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Large-Scale Synthesis of Eldecalcitol

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ABSTRACT: Industrial-scale synthesis of eldecalcitol is described. AA highly diastereoselective epoxidation of *p*-methoxybenzyl (PMB) protected dienol at room temperature provides the key epoxide intermediate with a secondary hydroxyl group, which is alkylated with a triflate to set up all of the subunits at the C-1, C-2, and C-3 positions of the A-ring fragment. Selective protecting group manipulation followed by palladium-catalyzed cyclization then provides the A-ring synthon. The C/D-ring fragment is obtained by (1) direct C-H hydroxylation of Grundman's ketone using in situ prepared trifluoropropanone dioxirane and (2) protection. Finally, the coupling of the A-ring with the C/D-ring fragment, global deprotection, and recrystallization provide the highly crystalline eldecalcitol.

KEYWORDS: *eldecalcitol, C_2-symmetric, C−H hydroxylation, Sharpless epoxidation, triflate alkylation*

INTRODUCTION

Vitamin D plays a crucial role as a hormonelike molecule in the control of phosphorous and calcium trafficking. It is uniquely converted into its biologically active form, calcitriol, via photoisomerization and subsequent oxidative hydroxylation.[1] Hinted by its prominent biological activities, a useful derivative that does not interfere with the major functions of endogenous calcitriol has been intensively searched for,[2] which led to the commercial launch of alfacalcidol, tacalcitol, maxacalcitol, paricalcitol, and eldecalcitol.[3]

Among them, eldecalcitol (**1**) has achieved prominent commercial success for the treatment of osteoporosis in Japan and has shown superior activity in lowering the risk of fracture and in increasing the bone mineral density over alfacalcidol.[4,5] In this context, extensive efforts have been made to devise an efficient synthesis of eldecalcitol.[6−10] These could be categorized into two main strategies: (1) the late-stage photoisomerization of a fully functionalized 7-dehydrocholesterol derivative (Figure 1, Route 1) and (2) the coupling reaction of the A- and the C/D-ring precursors (Routes 2 and 3). The former strategy was developed by Chugai Pharmaceutical, commencing from lithocholic acid, and is now used in the commercial process.[8] The final step of this route, however, requires a special photoreactor for its implementation and suffers from low chemical yield with the formation of many side products. This feature necessitates preparative HPLC purification (Route 1). The latter strategy was developed using either a coupling of the A-ring synthon via the Horner−Wittig reaction (Route 2)[9] or the transition-metal catalyzed cyclization of the A-ring ene-yne fragment with the appropriate C/D-ring-containing synthon (Route 3).[9d,10] These routes also suffered from low yields in the final cyclization and coupling reactions, respectively. Herein, we disclose a highly practical preparation of the A and C/D-ring fragments and their subsequent manipulation toward eldecalcitol.

RESULTS AND DISCUSSION

In general, the efficient stereoselective synthesis of the A-ring synthon represented a formidable challenge. The first attempt in 1993 by Takahashi et al. derived the C-1, C-2, and C-3 chiral centers of the A-ring from the C-2, C-3, and C-4 chirality of D-mannitol.[9a] Although this approach cleanly installed the three contiguous stereogenic centers with high fidelity, the early stage of this route was not suitable for scale-up due to low yield (30%) at the selective acetonide deprotection step. Another approach by Kubodera et al. in 1997 started from chiral tartaric acid,[9b] which was transformed into a C_2-symmetric epoxide via a multistep process.[11] Although the subsequent regioselective epoxide ring opening resulted in a highly stereocontrolled installation of the C-2 substituent, this route suffered from low stereoselectivity in installing the C-1 stereocenter. Taking these considerations into account, we have devised a highly stereoselective large-scale synthesis of the A-ring fragment by exploiting the C_2-symmetric structural features of D-mannitol (Figure 2).

The synthesis of the A-ring fragment started from the known C_2-symmetric divinyl diol **3**, which was obtained from D-mannitol via three steps (Scheme S1).[12] The diol moiety of **3** was protected as a *p*-methoxybenzyl acetal group to give **4**,

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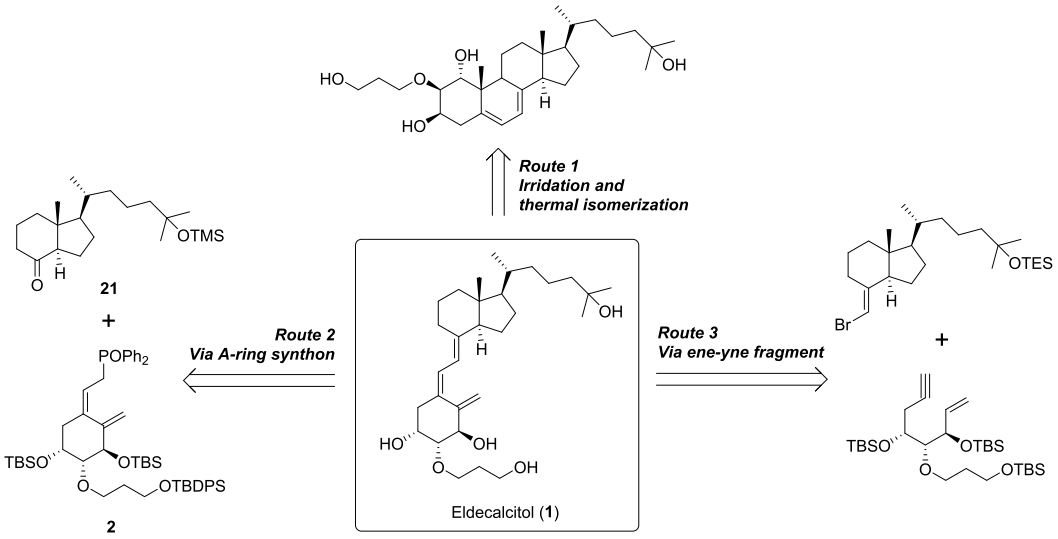


Figure 1. Synthetic strategies toward eldecalcitol (**1**).

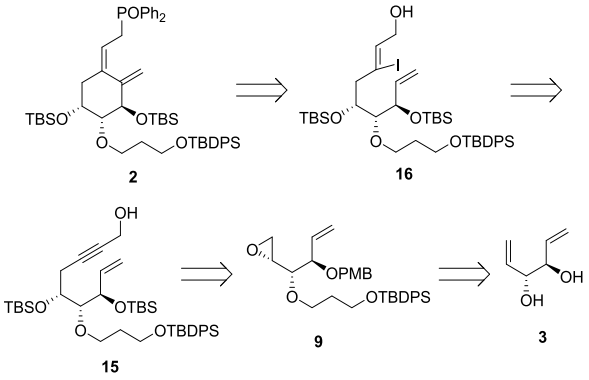
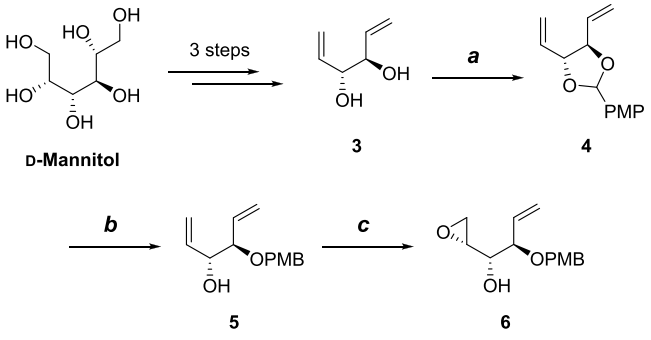


Figure 2. Retrosynthesis of A-ring fragment **2**.

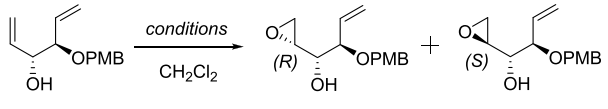
which was then reduced by DIBAL to afford *p*-methoxybenzy (PMB)-monoprotected intermediate **5**. Having **5** in hand, we studied the diastereoselective epoxidation to install the C-3 stereogenic center of **6** (Scheme 1). Initial attempts with mCPBA or $VO(acac)_2$ as an oxidant gave unsatisfactory diastereomeric ratios and chemical yields (entries 1–3, Table 1). In contrast, diastereoselective Sharpless epoxidation[11,13] at low temperature gave satisfactory diastereoselectivity, although

Scheme 1. Synthesis of 6[a]



[a]Reagents and conditions: (a) *p*-anisaldehyde, *p*-TsOH, C_6H_{12}, 40 °C, 4 h; (b) DIBAL, toluene, 0 °C, 1 h, 40% (for two steps); (c) $Ti(OiPr)_4$, (+)-DIPT, cumene hydroperoxide, 3 Å MS, CH_2Cl_2, rt, 5 h, 85%.

Table 1. Epoxidation of 5



entry	reagents and conditions	temp.	time (h)	ratio (**6**/**6′**)[a]	yield (%)[b]
1	mCPBA	0 °C to rt	25	46.5:53.5	20
2	$VO(acac)_2$	0 °C	23	64.8:35.2	23
3	$VO(acac)_2$	rt	23	70.3:29.7	30
4	$Ti(OiPr)_4$, (+)-DIPT, TBHP	−20 °C	94	98.9:1.1	59
5	$Ti(OiPr)_4$, (+)-DIPT, TBHP	−10 °C	43	98.6:1.4	69
6	$Ti(OiPr)_4$, (+)-DIPT, TBHP	0 °C	19	98.5:1.5	66
7	$Ti(OiPr)_4$, (+)-DIPT, TBHP	rt	5	97.9:2.1	85
8	$Ti(OiPr)_4$, (+)-DIPT, CMHP	rt	5	97.9:2.1	85

[a]Ratios were determined by ^1H NMR analysis. [b]Yields refer to the yields of mixed products.

a prolonged reaction time was required (entries 4–6). Propitiously, increasing the reaction temperature resulted in a significantly faster reaction with an enhanced chemical yield and minimal loss of diastereoselectivity (entry 7, **6**/**6′** = 97.9:2.1). Finally, we replaced TBHP with cumene hydroperoxide (CMHP), which is more viable for large-scale operation,[14] which afforded good results (entry 8, **6**/**6′** = 97.9:2.1).

After establishing the optimized reaction conditions for the preparation of epoxide **6**, we recognized that it will be highly efficient if intermediate **6** could be purified without the use of column chromatography. Toward this end, we successfully purified crude intermediates **5** and **6** via thin film distillation under a high vacuum. Considering that **5** and **6** represent key early intermediates toward the synthesis of fragment A, the removal of the need for chromatographic purifications encompassing all chemical steps leading up to **6** provides significant scale-up efficiency.

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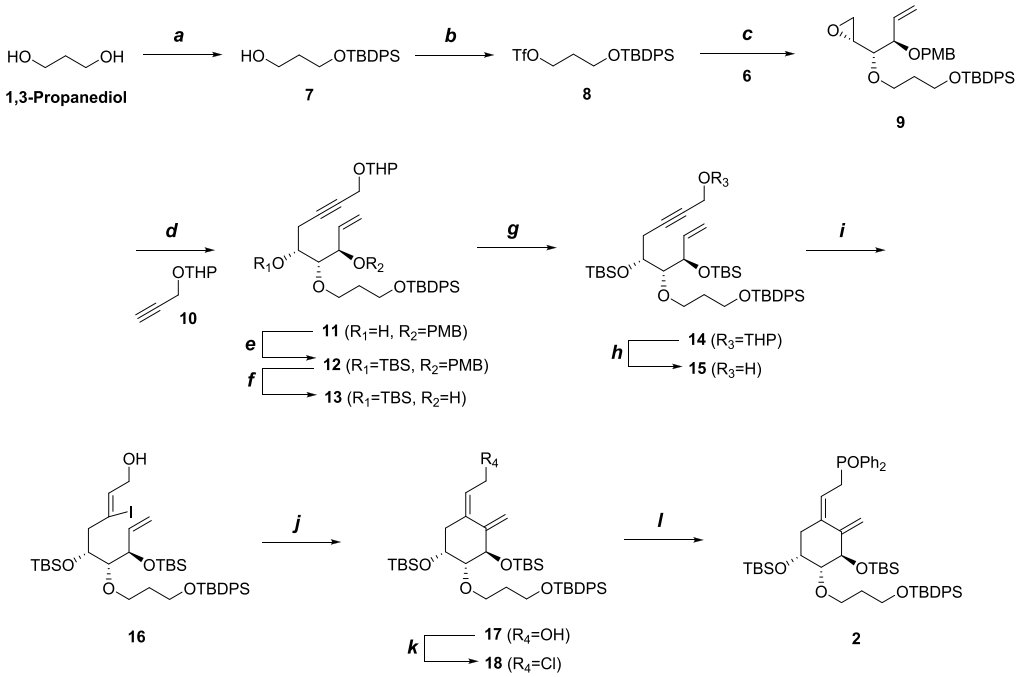
Scheme 2. Synthesis of 2[a]



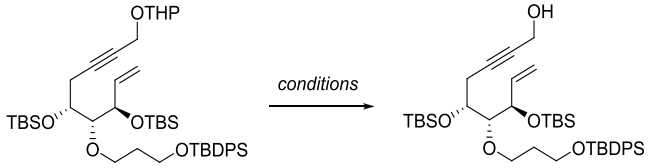
[a]Reagents and conditions: (a) Et_3N, TBDPSCl, CH_2Cl_2, rt, 15 h, 90%; (b) $(TfO)_2O$, DIPEA, *n*-heptane, 10 °C, 30 min, 95%; (c) **6**, NaH, CH_3CN, 0 °C, 10 min, then rt, 30 min, 85%; (d) **10**, *n*-BuLi, $BF_3{\cdot}OEt_2$, THF, −65 °C, 1 h, then rt, 1 h; (e) TBSCl, imidazole, DMF, 60 °C, 15 h; (f) DDQ, CH_2Cl_2, H_2O, rt, 2 h, 56% (for three steps); (g) TBSCl, imidazole, DMF, 60 °C, 6 h, 90%; (h) Me_2AlCl, CH_2Cl_2, rt, 5 h, 85%; (i): (i) Red-Al, Et_2O, rt, 4 h; (ii) I_2, THF, −65 °C, 30 min, then rt, 1 h, 70%; (j) $Ph(PPh_3)_4$, Et_3N, CH_3CN, reflux, 1 h, 90%; (k) NCS, Me_2S, CH_2Cl_2, −20 °C, 20 min, then rt, 30 min, 90%; (l): (i) $HPPh_2$, *n*-BuLi, THF, −60 °C, 1 h; (ii) 5% H_2O_2, $CHCl_3$, rt, 10 min, 80%.

Next, a Williamson ether reaction of secondary alcohol **6** was examined (Scheme 2). Early attempts at *O*-alkylation with analogs of **8**, which contained halide-leaving groups (−Br and −I), resulted in complex mixtures under various conditions. We then tested triflate **8**, which was synthesized from 1,3-propanediol in two steps. Initial attempts at alkylation using alkoxide bases or amine bases such as DIPEA did not afford the desired product. The use of NaH in tetrahydrofuran (THF), however, provided **9** in 60% yield. By careful TLC analysis, we found that triflate **8** was unstable in solvents such as THF, toluene, DME, and DCM, while good solution stability was observed in acetonitrile. With these observations in mind, coupling of **6** with **8** using NaH as a base in acetonitrile furnished **9** in 85% yield. It is important to note that excess triflate **8** should be quenched completely at the end of the reaction by the addition of MeOH. If not, residual triflate **8** slowly decomposes to generate triflic acid, which catalyzes the decomposition of the desired product **9**, especially when kept as a crude concentrate.

The reaction of THP-protected propargyl alcohol **10** with **9** in the presence of boron trifluoride etherate afforded **11**. The attempted deprotection of the PMB group using ceric ammonium nitrate (CAN) resulted in a cyclic side product instead of the desired diol. Due to this issue, a sequential *tert*-butyldimethylsilyl (TBS) protection of **11** to **12** and deprotection of the PMB group to **13** followed by TBS protection to **14** was effected.

Next, the required orthogonal deprotection of the THP group of **14** to yield **15** proved to be nontrivial. The well-known conditions using PPTS[15] were complicated by the concomitant partial deprotection of the silyl groups (entry 1, Table 2). The use of LiCl[16] at a high temperature afforded the desired product in a moderate yield (entry 2). The use of $NaCNBH_3/BF_3{\cdot}OEt_2$[17] led to a high yield, although a prolonged reaction time was required (entry 3). The reaction using $BF_3{\cdot}OEt_2/SiEt_3H$ provided a low yield (entry 4). Interestingly, the use of $MgBr_2$[18] as a Lewis acid showed a significant solvent effect: no reaction was observed in THF (entry 5); a high yield was achieved in Et_2O after a prolonged reaction time (entry 6); and a moderate yield was observed in CH_2Cl_2 (entry 7). Finally, the use of Me_2AlCl[19] (entry 8) led

Table 2. THP Deprotection of 14



entry	reagents and conditions	temp.	time (h)	yield (%)
1	PPTS (0.1 equiv), acetone, H_2O	0 °C to rt	24	5
2	LiCl (5.0 equiv), DMSO, H_2O	90 °C	8	50
3	$NaCNBH_3$ (1.5 equiv), $BF_3{\cdot}OEt_2$ (1.0 equiv), THF	rt	48	94
4	$BF_3{\cdot}OEt_2$ (2.0 equiv), $SiEt_3H$ (5.0 equiv), THF	rt	24	35
5	$MgBr_2$ (3.0 equiv), THF	rt	7	0
6	$MgBr_2$ (7.0 equiv), Et_2O	rt	24	90
7	$MgBr_2$ (3.0 equiv), CH_2Cl_2	rt	3	30
8	Me_2AlCl (2.0 equiv), CH_2Cl_2	0 °C to rt	5	85

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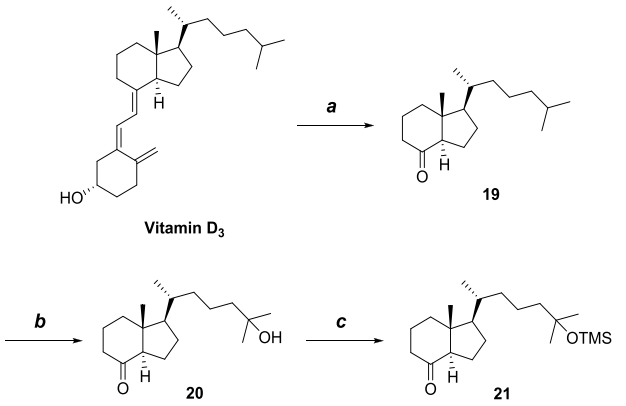
to a good yield in a short reaction time at ambient temperature and was selected as the final method for THP deprotection.

The partial reduction of the triple bond using Red-Al and subsequent iodination reaction conducted in the same pot gave vinyl iodide **16**. Its Pd(0)-catalyzed intramolecular Heck reaction afforded 6-exo cyclized (*Z*)-diene **17**. Chlorination of the allylic alcohol was achieved using the Corey–Kim reagent, and subsequent reaction with lithium diphenylphosphide furnished the required phosphine oxide **2** in a good overall yield.

The C/D-ring fragment **21**[20] was prepared via the direct hydroxylation of Grundman's ketone **19**, which was readily obtained from the ozonolysis of vitamin D_3 (Scheme 3).

Scheme 3. Synthesis of 21[a]



[a]Reagents and conditions: (a) O_3, $NaHCO_3$, CH_2Cl_2, MeOH, −65 °C, 4 h, 85%; (b) CF_3COMe, Oxone, $NaHCO_3$, CH_3CN, H_2O, 0 °C, 24 h, 53%; (c) TMS-imidazole, CH_2Cl_2, rt, 1.5 h, 78%.

Although the use of isolated dioxirane in this reaction provides high yield, we deployed in situ generated methyl(trifluoromethyl)dioxirane (TFDO), which was derived from Oxone and trifluoroacetone to mitigate the potential safety issues arising from this conversion.[21]

Finally, a Horner–Wittig reaction was required to unite the A-ring fragment **2** and the C/D-ring fragment **21**. The known conditions using *n*-BuLi were first attempted, which led to olefin **22** in a low to moderate yield (Scheme 4).[9e,f] Critically, the use of an excess amount of **2** (2.0–3.0 equiv) led to higher yields (Table 3, entries 4 and 5). With fully functionalized **22** in hand, the global deprotection of the silyl groups using *p*-TsOH in $MeOH/CH_2Cl_2$ afforded eldecalcitol (**1**), which was recrystallized in acetonitrile–water to provide the highly pure and crystalline product. Our synthetic sample was in good spectroscopic agreement with the reported eldecalcitol.[7a,9f,g] Its X-ray single-crystal structure is depicted in Figure 3.

Table 3. Optimization of Coupling Reaction between 2 and 21

entry	**2** (equiv)	*n*-BuLi (equiv)	**21** (equiv)	**22** yield (%)
1	1.0	1.0	1.0	>10
2	1.5	1.5	1.0	50
3	1.0	1.0	2.0	>10
4	2.0	2.0	1.0	89[a]
5	3.0	3.0	1.0	95

[a]0.7 equiv of **2** was recovered.

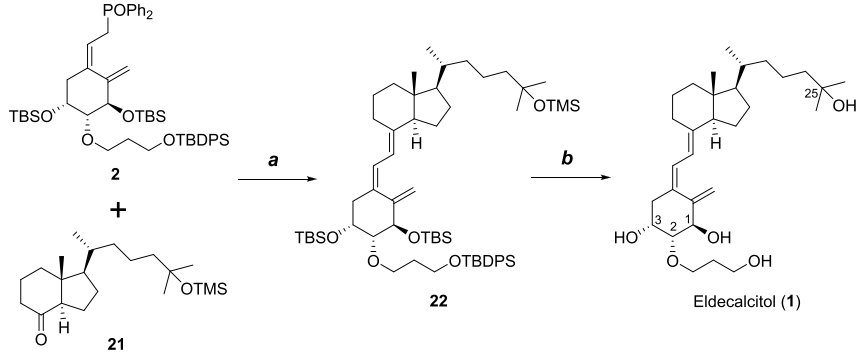
CONCLUSIONS

In summary, a large-scale synthetic route toward eldecalcitol (**1**) was devised. Our synthesis features no chromatographic purification for the preparation of the key early intermediate **6**, which is accessed from a highly efficient Sharpless epoxidation conducted at ambient temperature. The selective deprotection of the THP group of **14** is worthy of recognition for its efficiency. Finally, the coupling of A-ring phosphine oxide **2** with C/D-ring ketone **21** has been accomplished in high yield, and the final recrystallization of **1** afforded high-quality eldecalcitol as a crystalline solid.

EXPERIMENTAL SECTION

General Methods. Optical rotations were measured with a JASCO P-2000 polarimeter in ethanol solvent. ^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 the mixtures of ethyl acetate and hexane as eluents. Unless otherwise stated, all of the nonaqueous reactions were carried out under an argon atmosphere with commercial-grade reagents and solvents. THF was distilled

Scheme 4. Synthesis of Eldecalcitol (1)[a]



[a]Reagents and conditions: (a) *n*-BuLi, THF, −65 °C, 1 h, then −10 °C, 2 h, 89%; (b) *p*-TsOH·H_2O, CH_2Cl_2, MeOH, rt, 5 h, 80%.

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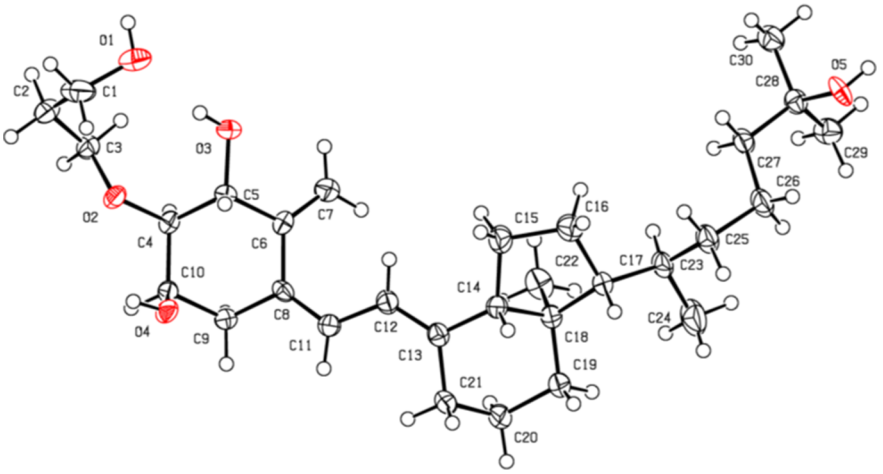

Figure 3. X-ray single-crystal structure of eldecalcitol (**1**).

from sodium and benzophenone. Dichloromethane was distilled from calcium hydride.

*(4R,5R)-2-(4-Methoxybenzyl)-4,5-divinyl-1,3-dioxolane (**4**).* To a solution of **3** (3.4 kg, 30 mol) in cyclohexane (34 L) were added *p*-anisaldehyde (4.7 L, 39 mol) and *p*-TsOH (4.3 kg, 22 mol) at rt. The reaction mixture was stirred at 40 °C for 4 h, cooled to rt, and quenched with aqueous 5% $NaHCO_3$ solution (56 L). The organic layer was separated and washed with aqueous 10% $NaHSO_3$ solution (133 L) for the removal of unreacted *p*-anisaldehyde. The organic layer was separated, washed with aqueous 3% $NaHCO_3$ solution (35 L) and water (35 L), dried over Na_2SO_4, and concentrated in vacuo. Crude oil **4** (6.9 kg, 30 mol) was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (2H, dd, J = 6.6, 1.8 Hz), 6.91 (2H, dd, J = 6.7, 1.9 Hz), 6.00 (1H, s), 5.94−5.85 (2H, m), 5.45−5.35 (2H, m), 5.33−5.24 (2H, m), 4.37−4.19 (2H, m), 3.81 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 134.4, 133.7, 130.3, 128.1, 119.4, 118.6, 113.9, 103.9, 84.0, 82.3, 55.5.

*(3R,4R)-4-((4-Methoxybenzyl)oxy)hexa-1,5-dien-3-ol (**5**).* To a solution of crude **4** (6.9 kg, 30 mol) in toluene (35 L) was added 1.2 M DIBAL in toluene (30 L, 36 mol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. MeOH (1 L) was added to the reaction mixture. The reaction mixture was cooled to 10 °C, quenched with aqueous 5% NaOH solution (48 L), and stirred for 10 min. The organic layer was separated, dried over Na_2SO_4, and concentrated in vacuo. Thin film distillation of the crude mixture at 120 °C under 0.2 Torr gave product **5** (2.8 kg, 12 mol, 40% for two steps) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (2H, d, J = 8.7 Hz), 6.89 (2H, dd, J = 6.7, 1.9 Hz), 5.86−5.67 (2H, m), 5.99−5.35 (2H, m), 5.32−5.28 (1H, m), 5.20 (1H, dt, J = 10.5, 1.5 Hz), 4.59 (1H, d, J = 11.1 Hz), 4.31 (1H, d, J = 11.1 Hz), 4.07−4.01 (1H, m), 3.80 (3H, s), 3.67 (1H, t, J = 7.5 Hz), 2.76 (1H, d, J = 3.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 136.3, 134.9, 130.1, 129.7, 120.3, 117.1, 114.0, 83.8, 74.8, 70.4, 55.4.

*(1S,2R)-2-((4-Methoxybenzyl)oxy)-1-((R)-oxiran-2-yl)but-3-en-1-ol (**6**).* To a solution of activated 3 Å molecular sieves (0.7 kg) in CH_2Cl_2 (8.5 L) were added $Ti(OiPr)_4$ (2.12 L, 7.16 mol) and (+)-diisopropyl tartrate (1.76 L, 8.35 mol) at rt. The reaction mixture was stirred at rt for 20 min. A dilute solution of compound **5** (1.40 kg, 5.98 mol) in CH_2Cl_2 (5.5 L) was added to the reaction mixture. The reaction mixture was stirred at rt for 20 min and cooled to 15 °C. Cumene hydroperoxide (80%, 1.14 L, 6.14 mol) was added dropwise to the reaction mixture using a dropping funnel. The reaction mixture was stirred at rt for 5 h and filtered through a pad of Celite. A solution of $FeSO_4 \cdot 7H_2O$ (1.99 kg) and citric acid (0.69 kg) in water (28 L) was added to the resulting solution. The organic layer was separated, filtered through a pad of Celite, and washed with a solution of NaOH (1.0 kg) in aqueous 20% NaCl solution (13 L). The organic layer was separated, washed with 1 N HCl solution (4.3 L), aqueous 4.6% $NaHCO_3$ solution (13 L), and water (13 L), dried over Na_2SO_4, and concentrated in vacuo. Thin-film distillation of the crude mixture at 80 °C under 0.2 Torr and further purification by thin film distillation at 140 °C under 0.2 Torr gave product **6** (1.27 kg, 5.07 mol, 85%) as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 (2H, d, J = 8.4 Hz), 6.89 (2H, d, J = 8.7 Hz), 5.92−5.80 (1H, m), 5.42 (1H, s), 5.40−5.35 (1H, m), 4.62 (1H, d, J = 11.4 Hz), 4.35 (1H, d, J = 11.4 Hz), 3.94−3.87 (1H, m), 3.81 (3H, s), 3.48 (1H, t, J = 5.1 Hz), 3.06−3.01 (1H, m), 2.78 (2H, d, J = 3.3 Hz), 2.46 (1H, brs); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 134.7, 130.0, 129.7, 120.1, 114.0, 81.4, 73.3, 70.3, 55.4, 51.9, 45.0.

*(3R,4S)-1-(4-Methoxyphenyl)-11,11-dimethyl-4-((R)-oxiran-2-yl)-10,10-diphenyl-3-vinyl-2,5,9-trioxa-10-siladodecane (**9**).* To a solution of 60% dispersion of NaH in mineral oil (0.28 kg, 7.0 mol) in CH_3CN (8.5 L) was added a dilute solution of compound **6** (1.27 kg, 5.07 mol) in CH_3CN (3.5 L) slowly at −5 °C. To this reaction mixture was added dropwise a solution of triflate **8** (3.40 kg, 7.60 mol) in CH_3CN (3 L) using a dropping funnel. The reaction mixture was stirred at 0 °C for 10 min, stirred at rt for 30 min, and quenched with MeOH (0.41 L, 10.1 mol). To the resulting solution were added water (12.5 L) and AcOEt (12.5 L) and stirred for 10 min. The organic layer was separated, washed with water (12.5 L), dried over Na_2SO_4, and concentrated in vacuo. Purification by silica gel column chromatography (hexanes/AcOEt = 7:1) gave product **9** (2.36 kg, 4.32 mol, 85%) as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67−7.61 (4H, m), 7.44−7.33 (6H, m), 7.25−7.22 (2H, m), 6.86−6.83 (2H, m), 5.91−5.81 (1H, m), 5.31−5.24 (2H, m), 4.60 (1H, d, J = 12.0 Hz), 4.34 (1H, d, J = 11.7 Hz), 3.92 (1H, q, J = 3.9 Hz), 3.78 (3H, s), 3.76−3.68 (3H, m), 3.64−3.56 (1H, m), 3.22 (1H, t, J = 4.5 Hz), 3.10−3.06 (1H, m), 2.76−2.72 (2H, m), 1.83−1.74 (2H, m), 1.03 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 135.7, 135.3, 134.9, 134.1, 130.5, 129.8,

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129.7, 129.5, 127.9, 127.8, 118.8, 113.8, 81.0, 80.5, 70.4, 68.8, 60.9, 55.4, 51.2, 45.5, 33.2, 27.0, 26.7, 19.4.

*(3R,4R,5R)-4-(3-((tert-Butyldiphenylsilyl)oxy)propoxy)-3-((4-methoxybenzyl)oxy)-9-((tetrahydro-2H-pyran-2-yl)oxy)-non-1-en-7-yn-5-ol (**11**).* To a solution of THP-protected propargyl alcohol **10** (1.81 kg, 12.9 mol) in THF (16.5 L) was added 2.5 M *n*-BuLi in *n*-hexane (4.83 L, 12.1 mol) dropwise at −65 °C. The reaction mixture was stirred at −65 °C for 1 h. To the reaction mixture were added dropwise a solution of compound **9** (2.36 kg, 4.32 mol) in THF (7 L) and $BF_3{\cdot}OEt_2$ (0.59 L, 4.75 mol) subsequently. The reaction mixture was warmed to rt, stirred at rt for 1 h, and quenched with aqueous 8.9% NH_4Cl solution (11.5 L). The organic layer was extracted with AcOEt (23 L), dried over Na_2SO_4, and concentrated in vacuo. The crude oil of **11** (2.96 kg, 4.31 mol) was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66−7.63 (4H, m), 7.45−7.34 (6H, m), 7.25−7.21 (2H, m), 6.86 (2H, dt, J = 9.2, 2.5 Hz), 5.98−5.86 (1H, m), 5.35−5.29 (2H, m), 4.79 (1H, t, J = 3.3 Hz), 4.59 (1H, d, J = 11.7 Hz), 4.30 (1H, d, J = 11.7 Hz), 4.27−4.23 (2H, m), 4.11−4.07 (1H, m), 3.87−3.82 (2H, m), 3.79 (3H, s), 3.75−3.65 (4H, m), 3.55−3.46 (1H, m), 3.37−3.34 (1H, m), 2.99 (1H, d, J = 4.8 Hz), 2.56−2.40 (2H, m), 1.82−1.49 (8H, m), 1.04 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 135.7, 135.0, 134.0, 129.9, 129.8, 129.7, 127.8, 119.1, 114.0, 96.9, 83.2, 82.1, 79.5, 78.2, 70.4, 69.6, 68.9, 62.2, 60.8, 55.4, 54.8, 33.2, 30.5, 27.0, 25.5, 24.0, 19.3, 14.3.

*(5R,6S)-6-((R)-1-((4-Methoxybenzyl)oxy)allyl)-2,2,3,3,13,13-hexamethyl-12,12-diphenyl-5-(4-((tetrahydro-2H-pyran-2-yl)oxy)but-2-yn-1-yl)-4,7,11-trioxa-3,12-disilatetradecane (**12**).* To a solution of crude compound **11** (2.96 kg, 4.31 mol) in DMF (30 L) were added imidazole (0.73 kg, 10.72 mol) and TBSCl (1.49 kg, 9.89 mol) subsequently at rt. The reaction mixture was stirred at 60 °C for 15 h, cooled to rt, and quenched with water (3 L) and aqueous 5% NH_4Cl solution (23 L). The organic layer was separated with AcOEt (30 L), washed with water (30 L), dried over Na_2SO_4, and concentrated in vacuo. The crude oil of **12** (3.45 kg, 4.31 mol) was used in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68−7.64 (4H, m), 7.43−7.33 (6H, m), 7.23−7.20 (2H, m), 6.82 (2H, dt, J = 9.2, 2.5 Hz), 5.93−5.81 (1H, m), 5.31−5.28 (1H, m), 5.25 (1H, s), 4.84−4.76 (1H, m), 4.49 (1H, d, J = 11.4 Hz), 4.30−4.21 (3H, m), 3.97−3.74 (10H, m), 3.53−3.47 (1H, m), 3.38−3.34 (1H, m), 2.51−2.49 (2H, m), 1.89−1.48 (8H, m), 1.04 (9H, s), 0.86 (9H, s), 0.07 (3H, s), 0.01 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 136.5, 135.7, 134.2, 130.9, 129.6, 129.5, 127.7, 118.5, 113.8, 96.8, 96.7, 85.6, 84.7, 84.6, 80.8, 71.6, 70.4, 70.2, 62.1, 61.2, 60.5, 55.4, 54.8, 54.7, 33.5, 30.5, 27.0, 26.0, 25.8, 25.6, 23.6, 21.2, 19.3, 18.2, 14.3, −4.3, −4.5.

*(3R,4S,5R)-5-((tert-Butyldimethylsilyl)oxy)-4-(3-((tert-butyldiphenylsilyl)oxy)propoxy)-9-((tetrahydro-2H-pyran-2-yl)oxy)non-1-en-7-yn-3-ol (**13**).* To a solution of crude compound **12** (3.45 kg, 4.31 mol) in CH_2Cl_2 (35 L) were added water (25 L) and DDQ (1.17 kg, 5.15 mol) at rt. The reaction mixture was stirred at rt for 2 h, quenched with aqueous 0.75% NaOH solution (35 L), and stirred at rt for 10 min. The organic layer was separated, and aqueous 10% $NaHSO_3$ solution (38 L) was added and stirred at rt for 10 min. The organic layer was separated, dried over Na_2SO_4, and concentrated in vacuo. Purification by silica gel chromatography (hexanes/AcOEt = 9:1) gave product **13** (1.64 kg, 2.41 mol, 56% for three steps) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67−7.64 (4H, m), 7.45−7.35 (6H, m), 5.99−5.88 (1H, m), 5.35 (1H, dt, J = 17.2, 1.7 Hz), 5.18 (1H, dt, J = 10.5, 1.5 Hz), 4.80 (1H, t, J = 3.1 Hz), 4.31−4.22 (3H, m), 3.93−3.79 (3H, m), 3.75−3.64 (3H, m), 3.54−3.47 (1H, m), 3.33 (1H, dd, J = 5.7, 3.9 Hz), 2.66 (1H, d, J = 6.3 Hz), 2.58−2.43 (2H, m), 1.87−1.65 (4H, m), 1.61−1.50 (4H, m), 1.04 (9H, s), 0.90 (9H, s), 0.11 (3H, s), 0.09 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 135.7, 134.0, 129.7, 127.8, 116.2, 98.7, 83.8, 83.4, 83.3, 78.2, 71.3, 70.9, 69.6, 62.2, 62.1, 60.9, 60.5, 54.6, 33.3, 30.5, 27.0, 25.9, 25.5, 24.1, 21.2, 19.3, 18.2, 14.3, −4.4, −4.6.

*(5R,6R)-6-((1R)-1-((tert-Butyldimethylsilyl)oxy)-5-((tetrahydro-2H-pyran-2-yl)oxy)pent-3-yn-1-yl)-2,2,3,3,13,13-hexamethyl-12,12-diphenyl-5-vinyl-4,7,11-trioxa-3,12-disilatetradecane (**14**).* To a solution of compound **13** (1.64 kg, 2.41 mol) in DMF (16.5 L) were added imidazole (0.263 kg, 3.86 mol) and TBSCl (0.546 kg, 3.62 mol) subsequently at rt. The reaction mixture was stirred at 60 °C for 6 h, cooled to rt, and quenched with water (1.6 L) and aqueous 5% NH_4Cl solution (13 L). The organic layer was separated with AcOEt (16.5 L), washed with water (16.5 L), dried over Na_2SO_4, and concentrated in vacuo. Purification by silica gel chromatography (hexanes/AcOEt = 10: 1) gave product **14** (1.65 kg, 2.17 mol, 90%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68−7.64 (4H, m), 7.44−7.34 (6H, m), 5.93−5.81 (1H, m), 5.24 (1H, dt, J = 17.4, 1.5 Hz), 5.14−5.10 (1H, m), 4.79−4.78 (1H, m), 4.30−4.25 (1H, m), 4.20−4.13 (2H, m), 3.98−3.94 (1H, m), 3.86−3.67 (5H, m), 3.54−3.47 (1H, m), 3.26 (1H, dd, J = 6.6, 1.5 Hz), 2.51−2.33 (2H, m), 1.86−1.47 (8H, m), 1.04 (9H, s), 0.89 (9H, s), 0.87 (9H, s), 0.08 (3H, s), 0.06 (3H, s), 0.04 (3H, s), 0.02 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 135.7, 134.2, 129.6, 127.7, 116.0, 98.9, 96.8, 74.4, 72.2, 69.6, 62.1, 61.3, 60.5, 54.9, 54.8, 33.5, 30.4, 27.0, 26.1, 26.0, 25.5, 23.6, 21.2, 19.3, 18.4, 18.2, 14.4, −4.3, −4.4, −4.5.

*(5R,6R,7R)-5,7-Bis((tert-butyldimethylsilyl)oxy)-6-(3-((tert-butyldiphenylsilyl)oxy)propoxy)non-8-en-2-yn-1-ol (**15**).* To a solution of compound **14** (1.65 kg, 2.17 mol) in CH_2Cl_2 (16.5 L) was added 0.9 M Me_2AlCl in heptane (4.83 L, 4.34 mol) dropwise at 10 °C. The reaction mixture was stirred at rt for 5 h, cooled to 0 °C, and quenched with MeOH (132 mL, 3.25 mol). To the resulting solution was added aqueous 3.6% NaOH solution (16.5 L) and stirred for 10 min. The organic layer was separated, dried over Na_2SO_4, and concentrated in vacuo. Purification by silica gel column chromatography (hexanes/AcOEt = 9:1) gave product **15** (1.42 kg, 1.84 mol, 85%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68−7.64 (4H, m), 7.44−7.34 (6H, m), 5.93−5.81 (1H, m), 5.24 (1H, dt, J = 17.3, 1.6 Hz), 5.13 (1H, dt, J = 10.5, 1.5 Hz), 4.29−4.21 (2H, m), 4.18−4.13 (1H, m), 3.98−3.93 (1H, m), 3.87−3.67 (4H, m), 3.27 (1H, dd, J = 6.6, 1.8 Hz), 2.49−2.34 (2H, m), 1.87−1.78 (2H, m), 1.37 (1H, t, J = 6.0 Hz), 1.04 (9H, s), 0.89 (9H, s), 0.88 (9H, s), 0.09 (3H, s), 0.06 (3H, s), 0.05 (3H, s), 0.02 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 135.7, 134.2, 129.7, 127.8, 116.0, 87.0, 85.4, 79.5, 74.4, 72.1, 69.7, 61.0, 51.7, 33.5, 27.0, 26.1, 26.0, 23.5, 19.4, 18.4, 18.2, −4.3, −4.4, −4.5.

*(5R,6R,7R, Z)-5,7-Bis((tert-butyldimethylsilyl)oxy)-6-(3-((tert-butyldiphenylsilyl)oxy)propoxy)-3-iodonona-2,8-dien-1-ol (**16**).* To a solution of compound **15** (1.42 kg, 1.84 mol) in Et_2O (18.5 L) was added 60% Red-Al solution in toluene (7.39 L, 2.65 mol) dropwise at 0 °C. The reaction mixture was stirred at rt for 4 h and cooled to 0 °C, and AcOEt (0.2 L) was

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added at 0 °C and cooled to −65 °C. A solution of I_2 (0.937 kg, 3.69 mol) in THF (2.5 L) was added to the reaction mixture at −65 °C. The reaction mixture was stirred at −65 °C for 30 min, stirred at rt for 1 h, quenched with aqueous 10% NH_4Cl solution (4.2 L), and stirred for 10 min. The organic layer was separated, washed with aqueous 10% $Na_2S_2O_3$ solution (11.7 L), dried over Na_2SO_4, and concentrated in vacuo. Purification by silica gel column chromatography (hexanes/AcOEt = 9:1) gave product **16** (1.08 kg, 1.29 mol, 70%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.69−7.62 (4H, m), 7.45−7.34 (6H, m), 5.93−5.76 (2H, m), 5.31 (1H, dt, J = 17.3, 1.5 Hz), 5.18 (1H, dt, J = 10.5, 1.4 Hz), 4.20−4.01 (4H, m), 3.89−3.69 (4H, m), 3.28 (1H, dd, J = 7.5, 0.9 Hz), 2.74−2.67 (1H, m), 2.61−2.56 (1H, m), 1.89−1.80 (2H, m), 1.39 (1H, t, J = 6.0 Hz), 1.05 (9H, s), 0.90 (9H, s), 0.84 (9H, s), 0.09 (3H, s), 0.06 (3H, s), 0.05 (3H, s), 0.02 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 136.5, 135.7, 134.2, 134.1, 129.7, 127.8, 116.8, 107.9, 87.5, 74.6, 71.2, 69.9, 67.5, 61.5, 60.5, 48.7, 33.6, 27.0, 26.1, 21.2, 19.4, 18.4, 18.1, 14.4, −3.8, −3.9, −4.4, −4.5.

(Z)-2-((3R,4R,5R)-3,5-Bis((tert-butyldimethylsilyl)oxy)-4-(3-((tert-butyldiphenylsilyl)oxy)propoxy)-2-methylenecyclohexylidene)ethan-1-ol (**17**). A solution of compound **16** (1.08 kg, 1.29 mol) in CH_3CN (32.5 L) was degassed under Ar gas for 30 min. To the reaction mixture were added $Pd(PPh_3)_4$ (90 g, 78 mmol) and Et_3N (19.5 mL, 1.39 mol). The reaction mixture was refluxed at 81 °C for 1 h. The reaction mixture was cooled to rt and concentrated in vacuo. Purification by silica gel column chromatography (hexanes/AcOEt = 9:1) gave product **17** (0.83 kg, 1.16 mol, 90%) as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67−7.64 (4H, m), 7.44−7.33 (6H, m), 5.52 (1H, t, J = 6.7 Hz), 5.23 (1H, s), 4.84−4.82 (1H, m), 4.25−4.09 (4H, m), 3.80−3.62 (4H, m), 3.18 (1H, dd, J = 6.9, 2.1 Hz), 2.43−2.36 (1H, m), 2.26−2.17 (1H, m), 1.88−1.79 (2H, m), 1.20−1.00 (1H, m), 1.04 (9H, s), 0.89 (9H, s), 0.86 (9H, s), 0.06 (3H, s), 0.04−0.03 (9H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.4, 139.2, 135.7, 134.1, 129.7, 127.7, 126.8, 84.5, 74.2, 69.1, 68.4, 61.4, 60.5, 60.0, 41.3, 33.5, 27.0, 25.9, 21.2, 19.4, 18.4, 18.3, 14.4, −4.5, −4.6, −4.7.

(((1R,2R,3R,Z)-2-(3-((tert-Butyldiphenylsilyl)oxy)propoxy)-5-(2-chloroethylidene)-4-methylenecyclohexane-1,3-diyl)bis(oxy))bis(tert-butyldimethylsilane) (**18**). A solution of NCS (0.318 kg, 2.38 mol) in CH_2Cl_2 (7.5 L) was cooled to 0 °C. To the reaction mixture was added Me_2S (0.19 L, 2.55 mol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min and cooled to −20 °C. A solution of compound **17** (0.83 kg, 1.16 mol) in CH_2Cl_2 (5 L) was added dropwise to the reaction mixture. The reaction mixture was stirred at −20 °C for 20 min, stirred at rt for 30 min, and quenched with water (7.5 L). The organic layer was separated, dried over Na_2SO_4, and concentrated in vacuo. Purification by silica gel column chromatography (hexanes/AcOEt/Et_3N = 10:1:0.1) gave product **18** (0.76 kg, 1.05 mol, 90%) as yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.67−7.63 (4H, m), 7.44−7.34 (6H, m), 5.52 (1H, t, J = 7.8 Hz), 5.29 (1H, s), 5.04−5.03 (1H, m), 4.25 (1H, d, J = 7.2 Hz), 4.19−4.09 (3H, m), 3.79−3.62 (4H, m), 3.17−3.15 (1H, m), 2.39 (1H, dd, J = 13.5, 6.9 Hz), 2.23−2.17 (1H, m), 1.88−1.79 (2H, m), 1.04 (9H, s), 0.89 (9H, s), 0.85 (9H, s), 0.06 (3H, s), 0.04 (3H, s), 0.03 (3H, s), 0.02 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.5, 135.7, 134.1, 129.7, 127.8, 123.1, 69.0, 68.5, 61.4, 44.9, 41.4, 33.5, 27.0, 26.0, 25.9, 19.4, 18.4, 18.3, −4.5, −4.7.

((Z)-2-((3R,4R,5R)-3,5-Bis((tert-butyldimethylsilyl)oxy)-4-(3-((tert-butyldiphenylsilyl)oxy)propoxy)-2-methylenecyclohexylidene)ethyl)diphenylphosphine oxide (**2**). A solution of $HPPh_2$ (0.27 L, 1.58 mol) in THF (9.5 L) was cooled to 0 °C. To the reaction mixture was added dropwise 2.5 M *n*-BuLi in *n*-hexane (0.63 L, 1.58 mol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min to generate $LiPPh_2$ solution. A solution of compound **18** (0.76 kg, 1.05 mol) in THF (9.5 L) was cooled to −60 °C. $LiPPh_2$ solution was added dropwise to the reaction mixture. The reaction mixture was stirred at −60 °C for 1 h, quenched with water (95 mL) at −60 °C, and evaporated. The resulting substance was diluted with $CHCl_3$ (13.5 L) and 5% H_2O_2 (4.5 L) was added at rt and stirred at rt for 10 min. The organic layer was separated, washed with aqueous 5% $Na_2S_2O_3$ solution (16.5 L), dried over Na_2SO_4, and concentrated in vacuo. Purification by silica gel column chromatography (CH_2Cl_2/THF = 15:1) gave product **2** (0.75 kg, 0.838 mol, 80%) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78−7.71 (4H, m), 7.70−7.66 (4H, m), 7.59−7.37 (12H, m), 5.36 (1H, dd, J = 14.4, 7.2 Hz), 5.26 (1H, s), 4.84 (1H, t, J = 1.8 Hz), 4.27 (1H, d, J = 7.5 Hz), 4.15−4.11 (1H, m), 3.79−3.64 (4H, m), 3.43−3.31 (1H, m), 3.28−3.15 (1H, m), 3.12 (1H, dd, J = 7.7, 2.0 Hz), 2.38−2.33 (1H, m), 2.23−2.15 (1H, m), 1.91−1.82 (2H, m), 1.07 (9H, s), 0.93 (9H, s), 0.83 (9H, s), 0.10 (3H, s), 0.05−0.03 (9H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.6, 135.7, 134.1, 131.9, 131.3, 131.2, 131.1, 129.7, 128.8, 128.7, 128.6, 127.7, 115.4, 69.2, 68.6, 61.5, 33.4, 27.0, 26.0, 19.3, 18.4, 18.3, −4.5, −4.6, −4.7.

(1R,3aR,7aR)-7a-Methyl-1-((R)-6-methylheptan-2-yl)-octahydro-4H-inden-4-one (**19**). To a solution of vitamin D_3 (1.46 kg, 3.80 mol) in CH_2Cl_2 (47 L) and MeOH (15 L) was added $NaHCO_3$ (0.022 g, 0.26 mol) at rt. The reaction mixture was cooled to −65 °C. Ozone was passed through the solution (0.1 MPa, 2.0 mL/min) for 4 h until the reaction is complete. The reaction mixture was warmed to −30 °C, quenched with DMS (1.42 L, 19.02 mol), warmed to rt, and stirred for 18 h at rt. To the resulting solution was added water (15 L) and stirred for 30 min. The organic layer was extracted with CH_2Cl_2 (30 L), dried over Na_2SO_4, and concentrated in vacuo. Purification by silica gel column chromatography (hexanes/AcOEt = 4:1) gave product **19** (0.91 kg, 3.44 mol, 85%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.47 (1H, dd, J = 11.7, 7.5 Hz), 2.29−2.25 (2H, m), 2.25−1.00 (17H, m), 0.97 (3H, d, J = 6.0 Hz), 0.90 (3H, d, J = 6.6 Hz), 0.88 (3H, d, J = 6.6 Hz), 0.66 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.2, 62.0, 56.7, 49.9, 41.0, 39.4, 39.0, 36.0, 35.5, 28.0, 27.5, 24.1, 23.8, 22.8, 22.5, 19.1, 18.7, 12.5.

(1R,3aR,7aR)-1-((R)-6-Hydroxy-6-methylheptan-2-yl)-7a-methyloctahydro-4H-inden-4-one (**20**). To a solution of compound **19** (0.91 kg, 3.44 mol) in CH_3CN (33 L) and water (3.6 L) was added trifluoroacetone (6.1 L, 68.8 mol) at 0 °C. Oxone (12.7 kg, 20.6 mol) and $NaHCO_3$ (3.5 kg, 41.7 mol) were added to the reaction mixture. The reaction mixture was stirred at 0 °C for 24 h, quenched with water (9 L) and CH_2Cl_2 (9 L), stirred at rt for 1 h, and filtered. Water (18 L) was added to the crude mixture, and the mixture was stirred at rt for 30 min. The organic layer was separated, dried over Na_2SO_4, and concentrated in vacuo. Purification by silica gel chromatography (hexanes/AcOEt = 4:1) gave product **20** (0.51 kg, 1.82 mol, 53%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.45 (1H, dd, J = 11.7, 7.2 Hz), 2.28−1.00 (19H, m), 1.22 (6H, s), 0.97 (3H, d, J = 6.0 Hz), 0.64 (3H, s); ^{13}C

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NMR (75 MHz, $CDCl_3$) δ 212.1, 71.0, 62.0, 56.7, 49.9, 44.3, 41.0, 39.0, 36.2, 35.5, 29.4, 29.2, 27.5, 24.1, 20.7, 19.1, 18.7, 12.5.

*(1R,3aR,7aR)-7a-Methyl-1-((R)-6-methyl-6-((trimethylsilyl)oxy)heptan-2-yl)octahydro-4H-inden-4-one (**21**).* To a solution of compound **20** (0.51 kg, 1.82 mol) in CH_2Cl_2 (5.1 L) was added TMS-imidazole (0.76 kg, 5.42 mol) at rt. The reaction mixture was stirred at rt for 1.5 h, quenched with water (5.1 L), and stirred at rt for 10 min. The organic layer was separated, dried over Na_2SO_4, and concentrated in vacuo. Purification by silica gel chromatography (CH_2Cl_2) gave product **21** (0.50 kg, 1.42 mol, 78%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.55−2.41 (1H, m), 2.38−1.15 (17H, m), 1.22 (6H, s), 1.15−1.00 (1H, m), 0.98 (3H, d, J = 6.3 Hz), 0.66 (3H, s), 0.12 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.2, 74.0, 62.0, 56.8, 50.0, 45.2, 41.0, 39.0, 36.3, 35.5, 30.0, 29.9, 27.5, 24.1, 20.8, 19.1, 18.7, 12.5, 2.6.

*(((1R,2R,3R,Z)-2-(3-((tert-Butyldiphenylsilyl)oxy)propoxy)-5-(2-((1R,3aS,7aR,E)-7a-methyl-1-((R)-6-methyl-6-((trimethylsilyl)oxy)heptan-2-yl)octahydro-4H-inden-4-ylidene)ethylidene)-4-methylenecyclohexane-1,3-diyl)bis(oxy))bis(tert-butyldimethylsilane) (**22**).* To a solution of compound **2** (0.146 kg, 0.17 mol) in THF (1.46 L) was added 2.5 M *n*-BuLi in *n*-hexane (0.065 L, 0.17 mol) dropwise at −65 °C. The reaction mixture was stirred at −65 °C for 1 h. A solution of compound **21** (0.029 kg, 0.083 mol) in THF (0.29 L) was added dropwise to the reaction mixture at −65 °C. The reaction mixture was warmed to −10 °C for 2 h, quenched with water (1.46 L), and warmed to rt, AcOEt (1.46 L) was added and stirred at rt for 30 min. The organic layer was separated, dried over Na_2SO_4, and concentrated in vacuo. Purification by silica gel chromatography (hexanes/AcOEt = 30:1) gave product **22** (0.075 kg, 0.073 mol, 89%) as colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71−7.59 (4H, m), 7.45−7.31 (6H, m), 6.21 (1H, d, J = 11.1 Hz), 5.99 (1H, d, J = 11.1 Hz), 5.29−5.18 (1H, m), 4.96 (1H, d, J = 2.4 Hz), 4.24−4.10 (2H, m), 4.12 (1H, q, J = 7.2 Hz), 3.83−3.62 (4H, m), 3.22 (1H, dd, J = 6.6, 2.1 Hz), 2.94−2.87 (1H, m), 2.50−2.38 (1H, m), 2.21 (1H, dd, J = 13.2, 3.6 Hz), 2.08−1.12 (18H, m), 1.20 (6H, s), 1.10−0.96 (10H, m), 0.93 (3H, d, J = 6.3 Hz), 0.90−0.80 (18H, m), 0.53 (3H, s), 0.10−−0.10 (21H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3, 135.7, 134.6, 134.2, 129.6, 127.7, 123.4, 118.0, 74.3, 69.6, 68.4, 61.4, 60.5, 56.8, 56.5, 45.9, 45.4, 40.8, 36.6, 36.3, 33.5, 30.1, 30.0, 27.9, 27.0, 26.0, 23.7, 22.3, 21.1, 19.4, 19.0, 18.4, 18.3, 14.3, 12.1, 2.8, −4.5, −4.7.

*(1R,2R,3R,Z)-5-(2-((1R,3aS,7aR,E)-1-((R)-6-Hydroxy-6-methylheptan-2-yl)-7a-methyloctahydro-4H-inden-4-ylidene)ethylidene)-2-(3-hydroxypropoxy)-4-methylenecyclohexane-1,3-diol [Eldecalcitol] (**1**).* To a solution of compound **22** (0.075 kg, 0.073 mol) in CH_2Cl_2 (0.56 L) and MeOH (0.56 L) was added *p*-TsOH·H_2O (0.014 kg, 0.073 mol) at rt. The reaction mixture was stirred at rt for 5 h, quenched with aqueous 3% $NaHCO_3$ solution (0.24 L), washed with aqueous 10% NaCl solution (0.24 L), dried over Na_2SO_4, and concentrated in vacuo. Purification by silica gel chromatography (CH_2Cl_2/MeOH = 30:1) gave eldecalcitol (**1**, 0.029 kg, 0.058 mol, 80%) as a white solid. Further purification by recrystallization from a mixture of CH_3CN (0.43 L) and water (0.43 L) gave **1** (0.020 kg, 0.041 mol). $[\alpha]^D_{20}$ = −39.4 (*c* 0.4, EtOH); IR (neat) ν max 3535, 3421, 3329, 2941, 2924, 2860, 1447, 1373, 1114, 1073, 1045 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35 (1H, d, J = 11.2 Hz), 6.04 (1H, d, J = 11.3 Hz), 5.50 (1H, t, J = 2.1 Hz), 5.08 (1H, t, J = 2.1 Hz), 4.33−4.29 (1H, m), 4.26−4.24 (1H, m), 3.95−3.87 (1H, m), 3.83 (2H, q, J = 5.3 Hz), 3.75−3.68 (1H, m), 3.27−3.23 (2H, m), 2.83−2.74 (2H, m), 2.63 (1H, d, J = 2.3 Hz), 2.54 (1H, dd, J = 14.5, 4.0 Hz), 2.41 (1H, d, J = 14.1 Hz), 2.02−1.93 (2H, m), 1.92−1.82 (3H, m), 1.71−1.63 (2H, m), 1.59−1.36 (8H, m), 1.29−1.20 (4H, m), 1.21 (6H, s), 1.09−1.00 (1H, m), 0.94 (3H, d, J = 6.3 Hz), 0.55 (3H, s), missing C-25 hydroxyl proton; ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 143.1, 132.3, 125.0, 117.4, 111.9, 85.5, 71.6, 71.2, 68.4, 66.7, 61.2, 56.7, 56.5, 46.0, 44.5, 40.6, 36.5, 36.2, 32.0, 29.5, 29.3, 29.2, 27.8, 23.8, 22.5, 20.9, 19.0, 12.1; HRMS(ESI+) $[M + Na]^+$ m/z calcd for $C_{30}H_{50}O_5Na^+$ 513.3550, found 513.3560.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.0c00436.

Synthesis of dienol **3** from D-mannitol (Scheme S1), experimental procedures of **23**, **24**, **3**, **7**, and **8**, and copies of ^{1}H and ^{13}C NMR spectra of all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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