wook Moon, Kee-Young Lee, Chang Young Oh, U Bin Kim, and Hyunik Shin*

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ABSTRACT: A highly convergent, gram-scale synthesis of vitamin D3 analogue tacalcitol **1** is disclosed, starting from *L*-valine and Inhoffen–Lythgoe diol. Key features of the synthesis include modified Julia olefination reaction of *β*-oxybenzothiazol-2-yl sulfone with C/D ring containing aldehyde to access decagrams of fully functionalized C/D ring synthon. The Horner–Wadsworth–Emmons (HWE) reaction between the C/D ring fragment and commercially available phosphonate completes the carbo-skeleton, which is elaborated into tacalcitol **1** in a gram-scale synthesis.

KEYWORDS: *tacalcitol, vitamin D3 analogues, modified Julia reaction, epimerization, debenzylation*

INTRODUCTION

The hormonally active metabolite of vitamin D3 (1*α*,25-dihydroxyvitamin D3, calcitriol, **2**; Figure 1) is a potent agonist

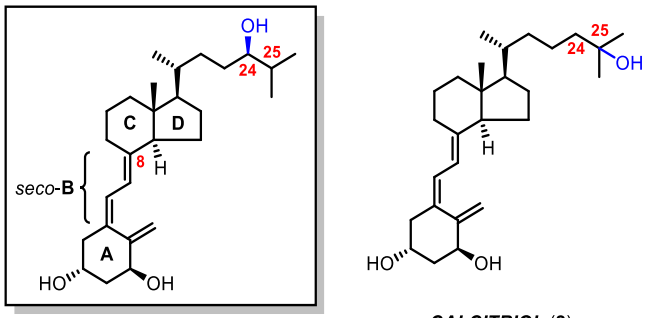

Figure 1. Structure of tacalcitol (**1**) and calcitriol (**2**).

of the transcription factor vitamin D receptor (VDR).[1] Endogenously, **2** is involved in calcium and phosphate homeostasis, cell differentiation, cell antiproliferation, and immunomodulation.[2] Despite its broad biological activity, the therapeutic use of **2** is limited by its adverse effects on calcium metabolism, which can lead to hypercalcemia,[3] hypercalciuria,[4] and bone decalcification.[5] In this context, structural modification efforts have been directed to discover an analogue of **2** having enhanced desired activity[6] with minimal side effects.[7] Currently, 14 such synthetic analogues of vitamin D are on the market as clinical drugs, including alfacalcidol, maxacalcitol, paricalcitol, eldecalcitol, and tacalcitol (**1**).[8]

Among them, tacalcitol (**1**) is used as an efficacious and well-tolerated dermatological treatment for psoriasis, chronic chapped lips, severe dry skin conditions, and other keratinization disorders.[9] Importantly, **1** displays a markedly reduced effect on calcium metabolism compared to **2**.[10−12] Structurally, **1** differs from **2** by hydroxylation of the side chain at the C24 position. Both **1** and **2** feature a central C/D ring connected by *seco*-B/A ring at the C8 position (Figure 1, steroidal numbering).

Over the previous decades, several intriguing approaches have been exploited for the synthesis of tacalcitol (**1**).[13−19] Representative routes include starting from 24-oxocholestrol, which latently contains the complete carbo-skeleton of **1** (Scheme 1, Route 1).[13] Through multistep elaboration, 24-oxocholestrol is converted into 5,7-diene **3**, which is then subjected to a photo-irradiation/thermal isomerization sequence. Although **1** is accessible in this way, the synthesis affords a 1:1 C24-diastereomeric intermediate, obliging an inefficient chromatographic separation. Addressing this issue, Tanaka and co-workers disclosed a diastereoselective isopropylation of **4** to set the C24-stereocenter (Route 2).[20] Subsequent coupling with an ene-yne fragment **5** yields **1**. Similar diastereoselective isopropylation of steroidal C24-aldehydes have also been disclosed, en route to **1**.[15] These routes however risk low asymmetric induction during the key diastereoselective isopropylation step.[21] In our ongoing investigations into the synthesis of vitamin D analogues[22] including **1**, we were particularly drawn to the route published by Fall and co-workers, who have utilized a modified Julia olefination reaction to functionalize the C/D ring containing sulfone **6** (Route 3).[19] This approach, however, is significantly limited by the reported low yield in the modified Julia reaction. Based on this observation, we proposed to reverse the functionality of the aldehyde and sulfone fragments, in which C/D ring containing aldehyde **7** and *β*-oxybenzothiazol-2-yl sulfone **8** would be united via the modified Julia coupling (Route 4). Subsequently, the Horner–Wadsworth–Emmons (HWE) reaction with commercially available **9** was foreseen to allow access to **1**. Herein, we disclose the development of this route, which led to gram-quantity preparation of **1**.

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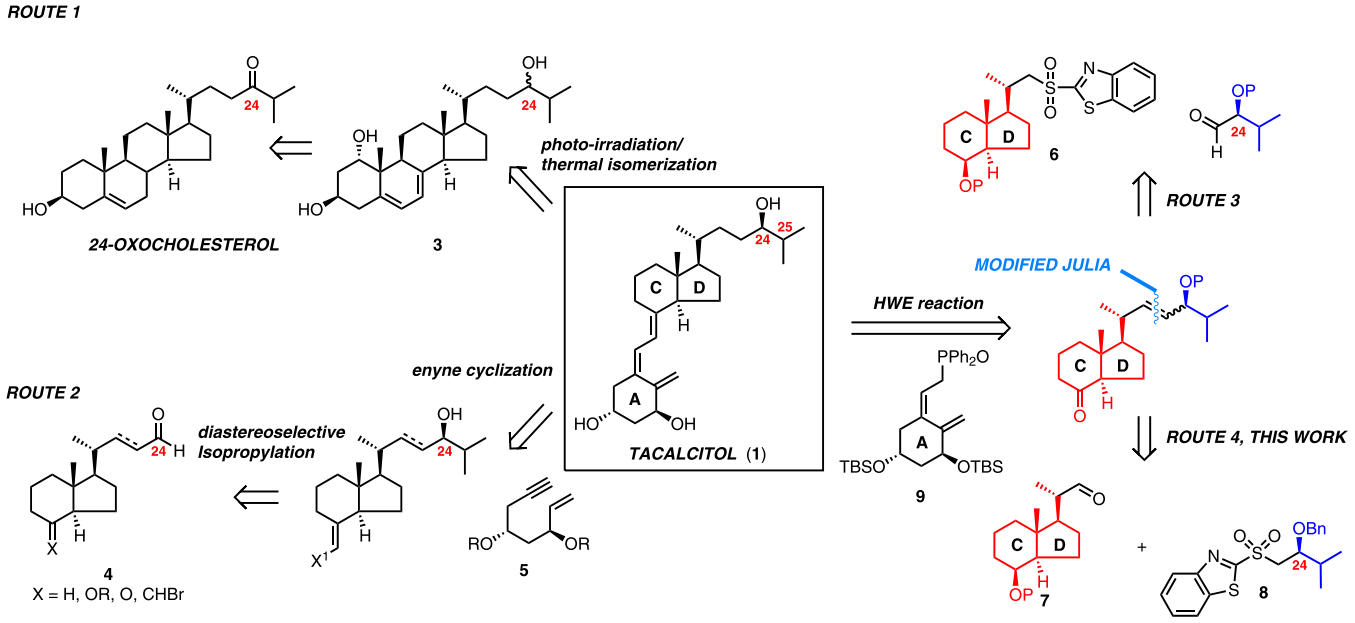
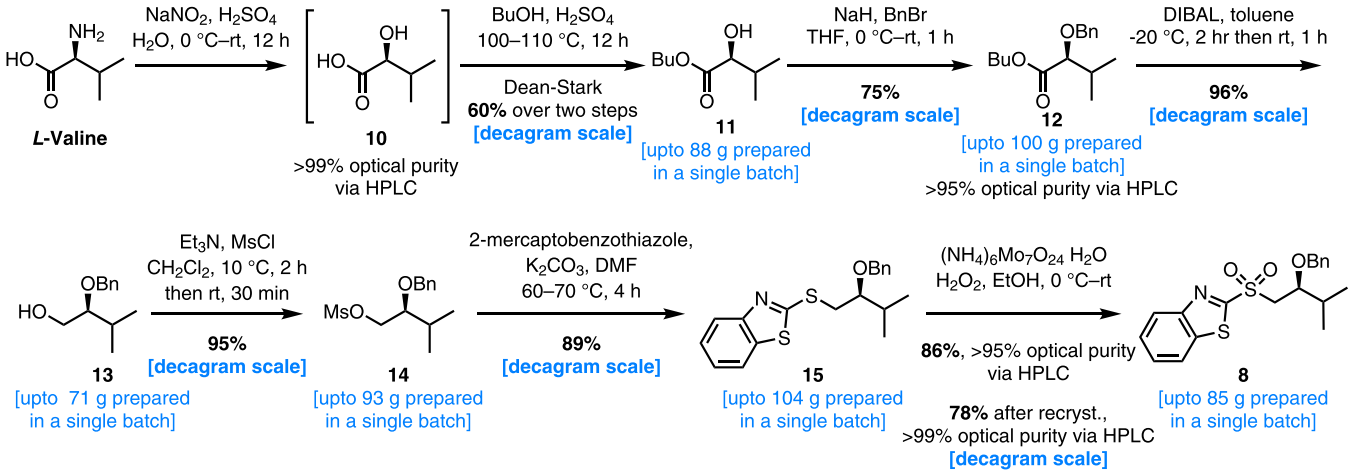
Scheme 1. Reported Synthetic Approaches towards 1 (Routes 1−3) and This Work (Route 4)



Scheme 2. Synthesis of β-Oxybenzothiazol-2-yl Sulfone 8



RESULTS AND DISCUSSION

Our synthesis commenced with the functionalization of *L*-valine (Scheme 2). Well-known double-inversion (nitration−hydrolysis) sequence afforded α-hydroxy acid **10**,[23] with an optical purity of >99%. Fischer esterification of crude **10** with BuOH furnished butyl ester **11** with an optical purity of >96.5%. The secondary alcohol was then alkylated with benzyl bromide to prepare protected alcohol **12**. During the benzyl protection, we noticed modest epimerization of the stereocenter, furnishing material with an optical purity of 95%. The DIBAL reduction of the ester afforded primary alcohol **13**, which was converted into mesylate **14** in high yield. Finally, treatment of **14** with 2-mercaptobenzothiazole in the presence of K_2CO_3 afforded sulfide **15**, which was oxidized with ammonium heptamolybdate[24] to furnish β-oxybenzothiazol-2-yl sulfone **8** with an optical purity of 95%. Through the recrystallization in hexane/ethanol, the eroded optical purity of **8** could be restored to >99%. All reactions were conducted in the multi-decagram scale, and over 80 g of **8** was secured.

With sulfone **8** in hand, we next turned our attention to the preparation of aldehyde **16** (Scheme 3). Starting with **17** derived from exhaustive oxidative cleavage of vitamin D2 and reduction using $NaBH_4$,[25] double-TES protection furnished bis-protected alcohol **18**, which was followed by the primary TES group deprotection with TBAF to yield **19**. Although an identical reaction sequence utilizing the TBS group was known,[19] we found that selective TBS deprotection of primary alcohol was troublesome, thus mandating the usage of the more labile TES group. Compound **19** was then oxidized with TEMPO, affording aldehyde synthon **16** in good yield.

With multi-decagrams of **8** and **16** in hand, we were ready to initiate the key, modified Julia coupling (Scheme 4). It should be noted that the use of β-oxybenzothiazol-2-yl sulfones such as **8** in the modified Julia couplings is relatively rare,[26,27] as these substrates can undergo base-mediated β-elimination reaction.[28,29] In the event, however, the reaction between **8** and **16** mediated by NaHMDS smoothly furnished C23−C26-appended C/D ring fragment **20** in >80% yield after purification by flash chromatography, heralding the success of our synthetic strategy. To set the stage for union with the

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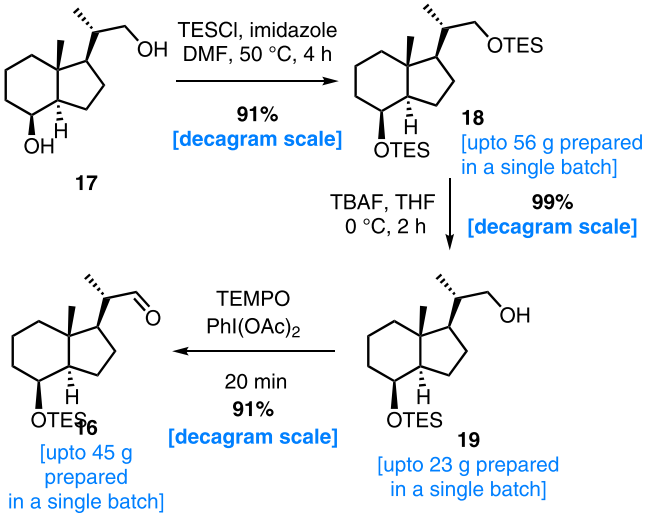
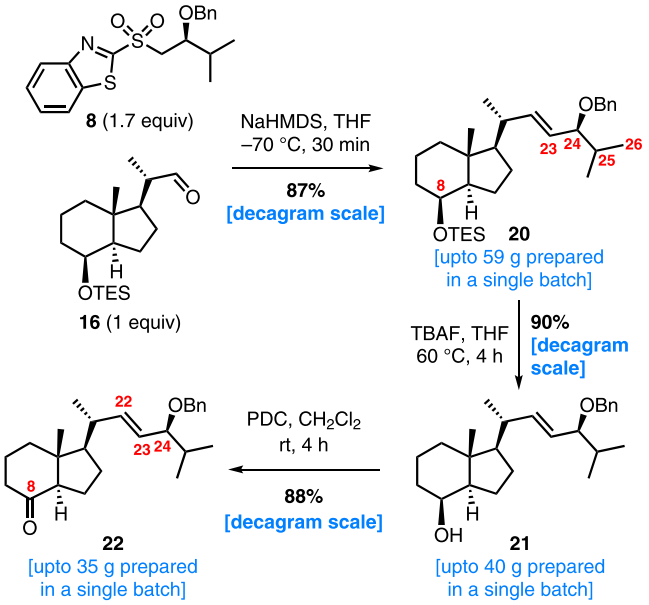
Scheme 3. Synthesis of C/D Ring Containing Aldehyde Synthon 16



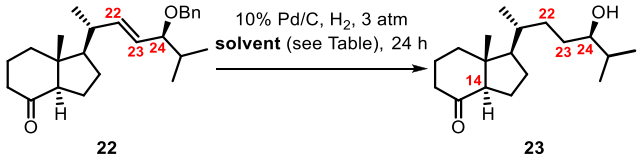
Scheme 4. Modified Julia Reaction of 8 and 16 and Further Elaboration into Ketone 22



seco-B/A ring fragment via HWE reaction, the C8-OTES group was deprotected with TBAF to yield alcohol **21**, which was oxidized with PDC to furnish ketone **22**.

As the *seco*-B/A ring of **1** features a reducible diene, benzyl protecting group, and the C22−C23 olefin of **22** had to be reduced before the anticipated union with the *seco*-B/A ring containing phosphonate. To our surprise, the concurrent debenzylation and reduction of C22−C23 olefin proved challenging and highly sensitive to the solvent used. Under reductive hydrogenation conditions mediated by Pd/C catalysis, solvation with ethyl acetate (Table 1, entry 1) or EtOH (entry 2) led to sluggish olefin reduction and sluggish debenzylation. EtOH/EtOAc solvent mixture afforded faster olefin reduction without facile debenzylation (entry 3). A similar result was obtained with MeOH (entry 4). Intriguingly, complete debenzylation was affected in THF, although the olefin reduction remained sluggish (entry 5). Based on these

Table 1. Solvent Effects on Concurrent C24-OBn Debenzylation/C22−C23 Olefin Reduction



entry	solvent	C22−C23 olefin reduction	C24-OBn debenzylation	23 yield (%)
1	EtOAc	slow	slow	n.d.[a]
2	EtOH	slow	slow	n.d.[a]
3	EtOAc/EtOH	moderate	slow	n.d.[a]
4	MeOH	fast	slow	n.d.[a]
5	THF	moderate	fast	n.d.[a]
6	MeOH/THF	fast	fast	74[b]

[a]n.d. = not determined. [b]51% after recrystallization.

observations, we were able to devise a solvent mixture of MeOH/THF, which afforded the fully reduced product **23** in 74% yield (entry 6). However, we unexpectedly observed modest yet noticeable epimerization at the C24 stereocenter to result in a ratio of C24(*R*)/C24(*S*) = 92.0: 8.0. This issue was rectified by recrystallization in hexanes, which restored the optical purity of **23** to 96.7% with a 51% yield.

Having **23** in hand, C24-OH was protected with the TES group to afford **24** (Scheme 5). Finally, the Horner−Wadsworth−Emmons reaction with the known[30] and commercially available phosphonate **9** smoothly furnished **25**, which after a global deprotection step afforded **1**. This material was recrystallized in a MeOH/H_2O solution to afford the highly pure tacalcitol monohydrate (>99% purity).

CONCLUSIONS

In summary, large-scale synthesis of tacalcitol (**1**) is disclosed. Key features in the synthetic route include modified Julia olefination reaction to append the side chain to the C/D ring fragment and use of the HWE reaction to unite the key fragments. The solvent effects of concurrent debenzylation/olefin reduction are also worthy of note. Using the disclosed synthetic route, gram quantity of pure **1** monohydrate was readily accessed.

EXPERIMENTAL SECTION

General Methods. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectroscopic data were recorded with a Fourier transform NMR (FT-NMR) spectrometer at 300 or 75 MHz. Chemical shift values are reported in parts per million (ppm) relative to TMS or $CDCl_3$ as the internal standard, and coupling constants are reported in hertz. Infrared (IR) spectra were measured with a Fourier transform IR (FT-IR) spectrometer. Mass spectroscopic data were obtained with a Jeol JMS 700 high-resolution mass spectrometer equipped with a magnetic sector--electric sector double-focusing analyzer. Flash chromatography was performed using mixtures of ethyl acetate and hexane as eluents. Unless otherwise stated, all the nonaqueous reactions were carried out under an argon atmosphere with commercial-grade reagents and solvents. Tetrahydrofuran (THF) was distilled from sodium and benzophenone. Dichloromethane was distilled from calcium hydride.

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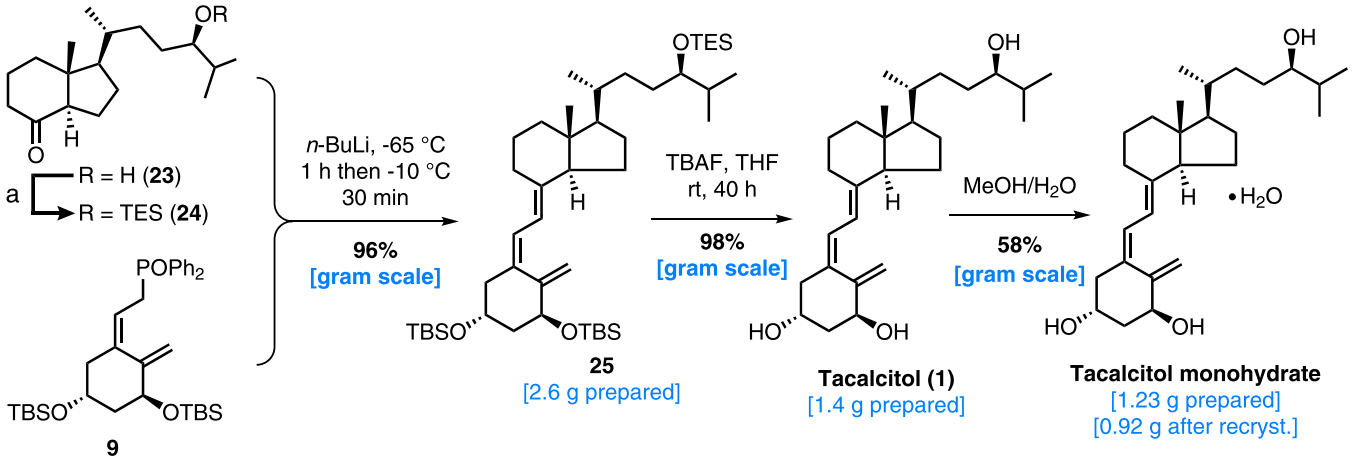
Scheme 5. Synthesis of Tacalcitol (1)



a. TESCl, imidazole, DMF, rt, 2 h, 99%. [Upto 1.4 g of **24** prepared in a single batch].

*(((1R,3aR,4S,7aR)-1-((2R,5S,E)-5-(Benzyloxy)-6-methylhept-3-en-2-yl)-7a-methyloctahydro-1H-inden-4-yl)oxy)triethylsilane (**20**).* To a chilled solution of sulfone **8** (78.1 g, 0.24 mol) in THF at −70 °C, NaHMDS (1.0 M, 187 mL, 0.19 mol) was added. The reaction mixture was stirred for 30 min at this temperature. A solution of aldehyde **16** (45.0 g, 0.14 mol) in THF (132 mL) was then added and the reaction mixture further stirred for 1 h at −70 °C. The reaction mixture was then warmed to room temperature and stirred for a further 4−5 h. Upon completion of the reaction, as monitored by TLC (hexanes/EtOAc = 30:1), the reaction mixture was quenched by the slow addition of NH_4Cl (250 mL, 10%, aqueous), followed by the addition of EtOAc (450 mL). Layers were separated, and the organic layer was dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (silica gel, hexanes/EA = 40:1) afforded the desired olefin **20** (59 g, 87%) as a pale yellow to colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.22 (5H, m), 5.46−5.14 (2H, m), 4.64−4.35 (2H, m), 4.33 (1H, m), 3.89 (1H, dd, J = 9.3 Hz, 6.6 Hz), 1.94−1.11 (13H, m), 1.00−0.89 (21H, m), 0.60−0.52 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.7, 139.4, 128.2, 127.5, 127.2, 126.6, 79.8, 70.0, 69.4, 57.0, 53.1, 42.1, 40.8, 34.6, 34.5, 33.2, 27.7, 23.0, 20.5, 18.8, 18.7, 17.7, 13.9, 7.0, 5.0.

*(1R,3aR,4S,7aR)-1-((2R,5S,E)-5-(Benzyloxy)-6-methylhept-3-en-2-yl)-7a-methyloctahydro-1H-inden-4-ol (**21**).* To a solution of protected alcohol **20** (59 g, 0.12 mol) in THF (43 mL), TBAF (183 mL, 0.18 mol) was added and the reaction mixture heated at 60 °C for 4−5 h. Upon completion of the reaction, as monitored by the TLC analysis (hexanes/EtOAc = 5:1), the reaction mixture was cooled to room temperature and quenched by the addition of H_2O (250 mL). EtOAc (400 mL) was added and after vigorous stirring, the layers were separated. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (silica gel, hexanes/EtOAc = 7:1) afforded the desired alcohol **21** (40 g, 90%) as a pale yellow to colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.33 (5H, m), 5.47−5.16 (2H, m), 4.64−4.33 (2H, m), 4.08 (1H, s), 3.91−3.86 (1H, m), 2.38 (1H, m), 1.99−1.16 (12H, m), 1.00−0.90 (13H, m);^{13}C NMR (75 MHz, $CDCl_3$) δ 140.4, 139.3, 128.2, 127.5, 127.2, 126.8, 79.9, 70.1, 69.3, 56.9, 52.6, 41.8, 40.4, 34.5, 33.6, 33.2, 27.5, 22.5, 20.5, 18.8, 18.7, 17.4, 13.9.

*(1R,3aR,7aR)-1-((2R,5S,E)-5-(Benzyloxy)-6-methylhept-3-en-2-yl)-7a-methyloctahydro-4H-inden-4-one (**22**).* To a solution of alcohol **21** (40 g, 0.11 mol) in CH_2Cl_2 (400 mL), PDC (61.5 g, 0.16 mol) was added and the reaction mixture stirred at room temperature for 4−5 h. Upon completion of the reaction as monitored by TLC analysis (hexanes/EtOAc = 5:1), Et_2O (800 mL) was added and the reaction mixture was stirred for 30 min. The reaction mixture was filtered through a pad of Celite and washed with Et_2O. The combined filtrate was concentrated in vacuo. Flash chromatography (silica gel, hexanes/EtOAc = 7:1) afforded the desired ketone **22** (35.6 g, 88%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.32 (5H, m), 5.48−5.21 (2H, m), 4.63−4.34 (2H, m), 3.90−3.85 (1H, dd, J = 9.3 Hz, 6.3 Hz), 2.50−1.48 (14H, m), 1.01−0.98 (6H, m), 0.92 (3H, d, J = 6.6 Hz), 0.61 (3H, s);^{13}C NMR (75 MHz, $CDCl_3$) δ 211.7, 139.6, 128.3, 127.4, 127.3, 79.6, 70.0, 61.9, 56.8, 49.7, 41.0, 39.0, 34.6, 33.1, 27.8, 24.0, 20.7, 19.0, 18.7, 18.7, 12.8.

*(1R,3aR,7aR)-1-((2R,5R)-5-Hydroxy-6-methylheptan-2-yl)-7a-methyloctahydro-4H-inden-4-one (**23**).* To a pressurizable reactor, a solution of ketone **22** (35.6 g, 96.6 mmol) in THF (534 mL) is loaded. A solution of Pd/C (10 wt % loading, 3.56 g, 3.34 mmol) in MeOH (534 mL) is further added. To the reactor, hydrogen gas was fed and the reaction mixture stirred for 24 h under 3−3.5 atm of H_2. Hydrogen gas was then purged, and the reaction mixture was filtered through Celite. The filtrate was concentrated in vacuo. Flash chromatography (silica gel, hexanes/EtOAc = 3:1) afforded the desired alcohol **23** [C24(R)/C24(S) = 92.0:8.0] (20.0 g, 74%) as a colorless oil. ***Recrystallization*: 23** furnished above (1.45 g, 5.21 mol) was diluted in hexanes (14.5 mL). The solution was warmed to 40−45 °C to fully dissolve the solids. The reaction mixture was stirred slowly and cooled down to room temperature. The solution was cooled and stirred at 15−20 °C for 4 h. The solids were filtered and washed with hexanes (6 mL). The solids were then dried and afforded the desired alcohol **23** [C24(R)/C24(S) = 95.7:4.3] (1.0 g, 69%) as white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.32−3.30 (1H, m), 2.48−2.42 (1H, m), 2.32−2.21 (2H, m), 2.19−2.06 (1H, m), 2.05−1.88 (3H, m), 1.81−1.50 (5H, m), 1.47−1.32 (6H, m), 1.30 (1H, d, J = 5.1 Hz), 0.97 (3H, d, J = 5.7 Hz), 0.93−0.89 (6H, m), 0.65 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ

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212.0, 76.6, 62.0, 56.6, 49.9, 41.0, 39.0, 35.5, 33.6, 31.9, 30.6, 27.6, 24.1, 19.1, 18.9, 18.7, 17.2, 12.5.

*(1R,3aR,7aR)-7a-Methyl-1-((2R,5R)-6-methyl-5-((triethylsilyl)oxy)heptan-2-yl)octahydro-4H-inden-4-one (**24**).* To a solution of alcohol **23** (10 g, 35.7 mmol) in DMF (100 mL), imidazole (3.16 g, 46.4 mol) and TESCl (7.18 mL, 42.8 mmol) were added and the reaction mixture stirred at room temperature for 2 h. Upon completion of the reaction as monitored by TLC analysis (hexanes/EtOAc = 5:1), the reaction mixture was quenched by the addition of NH_4Cl (100 mL, 5%, aq.), followed by the addition of EtOAc (100 mL). The reaction mixture was stirred vigorously then the layers were separated. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (silica gel, hexanes/EtOAc = 10:1) afforded **24** (14 g, 99%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.42−3.37 (1H, m), 2.49−2.42 (1H, m), 2.30−1.86 (6H, m), 1.77−1.65 (2H, m), 1.62−1.47 (2H, m), 1.43−1.12 (6H, m), 0.99−0.94 (12H, m), 0.87−0.84 (6H, m), 0.64−0.55 (9H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.1, 77.4, 62.0, 56.7, 49.9, 41.0, 39.0, 35.8, 33.1, 31.5, 29.7, 27.4, 24.1, 19.1, 18.8, 18.1, 7.0, 5.3.

*(((1R,3S,Z)-5-(2-((1R,3aS,7aR,E)-7a-Methyl-1-((2R,5R)-6-methyl-5-((triethylsilyl)oxy)heptan-2-yl)octahydro-4H-inden-4-ylidene)ethylidene)-4-methylenecyclohexane-1,3-diyl)bis(oxy))bis(tert-butyldimethylsilane) (**25**).* To a chilled solution of phosphonate **9** (6.3 g, 10.8 mmol) in THF (30 mL) at −65 °C, *n*-BuLi (2.5 M, 4.57 mL, 11.4 mol) was added. The reaction mixture was stirred at −65 °C for 1 h. The solution of ketone **24** (1.4 g, 3.55 mmol) in THF (6 mL) was then added to the reaction mixture and stirred further at −65 °C for 1 h. The reaction mixture was then warmed slowly to −10 °C and stirred at this temperature for 30 min. Upon completion of the reaction as monitored by the TLC analysis (hexanes/EtOAc = 30:1), the reaction mixture was quenched by the slow addition of H_2O (10 mL), followed by the addition of Et_2O (30 mL). The reaction mixture was stirred vigorously then the layers were separated. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (silica gel, hexanes/EtOAc = 50:1−30:1) afforded the desired product **25** (2.6 g, 96%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (1H, d, J = 16.4 Hz), 6.02 (1H, d, J = 14.8 Hz), 5.18−4.87 (2H, m), 4.39−4.36 (1H, m), 4.22−4.17 (1H, m), 3.42−3.37 (1H, m), 2.84−2.81 (1H, m), 2.47−2.21 (2H, m), 2.02−1.95 (2H, m), 1.90−1.77 (3H, m), 1.74−1.63 (4H, m), 1.51−1.43 (4H, m), 1.37−1.21 (5H, m), 1.17−1.09 (1H, m), 0.99−0.93 (9H, m), 0.91−0.84 (27H, m), 0.63−0.53 (9H, m), 0.06 (12H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.3, 141.1, 134.9, 123.2, 117.8, 111.2, 77.4, 72.1, 67.5, 56.5, 56.3, 46.1, 45.8, 44.8, 40.6, 36.4, 33.0, 31.6, 29.9, 28.9, 27.7, 25.9, 25.8, 23.5, 22.2, 18.9, 18.2, 18.0, 12.0, 7.1, 5.3.

*Tacalcitol (**1**). (1R,3S,Z)-5-(2-((1R,7aR,E)-1-((2R,5R)-5-Hydroxy-6-methylheptan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)-4-methylenecyclohexane-1,3-diol.* This reaction was performed with the strict exclusion of light. To a solution of **25** (5.5 g, 7.24 mmol) in THF (15 v/w), TBAF (1.0 M in THF, 36.21 mL, 36.21 mmol) was added and the reaction mixture stirred at room temperature for 40 h. Upon completion of the reaction as monitored by the TLC analysis (hexanes/EtOAc = 5:1 and 2:1), the reaction mixture was quenched by the addition of H_2O (50 mL), followed by the addition of EtOAc (100 mL). The reaction mixture was stirred vigorously then the layers were separated. The organic layer was dried (Na_2SO_4) and concentrated in vacuo. Flash chromatography (silica gel, hexanes/EtOAc = 1:2−1:3) afforded tacalcitol (**1**, 2.96 g, 98%) as a white solid in a ratio of C24(R)/C24(S) = 93.71:4.40. ^{1}H NMR (700 MHz, $CDCl_3$) δ 6.38 (1H, d, J = 11.2 Hz), 6.02 (1H, d, J = 11.2 Hz), 5.17−5.15 (2H, m), 4.43−4.41 (1H, m), 4.23−4.21 (1H, m), 3.33−3.31 (1H, m), 2.84−2.82 (1H, m), 2.62−2.60 (1H, m), 2.31−2.30 (1H, m), 2.05−1.91 (5H, m), 1.69−1.64 (3H, m), 1.55-1.36 (7H, m), 1.33−1.21 (4H, m), 0.95−0.91 (9H, m), 0.55 (3H, s); ^{13}C NMR (175 MHz, $CDCl_3$) δ 147.6, 143.3, 132.8, 125.1, 117.0, 111.8, 77.1, 70.9, 66.9, 56.5, 56.4, 45.9, 45.3, 42.9, 40.5, 36.0, 33.6, 32.0, 30.6, 29.1, 27.7, 23.6, 22.3, 18.9, 18.8, 17.2, 12.0.

Tacalcitol Monohydrate. *(1R,3S,Z)-5-(2-((1R,7aR,E)-1-((2R,5R)-5-Hydroxy-6-methylheptan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)-4-methylenecyclohexane-1,3-diol hydrate.* A warmed solution of **1** (2.0 g, 4.8 mmol) in MeOH (160 mL) and H_2O (110 mL) at 30 °C was stirred for 5−7 min. The reaction mixture was then warmed to 25−37 °C and further stirred for 10 min before being cooled to 30 °C. To this solution, tacalcitol monohydrate (5 mg) was added and the reaction mixture was left standing for 48 h at 20−25 °C. The produced solids were filtered and washed with MeOH/H_2O = 80:55 (10 mL) solution. The solids were dried to afford tacalcitol monohydrate (1.23 g, 58.9%) as a white solid in a ratio of C24(R)/C24(S) = 98.36:1.64. ***Recrystallization***: Tacalcitol monohydrate (1.2 g, 2.76 mmol) was stirred in MeOH (96 mL) until it was fully dissolved. The solution was warmed to 30 °C and H_2O (66 mL) was added over 5−7 min. The reaction mixture was then warmed to 35−37 °C and stirred for 10 min, before being cooled to 30 °C. Tacalcitol monohydrate seed crystal (5 mg) was added and the reaction mixture was left standing for 48 h at 20−25 °C. The produced solids were filtered and washed with MeOH/H_2O = 80:55 (10 mL) solution. The solids were dried to yield tacalcitol monohydrate (0.92 g, 76.7%) as a white solid in a ratio of C24(R)/C24(S) = 99.23:0.77. mp: 110.0−112.2 °C.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.1c00010.

Experimental procedures for the synthesis of **10**, **11**, **12**, **13**, **14**, **15**, **8**, **17**, **18**, **19**, and **16**, and copies of ^{1}H and ^{13}C NMR spectra of all novel compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Hyunik Shin − *R&D Center, Yonsung Fine Chemicals Co., Ltd., Suwon-si, Gyeonggi-do 16675, Republic of Korea;* orcid.org/0000-0002-0222-8418; Email: hishin@yonsungchem.co.kr

Authors

Seung Jong Lee − *R&D Center, Yonsung Fine Chemicals Co., Ltd., Suwon-si, Gyeonggi-do 16675, Republic of Korea*

Hyung Wook Moon − *R&D Center, Yonsung Fine Chemicals Co., Ltd., Suwon-si, Gyeonggi-do 16675, Republic of Korea*

Kee-Young Lee − *R&D Center, Yonsung Fine Chemicals Co., Ltd., Suwon-si, Gyeonggi-do 16675, Republic of Korea*

Chang Young Oh − *R&D Center, Yonsung Fine Chemicals Co., Ltd., Suwon-si, Gyeonggi-do 16675, Republic of Korea*

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U Bin Kim − *R&D Center, Yonsung Fine Chemicals Co., Ltd., Suwon-si, Gyeonggi-do 16675, Republic of Korea*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.oprd.1c00010

Notes

The authors declare no competing financial interest.

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